

Regulatory Implications of Hepatitis E Virus

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EMA/CHMP/BWP/196177/2014
Biologics Working Party (BWP)

Workshop on Viral safety of plasma-derived medicinal products with respect to hepatitis E virus

28 –29 October 2014, European Medicines Agency, London

Chair: J. Bluemel

Steering Committee: J. Bluemel, W. Oualikene-Gonin, K. Chidwick, K. Cristiano, M. Farshid, P. de Felipe, M. van de Bovenkamp, G. Silvester

Presenters: H. Dalton, R. Tedder, HL Zaaijer, R. Tedder, W. Oualikene-Gonin, A. van der Eijk, N. Kamar, JM Echevarria, AR Ciccaglione, SA Baylis, A. Andonow, J. Izopet, B. Flan, TR Kreil, A. Gröner, R. Gajardo, M. Yunoki, I. van Hoegen, F. Rossi.

Agenda – Key Questions

Session 1: Introduction

Session 2: Transfusion-associated infections and clinical experience with HEV-infections

- *How serious are HEV infections and which patient populations may be particularly at risk?*

Session 3: HEV-Detection and epidemiology of HEV in Blood/Plasma Donations

- *state of testing?*

Session 4: Solvent/Detergent treated (SD) Plasma and neutralisation by antibodies

- *Do serum antibodies against HEV significantly neutralise?*

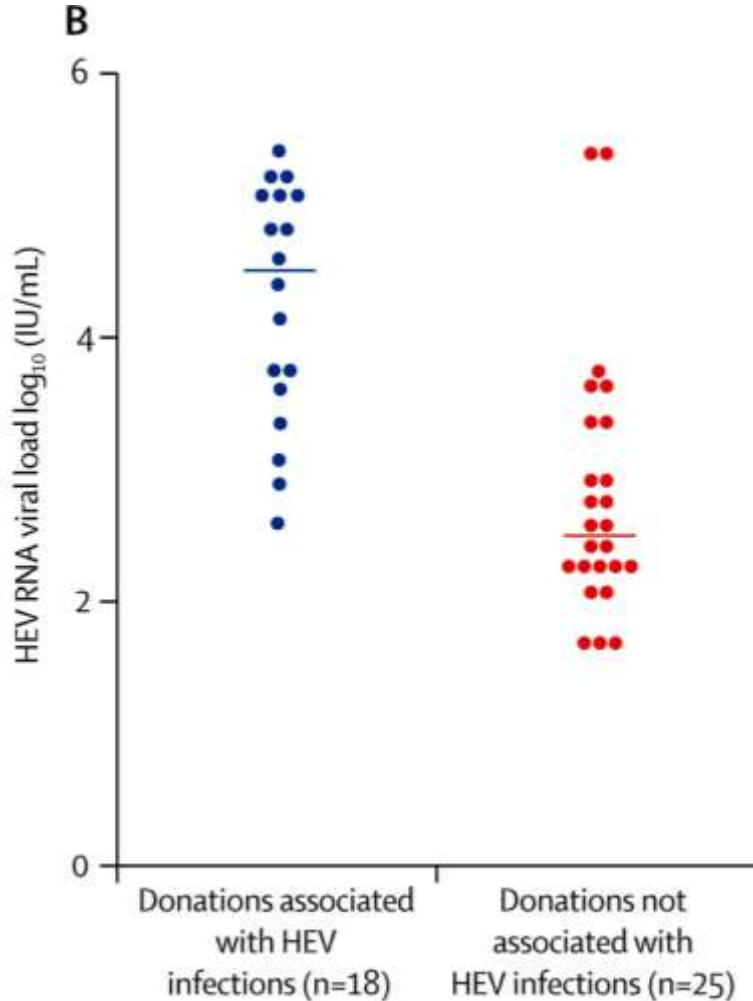
Session 5: Latest experience from studies on inactivation/removal of HEV

- *Which steps are efficient to remove / inactivate HEV? (and which model viruses can be used to assess that?)*
- *Do we need more virus validation data?*

Session 6: Risk assessment for plasma-derived medical products and implication for warning statements

- *Do we need risk assessments and/or warning statements?*
- *NAT testing will be required in the Ph. Eur. for SD plasma. Should this also be required for any other products?*

Evaluating the (minimum) infectious dose



1.1×10^5 GE/ml
1.1×10^5 GE/ml
8.9×10^4 IU/ml
3.2×10^4 IU/ml
3.2×10^4 IU/ml
2.8×10^4 GE/ml
1.7×10^4 IU/ml
3.2×10^3 IU/ml
6.5×10^3 IU/ml
6.0×10^3 IU/ml
3.0×10^3 GE/ml
541 GE/ml
380 GE/ml

ASNM:
Donations associated with infections
imputability grade 3, certain)

Hewitt et al., 2014 Lancet 384:1766-1733

Evaluating the (minimum) infectious dose

Donation 1: **120 IU/ml** plasma HEV RNA

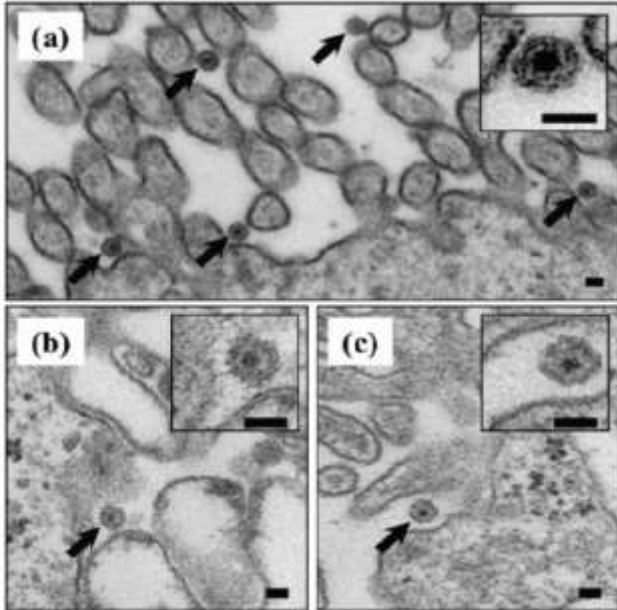
Donation 2: 495 IU/ml plasma HEV RNA

	Transfusion recipients				HEV status		
	Transfused infectious dose HEV RNA	Recipient, sex and age	Immuno-compromised	Outcome	HEV status determined, time after transfusion	HEV PCR	Anti-HEV IgG status
Blood products from donation 1							
Apheresis platelets (196 mL)	7,056 IU	#1, male 47 years	Yes	Chronic HEV infection	6 months	Positive	Positive
Apheresis platelets (247 mL)	8,892 IU	#2, male 6 years	No	Probable HEV infection	8 months	Negative	Positive
Apheresis platelets (243 mL)	8,748 IU	#3, female 70 years	Yes	Died, sepsis	NA	NA	NA
Blood products from donation 2							
Apheresis platelets (208 mL)	30,888 IU	#4, male 71 years	Yes	No HEV infection	5 months	Negative	Negative
Apheresis platelets (251 mL)	37,273 IU	#5, male 71 years	No	Died, arrhythmia	NA	NA	NA
Apheresis platelets (249 mL)	36,976 IU	#5, male 71 years	No	Died, arrhythmia	NA	NA	NA

Apheresis platelets with ca 0.33ml Plasma/ml

Huzly et al., 2014, Eurosurveillance:

Neutralisation

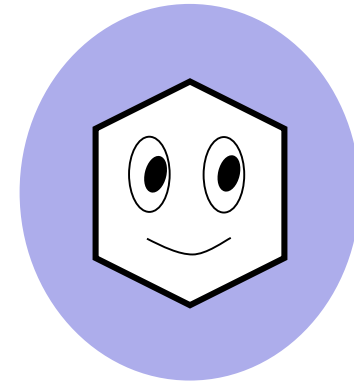


PLC/PRF/5 (a), HepG2 (b) and A549 (c) cells infected with cell culture-produced HEV (JE03-1760F strain). Arrows = extracellular membrane-associated virus-like particles. Scale bars: 50nm.

Nagashima et al, *J Gen Virol* 2014 95 2166-2175

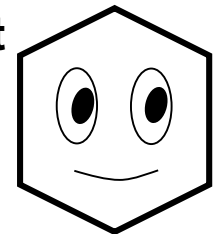
Takahashi et al, *J Clin Microbiol*, 2010 48 1112-25

Lipid-associated HEV
from plasma
from cell culture
infectious
more resistant
larger



~ 50 nm

Non-lipid-associated HEV
from stool
from cell culture+ detergent/solvent
from production intermediate?
infectious
less resistant
smaller



27-35 nm

Neutralisation

No *in vitro* neutralisation of lipid-associated virus

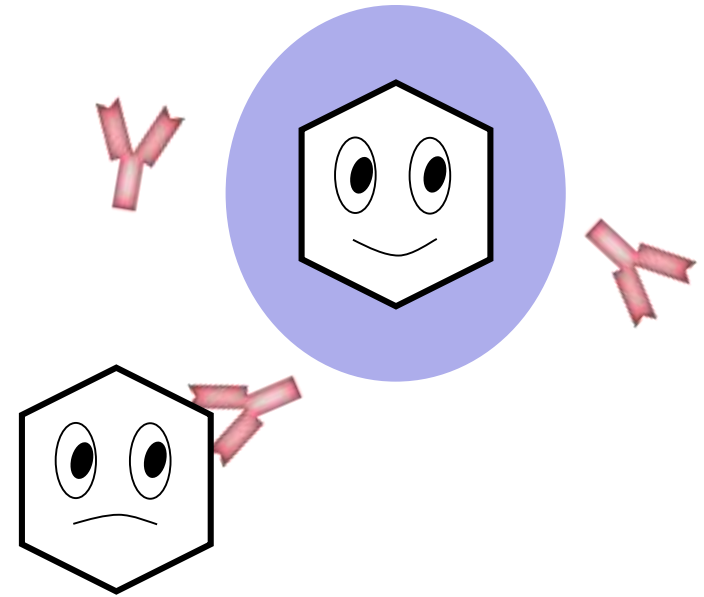
Limited *in vitro* neutralisation of naked particles (1-2 logs)

**Transmission cases by SD-Plasma
(anti-HEV present/likely in SD-plasma pools)**

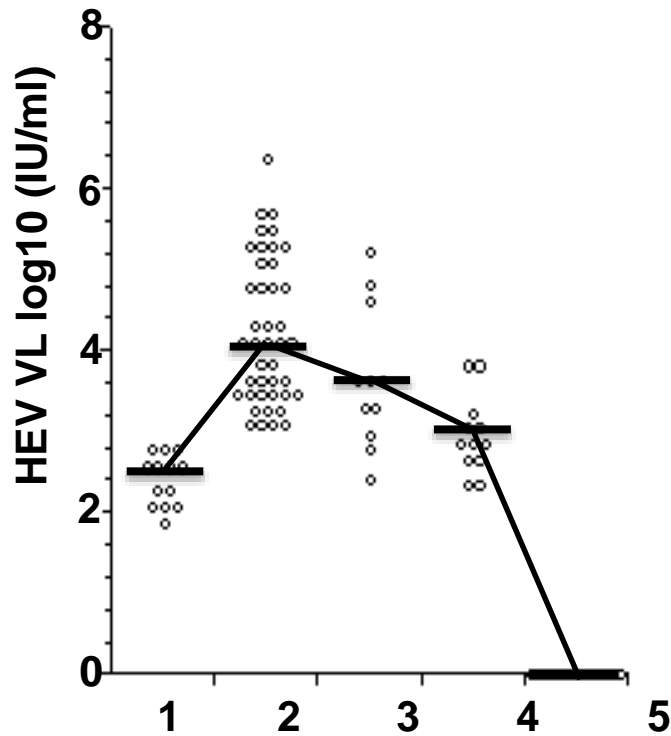
**Antibody titres decline in humans
(found for about 10 yrs after infection)**

**There are cases of human re-infections
(especially immunocompromised)**

- Do not expect too much from antibodies**



Viraemic RNA Concentration in plasma



Genoty pe	Virus strain	HEV RNA (copies/ml)
3a	HRC-HE104	1.6×10^7
3b	JRC-HE3	2.5×10^7
3f	RKI	1.3×10^6
4c	HRC-HE15	1.0×10^6

WHO
standard

NIID
standard

Baylis et al., 2013, EID

Viraemic loads for (worst case) risk assessments: 10^6 up to 10^7 /ml

HEV RNA in Plasma Pools

Source of pools	No. positive/ no. analysed
Europe	3/34
Europe/North America	0/3
North America	1/4
Middle East	0/11
Southeast Asia	4/23
Overall	8/75

8 (of 75) positive pools: HEV RNA 100- 1000 copies/ml

Baylis et al., 2013, Vox Sang

Simplified HEV Risk assessment:

A: HEV RNA in Plasma Pool: 1000 IU/ml

B: Plasma to produce a dose: 1-10l (product-specific)

C: HEV RNA per dose (A x B): 6-7 log₁₀ IU

D: ca 7000 IU HEV RNA can cause an infection

More than 4 to 7 log₁₀ HEV reduction capacity is needed.

Directive 2001/83 Article 115: *Member States shall take all necessary measures to ensure that the manufacturing and purifying processes used in the preparation of medicinal products derived from human blood or human plasma are properly validated, attain batch-to-batch consistency and guarantee, insofar as the state of technology permits, the absence of specific viral contamination....*

European Guideline EMA/CHMP/BWP/706271/2010: **An efficient virus inactivation/removal step (LRF 4, robust) for non-enveloped viruses has been required for plasma-derived medicinal products!**

How effective are the steps against HEV?

HEV Inactivation/Removal

Pasteurisation (10h, 60°):	similar to HAV?, product-specific Limited for albumin 2-3 log?
Dry heat treatment:	Effective for HAV. HEV?
20nm Nanofiltration:	product-specific effective removal expected/demonstrated
35-50nm Nanofiltration:	removal of HEV? product-specific
Ethanol fractionation steps:	virus-specific or unspecific? process/product-specific
Other purification steps:	process/product-specific
Low pH (pH4):	no inactivation

Outcome - Discussion

- **Clinical picture is evolving (frequently asymptomatic, risk groups)**
- **Many donations are positive (ca. 1:2000)**
- **Main risk from blood components**
- **Plasma pools are affected.**
- **Plasma products are (more or less) safe because of virus reduction (S/D plasma?)**
- **confirmation of HEV inactivation/removal is desired**
- **Write an Reflection Paper**

Aim of the reflection paper

1. Summarize current knowledge (report)
2. Request/encourage risk assessments
3. “Give guidance” for risk assessments
 - Infectious dose.
 - Virus input (epidemiology, viraemic titres, loads in plasma pools)
4. Encourage manufactures to perform more virus reduction studies
5. Identify „most risky“ product classes
6. Remind on effective reduction steps for non-enveloped viruses

Aim for publication August 2015 for 3 months consultation

Risk assessments?

Affected pools must be expected. Notification of affected specific pools may/will come...!

consider primarily products not including parvo-filters class of step

Do we need more virus validation data?

Yes, desired , encourage manufactures to proceed with investigations (investigational studies or formal validation data?)- For albumin?

Do we need warning statements for plasma-derived medicinal products?

lack of transmission is reassuring but need more investigations. Could be missing transmission because not looking. Need confirmation that understanding is correct that products are safe with respect to HEV.

Discuss SD-plasma:

(EP-Run control for plasma pool is **320 IU/ml**)

NAT testing has been required in the Ph. Eur. for SD plasma. Should this also be required for any other products?

Reflections:

- **No?, rather focus on effective state of the art virus inactivation/removal**
- **(NAT screening only an option for specific plasma-derivatives without sufficient HEV reduction)**

HEV: Safety approach relying on inactivation/removal only

Mitteilungen des Arbeitskreises Blut des Bundesministeriums für Gesundheit

Hepatitis-E-Virus

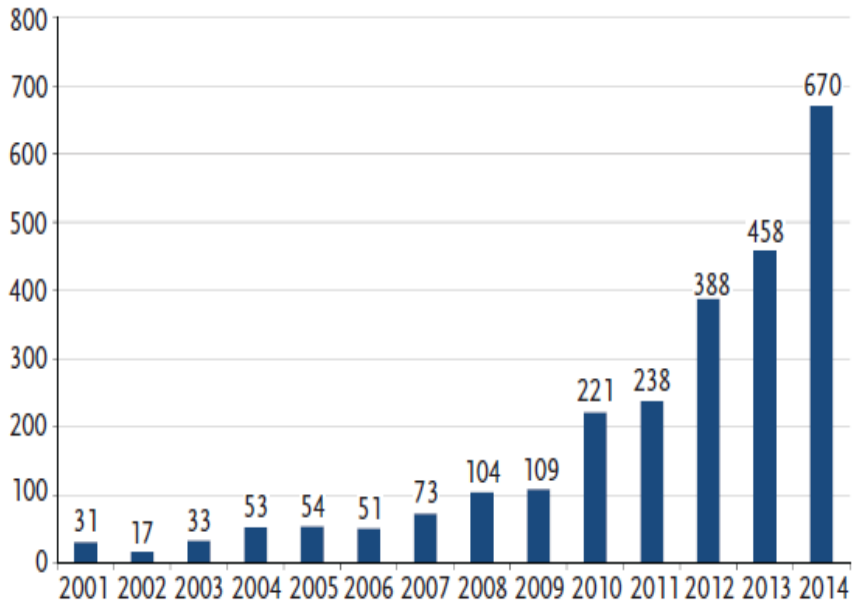
Stellungnahmen des Arbeitskreises Blut
des Bundesministeriums für Gesundheit

08.Okt 2014

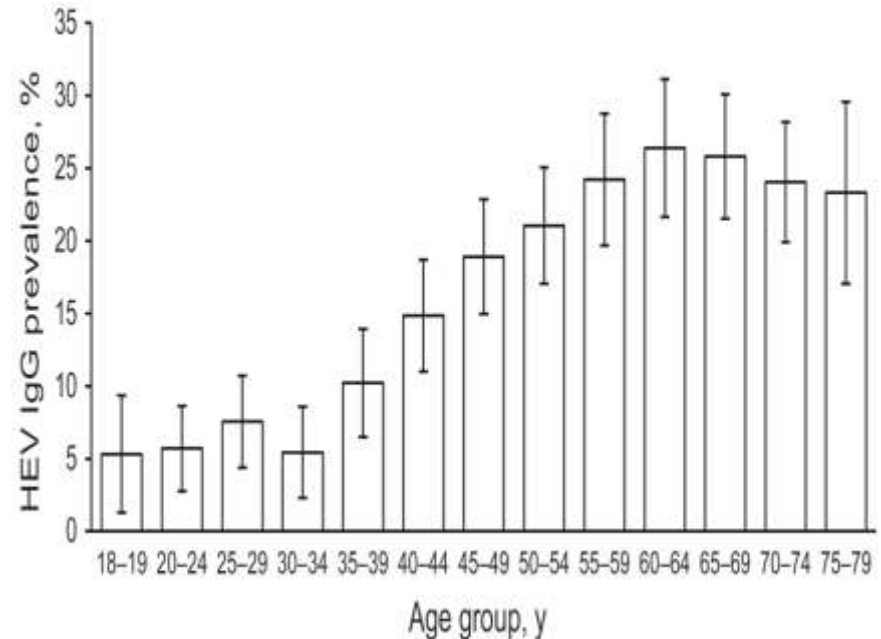
German version: Bundesgesundheitsblatt 58:198–218, 2015 · DOI
10.1007/s00103-014-2103-4.

English version : Transfusion Medicine and Hemotherapy, *in press*

HEV-Epidemiology in Germany



Notified cases in Germany
RKI, Epidem Bulletin 2015 no15
Increasing awareness?



Seroprevalence in Germany
Faber et al., 2012, Emerg Infect Dis 18:1654–1657

Ca. 320,000 infections (seroconversions) per year

Viraemic donations: 1:1.240 to 1:4.500

6 x 10⁶ blood components transfused in 2012

→ 4839 to 1333 affected blood components per year in DE?

For the screening of blood donations for HEV, the method of choice is at present NAT. A sensitivity of approximately 100 IU/ml HEV-RNA seems to be necessary to achieve a considerable reduction of HEV transmissions.

In principle, testing of all donated blood is possible, but this is not considered necessary because of the limited virulence of HEV for immunocompetent recipients of blood components.

However, HEV infections seem to pose a risk for heavily immunosuppressed patients according to previous findings, especially for patients following allogeneic stem cell and organ transplantation. These patients would potentially benefit from a provision of HEV RNA-negative blood components.

Research is needed regarding the extent to which an introduction of NAT for the screening of blood donations could reduce the risk of infection and disease in immunosuppressed transplant recipients.

Regardless of the risk of transmission of HEV by blood components, it has been recommended to continuously monitor immunocompromised patients, especially transplant recipients with regard to HEV infections.

Thank you!