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Changing rates but persisting seasons: patterns of enterovirus infections in hospitalizations and outpatient visits in Denmark 2015-2022

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Background: Enteroviruses (EV) constitute a diverse group of viruses manifesting a broad spectrum of clinical presentations in humans ranging from mild skin manifestations to more severe central nervous system (CNS) infection. Severe infections are reported with increased frequency globally, albeit the burden of diseases and the evolution of circulating viruses is largely unknown. We aimed to systematically explore contemporary trends in hospitalizations attributed to EV infections using national hospitalization discharge data.

Methods: We utilized the Danish National Patient Register which holds information on all contacts to Danish hospitals. We covered eight full years (2015-2022). Length-of-stay and administrative procedure codes were used to distinguish hospital admissions from outpatient visits. We utilized burden of disease estimates and distribution statistics.

Results: We identified 1029 hospitalizations and 1970 outpatient visits due to EV infections. The hospital admissions were primarily associated with CNS-infections (n=570, 55.4%) and skin (n=252, 24.5%), with variation over the studied period. The admitted patients were predominately children (43.8%) though patients were identified in all ages. The clinical manifestation was associated with age, with CNS infections dominating in the neonates and adults, and skin infections dominating in children 1-2 years (17.2%). Outpatient visits were predominantly observed among children 1-2 years (55.0%), presenting with skin symptoms (77.9%). We show a seasonal pattern of EV infections with summer/fall peaks and markedly impact on the EV hospitalization burden related to COVID-19 mitigation measures including national lockdown periods. 25% of hospital admissions occurred during 2020-2022.

Conclusion: EV infections caused both hospital admissions and outpatient visits in the period studied, predominately among children aged 1-2 years. Overall, skin

infections dominated the outpatient visits, while the majority of hospital admissions were due to CNS infections. The pandemic period did not change the seasonal pattern of EV infections but notably lowered the number of admissions to hospital with CNS infection and raised the number of outpatient admissions with skin infection.

KEYWORDS

enterovirus, epidemiology, cohort study, seasonality, meningitis, childhood infection, clinical presentation

1 Introduction

Human enteroviruses (EV) are common viruses, with over 300 EV types characterized genetically by phylogenetic clustering to this date. EV belongs to the genus Enterovirus of the Picornaviridae family, consisting of single-stranded RNA viruses. EV are classified into four species (*Enterovirus A- Enterovirus D*) and three rhinovirus species (*Rhinovirus A – Rhinovirus C*) (1–3). Five additional animal species (*Enterovirus E- Enterovirus J)* exist as well. Most EV infections are asymptomatic or cause mild upper respiratory or gastrointestinal infections but EV can cause severe infections, in particular in young infants with central nervous system (CNS) involvement and potential long-term impairment (1, 4, 5). EV have been the cause of major epidemics, with severe clinical manifestation such as poliomyelitis (6). A European review of EV laboratory data through national reference laboratories between 2015-2017 reported that 66% of infections documented were in children younger than 5 years and that 45% of cases presented with neurological symptoms (7).

Recently, EV have been linked with acute flaccid myelitis (AFM), in particular types EV-D68 and EV-A71 have been recognized as causal agents of flaccid paralysis similar to poliomyelitis in children (8–10). In Denmark, the first case of AFM caused by EV-D68 was reported in 2020, and the circulation is monitored closely by the national public health institute, Statens Serum Institute (SSI) (11, 12). Commencing with the onset of the COVID-19 pandemic, there has been a surge in reports detailing EV infections attributed to Echovirus-11 in newborns with severe clinical impact and mortality higher than usual (13–16).

With the recent trends of more severe EV infections emerging and re-emerging, attention should be given to documenting the impact of these infections, including a more detailed description of the disease burden caused by the viruses. A study of EV-positive samples showed a steady number of between 215-315 positive per year from 2010-2013 (17). Studies of EV infections in Denmark based on reviews of medical journals have shown higher number of EV meningitis in adults in 2017/2018 compared to the years before, but with a decline again in 2019 (18, 19). There is no systematic information on severe EV infections in children or in adults without CNS involvement available from Denmark, and it is the aim of this study to provide information on all severe EV infections. This is needed to guide public health decisions on surveillance and interventions.

We explored the Danish national health registries to assess the burden of documented hospital admissions associated with EV infection regardless of clinical presentation in the Danish population during an 8-year period.

2 Materials and methods

We conducted an observational study of patients admitted to hospitals in Denmark from January 1, 2015, to December 31, 2022, utilizing data from the Danish National Patient Register (NPR) (20), the Medical Birth Register (MFR) (21), and the Cause of Death Register (DAR) (22) to gain information on demographics, outcomes, and risk factors. The NPR serves as a comprehensive research register founded on the entirety of administrative registrations documenting hospital contacts throughout Denmark. Each contact within this register is assigned a primary diagnosis using the International Classification of Disease no. 10 (ICD-10), and the inclusion of optional and unlimited secondary diagnoses enhances the depth of clinical information (20). The MFR holds detailed records of Danish births, with clinical information on mother, child, and delivery. Additionally, the repository contains administrative information outlining the procedures involved in each birth (21). The Cause of Death Registry (DAR) compiles information concerning all Danish residents who have deceased within the borders of Denmark. The causes of death are listed in the registry as they are declared on the death certificate of the diseased person (22).

Contacts to hospital with EV diagnosis was extracted from the NPR, where only the ICD-10 diagnosis is available. The registry holds no specific clinical information and no information on patient samples, though we assume that patients with EV specific diagnosis have had confirmative testing leading to the specific diagnosis. Diagnostic testing primarily occurred based on clinical indication. All samples positive for EV were shipped to the SSI reference laboratory for confirmation tests and subtyping of samples as part

of the WHO polio surveillance framework (5, 17). EV are typically identified with polymerase chain reaction (PCR) tests on samples (cerebrospinal fluid (CSF), sputum, saliva, blood, skin, fecal) from patients with suspected EV infection. During the study period emergency departments and departments of infectious medicine invested in small point-of-care-test (POCT) PCR (POCT-PCR) machines, for syndromic testing. With this, most EV testing is conducted as real-time PCR tests at Departments of Clinical Microbiology (KMA) or the national reference laboratory at SSI, using in-house assays PCR-testing (17) or at hospitals using POCT with commercial syndromic assays PCR for CNS-, respiratory- or gastrointestinal infections (multiple manufacturers).

EV infections were defined by the ICD-10 codes and divided into groups based on diagnosis. Diagnostic groups were distinguished using ICD-10 codes. We divided the diagnosis into main groups after organ system and frequency, combining diseases in organ systems with few instances of registration into the group 'Other'. In organ system group central nervous system (CNS), infections with symptoms involving the CNS are included. In the group skin infections, infections with presentations predominantly in the skin, such as rashes, blisters, or ulcers, are included. The specific diagnoses are presented in Table 1. Contacts to hospital were included in the study if patients were given at least one EV diagnosis, primary or secondary, during admission. Patients with contacts starting on or between 1. January 2015 and 31. December 2022 were included in the study. Information on discharge and deaths were obtained on 13. July 2023. Contacts with no discharge date at the end of study were excluded. Contacts due to accidents and planned recurrent visits (i.e., for follow-up treatment or examination) were excluded using administrative procedure codes. Contacts shorter than 12 hours were considered outpatient visits and contacts with a minimum of 12 hours of hospitalization were considered a hospital admission. Two concurrent admissions were treated as one admission if the time between discharge and next admission were 7 days or less. Recurrent admission with EV diagnosis within 90 days of discharge was investigated individually to establish if the second admission was a part of the first registered admission or a new infection causing hospital admission.

We classified the patients into the following age groups by the age at admission: <1 month (30 days or less), 1-2 months (31 days -12 weeks), 3-5 months (13-24 weeks), 6-11 months (25-52 weeks), 1-2 years, 3-5 years, 6-17 years, 18-25 years, 26-45 years, 46-65 years, 66+ years.

We calculated length-of-stay (LOS) from the start of first registered admission, until last timestamp of the admission. If patients were transferred between departments or hospitals, the admissions were considered connected and counted as one admission.

Severe outcomes of the EV infection were defined as registered need for oxygen treatment, admission to the intensive care unit (ICU) or death. Patients who received oxygen treatment and/or admission to ICU were identified through procedure codes in NPR. Deaths during admission or within 30 days of discharge were identified in DAR.

Expected risk factors in the patients were identified through NPR and MFR. For children we investigated the distribution of preterm birth, low birth weight, and maternal smoking during pregnancy. In adults, we investigated the distribution of cancer, diabetes, ischemic heart disease, and chronic obstructive pulmonary disease (COPD).

We conducted descriptive analysis; frequency distributions and incidence rates pr. 100,000 person years, in age groups where appropriate. Population estimates were gathered from Statistics Denmark (23). We calculated medians and interquartile ranges (IQR) for continuous variables age and LOS. All analysis were performed using R version 4.3.1 (24).

3 Results

3.1 Hospital admissions

We identified 1029 patients admitted to hospitals with EV infections, and found they consisted of 1024 unique individuals based on the Danish civil registration system. 5 patients had multiple admissions with EV infection. 55.8% of patients were male, with male domination in all age groups except from 18-25 years (45% male) and 66+ *years* (36% male) (Table 2).

Patients younger than 3 years represented 42.7% (n=379) of all admissions and 262 admissions (25.5%) were in children younger than 1 year. The highest incidence rate of admission was found in the neonates (256 admissions pr. 100,000 children <1 month) (Table 2). Adults aged 26-45 years had the highest admission incidence rate (2.96 per 100,000), and this age group accounted for 33.1% of all patients admitted. Across all patients, the median length of stay (LOS) was 2.8 days (IQR: 1.2-9.0). Adults 66+ years had the longest median LOS, with 9.9 days (IQR: 2.6-22.7). In the adult age groups admissions with more than 30 bed days were not uncommon (26-45 years, median 3.8 (IQR: 1.2-68.7)) (Table 2). Among the youngest children (<1 month) the median LOS was 4.6 days (IQR: 3.1-7.2) (Table 2).

Our study covered eight full calendar years with a fluctuating number of admissions per year, reaching a maximum in 2018 (228 admissions, 22.2%) and a minimum in 2020 (52 admissions, 5.1%) (Table 3). Admissions by month followed a seasonal pattern, with few during the winter months of January to March, admissions increasing during the summer months of June and July, peaking either in the late summer months of August and September or in fall months October or November (Figure 1). During the COVID-19 pandemic period (2020–2022), the seasonal pattern continued but the number of cases was lower. The distribution between age groups changed during the study period, with a smaller portion of admissions occurring in adults during the pandemic period compared to the years 2017-2019 (Figure 2). A larger proportion of children (<18 years) admitted in the pandemic period were older than 6 months, while the proportion of children <1 month was not markedly different in this period (Figure 2).

The patients were predominately admitted to hospital due to EV infection in two major organ systems: the CNS (55.4%) or the skin (24.5%), though other organ systems were affected in 20.1% of the admissions (see Table 1 for included diagnosis, Table 2). The disease pattern varied with age as children were more prone to be

TABLE 1 ICD-10 codes and SKS-codes used to identify admissions with EV infection, severe outcomes, and comorbidities in adults.

ICD-10 code	Diagnostic definition	Notes	Organ system	N in study*
DA850	Enteroviral encephalitis		Central nervous system	73
DA870, DA870A, DA870B	Enteroviral meningitis	A: Coxsackievirus, B: Echovirus	Central nervous system	619
DA80	Acute poliomyelitis		Central nervous system	20
DA801	Acute paralytic poliomyelitis, wild virus, imported		Central nervous system	0
DA802	Acute paralytic poliomyelitis, wild virus, indigenous		Central nervous system	0
DA803	Acute paralytic poliomyelitis, other and unspecified		Central nervous system	5
DA804	Acute nonparalytic poliomyelitis		Central nervous system	<5
DA809	Acute poliomyelitis, unspecified		Central nervous system	13
DA880	Enteroviral exanthematous fever [Boston exanthem]		Skin	19
DB303A, DB303B	Acute epidemic hemorrhagic conjunctivitis (enteroviral)	A: Coxsackievirus type 24, B: Enterovirus type 70	Other organ systems	0
DB084	Enteroviral vesicular stomatitis with exanthem		Skin	1351
DB085	Enteroviral vesicular pharyngitis		Skin	349
DB088B	Enteroviral lymphonodular pharyngitis		Skin	73
DB330	Bornholm disease		Other organ systems	17
DB341, DB341A, DB341B	Enterovirus infection, unspecified site	A: Coxsackievirus, B: Echovirus	Other organ systems	261
DB971	Enterovirus as the cause of diseases classified to other chapters		Other organ systems	245
Comorbidity: ICD-10 codes				
DC**	All Cancer-diagnosis included			
DJ440, DJ441, DJ448, DJ449	Chronic obstructive pulmonary disease			
DE10, DE11, DE12, DE13, DE14, DP70, DR73, DR739	Diabetes			
DI20, DI21, DI22, DI23, DI24, DI25	Ischemic heart disease			
SKS-Codes for severity of disease	Explanation		Indicator	
BGDA2	High-flow oxygen treatment		Oxygen treatment	
BGXA5	Oxygen treatment		Oxygen treatment	
NABB	Intensive therapy		ICU-admission	
NABE	Intensive care observation		ICU-admission	
NABS	Anesthesiologic assistance		ICU-admission	
ZSAB0	Admission to intensive care unit		ICU-admission	

*Each patient may be registered with multiple diagnosis during the same admission.
**All subsidiary codes included.

TABLE 2 Hospital admissions with enterovirus infection.

	N (%) Admissions	IR (Admission incidence rate pr. 100,000 person years*)	Length of Stay in days pr admission Median (IQR)
Total	1029	2.2	2.8 (1.2-9)
Sex			
Male	574 (55.8)	2.5	2.8 (1.2-9)
Female	455 (44.2)	2.0	2.8 (1.2-9.1)
Age			
median (IQR)	11.0 (0 – 32)		
Age group			
<1 month	104 (10.1)	256.0	4.6 (3.1-7.2)
1-2 months	78 (7.6)	108.4	3.2 (1.9-5.9)
3-5 months	32 (3.1)	26.3	2.7 (1.2-4.1)
6-11 months	48 (4.7)	22.2	2.2 (1-3.4)
1-2 years	177 (17.2)	18.3	1.2 (0.8-3)
3 -5 years	42 (4.1)	2.9	2.1 (1-4.3)
6-17 years	72 (7.0)	1.1	1.7 (1.1-3.4)
18-25 years	71 (6.9)	1.5	2.9 (1.1-35.9)
26-45 years	341(33.1)	3.0	3.2 (1.3-32.1)
46-65 years	42 (4.1)	0.4	3.8 (1.2-68.7)
66+ years	22 (2.1)	0.3	9.9 (2.6-22.7)
Organ system			
Central nervous system	570 (55.4)	1.2	3.8 (1.7-31.9)
Skin	252 (24.5)	0.6	1.1 (0.8-2.5)
Other organ systems	207 (20.1)	0.5	3 (1.3-5.3)

*Background population is yearly total population, by age group where needed.

admitted with skin infections and adults more often admitted due to CNS infections (Figure 3).

The seasonal pattern differed by which organ system was infected (Figure 4). CNS-infections had clear seasonal peaks, while the seasonal variation was less pronounced for skin-infections and other infections. Skin- and other infections with EV occurred throughout the year, with small peaks at the same time as the CNS-infections, either in summer months around August or the fall month of October. During the COVID-19 pandemic period (2020-2022), the number of admissions with CNS-infections fell to exceptionally low levels and the expected peaks did not occur in 2020 and 2021, while admissions with skin and other infections did not change their seasonal pattern in this period.

When looking at severity of EV infections among the admitted patients, we found that 0.9% were admitted to the intensive care unit (ICU). Oxygen was required as a part of the treatment in 9.7% of admissions (n=100). Oxygen treatments were used in all age groups. In patients <1 month 5.8% received oxygen treatment, and children, the proportions receiving oxygen treatments varied between 2.6% (1-2 months) and 9.5% (3-5 years). In the age group 26-45 years 21.1% required oxygen treatment, which was the highest proportion among adults. Oxygen treatments were administered in 7% of CNS admissions, 2.6% of skin admissions and 1.1% of other admissions. Throughout the study period, there were 2 fatal cases within 30 days of EV-admission, all in adults above 45 years. There were no fatalities with EV-infection as registered cause of death (Data not shown).

We found that a possible risk factor in children admitted with EV was being born prematurely and with low birth weight (4.6% and 4.3% respectively in children <18 years, and in children younger than 1 year, 4.9% and 4.6% respectively) while 1.2% had low birth weight for their gestational age. Maternal tobacco usage during pregnancy occurred in 12.3% of admissions among children <18 years and 10.3% in children <1 year (Table 4).

For adults, we investigated the distribution of diagnoses of cancer, diabetes, heart disease, and chronic obstructive pulmonary disease (COPD) (Table 4). In 3.9% of adults admitted with EV, the patient had a diagnosis of at least one of these comorbidities within 5 years before admission.

3.2 Outpatient visits

We identified 1970 outpatient visits (i.e., hospital stays shorter than 12 hours and not a planned control) with EV infections, where 59.0% of patients were male. The incidence rate per 100,000 person years was 4.3 visits (Table 5). Children aged 1-2 years accounted for 55.8% of the outpatient visits (IR: 113.8) while children <1 month had almost no outpatient visits (6, 0.3%). Among outpatients, skin infections were most prevalent, with 77.9% of all visits. CNS-infections constituted 7.0% of outpatient visits (Table 5). Over time, the number of outpatient visits per month increased, and in 2019-2022 a seasonal pattern emerged, which remained unchanged during the pandemic period (2020-2022) (Figure 5).

4 Discussion

In this study we documented the number of patients diagnosed and admitted with EV infections in Danish hospitals over an 8-year period. This is the largest full-national systematic documentation of severe EV infections in a European country to this date. Utilizing the National Danish health care registers, we were able to identify all registered EV infections causing either admission to hospital or outpatient visits. The proportion of EV admissions caused by CNS-infections was highest among in-patients, whereas skin-infections were most common among patients seen as out-patients. EV infections were predominantly registered among young children. CNS-infections constituted the majority of hospital admissions. However, it was notable that this trend deviated among the youngest infants aged 3-5 months up to 3-5 years. Hospitalizations among these young children were mainly caused

TABLE 3 Yearly distributions for enterovirus admissions n (%).

	2015	2016	2017	2018	2019	2020	2021	2022
Total	103 (10)	107 (10.4)	179 (17.4)	228 (22.2)	151 (14.7)	52 (5.1)	81 (7.9)	128 (12.4)
Sex								
Female	40 (39)	47 (44)	75 (42)	99 (43)	71 (47)	28 (54)	35 (43)	60 (47)
Male	63 (61)	60 (56)	104 (58)	129 (57)	80 (53)	24 (46)	46 (57)	68 (53)
Organ system								
Central nervous system	39 (38)	73 (68)	123 (69)	161 (71)	90 (60)	13 (25)	15 (19)	56 (44)
Skin	38 (37)	19 (18)	36 (20)	34 (14)	29 (19)	25 (48)	38 (47)	33 (26)
Other organ systems	26 (25)	15 (14)	20 (11)	33 (14)	32 (21)	14 (27)	28 (35)	39 (30)
Age group								
<1 month	12 (12)	13 (12)	10 (5.6)	26 (11)	16 (11)	<10 (- -)	<5 (- -)	18 (14)
1-2 months	<10 (- -)	9 (8.4)	8 (4.5)	25 (11)	14 (9.3)	<5 (- -)	5 (6.2)	8 (6.3)
3-5 months	6 (5.8)	6 (5.6)	<5 (- -)	<5 (- -)	<5 (- -)	<5 (- -)	5 (6.2)	5 (3.9)
6-11 months	8 (7.8)	<5 (- -)	5 (2.8)	8 (3.5)	7 (4.6)	<5 (- -)	8 (9.9)	5 (3.9)
1-2 years	23 (22)	7 (6.5)	22 (12)	21 (9.2)	26 (17)	15 (29)	30 (37)	33 (26)
3-5 years	5 (4.9)	<5 (- -)	5 (2.8)	<5 (- -)	7 (4.6)	<5 (- -)	8 (9.9)	9 (7.0)
6-17 years	<5 (- -)	<10 (- -)	16 (8.9)	20 (8.8)	9 (6.0)	<5 (- -)	8 (9.9)	6 (4.7)
18-25 years	8 (7.8)	7 (6.5)	14 (7.8)	22 (9.6)	11 (7.3)	<5 (- -)	<5 (- -)	<5 (- -)
26-45 years	24 (23)	45 (42)	85 (47)	85 (37)	52 (34)	7 (13)	6 (7.4)	37 (29)
*46+ years**	8 (7.8)	7 (6.5)	10 (5.6)	16 (7.1)	8 (5.2)	5 (9.2)	<10 (- -)	<5 (- -)

*66+ years are added to 46-65 due to low cell-counts, for a combined group of 46+.

by EV-associated skin infections (dominating diagnose of Hand-Foot-and Mouth disease (HFMD)). Also notably, among children in the age group of 3- 5 years, the distribution of hospital admissions reached parity among skin, CNS and other EV-infections (Figure 3). Among the hospital admissions, LOS differed between age groups, with longer stays in neonates, which could possibly be explained by hospital admissions for EV occurring simultaneously with their birth, as well as neonates being at higher risk of admission due to their venerability. In adults aged above 66 years, the LOS was the highest, which may be explained by EV infections occurring simultaneously with other severe diseases or chronic conditions worsening with the infections.

We observed a seasonal pattern characterized by peak infection rates in either the months of August and September or October and

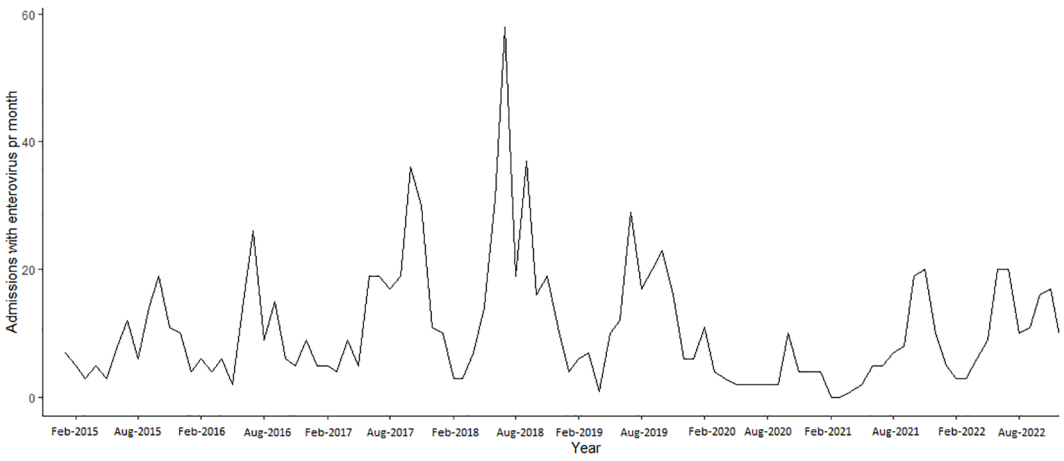

FIGURE 1
Enterovirus admissions per month 2015-2022.

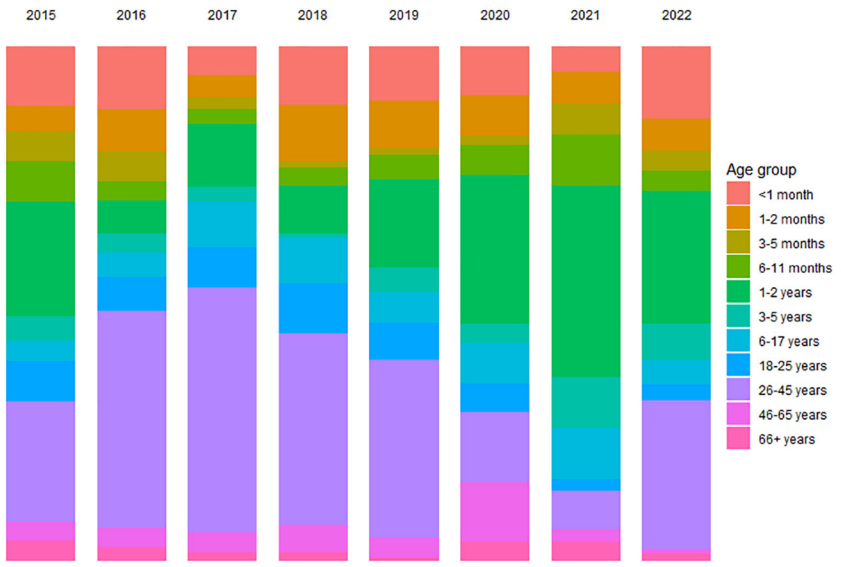

FIGURE 2
Age distribution in hospital admissions by year.

November. A trend that was less pronounced in hospital admissions during the pandemic period. This shift in pattern was attributed to a change in the prevalence of CNS infections, while skin infections and other infections maintained relatively low occurrences.

In 2018, hospital admissions with EV were at the highest during the study period. This peak can be explained by an echo 11 epidemic, as described by Broberg 2018 (25) The low number of hospitalizations in 2020 was explained by the COVID-19 pandemic control measurements such as lock downs and restrictions on public activities (13, 26).

The number of outpatient visits exhibited an increasing trend from 2019 onwards, with skin infections predominantly contributing to the rise in numbers. Notably, outpatient skin infections demonstrated a seasonal pattern since 2017, which became more distinct during this period marked by an increase in infections. In other locations such as Brazil, India, and China, changes to the seasonality of HFMD have been reported since the onset of the pandemic. China experienced a decrease in cases, while Brazil and India witnessed increases in HFMD cases (27–29). To our knowledge no European studies have been published on the latest trends in HFMD. We found an equal number of monthly outpatient visits and inpatient hospital admissions in 2017-2018, but the increased trend of outpatient visits from 2019 onwards shifted this distribution. Overall, there were 1970 outpatient visits versus 1029 inpatient hospitalizations. When considering the pathogen specific diagnosis, a positive test for EV is expected for a diagnosis of a disease with CNS-involvement, where skin lesions from EV infections can be differentiated from other skin infections by a trained physician. This difference may affect the number of outpatients presenting with CNS-symptoms correctly diagnosed with EV infections.

We observed that severe adverse outcomes such as ICU admissions or death were infrequent in our study, and we have not extended our follow-up information to include potential late presentations of severe sequelae including impaired motor functions or other disabilities. A longitudinal study conducted in Denmark revealed that across all age groups, individuals with EV infections exhibited a 10-fold higher 1-year mortality rate, with no discernible variation in subsequent years (5). Another Danish study focused on adults with EV meningitis and found that 20% of

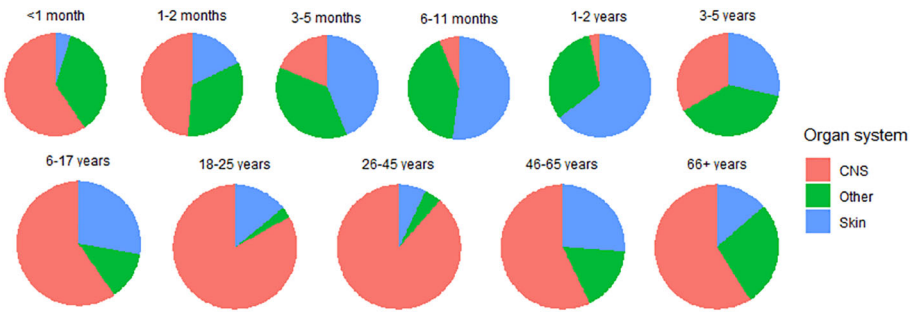

FIGURE 3
Distribution of infected organ systems in age groups.

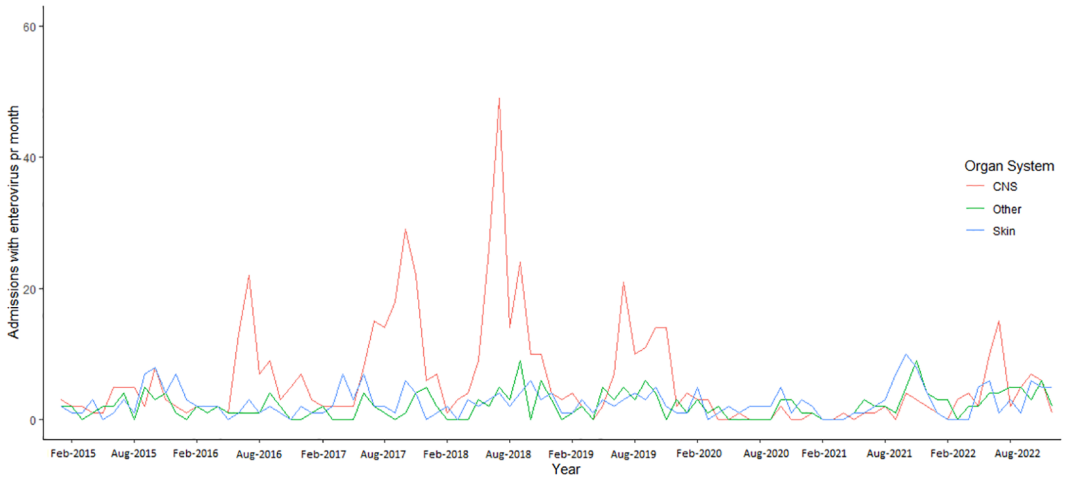

FIGURE 4
Enterovirus hospital admission by organ system affected 2015-2022.

patients experienced outcomes ranging from moderate disability to death within 30 days of discharge (18).

A comprehensive Danish clinical database dedicated to collecting information on infections in the CNS has systematically compiled data on adult EV meningitis from all hospitals in Denmark (19). Given that this data collection is prioritized by clinicians, we anticipate a near-complete representation of EV meningitis cases among hospital admissions. From 2015 to 2019, a total of 419 cases of adult EV meningitis were documented, a slightly lower figure than the overall number of adult admissions (476) disregarding the affected organ system or specific diagnoses over an extended study period.

TABLE 4 Risk factor distributions in admissions in children <18 and <1 years and adults.

Children's Comorbidities	*N (%)* N=553	*N patients <1 year (%)* N=262
Premature birth	26 (4.7)	13 (5.0)
Extremely premature	7 (1.3)	<5 (–)
Low birth weight	22 (3.9)	12 (4.6)
Low birth weight for gestational age	6 (1.1)	<5 (–)
Multiple birth	10 (1.8)	<5 (–)
Maternal tobacco usage during pregnancy	65 (11.7)	27 (10.3)
	N (%) N=476	
Adults' comorbidities *(Any of those below)*	19 (4.0)	
Cancer	9 (1.9)	
Diabetes	9 (1.9)	
COPD	<5 (–)	
Heart disease	<5 (–)	

TABLE 5 Descriptive statistics for enterovirus outpatient visits.

	N (%) out-patient visits	IR (Admission incidence rate pr. 100,000 person years*)
Total	1970	4.3
Sex		
Female	808 (41.2)	3.5
Male	1162 (58.8)	5.0
Age		
Median (IQR)	1.0 (1 – 4)	
Age group		
<1 month	6 (0.3)	38.6
1-2 months	29 (1.5)	40.3
3-5 months	33 (1.7)	30.7
6-11 months	205 (10.4)	96.8
1-2 years	1100 (55.8)	113.8
3 -5 years	157 (8.0)	10.7
6-17 years	103 (5.2)	1.6
18-25 years	60 (3.0)	1.4
26-45 years	205 (10.4)	1.8
46-65 years	47 (2.4)	0.6
66+ years	21 (1.1)	0.3
Missing	4 (0.2)	
Organ system		
Central nervous system	137 (7.0)	0.3
Skin	1534 (77.9)	3.3
Other organ systems	299 (15.0)	0.7

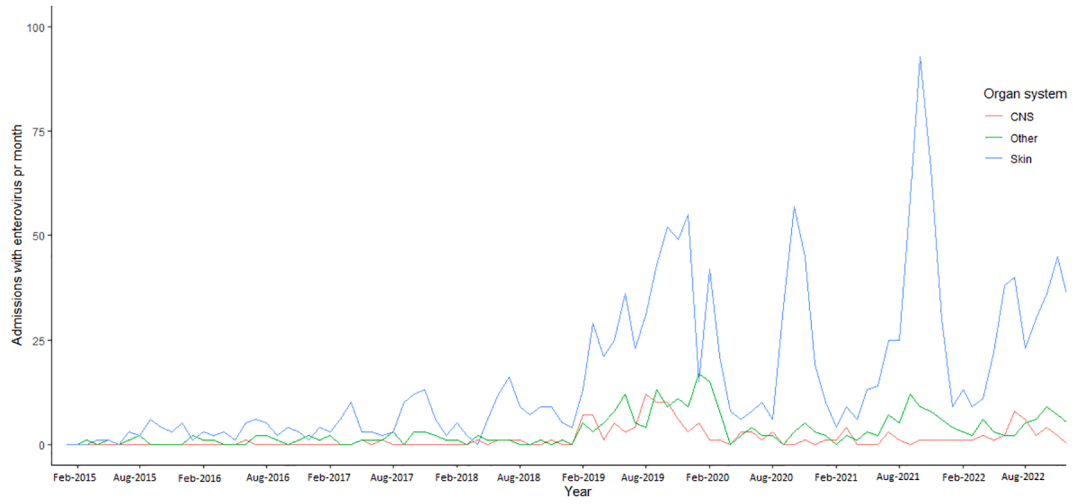

FIGURE 5
Enterovirus outpatient visits by organ system per month 2015-2022.

This observed discrepancy is likely attributable to underreporting of EV specific ICD-10 diagnosis in the healthcare registries, which primarily serve as administrative tools for the planning and financing of Denmark's health care system. Similar deficiencies in ICD-10 codes within administrative registries of infectious diseases have been previously demonstrated in other settings when compared to clinical datasets of confirmed positive cases (30).

Beyond the variations in preferences for specific ICD-10 codes, our observations suggest that limited awareness of EV in general, may contribute to divergent practices in testing and diagnosis outpatient visits, where the seasonal trends of EV infections only became evident after 2018, coinciding with the increased adoption of point-of-care testing.

This discrepancy was most pronounced in outpatient visits, where the seasonal trends of EV infections only became evident after 2018, coinciding with the increased adoption of point-of-care testing polymerase chain reaction (POCT-PCR) in emergency departments across Denmark. In the case of young children, the rarity of pathogen diagnosis in CNS-infections coupled with low C-reactive protein (CRP) counts, often leads pediatricians to refrain from performing lumbar puncture procedures. Consequently, in the absence of a confirmed infective pathogen, hospital admissions are less likely to be assigned EV-specific ICD-10 codes. While our work has documented registered EV infections in Denmark from 2015 to 2022, the challenges associated with ICD-10 coding may have led to an underestimation of the true burden of EV infections.

We advocate for the adoption of prospective study designs, akin to those implemented in the Danish clinical database for adults with infections in the brain, and the surveillance pilots proposed by the European non-polio enterovirus network (19, 31). These approaches, encompassing all age groups and considering diverse clinical presentations, will be instrumental in detecting EV infections more comprehensively. By further investigating EV infections and systematically collecting information on symptoms, outcomes, diagnoses, and treatments, we can enhance our understanding of the intricate landscape of EV infections.

5 Conclusion

In this retrospective national study of EV-associated hospitalizations, CNS-infections were most prevalent among hospitalized patients across all ages, while skin-infections and HFMD was most common among pediatric outpatient visits. The affected organ system leading to hospital admission exhibited age-related variations, with CNS infections prevailing in the youngest children and in adults. Interestingly, the seasonal pattern of CNS-infections causing admissions showed a diminished prominence during the pandemic period. In contrast, the seasonality observed in skin infections prompting outpatient visits remained unaffected. This intriguing divergence in the impact of the pandemic on the seasonal dynamics of different EV-infection types warrants further investigation and consideration in public health strategies.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: The datasets presented in this article are not readily available due to Danish data protection legislation. All register data in Denmark are accessible for researchers with approval for use from the relevant authorities. Requests to access the datasets should be directed to Sundhedsdatastyrelsen (The Danish Health Data Authority). Requests to access these datasets should be directed to e-sundhed.dk.

Ethics statement

Ethical approval was not required for the study involving humans in accordance with the local legislation and institutional requirements. Written informed consent to participate in this study was not required from the participants or the participants' legal guardians/next of kin in accordance with the national legislation and the institutional requirements.

Author contributions

CJ: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Visualization, Writing – original draft, Writing – review and editing. AE: Data curation, Writing – review and editing. MJ: Supervision, Writing – review and editing. TL: Supervision, Writing – review and editing. TK: Supervision, Writing – review and editing. UN: Supervision, Writing – review and editing. TF: Conceptualization, Funding acquisition, Supervision, Writing – review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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