



Hepatitis E: a curious zoonosis

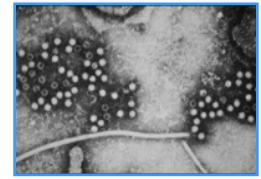
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Hepatitis E Virus

Hepeviridae, hepevirus

- Acute Hepatitis * enteric transmission
- Incubation time : 40 days
- Fulminate Hepatite : 1 -4% (20% pregnancy)

*chronic in recipient transplants and HIV+



Endemic Regions Asia, Africa, Central America

Water, soiled food



Genotypes 1, 2

Sporadic Cases US, Europe, Japan

US, Europe, Japan



Environment ?????

Genotype 3, 4

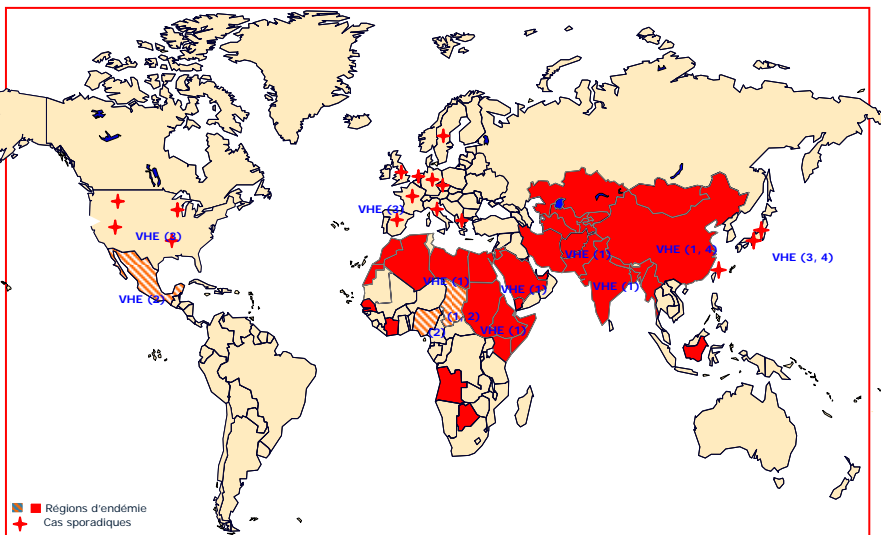


????? (Japan: grilled Liver, Sushi)



Genotypes 3 et 4

Q: Is the animal reservoir responsible for zoonotic transmissions ?



Possible animal Réservoirs

Animals	Countries	Ab Prevalence
Swine	Worldwide	30-80%
Rat	India, Brazil	50-80%
Cat	Japan	33%
Dog	Brazil	7%
Sheep	India, China, Brazil	
Goat	India, China, Brazil	
Wild boar	Japan, France, Germany, Italy, Spain, Hungary	5-42%
Deer	Japan, Hungary	2.6%
Chicken	USA, Brazil, Australia	20-30%
Bovine	Brazil	1.42%
<u>Horse</u>	Egypt	13%
<u>Mongoose</u>	Japan	8.3%



33% Japanese cats (n=135) Usui et al, 2004



Crossing the Species Barrier

<i>Genotype</i>	<i>Natural Host</i>	<i>Exp Models</i>	<i>Infection</i>
1 & 2	Human	Macaque	+
		Swine	-
		Rat	+
3	Human	Macaque	+
		Swine	+
	Swine	Macaque	+
		Swine	+
		Chicken	nd
		Rat	nd
		Lamb	+
Avian	Chicken	Macaque	-
		Swine	-
		Chicken	+
		Rat	nd
		Turkey	+



nd: not determined

HEPATITIS E IN SWINE

Natural infection

- Asymptomatic
- Occurs around 10 weeks (after weaning, lost Ab maternal)
- Viral excretion between 12 and 15 weeks, seroconversion at 16-20 weeks
- 90% herds are infected (USA, Europe, Asia)

Model of experimental infection in swine

- Asymptomatic (few liver lesions, no increase of ASAT,ALAT, feces excretion, seroconversion)
- Extra-hepatic sites of multiplication : small intestine, colon, lymph nodes, high excretion in bile, spleen, . (Williams et al JCM 2001).
- No effect in pregnant gilts (Kasorndorkbua et al 2003).
- Few differences of physiopathology between swine and human genotype 3 strains.
- Highly contagious $RO = 8.8$ (Bouwknegt et al Vet Res 2008)

HEPATITIS E IN SWINE

Model of experimental infection in swine

Table 2: HEV RNA in organs, excreta and bile from second-generation contact-infected pigs and *iv* inoculated pigs at 28 days post infection.

Pig	Contact infected					Inoculated						
	1	2	3	4	5	Total	Total	6	7	8	9	10
Faeces	+	-	-	-	+	2/5	5/5	+	+	+	+	+
Urine	+	-	-	+	+	3/5	0/5	-	-	-	-	-
Serum	-	-	-	-	+	1/5	4/5	+	+	-	+	+
Bile	+	-	-	-	+	2/5	5/5	+	+	+	+	+
Liver	+	-	-	-	+	2/5	5/5	+	+	+	+	+
Mesenterial LN	+	-	-	-	+	2/5	5/5	+	+	+	+	+
Bronchial LN	+	-	-	-	+	2/5	5/5	+	+	+	+	+
Hepatic LN	+	-	-	+	+	3/5	5/5	+	+	+	+	+
Pancreas	-	-	-	-	-	0/5	0/5	-	-	-	-	-
Spleen	+	-	-	+	+	3/5	5/5	+	+	+	+	+
Kidney	-	-	-	-	+	1/5	4/5	+	+	-	+	+
Ileum	-	-	-	-	.	1/4	4/5	+	+	-	+	+
Jejunum	-	-	-	-	+	1/5	4/4	+	+	.	+	+
Colon	+	-	-	-	+	2/5	4/5	+	+	-	+	+
Tonsil	-	-	-	-	-	0/5	3/5	+	-	-	+	+

'+' indicates the presence of HEV RNA; '-' indicates the failure to detect HEV RNA; '.' indicates that samples were not examined



Day*	Type	Pig ID	Type of muscle		
			Longissimus	Biceps femoris	Iliopsoas
13	C3	21	+	+	-
13	C3	22	+	+	+
15	C3	23	+	+	+
18	C3	24	-	-	-
19	C2	19	+	+	+
23	C1	15	-	-	+
24	C1	16	+	+	+
25	<i>iv</i>	6	-	+	+
25	<i>iv</i>	7	+	+	+
25	<i>iv</i>	8	-	+	-
25	<i>iv</i>	10	+	+	+
27	C2	3	-	-	-
27	C2	5	+	+	+
27	<i>iv</i>	9	+	+	+
29	C1	17	-	-	-
30	C2	4	-	-	-
31	C1	18	-	+	-
32	C2	20	-	-	+
53	<i>iv</i>	14	-	-	-
55	<i>iv</i>	13	-	-	-

DÉCOUPE DE LA VIANDE DE PORC



Evidence of Zoonotic transmissions

✓ Zoonotic transmissions through direct contact with swine or infected pork meat

➤ Increased HEV sero prevalence in exposed personnel (veterinaries, butchers, slaughterhouse).

USA	26% (<i>Meng et al 2002</i>)
Sweden	13% (<i>Olsen et al 2006</i>)
Moldavia	51.1% (<i>Drobeniuc et al 2001</i>)
The Netherlands	11% (<i>Bouwknegt et al 2007</i>)

✓ Zoonotic transmissions through infected food product

Species of origin	Mode of contamination	Geno-type	Reference
Sika deer	Uncooked meat (sushi)	3	Tei et al, 2003
Wild boar	Barbecue (partially undercooked)	3	Tamada et al, 2004
Wild boar	Barbecue (partially undercooked)	3	Masuda et al, 2005
Pig	Grilled or uncooked pig liver	3	Yasuyuki et al, 2003

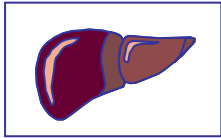
✓ Possible transmissions zoonotic with pork products

Confession	Muslim	Hindu
Prevalence	2%	20%

Indonesian study
(*Surya et al 2005*)

Source of HEV exposure

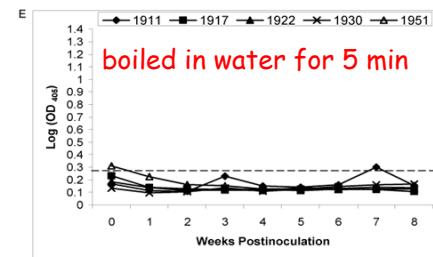
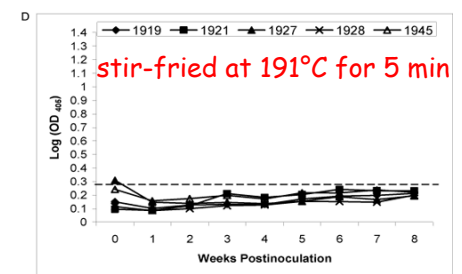
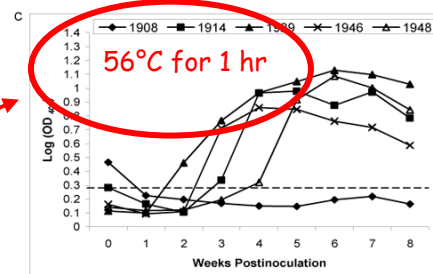
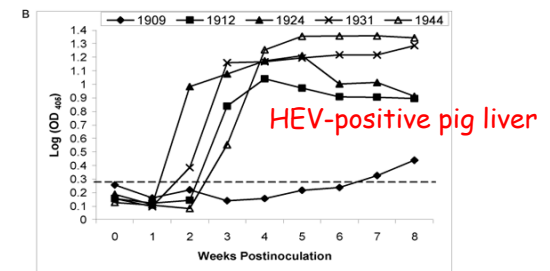
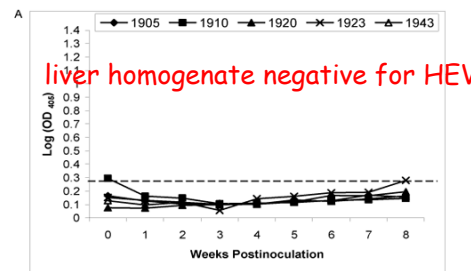
✓ Food product infected by HEV: pork liver in grocery stores



USA (Feagins *et al* JGV 2007); ARN + = 14/127 (11%); 2/3 infectious
The Netherlands (Bouwknegt *et al* J Food Prot 2007); ARN+ 4/62 (6.5%)
Japan (Yazaki Y *et al* J Gen Virol 2003); ARN + = 7/363 (1.9%)

Inactivation of infectious hepatitis E virus present in commercial pig livers sold in local grocery stores in the United States

R. Feagins, *et al* Int J Food Microbiol. 2008 March 31; 123(1-2): 32-37.



✓ Other risk factors:

Consumption of offal or wild-boar meat (Wichmann O *et al*, J Infect Dis. 2008)

Source of HEV exposure

✓ Sea shell



Japan (Li et al Am J Trop Med Hyg. 2007) *Corbicula Japonica*

✓ Wastewater in non endemic regions



US, Spain and France RNA +
Clemente-Casares et al, EID 2003

✓ Surface water in non endemic regions (Rutjes SA, EID 2009)

Hepatitis E in France



>150 human indigenous cases per year (source: National reference centre)

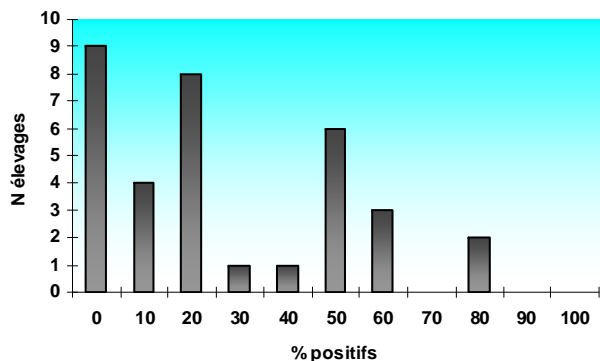
<http://www.cnr.vha-vhe.aphp.fr/cadrecnr.htm>

- ✓ 1 to 2 cases of fulminate hepatitis/year
- ✓ Chronic cases (transplant recipient)
- ✓ Genotype 3 HEV strains
- ✓ Seroprevalence :
 - 3.2% in blood donors from Paris area and north west
Boutrouille et al JCM 2007)
 - 16.4% in blood donors from Toulouse area (30% in
hunters *Mansuy et al JMV 2008*)

HEV Prevalence in French swine herds

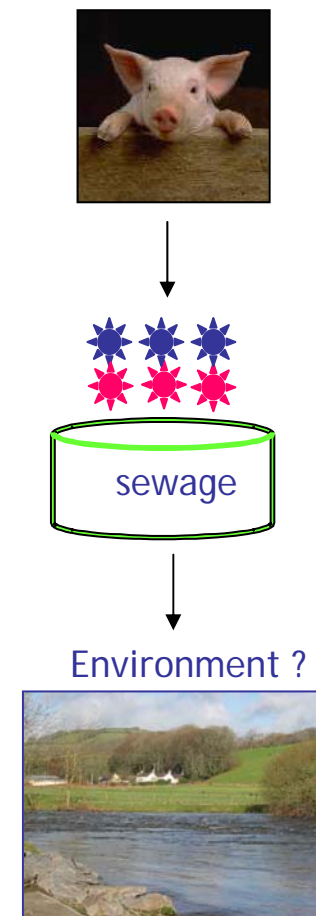
Serology

- > 70% Swine Herds are infected (n=51)
- Intra herd prevalence : 25% (2.5 to 80%)

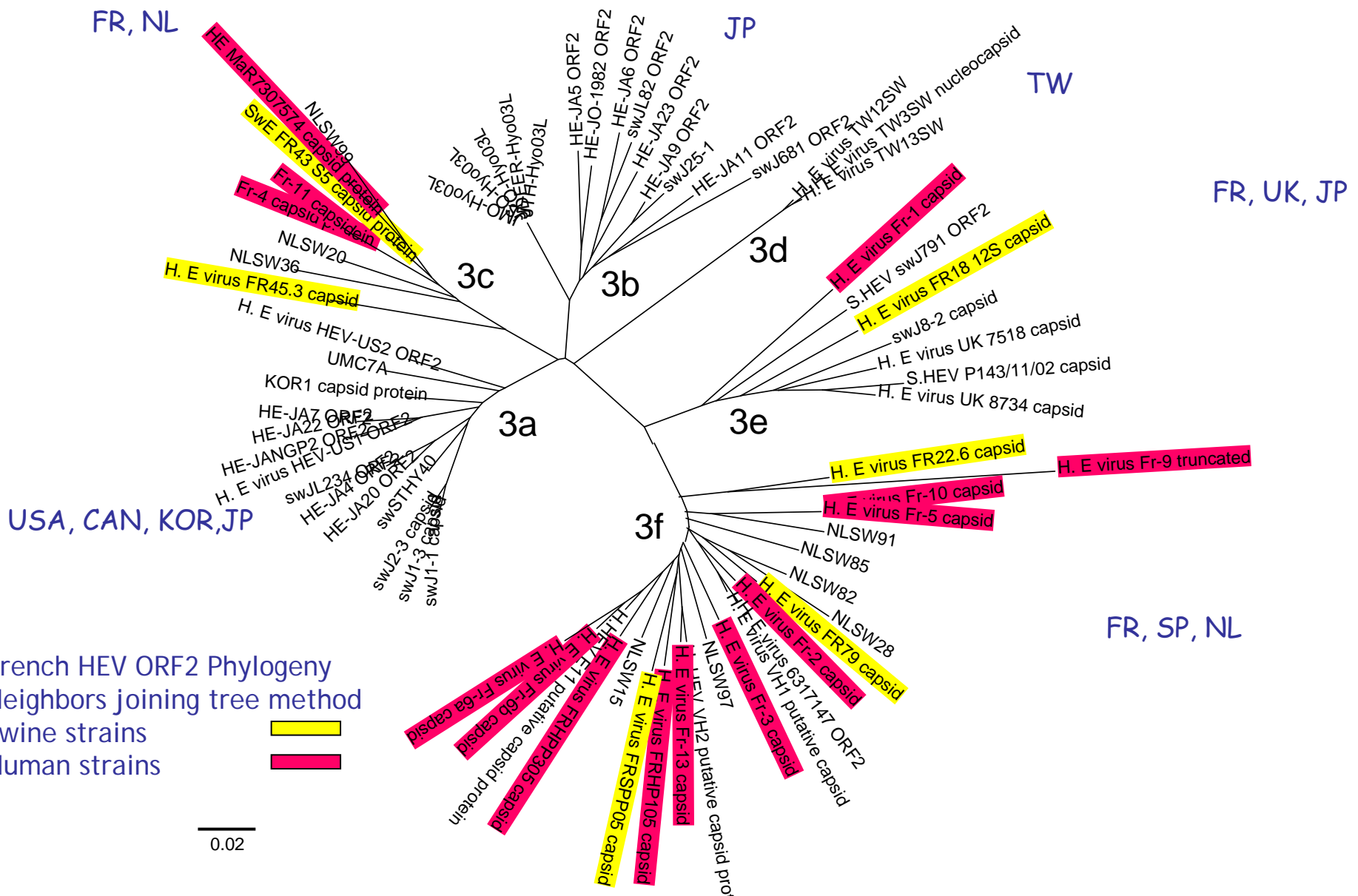


Virology

- HEV RNA is present in individual fecal samples
- HEV RNA is present in slurry manure storage
- HEV RNA present in manure storage is infectious (as confirmed by experimental infection of pig)
- HEV RNA sequences present in swine are closely related to human strains (Genotype 3c, 3e and 3f).

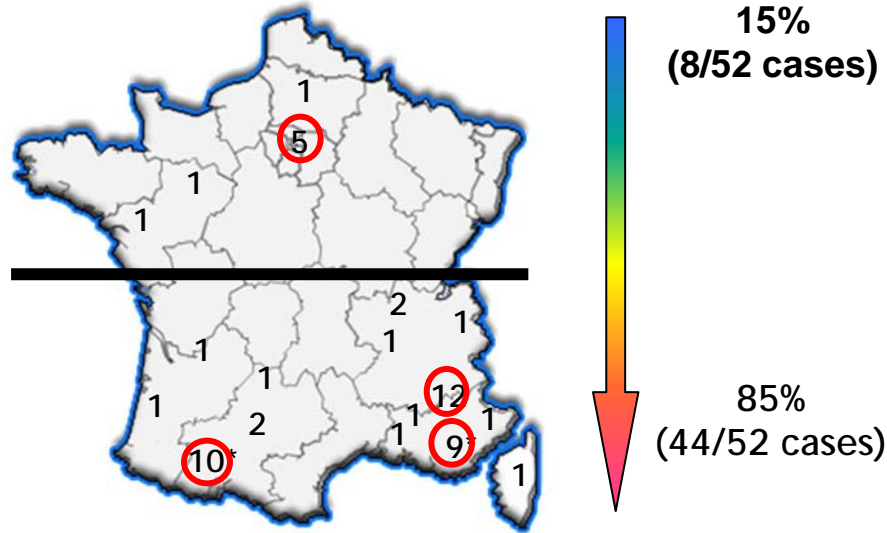


Molecular Virology : phylogenic analyses of French isolates



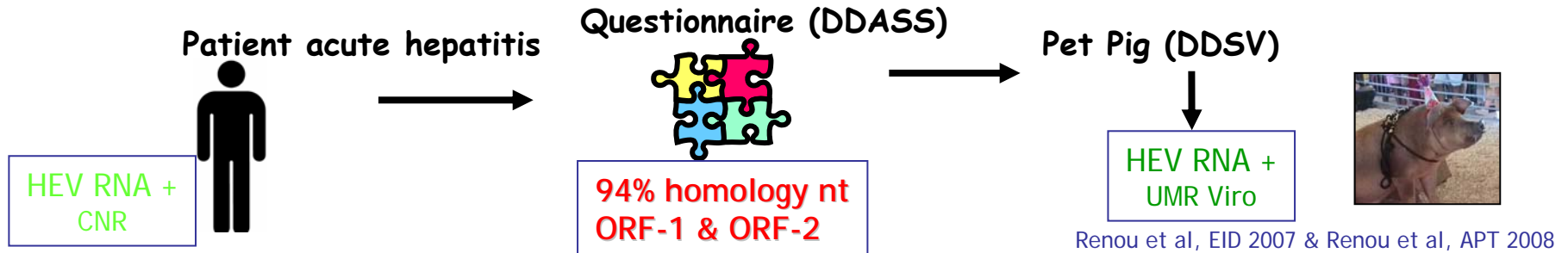
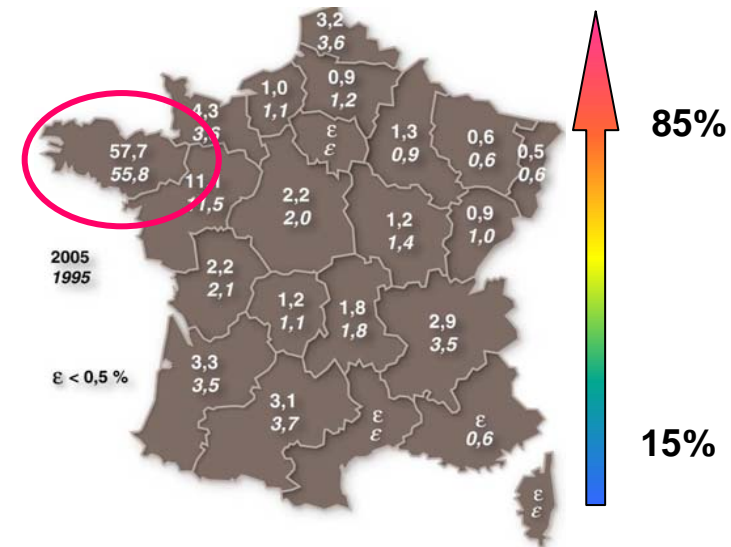
Epidemiology: study of clinical cases of HEV within the ANGH network

Geographic Distribution of 53 cases:
Increasing Gradient North-> South

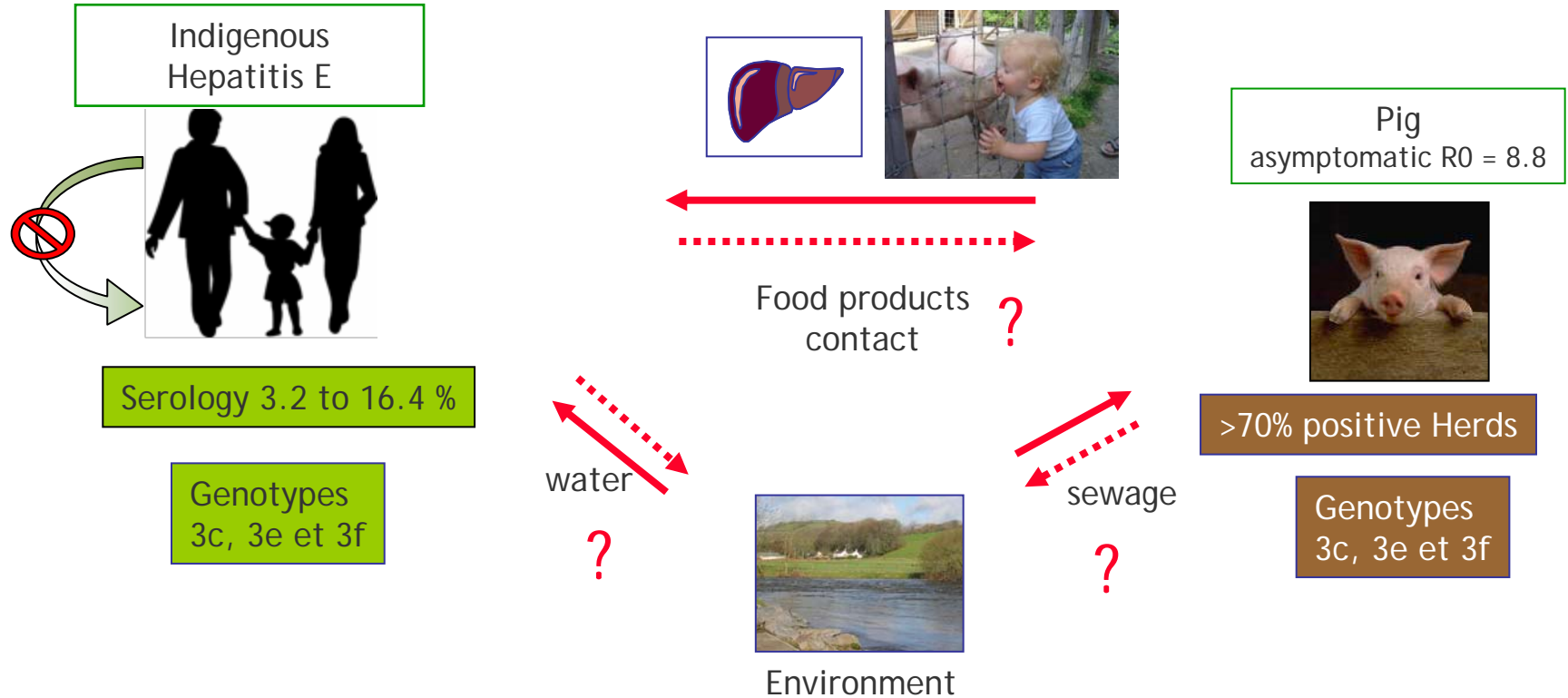


French Guinea = 1 case
 Indigenous cases (no Travel) = 47 cases (89%)
 1 case of fulminate hepatitis
 No particular risk factor identified (private well)

Geographic distribution of swine herds
Increasing Gradient South-> North



Conclusions



Acknowledgments

➤ UMR 1161 Eq VHE

Annie Boutrouille

Aurélie Lunazzi

Audrey Fraisse

Gaetana Di Liberto

Marc Eloit

➤ AFSSA Ploufragan

➤ Jean-Pierre Jolly

➤ Virginie Dorenlor

➤ Christelle Fablet

➤ CHU Purpan

➤ J. Izopet, JM. Mansuy

➤ CHG Hyères

➤ Christophe Renou

➤ CNR VHE

➤ E. Nicand

➤ Inserm U618

➤ P. Coursaget

➤ InVS

➤ E. Delarocque-A

➤ DERNS

➤ A. Thebault