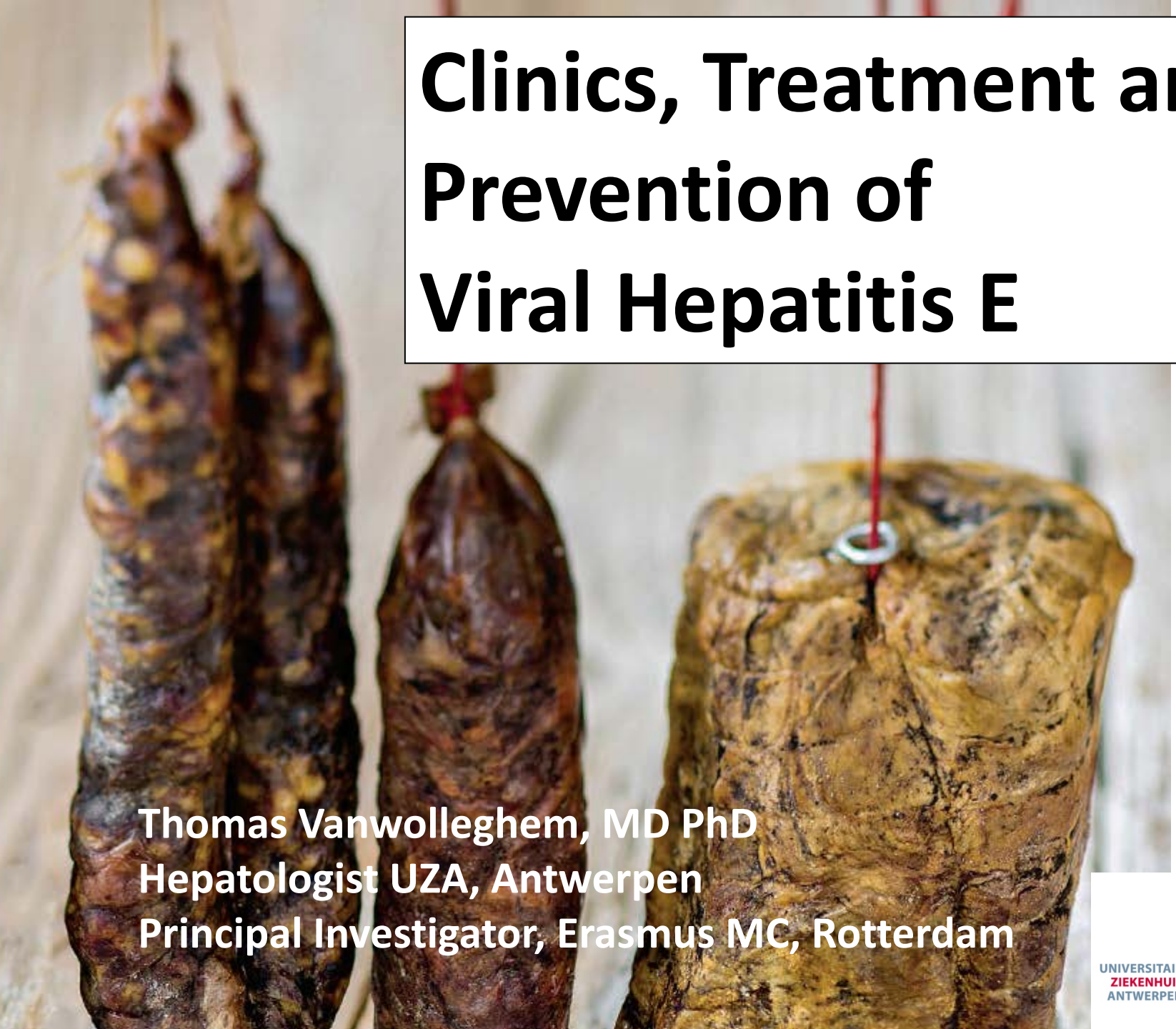


Clinics, Treatment and Prevention of Viral Hepatitis E

Thomas Vanwolleghem, MD PhD
Hepatologist UZA, Antwerpen
Principal Investigator, Erasmus MC, Rotterdam

UNIVERSITAIR ZIEKENHUIS ANTWERPEN
UZA
kennis / ervaring / zorg

Scheme

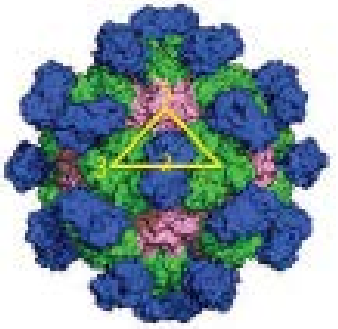
- HEV Virology
- HEV Transmission and Prevention

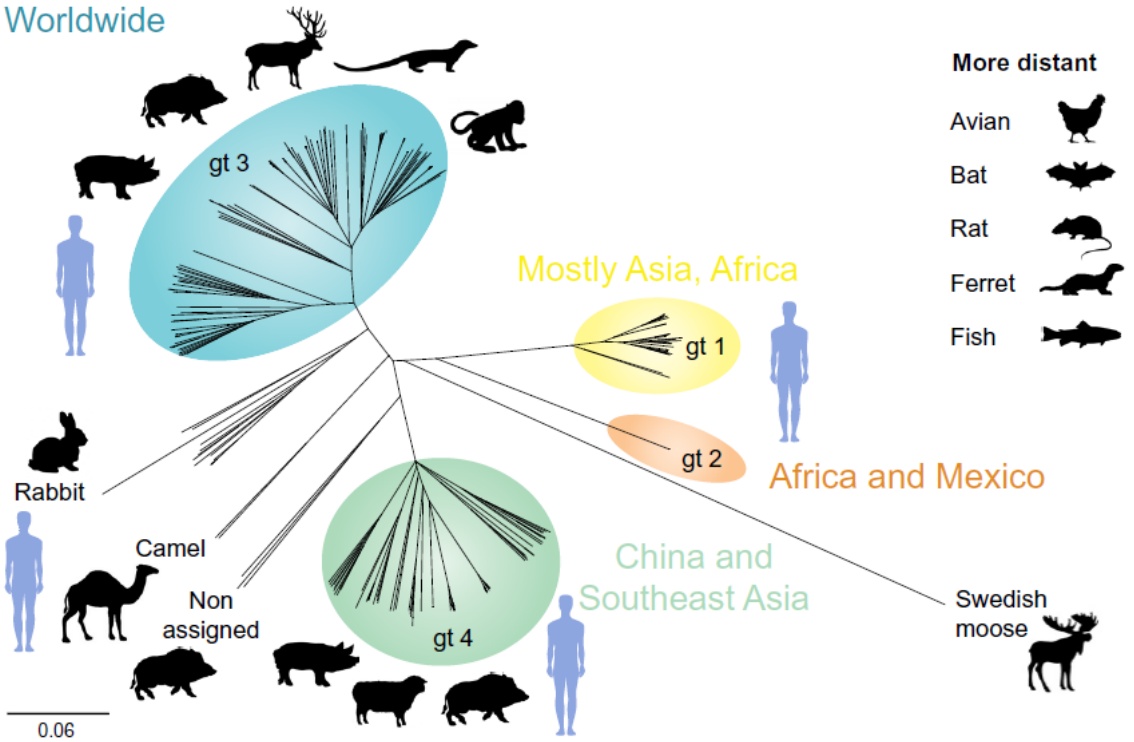
- HEV Clinical presentation
- HEV Treatment

- Wrap up

Hepatitis E virus and the global disease burden

- Nonenveloped +sense single stranded RNA virus (27-34 nM)
- 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

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**

- In Belgium?
  - 2018 planned age-specific seroprevalence study (WIV/ISP, UA, UZA)
  - 2 systematic serum banks obtained in 2006 and 2014

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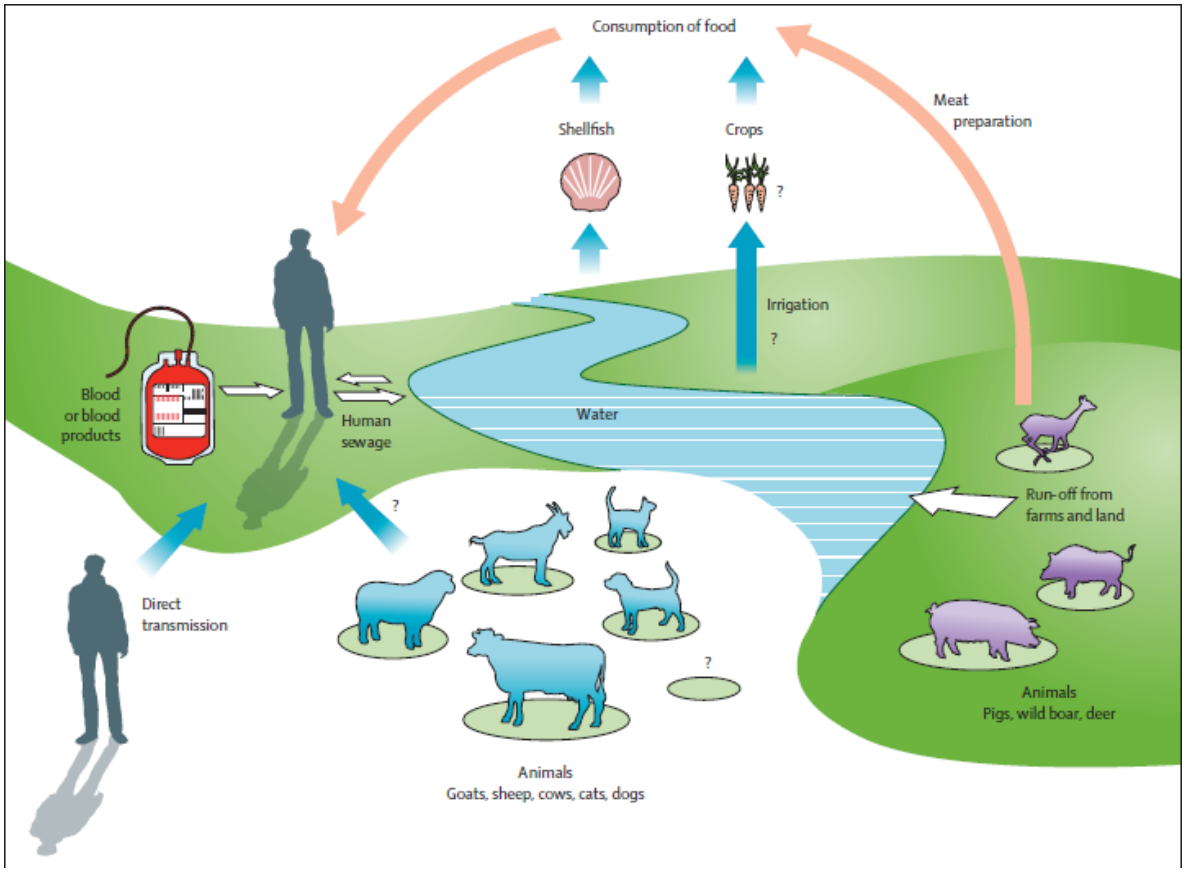
Hogema BM, Transfusion 2014, Wenzel JJ, Hepatol 2014, Zaaijer HL, Hepatol 2015

HEV Transmission

Transmission mainly via fecal-oral route

Transfusion: possible



Lancet June 30, 2012

Van der Poel. Curr Opinion Virology 2014

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How big is the

Identical HEV strai
consumed meat ar

Rijksinstituut voor Volksgezondheid en Milieu
Ministerie van Volksgezondheid, Welzijn en Sport

Signaleringsoverleg

Wekelijks overzicht van infectieziektesignalen: 23 juni 2016 (week 25)

Binnenlandse signalen

2854 Hepatitis E-virus-RNA in diverse varkensleverproducten

In recent onderzoek naar de bronnen van HEV-infectie bij mensen heeft Sanquin 43 van 55 (78%) leverworsten en 12 van 15 (80%) varkenspatémonsters, afkomstig van diverse producenten, positief getest op HEV-RNA met een PCR-test. De NVWA heeft

Lancet 2003; 362: 371–73; Emerg Infect Dis, 2005. **11**(12):1958; J Infect Dis, 2010. **202**(6):825; Food Environ Virol, 2012. **4**(4):179; Emerg Infect Dis, 2012. **18**(12):2085; Appl Environ Microbiol, 2012. **78**(10):3763; PNAS,1997,**94**(18):9860

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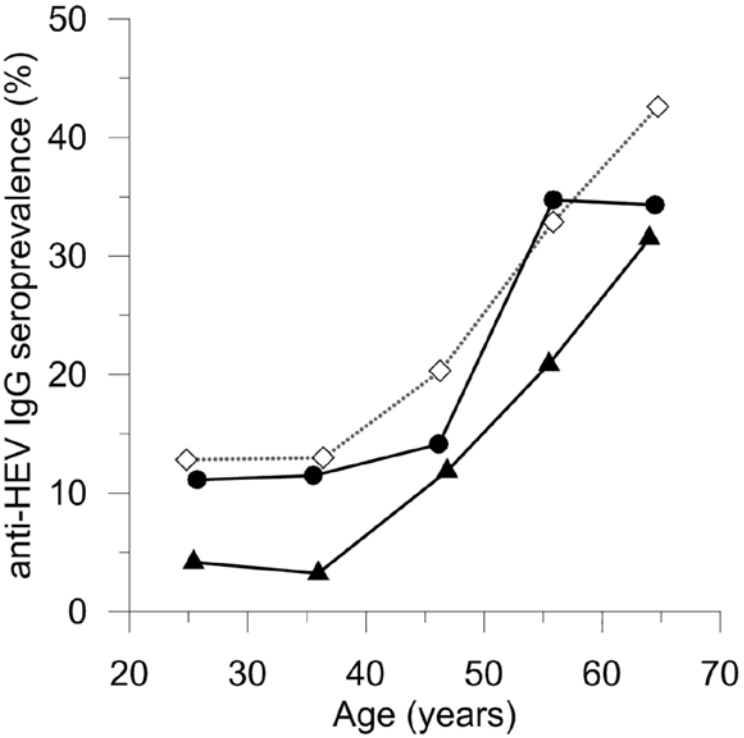
How big is the zoonotic risk?

Holland: HEV IgG+
meat vs vegetarians: OR 1.78

UK: HEV IgM+
OR > 2.48- 10.12 (P = 0.002)



Exposure	OR	95% CI	*P* value
Consumed pork pie			
No	1·00	Baseline	
Yes	6·33	(1·41–28·48)	0·009
Consumed ham or sausages purchased from a major UK supermarket chain			
Neither	1·00	Baseline	
Either	2·48	(0·32–18·96)	
Both	10·12	(1·68–60·81)	0·023

Slot et al. PLOS ONE 2017;April 27.
Said et al Epidemiol Infect 2014; 144:1467

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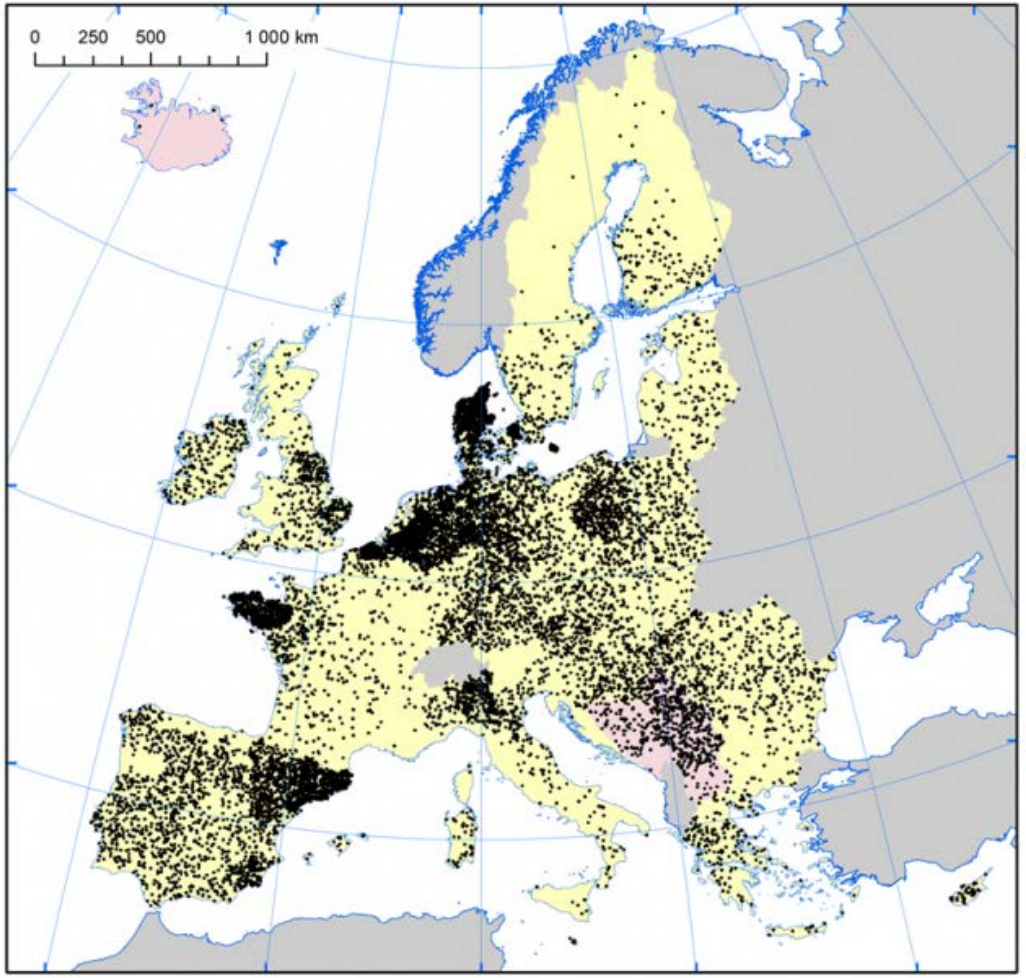
Zoonotic Risks in Belgium: “Pig Belt”



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

- 70% of fatteners HEV RNA+
- @ 1month:
  serum HEV RNA-
  faeces HEV RNA+
- transmission to newborn pigs

→True pig reservoir

Belgium (2010): slaughterhouse

→ 5/23 farms HEV RNA+
→ 8/115 (7%) pigs HEV RNA+

BMC Res Notes, 2012. PLOS one 2011

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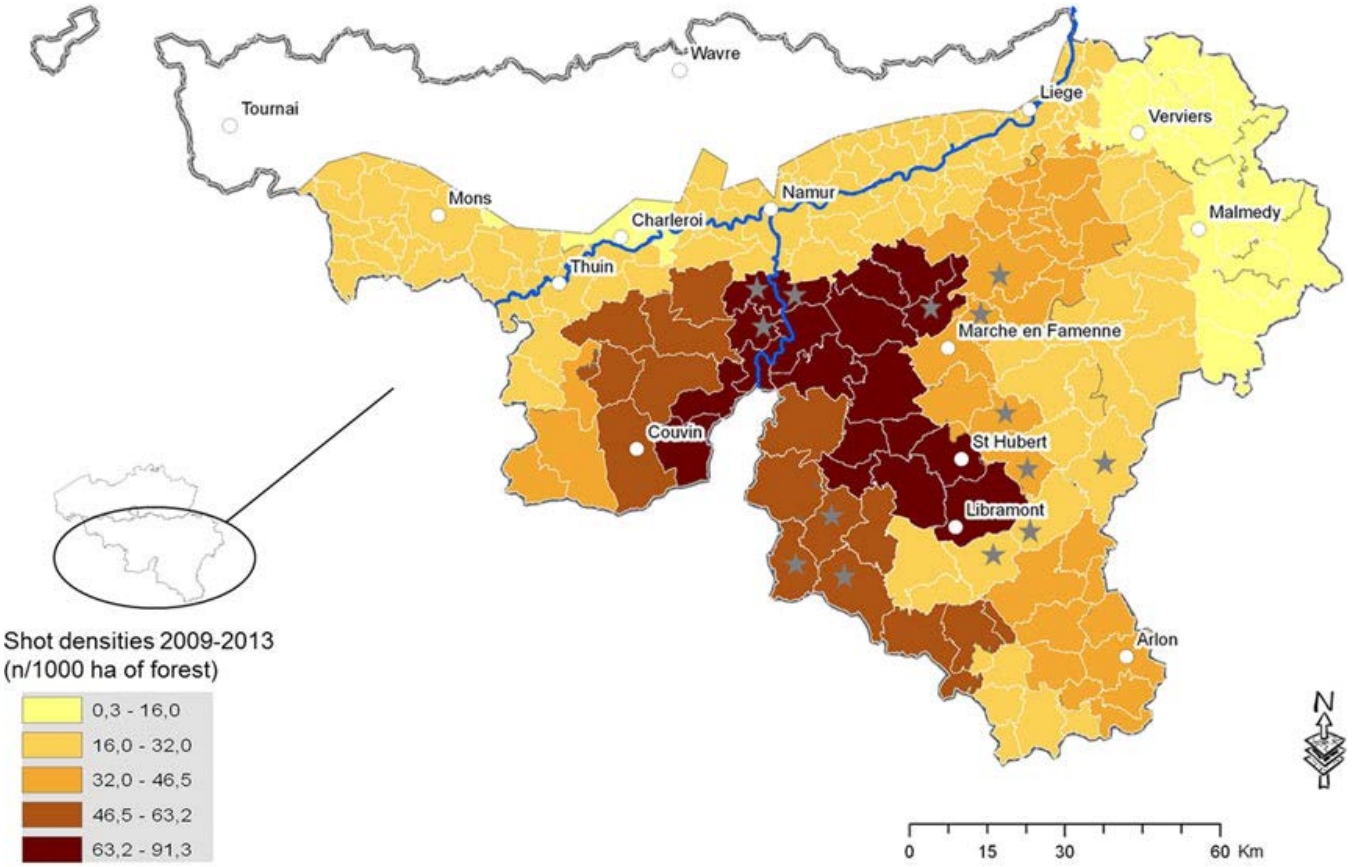
Zoonotic Risks in Belgium: … and Wildlife



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

Wild boar density shot per region (2009-2013)

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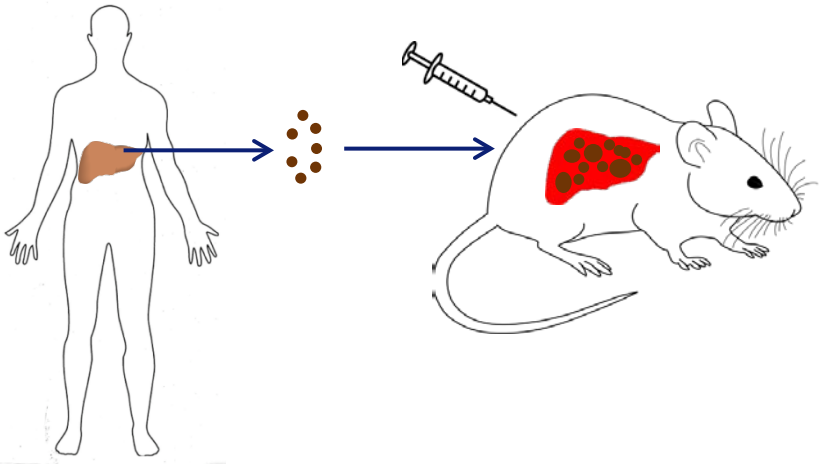
Transboundary and Emerging Diseases. 2015

Minimal infectious dose? Inactivation?

- MID ?: Experimental inoculation

pigs, rhesus macaque and chimeric mice



- Inactivation ?

  > 71°C for ≥ 20': 0/4 pigs infected

TABLE 2 HEV fecal excretion in experimentally infected pigs

			No. of pigs excreting HEV/no. of pigs in group on the following day postinoculation:														
Group	Temp (°C)	Time	−4	2	4	7	9	11	14	16	18	22	25	28	30	32	35	Total
1	71	5	0/3	0/3	0/3	0/3	0/3	2/3	2/3	2/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	2/3
2	71	10	0/3	0/3	0/3	0/3	0/3	0/3	0/2[a]	0/3	1/3	2/3	2/3	1/3	1/3	1/3	0/3	2/3
3	71	20	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/3[a]	0/4	0/4	0/4	0/4	0/4	0/4	0/4	0/4
4	68	5	0/3	0/3	0/3	0/3	1/3	1/3	1/3	1/3	0/3	0/3	0/3	0/3	0/3	0/3	0/2[a]	1/3
5	68	10	0/3	0/3	0/3	0/3	1/3	1/3	0/3	2/3	1/3	1/3	1/3	0/3	0/3	0/3	0/3	2/3
6	68	20	0/4	0/4	0/4	0/4	1/4	1/4	3/4	3/4	2/4	1/4	0/4	0/4	0/4	0/4	0/4	3/4
7	62	5	0/3	0/3	0/3	0/3	3/3	3/3	2/3	2/3	1/3	1/3	1/3	1/3	1/3	1/3	1/3	3/3
8	62	20	0/3	0/3	0/3	1/3	3/3	3/3	3/3	3/3	1/2[a]	2/3	2/3	1/3	0/3	0/3	0/3	3/3
9	62	120	0/4	0/4	0/4	0/4	1/4	1/4	2/4	3/4	3/4	3/4	1/4	1/4	0/4	0/4	0/4	3/4
10	HEV positive, no heating		0/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4	4/4	3/4	3/4	3/4	3/4	3/4	3/4	4/4
11			0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/3	—[b]	—	—	—	—	—	—	0/6

Vanwolleghem T, Gastroenterology, 2007; Vanwolleghem T, Hepatol 2008; Vanwolleghem T, J.Hepatol, 2010; Van de Garde,..,Vanwolleghem, T J Virol 2016; Van de Garde,…, Vanwolleghem,T Sci Rep 2017.
J Gen Virol, 2007,**88**(3):912; Hepatology 2016; Appl Environ Microbiol. 2012;78(15):5153

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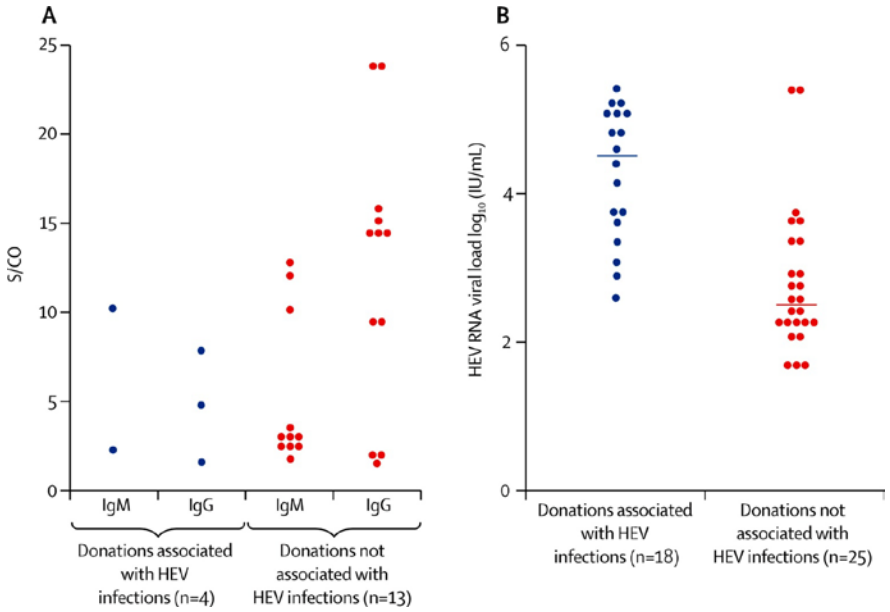
Transfusion?



42% (18/43) recipients infected

Risk of HEV transmission:
RBC < platelets << plasma
~ low/absent HEV IgG
~ higher HEV RNA (p<0·0001)

Absolute risk low: HEV RNA+ donations

The Netherlands	0.037%	(17/45,415)
Denmark	0.04%	(11/ 25,637) --> 0 infections
UK	0.04%	(79/225,000) --> 18 infections
Japan	0.012%	(231/2,000,000)

Lancet, 2014. **384**(9956):1766; Transfusion 2016;56:2225; Euro Surveill 2013;18:20550.

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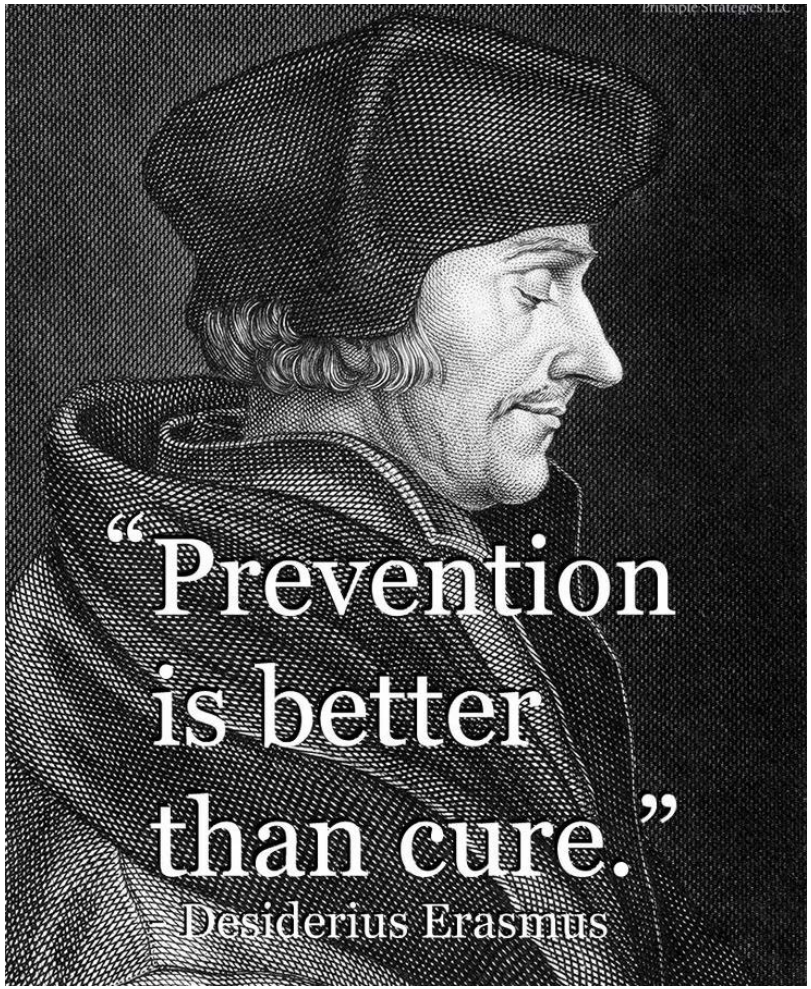
How to translate this knowledge in Preventive Measures



HEV Prevention

- HEV vaccine:

  Chinese HEV genotype 1, not FDA or EMA approved

  4.5 yr efficacy of 86.8% (7 infections in vaccinees, vs 60 in controls)

  Efficacy in HEVgt 3 infections?

- Zoonotic Risk:

  SOT recipients: NO liver sausage/paté; shellfish; uncooked pork

  Food processing techniques?

N Engl J Med 2015;372:914.

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

HEV Prevention

- Blood donation screening? Cost-effective?

  0.2% of all HEV infections in The Netherlands (H Zaaijer)

  1 year dietary risk ~ blood from 13 donors (UK)

plasma polytransfused

Country	HEV RNA positive donations	Population at risk		Reported TT HEV infections	Screening of blood donations			
		allo-HSCT [51] AN (AR/p1omp)	SOT [52] AN (AR/pmp)		Implemented	Under Consideration	In evaluation	Not recommended
Denmark	1:2,331(2016) [16]	144 (201 – 300)	356 (63.6)					x
France	1:2,218 (2012–3) [18]	1,724 (201 – 300)	5,141(79.6)	x		x[a]		
Germany	1:1,241 (2012) [24]	2,892 (›300)	3,710 (44.9)	x		x[b]		
Greece	NA	169 (151 – 200)	171 (15.4)				x	
Ireland	1:2,778 (2016)	77(151 – 200)	246 (52.3)		x[c]			
Italy	NA	1,625 (201 – 300)	3,252 (53.2)				x	
The Netherlands	1: 726 (2016) [7]	1175 (›300)	1,315 (78.3)			x[d/e]		
Portugal	NA	137 (101 – 150)	739 (69.7)				x	
Spain	1:3,333 (2014) [53]	1,072 (201 – 300)	4,247 (90.2)	x			x	
Switzerland	NA	191 (201 – 300)	504 (61.5)			x		
United Kingdom	1:1,340–5,000 (2016)	1,602 (201 – 300)	4,561 (71.8)	x	x[e/f]			

Belgium? Luxemburg?

HEV RNA+ donations = 0.04%

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Euro Survell 2017;22(16):30514; TRANSFUSION 2017;57;267

Scheme

- HEV Virology
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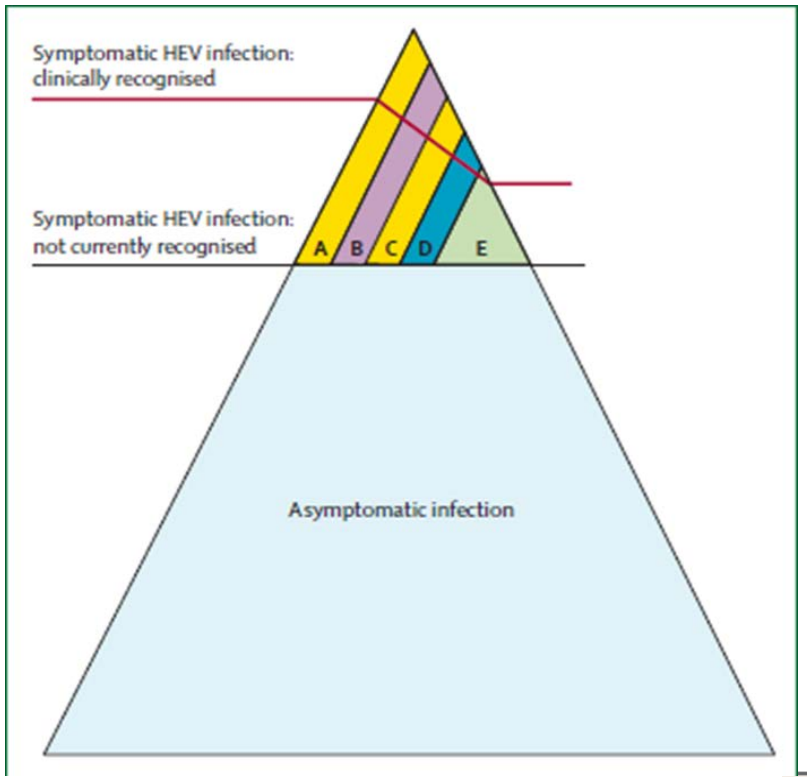
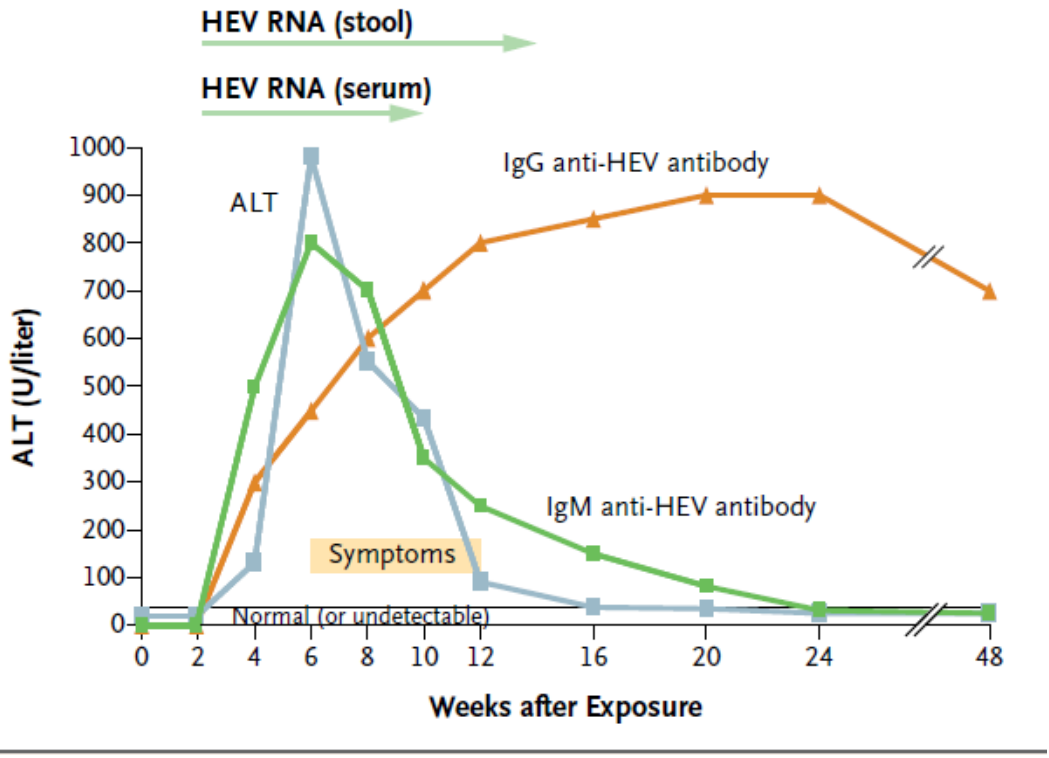
Acute HEV (gt 1/2/3/4)





Out of 40 symptomatic Acute HEV patients:

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; . Lancet June 30, 2012

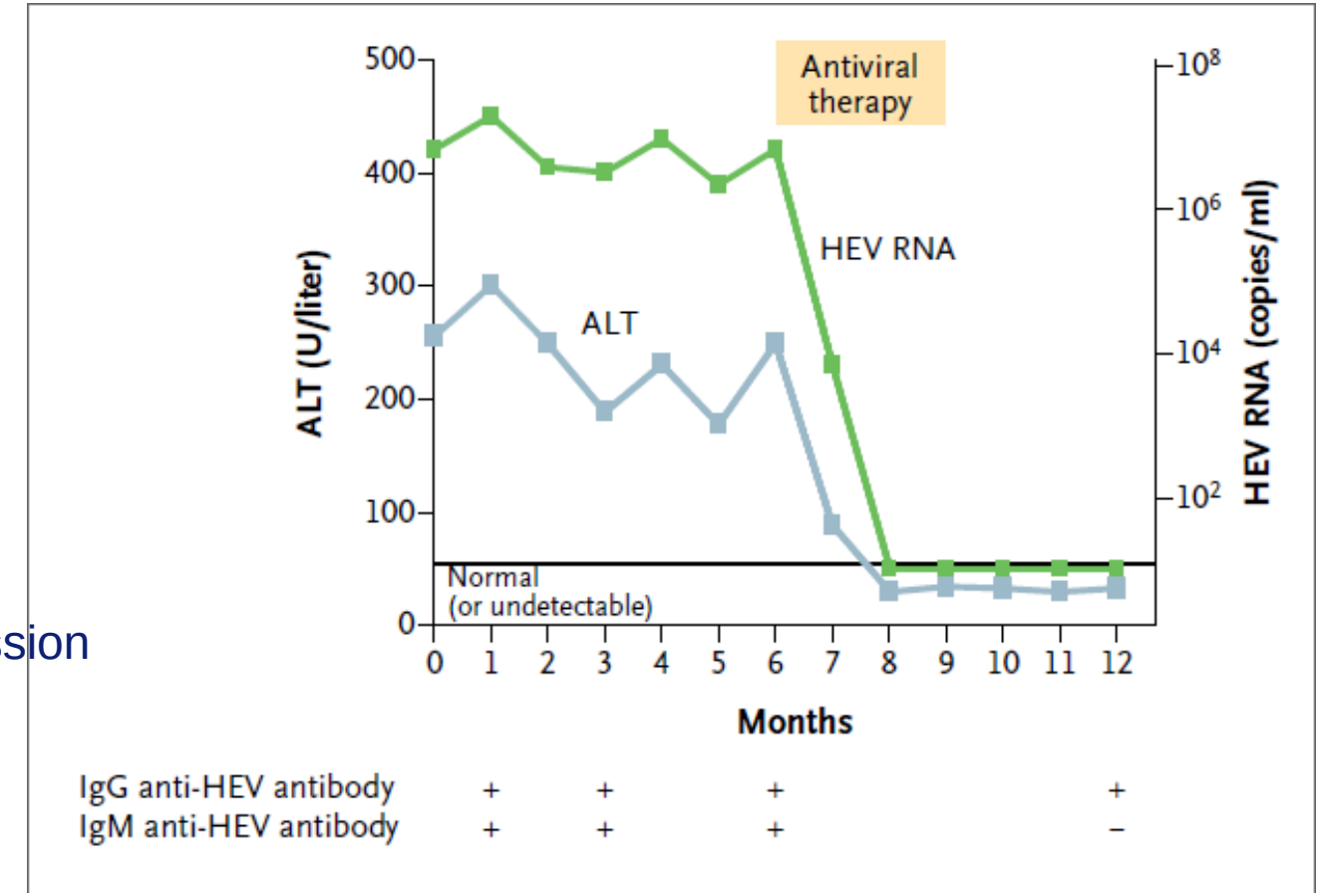
Chronic HEV genotype 3

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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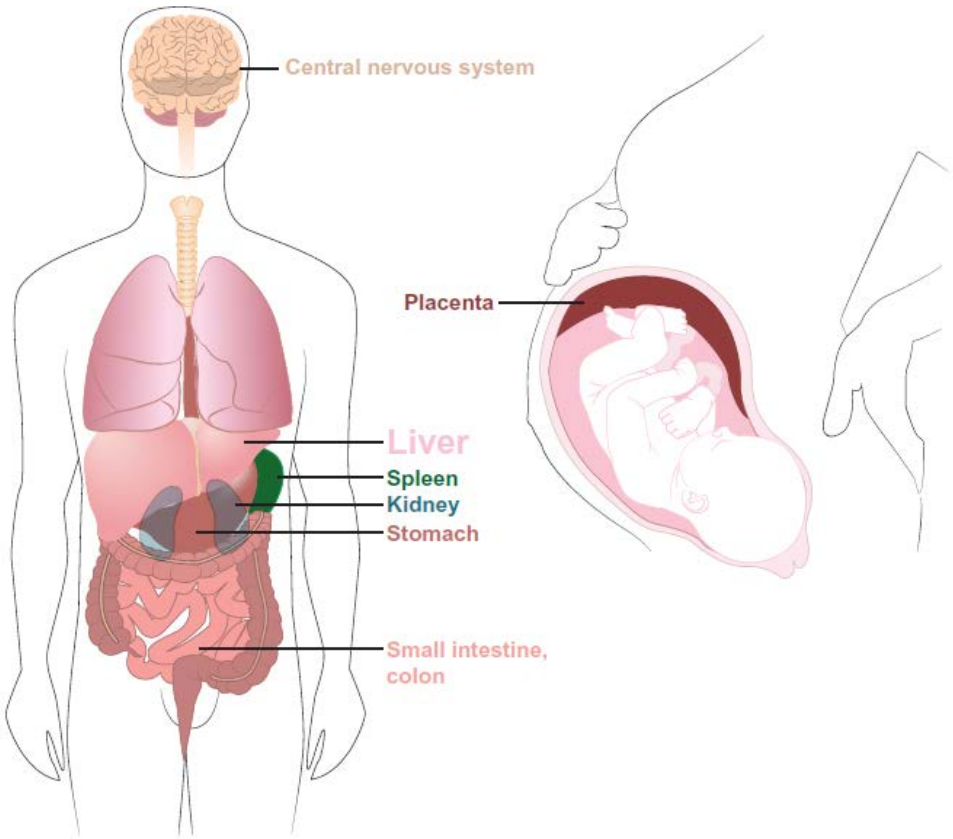
Extrahepatic manifestations



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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Scheme

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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

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

Conclusions: HEV

- Belgiums HEV transmission risks and preventive measures remain uncertain:
  - HEV present in pig stock and wild boars
  - Immunocompromised: no uncooked pork meat, seafood, liver sausage/liver pate
  - Transfusion: limited contribution to HEV epidemics

- Acute, mostly asymptomatic in immunocompetent
- Possible chronic in immunocompromised
- HEV PCR necessary in immunocompromised

- Treat chronic HEV with RBV
- Relapsers difficult to cure

Ackowledgements

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Erasmus MC Fellowship 2011

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Stichting tegen Kanker

Questions?

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