HEV Update – Blood Components

Dragoslav Domanović, European Centre for Disease Prevention and Control (Sweden)

Outline

ECDC activities started in 2015

- to understand the epidemiology and burden of HEV infection in humans across the EU/EEA Member States and
- to harmonise EU/EEA MS response to the threat posed by the virus to human health and the safety of blood supply

Hepatitis E

Most common cause of acute viral hepatitis world-wide;

HEV 1 & HEV 2 infections in developing countries- waterborne

- 3.4 million symptomatic cases, including 70,000 deaths and 3,000 stillbirths in 9 endemic regions*

HEV 3 & HEV 4 infections - endemic in developed world – zoonotic, under-reported

- Many cases - subclinical
- Significant proportion of symptomatic cases – misdiagnosed or unrecognized
- Surveillance system sometimes not established

European Union – Hep E – increasing in last decade

- Hep E gradually becoming the dominant cause of new hepatitis cases (imported + autochthonous HEV3)
- burden of HEV infection in humans - poorly documented.
- HEV infection is not under EU surveillance,
- Picture of the hep E endemic in EU not complete.

* Rein BD et al. The global burden of hepatitis E virus genotypes 1 and 2 in 2005.Hepatology 2012;55:988-997

ECDC activities

2013

- HEV threat to the blood safety discussed at the meeting NCA for blood and blood components

2015

- 1st expert group meeting on the Epidemiology and surveillance of Hepatitis E virus in EU/EEA, ECDC, Stockholm, 09-10/12/2015

2016

- Expert group meeting on Assessing the risk and prevention of HEV transmission via SoHO
- 2nd expert group meeting on the Epidemiology and surveillance of Hepatitis E virus in EU/EEA, ECDC

ECDC activities

1. Establishment of an expert group

Members are nominated experts from the EU/EEA MS + 3 external scientific experts + EFSA + WHO

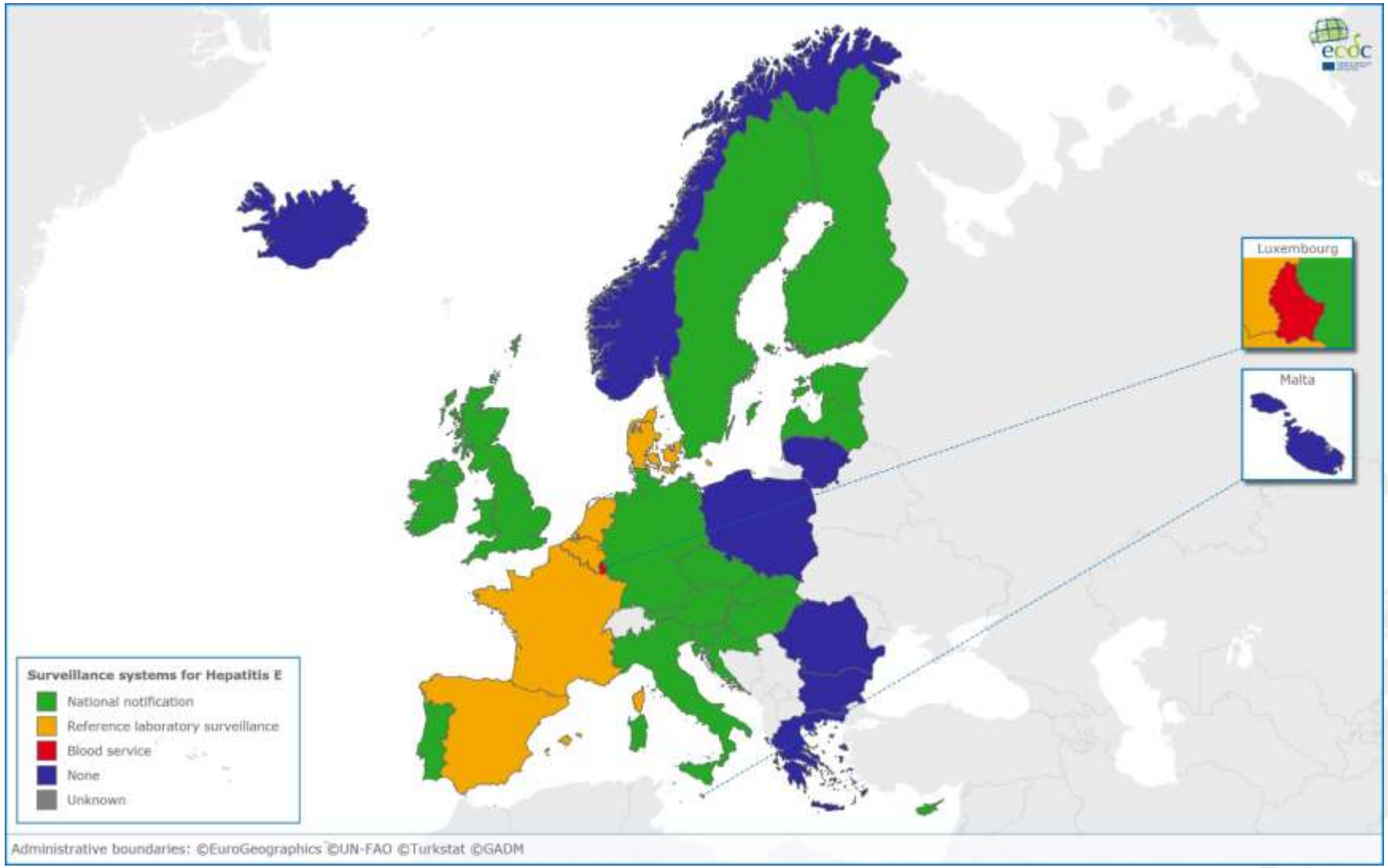
2. Member State survey

Ask EU/EEA MS to describe surveillance systems in place, applied case definitions and laboratory methods for diagnosis, collect case numbers, where possible

3. Systematic literature review

"What is the seroprevalence and/or incidence of HEV antibodies over the last 10 years (2005-recent) in different populations surveyed in the EU/EEA MS by country and/or region"

Member State survey: HEV surveillance in EU/EEA, 2015 - preliminary results



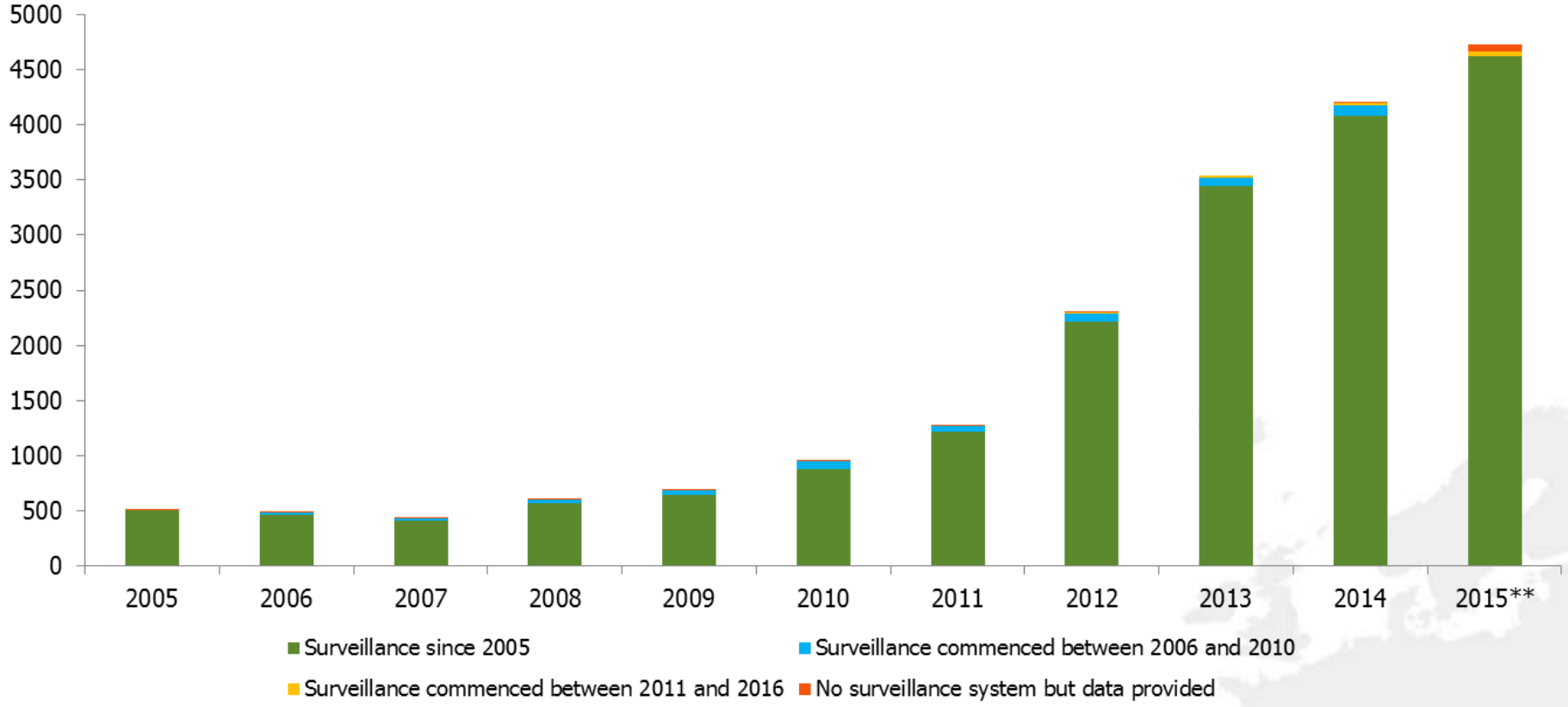
Surveillance systems:

National notification-
17 (55%)
Reference laboratory-
5 (16%)
Blood service-
1 (3%)
Not exisiting –
8 (26%)

Case definitions:

variable

Number of laboratory-confirmed cases of HEV by year and start of surveillance, EU/EEA 2005–2015*



* Data available for: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Estonia, Finland, France, Germany, Hungary, Italy, Latvia, Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden, United Kingdom

** Number of confirmed cases in France derived from linear regression projections for the year 2015

ECDC action plan

- Facilitate establishment of **'HEVnet' database** at RIVM
- Support development of **harmonised sequencing protocol** for genotyping and subtyping of HEV strains;
- Central **coordination of communication**;
- **Collaboration with EFSA** to assess risk due to food;
- **Assess** the risk of HEV transmission through blood transfusion, blood products and transplantation;

Objectives of the 'HEVnet' database

- To support epidemiological investigations on a European level;
- To explore association between viral subtypes and clinical picture;
- To map the population structure of HEV strains associated with outbreaks and other incidents with public health impact;
- To collect HEV sequences from both human and animal populations to identify epidemiological relationship and inform options for control;
- To develop common protocols for genotyping and subtyping of HEV strains;

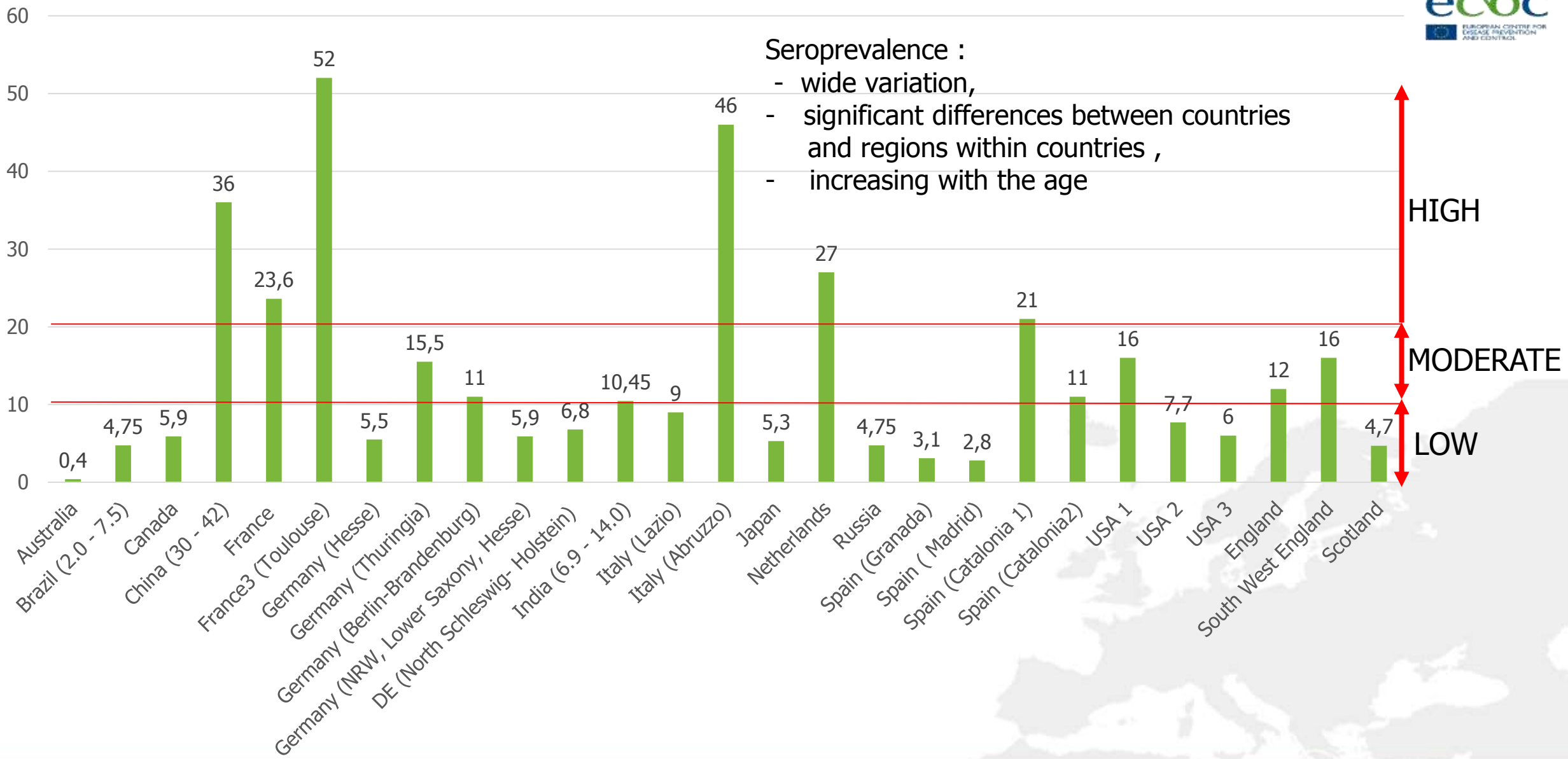
HEV expert group

ECDC, Stockholm, 09-10/12/2015

HEV = Transfusion transmitted pathogen

- Present in the asymptomatic donor's blood;
- Survives in the donated blood during processing and storage;
- Responsible for a clinically apparent outcome in at least a proportion of recipients who become infected.

Seroprevalence of anti-HEV IgG (%) - blood donors



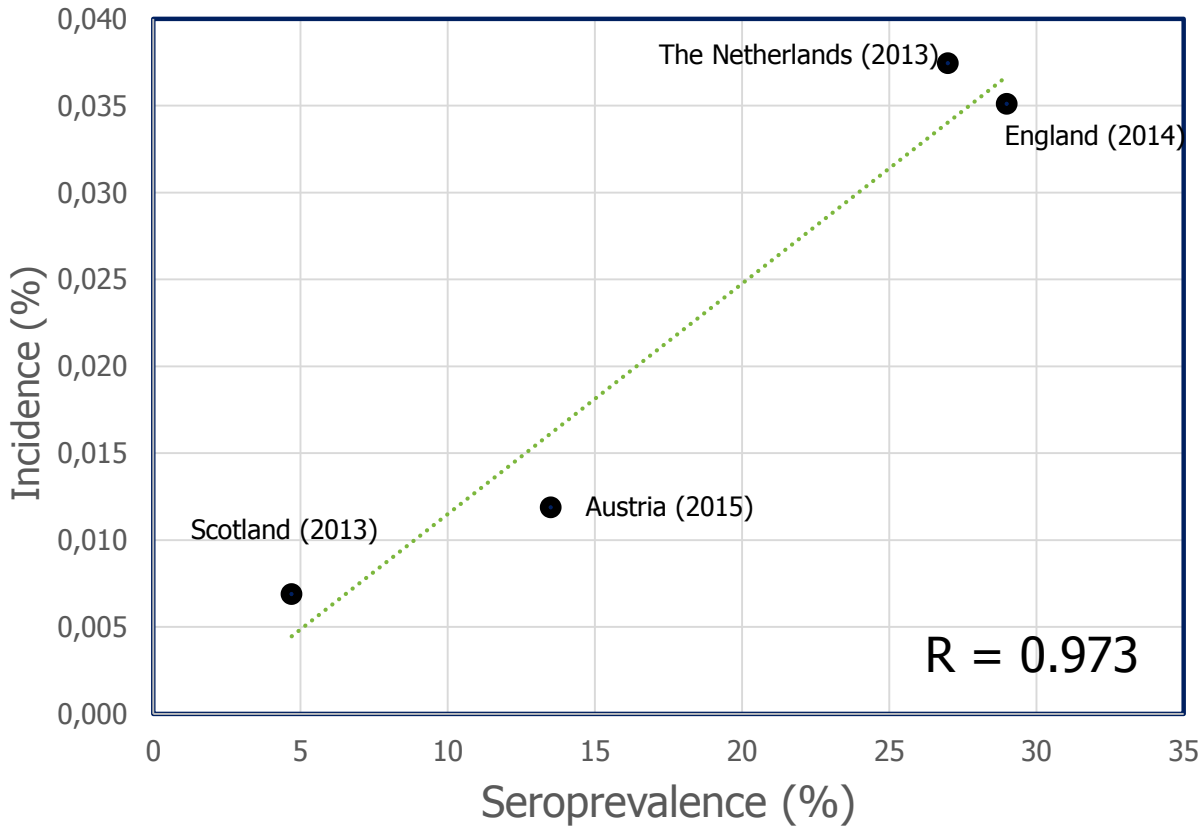
Adapted from: Petrik J et al. Hepatitis E. International forum. Vox Sanguinis, 2015

Incidence HEV3 RNA - blood donors EU

Year	Countries	Technique	No. tests	Ratio of positives	Ref.
2011	England	PCR	42000	1:7040	Ijaz et al.
2013	Scotland	PCR	43560	1 :14520	Cleland et al.
2011	Germany	RT-PCR	18100	1:4525	Baylis et al.
2011	Sweden	RT-PCR	95835	1:7986	Baylis et al.
2011	Germany	RT-PCR	16125	1:1241	Vollmer et al.
2011-2012	Netherlands	RT-PCR	45415	1:2672	Slot et al.
2012-2013	England	RT-PCR	225000	1:2848	Hewitt et al.
2012	France	RT-PCR	53234	1:2218	Gallian et al.
2013	Spain	TMAA	9998	1:3333	Sauleda et al.

PCR: Polymerase Chain Reaction; RT-PCR: Real Time Polymerase Chain Reaction; TMAA - transcription mediated amplification assay

Possible correlation between seroprevalence and incidence of HEV among blood donors in EU/EEA



Proposed HEV endemicity classification

Endemicity	Seroprevalence	Incidence
Low	< 10%	< 1:10,000
Intermediate	10% - 20%	1:10,000 – 1:2,500
High	> 20%	➢ 1:2,500

Clinical characteristics of HEV 3 (4) infection

Acute hepatitis

- Acute, self-limiting, clinical & biochemical recovery after few weeks
- Subacute liver failure (patients with chronic liver disease)
- Male/female ratio = 3.2 : 1, mean age 63.7 years

Chronic hepatitis

- Immunosuppressed patients (recipients SOT, HSCT) (60% of exposed to HEV)
- Imported HEV4 fatal case in SOT USA (2015)

Extra-hepatic manifestations

- Neurological (Guillain-Barre synd., neuralgic amyotrophy, transverse myelitis, meningoencephalitis)

Transfusion transmitted HEV infection

- ~ 40 cases of HEV transmission through blood product recipients in Europe/Japan
- Underreporting: non-recognition, miss-diagnosis, subclinical cases

Cases of molecularly confirmed TTI HEV in non-endemic countries (Matsui, 2015)

Author	Transmission (y)	HEV Genotype	Blood component	Patient age	Patient gender
Matsubayashi K, et al. 2004	2002	4	FFP	67	M
Matsubayashi K, et al. 2008	2004	4	PLT	69	M
Boxall E, at al. 2006	2005	3	FFP	60	M
Colson P, et al. 2007	2006	3	RBC	7	M
Tamura A, et al. 2007	-	3	RBC	21	M
Matsui T, et al. 2015	2005	3	PLT	72	M

M=male; FFP=fresh frozen plasma; PLT=platelets; RBC=red blood cells, y=year

Transfusion transmitted HEV3

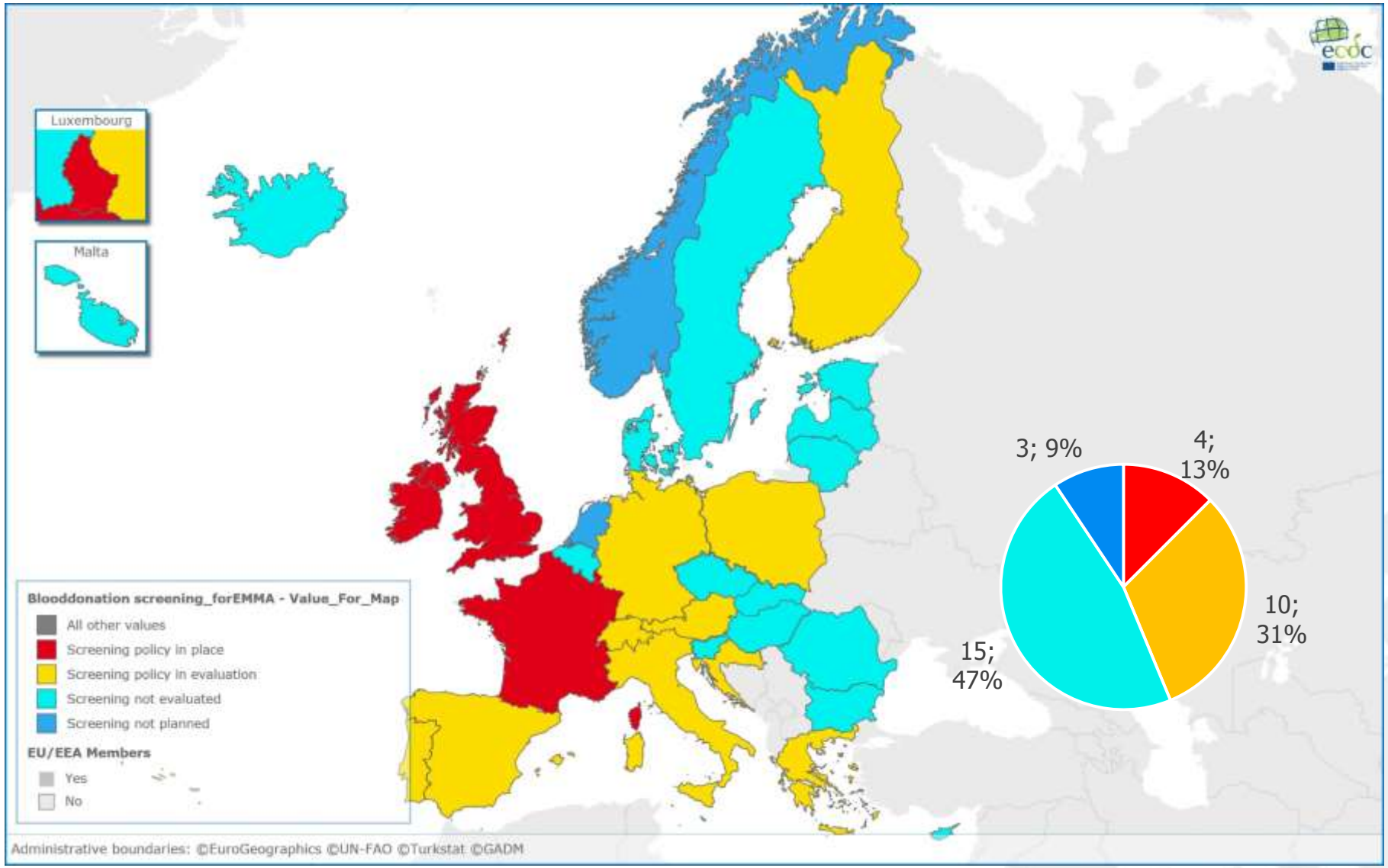
- **Hewitt P, Lancet 2014.**
- Sample – 225 000 blood donations
- 79 donations /129 components HEV3 RNA positive
- 62 transfused
- 43 recipients followed – 18 (42%) evidence of infection = transmission rate
- Transmission is increasing with a higher plasma content

Component	Number of * recipients	Infected Recipients (%)	Uninfected Recipients (%)
Red Blood Cells	16	4 (25%)	12 (75%)
Pooled Platelets	10	4 (40%)	6 (60%)
Apheresis platelets	14	7 (50%)	7 (50%)
FFP	2	2 (100%)	0 (0%)
Pooled Granulocytes	1	1 (100%)	0 (0%)
TOTAL	**43**	**18 (42%)**	**25 (58%)**

Status of HEV blood safety measures in EU MS – EU Commission DG SANTE D4 survey

- **No legal requirement to test blood donations for hepatitis E in the EU**
- **Hepatitis E discussion at CAs meeting in April 2015 revealed different approaches in those MS that described their current situation**
- **Agreed that it would be useful to understand the current situation related to HEV and blood donations in all MS through a simple email survey**
- **Results circulated to the group in August 2015**

Screening policy of blood donations for HEV in EU/EEA



Current types of screening policies in EU/EEA

Screening in place (NAT HEV RNA)

- Universal (all donations)
- Partial (subset of donations to be transfused to the risk patients)
- "HEVnet" database

Screening not implemented

- Use pathogen inactivated blood components for patients at risk.
- No measures

SaBTO recommendations on the use of HEV-screened blood components - summary

NAT HEV RNA negative blood components for:

Solid Organ transplantation

- SOT recipients (who are taking immunosuppressive medication)
- Potential SOT recipients (3 months prior transplantation)
- Any patient who is receiving immunosuppressive therapy before SOT
- SOT patients undergoing extracorporeal circulatory support

Haematopoietic Stem Cell Transplantation

- Allogeneic HDCT patients 3 months before and 6 months after transplantation or as long as the patient is under immunosuppression.

Revision planned in 2018

Issues for consideration before the introduction of screening for TTIs

	Y	N
Is the infectious agent readily transmissible through the transfusion of infected blood or blood products?		
Could the infection result in severe morbidity or mortality in recipients?		
Is the infection widespread or endemic to the country or region?		
Can blood donors at risk of the specific infection be identified and deferred through the donor selection process?		
Is the infectious agent identifiable by blood screening?		
Is an effective screening assay readily available that can specifically identify infected donations?		
Are confirmatory assays available to distinguish between true and false positive results?		
What are the benefits of screening for an additional TTI in relation to resource and logistics requirements?		
What might be the impact on the blood supply if such a test is introduced?		
What are the wider social, political and legal context?*		
Risk of transmission by different routes?*		

World Health Organization. Screening Donated Blood for Transfusion Transmitted Diseases.
* Added to the WHO list

Instead of conclusion

Expert meeting on assessing the risk and prevention of TTHEV (Lisbon, Portugal27/05/2016)

Assess the current status of

- TTHEV cases in EU
- Screening policies

Discuss the approach to risk assessment

Discuss prevention strategies

"The essence of strategy is choosing what not to do"

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