# Hepatitis E and Neurological disease

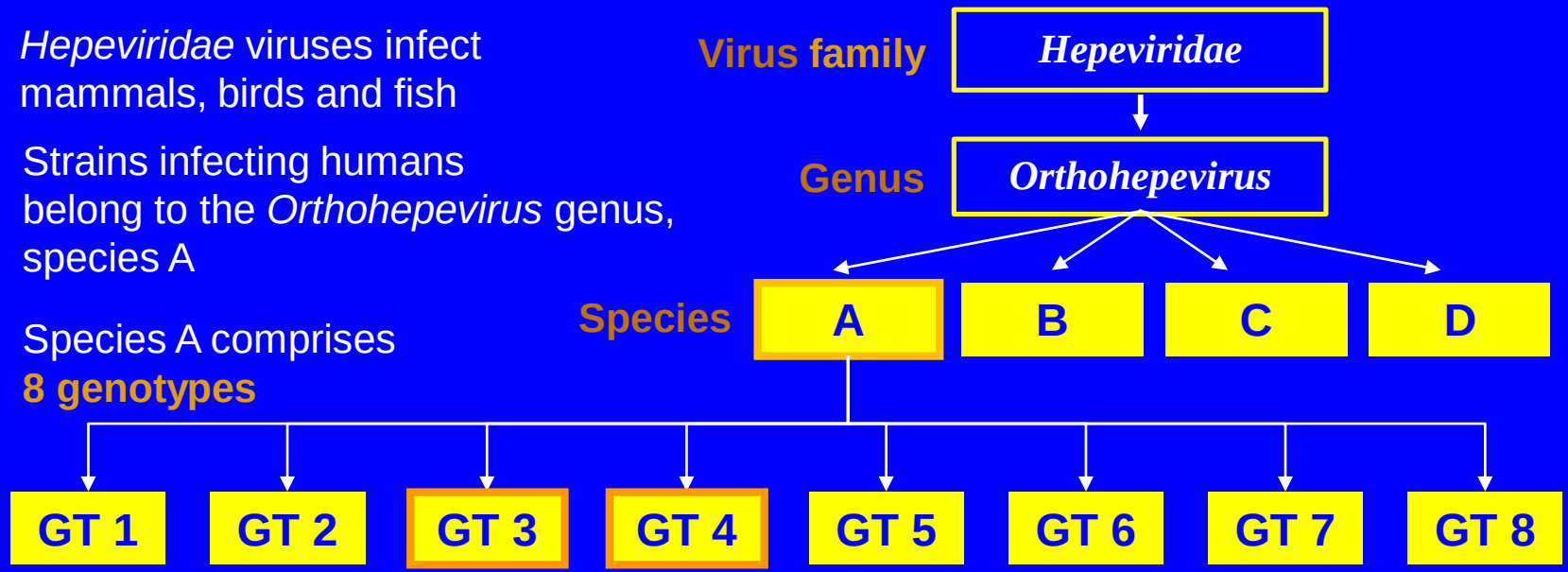
Harry Dalton

# Virology of HEV

*Hepeviridae* viruses infect mammals, birds and fish

Strains infecting humans belong to the *Orthohepevirus* genus, species A

Species A comprises **8 genotypes**




- Only infect humans
- **Faecal–oral spread** via contaminated water
- Large **outbreaks**
- Brief, **self-limiting**
- Never chronic
- High mortality in **pregnancy** (25%)

- **Endemic** in animal species; eg, pigs and wild boar
- **Zoonotic** infections in humans
- **High-income countries**
- China: GT 4 most common
- Japan GT3 & GT4
- S. America: GT 3 only

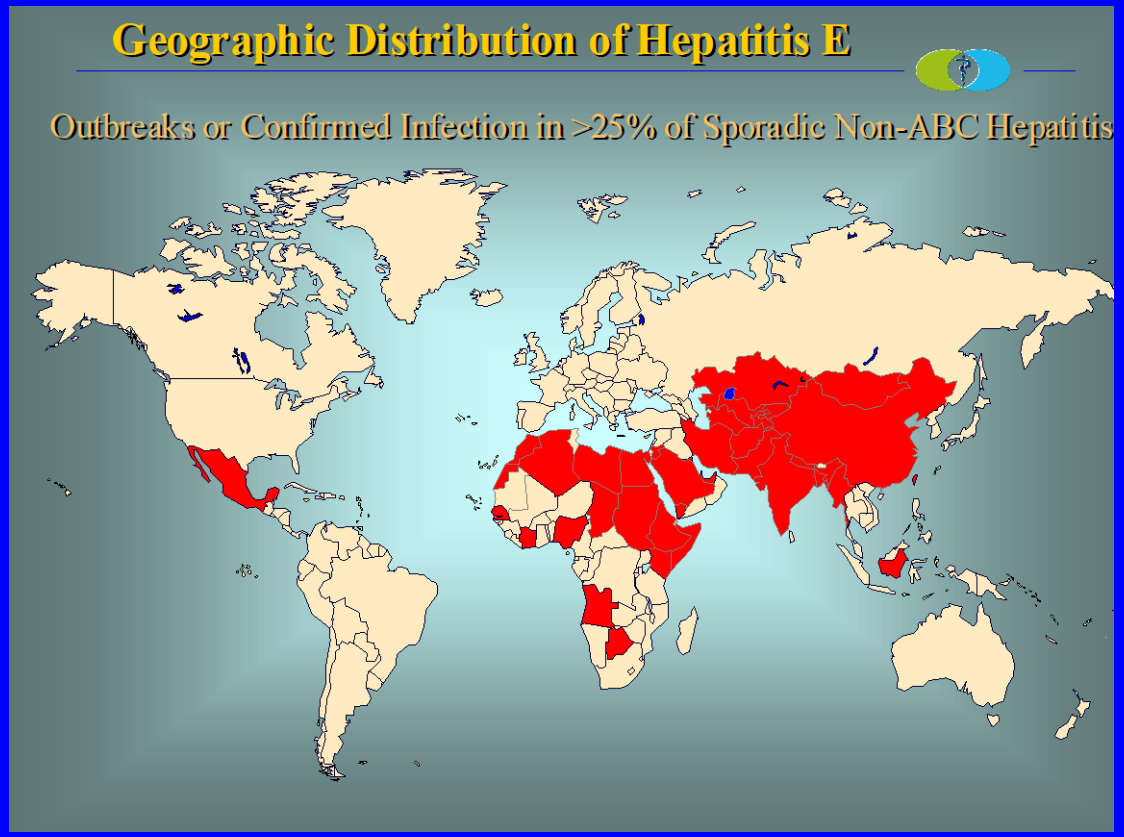
- Have only been reported in wild boar

- GT 7 identified in patient regularly consuming camel meat and milk
- Have since been identified in camels

EASL CPG HEV. J Hepatol 2018

# HEV in developing countries

- Major health issue
- Genotypes 1 & 2
- Faeco-oral route via infected water
- Affects young adults
- **Mortality in pregnant women 25%**



# HEV in developed countries: received wisdom

- Seen in travellers
- Of little relevance in developed countries

# acute HEV Gt 3 (and 4)

- Commonest cause acute viral hepatitis in many European countries
- **? ≥2 million locally acquired HEV infections in Europe per year**
  - Mostly zoonotic, Pigs primary host
- Mostly Gt 3 (occasionally Gt4)
  - Locally acquired, travel history irrelevant
  - M:F ratio 3:1; median age 63 years[1]
  - Self limiting hepatitis
  - Deaths in patients with pre-existing chronic liver disease
  - **No deaths in pregnancy**

1. Dalton HR, et al. Eur J Gastroenterol Hepatol 2008;20:784–90;
EASL CPG HEV. J Hepatol 2018

# Acute HEV3: symptoms

**COMMON**

- Jaundice
- Anorexia
- Lethargy
- Abdominal
- pain
- Vomiting
- Fever
- Myalgia

**LESS COMMON**

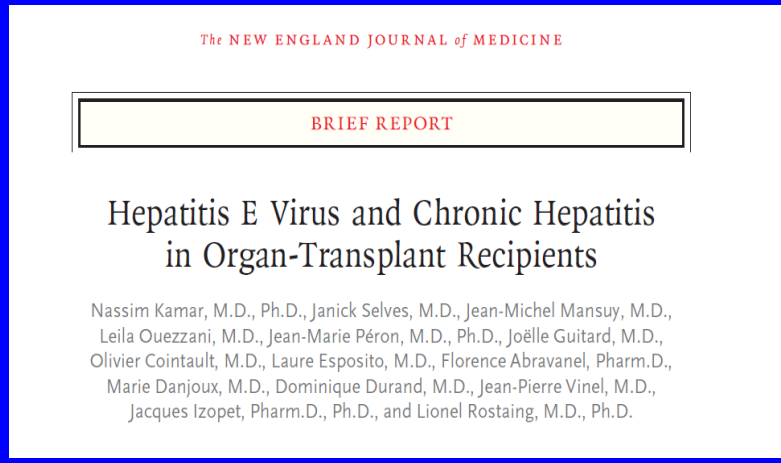
- Pruritis
- Weight loss
- Headaches
- Arthralgia
- **Neurological**
- No symptoms

*Dalton et al EJGH 2008, Woolson et al APT 2014*

# Chronic HEV infection: immunosuppressed

- Chronic HEV3 infection in transplant patients
  - No symptoms, anicteric, ALT 200-300IU/L
  - **10% cirrhotic in 2 years**

*Kamar et al NEJM 2008*



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Hepatitis E Virus and Chronic Hepatitis in Organ-Transplant Recipients

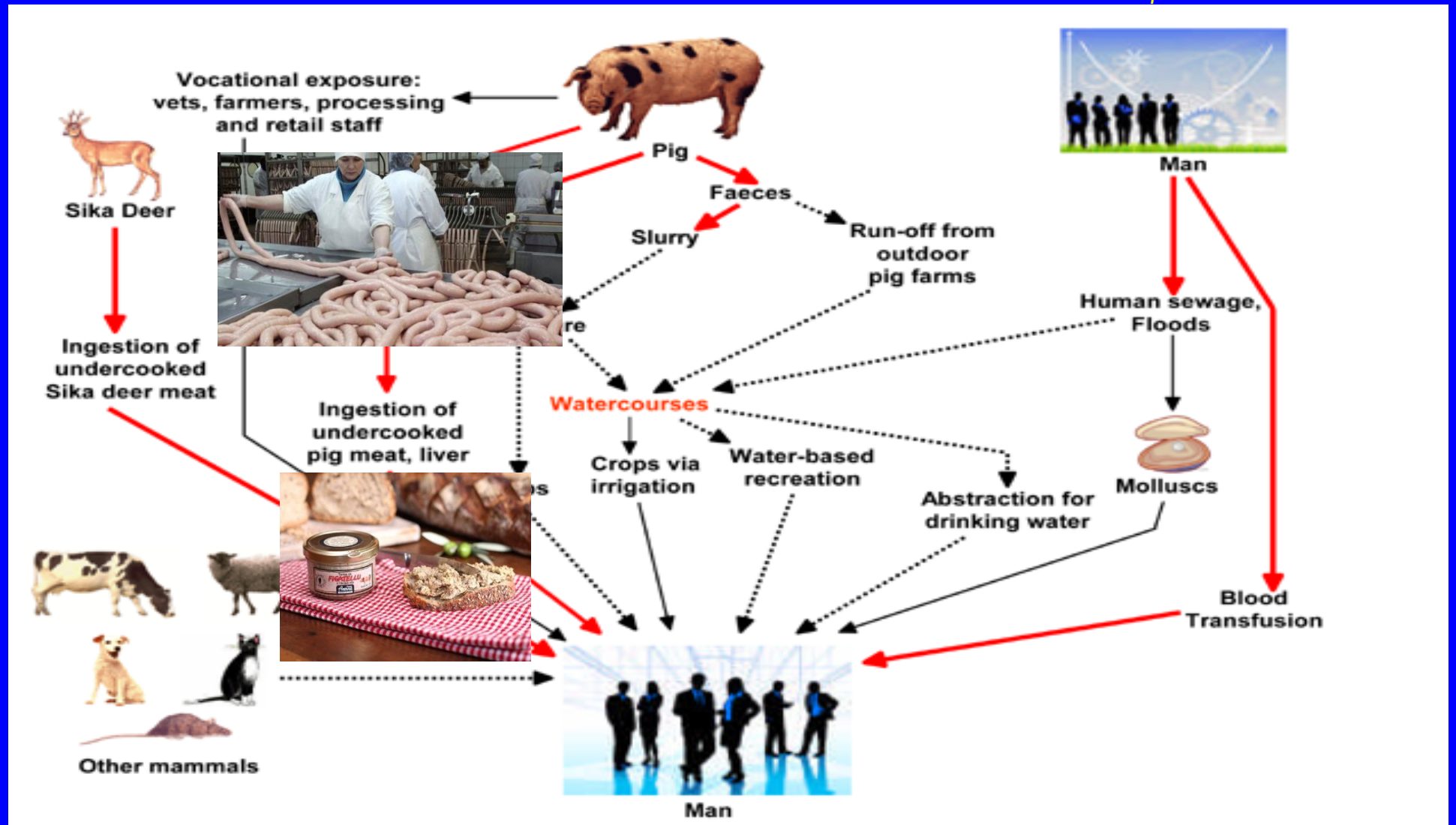
Nassim Kamar, M.D., Ph.D., Janick Selves, M.D., Jean-Michel Mansuy, M.D., Leila Ouezzani, M.D., Jean-Marie Péron, M.D., Ph.D., Joëlle Guitard, M.D., Olivier Cointault, M.D., Laure Esposito, M.D., Florence Abravanel, Pharm.D., Marie Danjoux, M.D., Dominique Durand, M.D., Jean-Pierre Vinel, M.D., Jacques Izopet, Pharm.D., Ph.D., and Lionel Rostaing, M.D., Ph.D.

- Prevalence of chronic HEV
  - High in French transplant centres
  - Other European transplant centres: 1-2%

*Pas et al EID 2012*
*Koning et al J Heart Lung Tran 2013*
*Moal et al JMV 2013*
*Halac et al Gut 2012*
*Pischke et al Am J Transpl 2012*

# Source and route of infection

*Dalton et al Lancet Inf Dis 2008*



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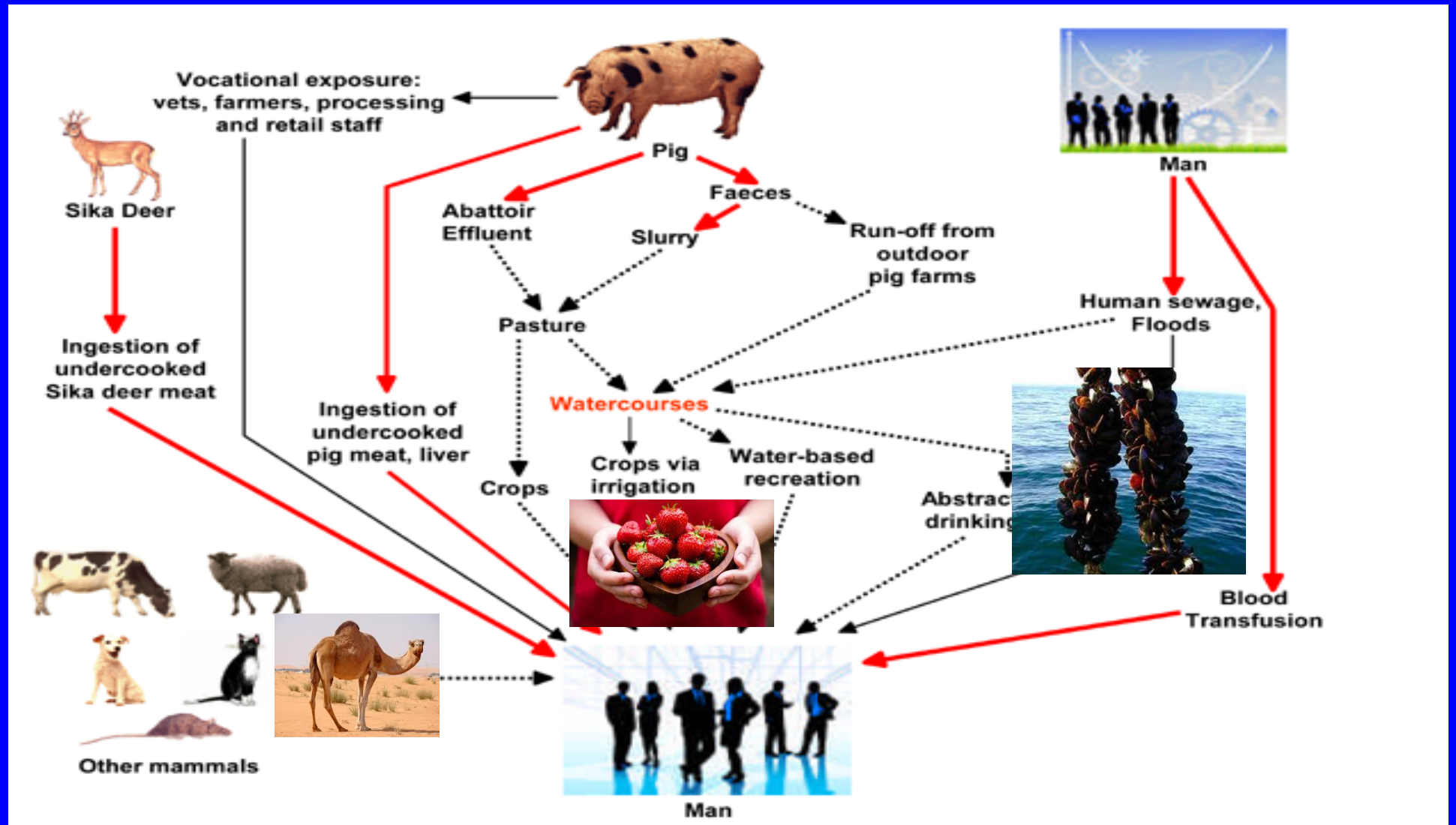
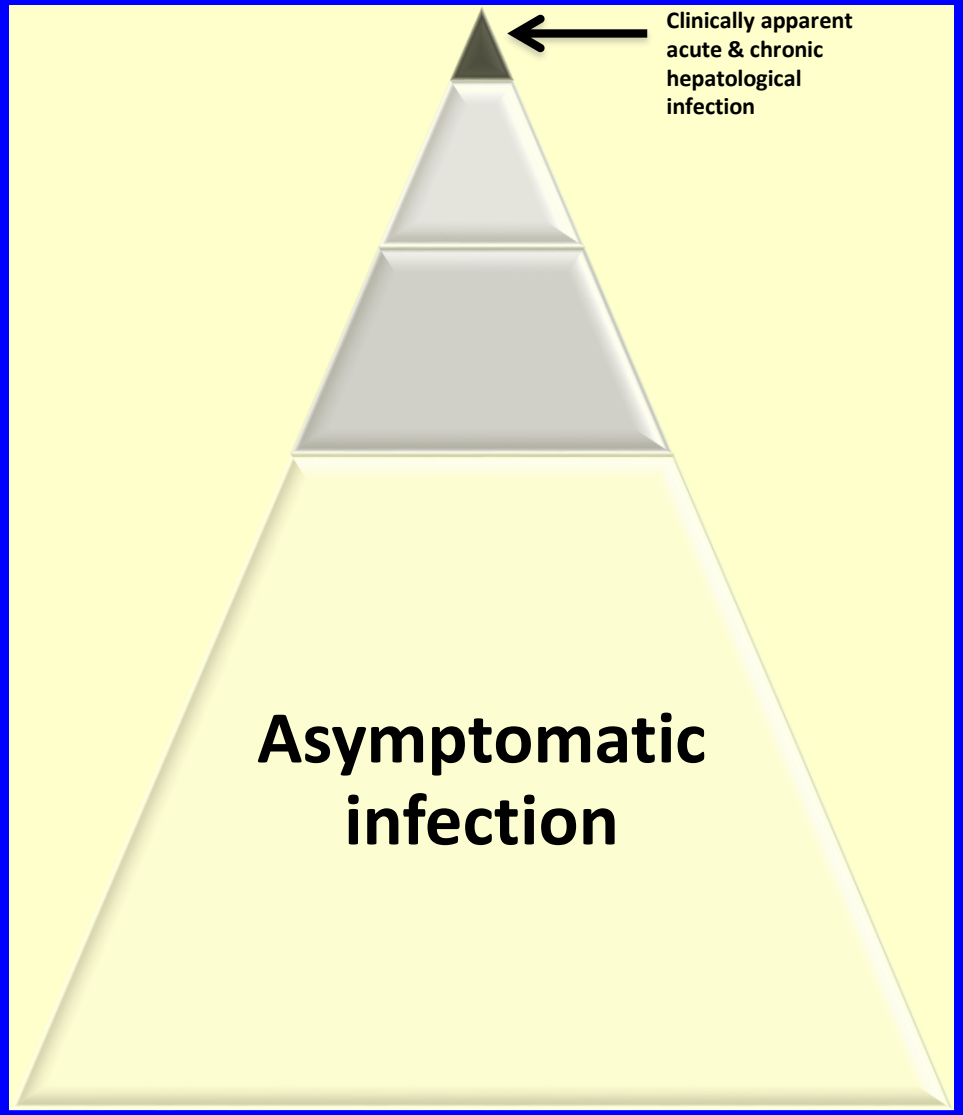


# HEV3: incidence varies between & within countries & over time

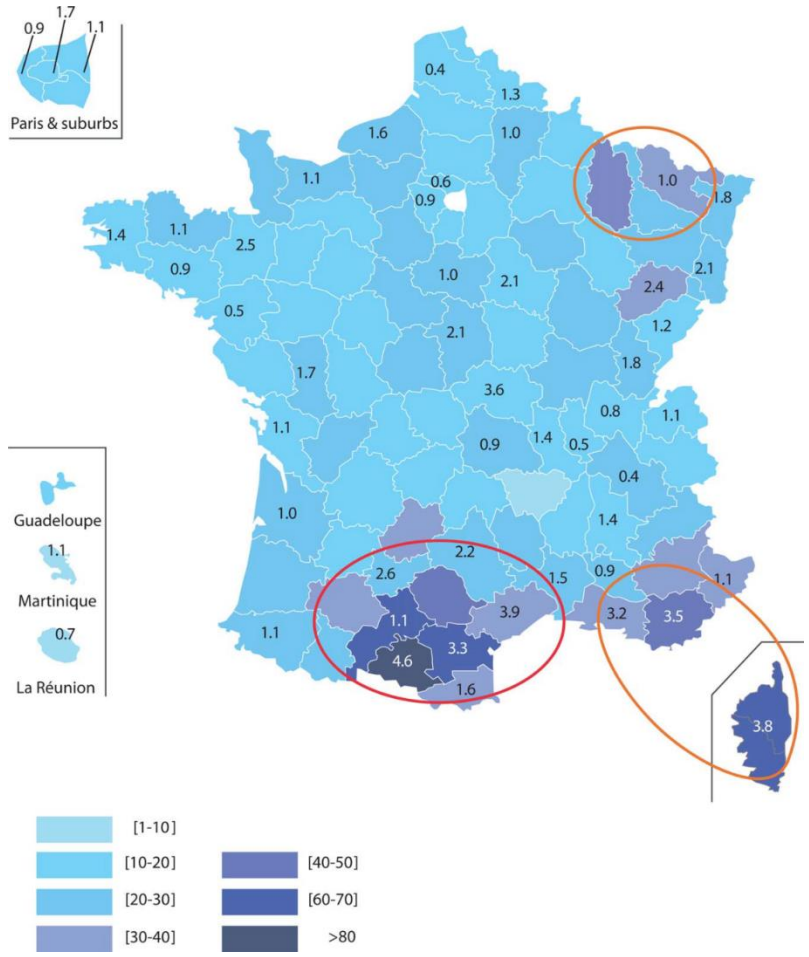
- UK: 0.2% *Ijaz et al 2009 JClinVirol*
  *Ijaz et al JID 2014*
- Netherlands: 1.1% *Slot et al Eurosurv 2013*
- SW France: 3.2% *Abravenal et al JID 2014*

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



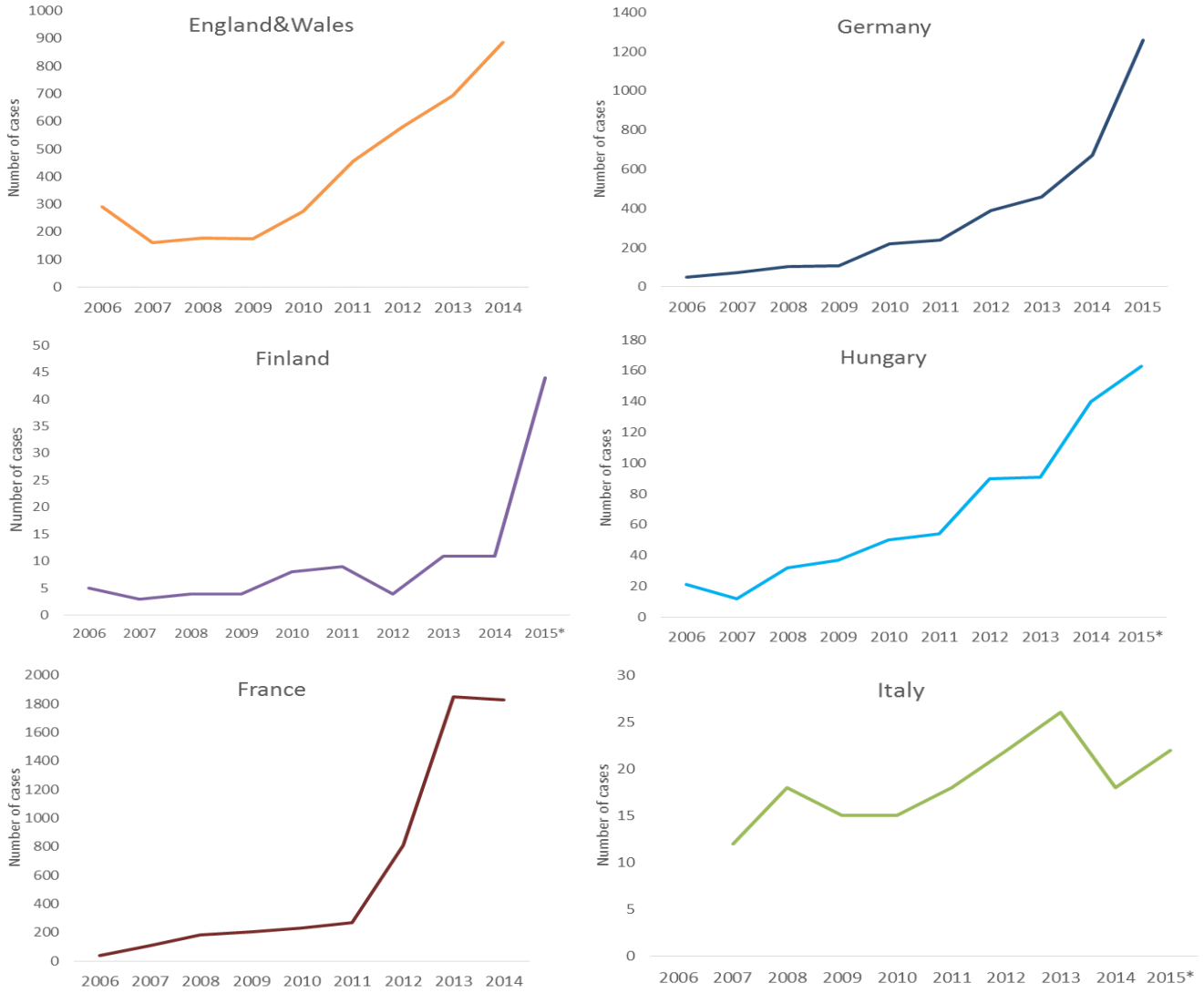

*Hewitt et al Lancet 2014, Tedder et al Transfusion 2016*

# HEV seroprevalence: varies within countries




*Mansuy et al 2016 Hepatology*

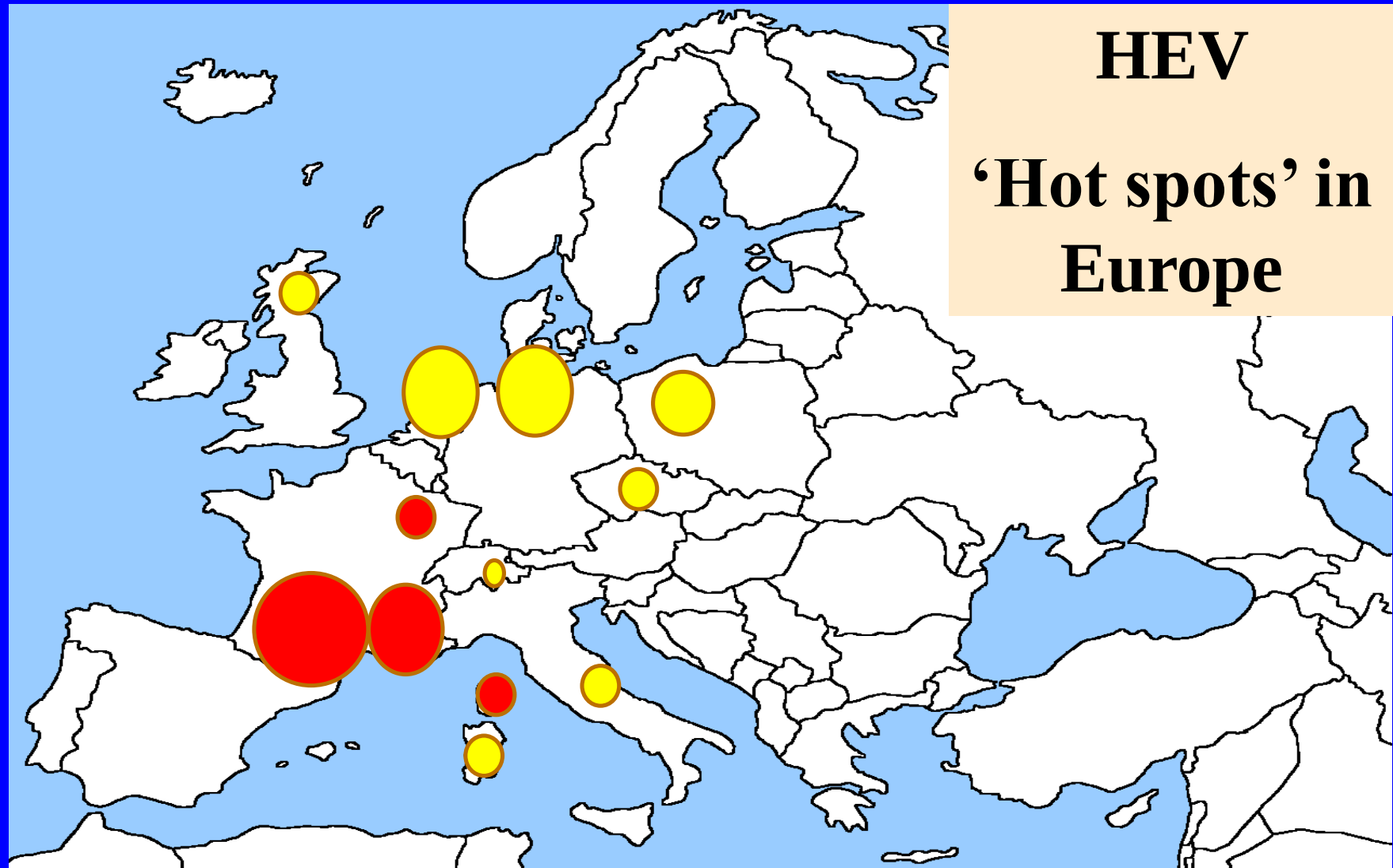
# HEV incidence varies over time




*Adlhoch et al JCV 2016*

# HEV

# ‘Hot spots’ in Europe



*Thom et al EuroSurveill 2018*
*Niederhauser et al Eurosurv 2018*
*Westhölter et al J Hepatol 2018*
*Bura et al IntJInfDis 2017*
*Adlhoch et al J Clin Virol. 2016*
*Mansuy et al Hepatology 2016*
*Zaaijer Hepatology. 2015*
*Müller et al TrMedHemo 2015*
*Lucarelli et al EuroSurveill 2016*
*Grabarczyk et al Transfusion 2018*

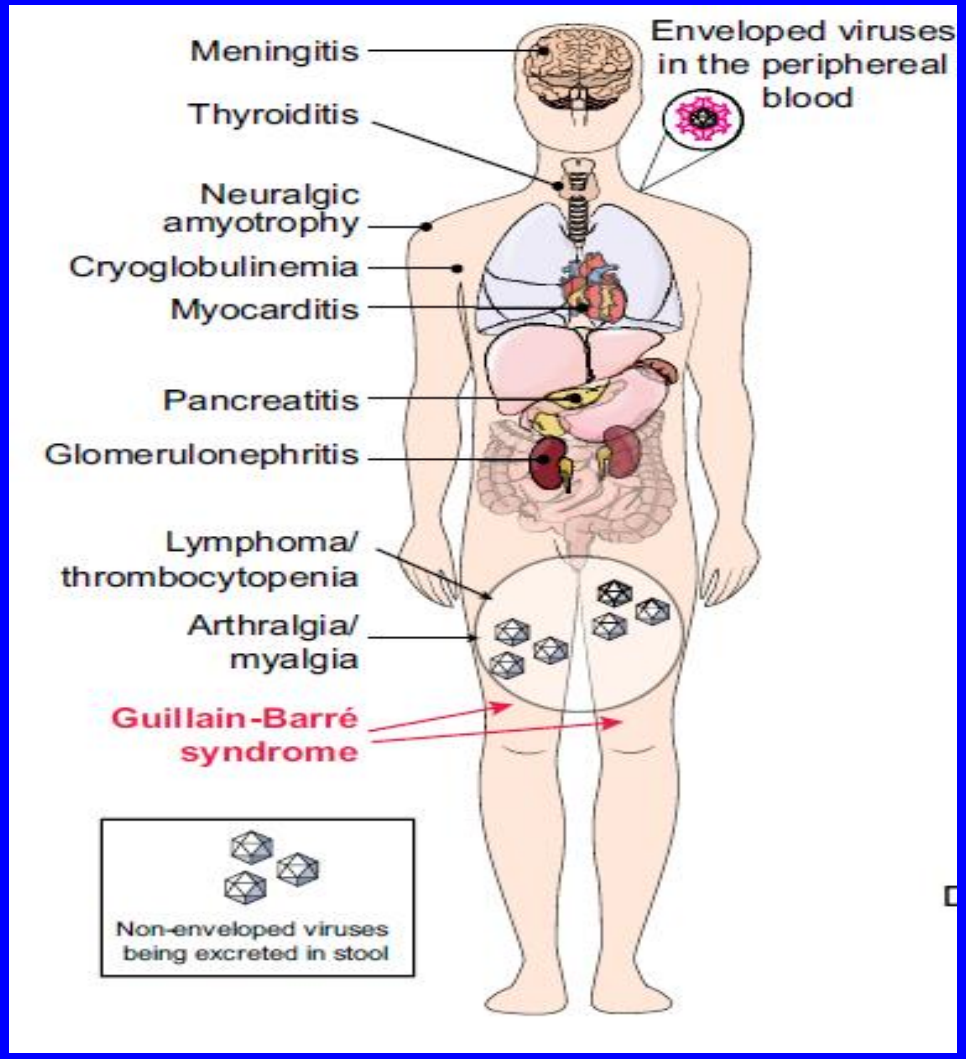
| Country | Blood donors HEV RNA positive | HEV IgG seroprevalence | Assay | Reference |
|---|---|---|---|---|
| **France Midi-Pyrénées** | **1:1595** | **52%**<br>16% | Wantai<br>Genelabs | *Gallian et al, 2014*<br>*Mansuy et al, 2011*<br>*Mansuy et al, 2008* |
| **Japan** | **1:1781** | | | Fukuda 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 RNA donor screening

- Universal screening:

**Germany: summer 2019**
**Swiss: Nov 2018**
**UK: April 2017**
**NL: July 2017**
**Ireland: Jan 2016**

# HEV: extrahepatic manifestations



# HEV and neurological injury

- ~200 cases worldwide:
  - Guillain−Barré syndrome
  - Neuralgic amyotrophy
  - Meningoencephalitis
  - Myasthenia gravis
  - Miscellaneous
    - Bells Palsy, myosotis, mononeuritis multiplex, vestibular neuritis
- Occurs in:
  - Acute and chronic HEV
  - Developed and developing countries
- **Neurological symptoms and signs dominate clinical picture**

*Kamar et al Emerg Inf Dis 2011, Dalton et al Nature Neurol Rev 2016*

# Guillain-Barré Syndrome (GBS)

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

*Oomes et al Neurology 1996*

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

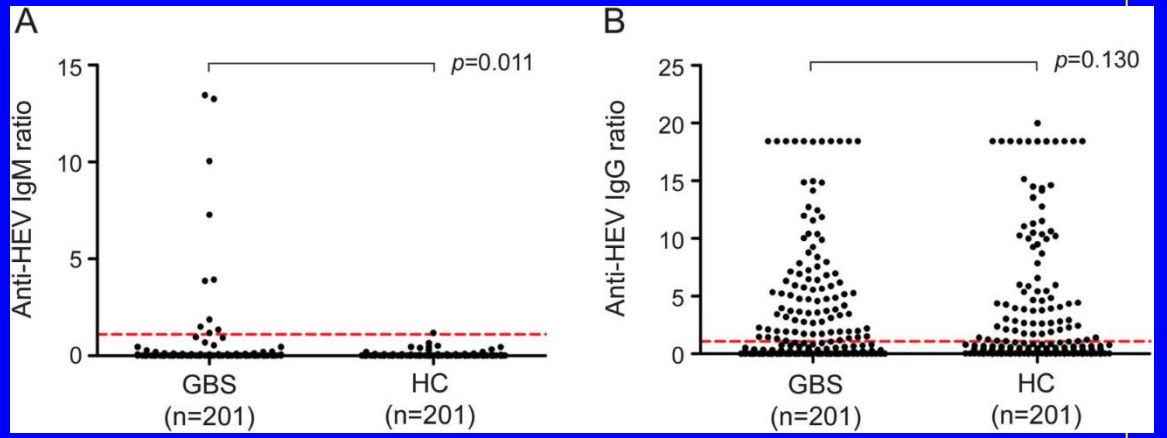
Article abstract-In 100 consecutive patients with Guillain-Barre syndrome, we assessed liver function on admission and at fixed intervals after either intravenous immunoglobulin (IgIV) or plasma-exchange (PE) treatment. On admission, 38% showed a plasma alanine aminotransferase elevation, gamma glutamyl 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

# 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)

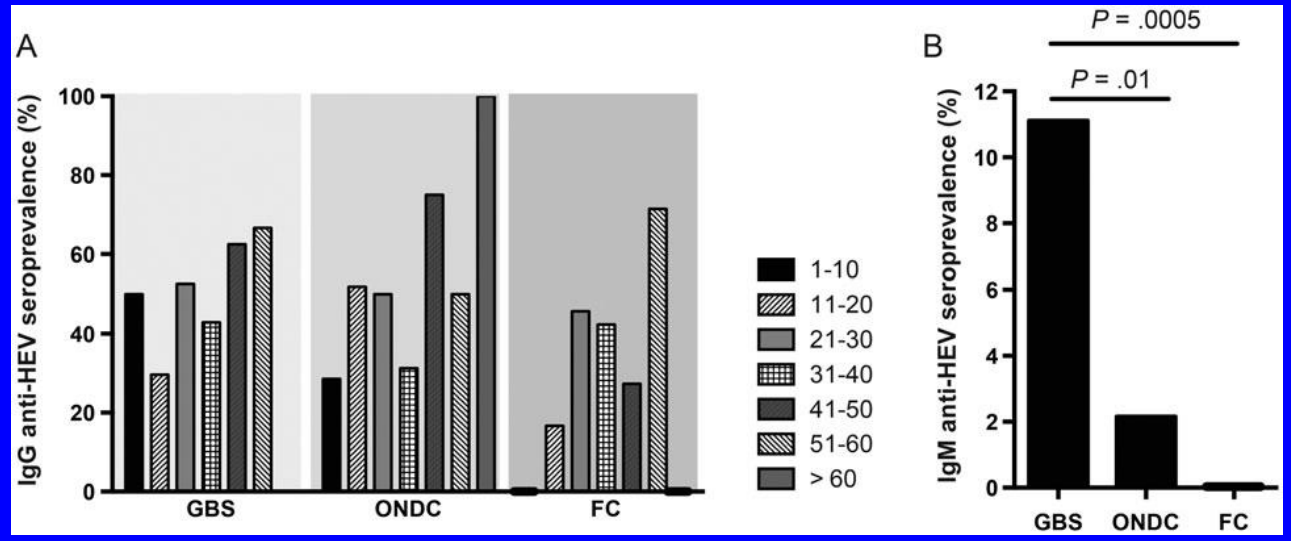



- Liver function tests:
  - Not jaundiced
  - Normal liver function n=3
- Outcome:
  - 1 required ventilation, 7 have significant disability at 6 months

*van den Berg et al Neurology 2014*

# HEV and GBS

- Case control study of Bangladeshi patients with GBS (n=100)
  - 11% of GBS have HEV infection (HEV genotype 1, n=1)




*Geurtsvankessel et al. Clin Infect Dis, 2013*

# HEV & meningoencephalitis

- 14 cases: Europe n=9, Asia n=4, USA n=1
- Immunosuppressed (n=5)
    - Ataxic syndrome
- HEV RNA (genotype 3) serum and CSF (n=6)
    - Quasisepcies compartmentalisation
- LFTs modestly elevated
- Outcome variable: Worse in immunosuppressed

*Dalton et al Nature Neurol Rev 2016*

# 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 liver function: ALT 100-300, **normal bilirubin**
  - 4 PCR positive: HEV genotype 3

*Van Eijk et al, Neurology 2014*

# Neuralgic amyotrophy and HEV:
## Multi-centre international study

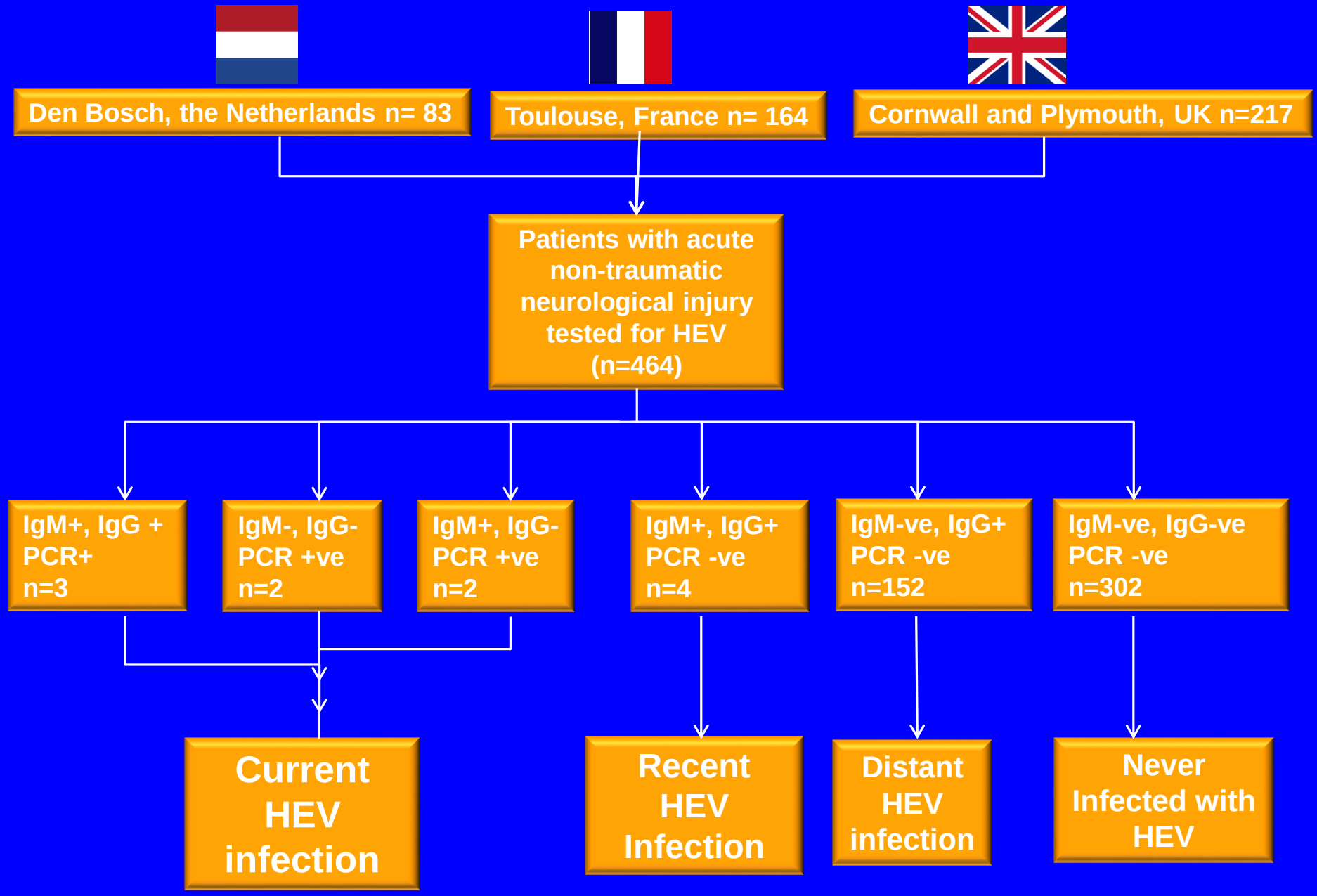
- Cornwall UK, Holland, Germany, Switzerland, France, Italy
- Retrospective study
- **NA cases:**
  - **HEV +ve n=57**
  - **HEV –ve n=61**
- Outcome measures:
  - Clinical phenotype & Outcome

*Van Eijk et al, Neurology, 2017*

# Neuralgic amyotrophy and HEV:
## Multi-centre international study

| | HEV +ve | HEV -ve | P value |
|---|---|---|---|
| Age | 51 (23-83 yrs) | 44 (25-79) | <0.01 |
| Male | 82% | 75% | NS |
| ALT | 259 (12-2961) | 23 (7-396) | <0.01 |
| **Bilateral involvement** | **80%** | **8%** | **<0.001** |
| **Phrenic/lumbar involvement** | **58%** | **10%** | **<0.01** |
| | | | |
| Clinical outcome | Variable | Variable | NS |

*Van Eijk et al, Neurology, 2017*




*Dalton et al. Journal of Hepatology, 2017*

| Acute neurological event | Number tested (n=) | HEV infection; n= (%) |
|---|---|---|
| **Neuralgic amyotrophy** | **5** | **3 (60%)** |
| Guillain-Barré syndrome | 11 | 0 (0%) |
| **Encephalitis** | **7** | **1 (14%)** |
| Meningitis | 7 | 0 (0%) |
| **Cranial Nerve palsies** | **31** | **1 (3%)** |
| **Seizure(s)** | **44** | **3* (7%)** |
| **Cerebrovascular accident** | **170** | **4 (2%)** |
| Transient ischaemic attack | 68 | 0 (0%) |
| Migraine/headaches | 51 | 0 (0%) |
| Multiple sclerosis | 12 | 0 (0%) |
| Myelitis | 14 | 0 (0%) |
| Miscellaneous | 25 | 0 (0%) |
| Other | 28 | 0 (0%) |

“Harry. Has this virus been misnamed?”

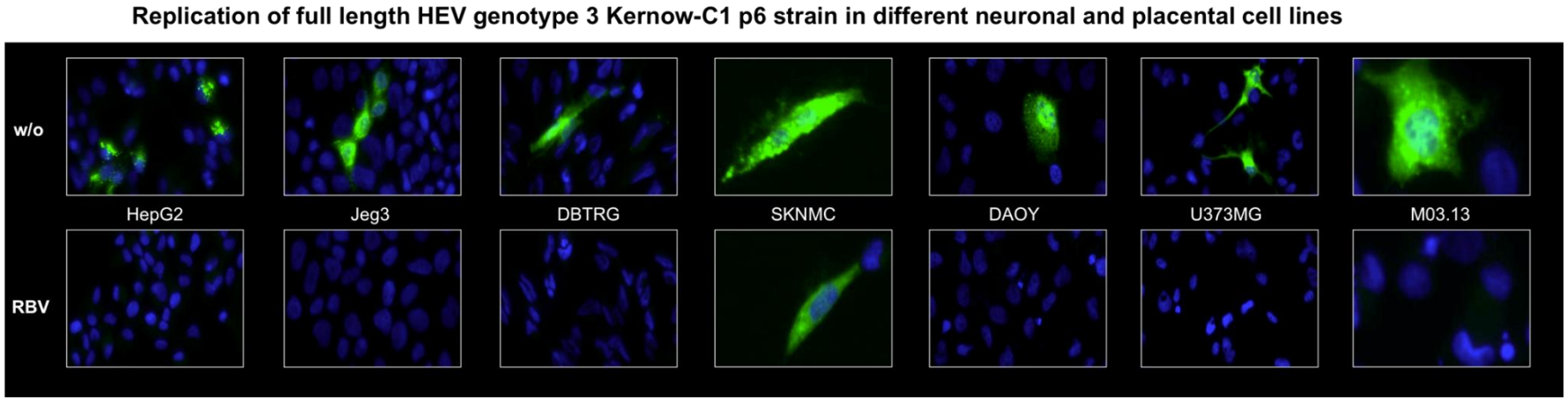
“These patients have profound neurological injury, but not much of a hepatitis”

# HEV & neurological syndromes: evidence for causality

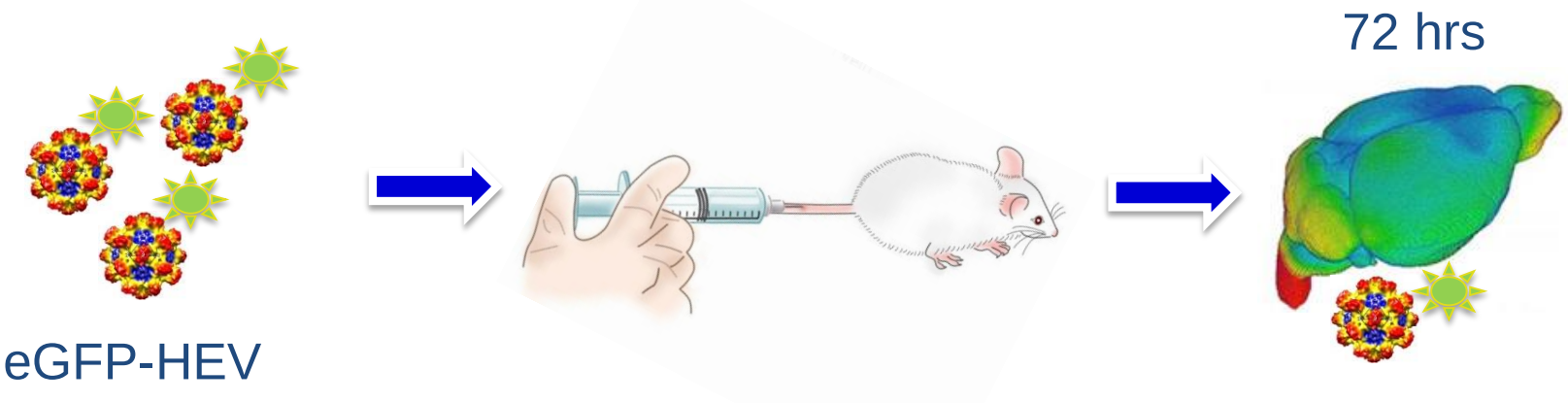
- Number and homogeneity of cases
  - Over time and geographical location
- Case-control data (GBS) *van den Berg et al, Neurol 2014, Geurtsvankessel et al Clin Inf Dis 2013*
  - Netherlands (HEV3) & Bangladesh (HEV1) & Japan *Fukae et al Neurol Sci 2016*
- Intrathecal anti-HEV IgM synthesis *Silva et al 2016*
- HEV RNA
  - Serum and CSF
- Resolution of neurological symptoms with viral clearance *Dalton et al Ann Int Med 2010*
- Kernow C1p6 *Shukla et al PNAS 2011 & J Virol 2012*
  - Grows on a range of cell lines, including neurological

# HEV & neurological syndromes: evidence for causality

**HEV infects neurological cell lines:**



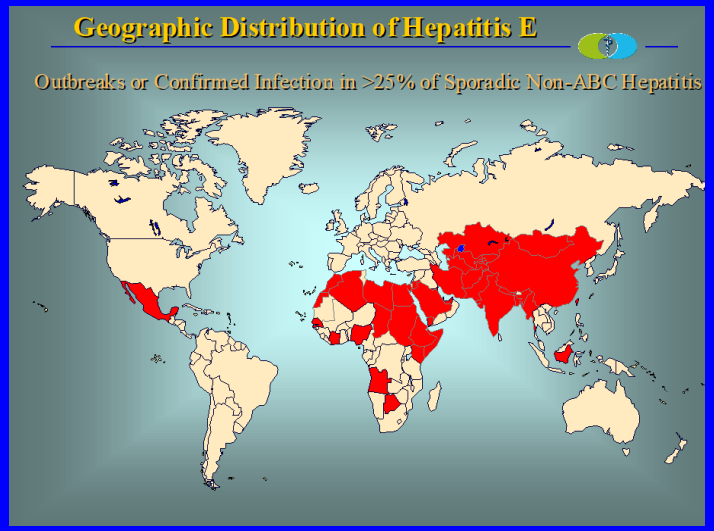

**HEV crosses blood brain barrier in mice:**



# HEV burden of disease

**Genotype 1 and 2**

- 3 million cases/year
- 70,000 deaths




**Genotype 3 and 4**

- Unknown
- On going international study

*Rein et al Hepatology 2012*

# HEV gt3 burden of disease: lab confirmed HEV cases (n=283)

**outcome**

- 69% admitted to hospital (1892 bed days)
- Liver failure n= 21
- Acute kidney injury n=28

- Neurological disease n=25
  - 50% long term residual symptoms

- **9 deaths (2.8%)**
  - **Liver failure n=7**
  - **Chronic HEV n=2**

*Wallace et al, BASL 2018*

# Conclusions: HEV

- Very common worldwide
- Europe: porcine zoonosis (gt3 and4)
  - Acute and chronic infection
  - Extrahepatic manifestations
  - **Neurological (~10% cases)**
    - Not jaundiced
    - Disease mechanisms and treatment: unknown

# Hypothesis:
# Can HEVgt3/4 cause miscarriage in humans?

- HEV gt1  pregnant women 25% maternal mortality
  - 3rd trimester, liver failure

- **HEV gt3 can cause extrahepatic damage without liver injury**
- Cause of miscarriage unknown >25%
  - ?unidentified virus
- HEVgt3:
  - Grows on placental cell lines; high foetal loss in infected pregnant rabbits
  - There is a lot of it about!!!