# Hepatitis E:

## Diagnosis

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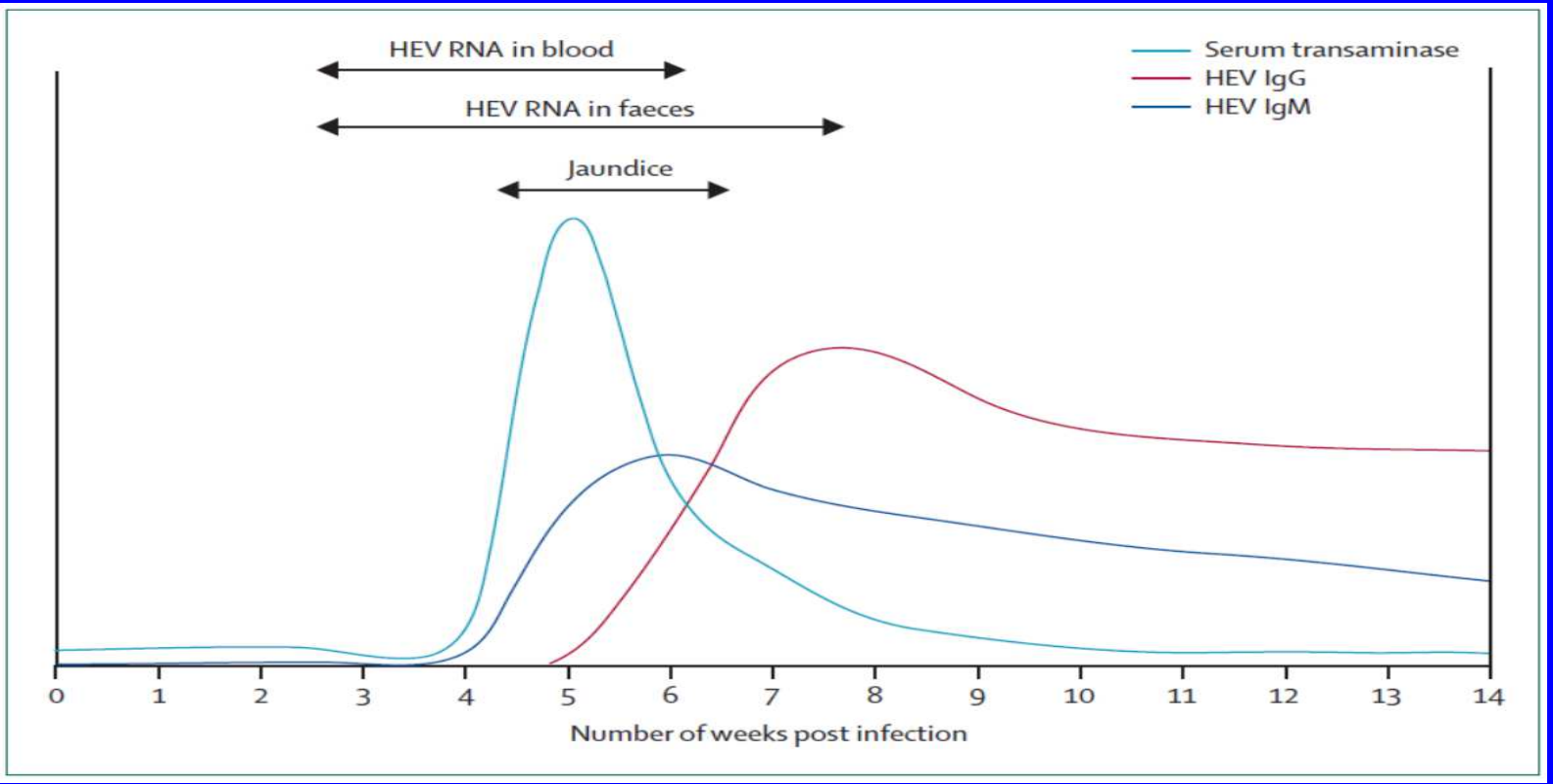
European Centre for Environment & Human Health
University of Exeter Medical School
Cornwall, UK

# Talk outline

Diagnosis:

- Acute HEV
- Chronic HEV
- Epidemiology & diagnosis
- Neurological HEV

# acute HEV: serological response

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# Acute HEV: Laboratory Diagnosis

## Serology

- Anti-HEV IgM
- Anti-HEV IgG

## Nucleic Acid testing

- RT-PCR, HEV RNA
  - Serum
  - Stool
- genotyping

# Acute HEV: Laboratory Diagnosis

## Serology

- Anti-HEV IgM
- Anti-HEV IgG

- variable kit performance
- False +ve: autoimmune hepatitis

## Nucleic Acid testing

- RT-PCR, HEV RNA
  - Serum
  - Stool
- genotyping

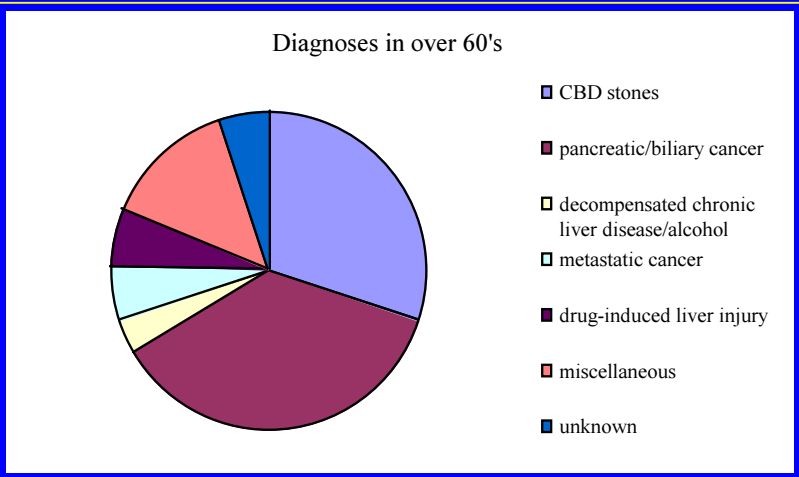
- Varied lab procedures
- 20 labs = 20 different answers!
- Laboratory testing harmonised to WHO standard 2012

*Baylis et al Emerg Inf Dis 2013*

# Hepatitis: Differential Diagnosis

1. DILI
2. Autoimmune hepatitis
3. **Acute HEV**
4. Seronegative hepatitis
5. EBV hepatitis
6. Acute HBV
7. HAV
8. Acute HCV

Jaundice Hotline 1998-2015 >3,00 patients



# Hepatitis: Differential Diagnosis

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**HEV: clinical phenotype**

Older males

- Median age: 63 years
- M:F = 3:1

Travel history: irrelevant

*Dalton et al J Viral Hepatitis 2007, Dalton et al EurJGastro 2008, Vine et al APT 2012., Woolson et al 2014, APT*

# Hepatitis: Differential Diagnosis

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**Drug-induced liver injury (DILI)**

- Common in the elderly
- 13% of patients with DILI have HEV3

*Dalton et al APTherap 2007*

- Diagnosis of DILI not secure without testing for HEV

# Hepatitis: Differential Diagnosis

1. DILI
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## Autoimmune hepatitis

Occurs in elderly as well as young

Diagnosis suggested by:

- Impaired synthetic function
- Raised IgG
- +ve auto-antibodies

*Panyani et al EJGH 2013*

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# HEV
# and decompensated chronic liver disease

Poor prognosis

*Dalton et al Lancet 2007*

**Anglo/French study (CLD n=343)**

Mortality = 27%

*Blascoe Perrin et al AP&T 2015*

**Making a diagnosis**

- No clues:
  - Diet
  - Travel history
- Need to test for it !
  - Incidence varies geographically
  - SW France: 8%
  - Cornwall: 1%
  - Glasgow: 0%

# Chronic HEV: diagnosis

## Patients

- Solid organ transplant recipients
- Stem cell transplant recipients
- HIV patients
- Haematological malignancy
- Other cause of immunosuppression

## Clinical phenotype

- No symptoms
- ALT 100-200 iu/L

# Chronic HEV: diagnosis

## Patients

- Solid organ transplant recipient
- Stem cell transplant recipient
- HIV patient
- Haematological malignancy
- Other cause of immunosuppression

## Clinical phenotype

- No symptoms
- ALT 100-200 iu/L

**Virological testing**

IgM & IgG serology unreliable

Diagnosis made by RT-PCR

PCR and viral load guides therapy

# Chronic HEV: differential diagnosis

1. Graft rejection
2. ‘DILI’
3. Recurrence of primary liver pathology
4. Graft versus host disease
5. Inter-current infections (sepsis etc)
6. **Chronic HEV**
7. Chronic EBV and CMV

# Re-infection with HEV

## Genotype 4, China:

- 20% are re-infections
- More common in females
- Milder hepatitis than primary infection

- **IgM negative**
- **IgG and PCR positive**

*Kamar et al Lancet 2012*

# Re-infection with HEV

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- 20% are re-infections
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- **IgM negative**
- **IgG and PCR positive**

*Kamar et al Lancet 2012*

## Genotype 3, Toulouse, France:

- Reinfections quite common
- IgG <7 WHO units/ml

*Abravanel et al JID 2014*

## Genotype 3, EU blood donors

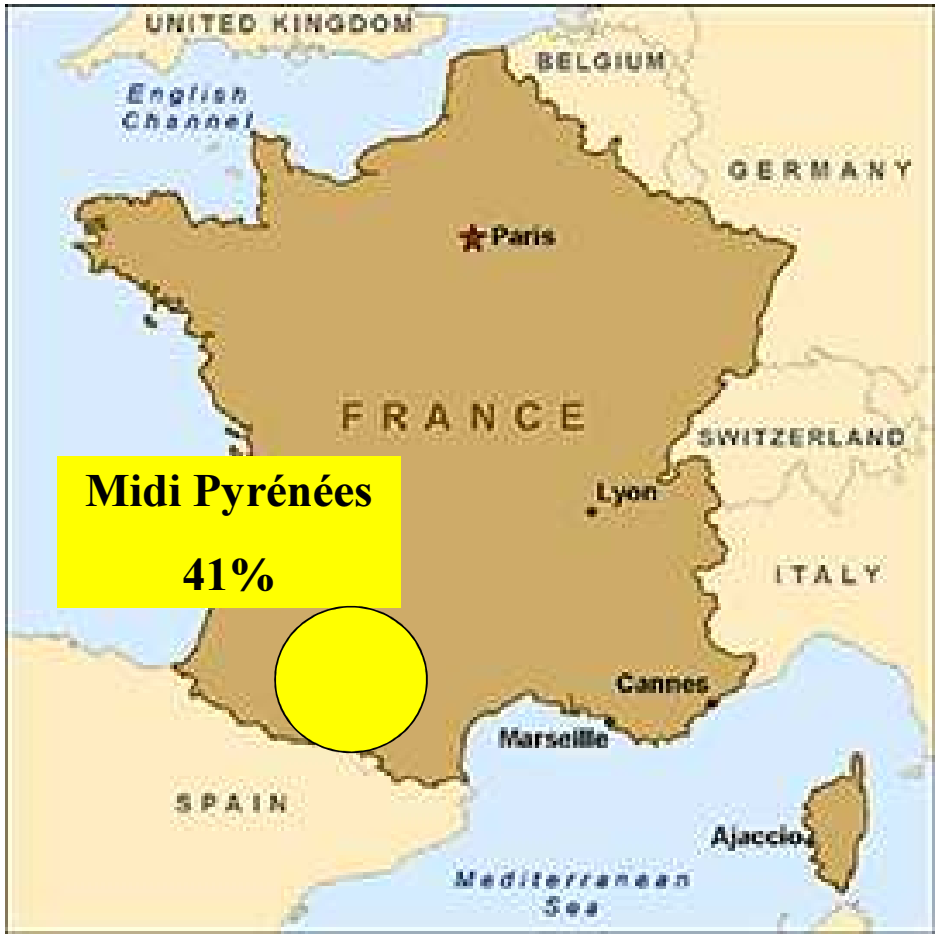
- Some donors have reinfections

*Baylis et al Vox Sang 2015*

# HEV and blood donors

| Country | Blood donors HEV RNA positive | HEV IgG seroprevalence | Assay | Reference |
|---|---|---|---|---|
| **France**<br>**Midi-Pyrénées** | **1:1595** | **52%**<br>16% | Wantai<br>Genelabs | *Gallian et al, 2014*<br>*Mansuy et al, 2011*<br>*Mansuy et al, 2008* |
| **Japan** | **1:1781** | | | Fukuda et al, 2004 |
| **Germany** | **1:1200**<br>**1:4525** | **29.5%**<br>18.0%<br>4.5% | Wantai<br>Mikrogen<br>MP diagnostics | *Vollmer et al, 2012*<br>*Baylis et al, 2012*<br>*Wenzel et al, 2013* |
| **Netherlands** | **1:2671** | **27.0%**<br>1.1% | Wantai<br>Abbott | *Slot et al, 2013*<br>*Zaaijer et al, 1993* |
| **Sweden** | **1:7986** | 9.2% | Abbott | *Baylis et al, 2012*<br>*Olsen et al, 2006* |
| **England** | **1:2848**<br>**1:7000** | **12.0%**<br>5.3 | Wantai<br>Abbott | *Hewitt et al, 2014*<br>*Ijaz et al, 2012*<br>*Beale et al, 2011*<br>*Bernal et al, 1996* |
| **Scotland** | **1:14520** | **4.7%** | Wantai | *Cleland et al, 2013* |

# HEV IgG seroprevalence: varies within countries




*Mansuy et al Eurosurveillance 2015*

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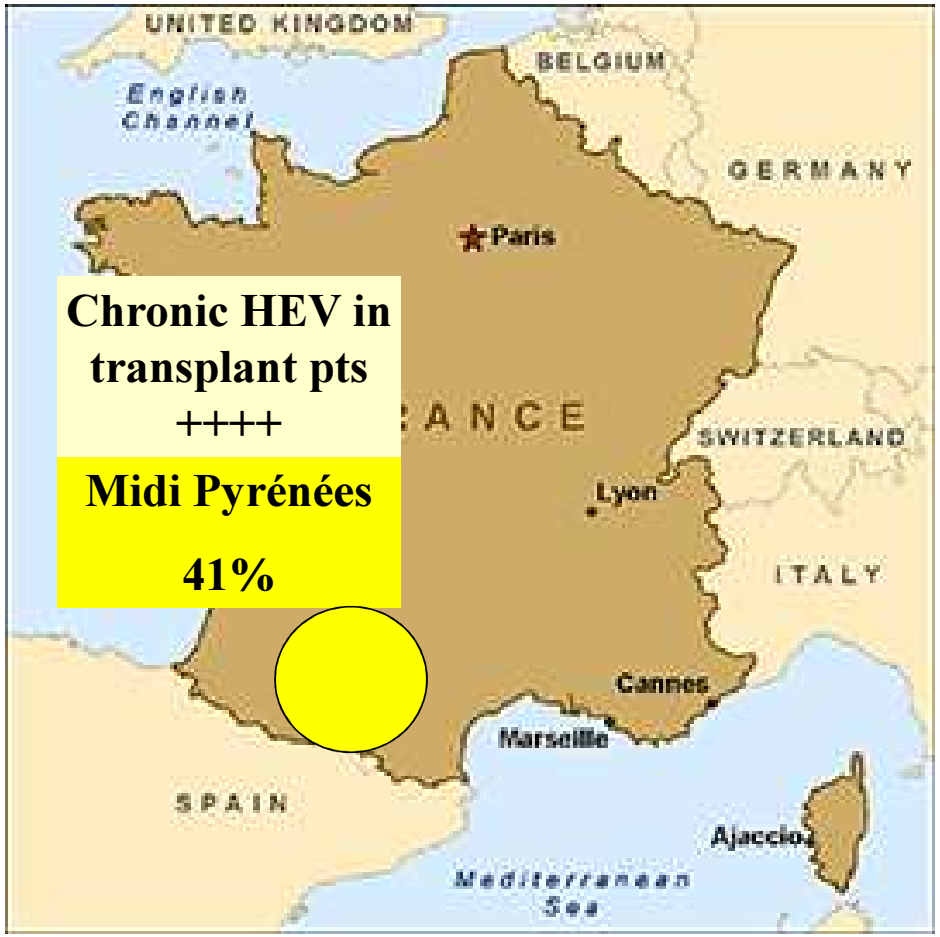
# HEV IgG seroprevalence: varies within countries




*Mansuy et al Eurosurveillance 2015*

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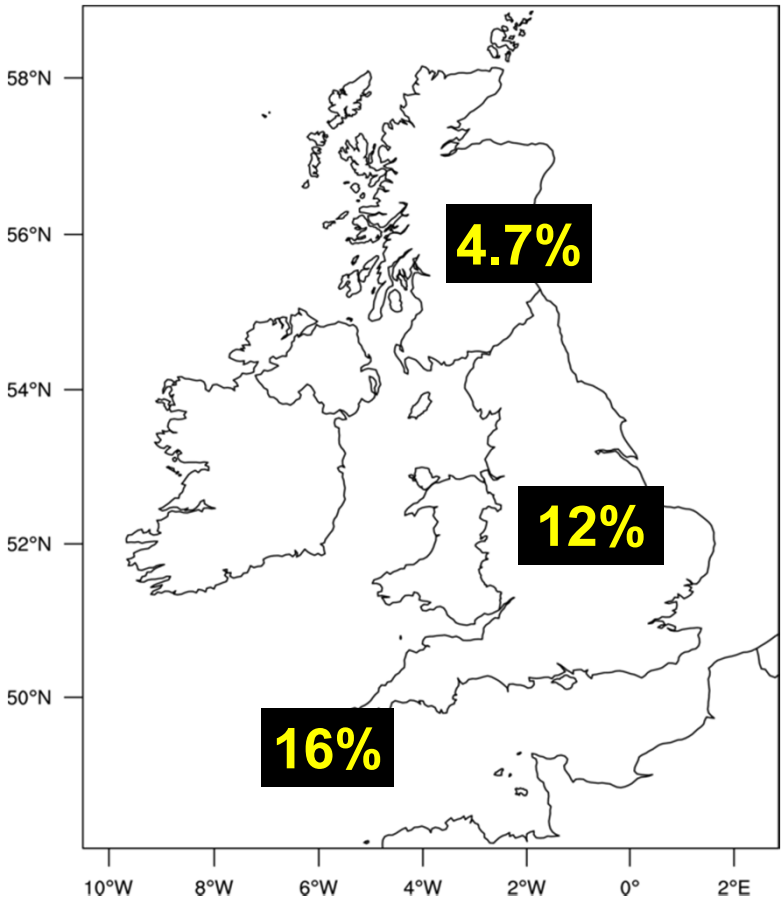
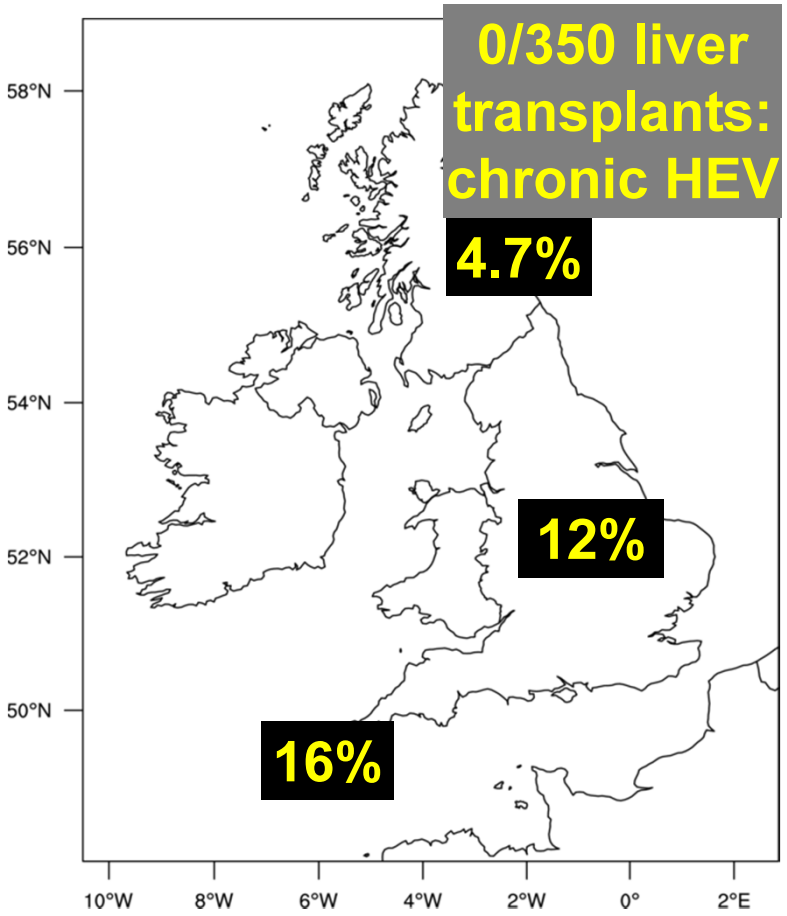
# HEV IgG seroprevalence: varies within countries

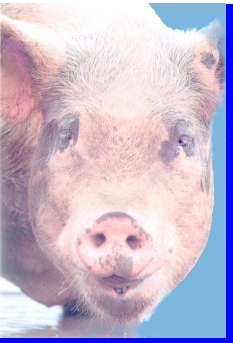



*Hartl et al, submitted*

# HEV IgG seroprevalence: varies within countries




*Hartl et al, submitted*



# Something is happening!!!

Increased seroprevalence in young Dutch adults

*Hogema et al Transfusion 2014*

Dutch blood donors 2014

- **1 : 600 are HEV RNA +ve**

*Zaaijer et al Hepatology 2014*

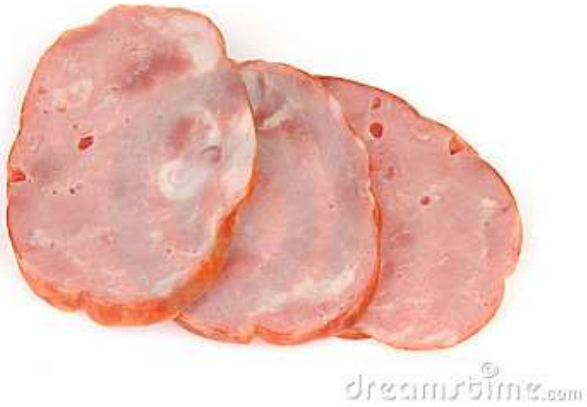
Increased incidence in England

- HEV RNA similar to European pigs

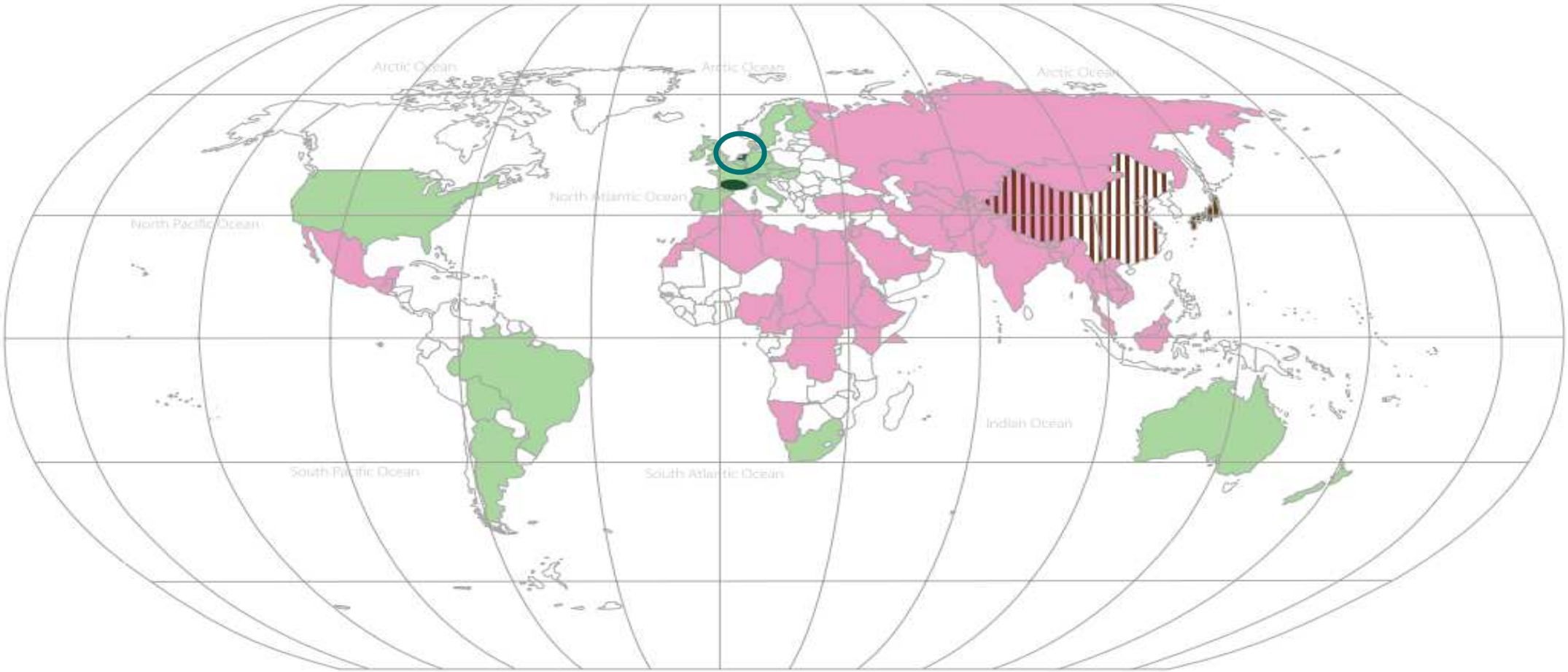
*Ijaz et al JID 2014*

Changes in EU food chain?

- Processed ham and pig serum



## Geographic distribution of human cases of Hepatitis E




**Genotype 1 and 2**
- endemic
- waterborne

**Genotype 3**
- sporadic
- zoonotic

**Genotype 3**
- hyperendemic area

**Genotype 4**
- sporadic
- zoonotic

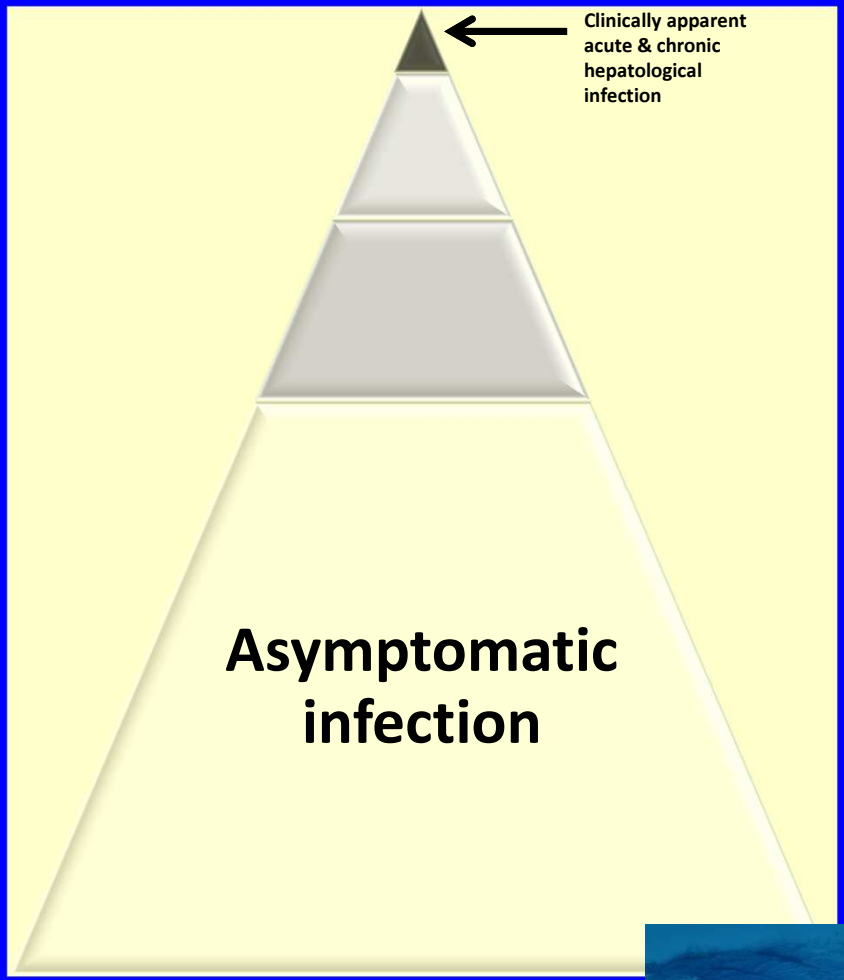
# HEV3: incidence

- UK: 0.2% *Ijaz et al JClinVirol 2009* *Ijaz et al JID 2014*

**100,000 infections per year**

- USA: 0.7% *Faramwi et al EpiInf 2011*
- Netherlands: 1.1% *Slot et al Eurosurv 2013*
- SW France: 3.2% *Abravenal et al JID 2014*

- England and Wales:
  - 869 lab confirmed cases of HEV ( 2014)
- England:
  - incidence HEV: 100,000/yr




*Hewitt et al Lancet 2014*

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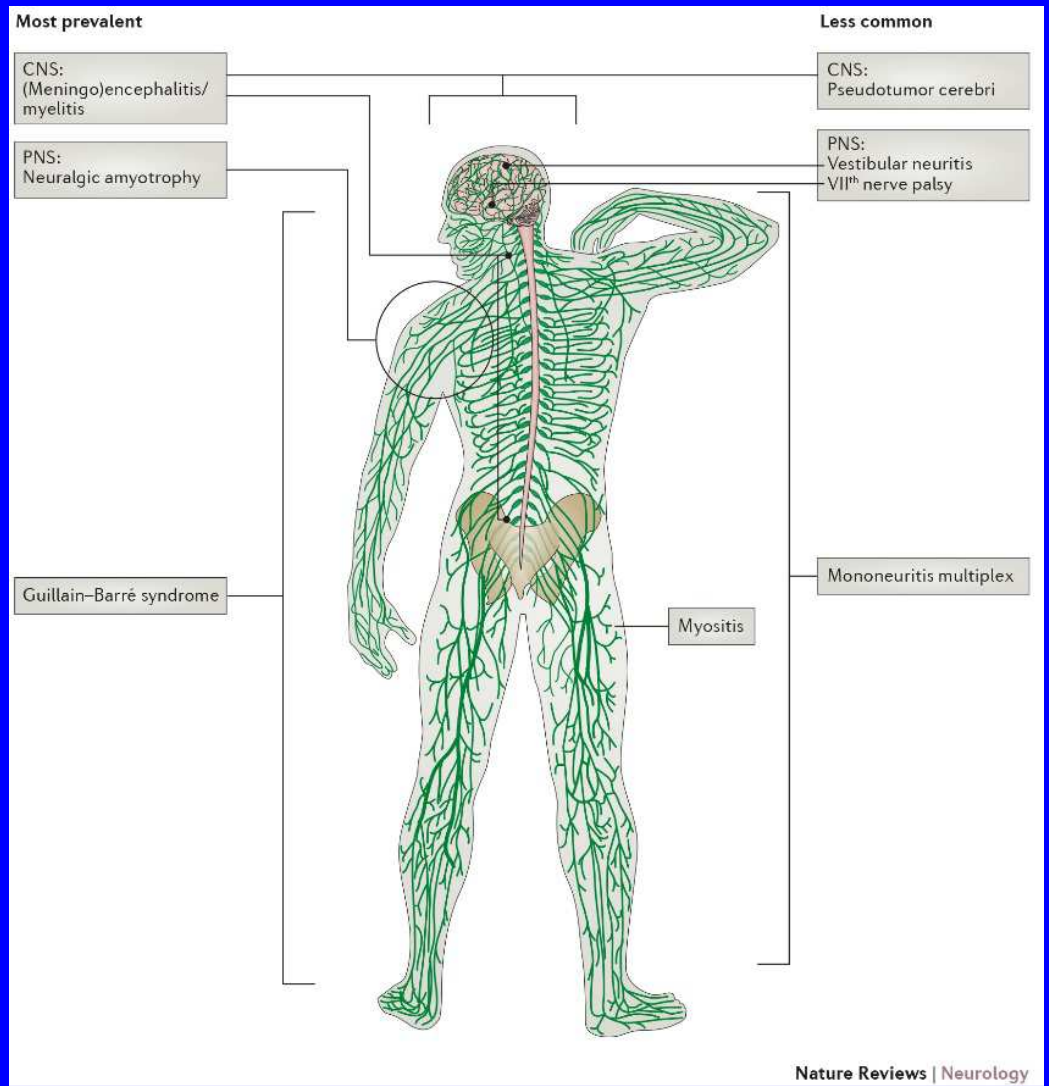
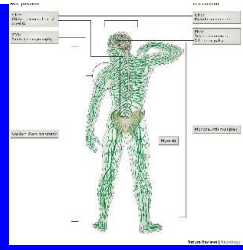
# HEV and neurological syndromes



# HEV and neurological syndromes



HEV associated neurological syndromes:

- Guillain−Barré syndrome
- bilateral brachial neuritis
- Encephalitis
- Mononeuritis multiplex, Bell's Palsy, peripheral neuropathy, mysotitis, vestibular neuritis

5.5% of Toulouse/Cornwall patients with HEV have neurological injury

*Kamar et al Emerg Inf Dis 2011*

- **LFTs only mildly abnormal and most cases anicteric**

Occurs in:

- acute and chronic HEV
- Developed and developing countries

*Dalton et al Nature Rev Neurol, in press*

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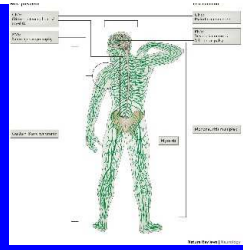
# Guillain-Barré Syndrome (GBS)



- Post infectious immune-mediated polyradiculopathy
- Infectious triggers:
  - Campylobacter: 35%
  - Unknown: 50%
- **30% abnormal LFTs ? Cause**

Article

**Liver function disturbances in Guillain-Barre syndrome**

**A prospective longitudinal study in 100 patients**

P. G. Oomes, MD, F.G.A. van der Meche, MD, PhD and R. P. Kleyweg, MD, PhD

+ SHOW AFFILIATIONS

doi: 10.1212/WNL.46.1.96
*Neurology* January 1996 vol. 46 no. 1 96-100

Abstract | Full Text | Full Text (PDF)

Also available: Figures Only PPT Slides of All Figures

ABSTRACT

Article abstract-In 100 consecutive patients with Guillain-Barre syndrome, we assessed liver function on admission and at fixed intervals after either intravenous immunoglobulin (IgIV) or plasma-exchange (PE) treatment. On admission, 38% showed a plasma alanine aminotransferase elevation, gamma glutamyl transferase elevation, or both of more than 1.5 times the upper limit of normal. Ten of these patients had serologic evidence of recent cytomegalovirus infection. The remaining 28 patients were negative for other known causes of liver damage, including infection with Epstein-Barr virus or hepatitis A, B, and C; alcohol abuse; hepatotoxic drugs; recent surgery; and concurrent liver disease. In a hospital control group of 100 consecutive patients with subarachnoid hemorrhage, only 5 had unexplained liver function disturbances on admission ($p < 0.0001$). In the IgIV-treated group, the percentage of patients with elevated liver function tests increased from 35% before to 69% shortly after treatment at 2 weeks postadmission ($p < 0.005$). In the PE-treated group, this percentage decreased somewhat from 41% to 36% (not significant). There was also a significant rise in median plasma activity of the various liver enzymes in the IgIV group. At 1 month, however, significant difference had disappeared. At 3 and 6 months, the percentage of patients with liver function disturbances reached a significantly lower level in both treatment groups compared with the time of admission. We concluded that many patients with Guillain-Barre syndrome had mild liver function disturbances without obvious cause. In addition, IgIV treatment was associated with mild transient liver function disturbances through an unknown mechanism.

**NEUROLOGY 1996;46:** 96-100

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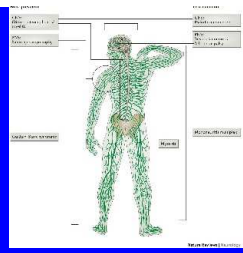
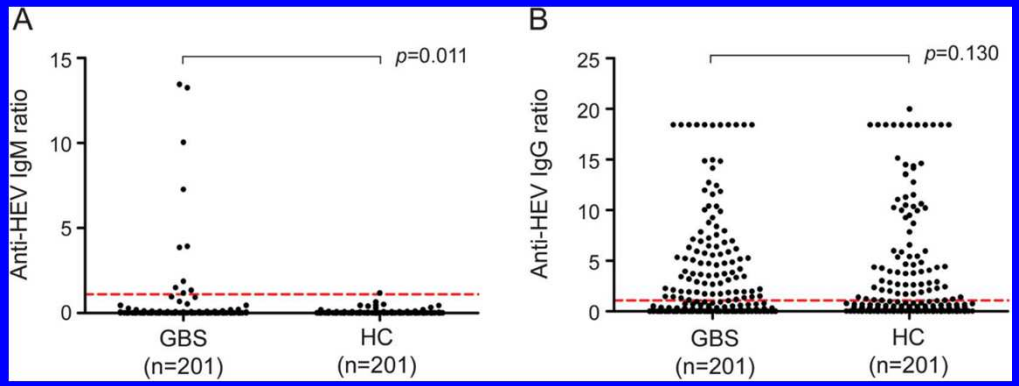
*Oomes et al Neurology 1996*

# HEV & Guillain-Barré syndrome



## Case control study of Dutch patients with GBS (n=201)

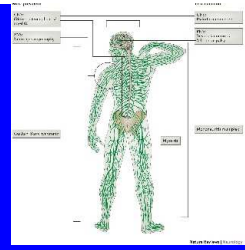
- 5% of GBS have HEV infection (10/201, p=0.01 vs controls)




*van den Berg et al Neurology 2014*

- Mildly abnormal LFT's:
  - normal bilirubin
  - ALT: 70 (range 26-921); abnormal n=7
- Outcome:
  - 1 required ventilation, 7 have significant disability at 6 months
- Some patients are viraemic (HEV3) at presentation
  - ?role for early therapy with ribavirin

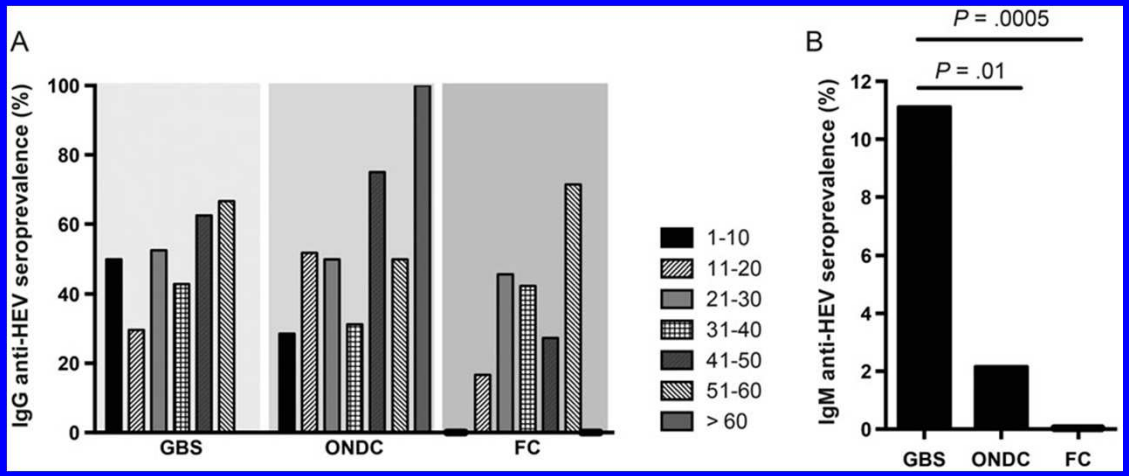
# HEV & Guillain-Barré syndrome



## Case control study of Bangladeshi patients with GBS (n=100)

- 11% of GBS have HEV infection (genotype 1, n=1)

*Geurtsvankessel et al Clin Infect Dis 2013*




## Worldwide HEV & GBS: n=36

- Age 2-73 years, 72% male
- All but one: immunocompetent

*Dalton et al Nature Rev Neurol, in press*

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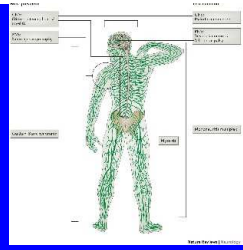

# HEV & Guillain-Barré syndrome: outstanding questions

30% of GBS have abnormal LFT's:

- Are the other 25% caused by re-infection with HEV?

If HEV re-infection is 4 weeks prior to symptom onset:

- IgM –ve
- IgG +ve
- PCR –ve
- Indistinguishable from distant infection

*Dalton et al Nature Rev Neurol, in press*

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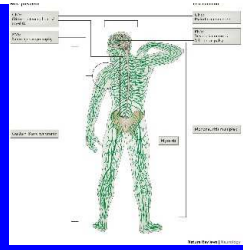

# HEV & Guillain-Barré syndrome: outstanding questions

30% of GBS have abnormal LFT's:

- Are the other 25% caused by re-infection with HEV?

What are the pathogenic mechanisms?

Role of HEV in other neurological syndromes?

*van den Berg et al Neurology 2014*

If HEV re-infection is 4 weeks prior to symptom onset:

- IgM –ve
- IgG +ve
- PCR –ve
- Indistinguishable from distant infection

*Dalton et al Nature Neurology Rev, in press*

# HEV & Neuralgic amyotrophy (brachial neuritis, Parsonage Turner syndrome)

- LFTs abnormal in some patients, ? Cause
- Anglo/Dutch cohort study: 47 patients tested for HEV
  - 5 (10%) had HEV at the start of the illness
  - Age 30-40 years
  - Mildly abnormal LFT's: ALT 100-300, normal bilirubin
  - 4 PCR positive: HEV genotype 3

*Van Eijk et al, Neurology 2014*

- Worldwide:
  - HEV & NA n=30, nearly all from Europe
  - Genotype 3
  - Median age 49 years, 88% males
  - Bilateral symptoms +/- phrenic nerve involvement

*Dalton et al Nature Rev Neurol, in press*

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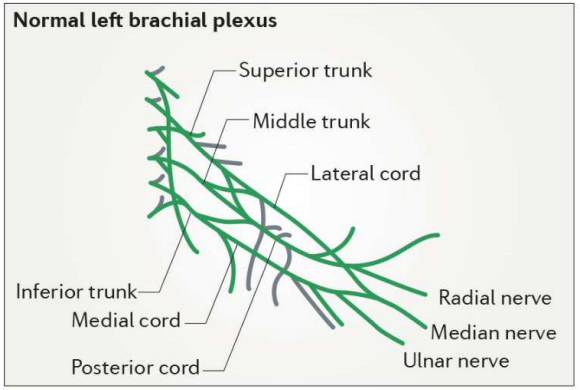
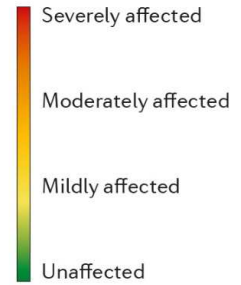
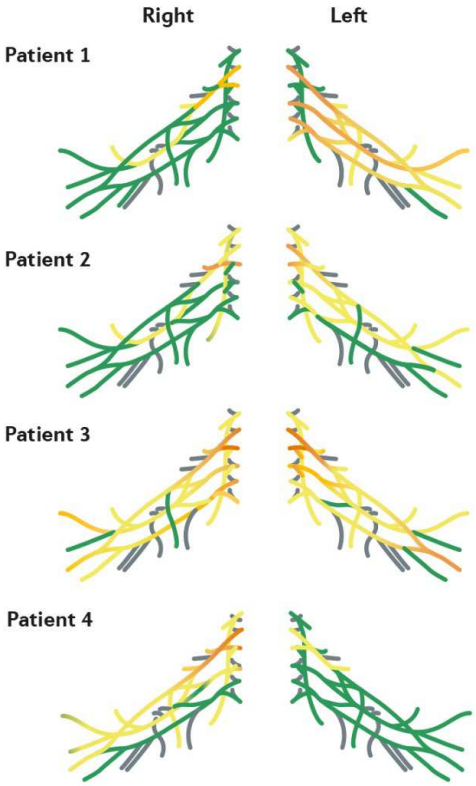
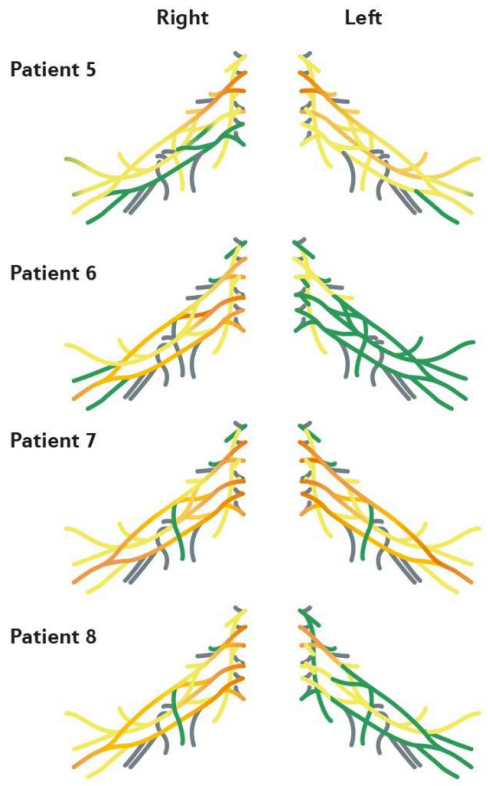



Nature Reviews | Neurology

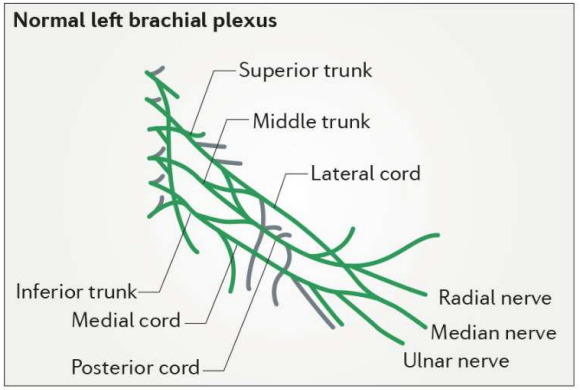
*Dalton et al Nature Rev Neurol, in press*

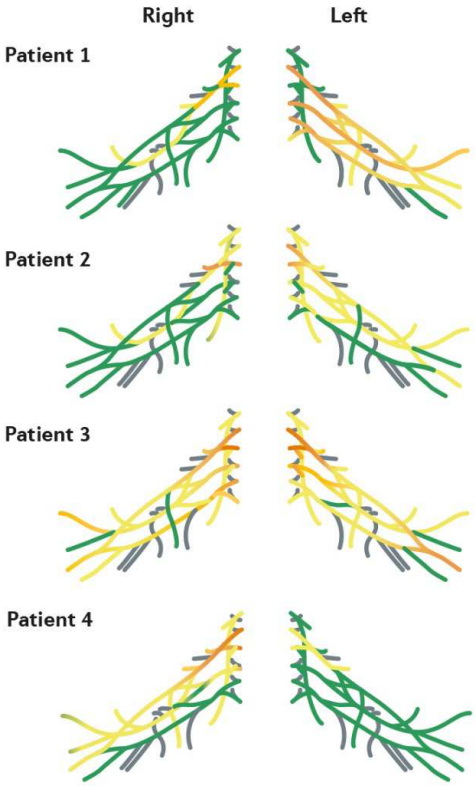
***Diagnostic tip:***

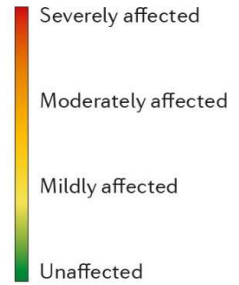
- *Bilateral non-traumatic shoulder pain*
- *Middle aged male*
- *Abnormal LFTs*

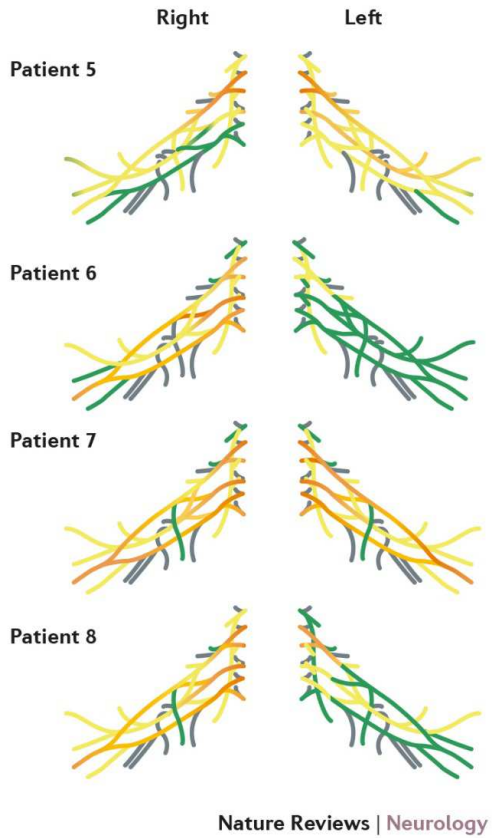
***Diagnosis = HEV***

*Dalton et al Nature Rev Neurol, in press*



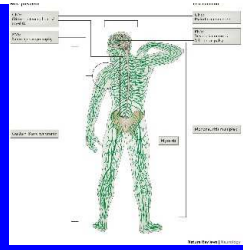



# HEV & Meningo-encephalitis

## 12 cases reported



- Europe, Asia, USA
- **Not jaundiced**
- HEV RNA in serum and CSF (n=6)
- Immunocompromised, chronic infection (n=5)
  - Ataxic component
  - Poor outcome
  - 2 deaths

*Dalton et al Nature Rev Neurol, in press*

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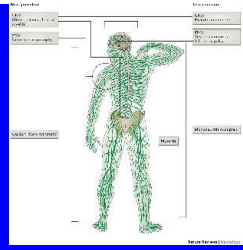
# Bart Jacobs
# Erasmus MC Rotterdam

# Bart Jacobs
# Erasmus MC Rotterdam

"Harry. Has this virus been misnamed?"

"These patients have profound neurological injury, but not much of a hepatitis"

# HEV & neurological syndromes: evidence for causality



## Number and homogeneity of cases

- Over time and geographical location

## Case-control data (GBS)

*van den Berg et al, Neurol 2014, Geurtsvankessel et al Clin Inf Dis 2013*

- Netherlands (HEV3) & Bangladesh (HEV1)

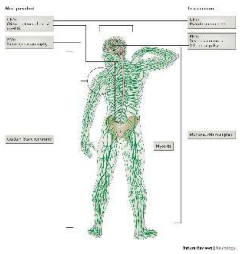
## HEV RNA

- Serum and CSF

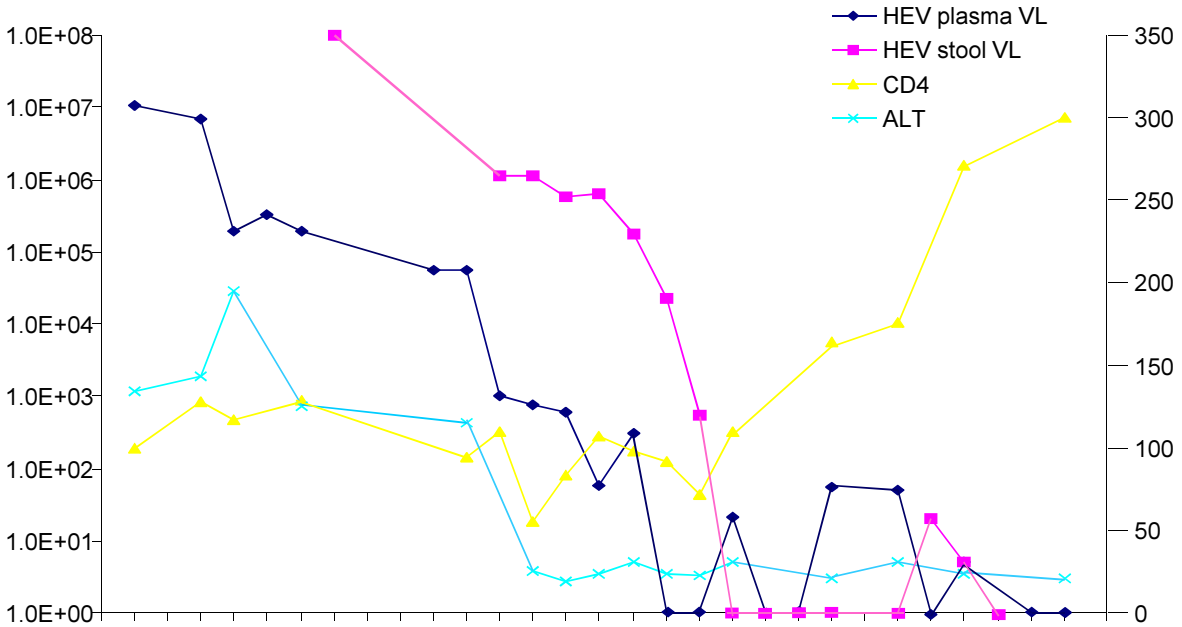
## Kernow C1p6

*Dalton et al NEJM 2009, Shukla et al PNAS 2011 & J Virol 2012*

- Strain of HEV incorporating a section of host genome
- Isolated from a patient with HIV and chronic HEV infection
- Grows on a range of cell lines, including neurological

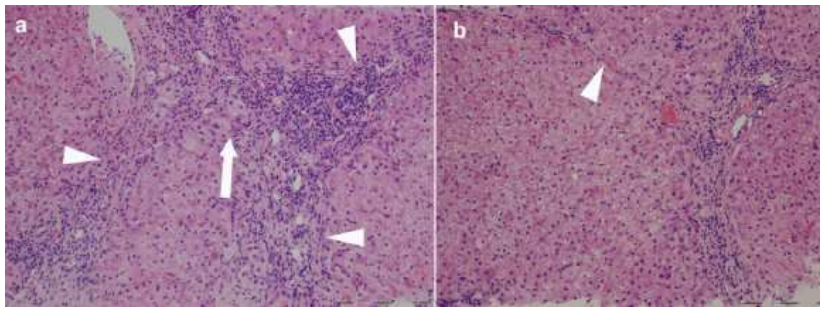


# HEV and neurology: response to treatment




***Interferon*** →

***Ribavirin*** →




*Dalton et al NEJM 2009*

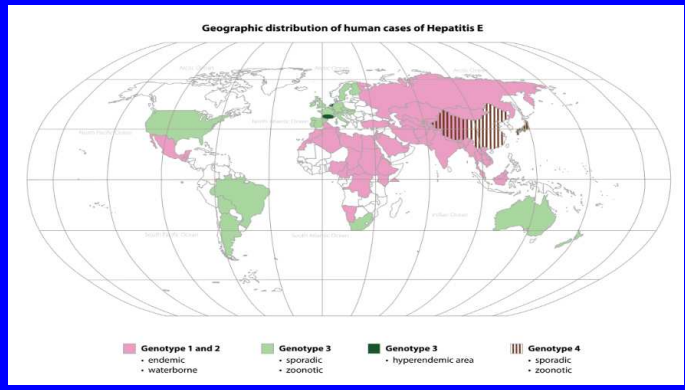
*Dalton et al Ann Int Med 2010*

# HEV: who should we test?

## Immunocompetent

- ALT >300 or
- Decompensated chronic liver disease
- DILI
- Guillain-Barré Syndrome
- Neuralgic amyotrophy
- Acute neurological syndromes, with raised ALT

*Wallace et al, 2015, submitted*




## Immunosuppressed

- Raised ALT
- Annual PCR

*Dalton et al Nature Rev Neurol, in press*
*Kamar et al Liver Int, in press*

# Conclusions: Diagnosis of HEV

- Serology
  - IgM and IgG
- PCR
- Quality of diagnostics good

- Need to think of diagnosis
- Travel history irrelevant, but chance of diagnosis varies geographically

- **Clinic phenotype of HEV is still emerging**

# Acknowledgments


- Lemon Street Gallery, Truro
- Sheila Sherlock Travelling Bursary 2011

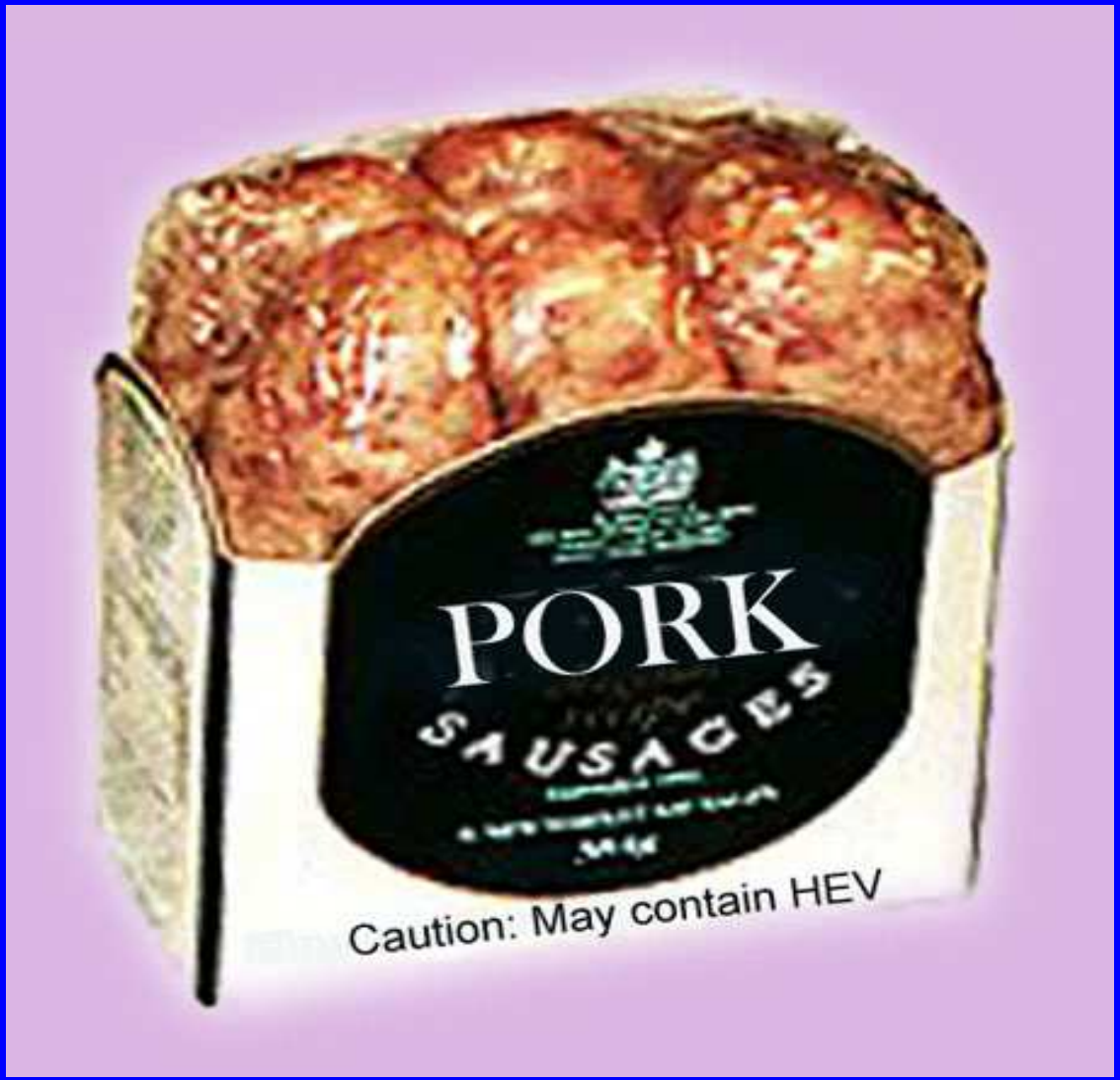
Royal College of Physicians
Setting higher medical standards

- Office of Chief Scientist Scotland
- Duchy Charity
- British Medical Association

European Centre for Environment & Human Health

# research collaborators

- Colleagues in SW England:
  - **Dr Richard Bendall**
  - Dr Frances Keane, Renal and Neurological physicians (Truro),
  - Medical Students: UoE & PCMD
  - Colleagues from Plymouth
  - Dr Mark Gompels (Bristol)
- UK, national:
  - Malcolm Banks: Veterinary Laboratory Association (Surrey)
  - Linda Scobie: Glasgow Caledonian University, Scotland
  - Adrian Stanley: Glasgow Royal Infirmary
  - Ken Simpson, Scottish Liver Transplant Unit, Edinburgh
  - Prof Richard Tedder, Dr Samreen Ijaz: Health Protection Agency (London)
  - Ellie Barnes: University of Oxford
- International:
  - Bob Purcell/Sue Emerson, NIH, Bethesda, Maryland, USA
  - **Bart Jacobs and colleagues, Erasmus MC and Nijmegen, The Netherlands**
  - Hans Zaaijer, Sanquin,Amsterdam, The Netherlands
  - Alessandro Bartoloni, Florence, Italy
  - Prof Ting Wu, Xiamen University, China
  - **Jacques Izopet, Nassim Kamar & colleagues, Toulouse, France**


PORK
SAUSAGES
Caution: May contain HEV

# Hepatitis: Differential Diagnosis

1. DILI
2. Autoimmune hepatitis
3. **Acute HEV**
4. Seronegative hepatitis
5. EBV hepatitis
6. Acute HBV
7. HAV
8. Acute HCV

**Drug-induced liver injury (DILI)**

- Common in the elderly
- 13% of patients with DILI have HEV3

*Dalton et al APTherap 2007*

- Diagnosis of DILI not secure without testing for HEV

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