



HEV Screening of blood: EU wide data

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Surveillance & Screening of Blood borne pathogens

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Hepatitis E and blood donation safety in selected European countries: a shift to screening?

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Hepatitis E virus infection in Europe: surveillance and descriptive epidemiology of confirmed cases, 2005 to 2015

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FIGURE 2

Reported number of cases of hepatitis E virus infection by year of notification and year of surveillance commencement, 22 European Union/European Economic Area (EU/EEA) countries, 2005–2015^a



^a Data available for the following countries (year of commencement of HEV surveillance/year since cases reported during study period 2005–2015): Austria (1980/2012), Belgium (2010/2010), Bulgaria (no surveillance/2015), Croatia (2009/2009), Cyprus (no surveillance/2009), Czech Republic (1996/2005), Estonia (1997/2005), Finland (1995/2005), France (2002/2005), Germany (2001/2005), Hungary (1993/2005), Italy (2007/2007), Latvia (commencement unknown/2007), the Netherlands (2012/2012), Norway (no surveillance/2005), Poland (no surveillance/2014), Portugal (commencement unknown/2014), Slovakia (2007/2005), Slovenia (1995/2005), Spain (commencement unknown/2006), Sweden (1993/2005), and UK (England and Wales (2003/2005), Scotland (2000/2005) and Northern Ireland (unknown/2005)).

Factors influencing your HEV screening strategy



- Source of infection = Food
- Research indicates prevalence & viral loads
- Evidence/reports of TT-HEV
- Cost of screening
- Logistics of selective v universal testing / MP size
- Transmissibility of infected blood
- Protect high risk patients from being exposed
- Educating our donors and patients

Factors influencing HEV screening in Ireland



- Food and shopping habits
 - Prevalence
 - Viral load detected
 - TT-HEV
 - Cost of screening
 - Logistics
 - Transmissibility
 - High risk patients
 - Educating donors
- ✓ Pork; no vegetarians
 - ✓ No supermarket loyalty
 - ✓ 1 in 5,000 RNA reactive
 - ✓ $VL < 260,000$ IU/mL
 - ✓ No reports of TT-HEV
 - ✓ Government funding
 - ✓ ID-NAT; Universal
 - ✓ 70% asymptomatic

Situation 1: Evaluating local situation in 18 EU States



Limited/No data on blood
donor prevalence (n=14)

Belgium	Greece
Bulgaria	Hungary
Croatia	Latvia
Cyprus	Lithuania
Czech Republic	Romania
Estonia	Slovakia
Finland	Slovenia

Blood donor prevalence
data available (n=4)

Italy
Poland
Portugal
Malta

Situation 2: Decision taken to not implement HEV screening in 2 States



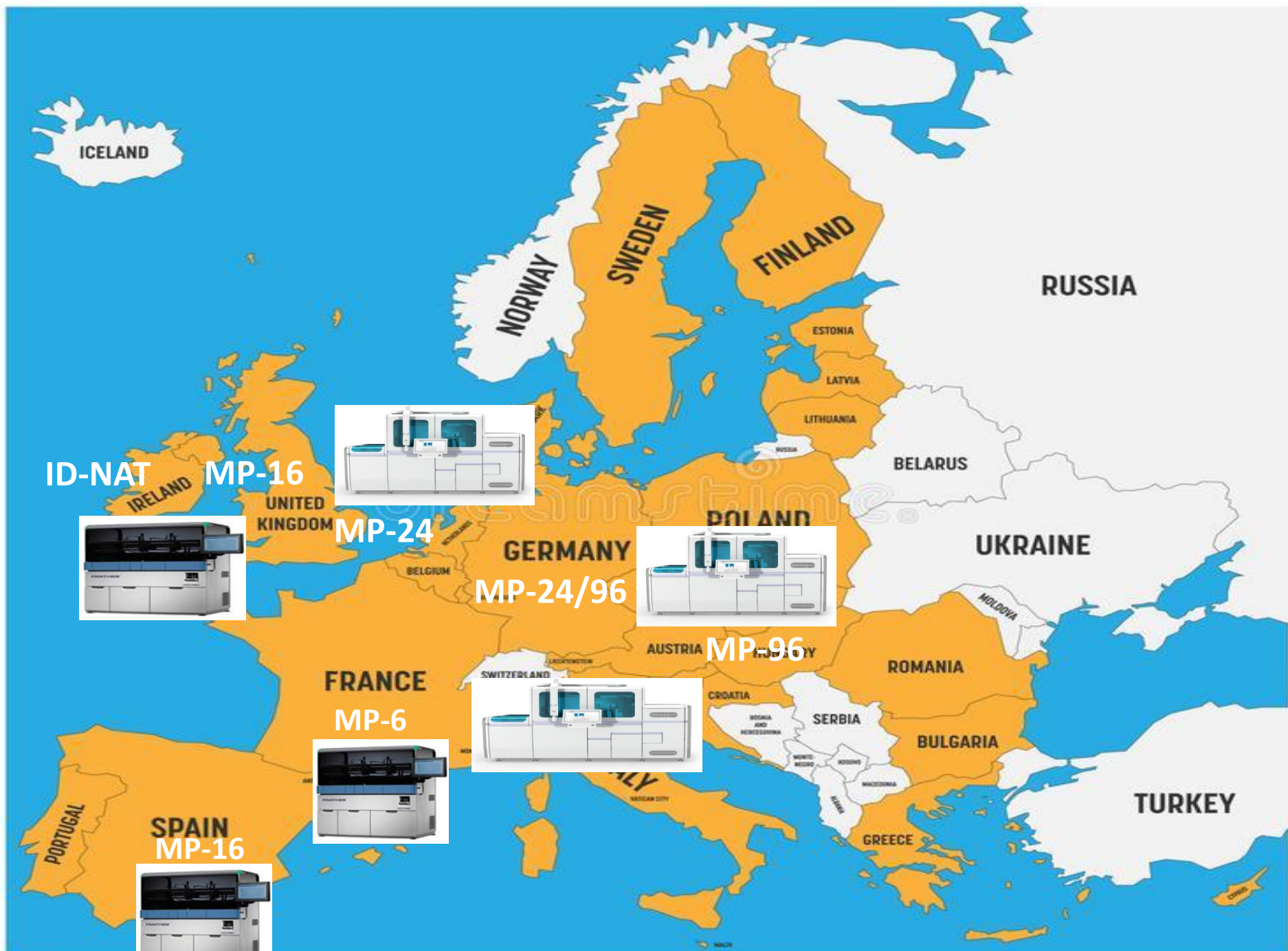
Denmark ¹
1 in 2,331 donors HEV (+)
11 / 25,637 donors
Median VL = 13 IU/mL
ID-NAT
No TT-HEV in 7 recipients; Median <100IU/mL/component

Sweden ^{2,3}
1 in 7,986 donors HEV (+)
5 / 95,835 donors
Median VL ~7,250 IU/mL
MP-96
Few reported cases of HEV infection each year (< 30)

1. Harritshoj *et al.* 2016 Transfusion Vol 56; pp. 2225-2232. 2. Baylis *et al.* 2012 Vox Sang Vol 103, pp. 89-90
3. Public Health Agency of Sweden. Number of Reported Hepatitis E Cases in Sweden. Available online:
<https://www.folkhalsomyndigheten.se/about-folkhalsomyndigheten-the-public-health-agencyof-sweden/> (accessed on 20 June 2016).

Situation 3: HEV screening in 8 EU States





ID-NAT MP-16



MP-24

MP-24/96



MP-96

FRANCE
MP-6



SPAIN
MP-16



Ireland

2016 & 2017 data



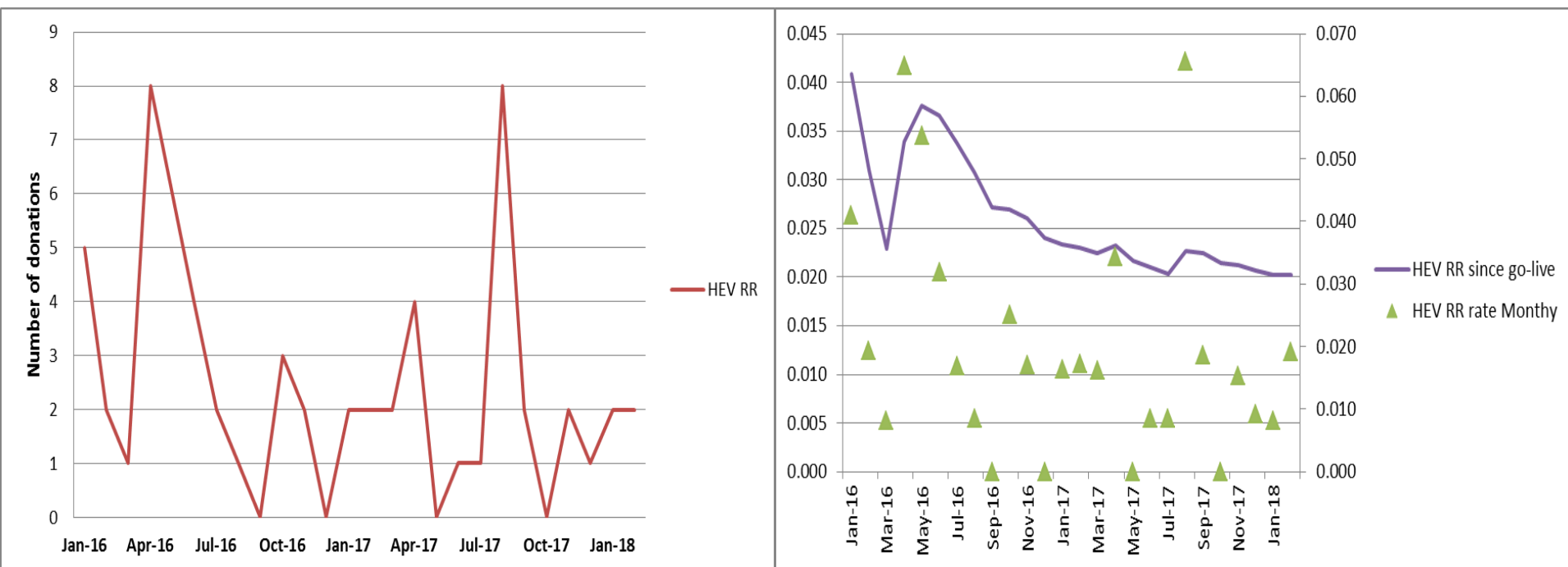
- 279,938 ID-NAT : 167 IR (0.06%), 59 RR (0.02%) or 1:4,745 donations (S/Co r: 1.06 – 53.03)
- HEV confirmation: Wantai IgM & IgG & PCR for all IRs
- 33/59 Window Period infections (56%; PCR +/-)
- 108 NRR (Rpt 1-4): 99 FP (92%)
 - 6 HEV NRR (Rpt 1-4) with serology (IgG ↑ reactivity)
 - 3 NRR IgG wk(+) index & f/up (? Past infection v non-specificity)
- 84% PCR(+)(Altona); 61% Sero(-)
- All Gt 3 (3c=44%; 3e=32%; 3f=12%; 3 outlier=9%; 3a=3%)
- Viral loads r:14 – 260,000 IU/mL (Median = 310 IU/mL)

Ireland

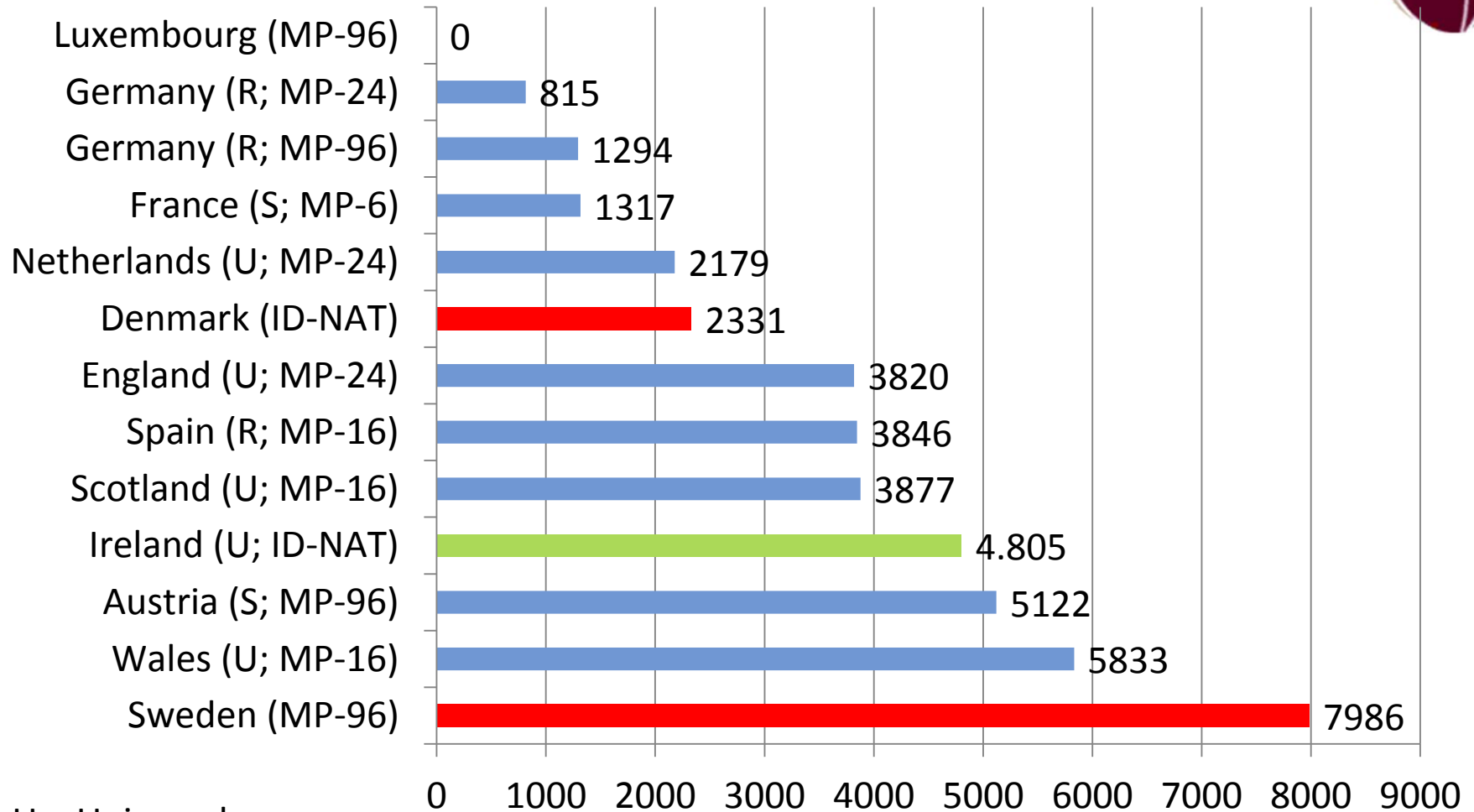
2016 & 2017 data



- No donor eating/travel/occupational patterns
- Lookback for donations less than 3 months old
- Donor deferred until NAT(-) and sero(+) (3-6 months)



HEV RNA positive donors rates across EU

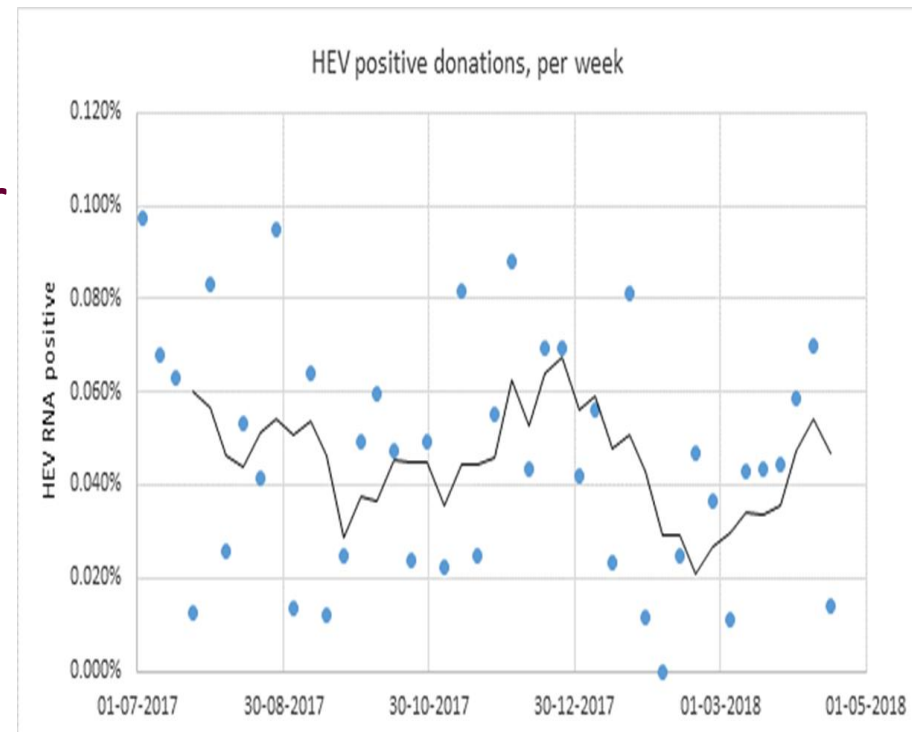


U = Universal
S = Selective
R = Regional

The Netherlands



- Screening of pooled solvent-detergent treated plasma started in 2013 (~30,000 donations/yr)
- 155 / 337,816 HEV positive (0.046%; 1 in 2,179)
- 100% PCR(+) 73% sero(-)
- Lookback up to 3 months
- 1/47 Archives (+) in FT donor
- Defer donors for 3 months
- Check donor seroconversion



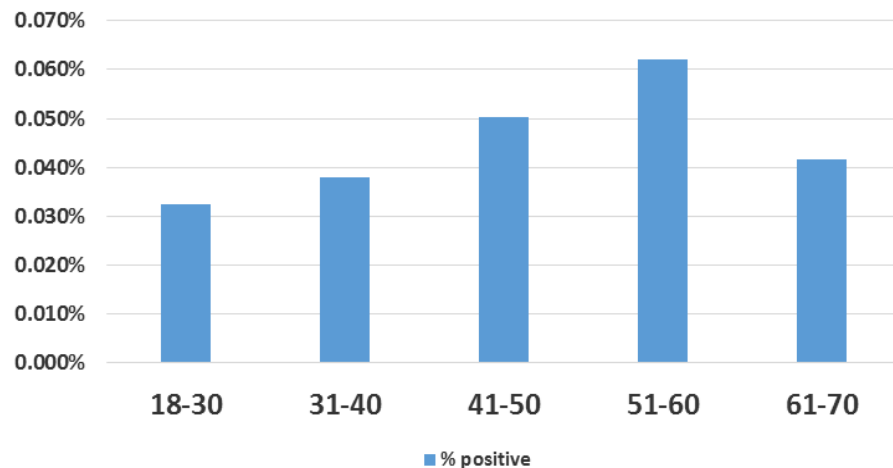
Age distribution of HEV positive donors



DUTCH DONORS

Age category	Donations screened	HEV RNA (+)	% HEV (+)
18-30	74051	24	0.032% (1:3085)
31-40	39413	15	0.038% (1:2630)
41-50	53575	27	0.050% (1:1985)
51-60	75599	47	0.062% (1:1610)
61-70	55214	23	0.042% (1:2400)
Total	297852	136	0.046% (1:2190)

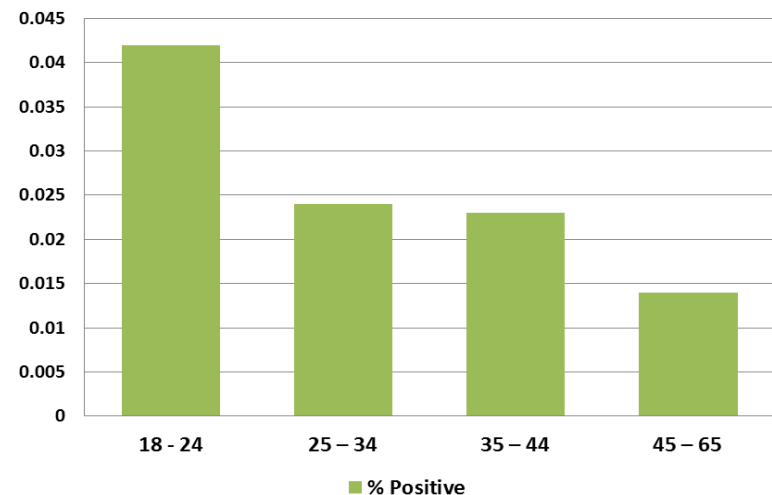
Incidence of HEV infection per age category



IRISH DONORS

Age group	Donations screened	HEV RNA(+)	% HEV (+)
18 - 24	28,398	12	0.042 (1:2367)
25 – 34	54,506	13	0.024 (1:4193)
35 – 44	66,412	15	0.023 (1:4427)
45 – 65	130,622	19	0.014 (1:6875)
Total	279,938	59	0.021 (1:4745)

HEV Infection by age group (2016 & 2017)



HEV NAT screening: Blood & Tissue Bank (Catalonia, Spain)



- 01/NOV/2017 to 30/APR/2018: 110,000 donations
- 29 HEV RNA positive donations (1 in 3,846)
- Characteristics of donors:
 - 65% males; Age at donation 39 ± 13 years
 - Viral load r: <40 to >1,000,000 IU/mL
 - 68% IgG/IgM (-) at donation (Mikrogen)
 - Gt 3f & 3c; 5 donors with elevated ALT levels
- F/Up: 73% HEV (+) (median time to F/U= 20 days)
- 87% IgG and/or IgM (+); 4 donors with elevated ALT

UK: England, Scotland, Wales



NHSBT

- March 2016 to Dec 2017: 475 / 1,814,286 HEV positive (1: 3,820); Genotype 3; VL r: 1 -3,230,000 IU/mL
- Confirmation of Reactive samples from pools at NTMRL using complimentary Panther system

SNBTS (U&S): 38 / 94,302 positive (1 : 2,481)

- 29/38 (76%) sero(-); Gt 3 Clade 1 group 2
- HEV notifiable since 2009 – steady increase
- Evidence of TT-HEV in liver tx patients (Thom et al. 2018 Euro Surveill 23(12))
- Sept '17 (U): 18 / 69,779 positive (1:3,877 donations)



France

- Nov '12 – Dec '14: RealStar RT-PCR (Altona) MP-96; VL R; <60 – 29,796 IU/mL; Gt 3 (3c, 3f) with 1:2,218 plasma donations RNA(+)
- Dec 2014 – Dec 2017: MP-6 Altona; Gt 3 with 1:1,317 plasma donations RNA(+)
- First TT-HEV case in 2006; 16 cases up to end 2013; mostly tx patients; all Gt 3; phylogenetic confirmation; related to blood usage areas (Paris 19%)
- HEV diagnosis increasing (testing; awareness; high risk tx patients)

Germany

- Waiting for the official “guidance” consultation process
- German Advisory Committee recommend NAT sensitivity of 100 IU HEV RNA/mL per single donation (Pauli *et al* 2015)
- German Red Cross (DRK Frankfurt) – customer demand
- 5 other ctrs (Bad Oeynhausen, Bochum, Hamburg-Eppendorf)

University hospitals of Ruhr University Bochum (UK RUB) ¹

- Jan ‘15 – July ‘17: 235,524 donations MP-96 (S; Altona); 1:1,294 donations PCR(+); Gt 3 most prevalent

University Medical Center, Hamburg-Eppendorf ²

- Oct ‘16 – May ‘17: 23 / 18,737 confirmed donors (1:815; Cobas HEV 6800) in MP-24. No vegetarians. TT-HEV cases.
- 3/23 seropositive; low VL (< 1,000 IU/mL; 65%); 6/7 Gt 3 group 2

Austria & Luxembourg



AUSTRIA

- Seroprevalence & Incidence of hep E in blood donors (Fischer C et al. 2015) – recommended donor HEV screening
- 2016: 18 / ~92,000 donors HEV(+) (1:5,122)(MP-96; Roche)
- Testing ~50% of donations for plasma industry; All Genotype 3
- HEV Reactive Donors deferred for 4 months
- Clinicians in Austria are currently not asking for HEV tested blood, but in principle HEV tested blood products are available.

LUXEMBOURG

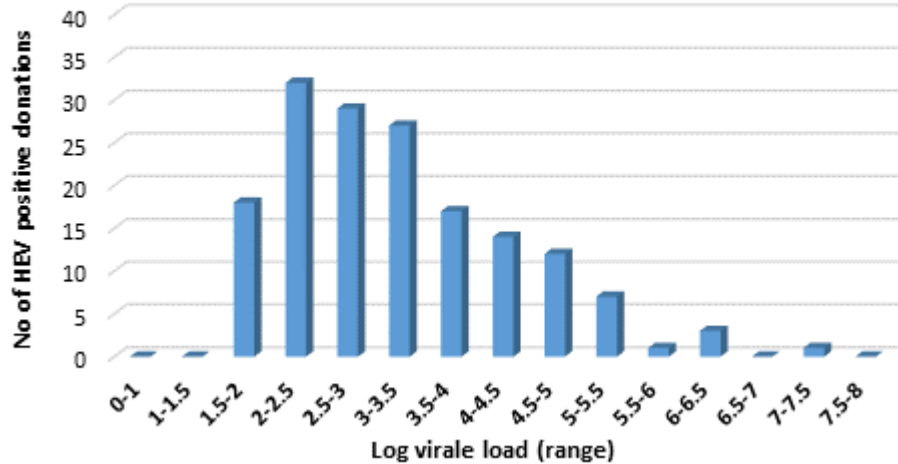
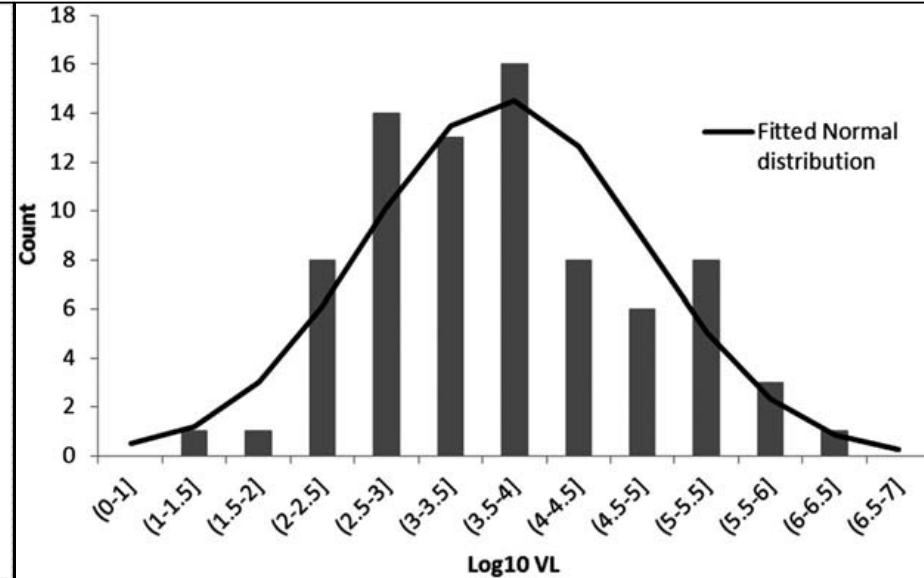
- 2017: 2,181 Male plasma donors (group O & A for SD treatment) screened (Roche), all the test were negative
- Lookback process for positive donors; HEV donors deferred for 3 months before re-instatement. Supply to high risk patients.

Viral Load Distribution of HEV(+) donors

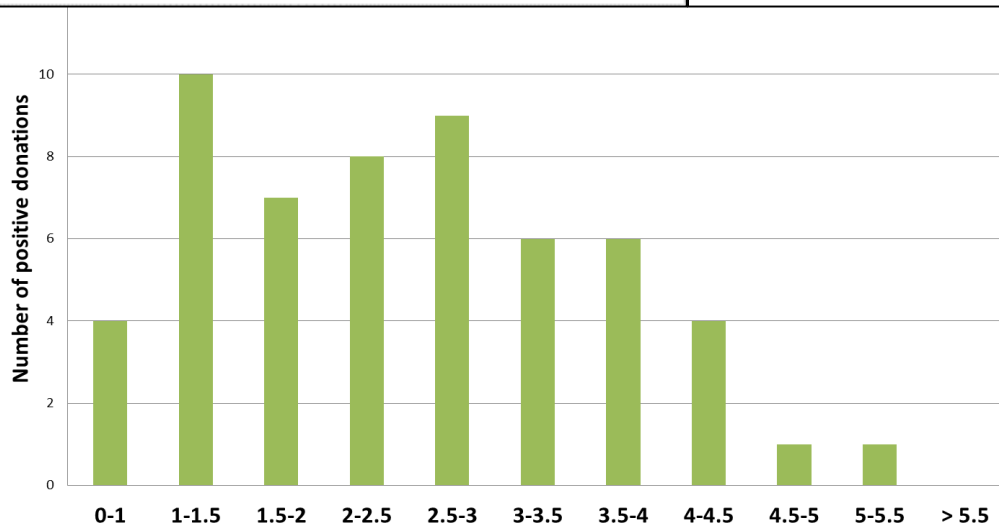
Dutch donors MP-24 (B. Hogema April 2018)

English donors MP-24 (Tedder et al. 2017)

Viral load distribution



**Irish
donors
ID-NAT**



Ireland

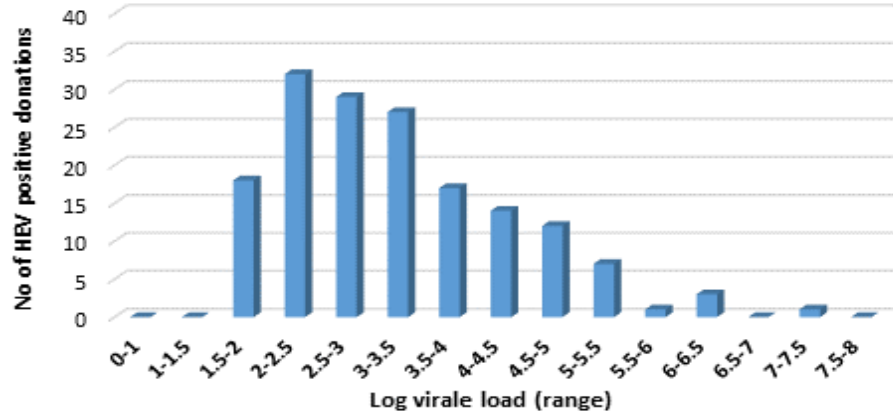
14 / 56 RR (25%)
have VL < log 1.5

21 / 56 RR (37.5%)
have VL < log 2.0

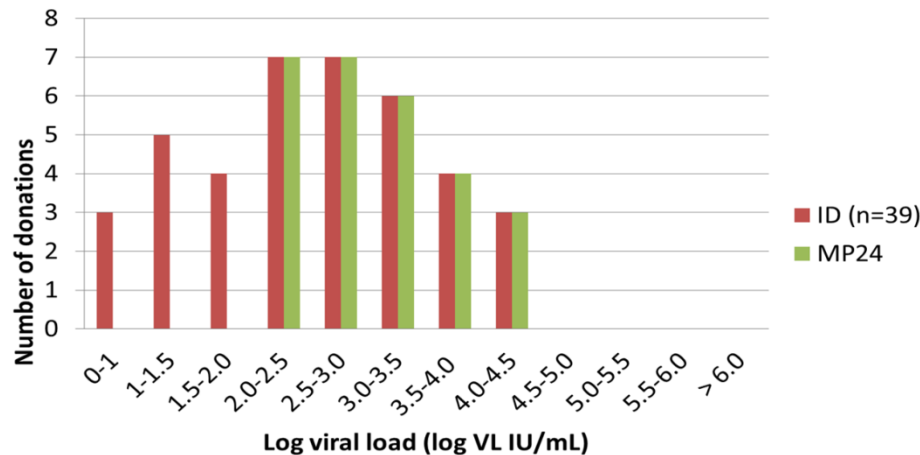
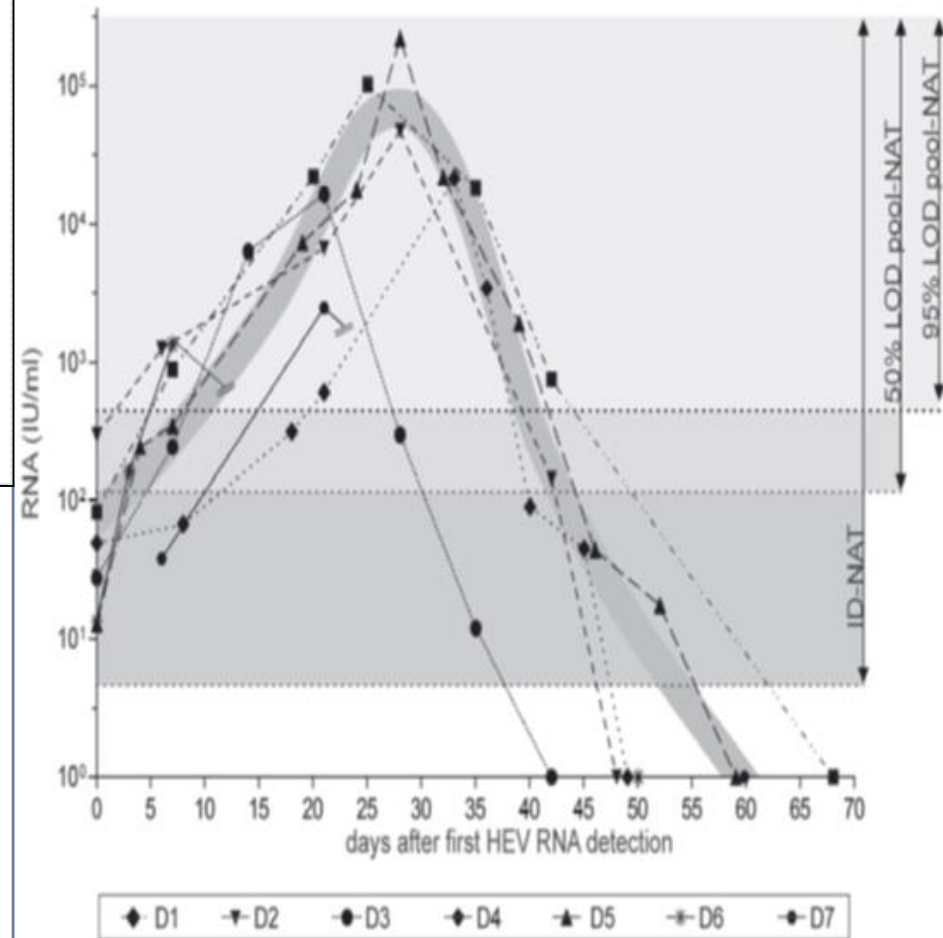


HEV Detectable Viral load compared to screening strategy

Viral load distribution



ID-NAT v MP-24
Distribution of HEV Viral Loads



Proven / Probable TT-HEV (2004 – 2017)

Dreier et al. 2018



Donor age, sex	VL (IU/mL)	Gt	Infectious dose (IU)	IgM/ IgG	Country/ year	Patient age,sex	Outcome post tx	Product
24, M	N/A	3f	N/A	Neg/ Neg	France 2005	7, M	Acute infection	RBC
40's, M	N/A	3	N/A	Pos/ Pos	UK	65, M	Acute infection	RBC
53, F	1,700	3f	17,000	Neg/ Neg	France 2011	53, F	Acute infection	Platelet Conc
32, F	N/A	3f	N/A	N/A	France 2012	36, M 61, M	Chronic Chronic	ICT plasma
41, M	3,160	3c	31,600	Neg/ Neg	France 2012	55, M	Acute infection	RBC
40's, M	120	3f	7,060 – 8,890	Neg/ Neg	Germany 2013	47, M 6, M	Chronic Probable	Apheresis platelet
41, M	75,000	3f	750,000	Neg/ Neg	Spain 2015	61, M	Acute infection	RBC
N/A	100,000	3	$10^5 / 10^7$	Neg/ Neg	Germany 2013	33, M 71, M	Chronic Chronic	RBC FFP

No TT-HEV (2004 – 2017)

Dreier et al. 2018



Donor age, sex	VL (IU/mL)	Gt	Infectious dose (IU)	IgM/ IgG	Country/ year	Patient age,sex	Outcome post tx	Product
40's, M	N/A	3	N/A	Pos/ Pos	UK	55, F	No infection	Platelet Conc
40's, M	495	3f	30,900	Neg/ Neg	Germany 2013	71, M	No infection	Apheresis platelet
32, M	< 10	NS	< 100	Neg/ Neg	Denmark 2015	54, M	No infection	RBC
27, M	< 10	NS	< 100	Pos/ Pos	Denmark 2015	62, M	No infection	RBC
48, M	191	NS	5,730	Pos/ Pos	Denmark 2015	0, F	No infection	Cryo
NS	100,000	3	2,500,000	Neg/ Neg	Germany	61, M	No infection	PPC
29, M	< 25	3	7,970	Neg/ Neg	Germany 2017	79, F	No infection	2 APC

Hepatitis E and blood donation safety in selected European countries: a shift to screening?



- Sharing of HEV sequences/data



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1st Hepatitis E virus network (HEVnet) meeting

event

 26 Oct 2017 - 27 Oct 2017

 RIVM, Bilthoven

 ECDC



The key objective of this meeting is to verify the rationale and objectives of molecular typing for surveillance of hepatitis E virus (HEV) through the hepatitis E network (HEVnet). The workshop will review HEVnet as a tool for molecular surveillance of HEV in Europe.

The other objectives of this meeting are:

- to review HEVnet as tool for molecular epidemiological investigations
- to provide an overview of the data uploaded to HEVnet
- to agree on a data analysis and perform data analysis
- to draft a manuscript/report outlining the findings
- to confirm the rationale and objectives of molecular typing for surveillance of HEV
- to recommend next steps.



Conclusion

- Screening strategy must focus on preventing TT-HEV
- Since 2017, 8 EU countries are screening for HEV RNA in blood donors (1 country in 2012)
- Country specific decision making
- Challenges:
 - political, socio-economic, cultural, clinical factors
 - Protecting our high risk patients
 - Approach to risk-based decision making
 - Clinical demands for HEV screened blood vary
- Collaboration is key
- Screened blood v dietary exposure

My Thanks go to..



- NAT laboratory & IBTS team
- Dr. Niamh O’Flaherty, Laboratory Director
- Boris Hogema & Hans Zaaijer & team, Sanquin
- PHE, UK, & NHSBT, SNBTS, WBS
- Silvia Sauleda & team, Spain
- Pierre Gallian & team, France
- Sally Baylis, Germany
- Christof Jungbauer & team, Austria
- Christine De Pauw & team, Luxembourg

6 NRR Sero(+) donors



Donation Number	Donor Age/ Sex	Previous donation date	IR HEV S/Co	RR HEV S/Co	FT or Rpt donor	NVRL results	Index IgM	Index IgG	Follow up sample	NAT	Follow up results	Days to follow up	Re-instated
R00011601 2050 B	33 yrs; Female	N/A	1.38	Rpt 1 & 2 Negative	SOND	PCR Not Detected (x 2); IgG Negative IgM Weak Positive	2.799	0.021	R0001160 27871 A	Negx2	IgM Positive (3.208) IgG Positive (10.468)	71	Yes 26/07/16
R00011615 4394 Z	53 yrs; Male	N/A	2.3	Rpt 1 - Rpt 5 Negative	Rpt	PCR Not Detected (x 2); IgM Negative; IgG weak positive	0.129	1.168	R0001160 28085 9	Negx2	IgM Negative (0.109) IgG Positive (6.200)	65	Yes 22/10/16
R00011610 7899 N	38 yrs; Male	25/08/15	1.12	Rpt 1 - Rpt 5 Negative	Rpt	PCR Not Detected (x 2); IgM Weak Pos & IgG Positive	2.521	17.505	R0001160 28051 T	Negx2	IgM Wk Positive (1.364) IgG Positive (17.211)	37	Deferred
R00011706 0054 6	56 F	N/A	1.17	Rpt 1 - Rpt 5 Negative	FT	PCR Not Detected (x2) IgM negative & IgG weak Positive	0.004	2.616	R0001171 00572 G	Negx2	IgM Negative (0.011), IgG Positive (3.795)	97	Yes 29/11/2017
R00011712 2569 L	63 M	09/03/2017	1.24	Rpt 1 - Rpt 5 Negative	Rpt	PCR Not Detected (x2) IgM negative & IgG Positive	0.14	7.579	R0001171 28252 4	Negx2	IgG positive (10.784) , IgM negative (0.118)	89	Yes 12/12/2017
R00011714 1459 M	46 M	N/A	1.78	Rpt 1 - Rpt 5 Negative	Rpt	PCR Not Detected (x2) IgM negative & IgG Positive	0.011	14.374	R0001171 42602 O	Negx2	IgG positive (14.674) , IgM negative (0.027)	22	Yes 17/02/2018

IR HEV S/Co	RR HEV S/Co	FT or Rpt donor	NVRL results	Index IgM (NVRL)	Index IgG (NVRL)	PHE Results
16.67	2.08, 4.95	Rpt	PCR Detected (x2) IgM Negative IgG Positive	0.342	9.153	RNA Not Detected, too low for genotyping
1.54	6.10, 1.36	SOND	PCR Detected (x2) IgM & IgG Negative	0.026	0.053	26 IU/ml viral load too low for genotyping
8.54	8.12, 7.03	Rpt	PCR Not Detected (x2) IgM Positive & IgG Positive	8.384	5.242	HEV RNA Not Detected, too low for genotyping
22.06	31.09, 30.99	FT	PCR Detected (x2) IgM & IgG Negative	0.019	0.042	VL 210 IU/mL; too low for genotyping
34.58	24.98 & 11.46	Rpt	PCR Not Detected (x2) IgM and IgG Negative	0.019	0.174	14 IU/ml; too low for genotyping
23.13	10.60, 17.12	FT	PCR Detected (x2) IgM & IgG Negative	0.038	0.111	HEV RNA Not Detected, too low for genotyping
50.13	49.77, 52.29	Rpt	PCR Detected (x2) IgM & IgG Negative	0.004	0.142	VL 6,700 iu/ml - 3f
32.65	39.23, 35.63	Rpt	PCR Detected (x2) IgM & IgG Negative	0.004	0.174	520 IU/ml - too low for genotyping
62.25	65.47, 58.01	Rpt	PCR Detected (x2) IgM & IgG Negative	0.792	0.089	260,000 IU/mL; genotype 3c
12.11	10.96, 9.01	Rpt	PCR Detected (x2) IgM Positive IgG Positive	13.573	11.568	66 IU/ml too low for genotyping
3.1	1.80, 0.00	Rpt	PCR Not Detected (x2) IgM Positive & IgG Positive	12.224	14.611	HEV RNA Not Detected; unable to genotype
1.33	0.1, 2.72, 0.16, 0.51, 1.00	Rpt	PCR Not Detected (x2) IgM and IgG Negative	0.067	0.25	HEV RNA Not Detected; unable to genotype
12.74	27.49 & 27.66	Rpt	PCR Detected (x1), PCR not detected (x1) IgM and IgG negative	0.023	0.095	20 IU/mL; too low to genotype
54.49	52.42 & 56.28	Rpt	PCR Detected (x2) IgM & IgG Negative	0.008	0.1	66,000 IU/mL; genotype 3f
17.73	27.99, 24.07	Rpt	PCR Detected (x2) IgM Negative & IgG Positive	11.495	0.822	4 IU/mL; unable to genotype
21.74	24.02, 26.49	Rpt	PCR Detected x 2, IgM and IgG Negative	0.015	0.163	350 IU/mL; too low to genotype
53.26	39.09, 45.43	Rpt	PCR Detected x 2; IgM positive & IgG negative	1.24	0.895	21,000 IU/mL; Genotype 3c
3.53	4.20, 1.77	FT	PCR Not Detected (x 2), IgM and IgG Negative	0.011	0.1	40 IU/ml; too low for genotyping
1.85	6.62, 4.92	Rpt	PCR Detected (x2) IgM Positive & IgG Positive	6.519	21.053	HEV RNA Not Detected; unable to genotype
9.95	12.13, 23.47	Rpt	PCR Detected (x2) IgM weak Positive & IgG Positive	1.745	16.242	69 IU/mL; too low to genotype
20.05	19.23, 7.32	Rpt	PCR Not Detected (x2) IgM and IgG Negative	0.015	0.021	18 IU/ml; too low for genotyping
53.31	52.39, 52.88	Rpt	PCR Detected (x2) IgM Positive IgG Positive	10.527	10.721	10,000 IU/mL; unable to genotype
32.01	32.17 & 30.92	Lapsed	PCR Detected (x2) IgM and IgG Negative	0.011	0.011	160 IU/mL; too low for

3 NRR IgG Weak positives



M, 65	19/08/16	1.11	Rpt 1-5 Neg	Rpt	PCR Not Detected (x 2); IgM Negative IgG Weak Positive	0.045	1.874	R00011710 0217 H	Neg x 2	IgM Negative (0.095) IgG Weak Pos (2.495)	08/03/17
M, 71	23/08/16	2.63	Rpt 1-5 Neg	Rpt	PCR Not Detected (x 2); IgM Negative IgG Weak Positive	0.026	1.784	R00011710 0166 7	Neg x 2	IgM Negative (0.034) IgG Weak Positive (1.963)	21/02/17
F, 47	31/01/17	1.75	Rpt 1-5 Neg	Rpt	PCR Not Detected (x 2); IgM Negative IgG Weak Positive	0.011	1.3	R00011710 0655A	Neg x 2	IgM negative (0.008) IgG equivocal (0.942)	31/07/17