EUROPE'S NEW HEPATITIS PROBLEM

Many get infected with hepatitis E, and a few get very sick. How can the virus be stopped?

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Onderzoeker, Erasmus MC

UNIVERSITAIR ZIEKENHUIS ANTWERPEN

UZA

kennis / ervaring / zorg

Scheme

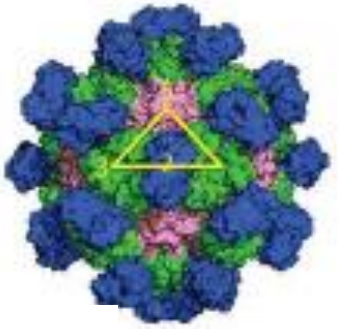
- HEV virology
- HEV (sero)-epidemiology

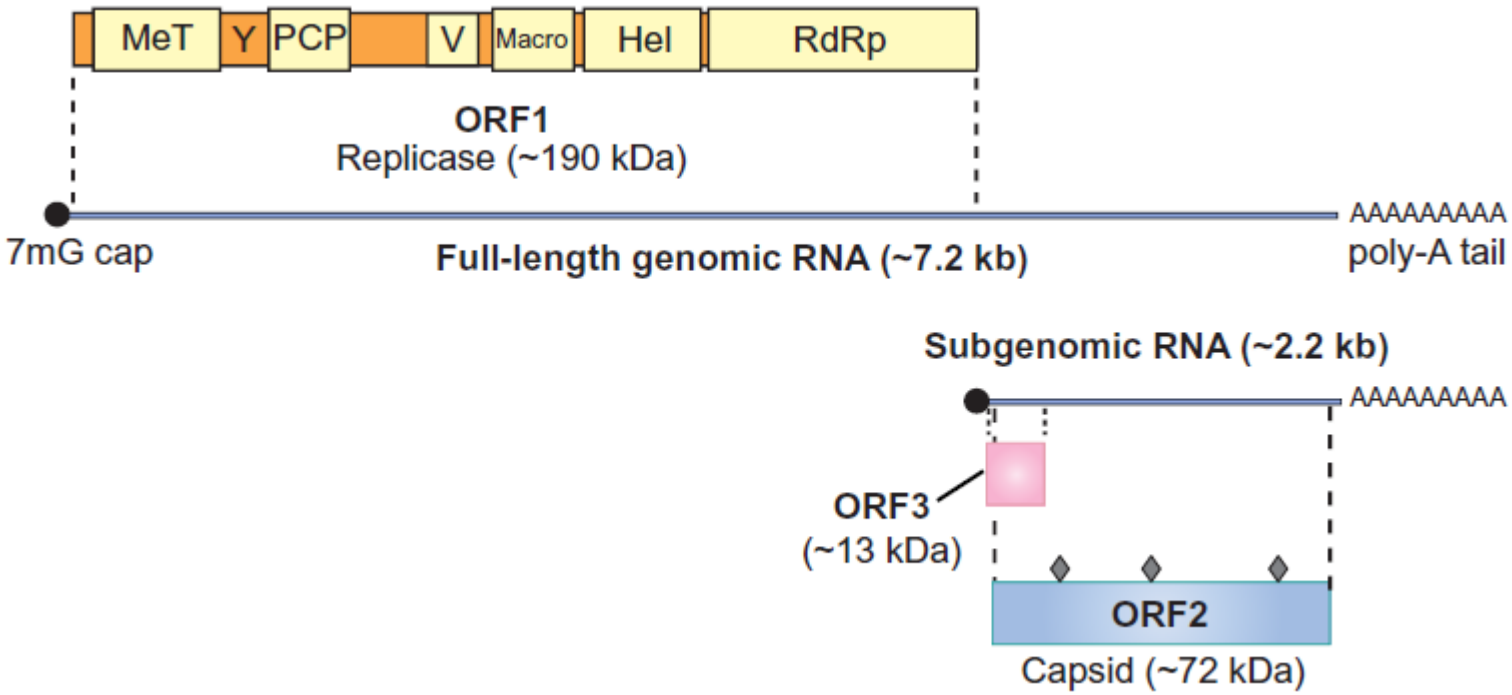
- HEV clinical presentation – treatment
  - HEV clinical cases- diagnosis

- HEV animal reservoirs- zoonotic risk
- HEV experimental models

Hepatitis E virus and the global disease burden

- Nonenveloped +sense single stranded RNA virus (27-34 nM)
- Family *Hepeviridae,* Genus *Orthohepevirus*
- 3 ORF





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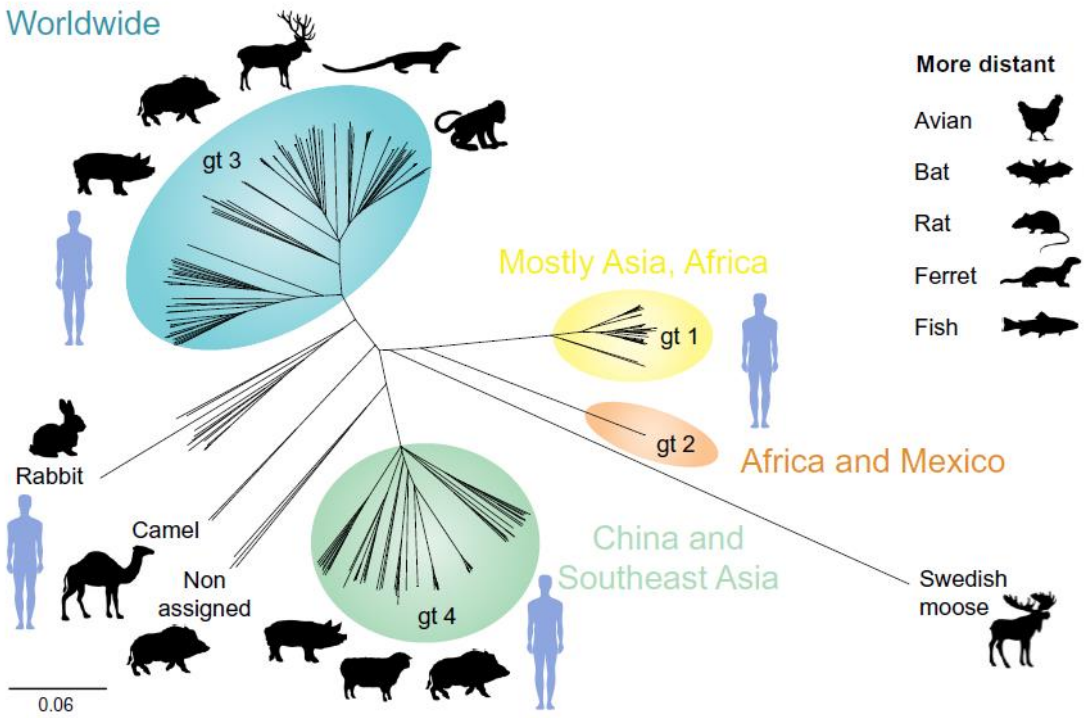
Aggarwall R, Hepatol 2011; Debing Y. J Hepatol 2016

Hepatitis E virus and the global disease burden

- 4 major genotypes:
  - 1+2 restricted to humans
  - 3+4 broad host range (zoonotic)



Aggarwall R, Hepatol 2011; WHO 2014, Debing Y J Hepatol 2016

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Hepatitis E virus is emerging

- Seroprevalence :
  - Overall↓ until 2011 (Germany and the Netherlands)
  - ↑ young (largely unexposed) adults

- ↑ HEV RNA positive blood donations in the Netherlands
  - Oct 2012 – Mar 2013 **1:2742**
  - Apr 2014 – Sep 2014 **1:611**

Hogema BM, Transfusion 2014, Wenzel JJ, Hepatol 2014, Zaaijer HL, Hepatol 2015

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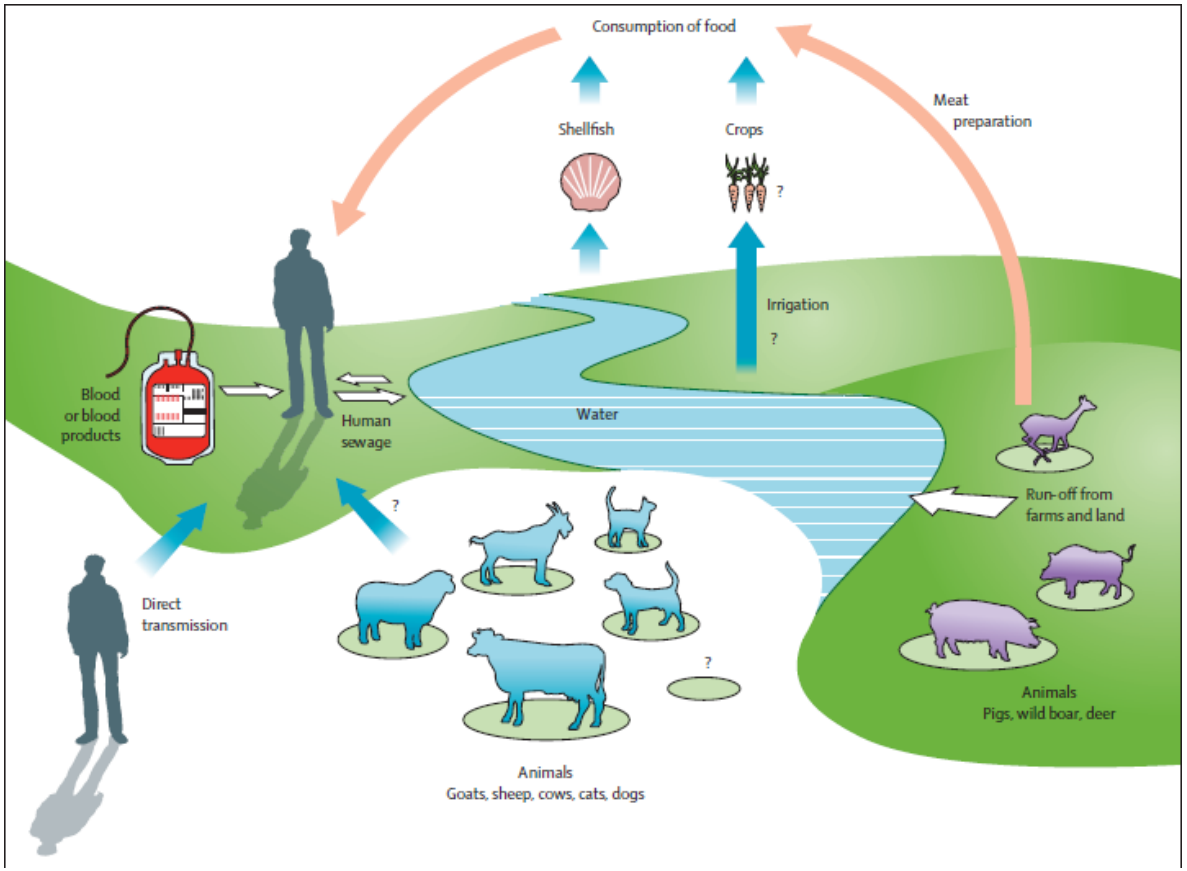
HEV Transmission

Transmission mainly via fecal-oral route



Lancet June 30, 2012
Van der Poel. Curr Opinion Virology 2014

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Sero-epidemiological surveys in Europe/US

Acute Fulminant HEV

US: zeldzaam (0,4%), totale ALI

Meer frequent in HEV gt 1 infecti

Acute on Chronic LF/ Decompensate

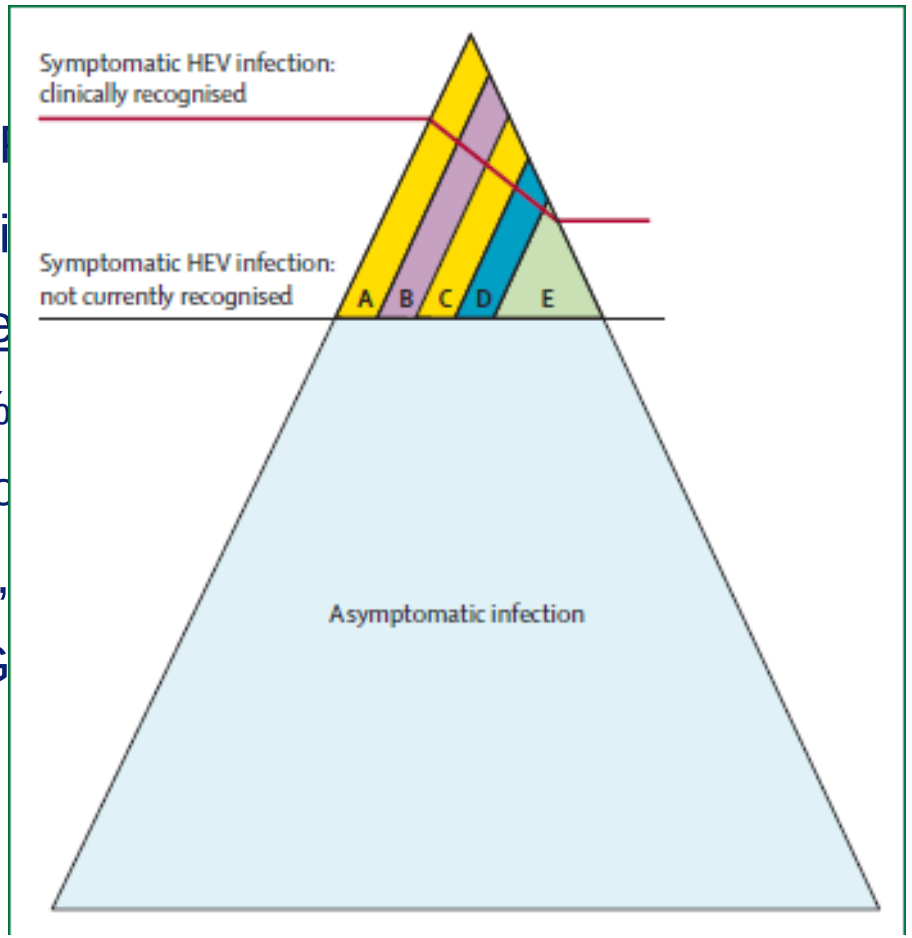
Prospective UK/French series: 3,2%

8 yr Retrospective Single Center (Tc

Acute alcoholic hepatitis: 3,6% (total,

Chronic liver disease: 21% HEV IgG

DILI: 3% HEV IgM+ (total n= 318)



Hepatol 2016 May 23. Lancet June 30, 2012. JVH 2007, 14, 298. Liv Int 2015;35:870. AP&T 2015;42:574. Eur J Gastroenterol Hepatol 2016. Gastro 2011;141:1665.

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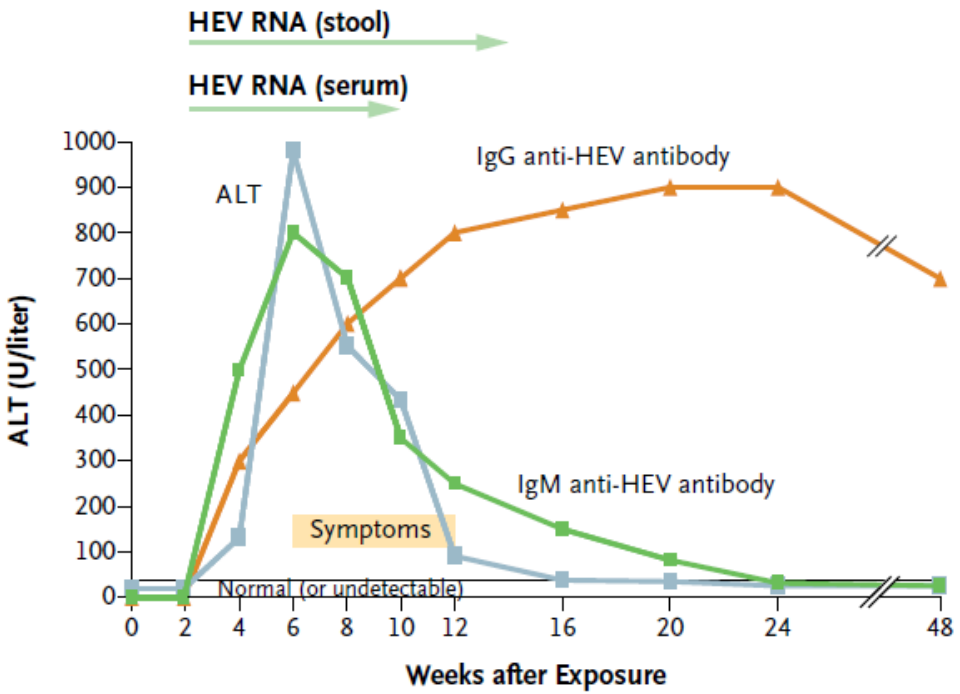
Scheme: HEV Zoonosis

- HEV virology
- HEV (sero)-epidemiology

- HEV clinical presentation – treatment
  - HEV clinical cases- diagnosis

- HEV animal reservoirs- zoonosis
- HEV experimental models

Classical acute HEV (gt 1/2/3/4)



40 cases of autochthonous

Symptom/frequency	Symptom/frequency
Jaundice $n=30$	Pruritis $n=4$
Anorexia $n=15$	Weight loss $n=3$
Malaise/lethargy $n=15$	Headaches $n=3$
Abdominal pain $n=14$	Back pain $n=2$
Nausea $n=13$	Arthralgia $n=2$
Fever/chills $n=8$	Rash $n=1$
Vomiting $n=7$[a]	Paraesthesiae $n=1$[b]
Myalgia $n=5$	No symptoms $n=2$

NEJM 2012. Eur J Gastroenterol Hepatol 2008,20:784

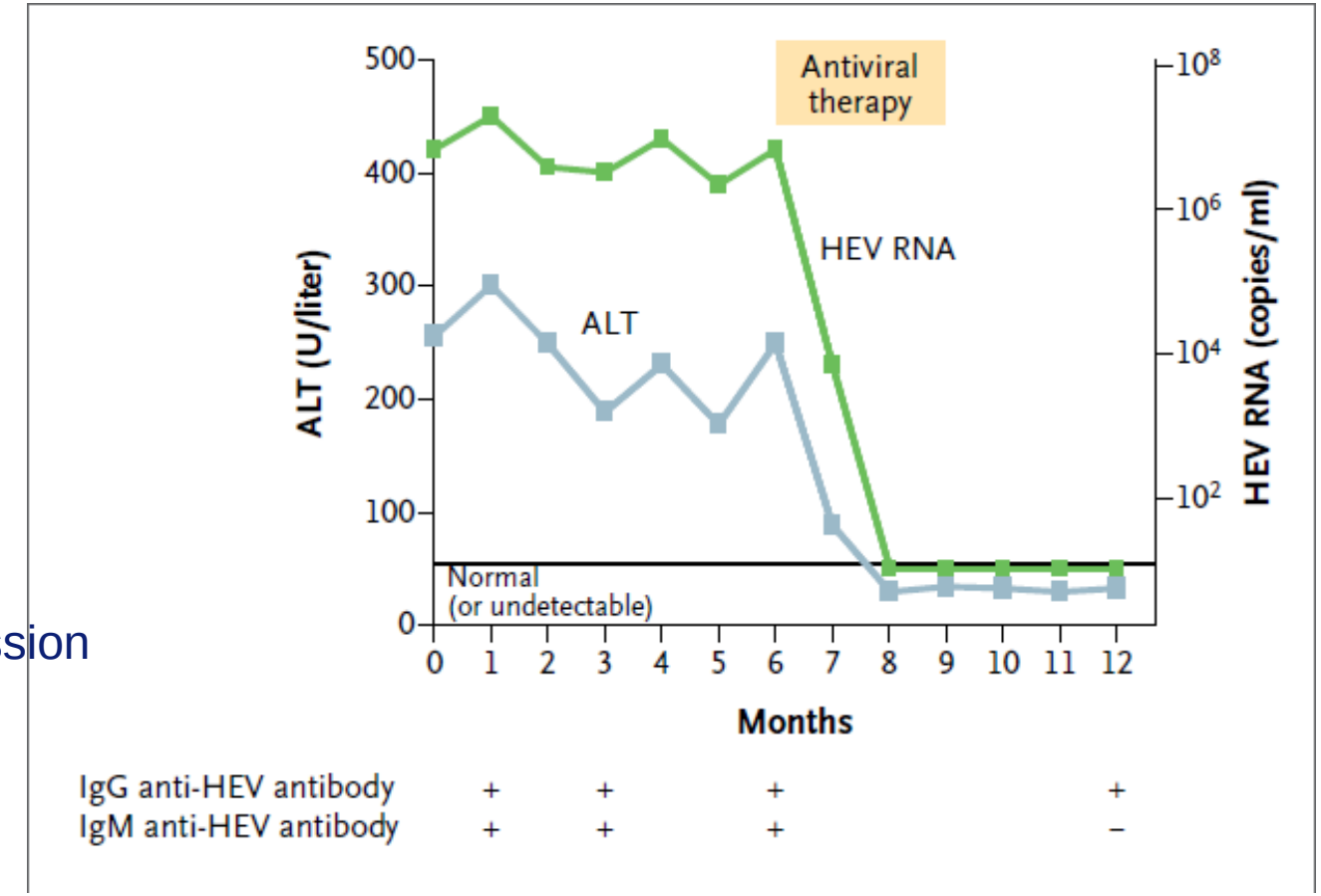
Chronic HEV genotype 3

Chronicity rate= 65,9% in SOT recipients (n=65/85)

HIV
SOT
BMTx
Cancer chemotherapy

“Immunocompetent” :
immune suppressive R/
undefined CD4 defect

-> Rapid fibrosis progression



NEJM 2012, Blood 2013;122:1079
GASTROENTEROLOGY 2011;140:1481 ; Hepatology 2014,60 (3).

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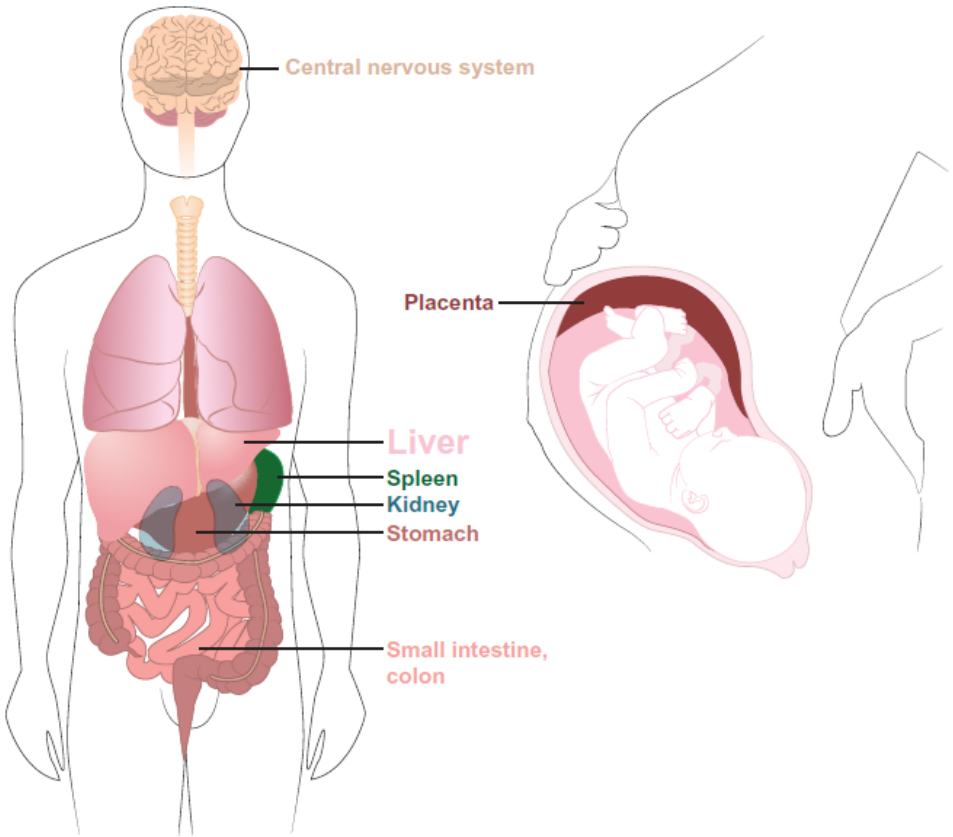
Extrahepatic manifestations



Neurological: (~100 cases)
Guillain-Barre
Brachial neuritis
Meningo-encephalitis

Kidney disease:
glomerulonephritis
± cryoglobulinemia

Replication vs HEV RNA Detection?
Animal models
Seldom HEV negative strand PCR (Placenta)

J Hepatol 2016 ;65:200. Liv Int April 2016. Lancet Infect Dis 2014;14:678-679

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Treatment for chronic HEV

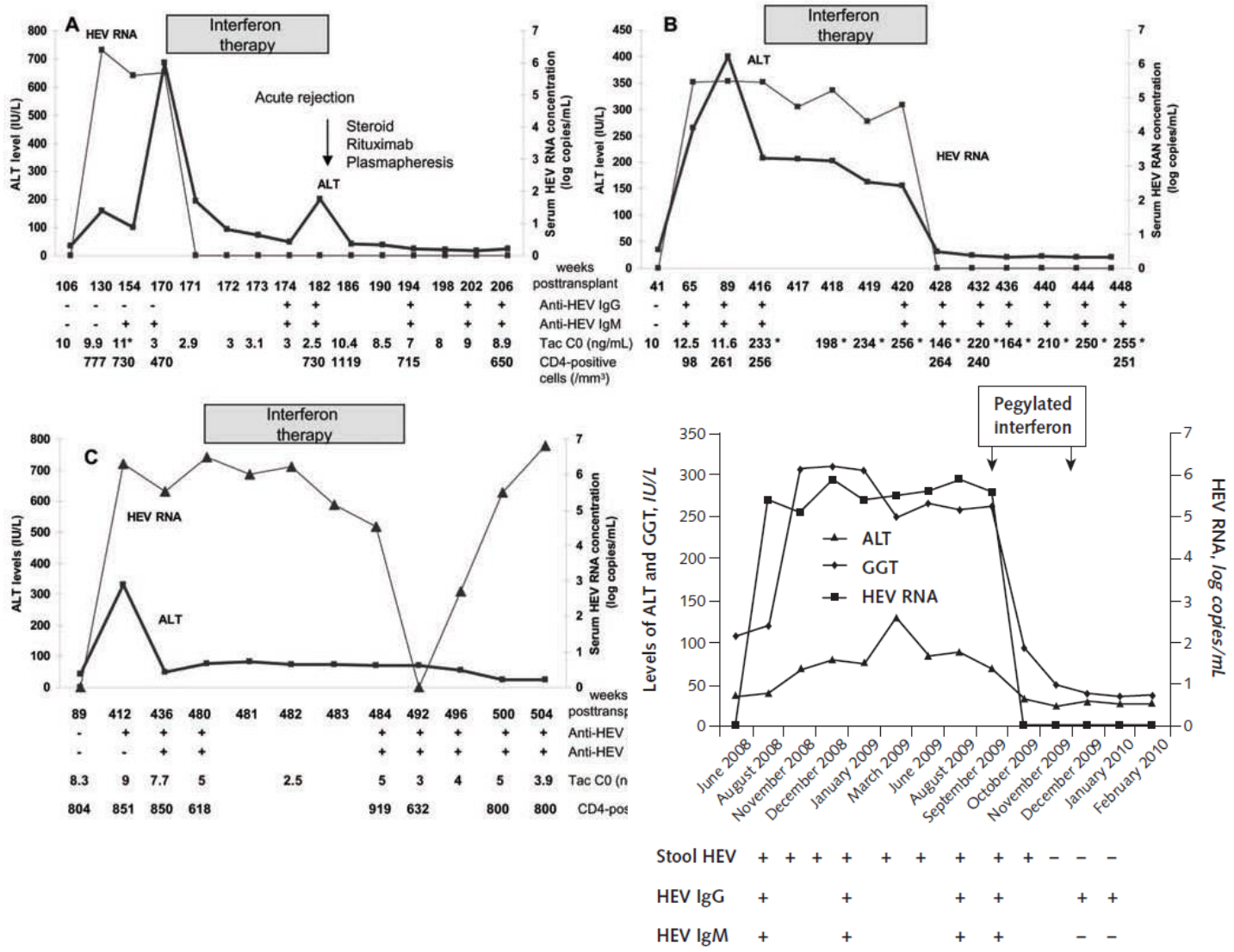
Reduction of immune suppression --> successfull in 32,1%

Table 1. Overview of approved drugs affecting hepatitis E virus (HEV) replication.

Drug	*In vitro* effect	*In vivo* effect	Mechanism of action
Ribavirin	Inhibition of HEV replication	HEV clearance in chronic hepatitis E; occasional cases of treatment failure	Intracellular GTP depletion through inosine 5'-monophosphate dehydrogenase inhibition
PegIFNα	Inhibition of HEV replication	HEV clearance in chronic hepatitis E	Immune activation
Sofosbuvir	Inhibition of HEV replication	Unknown	Nucleotide analog; inhibition of the viral RNA-dependent RNA polymerase
Mycophenolic acid (including prodrug mycophenolate mofetil)	Inhibition of HEV replication	Unclear, possibly associated with HEV clearance in chronic hepatitis E	Intracellular GTP depletion through inosine 5'-monophosphate dehydrogenase inhibition; immune suppression
mTOR inhibitors (rapamycin, everolimus)	Stimulation of HEV replication	Higher HEV RNA levels in patients with chronic hepatitis E on mTOR inhibitors	Inhibition of an eIF4E binding protein 1-dependent antiviral signaling pathway downstream of mTOR
Calcineurin inhibitors (cyclosporin A, tacrolimus)	Stimulation of HEV replication	Unknown; tacrolimus use associated with increased risk of viral persistence	Inhibition of cyclophilin A and B

Gastro 2011;140:1481 . J Hepatol2016 vol. 65:200–212

Treatment PegIFN?



3-month course
LTX n=3
135 µg/week
2 clear
1 relapse

Leukemia n=1
PegIFNα2b 1 µg/kg BW/week

2 rapid response
2 slow response

Not in KTX

Clin Infect Dis 2010;50:e30-33.
Ann Int Med 2010

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RBV for chronic HEV

Retrospective series (n=59)

- Median 3 months
- Median dose: 600 mg per day (upto 1200mg), ~ 8,1mg/kg
- EOT= 95%
- “SVR24 wks” =78%

~ weight based RBV (12 mg/kg): 1000 mg vs 1200 mg (anemia!)

Prediction of response: monitor HEV RNA in stool

- + @ 1 month in 100% of relapsers
- + @ 3 months in 66% of relapsers vs 0% of responders

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CID 2015;60(1):96–9. N Engl J Med 2014;370:1111. Ann Intern Med. 2010;153(2):85

UZA case 1: HTx recipient; feb 2014

UZA case 2: HTx + KTx recipient; 2016

Creatinine		+ 2.29	+ 2.30	+ 2.27	+ 2.02	+ 2.14	+ 2.30
eGFR CKD-EPI		- 28 *	- 28 *	- 28 *	- 32 *	- 30 *	- 28 *
Ureum		+ 71	+ 85	+ 96	+ 96	+ 102	+ 98
Natrium		142	141	139	142	141	141
Kalium		4.9	+ 5.2	4.6	4.7	4.5	4.2
CRP (mg/L)		+ 10.1	+ 12.3	+ 13.4	+ 12.3	+ 8.4	+ 5.2
LDH		209	199	+ 283	+ 271	+ 249	231
AST (GOT)		12	13	22	+ 42	+ 45	+ 41
ALT (GPT)		23	25	+ 64	+ 142	+ 156	+ 126
Alk. fosfatase		103	+ 127	+ 173	+ 204	+ 179	+ 173
Gamma-GT		+ 284	+ 422	+ 761	+ 997	+ 1005	+ 951
Tot. bilirubine		1.2	1.2	+ 1.5	0.99	0.99	0.79
Geconjugeerde bilirubine		+ 0.43	+ 0.50	+ 0.68	+ 0.50	+ 0.47	+ 0.38
Ongeconj. Bilirubine		0.77	0.7	0.82	0.49	0.52	0.41

HEV PCR (WIV) + : 1/7 ; 23/8 en 26/9
HEV serology : IgG+ en IgM+ 1/7

Start RBV

HEV infectie april-juni '16

Start RBV on 10/10

HEV RNA 1,30 E6 IU/mL (2/11) < 4,76 E7 IU/mL (7/10)

RBV monitoring (Nijmegen): 1.01 mg/L. (2-3 mg/L)

RBV monitoring (Nijmegen): 1.07 mg/L

HEV PCR-Juni 2015

UZA case 3: KTx recipient; 2016

uitgevoerde test		03/11/2016 08:40	25/10/2016 08:15 ^	28/09/2016 08:10 ^	13/09/2016 08:10 ^	11/08/2016 10:00 ^	26/07/2016 >>08:20<< ^	19/07/2016 08:10 ^	24/05/2016 08:20 ^
ED									
LGEMENE BIOCHEMIE									
Creatinine	>	+ 1.44	+ 1.28	+ 1.39	+ 1.40	+ 1.48	+ 1.45	+ 1.60	+ 1.28
eGFR CKD-EPI		- 50 *	- 58 *	- 52 *	- 52 *	- 49 *	- 50 *	- 44 *	
Ureum	>		33	39	36	38	38	46	34
Natrium	>		141	141	140	141	143	142	142
Kalium	>	4.4	4.1	4.8	4.0	4.2	4.3	4.5	4.0
Chloride	>		106	105	106	+ 108	+ 110	+ 108	106
Bicarbonaat			30	29	29	29	27	29	27
Anion gap (berekend)	>		- 5 *	7 *	- 5 *	- 4 *	- 6 *	- 5 *	9 *
Calcium (mmol/L)	>		2.32	2.48	2.23	2.44	2.35	2.38	2.27
Fosfaat (mmol/L)	>		1.03	1.10	0.93	0.92	1.07	1.05	0.97
Product Calcium*Fosfaat (bereke			2.4	2.7	2.1	2.2	2.5	2.5	2.2
Magnesium in serum (mmol/L)	>		- 0.61	0.66	- 0.55		- 0.61		
Urinezuur			5.8 *	5.3 *	5.8 *	6.3 *	6.9 *	7.2 *	5.9
CRP (mg/L)	>		+ 3.7	+ 18.9	<2.9	<2.9	<2.9	<2.9	<2.9
Tot. proteinen (g/L)	>		72	69	71	69	66	68	68
Albumine (g/L)	>		42	38	38		38	37	39
Glucose (serum)	>		+ 103	+ 101	97		91	98	94
LDH			199	222	185	181	184	205	
AST (GOT)			+ 47	34	+ 64	+ 57	+ 55	+ 49	
ALT (GPT)	>		+ 96	+ 63	+ 145	+ 121	+ 120	+ 91	31
Alk. fosfatase	>		+ 213	+ 281	+ 185	+ 173	+ 181	+ 171	
Gamma-GT	>		+ 329	+ 313	+ 299	+ 273	+ 324	+ 303	+ 117
Lipase	>		286	201	203	200	215	198	
Tot. bilirubine	>		0.77	1.0	0.94	1.0	0.60	0.83	
Geconjugeerde bilirubine	>		+ 0.28	+ 0.38	+ 0.33	+ 0.30	0.20	+ 0.23	
Ongeconj. Bilirubine			0.49	0.62	0.61	0.7	0.4	0.6	

HEV PCR (WIV) + : 11/8 en 12/10
HEV serology : IgG- en IgM+ 11/8

HEV RNA 5,32 E+6 IU/ml (12/10)

HEV infectie
mei-juli ’16
HEV PCR-
Jan 2016

Chronic HEV diagnosis UZA

Immune compromised patient with consistent ALT rise >1 month:

- HEV PCR (qualitative) (WIV)

→ Voorgedefinieerde DOTS test

(ism Veerle Matheeussen, Microbiologie UZA)

- HEV serology: (WIV Recomline --> Wantai)
  low NPV, to be combined with HEV PCR

Voedingsadviezen voor transplant pt

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Levertransplantatiecentrum › Nieuws › Voorlopig geen leverworst of paté

Nieuwsoverzicht

Archief

Voorlopig geen leverworst of paté

Print

22 juni 2016

Vanuit Sanquin is voorgesteld om het dieetadvies van orgaan- en allo-stamcel-transplantatiepatiënten uit te breiden met het advies om voorlopig geen leverworst of paté te eten in verband met risico's op hepatitis E infecties.

De onderbouwing hiervoor vindt u hieronder en verdere informatie kunt u vinden in de publicatie van Nijskens et al. Journal of Clinical Virology 74 (2016) 82–87

Merendeel leverworsten HEV RNA+
Cfr Figatellu Corsica/Zuid-Frankrijk

Scheme: HEV Zoonosis

- HEV virology
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- HEV clinical presentation – treatment
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- HEV animal reservoirs- zoonotic risk
- HEV experimental models

Zoonotic Risk? Animal Reservoirs?

Natural animal host	Classification (genus/species, genotypes [gt])	Experimental hosts for cross-species infection	Zoonotic infection in humans
	Orthohepevirus A		
Human	gt 1, 2, 3, 4	Non-human primates, pigs (gt 3, 4), rabbits (gt 1, 4), lambs (gt 1), Wistar rats (gt 1)	
Domestic swine	gt 3, 4	Non-human primates, rabbits, Mongolian gerbils (gt 4), Balb/C mice (gt 4)	Yes
Wild boar	gt 3, 4, 5, 6		Yes (gt 3, 4), likely (gt 5, 6)
Deer	gt 3		Yes
Rabbit	gt 3	Pigs	Likely
Mongoose	gt 3		Likely
Camel	gt 7		Yes
Moose	unknown		Not known
	Orthohepevirus B		
Chicken	Avian HEV gt 1, 2, 3	Turkeys	No
	Orthohepevirus C		
Rat			Unlikely
Ferret			Unlikely
Greater bandicoot			unlikely
Asian musk shrew			unlikely
Mink			unlikely
Bat	***Orthohepevirus D***		No
Cutthroat trout	***Piscihepevirus***		No

PLOSPathog2016

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Restricted Enzooticity of Hepatitis E Virus Genotypes 1 to 4 in the United States[▽]

CDC study

N= 4936 dieren (35 genera)

457 HEV IgG+:

Bizon (4,3%), Runderen (15%), Honden (0,9%), Ratten (0,6%)

Varkens (41,2%), Wilde zwijnen (2,9%)

Alleen hoge titers bij varkens (HEV gt3)

J Clin Microbiol 2011

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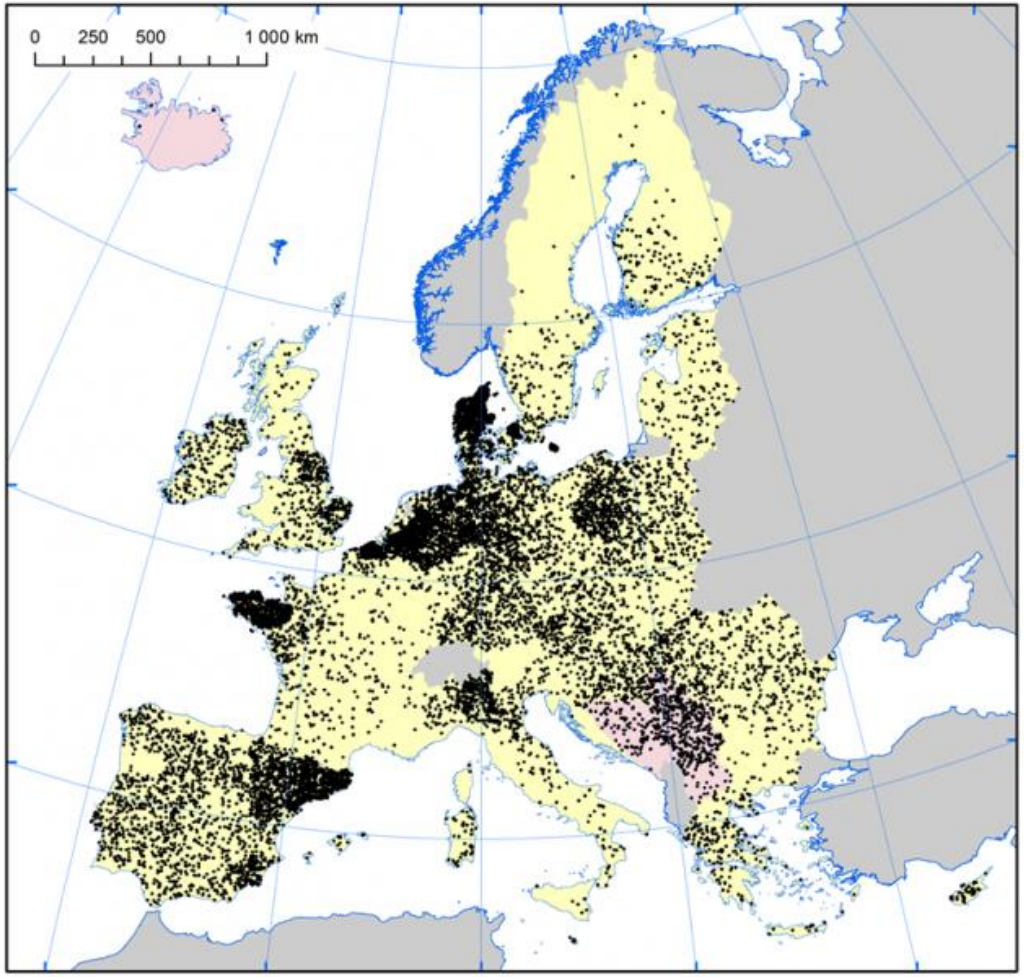
Zoonotic Risks in Belgium: “Pig Belt”



Number of sows by region (2013) - Source: Eurostat

- Overall 70% of fatteners HEV RNA+
- serum HEV RNA- within 1 month, but ongoing fecal secretion
- infection of newborn pigs

→True pig reservoir

Belgium (2010): slaughterhouse
→ 5/23 farms HEV RNA+
→ 8/115 (7%) HEV RNA+

BMC Res Notes, 2012. PLOS one 2011

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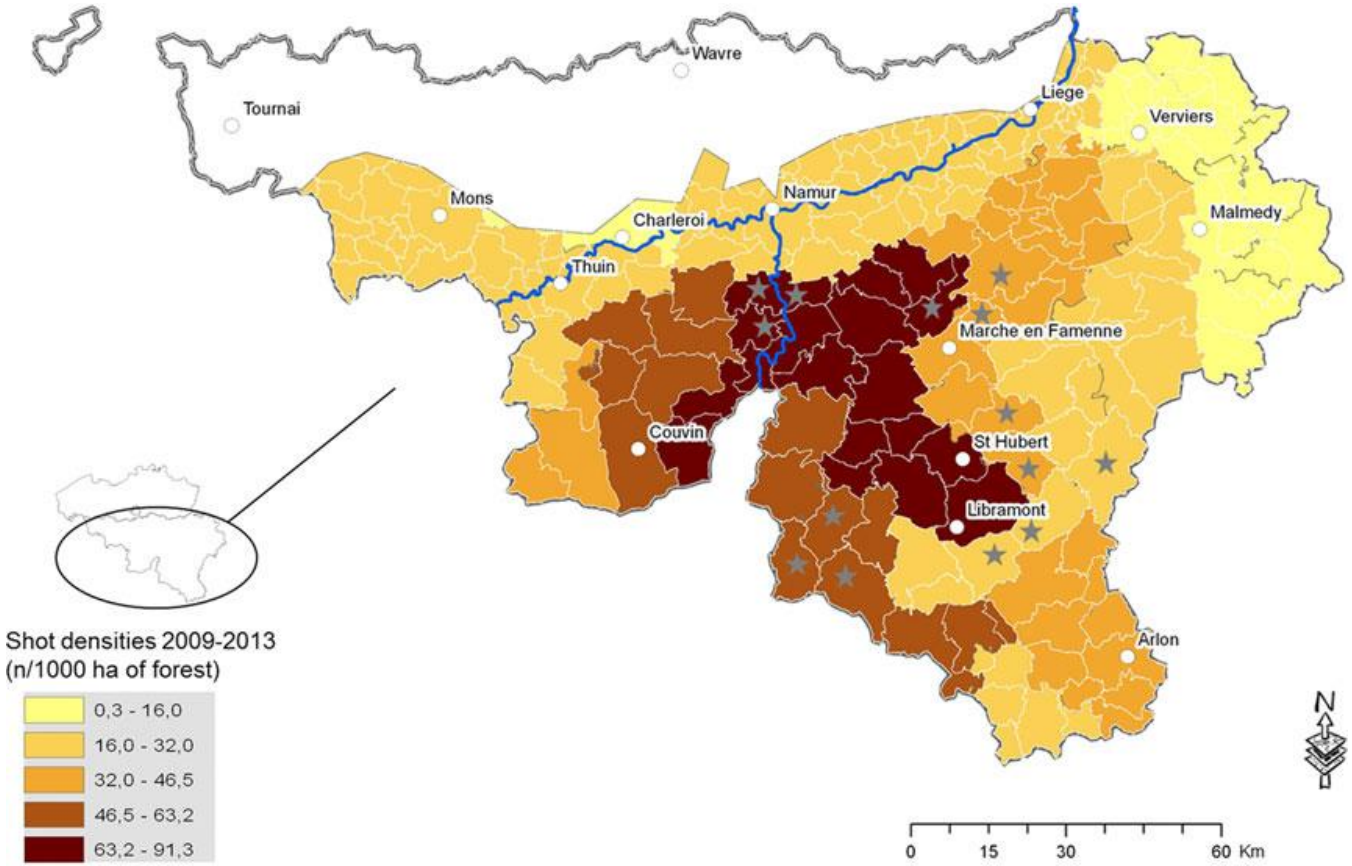
Zoonotic Risks in Belgium: … and Wildlife



- Wild Boar: 34% HEV IgG+
- Deer : 1-3% HEV IgG+

Wild boar density shot per region (2009-2013)

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Transboundary and Emerging Diseases. 2015

HEV experimental models

- In vitro, infection of various cell lines
- In vivo, acute HEV infection in pigs, ferrets, chimpanzee, and rhesus monkeys
- Recently, in vivo, chronic HEV infection in human-liver chimeric mice
  - uPA$^{+/+}$NOG (van de Garde et al. JVI 2016)
  - uPA$^{+/+}$SCID/beige (Alweiss et al. J Hepatol 2016)
  - uPA$^{+/+}$SCID (Sayed et al. Gut 2016)

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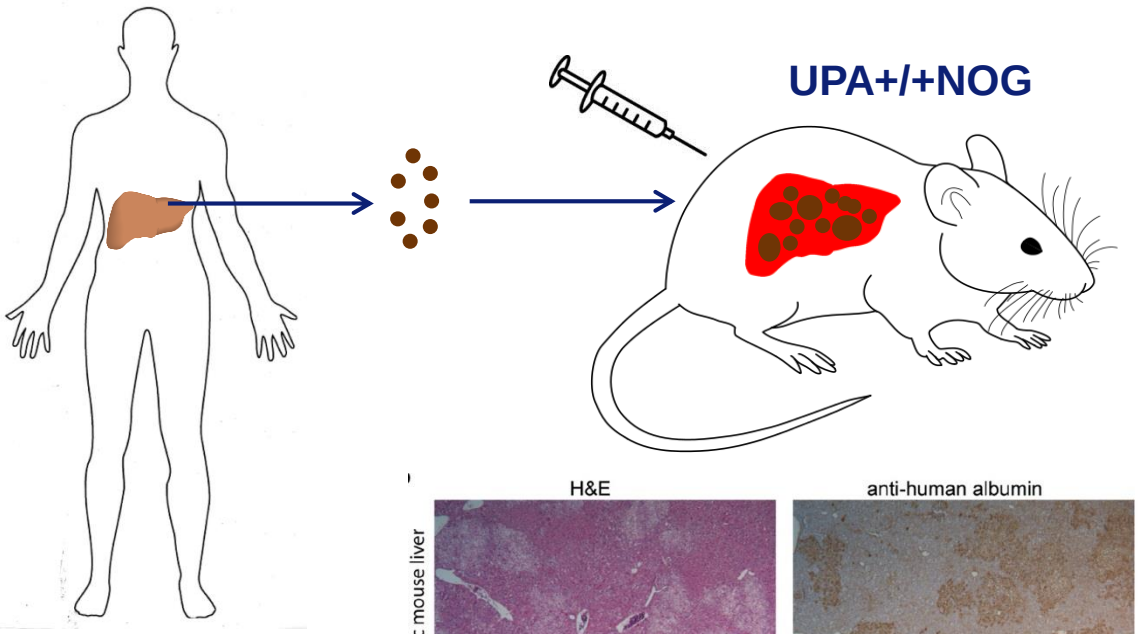
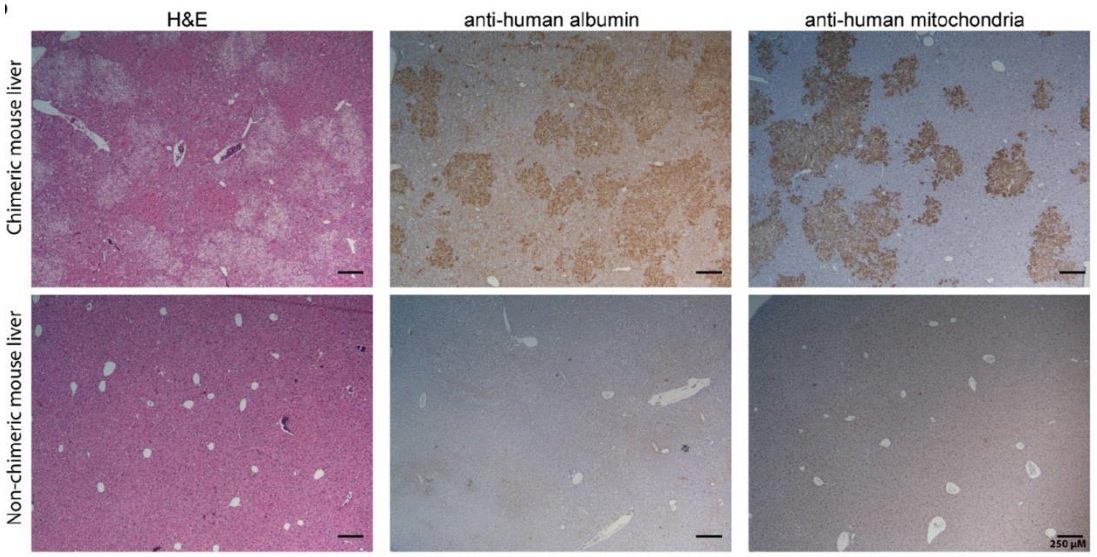
Principle of human liver chimeras





Vanwolleghem T, Gastroenterology, 2007; Vanwolleghem T, Hepatol 2008; Vanwolleghem T, J.Hepatol, 2010; Bissig KD, J Clin Invest, 2010; Lucifora J, Science, 2014; Giersch K, J Hepatol, 2015;

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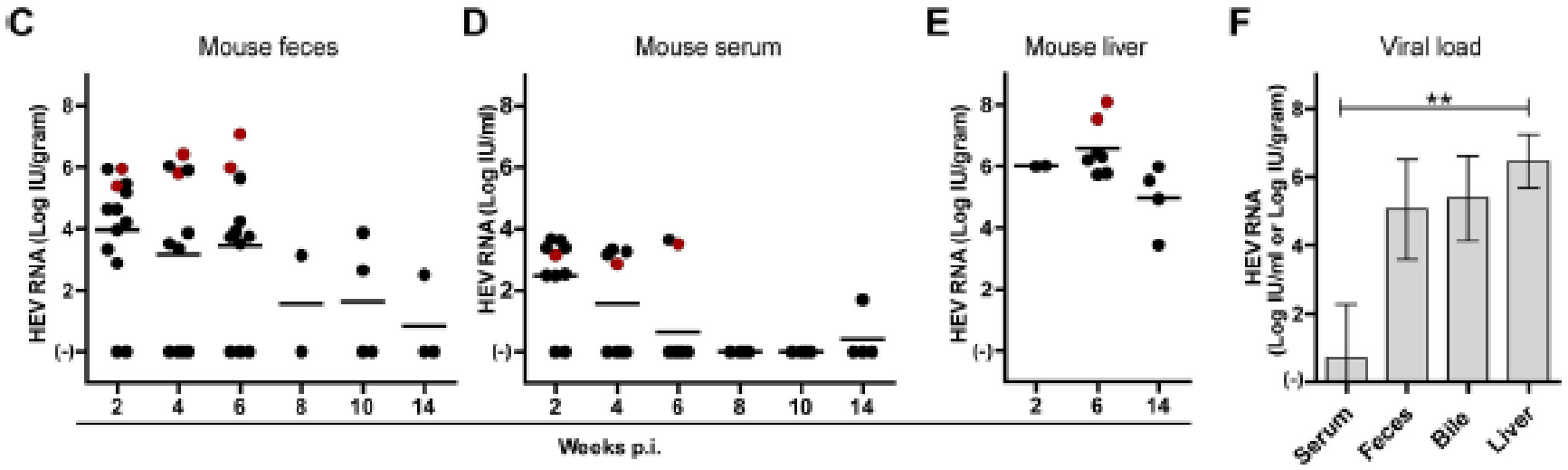
HEV gt3 infection of human-liver chimeric mice

- Infection with HEV gt3 derived from feces and liver but not from plasma/serum



Van de Garde et al. JVI 2016

Conclusion: HEV

- HEV gt 3 emerging in Europe
- Acute, mostly asymptomatic in immunocompetent
- Possible chronic in immunocompromised
- Viral hepatitis serology may be negative --> PCR
- Treat with RBV
- Uncooked pork meat, seafood, leverworst/paté
  - In Belgium: Deer safer than Wild Boar?
  - Many issues on food safety remaining

- Preclinical models for infectivity and antiviral studies

Ackowledgements

Division of Viral Hepatitis, CDC, USA

Department of Molecular and Comparative Pathobiology, The Johns Hopkins University School of Medicine, USA

Erasmus MC Fellowship 2011

Erasmus MC Pilot Grant 2015

Stichting tegen Kanker

Questions?

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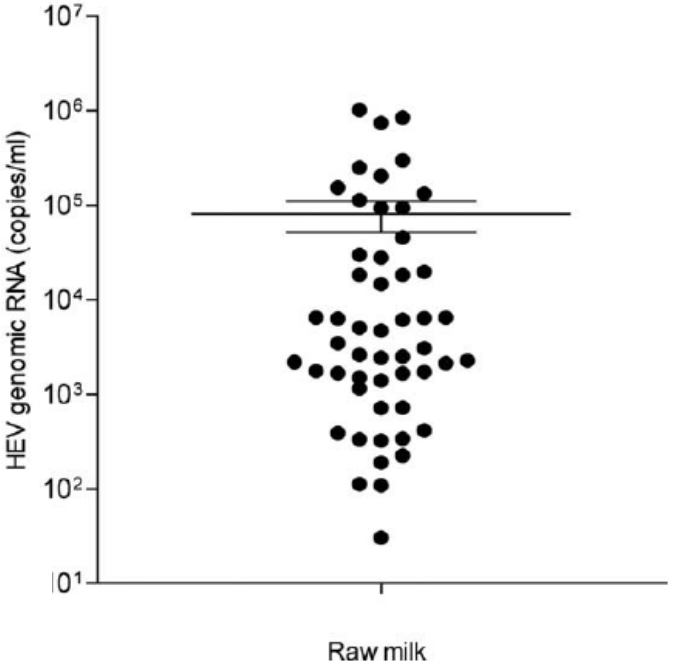
Excretion of Infectious Hepatitis E Virus Into Milk in Cows Imposes High Risks of Zoonosis

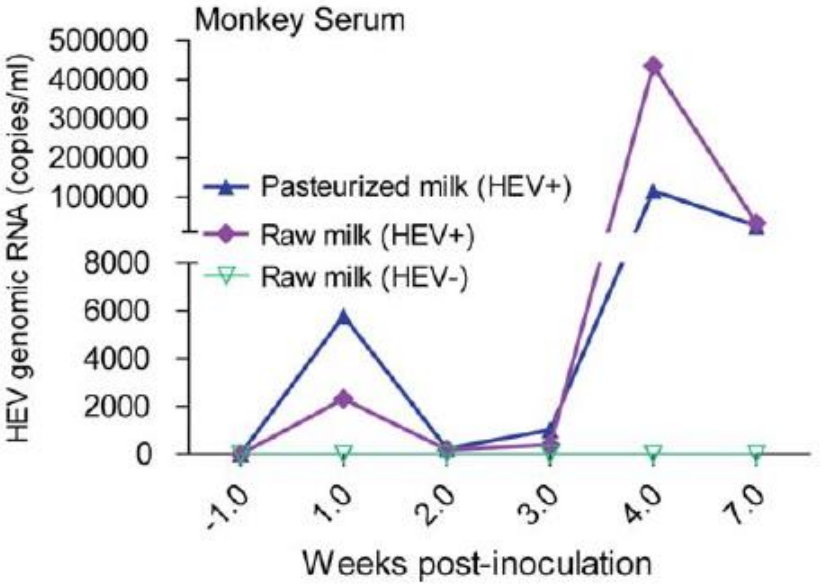
HEV gt 4 RNA in Feces (37,1%), bloed en melk (Yunnan, China)

Transmissie nr Rhesus monkey (gavage):

Pasteurisatie (30’ 62°C of 72°C): onvoldoende

Koken (3’ 100°C) = sterilizatie





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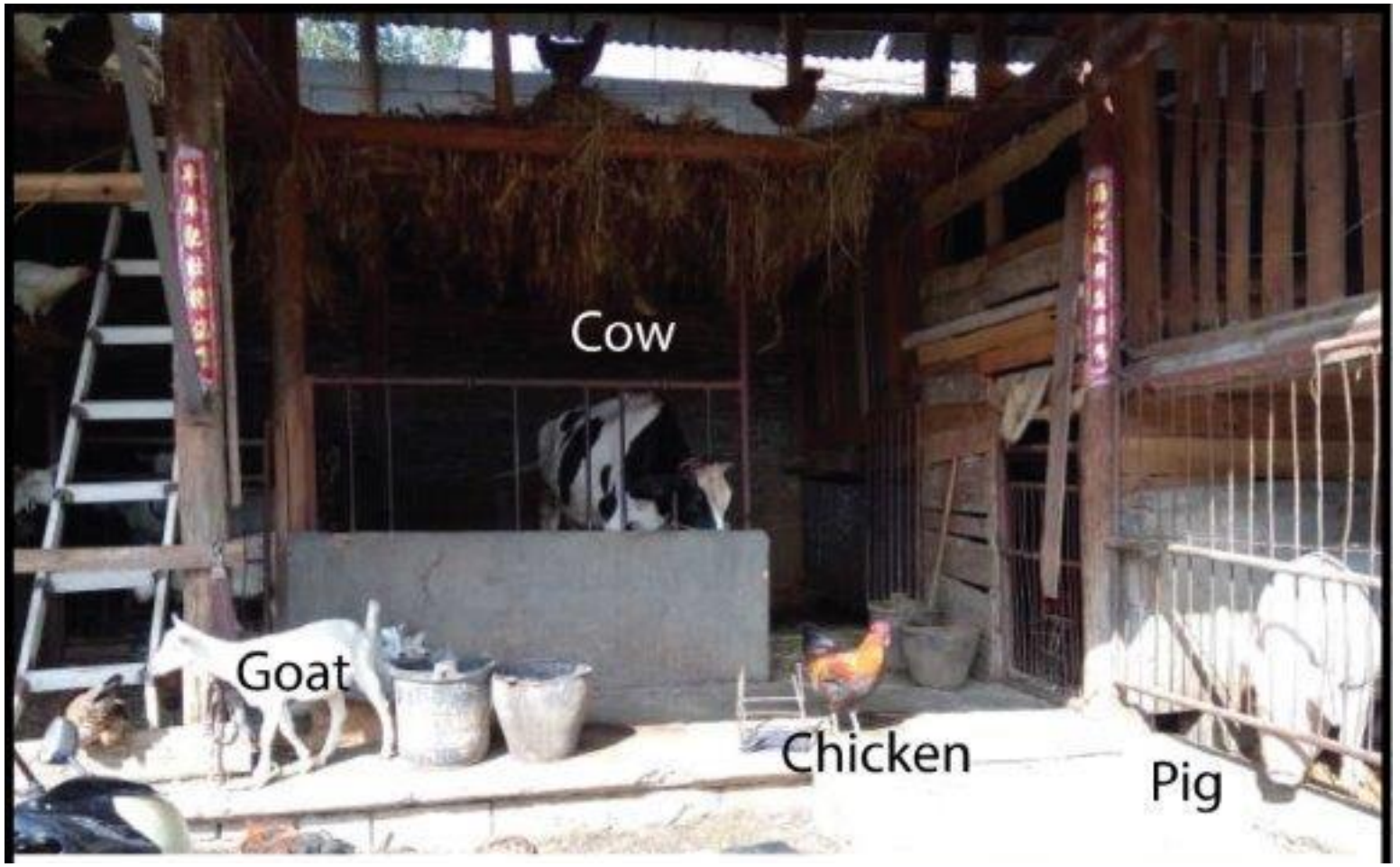
Rural China: Mixed Farming



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