

# HEV infection in developed countries

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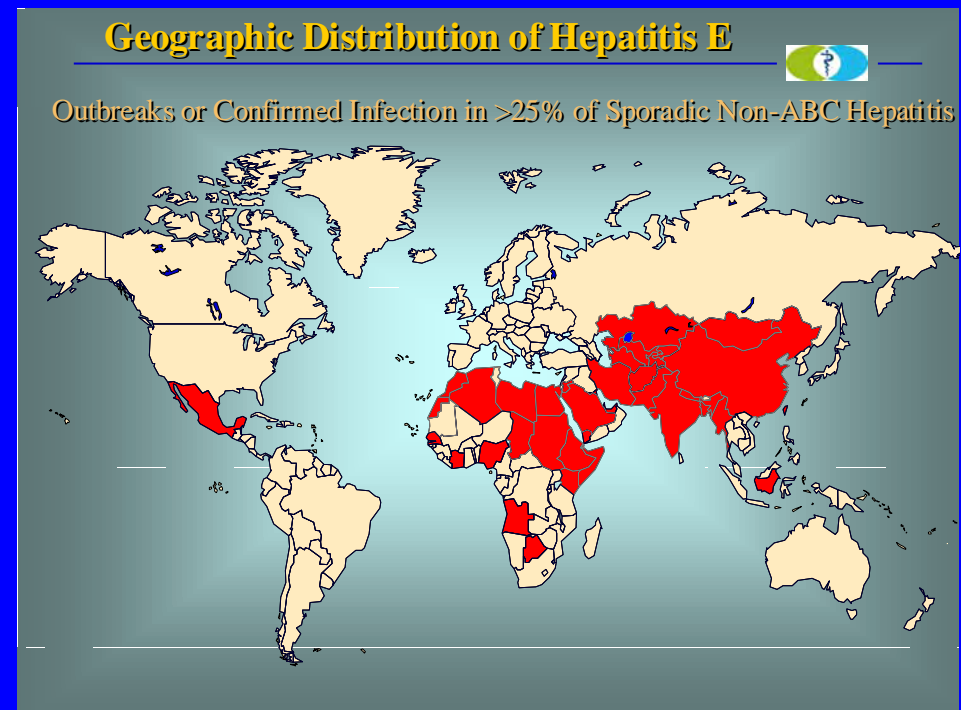


# Talk outline: HEV

- HEV in developed countries
  - Acute
  - Chronic
- Seroprevalence
  - Hypothesis #1
- Places HEV hides: unrecognised infection
- Speculation: Pork Consumption and liver deaths
  - Hypothesis #2

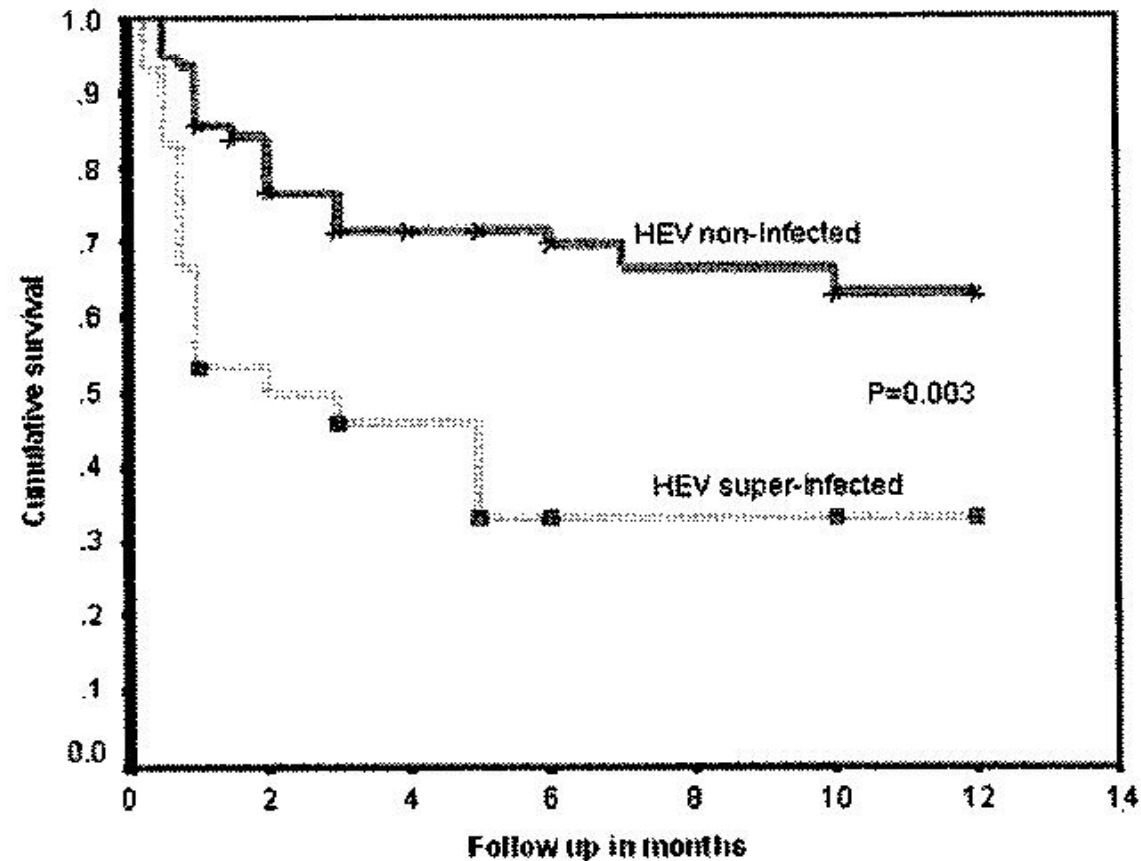
# HEV in developing countries

- Major health issue
  - Large outbreaks
- Faeco-oral route via infected water
- Affects young adults
- Mortality in pregnant women 25%

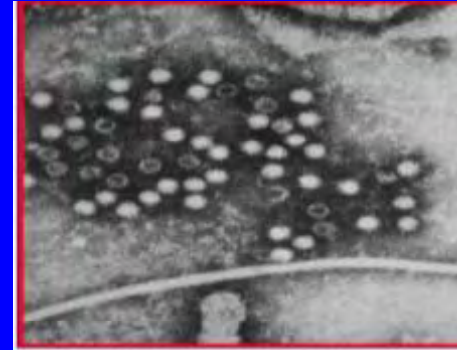


# HEV: in chronic liver disease

*Kumar Acharya et al J Hepatol 2007*



# HEV



- RNA virus
- Genotypes 1 & 2: human disease only
- Genotype 3 (& 4):
  - Human disease
  - Found in animals (asymptomatic)
    - Pigs
      - Worldwide
      - 85% UK pigs affected
      - 20% of pig herd excrete HEV in faeces
    - Boar, deer, mongoose



# HEV in developed countries: received wisdom

- A bit like HAV
  - Acute illness
  - Self-limiting
- Mainly seen in travellers
- v. rare in non-travellers
- Of little relevance in developed countries

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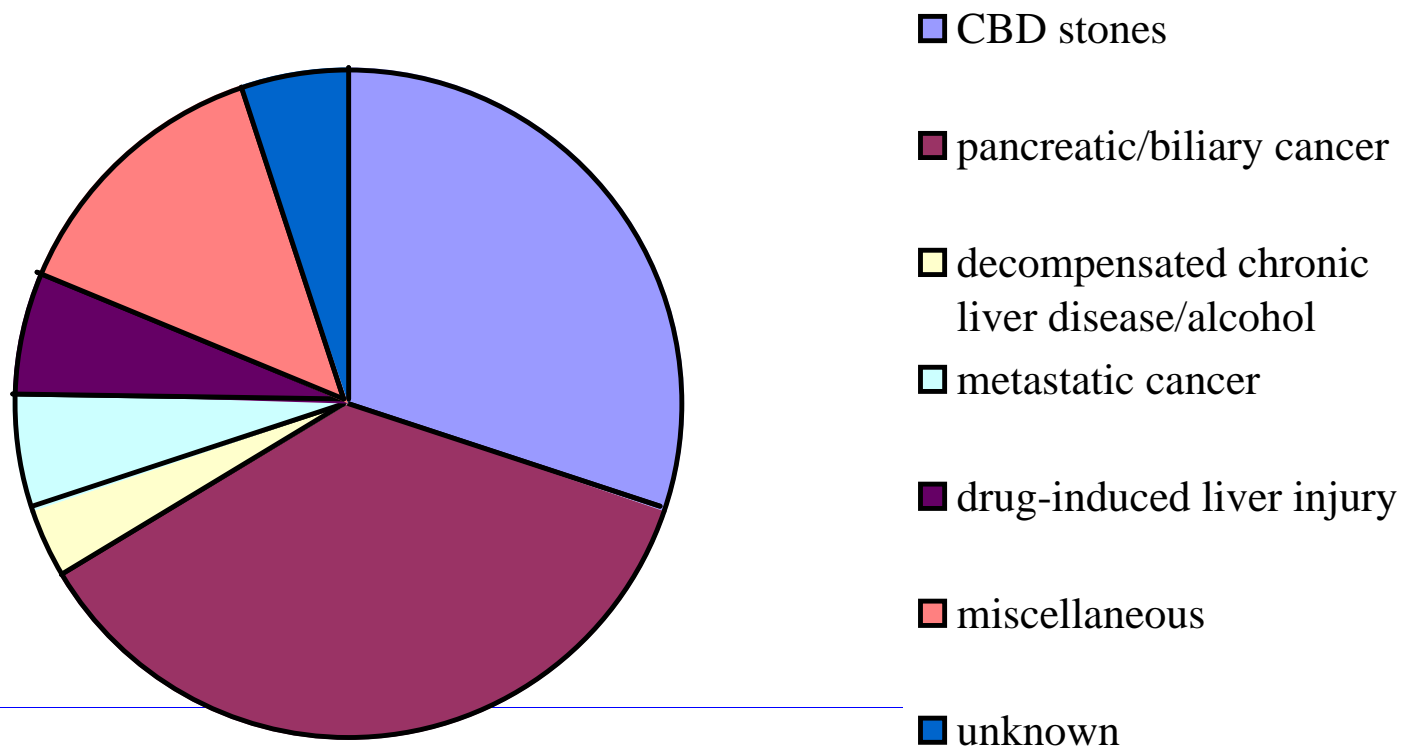
# Cornwall



- Good location to do epidemiological studies
- <0.5% immigrants

# Jaundice hotline clinic: 1998-2011 (n = 2100)

Diagnoses in over 60's



# Acute HEV3: clinical features

- 62 cases of HEV in non-travellers
  - 42/62 HEV PCR +ve, all genotype 3
- M:F = 3:1
- All Caucasian
- Median age 63.5 years (range 35-86)

*Dalton et al J Viral Hepatitis 2007*

*Dalton et al EurJGastro 2008*

# Acute HEV3: symptoms

- Jaundice (n=44)
- Anorexia (n=27)
- Lethargy (n=27)
- Abdo pain (n=25)
- **Vomiting (n=12)**
- Fever (n=12)
- Myalgia (n=11)
- Pruritis (n=10)
- Weight loss (n=7)
- Headaches (n=6)
- Arthralgia (n=6)
- **Paraesthesiae (n=3)**
- No symptoms (n=3)

## Acute HEV3: Spectrum of severity

- Asymptomatic – mild hepatitis – liver failure
- Bilirubin 120  $\mu\text{mol/l}$  (range 3-417)
- ALT 1465 IU/L
- 59/62 recovered (usually in 4 – 6 weeks)
- 3 patients died

# Hepatic complications

- Cornwall

- All had pre-existing cirrhosis
- Self-limiting encephalopathy (n=1): survived
- Sub-acute liver failure (n=2): died at 4 and 5 months

*Dalton et al Lancet 2007*

- France

- Poor prognosis in patients with chronic liver disease
- 70% mortality

*Peron et al J Viral Hepat 2007*

# HEV: Other developed countries

- |                                     |                                 |
|-------------------------------------|---------------------------------|
| • <b>USA</b>                        | <i>Halbur JClinMicro 2001</i>   |
| • Japan                             | <i>Miuzo ClinMicro 2002</i>     |
| • <b>France</b>                     | <i>Mansuy JMedVirol 2004</i>    |
| • Netherlands                       | <i>Widdowson JMedVirol 2004</i> |
| • Spain                             | <i>Buti JVirolMethods 1995</i>  |
| • Italy                             | <i>Romano J Hepatol 2010</i>    |
| • New Zealand                       | <i>Dalton JGastHepatol 2007</i> |
| • Denmark, Germany, Hungary, Sweden | <i>2009-10</i>                  |



# HEV: demographics and outcome

	<b>UK</b> <i>Dalton et al 2008</i>	<b>France</b> <i>Peron et al 2006</i>	<b>Japan</b> <i>Okamoto et al 2003</i>
<b>Cases</b>	40	23	46
<b>Mean age</b>	65 yrs	54.4 yrs	59.6 yrs
<b>% males</b>	77.5%	73.9%	87%
<b>Deaths</b>	7.5%	8.7%	10.8%
<b>Liver deaths</b>	5%	8.7%	10.8%

# HEV3: incidence

- Uncertain
- Geographical variation:
  - **UK: 0.2% (130,000 cases/year)**

*Ijaz et al 2009 JClinVirol*

- **Toulouse: 3.2%**

*Legrand-Abravanel et al Emerg Inf Dis 2011*

# HEV vs HAV

## Devon and Cornwall 2005-6

	HEV	HAV
• Tests	838	4503
• Cases	28	20
• Age*	65 (35-86)	41 (8-74)
• M:F	4.6	1.6
• Complications	n=5	n=0
• Death	n=2	n=0

\*p<0.05

*Dalton et al EurJClinMicro 2008*

# HEV 3:

## Asymptomatic infection

- Asymptomatic infection probably very common
- Aurora outbreak 2008
  - 33 cases hepatitis E
  - HEV 3: identical on sequencing
  - Foodborne outbreak
  - Source uncertain
    - ?shellfish
  - **>50% asymptomatic**

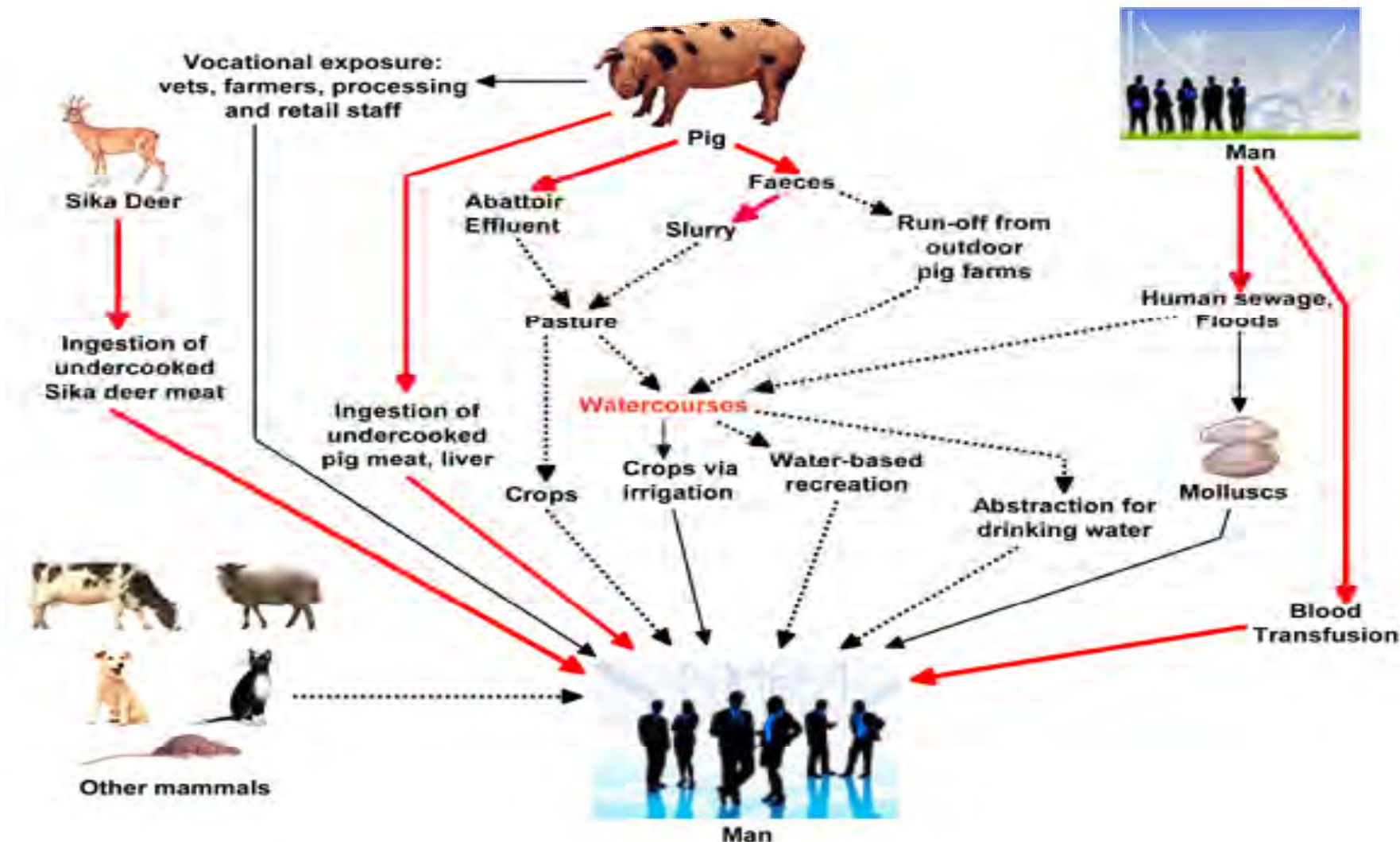
*Said et al EmInfDis 2009*



# HEV: re-infection

- Does occur
- May be quite common???
- Level of protective antibody uncertain

# HEV3: Source and route of infection



## Summary: acute HEV

- Older males, Genotype 3
- Porcine zoonosis, route of infection uncertain
- Range of severity and complications
- High incidence of infection
- Prognosis poor in chronic liver disease

# Chronic HEV infection in the immunosuppressed



# Chronic HEV infection: Transplant recipients

- Chronic HEV3 infection in transplant patients

*Kamar et al NEJM 2008, Gerolami et al NEJM 2008, Haagsma et al LivTrans 2008*

- Chronicity occurs in 60% of HEV3 infections

- Tacrolimus
- Low platelet count

*Kamar et al Gastroenterology 2011*

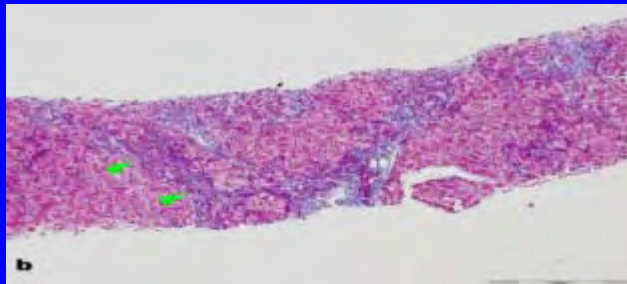
- Cirrhosis rapidly progressive

*Kamar et al Transplantation 2010*

- Very high incidence of chronic HEV in French transplant centres

# Chronic HEV infection: HIV

- 48-yr old bisexual male, alcohol ++
- HIV-1 since 2001, SE Asia
- TB treated 2003
- Anti-retroviral therapy started 2007
  - CD4: 30 cells/mm<sup>3</sup>
  - viral load: 82649 copies/ml
- LFT's abnormal, neurological symptoms
  - ?Drug reaction
- Chronic HEV3 infection



*Dalton et al NewEngJMed 2009*

# HEV & HIV co-infection

- Spain
  - 93 HIV patients, 43 with abnormal LFTs
  - All HEV PCR –ve

*Madejon et al JViralHep 2009*

- France:
  - 108 HIV patient with abnormal LFTs
  - No cases of chronic HEV infection

*Sellier et al Virology J 2011*

- UK:
  - 138 unselected HIV cases
  - No cases of chronic HEV infection
  - No evidence of sexual transmission of HEV

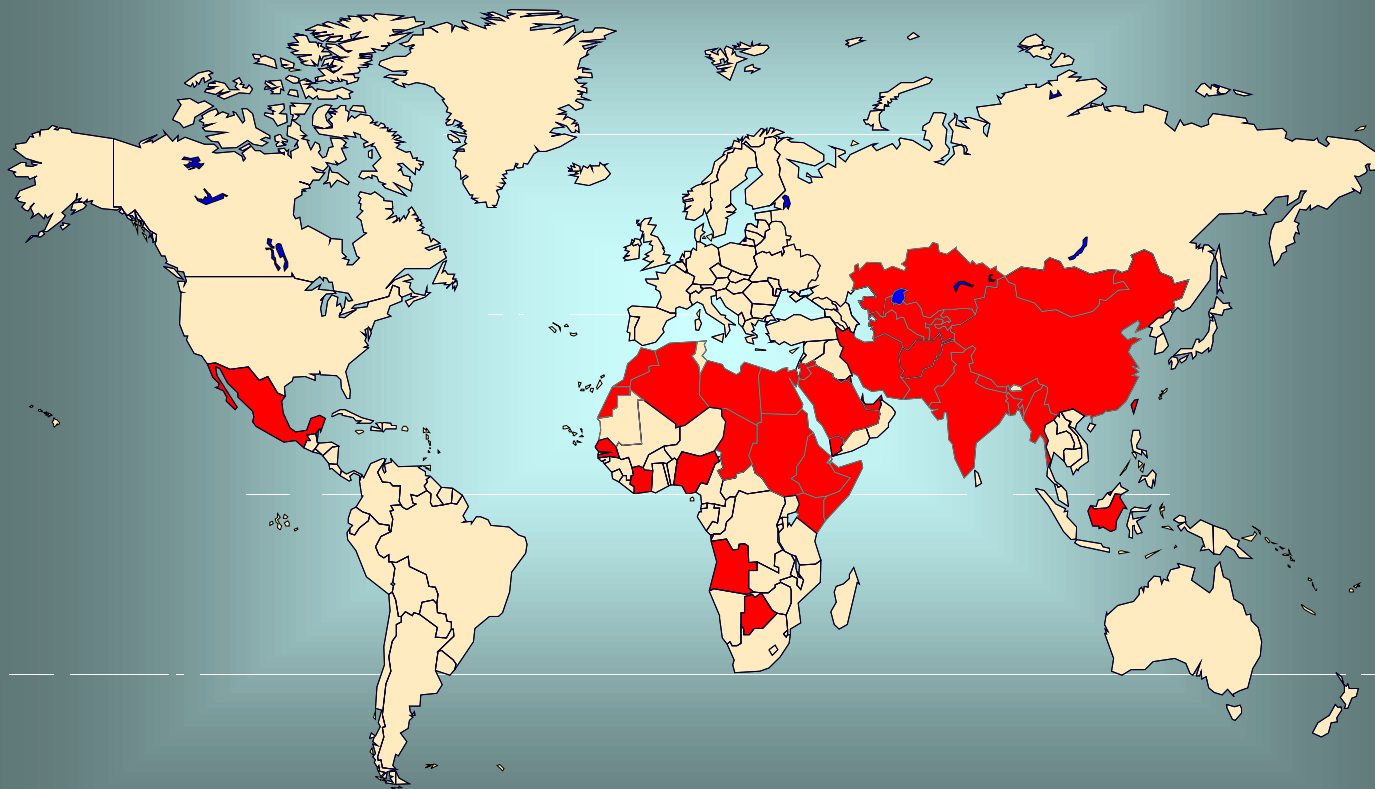
*Keane et al 2011, HIVmed 2011*

# HEV & HIV chronic co-infection: potential burden of disease

## Geographic Distribution of Hepatitis E



Outbreaks or Confirmed Infection in >25% of Sporadic Non-ABC Hepatitis



# HEV: Treatment

- **Acute HEV**

- No treatment required in most cases
- Ribavarin monotherapy in patients with chronic liver disease

*Peron et al J Hepatol 2011*

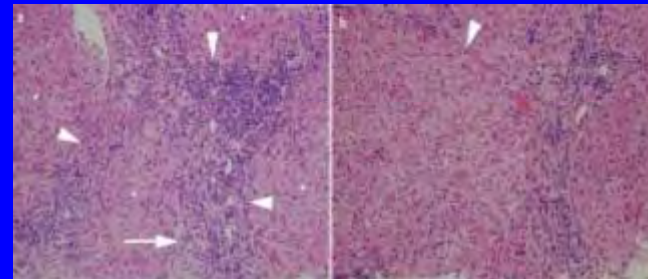
- **Chronic HEV**

- Transplant patients:
  - Reduce immunosuppression
  - $\alpha$ -interferon monotherapy
  - Ribavarin monotherapy

*Kamar et al ClinInfDis 2010*

*Kamar Gastroenterol 2010*

- HIV patient:
  - $\alpha$ -interferon and ribavarin



# HEV: prevention

- Chinese HEV vaccine is effective & safe  
*Lancet 2010*
- Not yet licensed for use





# HEV IgG seroprevalence in developed countries



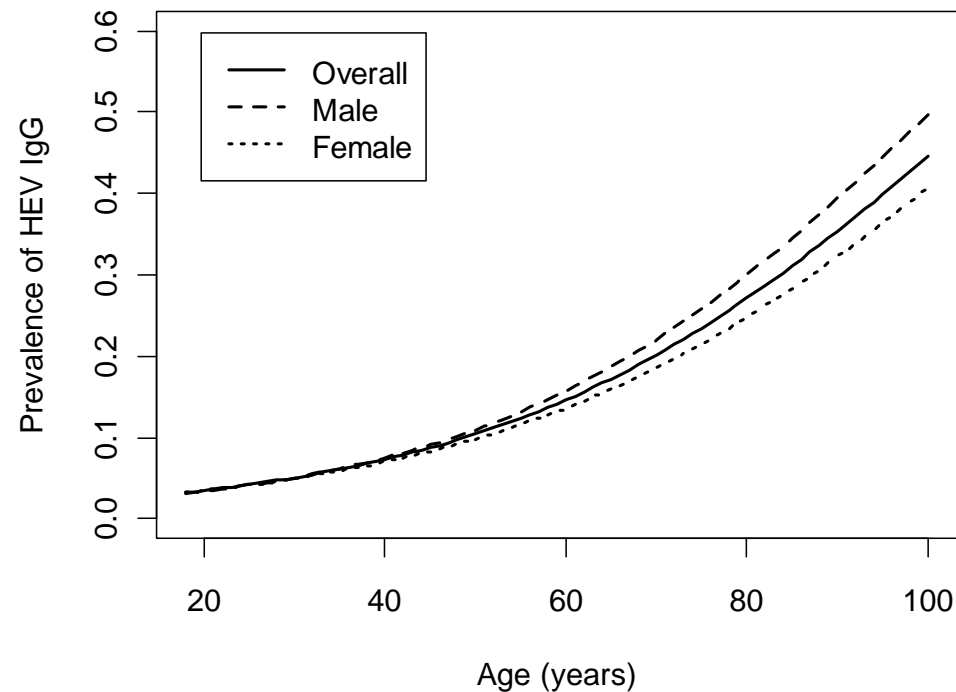
# HEV IgG seroprevalence in developed countries

- Wide range of results:
  - Demographics of population studied
  - True differences in seroprevalence
  - Differing assays used

# HEV IgG seroprevalence

## 16% : blood donors SW England

*Dalton et al EuroJGastroHep 2008*



# HEV IgG seroprevalence in developed countries



# HEV IgG seroprevalence in developed countries



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# HEV IgG seroprevalence in developed countries



# Wantai vs Genelabs HEV IgG assay

*Bendall et al J Med Virol 2010*

- PCR proven HEV3 cases (n=18)
- Serial samples n=50 (up to 7 years)
  - Wantai +ve 98%
  - Genelabs +ve 50%
    - » High negative seroconversion rate after 12 months
  - Genelabs cut off 10X higher than Wantai
    - » Genelabs = 2.5 WHO units
    - » Wantai = 0.25 WHO units
- HEV IgG seroprevalence in UK blood donors (n=500)
  - Wantai = 16.2%
  - Genelabs = 3.6%
- **Genelabs underestimates true seroprevalence by a factor of 4**





# Seroprevalence



	<b>SW England</b> <i>Bendall et al, 2008 &amp; 2010</i>	<b>SW France</b> <i>Mansuy et al 2004</i>
Blood donors	Yes	Yes
Anti-HEV seroprevalence	16%	16%
<b>Assay used</b>	<b>Wantai</b>	<b>Genelabs</b>

Hypothesis #1:  
HEV may be hyper-endemic in SW France

# Hypothesis #1:

## HEV may be hyper-endemic in SW France

- Observed incidence in Toulouse transplant population = 3.2%
- Molecular techniques used

*Legrand-Abravanel et al Emerg Inf Dis 2011*

# HEV IgG seroprevalence in developed countries



# HEV IgG seroprevalence in developed countries





*Hamish MacDonald 2002*

Places HEV hides

# HEV Seroprevalence UK: 16%

## why so high???

- ? Inaccurate HEV IgG assay
  - validated against HEV3 convalescent sera  
*Bendall et al JClVirol 2010*
- ? Sub-clinical infection
  - >50% of HEV infections are asymptomatic (Aurora outbreak)  
*Said et al EmInfDis 2009*
- ?Unrecognised infection
  - HEV hides in unusual places.....



# Unrecognised infection (1): Drug-induced liver injury (DILI)

- 13% of patients with DILI have HEV
- Diagnosis of DILI not secure without testing for HEV

» *Dalton et al*  
*A Pharm Therap*  
2007





# Unrecognised infection (2): HEV neuropathy



*Kamar et al Emerg Inf Dis 2011*

- Occurs in about 5% of cases (acute & chronic)
- LFTs only mildly abnormal
  - Inflammatory polyradiculopathy (n=6)
    - Complete resolution (n=4), Partial improvement (n=2)
  - Encephalitis (n=1)
    - Patient died
- HEV isolated from CSF (n=4)
  - CSF viral clearance coincides with symptom improvement
- ?other neurological syndromes: ? Guillian Barre Syndrome

# Unrecognised infection (3):

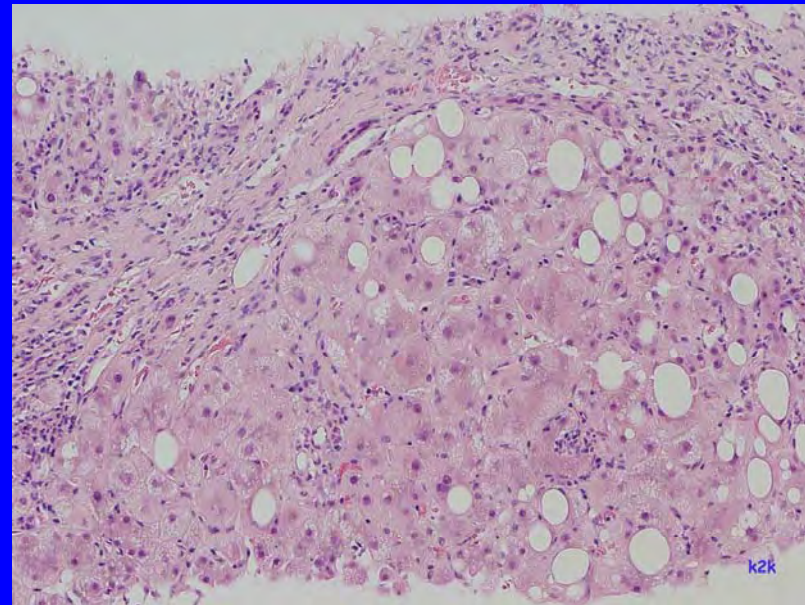
- 72 year old male
- Vomiting ++++
- ALT 600
- Ruptured oesophagus
  - Surgical repair
  - Intensive Care for 2 months



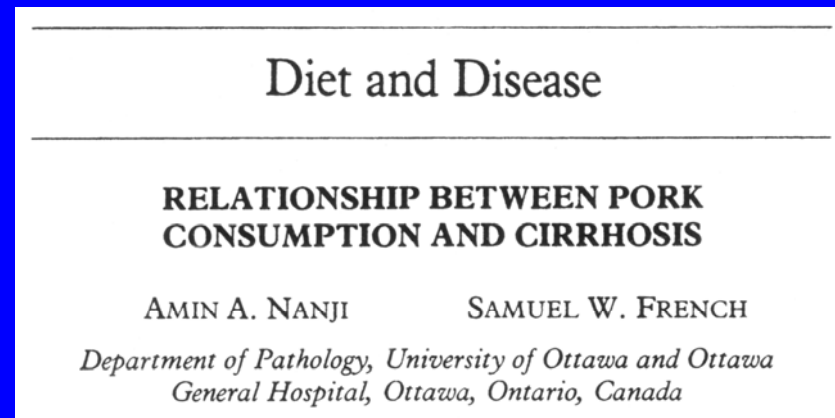
*Kurt Jackson 2007*

# Unrecognised infection (4): in chronic liver disease

- 76 yr old male
- Alcohol 35U/week
  - Bilirubin 86
  - ALT 2286
- Decompensated +++
- Transferred to another hospital
- Died at 4 months of ‘decompensated alcoholic liver disease due to alcoholic hepatitis’

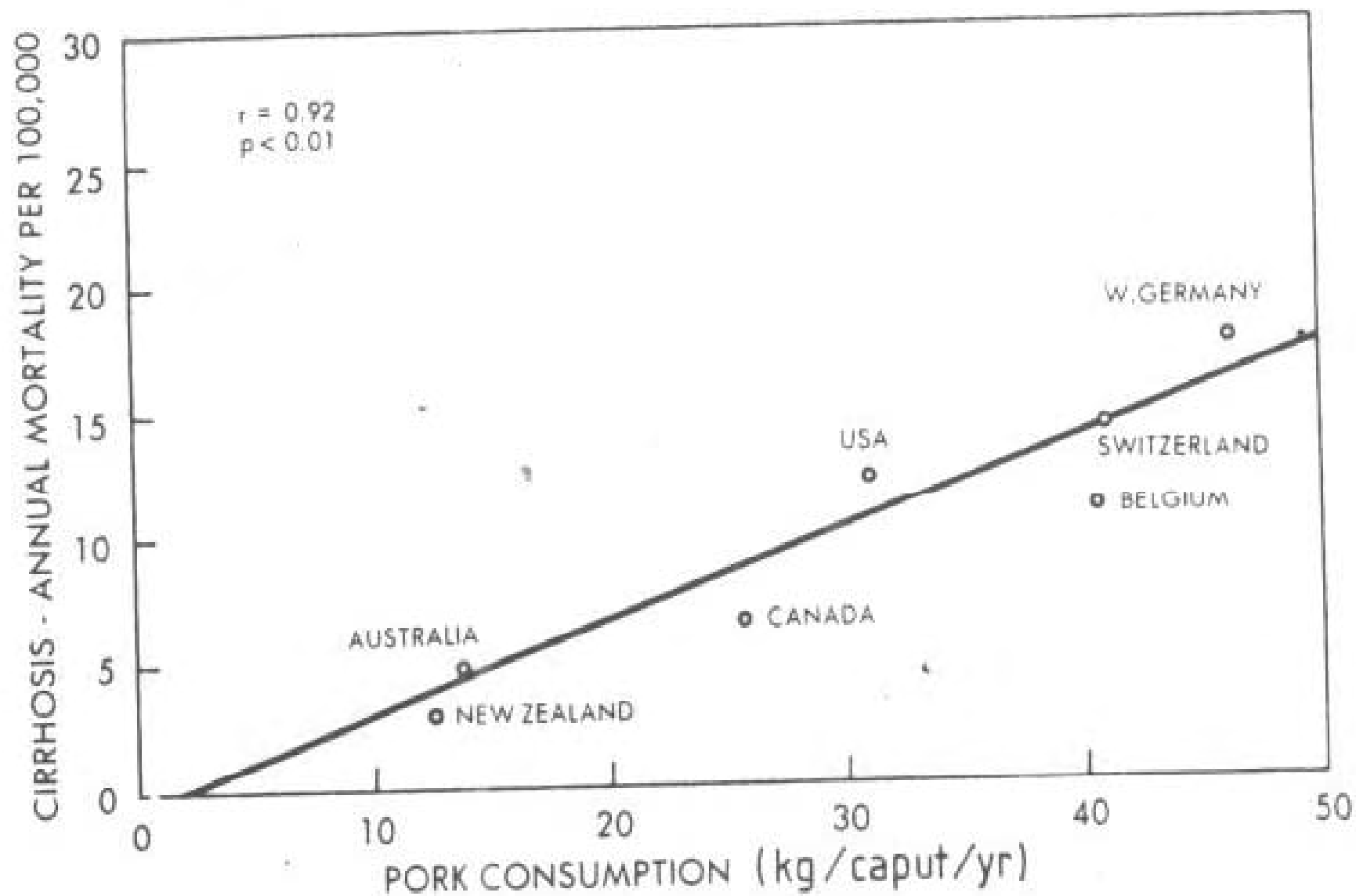


# Speculation: Pork consumption & liver deaths



- Deaths from cirrhosis vs ethanol consumption & pork consumption
  - Developed countries (1965, mid 1970's)
  - Provinces of Canada (1978)

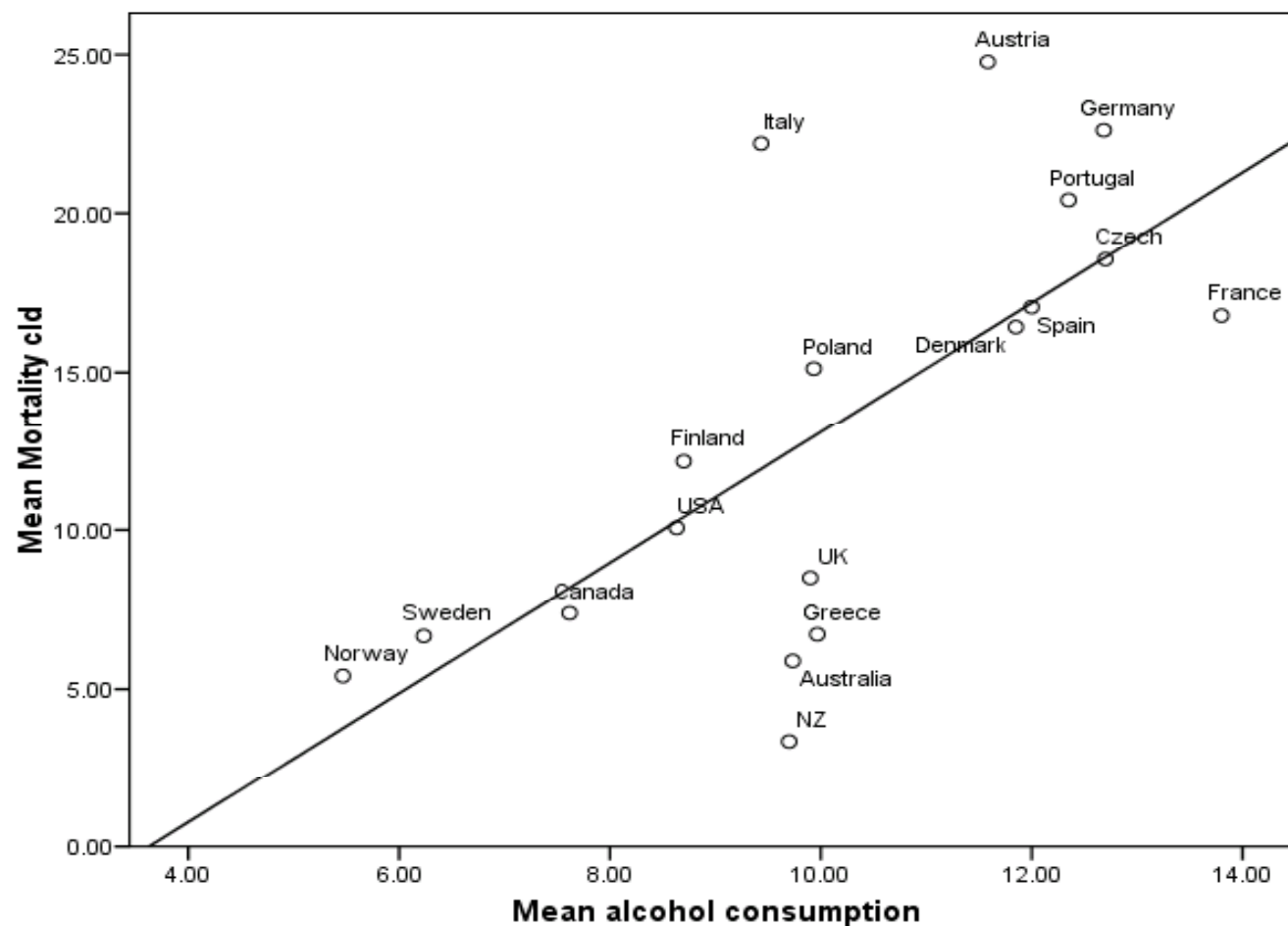
*Lancet 1985*



**Fig 3—Relationship between cirrhosis mortality and pork consumption.**

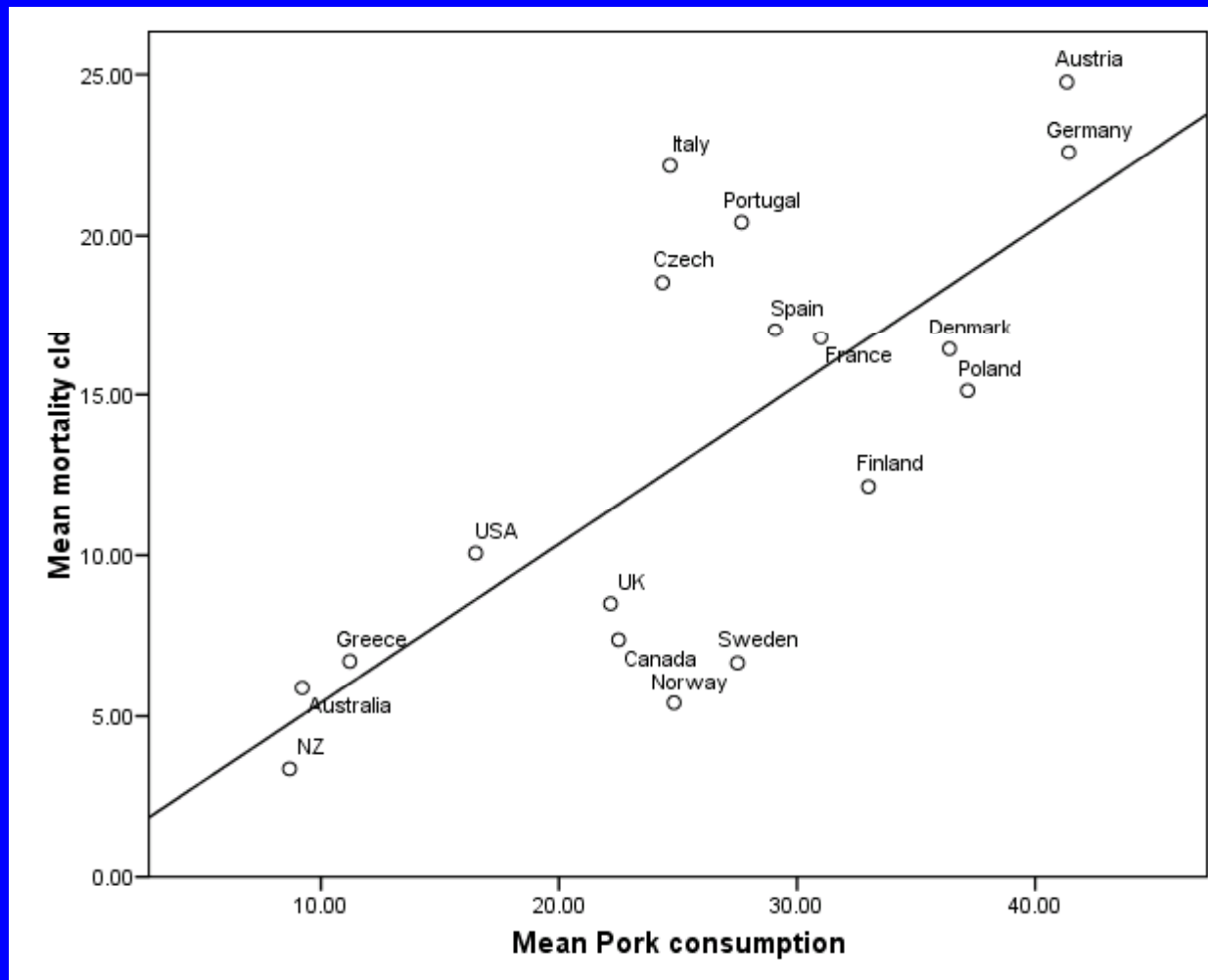
# Mortality from chronic liver disease vs alcohol consumption 1990 -2000

*Dalton et al Epidemiol Infect 2010*



$R^2=0.473$   $p=0.002$

# Mortality from chronic liver disease vs pork consumption 1990 -2000



$R^2=0.531$   $p=0.001$



# Multiple regression:

- Independent predictors of mortality:
  - Alcohol consumption (p=0.005)
  - HBV seroprevalence (p=0.037)
  - Pig meat consumption (p<0.001)

# Possible explanations:

1. Epiphenomenon
2. A factor in pork causes cirrhosis
3. A factor in pork causes death in patients with pre-existing cirrhosis ? HEV3

- HEV3 found in retail pig meat
  - » USA, Holland, Japan, UK & France

*Colson et al JID 2010*

- HEV survives cooking at 56C & can be transmitted by eating infected meat
- HEV mortality in chronic liver disease = 70%

# Hypothesis #2

## HEV: potential mortality in developed countries



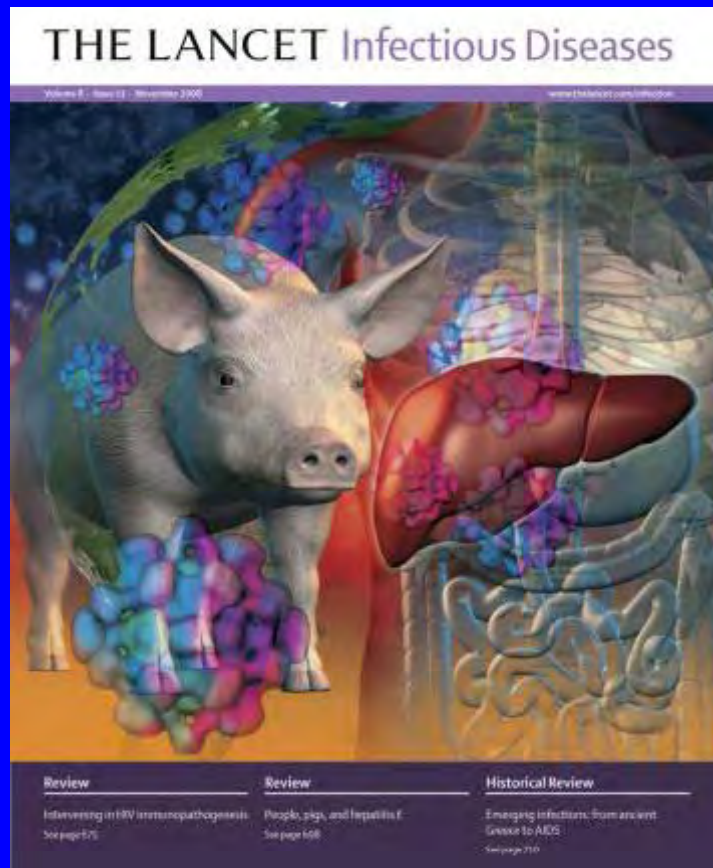
- Assuming:
  - Prevalence of chronic liver disease = 1%
  - Mortality HEV in chronic liver disease = 70%
  - Population of USA, Canada, EU, Japan, Australia & NZ = 931million
  - Annual HEV seroconversion rate – 0.2%
- **13,000 deaths/annum attributable to HEV infection in patients with chronic liver disease**

# HEV in developed countries: received wisdom

- A bit like HAV
  - Acute illness
  - Self-limiting
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# Conclusions:

## HEV in developed countries



- Commonest cause of acute viral hepatitis
- ?hyper-endemic SW France
- Probably porcine zoonosis
- Significant morbidity & mortality
- Prognosis poor in chronic liver disease
- May cause up to 13,000 deaths per year
- Burden of chronic infection unknown

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# research collaborators

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  - Dan Webster: University of Brighton
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  - Centres for Disease Control (CDC), Atlanta, Georgia
  - Prof Ting Wu, Xiamen University, China
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