IPFA/PEI 31st International Workshop on Surveillance and Screening of Blood-borne Pathogens

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Rat hepatitis E virus

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Disclosures:

I have no conflicts of interests regarding this presentation

Human health and rats: Two dramatic examples



14th Century in Europe: Black death
Rodents spread *Yersinia pestis*
Estimated 25-50 million deaths



Rattus sp.



21st Century:
Hantavirus respiratory syndrome
Mrs Hackman's official cause of death

- Rats can host a high diversity of zoonotic pathogens
- The risk for humans increases in environments with abundance of rats, direct contact with rat secretions (faeces, urine) and is usually associated with **poor hygienic conditions**

Spyrou et al, 2022; De Cock et al, 2023

JOURNAL OF
GENERAL VIROLOGY
Volume 91, Issue 3
Other

Detection of a novel hepatitis E-like virus in faeces of wild rats using a nested broad-spectrum RT-PCR

Reimar Johne[1], Anita Plenge-Bönig[2], Michael Hess[3], Rainer G. Ulrich[4], Jochen Reetz[1] and Anika Schielke[1]

BANC DE SANG I TEIXITS

The identification of a novel hepatitis E-like virus in wild rats was published in 2010

Authors from:

- Federal Institute for Risk Assessment, Berlin, Germany
- Institute of Hygiene and Environment, Hamburg, Germany
- Friedrich-Loeffler-Institut (Animal Health), Greifswald–Insel Riems, Germany
- Swiss Institute of Bioinformatics, Lausanne, Switzerland

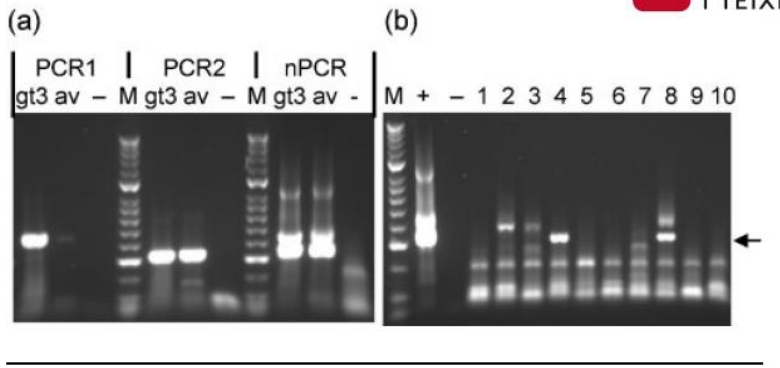
Hypothesis:

- ***Multiple reports on the detection of HEV-specific antibodies in rats have suggested the presence of an HEV-related agent; however, infectious virus or a viral genome has not been demonstrated so far***

Methods:

- 30 faecal samples from wild rats (Rattus norvegicus) from Hamburg (Germany)
- Broad-spectrum HEV nested RT-PCR

Identification of a novel hepatitis E-like virus in wild rats



- Two fragments were identified (HEV expected size):

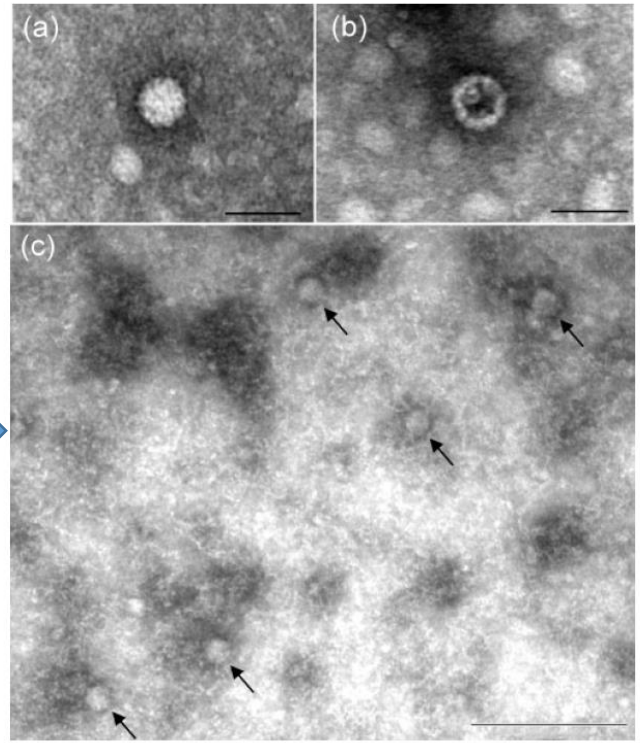
  - Sample R4: 4019 nt fragment
  - Sample R8: 1545 nt fragment

→ 90.4% homology

49.9% homology with avian HEV
59.9% homology with human HEV genotype 1

Electron microscopy in R4 faecal sample shows HEV-like viral particles:

Figure a: Filled particle 32 nm diameter
Figure b: Empty particle 34 nm diameter
Figure c: Immunocomplexes after incubating with anti-HEV antibodies



Novel Hepatitis E Virus Genotype in Norway Rats, Germany

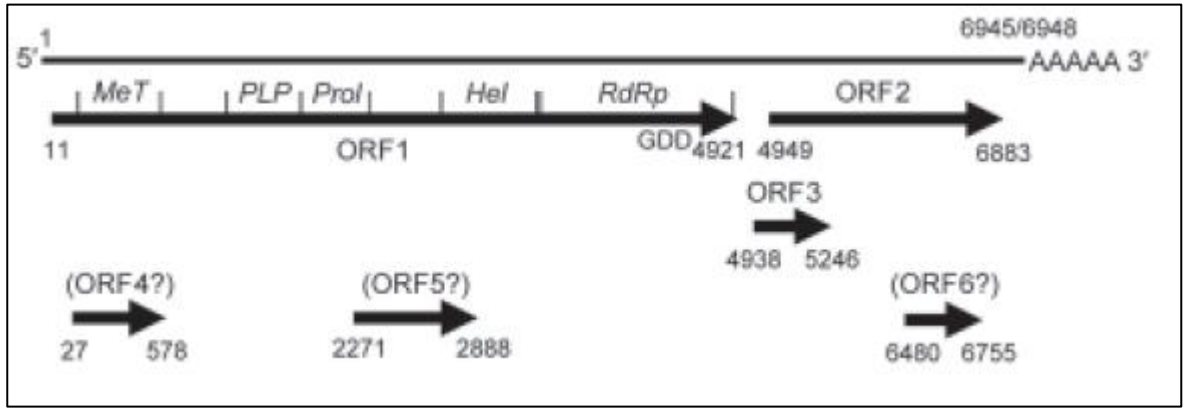
Reimar Johne, Gerald Heckel, Anita Plenge-Bönig, Eveline Kindler, Christina Maresch, Jochen Reetz, Anika Schielke, and Rainer G. Ulrich

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 16, No. 9, September 2010

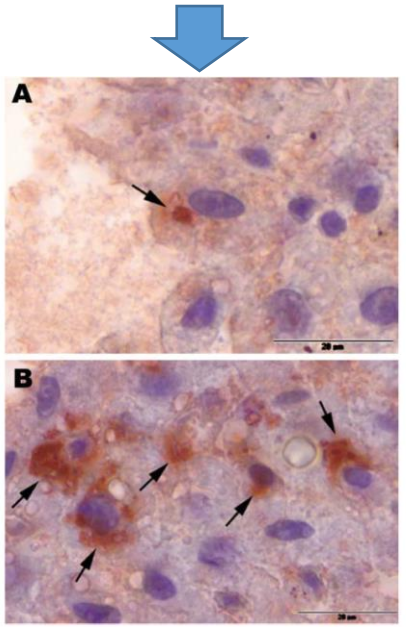


- The complete genome of the novel hepatitis E-like virus was sequenced
Single stranded RNA ≈6,900 nt

- The authors suggest a genomic organization similar other hepatitis E viruses



- Immunohistochemical staining: Positive reaction in **hepatocyte cytoplasm** of liver rats



TAXONOMY: Former nomenclature

Family	Hepeviridae				
Genus	Orthohepevirus				Piscihepevirus
Species	Orthohepevirus A	Orthohepevirus B	Orthohepevirus C	Orthohepevirus D	Piscihepevirus A
Genotype	1 (human) 2 (human) 3 (human, pig, wild board, deer) 4 (human, pig) 5 (wild boar) 6 (wild boar) 7 (camel, human?) 8 (camel)	(avian)	C1 (rats) C2 (mustelids)	(bat)	(fish)

Smith et al, 2014; Pérez-García et al, 2015; Takhur et al, 2020

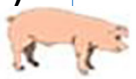
TAXONOMY: Current nomenclature

Family	Hepeviridae (Subfamily *Orthohepevirinae*)				Hepeviridae Subfamily *Parahepevirinae*)
Genus	*Paslahepevirus*	*Avihepevirus*	*Rocahepevirus*	*Chirohepevirus*	Piscihepevirus
Species	*Paslahepevirus balayani*		*Rocahepevirus ratti*		
Genotype	1 (human) 2 (human) 3 (human, pig, wild board, deer) 4 (human, pig) 5 (wild boar) 6 (wild boar) 7 (camel, human?) 8 (camel)		C1 (rats) C2 (mustelids)		Hepeviridae (Subfamily *Orthohepevirinae*)









Smith et al, 2014; Pérez-García et al, 2015; Takhur et al, 2020; Benavent et al, 2023
https://ictv.global/report/chapter/hepeviridae/hepeviridae/orthohepevirinae/rocahepevirus

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Species	*Paslahepevirus balayani*		*Rocahepevirus ratti*		
Genotype	1 (human)		C1 (rats) 		Hepeviridae (Subfamily *Orthohepevirinae*)
	2 (human)				
	3 (human, pig, wild board, deer) 		C2 (mustelids)		
	4 (human, pig) 				
	5 (wild boar)				
	6 (wild boar)				
	7 (camel, human?)				
	8 (camel)				

Paslahepevirus balayani genotype 3
HEV

Rocahepevirus ratti C1
ratHEV

Smith et al, 2014; Pérez-García et al, 2015; Takhur et al, 2020; Benavent et al, 2023
https://ictv.global/report/chapter/hepeviridae/hepeviridae/orthohepevirinae/rocahepevirus

RatHEV detection in rats



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- Surveillance of **ratHEV** in wild rats and Black rats (*Rattus rattus*) in 12 European countries (Ryll et al, 2022):
  - Detected in Germany, Denmark, Austria, Switzerland, Czech Republic, Belgium, France, Greece, Italy, Spain
  - Not detected in rats from Slovenia
  - **HEV** not detected in any rat sample
- RatHEV detected in rats in Romania (*Porea et al, 2023*)
- RatHEV detected in rats in Helsinky (Finland) (*Aivelo et al, 2024*)

EUROPE

- RatHEV detected in rats of 5 prefectures of Japan (*Takahashi et al, 2022*)
- RatHEV in wild rodents in Seoul (Korea) (*Park et al, 2024*)
- RatHEV in wild rodents in Hubei province and Yunnan province (China) (*Ding et al, 2024; Wu et al, 2024*)

ASIA

- RatHEV in 5,6% of *Rattus norvegicus* tested in Hamilton and Toronto area (Ontario, Canada); absence of HEV detection (*Robinson et al. 2023*)
- RatHEV complete genome from rats trapped in urban Los Angeles (USA)(*Debing et al, 2014*)

NORTH AMERICA

RatHEV surveillance in sewage and wastewater

Sewage monitoring: a useful tool to circulation of poliovirus, SARS-CoV-2





Barcelona Metropolitan Area, Spain:
6 wastewater sites
ratHEV detection rate: 100%
HEV not detected

Gothenburg, Sweden:
1 wastewater site (51 samples)
ratHEV detection rate: 98%

Córdoba, Spain:
1 wastewater site
106 samples
ratHEV detection rate: 94.3%
HEV detection rate: 0.6%

Abruzzo, Italy:
14 wastewater sites
ratHEV detection rate: 43%
HEV not detected

Benedetti et al, 2024; Churqui et al, 2024; Palombieri et al, 2023; Casares-Jimenez et al, 2024; Mari Costafreda and Albert Carceney personal communication

Is ratHEV an emerging zoonotic infection to humans?

- Retrospective study in South-Western France, an hyperendemic region for HEV (*Parraud et al, 2021*)
  - No evidence of ratHEV infection in a cohort of 224 patients, mostly immunocompromised, at risk of acquiring HEV infection

- Retrospective study in Germany (*Faber et al, 2022*):
  - No evidence of ratHEV infection in 200 patients with positive or borderline positivity to HEV IgM (HEV RNA negative)

The Hong-Kong case: First evidence of ratHEV infection in humans

Rat Hepatitis E Virus as Cause of Persistent Hepatitis after Liver Transplant

Siddharth Sridhar, Cyril C.Y. Yip, Shusheng Wu, Jianpiao Cai, Anna Jin-Xia Zhang, Kit-Hang Leung, Tom W.H. Chung, Jasper F.W. Chan, Wan-Mui Chan, Jade L.L. Teng, Rex K.H. Au-Yeung, Vincent C.C. Cheng, Honglin Chen, Susanna K.P. Lau, Patrick C.Y. Woo, Ning-Shao Xia, Chung-Mau Lo, Kwok-Yung Yuen

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 24, No. 12, December 2018

- Retrospective review of 518 organ recipients:
  - 52 patients met criteria for **persistent hepatitis**
    - 5 patients were positive for HEV IgM :

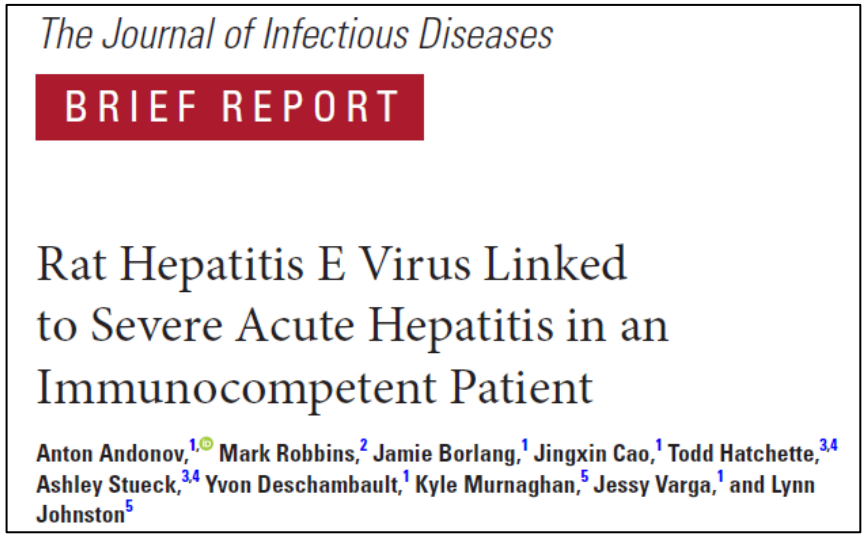
One patient tested positive for ratHEV RNA

- 56-year-old male, hepatocellular carcinoma due to HBV, liver recipient
- In a pre-transplant sample, the patient tested HEV IgG positive, IgM negative, which did not protect from acquiring ratHEV and developing persistent infection
- Treatment:
  - Decrease of the immunosuppression was not successful
  - Sustained virological response (negative ratHEV RNA) after ribavirin treatment
- The patient lived in a rat infested neighborhood
- In Hong Kong, around 17 cases of ratHEV have been reported to the Health System since 2017

(*Sridhar et al, 2018; Hon et al, 2020; Sridhar et al, 2021; Cheung et al 2024*)

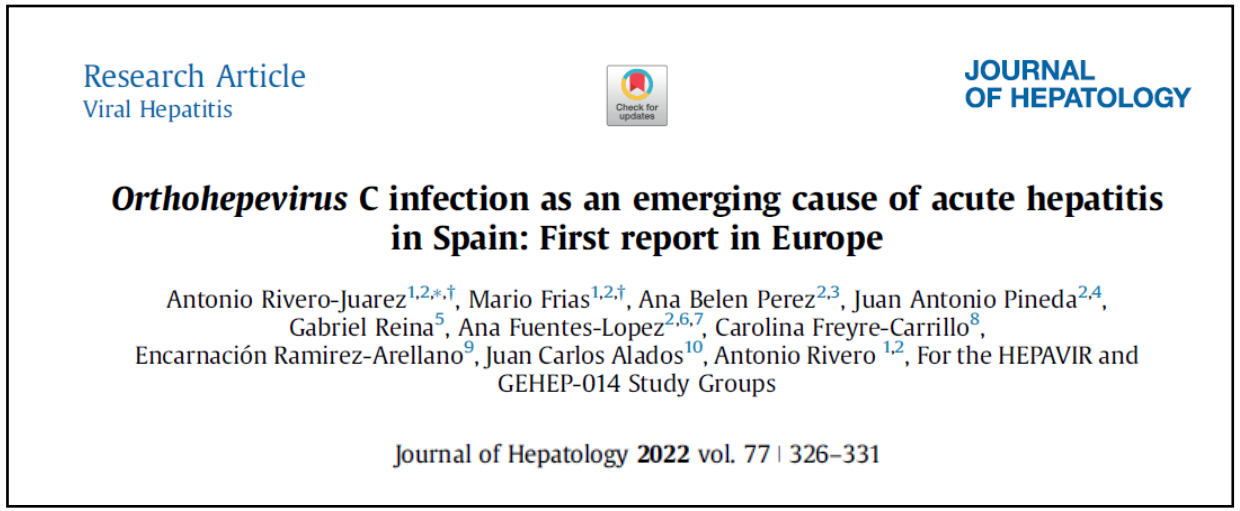
The Canada case: ratHEV infection imported from Africa
2nd ratHEV human case described

- 49-year-old male, former employee of the United Nations, was admitted to a hospital in Halifax (April 8, 2017)
- Severe acute hepatitis (anorexia, nausea, jaundice, fatigue, rash)
- Worked in Africa (Gabon, DR Congo) from January to 12 March; short vacations in Caiman Islands (29 March to 4 April)
- A blood sample collected on 10 April tested negative for HEV RNA (RT-PCR, Altona), **ratHEV RNA positive** (in-house RT-PCR)
- Authors state that the patient was infected in Africa, but no obvious contact with rodents was identified



(*Andonov et al, 2019*)

The Spanish cases: First report in Europe



Research Article
Viral Hepatitis

JOURNAL OF HEPATOLOGY

***Orthohepevirus* C infection as an emerging cause of acute hepatitis in Spain: First report in Europe**

Antonio Rivero-Juarez[1,2,*,†], Mario Frias[1,2,†], Ana Belen Perez[2,3], Juan Antonio Pineda[2,4], Gabriel Reina[5], Ana Fuentes-Lopez[2,6,7], Carolina Freyre-Carrillo[8], Encarnación Ramirez-Arellano[9], Juan Carlos Alados[10], Antonio Rivero [1,2], For the HEPAVIR and GEHEP-014 Study Groups

Journal of Hepatology **2022** vol. 77 | 326–331

- Cohort 1: 169 patients with suspected viral hepatitis:
  - Two patients were positive for ratHEV RNA
- Cohort 2: 98 immunocompromised patients with acute HEV infection (HEV IgM and/or HEV RNA positive):
  - One patient was positive for ratHEV RNA

  (*HEV IgM positive/HEV RNA negative*)

- Cohort of 11 pediatric patients: Two children infected with ratHEV, no obvious route of ratHEV acquisition
- Cohort of 842 HIV positive patients: One patient infected with ratHEV, no obvious route of ratHEV acquisition
- Cohort of 341 drug users:
  - One female was ratHEV RNA positive (negative for ratHEV specific antibodies), homeless and with multiple addictions
  - 17 individuals with specific anti-ratHEV IgG antibodies (*ELISA in-house method*)

(*Rivero-Juárez et al, 2022; Caballero-Gómez et al, 2024; Casares-Jiménez et al, 2023; Casares-Jiménez et al, 2024*)

ratHEV possible routes of acquisition

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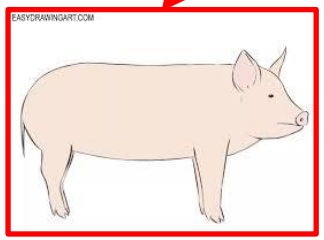
Direct contact with secretions

Unknown



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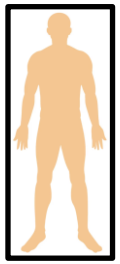


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ratHEV in blood donors?





(Yadav et al, 2024; *Rios-Muñoz et al, 2024; Shun et al, 2024)*

HEV vs ratHEV: Clinical characteristics and diagnosis

	HEV	ratHEV	Comments
Asymptomatic infections	Yes	Probable	
Acute hepatitis	Yes	Yes	
Persistent hepatitis	Yes	Yes	Immunosupressed patients
Treatment of persistent hepatitis	Reduce immunosuppression Ribavirin	Reduce immunosuppression Ribavirin	Not 100% effective
Extrahepatic manifestations (neurological) Mortality	Yes Yes	Yes (?) Yes (?)	One case in Hong Kong (meningencephalitis)
Diagnostic tools RNA detection IgG/IgM	 Commercial RT-PCR Commercial ELISA	 In-house RT-PCR, qRT-PCR In-house ELISA	

HEV vs ratHEV: Blood and plasma safety

	HEV	ratHEV
Prevalence in blood donors (IgG/IgM/RNA)	Varies among regions, extensively studied	No published data
Screening of blood donations	Implemented in some blood banks **(lack of consensus in Europe)**	**Commercial HEV NAT platforms do not detect ratHEV**
Post-transfusional transmission	Yes; extensively documented morbidity/mortality	Unknown
Post-transfusional infection outcome	Depends on the recipient's immunological status and clinical conditions	Depends on the recipient's immunological status and clinical conditions?

- **Plasma for fractionation: No impact?**

Reflection paper on viral safety of plasma-derived medicinal products with respect to Hepatitis E virus
(23 June 2016 EMA/CHMP/BWP/723009/2014 Committee for Medicinal Products for Human Use (CHMP))

SUMMARY

- RatHEV is an emerging zoonotic infection affecting humans, worldwide detected in rats
- For the moment, active infection in humans has been reported only in:
  - Hong Kong (≈20 cases)
  - Spain (≈7 cases)
  - Canada (1 case, imported from Africa)
- Lack of commercial diagnostic tools might explain the low number of clinical cases reported
- RatHEV can cause acute hepatitis, and persistent hepatitis in immunosuppressed patients
- There is no obvious route of contagion in most patients
- **RatHEV transfusion transmission has not been demonstrated but cannot be ruled out**

Thank you!

Muchas gracias!

Moltes gràcies!

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