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Hepatitis E Virus in England and Wales

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‘The two faces of hepatitis E virus’

Characteristic	Developing countries
Virus genotype	1, 2
Transmission	Waterborne/faecal-oral
Reservoir	Human
Outbreaks	Small to very large
HEV as % of hepatitis	Common
Age distribution	Young
Pregnant women	High mortality
Chronic infection	No

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HEV in England and Wales

- In the UK, hepatitis E disease traditionally associated with imported infections
- Established that HEV infections can be acquired indigenously
- Molecular characterisation indicates genotype 3 circulates in the UK
    - (genotypes 1 and 2 circulate through the developing world)
- Seroprevalence studies undertaken in the general population indicate a rate of ~13%
- 100 000 infections occur per year in England

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Investigating transmission routes

- The detection of HEV Abs and RNA in swine and other animals has led to suggestions of a potential zoonosis with animals acting as reservoirs for HEV infection in humans
- Studies from Japan/France where individuals became infected after consuming raw/undercooked pig, deer or boar meat
- PHE case control study based on food questionnaires
    - analysis suggests an association between the consumption of pork based products and HEV infection
- Berto et al., 2012 provided evidence of HEV contamination in the pork production chain

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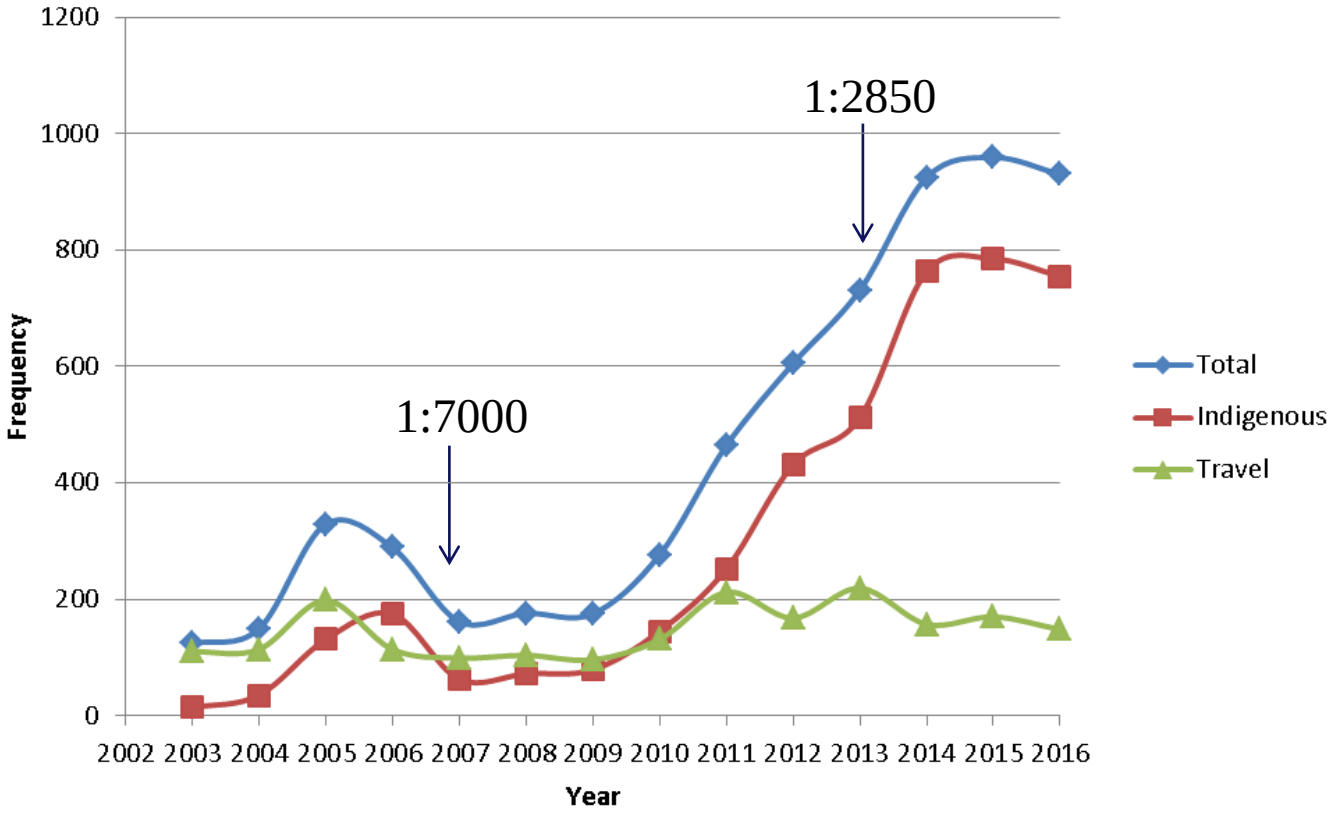
Enhanced surveillance of hepatitis E in England and Wales



Incidence in blood donors

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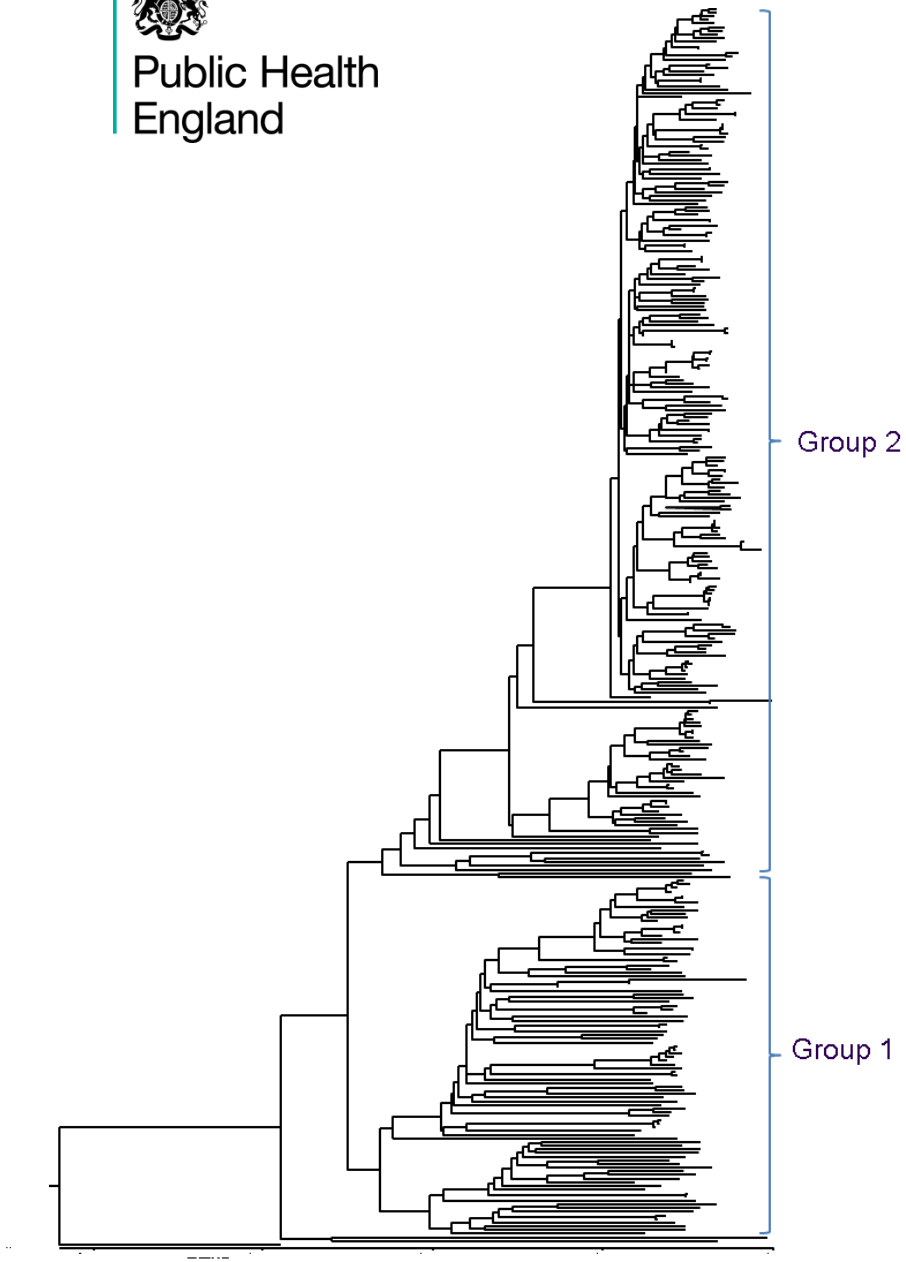
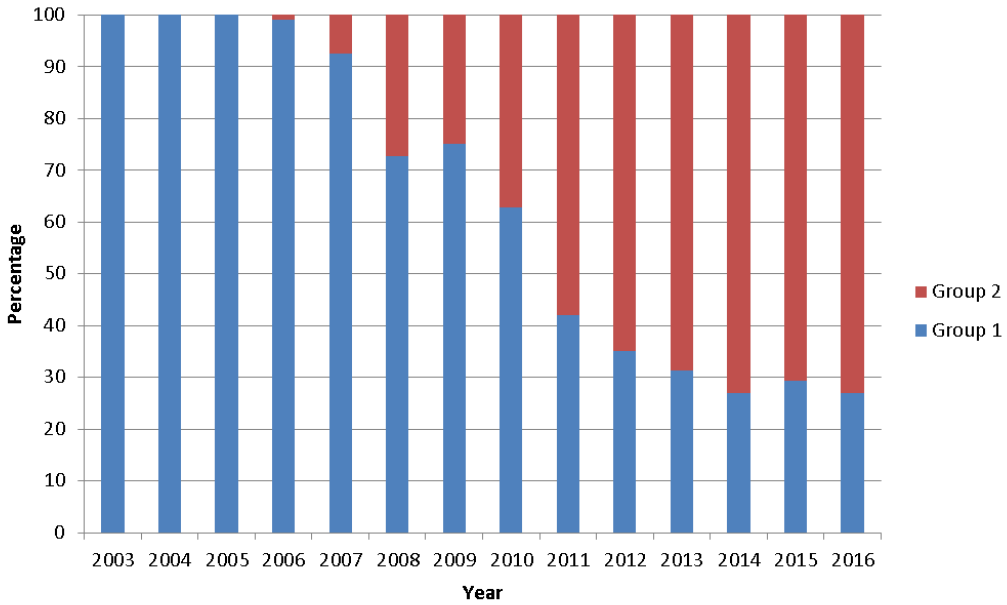
Frequency of group 1 and 2 viruses by year





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Change in the magnitude of risk

- Rise is case numbers associated with the emergence of a clade of viruses not commonly circulating prior to 2010
  - *are these viruses more transmissible?*
  - *are these viruses more pathogenic?*

- How have the risk factors changed?
  - *Changes in farming practices or animal husbandry?*
  - *Changes in food processing or importation of meat?*

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Public health implications of HEV have grown

- Recognition of chronic HEV infections in the immunosuppressed population

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 Olivier Cointault, M.D., Lau Marie Danjoux, M.D., Do Jacques Izopet, Pharm

CORRESPONDENCE

Chronic Hepatitis E with Cirrhosis in a Kidney-Transplant Recipient

TO THE EDITOR: Hepatitis E virus (HEV) is an important cause of acute viral hepatitis worldwide.[1] Kamar et al. in this issue of the *Journal*[2] and others[3,4] have recently suggested that HEV infection might result in chronic hepatitis in immunocompromised patients. We report a rapidly progressing case of cirrhosis in a renal-transplant recipient with chronic HEV infection.

A 52-year-old man who had undergone kidney transplantation in March 2005 presented with increased aminotransferase levels in June 2006. Four months later, the alanine aminotransferase level reached 126 U per liter and thereafter plateaued at three times the upper limit of the normal range. Serologic testing for hepatitis C virus (HCV) and HCV RNA had been

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Persistent, chronic hepatitis E

- Defined as persistence of plasma HEV RNA for > 3 months
- Infections can be difficult to identify
  - Patients have no clear symptoms and are anicteric
  - Modestly raised ALTs
- Diagnosis is often overlooked or mistaken for DILI or graft rejection
- Rapid progressive liver disease with 10% of patients developing cirrhosis within 2 years
- Majority of reported persistent cases in genotype 3
  - ~3 cases of genotype 4
  - 1 case of genotype 7 (camelid HEV)
  - No cases of genotype 1 and 2

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Treatment

- Prognosis for patients with persistent infections is poor
- Reduction in immunosuppression leads to viral clearance in 25% of patients
- Initial cases treated with pegylated interferon α (HIV setting)
- Ribavirin has become the drug of choice
  - Overall SVR reported at 85%
- Increasingly recognising relapses
- Re-treatment with ribavirin has been successful but not in all cases
- Sofosbuvir and daclatasvir shown not to be effective
- Role of amino acid changes acquired during treatment?

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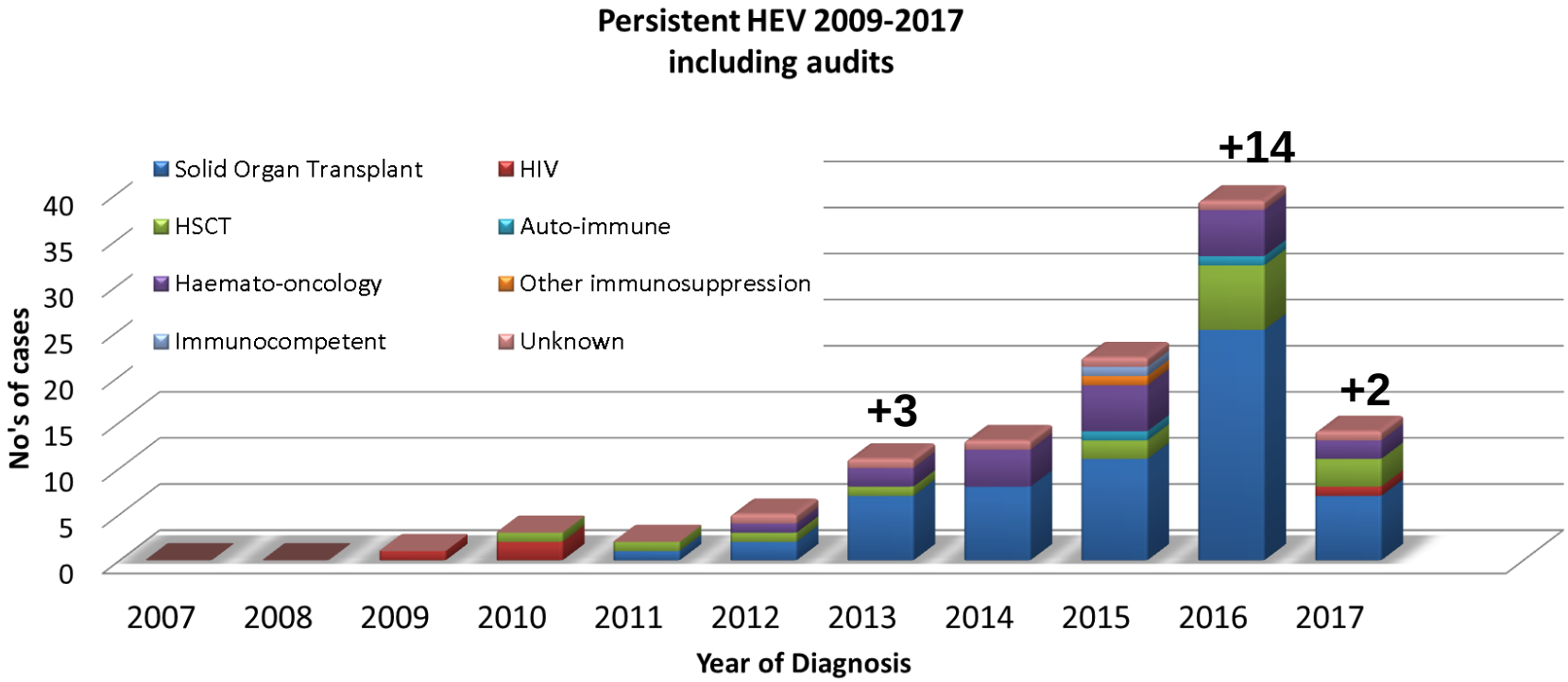
Persistent HEV infections across England and Wales 2009-17

90 cases; 109 including audits/studies



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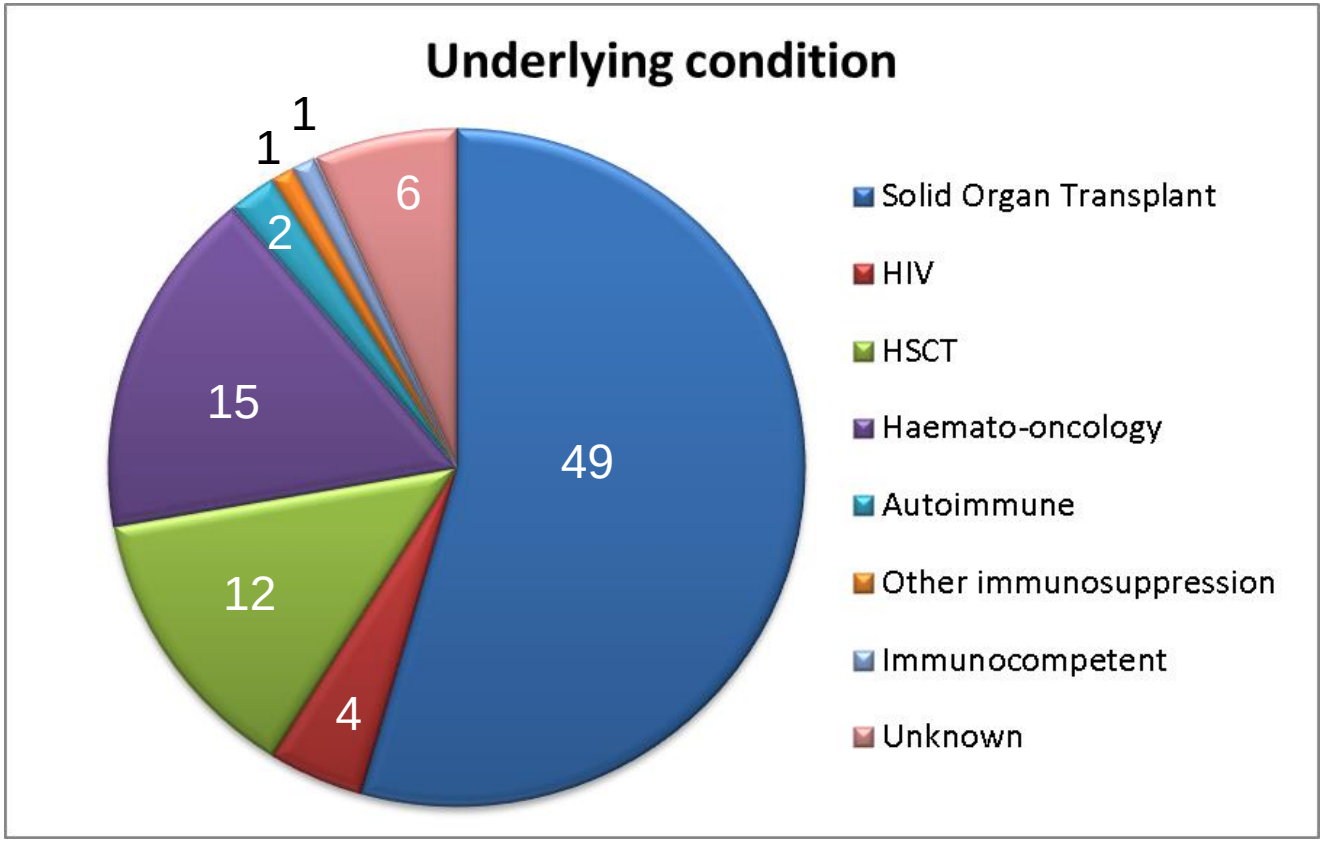
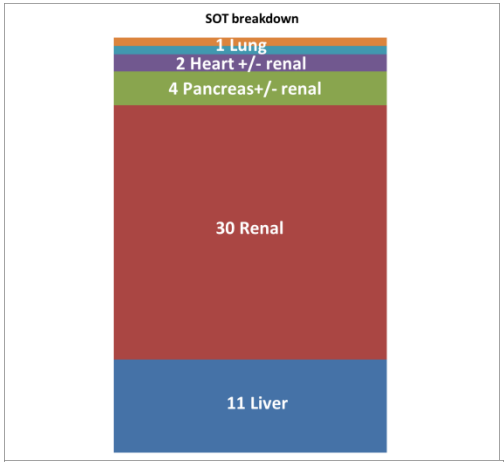
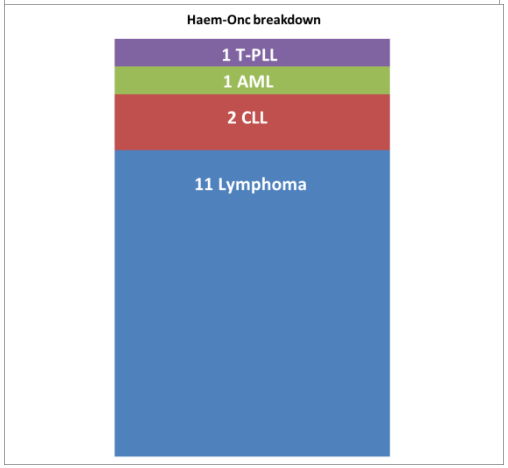
Breadth of underlying disease







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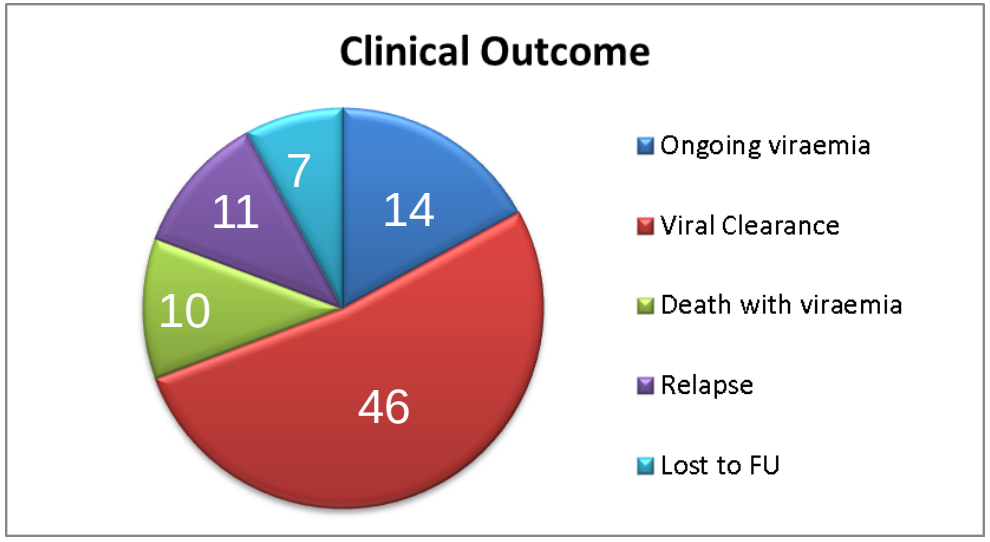
Outcome

- Outcome data incomplete but show
  - At least 5 (50%) of those that died whilst viraemic had evidence of liver failure
  - Relapses after treatment cessation are relatively common, we are aware of 11 (11%)



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Relapsers

patient no.	Underlying condition	Immunosuppression	Serostatus at time of viral clearance (IgG S/CO)	RBV treatment [daily dose, duration (wks)]	eGFR	Toxicity	RBV dose reduction?	clearance in stool?
1	Lymphoma	-	POS 3.10	-	-	-	-	-
2	nil	nil	POS 19.18	1000mg , 11	-	no	no	yes x 2 (15d)
3	Heart/Renal Tx	Tacrolimus, Prednisolone	POS 9.86	600mg, 12	-	anaemia	yes	yes x 2 (30d)
4	Liver Tx	Tacrolimus, Prednisolone	NEG	11	-	-	-	yes x 1
5	Lymphoma	Chemotherapy	POS 18.84	-	-	-	-	-
6	Renal Tx	Tacrolimus, MMF, Prednisolone	NEG	1000mg	63	anaemia	yes	-
7	Renal Tx	Sirolimus	NEG	800mg	> 90	anaemia	yes	-
8	CLL	-	POS 16.94	-	-	-	-	-
9	Lymphoma	Chemotherapy	POS 20.01	800mg, 13	70	anaemia	yes	yes x 2 (27d)
10	Allograft BMT	-	NEG	-	70	anaemia	yes	yes x 2 (36d)
11	Lymphoma/CVID	-	NEG	-	-	anaemia	yes	yes x 2 (24d)

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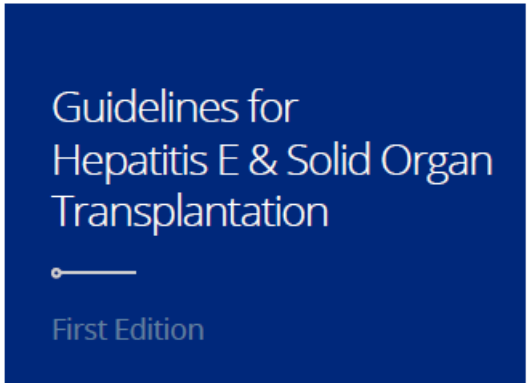
BTS British Transplantation Society
The Voice of Transplantation in the UK



Increased numbers of treatment failures, including ‘relapses’

- Dosage of ribavirin? Treatment duration?
- Testing for viral clearance?
- Other factors?
- Future treatment options remain limited

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Audit of HEV in transplant setting (in collaboration with QEH, Birmingham)

- Prevalence study of HEV viraemia in SOT/HSCT
- ~3000 patients undergoing TDM (ciclosporin/tacrolimus)
- 19/2826 HEV RNA pos (prevalence of 0.67%; 1:149)
  - 3 (15.8%) allogeneic HSCT recipients
  - 16 (84.2%) SOT recipients (6 kidney, 9 liver, 1 heart)

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HEV Audit – predictive factors for HEV viraemia

- Comparison with the uninfected aviraemic patients
  - Statistically significant higher
    - ALT ($p<0.0001$)
    - Bilirubin ($p=0.01$)
    - Tacrolimus levels ($p=0.002$)
    - Ciclosporin levels ($p=0.02$)

- 88% of HEV-infected patients had an abnormal ALT value at the time of screening (>41 IU/L) compared with only 452 (16%) of the HEV RNA-negative patients.

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HEV Audit – viraemic patients

- The diagnosis of hepatitis E infection was only considered clinically in one patient despite 88% have an abnormal ALT
- Development of antibody response does not lead to viral clearance
- Outcomes in 19 patients:
  - n=4 no/insufficient follow up
  - n=1 cleared at follow up
  - n=2 acute infections
  - n=12 persistent, chronic infections

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Chronic hepatitis E in HIV-infected individuals

- Rarely reported – 4 cases in England and Wales
- Low CD4 counts, ART, HIV VL not detected
- Persistently raised LFTs
- All patients treated
  - n=1 – RIP
  - n=3 – successfully cleared virus
    - Peg IFN and Ribavirin, PegIFN, Ribavirin,
- HEV VL clearance following treatment associated with recovery of CD4

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HEV and Blood Safety

- Growing momentum both in the UK and across Europe to address HEV and blood safety
- Joint NHSBT/PHE study established to look at blood safety
- Incidence in blood donors
  - Screened 225 000 donations
  - 1:2850 donations to be HEV RNA positive
- Transmission rates
  - Follow up of recipients of HEV containing blood products
  - 42% transmission rate

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Clinical sequelae of HEV infection in 18 recipients

Inferred immun-suppression	Number of recipients	Median weeks*			Proportion (%) who developed		
		to RNA detection	to seroconvert	duration infection	anti-HEV	clearance	clinical hepatitis
None or mild	8	5	7	10	8 (100%)	8 (100%)	1 (12.5%)
Moderate	6	8	11	18	5/6 (83%)**	3/4 (75%)**	0
Severe	4	9	37.5	30	2/3 (66%)**	2/3 (66%)**	0

* Only numerate values included
** excludes those who died whilst infected

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HEV and Blood Safety

- SaBTO (Advisory Committee on the Safety of Blood, Tissues and Organs) formed a working group
- 2016 - recommendation for the implementation of selective screening
  - Donations given to SOT and SCT patients
  - NHSBT extended this to neonates <1 year
- 2017- recommendation extended to universal screening
  - Blood donations (May 2017)
  - Tissues/organs/stem cells (October 2017)
- NB: blood screening will only **reduce** exposure as risk from diet still exists

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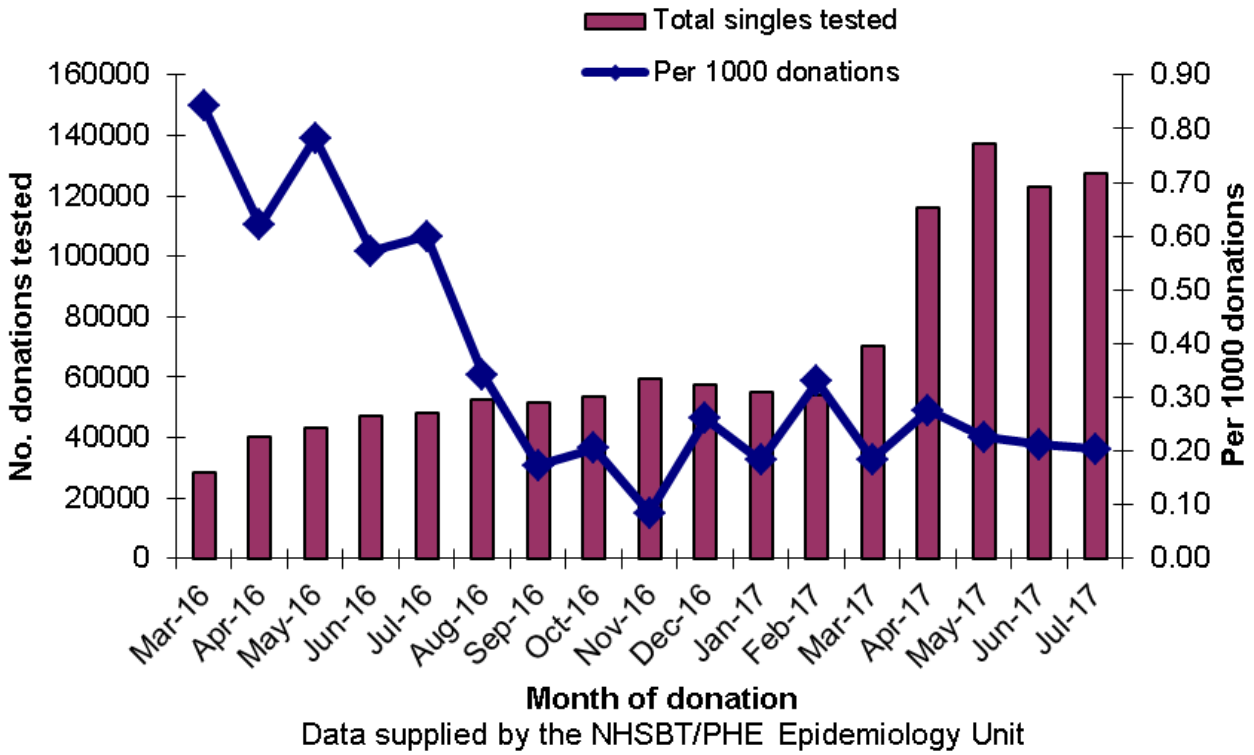
HEV and Blood Safety

- 2016 – selective screening of blood donations for vulnerable patient groups
- 2017- extension to universal screening by HEV RNA



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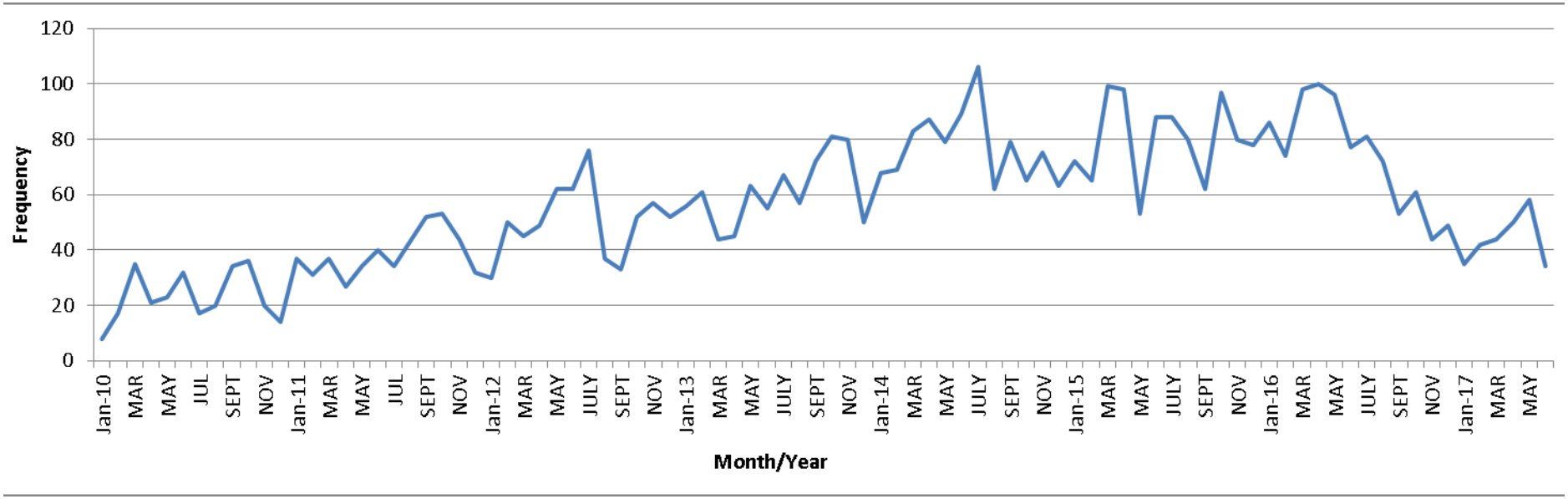
HEV clinical cases

Year	January	February	March	April	May	June	July	August	September	October	November	December	Total
2010	8	17	35	21	23	32	17	20	34	35	20	14	276
2011	37	31	37	27	34	40	34	43	52	53	44	32	464
2012	30	50	45	49	62	62	76	37	33	52	57	52	605
2013	56	61	44	45	63	55	67	57	72	81	80	50	731
2014	68	69	83	87	79	89	106	62	79	65	75	63	925
2015	72	64	99	98	53	88	88	80	62	97	80	78	959
2016	86	74	98	100	96	77	81	72	53	61	44	49	891
2017	35	42	33	-	-	-	-	-	-	-	-	-	110



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HEV summary

- Differences in transmission routes, genotype distribution and disease pattern between HEV in the developed vs developing world
- Now recognised as a widespread zoonosis associated with rolling infections in England and Wales
- Currently in a period of heightened HEV activity; associated with the emergence of a novel phylotype
- Public health remit has changed following recognition of chronic hepatitis (need more testing in immunosuppressed patients)
- More work needed to look at possible sources of infection and control

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Acknowledgements

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