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Enterovirus and Parechovirus infections in children

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B.G. 34 days of life

- ▶ Attended in A&E with:
 - 3 hours of fever up to 38.6 C
 - Slightly irregular feeds during the last 24 hours
 - No other signs or symptoms.
- ▶ Personal history: Full term baby (38+6 w), with **no risk factors of sepsis**
- ▶ Family history: Mother 29 years, healthy. Father 27 years, healthy. Older brother 2 y, healthy, without any current infection.



B.G. 34 days of life

▶ Examination:

- T 38.4 C, HR 200, RR 44, Sats 99 %.
- **Mottled. CR 3 secs. Crying/grunting**
- Chest– no recessions, bilateral air entry, no pathological sounds. No murmurs
- Abdomen, soft, no organomegaly
- No rash. No other findings.



B.G. 34 days of life

► Initial approach:

- IV access: gas (lactate 2.4, glucose 6.1), bloods, blood cultures.
- Fluid bolus and IV ceftriaxone (80 mg/kg)
- Urine: microscopy and culture
- NPA
- Lumbar puncture: microscopy, proteins, glucose, culture and viral PCR.

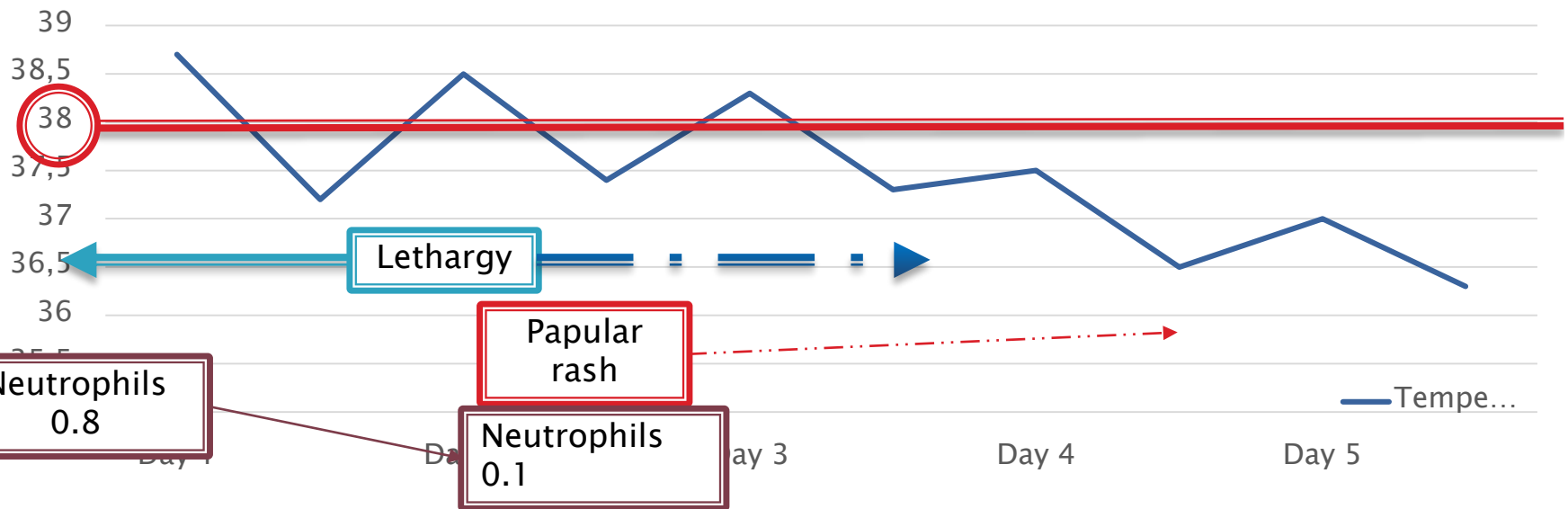
► First results:

- WBC $3.3 \times 10^9/\text{L}$ (N 0.8). CRP 3.7 mg/dL
- CSF WBC 4/mm³. Prot 0.39 g/L



B.G. 34 days of life

▶ Course of the infection:





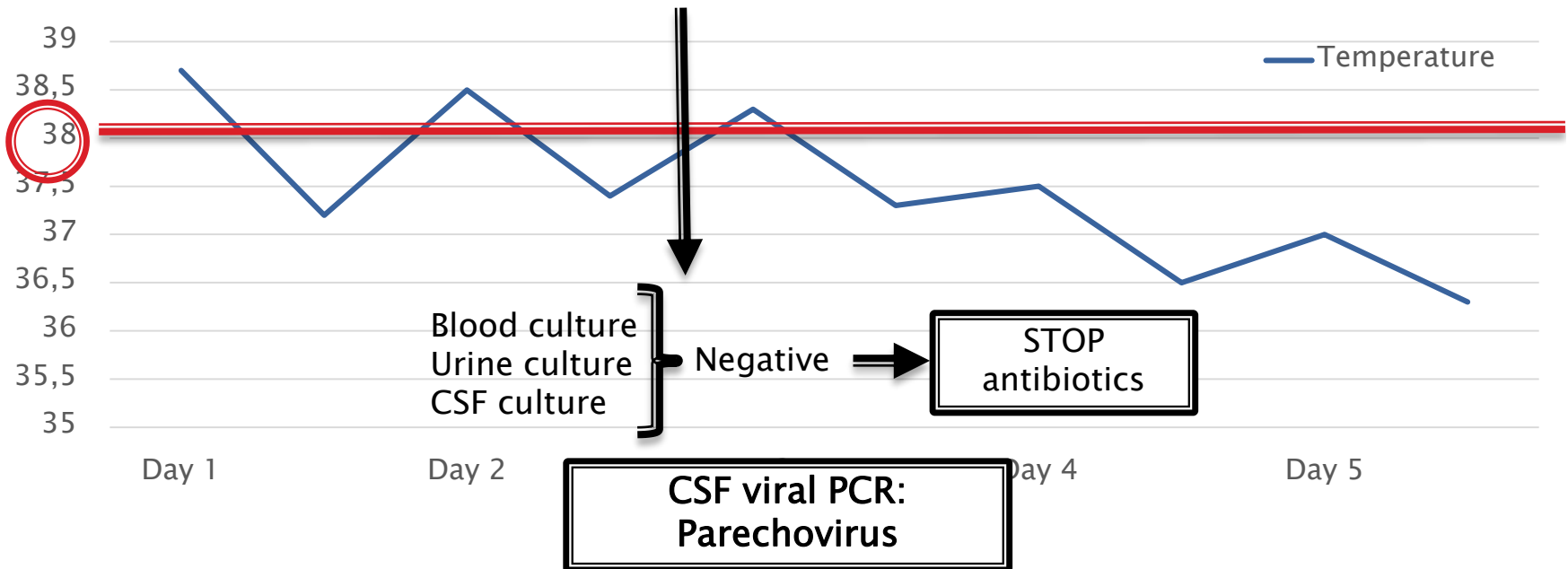
B.G. 34 days of life

Lethargy

Papular rash

Severe neutropenia

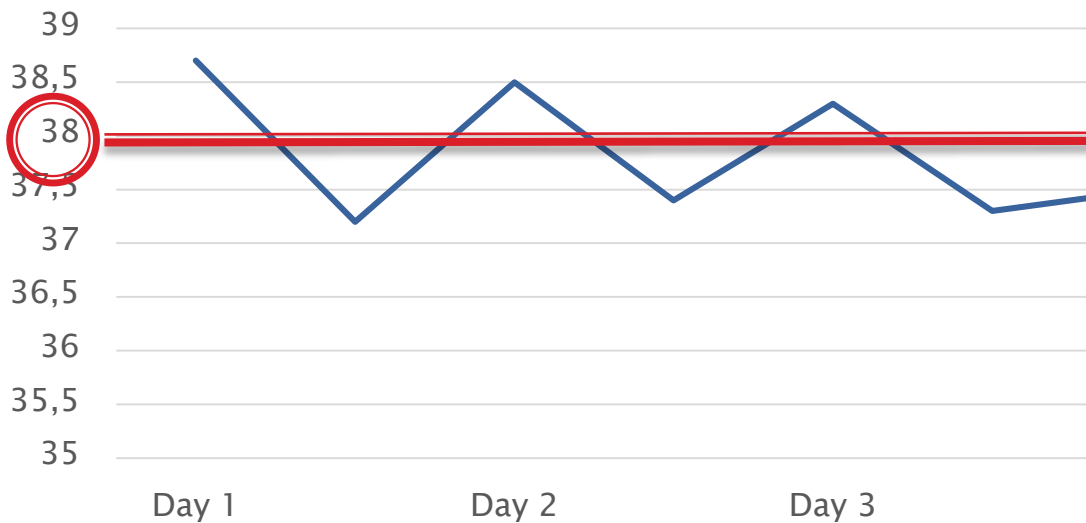
Course of the infection:





B.G. 34 days of life

▶ Course of the infection:



Lethargy

Papular rash

Severe neutropenia



Neutropenia recovered
after 2 months
No concerns after 6
months follow up

Bacterial vs. Viral Infections

Very low rates of culture-confirmed invasive bacterial infections in a prospective 3-year population-based surveillance in Southwest London

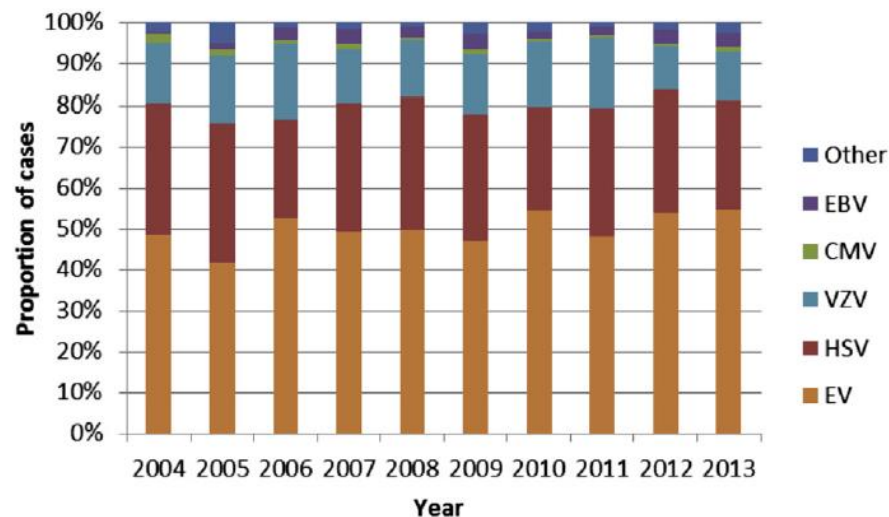
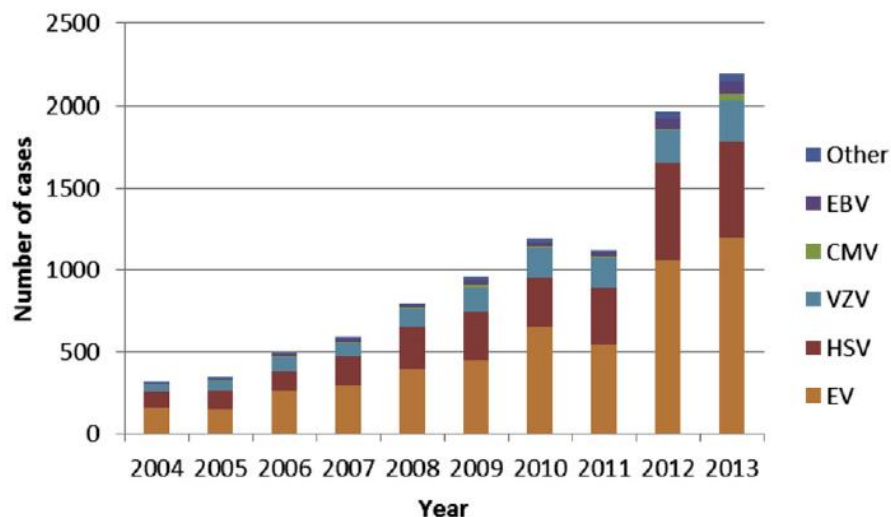
Kirsty Le Doare,^{1,2} Anna-Louise Nichols,¹ Helen Payne,¹ Rosy Wells,¹ Sonia Navidnia,¹ Gayle Appleby,¹ Elizabeth Calton,¹ Mike Sharland,¹ Shamez N Ladhani,^{1,3}
the CABIN Network

Table 1 Population rates of invasive bacterial infection by age 2009–2011 (episodes)

Episodes	1 month to <1 year	1–4 years	5–15 years	Total
Population	117 975	525 525	1 144 260	1 787 760
Admissions	10 306	16 484	19 249	46 039
Admission Rate/100 000 population	8736	3137	1682	2575
Total BC/CSF tests	6381	7806	6391	20 578
% admissions due to suspected infection	61.9%	47.4%	33.2%	44.7%
TOTAL positive BC/CSF	480	598	452	1530
Admission for presumed infection/100 000 population	407	114	40	86
% of suspected infections with positive cultures	7.5%	7.7%	7.1%	7.4%
Total significant BC/CSF	190 (37.7%)	151 (29.9%)	163 (32.3%)	504
Positive significant culture rate/100 000 population	161 (139–186)	28.7 (24.3–33.7)	14.3 (12.1–16.6)	28.2 (25.8–30.8)
% of total admissions due to infection	1.8%	0.9%	0.8%	1.1%
% of suspected infections with positive cultures	3.0%	1.9%	2.6%	2.4%
% of infections from all positive cultures	39.6%	25.3%	36.1%	32.9%
Total hospital-acquired infection (%)	115 (62.2%)	30 (16.2%)	40 (21.6%)	185
Total community-onset infections, with comorbidities (%)	30 (14.7%)	77 (37.7%)	97 (47.5%)	204
Total community-onset infections, no comorbidities (%)	45 (39.0%)	44 (38.3%)	26 (22.6%)	115
Rate for community-onset infections in healthy children per 100 000 population	38.1 (27.8–51.0)	8.4 (6.1–11.2)	2.3 (1.5–3.3)	6.4 (5.3–7.7)
Total community-onset BACTERIAL MENINGITIS, no comorbidities	11 (5.8%)	6 (4.0%)	2 (1.2%)	19
Rate for community-onset BACTERIAL MENINGITIS in healthy children per 100 000 population	9.3 (4.7–16.7)	1.1 (0.4–2.5)	0.2 (0.02–0.6)	1.1 (0.6–1.7)

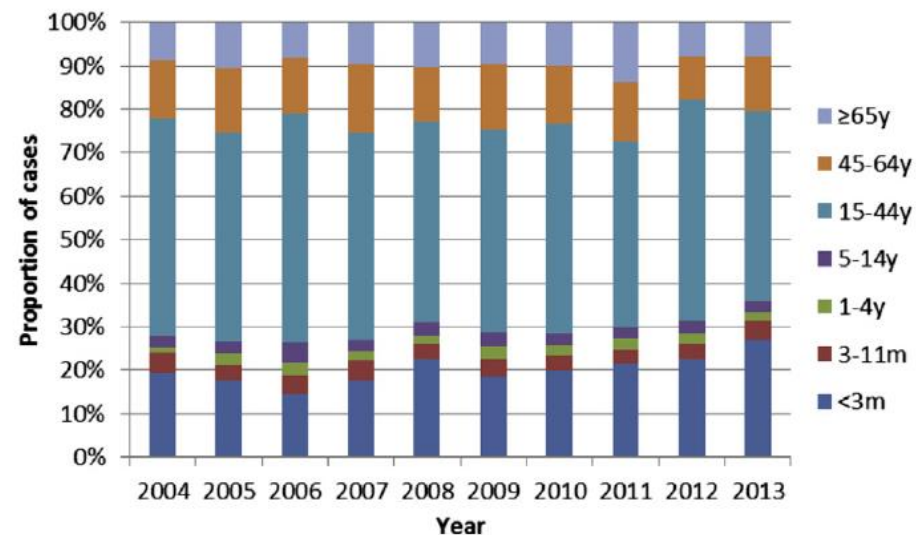
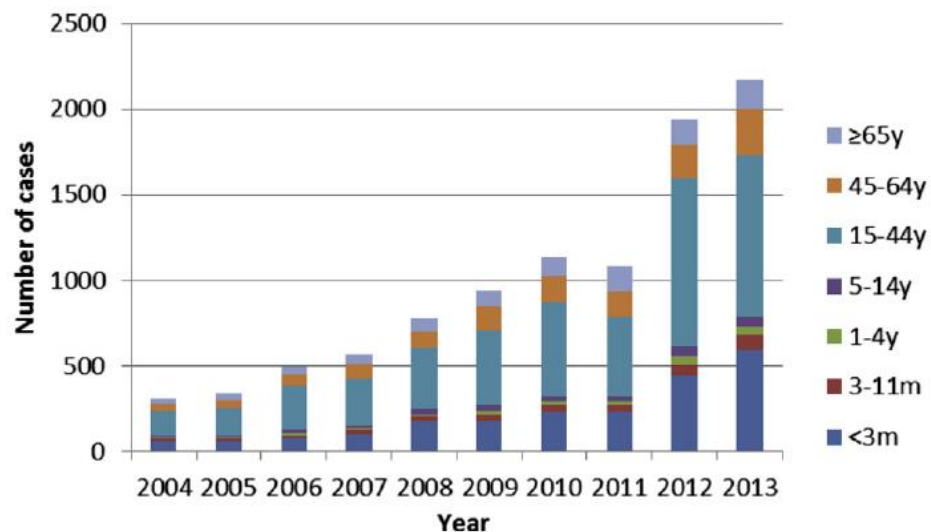
Seven-fold increase in viral meningo-encephalitis reports in England and Wales during 2004–2013

Seilesh Kadambari^a, Ifeanyichukwu Okike^a, Sonia Ribeiro^b, Mary E. Ramsay^b, Paul T. Heath^a, Mike Sharland^a, Shamez N. Ladhani^{a,b,*}



Seven-fold increase in viral meningo-encephalitis reports in England and Wales during 2004–2013

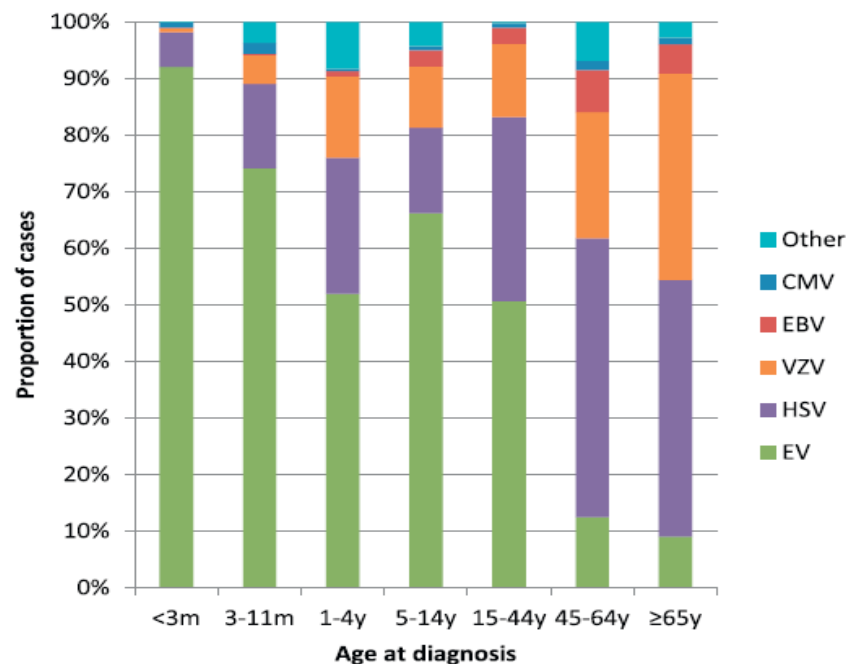
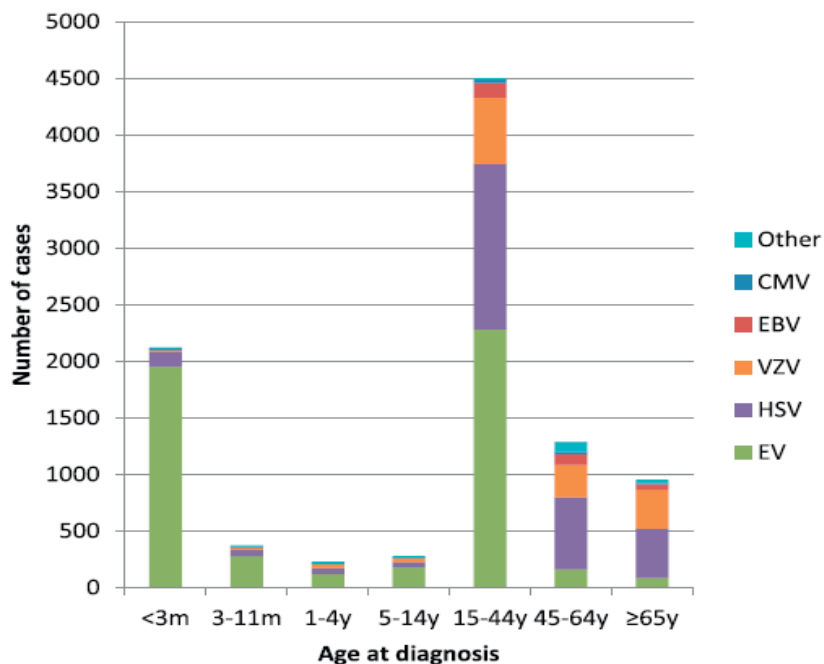
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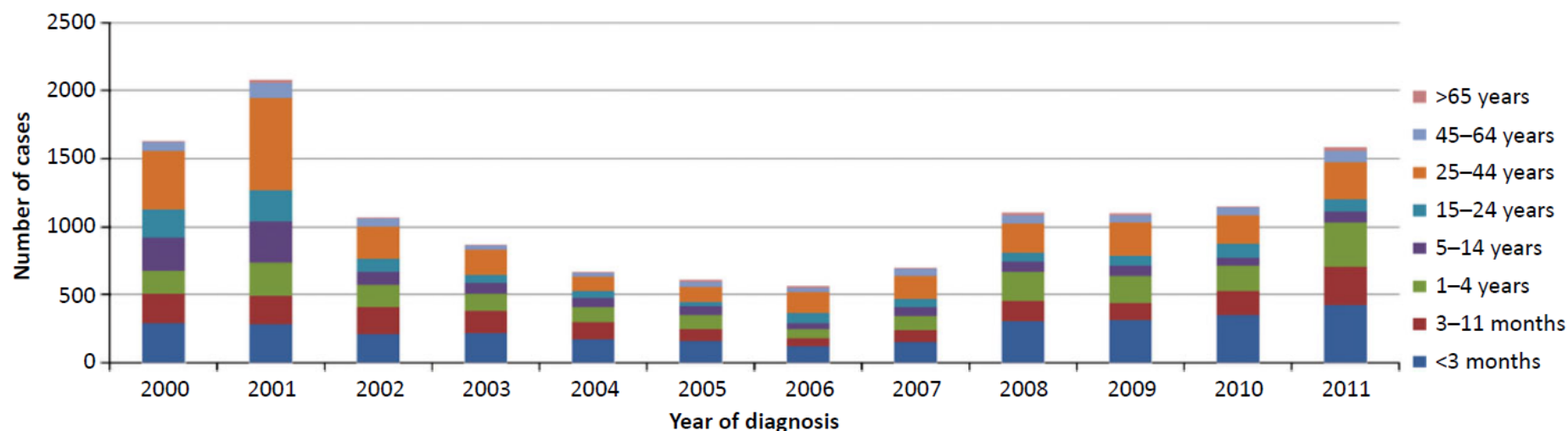
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Pathogens	Enterovirus
Age group	
<3 m	312.5 (559)
3–11 m	13.6 (73)
1–4 y	0.86 (24)
5–14 y	0.45 (29)
15–44 y	2.01 (456)
45–64 y	0.24 (34)
65 + y	0.18 (17)
Total ^a	2.13 (1192)



Enterovirus infections in England and Wales, 2000–2011: the impact of increased molecular diagnostics

S. Kadambari¹, A. Bukasa², I. O. Okike¹, R. Pebody³, D. Brown⁴, C. Gallimore⁴, J. Xerry⁴, M. Sharland¹ and S. N. Ladhani²



Source of Specimen

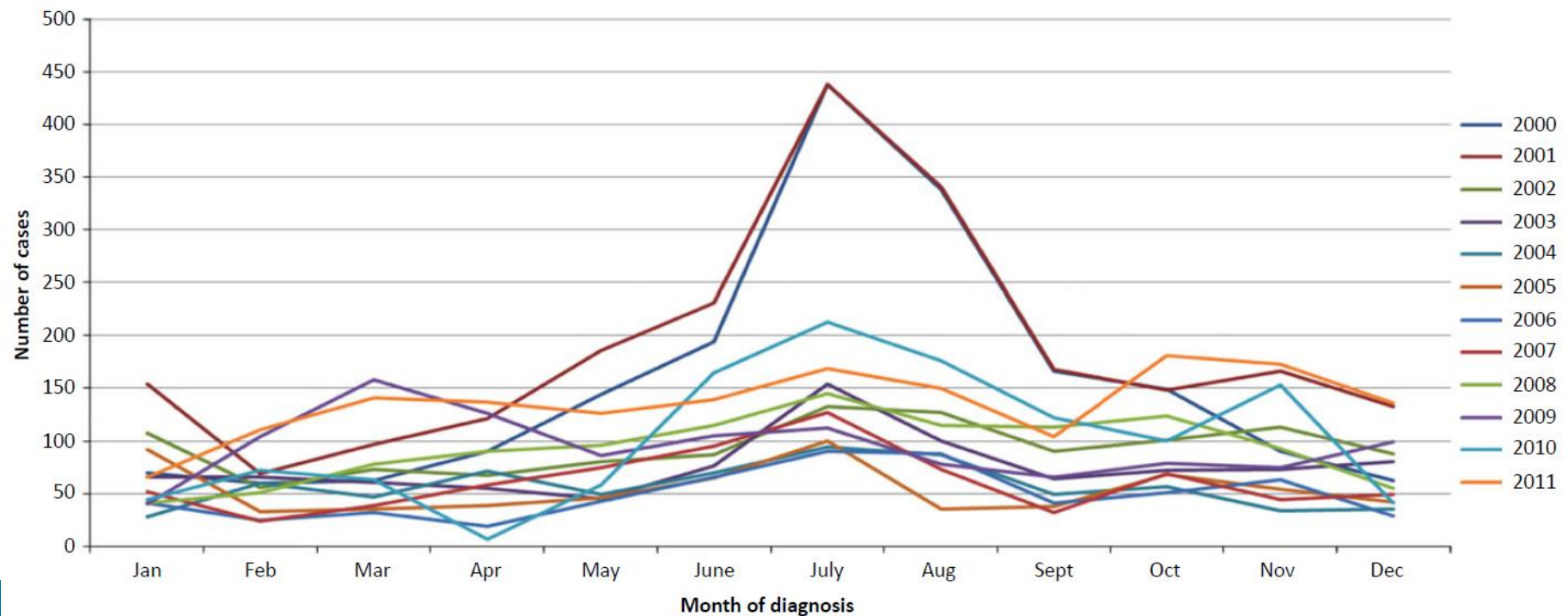
- ▶ CSF (n=5032): 36%
- ▶ Respiratory (n=3563): 26%
- ▶ Gastrointestinal (n=2394): 17%
- ▶ Blood (n=1602): 12%

Enterovirus Type

- ▶ Echovirus (n=2143): 55%
- ▶ Coxsackie B (n=904): 23%
- ▶ Coxsackie A (n=194): 5%
- ▶ EV type 70 (n=351): 0.9%
- ▶ EV type 71 (n=24): 0.6%

Enterovirus infections in England and Wales, 2000–2011: the impact of increased molecular diagnostics

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Enterovirus meningitis in infants

BPSU study



Public Health
England



St George's
University of London

British Paediatric Surveillance Unit Report Card

NOTHING TO REPORT ☐

2011

CODE No []

Specify in the box number of cases seen

- ☐ AIDS/HIV
- ☐ Congenital rubella
- ☐ Progressive Intellectual & Neurological Deterioration
- ☐ Severe Neonatal Hypernatraemia
- ☐ Guillain-Barré syndrome / Fisher syndrome
- ☐ CNS Inflammatory Demyelinating Disease
- ☐ Gonorrhoea, Syphilis, Chlamydia, and Trichomonas infections
- ☐ Congenital Syphilis

neoEntero BPSU: objectives

- **Primary Objective:**

Estimate the number of infants younger than 90 days who are hospitalised for EV/HPeV meningitis in the UK and Ireland every year (age group specific hospitalisation rates per 1,000 live births)

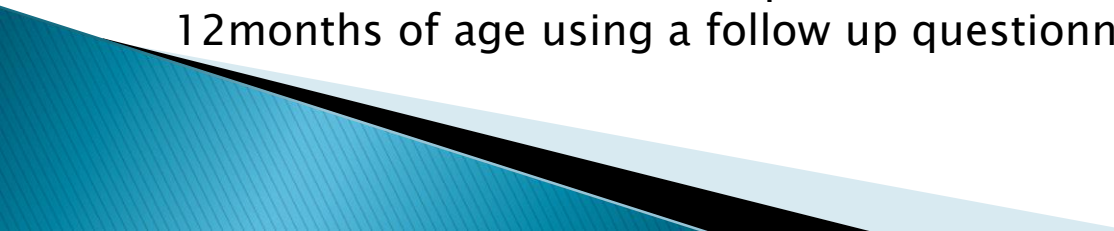
- **Secondary Objectives:**

Describe the clinical presentation, laboratory parameters, complications and outcome at hospital discharge of EV/HPeV meningitis

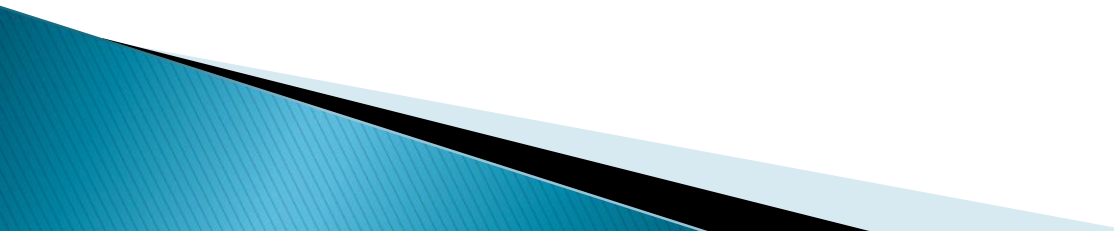
Identify any association between severity of clinical disease, EV/HPeV molecular types and/or viral load

Describe the investigations performed by paediatricians and management of infants suspected with EV/HPeV meningitis

Describe survival and developmental outcomes of EV/HPeV meningitis at 12 months of age using a follow up questionnaire



Results

- ▶ June 2014 – June 2015
 - ▶ 754 cases reported, 703 included fulfilled case definition
 - 668 EV (95%) and 35 HPeV (5%) meningitis
 - ▶ Majority between 15 and 89 days of age and
 - ▶ Only 6% born prematurely (<37 weeks gestation)
 - ▶ Annual incidence:
 - EV meningitis (0.79/1,000 live-births)
 - HPeV meningitis (0.04/1,000 live-births)
- 

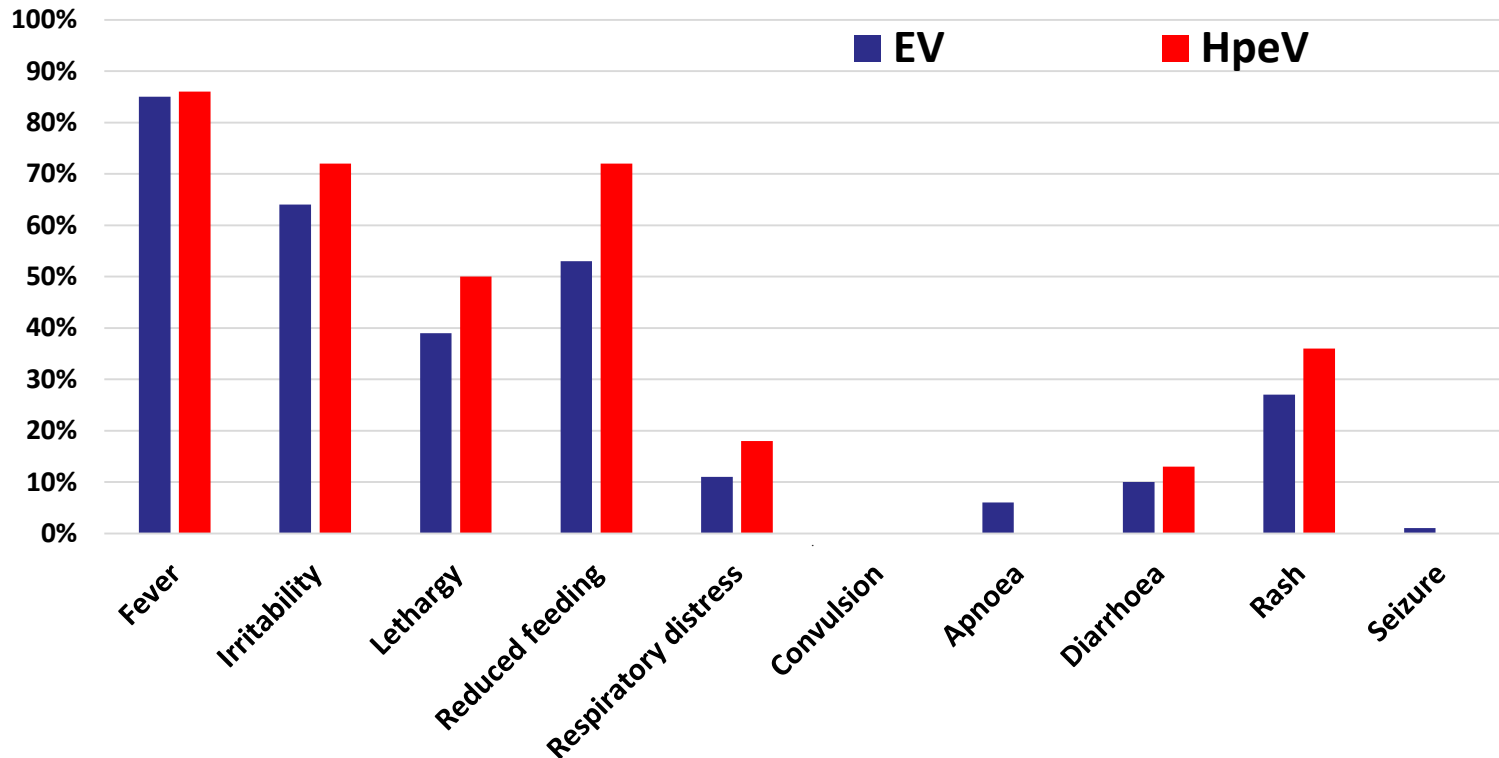
Results

- ▶ **3 commonest clinical presentations:**
 - fever (85%, 570/668),
 - irritability (66%, 441/666),
 - reduced feeding (54%, 363/668)

- ▶ **2 commonest examination findings:**
 - signs of shock (EV: 27%, 182/668; HPeV: 43%, 15/35)
 - respiratory distress (EV: 12%, 79/668; HPeV: 26%, 9/35)

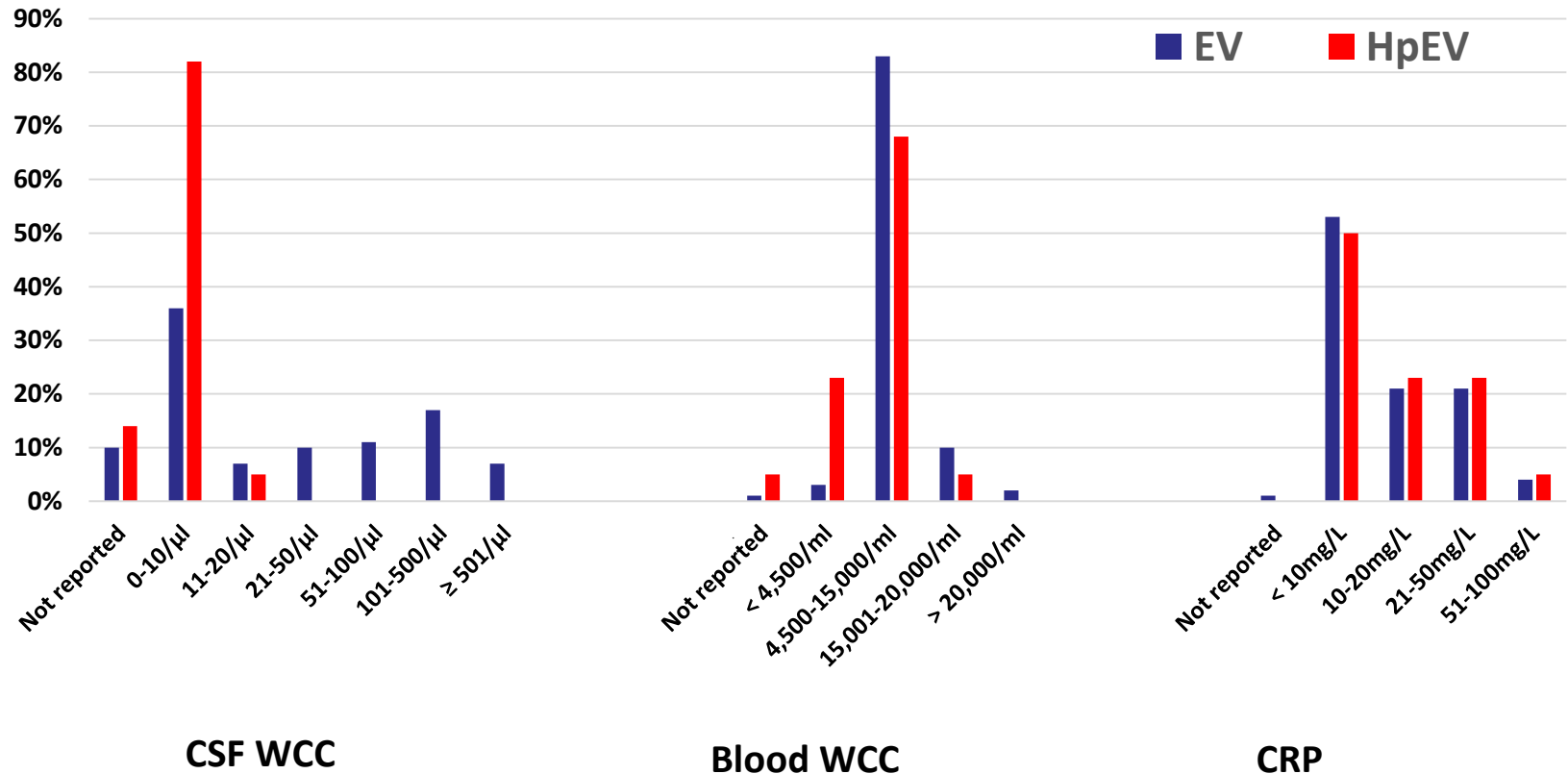
- ▶ **Intensive Care Unit Admission:**
 - 7% of (46/668) EV and 17% (86/35) HPeV cases
 - Intubation: 50% (23/46) EV cases and all 6 HPeV cases
 - Inotropes: 20% (9/46) cases and all 6 HPeV cases

Clinical Presentation



Symptoms and signs of EV/HPeV meningitis at onset

Laboratory Tests

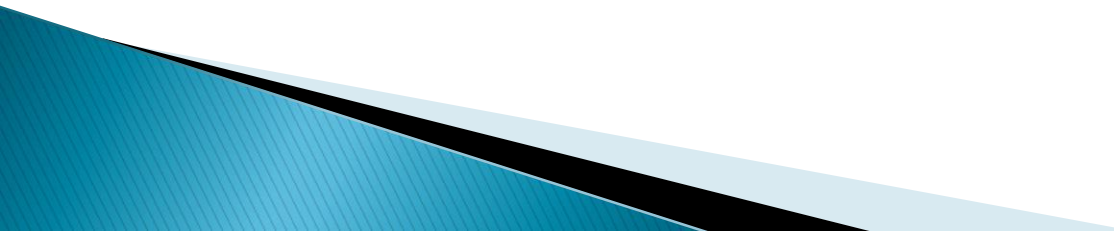


Laboratory markers of EV/HPeV meningitis

Results

- ▶ 95% (768/712) → virus was confirmed in CSF by PCR
 - 53% had a CSF white cell count (WCC) $<20/L$
- ▶ 77% had a CRP level $<20\text{mg/L}$
- ▶ None had a secondary bacterial infection (*6 coagulase-negative staphylococci – all contaminants*)
- ▶ Two infants with EV meningitis died
 - 2/668; case fatality rate, 0.3%; 95% CI, 0.04–1.1%.
- ▶ Of the survivors, 2 had long-term neurological complications
- ▶ HPeV meningitis: none died or had long-term complications

12 Months Follow-up

- ▶ 38% (254/668) of EV + 46% (16/35) HPeV infants reviewed by clinician during 12 months after hospital discharge.
 - ▶ 70% (189/270) had a formal hearing test after discharge – none had sensorineural hearing loss.
 - ▶ 2 infants with EV meningitis (well at discharge) had neurological complications by 12 months.
 - ▶ Risk of long-term sequelae in infants with EV meningitis was 0.6% (4/666; 95% CI, 0.2–1.5%).
- 

Human Parechovirus in infants

Human Parechovirus (HPeV): Epidemiology

- HPeV are in the picornavirus family, which includes enterovirus, hepatovirus and rhinoviruses.
- There are 16 HPeV genotypes, differences on clinical presentation.
 - HPeV1, HPeV2 and HPeV4–8 mainly cause mild gastrointestinal or respiratory illness (occasionally serious disease)
 - **HPeV3 causes severe illness** in you infants (mainly < 3 months): sepsis-like and CNS infections.
 - Transmission occurs by contact
- fecal-oral route (shedding up to

*Esposito,
2014
Renaud,
2015*

Isolation and identification of a novel human parechovirus

Miyabi Ito,¹ Teruo Yamashita,¹ Hideaki Tsuzuki,¹ Naokazu Takeda²
and Kenji Sakae¹

Ito, 2004

HPeV: Clinical presentation

- Non-HPeV3:
 - Mild respiratory or gastrointestinal disease (often >90 days).
- HPeV3 (often <90 days):
 - Fever and no focus
 - Sepsis-like syndrome
 - Encephalitis/meningitis
 - Seizures, particularly when seizures are difficult to control

Table 1. Number and Percentage of Children With Human Parechovirus Infection Who Demonstrated Specific Clinical Features

Clinical Feature	No. With Data Available	No. Presenting With Each Clinical Feature	% Presenting With Each Clinical Feature
Tachycardia	118	115	97.5
Fever	115	108	93.9
Irritability/pain	118	110	93.2
Tachypnea	117	107	91.5
Rash	117	84	71.8
Poor feeding	118	83	70.3
Poor perfusion	118	65	55.1
Diarrhea	118	52	44.1
Lethargy	118	49	41.5
Upper respiratory tract infection	118	17	14.4
Abdominal distension	118	15	12.7
Vomiting	118	14	11.9
Edema	118	11	9.3
Seizures	118	7	5.9
Apnea/preapnea	118	7	5.9
Myoclonic jerks	118	6	5.1

Aizawa 2015, Khatami 2015

HPeV: Clinical presentation



Table 1. Number and Percentage of Children With Human Parechovirus Infection Who Demonstrated Specific Clinical Features

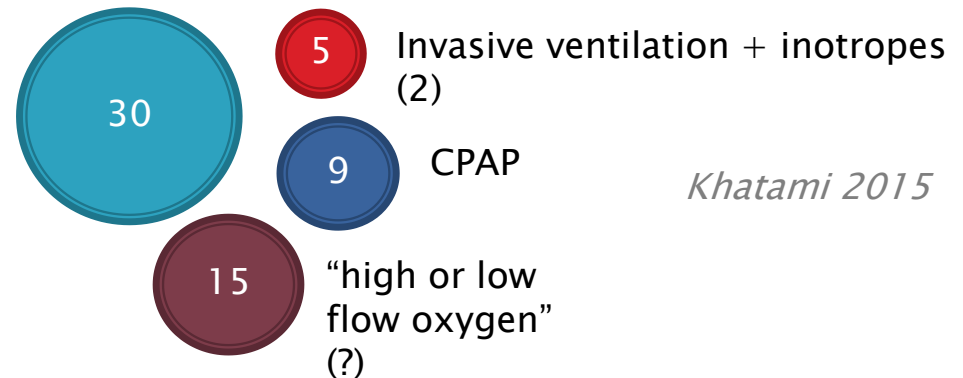
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Seizures	118	7	5.9
Apnea/preapnea	118	7	5.9
Myoclonic jerks	118	6	5.1

Aizawa 2015, Khatami 2015

HPeV: Severity



❖ N= 118 → 25% patients admitted in PICU
(n=30) → 16.5 d (p 0.0004)



Khatami 2015

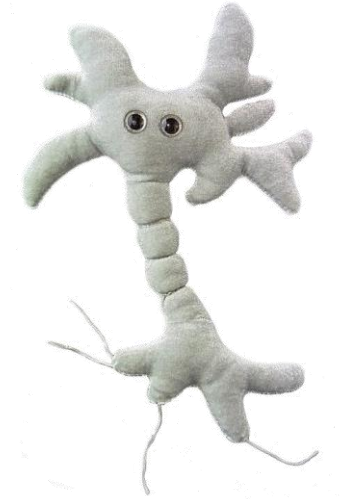
❖ N= 50 → 50% patients admitted in PICU
(n=25)



Vergnano, 2015

HPeV: Neurological symptoms

- Challenge in studying childhood encephalitis in very young children
- Nonspecific features of illness in young infants
- ? Enterovirus infection.



Parechovirus Encephalitis and Neurodevelopmental Outcomes

Philip N. Britton, FRACP,^{a,b,c} Russell C. Dale, MRCP PhD,^{a,d} Michael D. Nissen, FRACP, FRCPA,^e Nigel Crawford, FRACP, PhD,^{f,g,h} Elizabeth Elliott, FRACP, MD,^{a,c,i} Kristine Macartney, FRACP, MD,^{a,c,j} Gulam Khandaker, PhD,^{a,j} Robert Booy, FRACP, PhD,^{a,b,c,j} Cheryl A. Jones, FRACP, PhD,^{a,b,c} on behalf of the PAEDS-ACE Investigators

Britton et al., 2016

HPeV: Diagnosis

Blood

- Normal (low) peripheral leukocyte count
- C-reactive protein (CRP) normal/mild increase

CSF

- The absence of CSF pleocytosis is virtually universal (up to 90%)
- CSF abnormalities are less common with HPeV3 than other viral CNS infections
- CSF protein levels may be modestly increased in <50% of patients with HPeV3.

*Renaud,
2015*

Laboratory data	Median (range)
White blood cells (/μL)	5200 (2200–8270)
C-reactive protein (mg/dL)	0.23 (0–2.4)
Aspartate aminotransferase (IU/L)	38 (19–308)
Alanine aminotransferase (IU/L)	19 (7–92)
Lactate dehydrogenase (IU/L)	305 (226–621)
CSF cell count (cells/μL)	3 (0–25)
CSF glucose (mg/dL)	60 (36–81)
CSF protein (mg/dL)	45 (24–89)
Real-time RT-PCR	
Serum Ct value	22.07 (17.20–31.01)
HPeV3 RNA levels (log ₁₀ copies/μL)	4.41 (2.23–6.14)
CSF Ct value	33.02 (24.04–39.01)
HPeV3 RNA levels (log ₁₀ copies/μL)	1.30 (–0.52 to 4.09)

Aizawa 2015

CSF HPeV vs EV?

Table 2

Characteristics of the children with EV and HPeV infection.

	EV positive (n = 140)	HPeV positive (n = 44)	p-value
Median age in days (range)	50 (3–4955)	68 (3–4677)	0.59
Sex (male/female)	1.9 (91/49)	2.4 (31/13)	0.50
Diagnosis (%): meningitis	75 (54%)	16 (36%)	0.046 ^a
Gastro-enteritis	21 (15%)	13 (30%)	0.030 ^a
Other organ involvement	44 (31%)	15 (34%)	0.74
No. of hospitalized children (%)	118 (86%) ^A	43 (98%)	0.029 ^a
Median duration of hospitalization in days (range)	3.1 (1–12)	3.0 (1–10)	0.24
No. children who received antibiotic treatment (%)	66 (52%) ^B	21 (49%)	0.669
Mortality (%)	0 (0%)	0 (0%)	–
CRP [mg/l] (range)	14.5 (<1–181)	5.75 (0–91)	0.61
Blood: WBC count [$\times 10^9$ per liter] (range)	12.0 (3.6–88)	6.7 (2.9–24.6)	0.51
Thrombocytes [$\times 10^9$ per liter] (range)	377 (186–696)	316 (87–583)	0.49
CSF: WBC count [$\times 10^6$ per liter] (range)	159 (1–1008)	7.1 (0–40)	0.49
CSF: protein [G/l] (range)	0.53 (0.16–1.09)	0.48 (0.18–0.91)	0.43
CSF: glucose [mmol/l] (range)	3.0 (1.5–4.2)	3.0 (2.0–3.6)	0.88

The columns describes the characteristics for the EV vs. HPeV positive patients.

No. = number; WBC = white blood cell; CSF = cerebrospinal fluid.

^a Significant, ^A missing data in 2 patients, ^B missing data in 13 patients.

Lack of pleocytosis: 42% vs 77%

HPeV: Diagnosis

- CSF and blood are the preferred samples to prove active HPeV infection
- PCR detection can also be performed in respiratory samples, including throat and nasopharyngeal swabs, or stool samples.

*Renaud,
2015*

Table 3. Number of Clinical Isolates With Human Parechovirus RNA Detected by Polymerase Chain Reaction for Each Child

Isolates Tested	No. of Children With Positive Results
CSF only	42
Stool only	34
NPA only	4
Rectal swab only	2
Throat swab only	1
CSF and stool	28
Stool and NPA	1
Rectal swab and NPA	1
CSF, stool, and NPA	4
CSF, stool, NPA, and blood	1
Total	118

35%

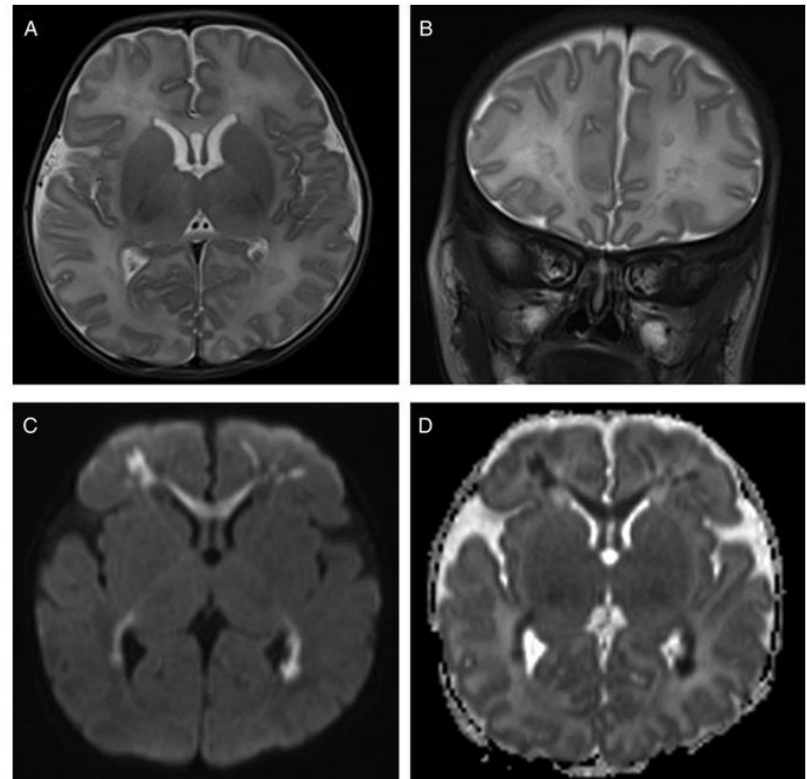
Abbreviations: CSF, cerebrospinal fluid; NPA, nasopharyngeal aspirate.

*Khatami,
2015*

HPeV (HPeV3): Diagnosis

- Cranial US should not be used as a screening
- MRI: diffusion restriction
- EEG (seizures)

Study	Khatami, 2015	Vergnano, 2015
Number of infants	118	50
Neurological symptoms*	NS	21
MRI performance	11	12
MRI pathological findings	7	10



Khatami, 2015

*Lethargy, irritability, seizures

HPeV3: Outcomes

- The outcomes of HPeV3 CNS infections are mostly benign.
- Cognitive and motor deficits can occur → illnesses that have neurologic findings during acute disease.

(A) Sepsis-like Syndrome <90 d of Age	(B) Clinical Infant Encephalitis	(C) Febrile Coagulopathy	(D) Myocarditis
<i>Clinical</i>			
Fever Irritability Decreased activity	Fever Irritability Decreased activity plus Seizures; may be difficult to control	Same as (A) plus Ecchymoses or purpura	Same as (A) plus Dilated myocardium and pulmonary edema
<i>General laboratory</i>			
Peripheral leukopenia or lymphopenia Modestly increased C-reactive protein level	Same as (A)	Same as (A) plus Abnormal clotting studies Increased liver function studies	Peripheral leukopenia or lymphopenia Modestly increased C-reactive protein level
<i>CSF</i>			
No pleocytosis Mildly increased protein levels (+) RT-PCR for HPeV3	No pleocytosis Modestly increased protein levels (+) RT-PCR for HPeV3	Same as (B)	Same as (A)
<i>MRI brain</i>			
In general not performed	White matter changes	Data not available	Data not available
<i>Outcome</i>			
In general no sequelae	Subset with cognitive or motor sequelae	May be lethal	May be lethal

Renaud, 2015

HPeV: Outcomes

Parechovirus Encephalitis and Neurodevelopmental Outcomes

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Study	Khatami, 2015	Vergnano, 2015
Number of infants	118	50
Deaths	0	1
Development delay	NR	19
Neurological sequelae	4	3

All 3: Seizures and MRI changes

- Australian Childhood Encephalitis (ACE) from May 2013 to Dec 2014.
 - 133 children < 14
 - 9 infants with HPeV** (13 initial cases)

Clinical features

5 premature
9 < 2 mths
9 lethargy / irritable
8 seizures

Diagnostics

9 CSF HPeV PCR
9 HPeV3
9 No WBC CSF (median 0, 0–6)
2 Cranial Us abnormal
9 Brain MRI abnormal
6/7 EEG abnormal

Outcome

Short-term:
3 Neuro. sequelae
12 Months:
5 Neuro. sequelae

Increasing Awareness Worldwide

Parechovirus Genotype 3 Outbreak among Infants, New South Wales, Australia, 2013–2014

Germaine Cumming,¹ Ameneh Khatami, Brendan J. McMullan, Jennie Musto, Kit Leung,
Oanh Nguyen, Mark J. Ferson, Georgina Papadakis, Vicky Sheppeard

Clinical utility of serum samples for human parechovirus type 3 infection in neonates and young infants: The 2014 epidemic in Japan

Yuta Aizawa ^a, Yuko Suzuki ^a, Kanako Watanabe ^b,
Tomohiro Oishi ^a, Akihiko Saitoh ^{a,c,*}

Centers for Disease Control and Prevention

MMWR

Morbidity and Mortality Weekly Report

Weekly / Vol. 64 / No. 34

September 4, 2015

Enterovirus and Human Parechovirus Surveillance — United States, 2009–2013

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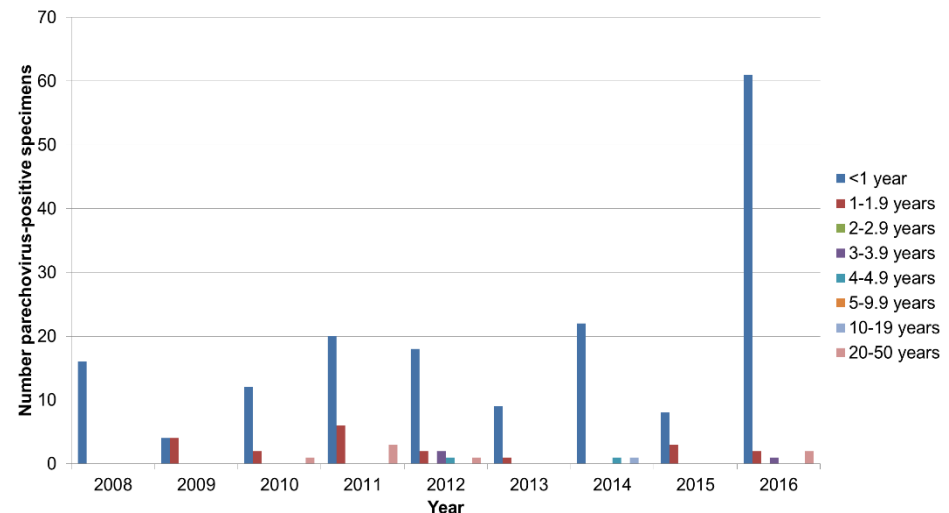


Public Health
England

Protecting and improving the nation's health

Year	Total Tested	Total Positive	Positive rate
2008*	214	15	7.0%
2009	578	7	1.2%
2010	433	7	1.6%
2011	689	20	2.9%
2012	1263	22	1.7%
2013	1351	8	0.6%
2014	476	23	4.8%
2015	467	11	2.4%
2016*	139	65	46.8%

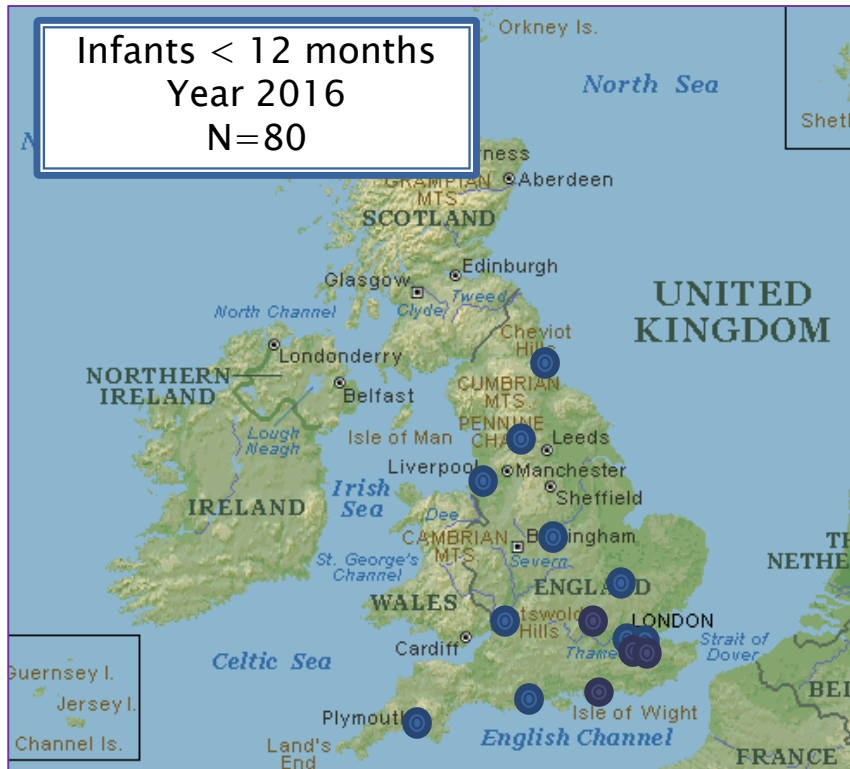
Specimen referral patterns to the Virus Reference Department (VRD), 2008–2016.



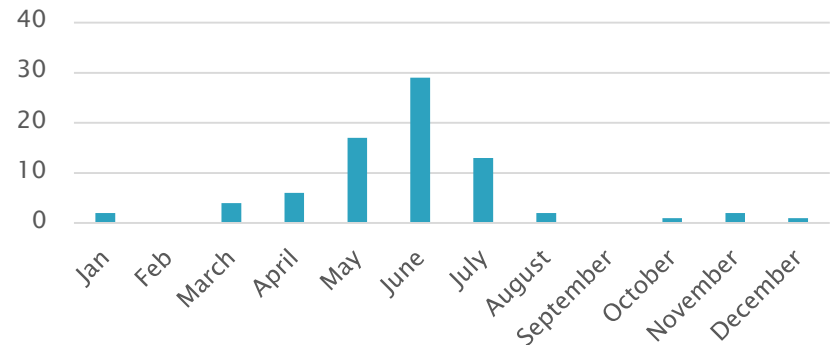
Age distribution of human parechovirus infections detected among specimens referred to the VRD, 2008–2016.

PHE. Press note: Detection of Parechovirus in the UK, 2008–2016

UK (2016) HPeV Outbreak



Month distribution



- Age median 43.3 d (1–314d)
- Prematurity 3.7%
- Symptoms: Fever 85%, lethargy 62.5%, reduced feeding 43.7%
- Examination: rash 26.2%, shock 30%
- PICU admission 11 cases (13.7%)--> 7 invasive ventilation (5 inotropes)
- CSF: 90% <5 WBC. 80% <0.6 g/L
- All survived
- No sequelae

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**Twenty-Nine Cases of Enterovirus-D68 Associated Acute Flaccid Myelitis in Europe 2016;
A Case Series and Epidemiologic Overview**

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Leer-Buter¹, MD, PhD, Oebele F. Brouwer², MD, PhD, and Hubert G.M. Niesters¹, MD, PhD,
on behalf of the 2016 EV-D68 AFM Working Group³

Conclusions

- ▶ Bacterial infections very rare in infants and young children
- ▶ Incidence of EV/HPeV meningitis in infants at least as high as bacterial meningitis (5 x higher than GBS meningitis)
- ▶ Often associated with severe clinical presentations
- ▶ Normal blood WCC * Normal/ Mild CRP * Normal CSF WCC
- ▶ Long-term sequelae very rare (but not zero)
- ▶ Sequelae associated with severe neurological presentation
- ▶ No association with hearing loss after infection
- ▶ Need for long-term follow-up (? 12 months)
- ▶ Beware emerging new strains (EV D68)
- ▶ More studies needed on severe presentations
 - Sepsis-like, neurological, cardiac



Thank you