

24th **ECCMID** Barcelona, Spain
10-13 May 2014

 **ESCMID** EUROPEAN SOCIETY
OF CLINICAL MICROBIOLOGY
AND INFECTIOUS DISEASES



Educational Workshop

Hepatitis E in pregnancy

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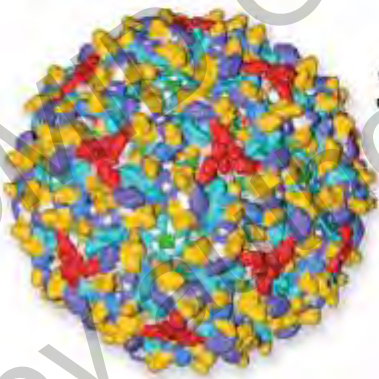
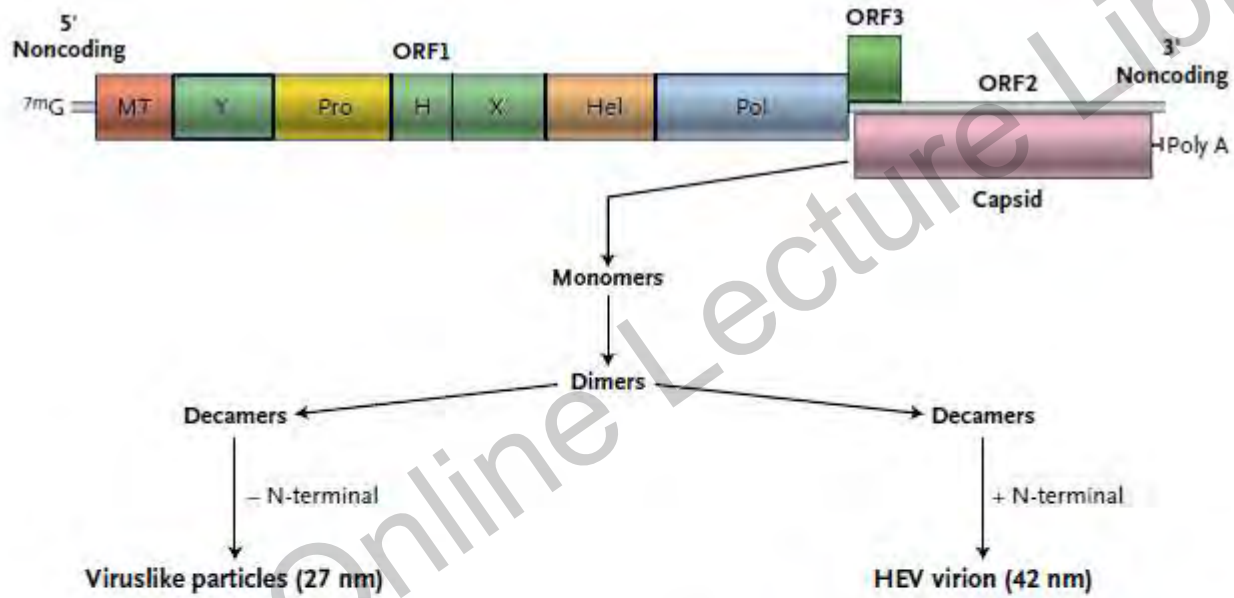
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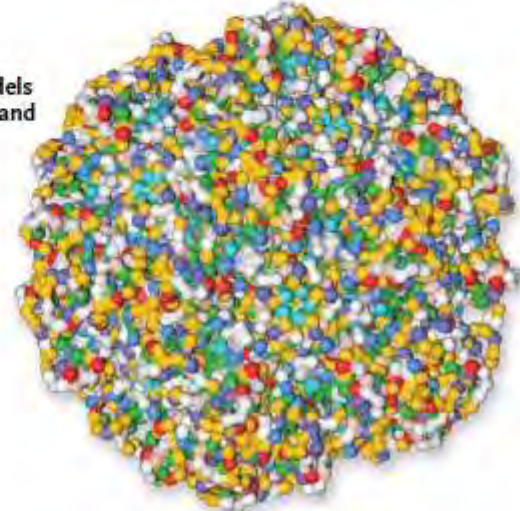
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Hospital Universitari

Advisory Boards: Janssen, MSD, Gilead
Educational presentations: Gilead, Bristol,
Janssen, MSD

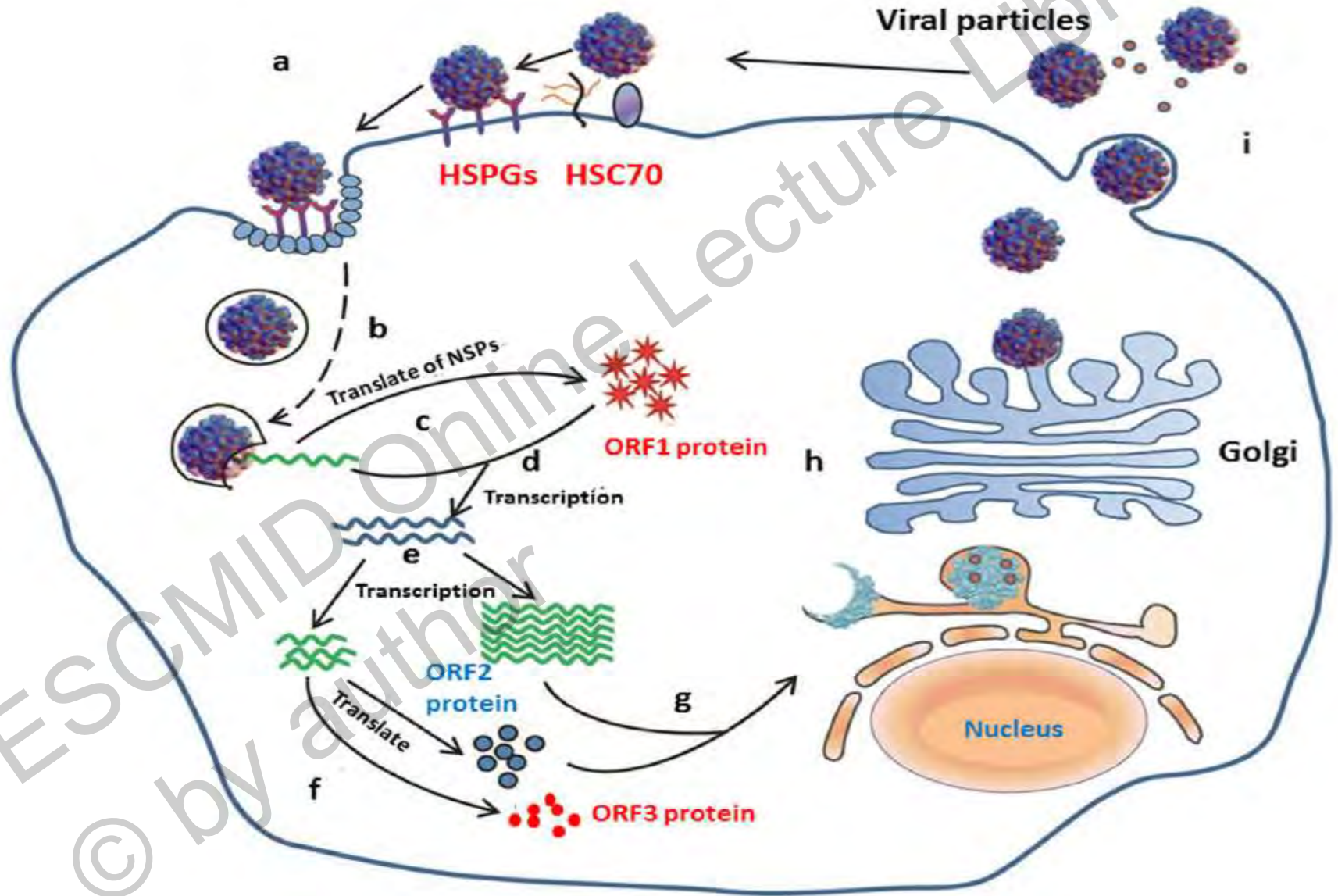
The virus



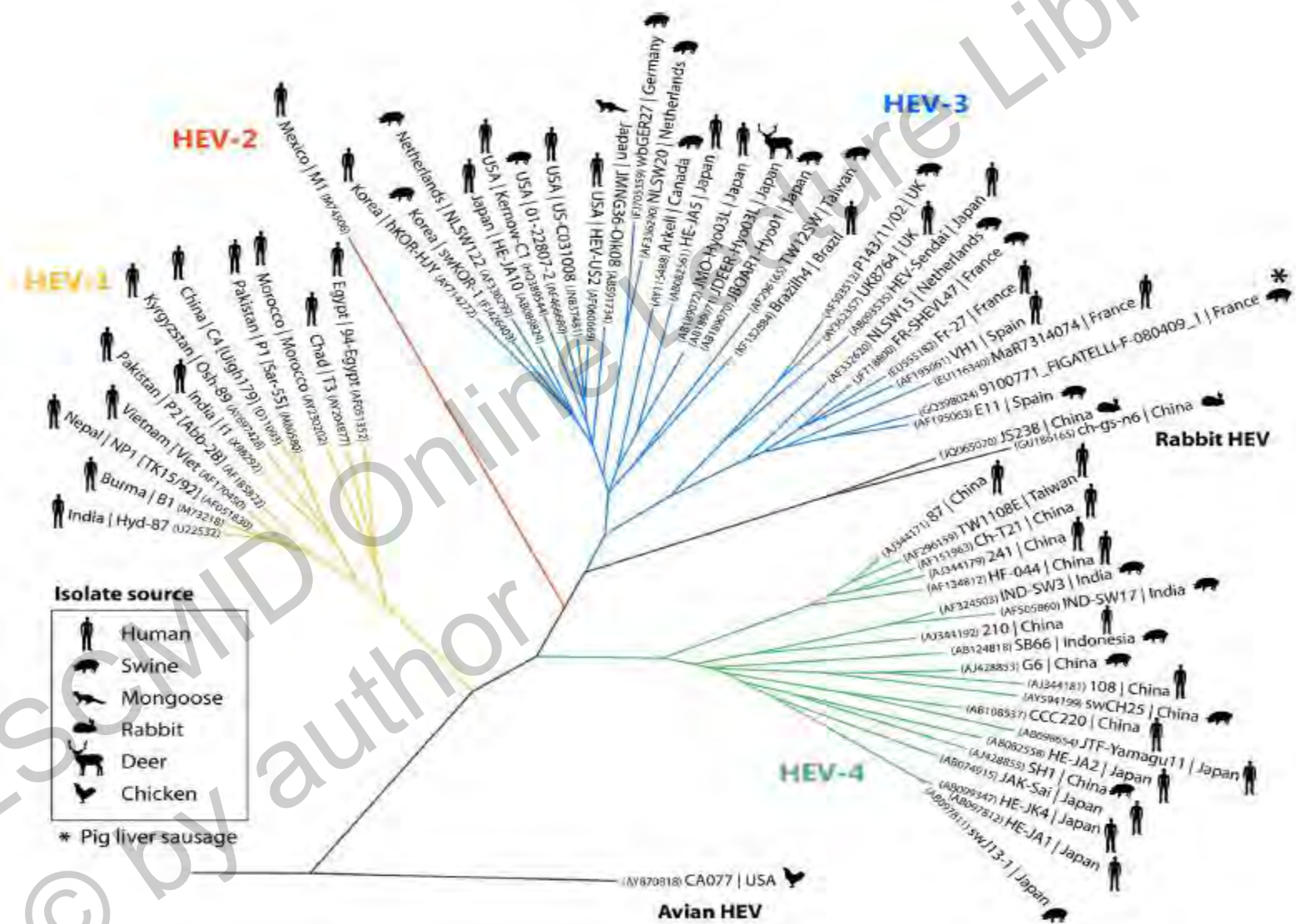
Color-enhanced surface models of the HEV viruslike particle and virion structures



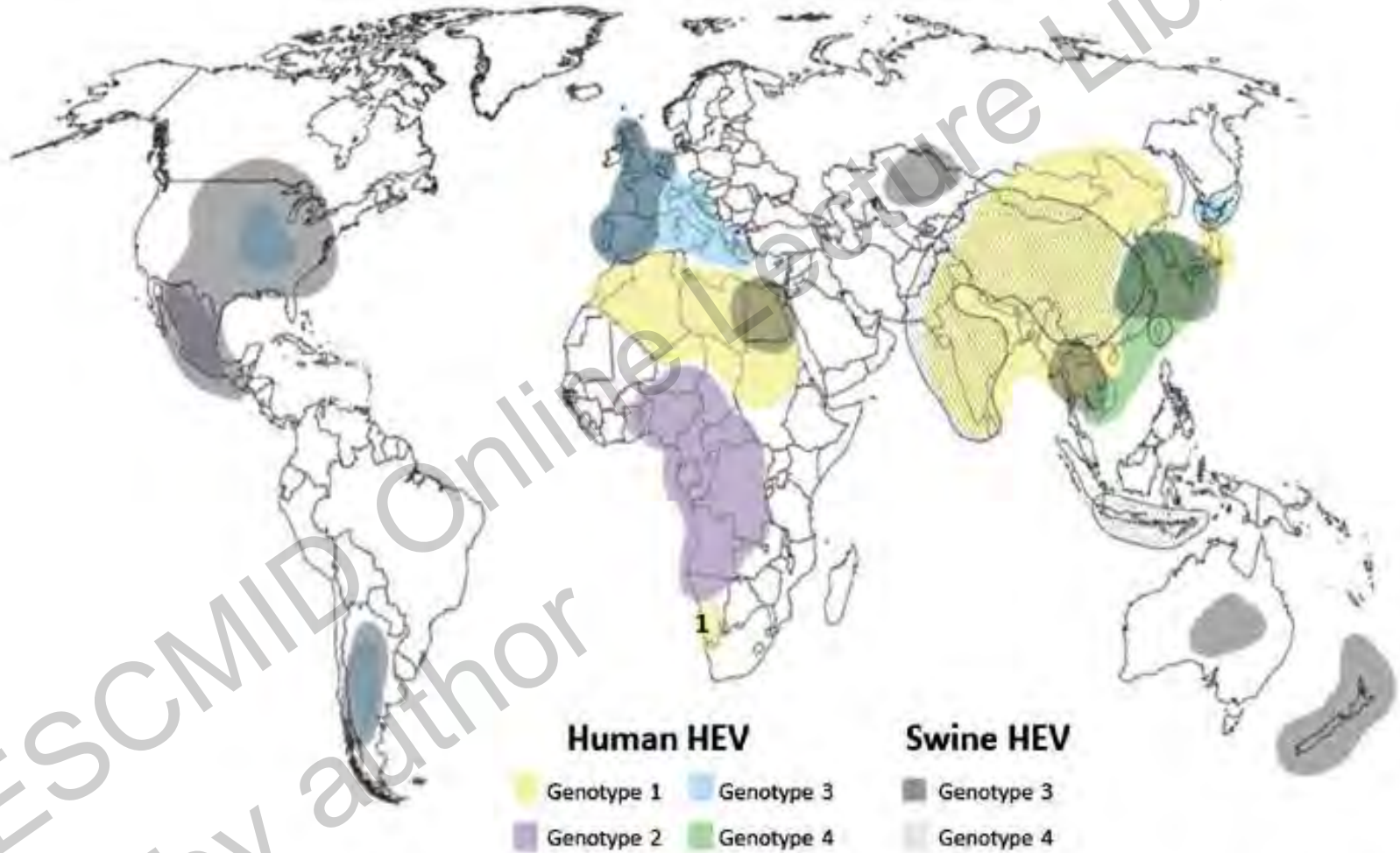
Replication cycle



HEV Genotypes

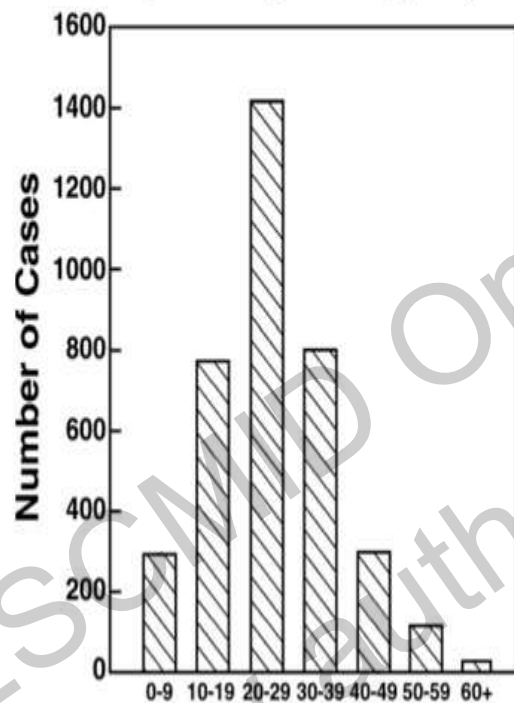


Geographic distribution

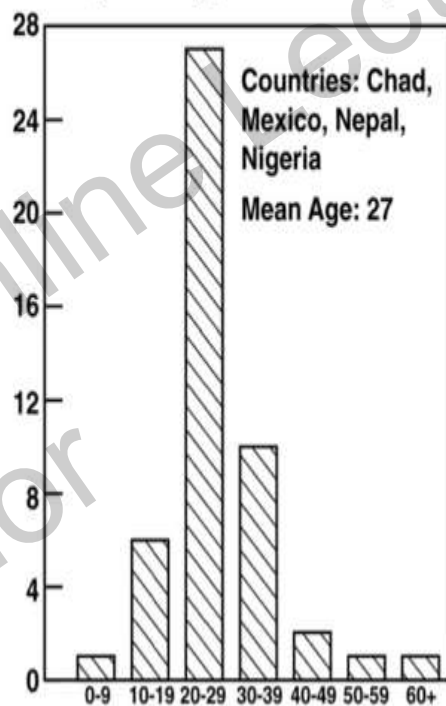


Age distribution

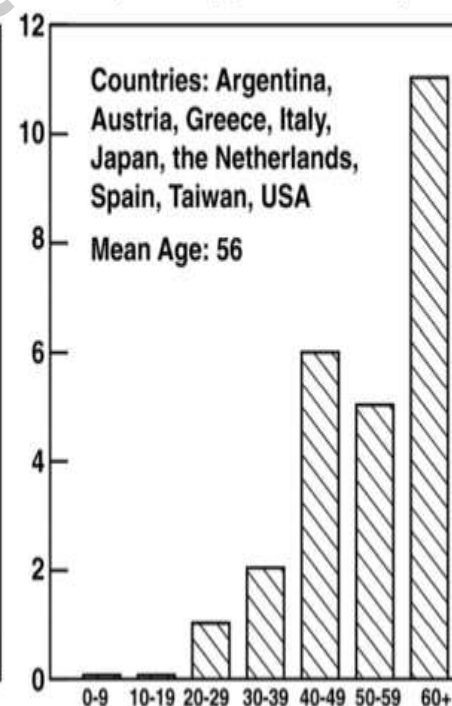
**Epidemic Hepatitis E:
Delhi, India, 1955
(Probably Genotype 1)**



**Sporadic Hepatitis E:
Developing Countries
(Genotypes 1 and 2)**



**Sporadic Hepatitis E:
Industrialized Countries
(Genotypes 3 and 4)**



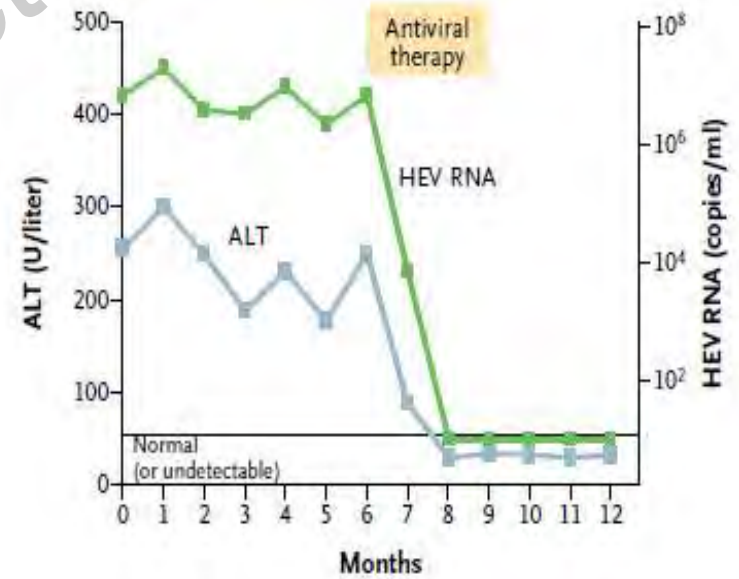
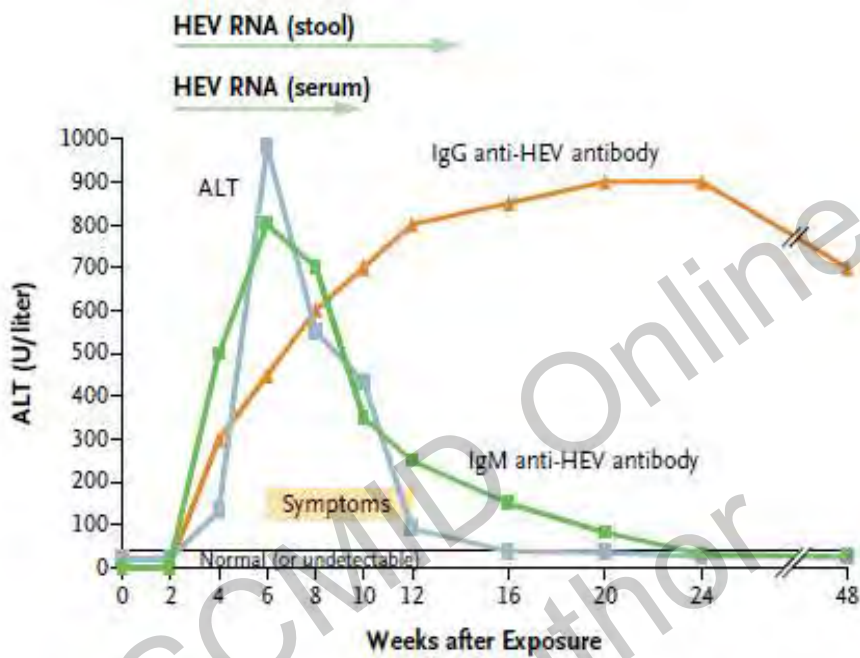
Age (Years)

Age (Years)

Question 1.

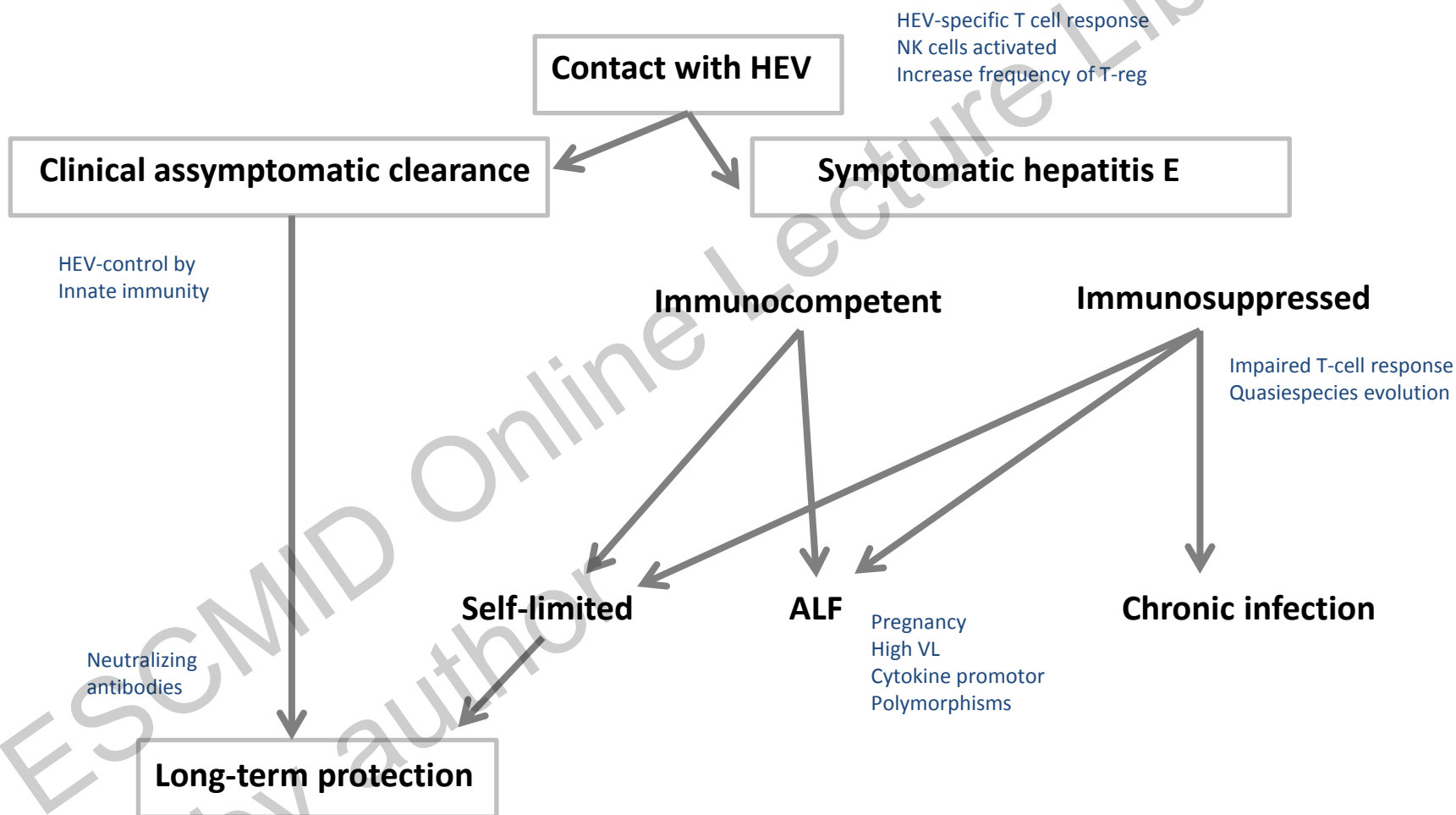
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HEV infection



IgG anti-HEV antibody	+	+	+	+
IgM anti-HEV antibody	+	+	+	-

Immune responses to HEV infection



HEV treatment

➤ Prevention: vaccine

Shrestha, NEJM 2007

Zhu, Lancet 2010

➤ If severe acute infection

Ribavirin: 5 cases

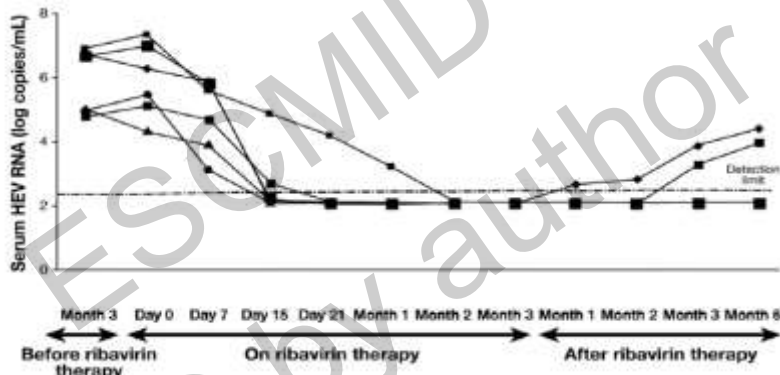
Pischke, Liver Int. 2013

Del Bello, J Hepatol 2012

Gerolami, J Clin Virol 2011

Goyal, Antivir Ther 2012

Tandon, Hepatol Res 2002



➤ If immunosuppression: adjust levels

Moal, J Med Virol 2013

➤ If chronification:

Peg-interferon:

Haagsma, Liver Transpl 2010

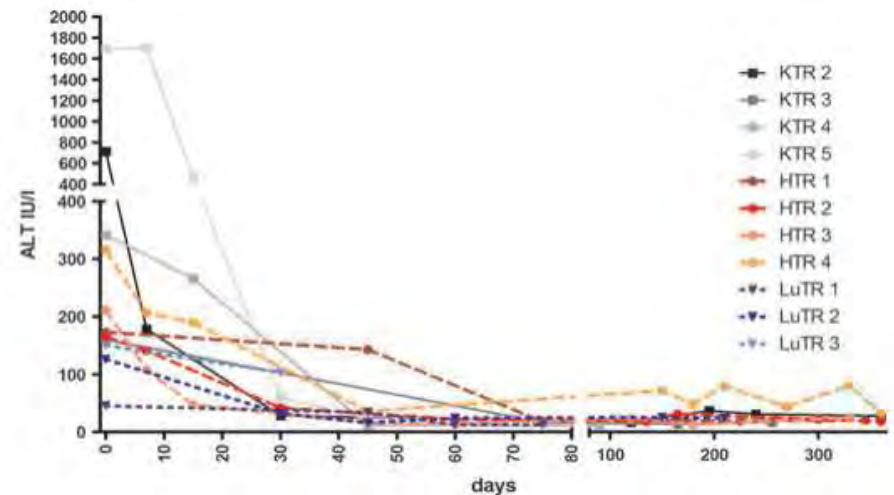
Kamar, Nephrol Dial Transpl 2010

Ribavirin:

Mallet, Ann Int Med 2010, AASLD 2010

Kamar, Gastroenterology 2010

Pischke, Liver Int. 2013



HEV: so many differences among genotypes

Characteristics	Genotypes 1 and 2	Genotypes 3 and 4
Geographic distribution	Developing countries only	Both developing and developed
Pattern of spread	Epidemic/Sporadic	Sporadic
Species specificity	Human	Swine, human
Major mode of spread	Fecal-oral, waterborne	Foodborne
Age	Adolescents and young adults	Disease rates higher among older adults
Sex	Similar	Men
Mortality	High in pregnant women	High among older adults
Extrahepatic features	Rare	Yes
Chronic infection	No	Immunosuppressed
Therapy	None (vaccine)	RBV, IFN

HEV in pregnancy

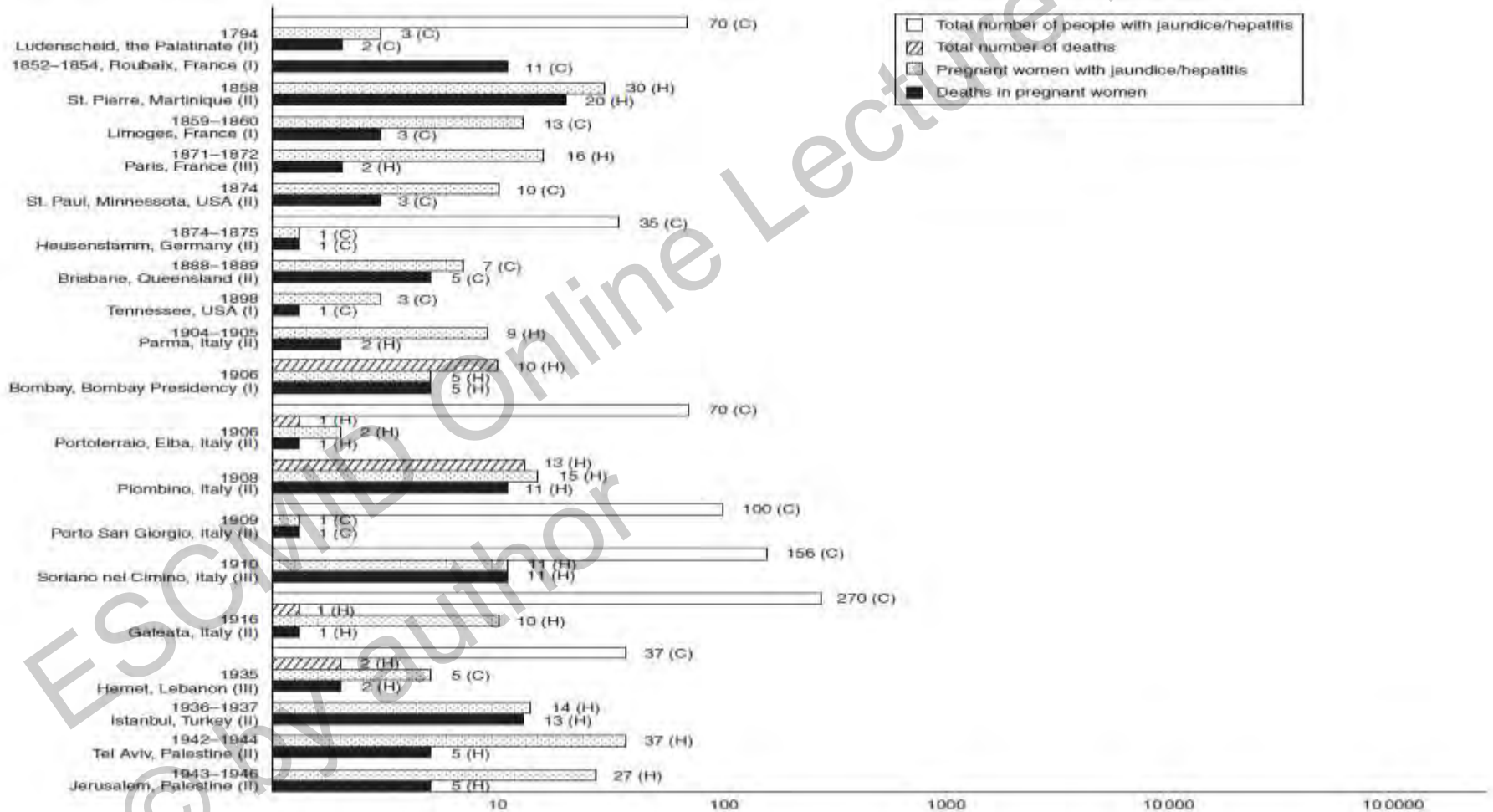
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Question 2.

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HEV in pregnancy

Morbidity and mortality frequencies in hepatitis E-like epidemics of jaundice or viral hepatitis with pregnancy deaths, 1794–1946.



HEV in pregnancy

Seroprevalence of IgG antibodies to HEV among asymptomatic pregnant woman:

Study location	Time	Seroprevalence n/N (%)	Risk factors
Egypt	(1997-2003)	2046/2428 (84.3%)	Older age, village, unwashed food
India	(2006-2007)	101/300 (33.7%)	Lower education / economic status
Bali	(2003)	501/819 (18.4%)	District of residence
Gabon	(2005)	119/840 (14%)	Urban>rural
Turkey	(2000-2002)	31/245 (12.6%)	Older age
Tunisia	(2006)	49/404 (12%)	Older age, high parity
China	(2012)	30/293 (10.2%)	Not described
Spain	(2004)	2/365 (0.6%)	Not described

HEV in pregnancy

Undeveloped countries & Genotype 1-2

¿Host related factors or viral factors?

- Genotype / viral load
- Coinfection
- Nutritional status
- Environment: seasonal rainfall patterns, sanitation systems, animal exposures

Mother:

- High incidence of fatal outcomes
- Peripartum Haemorrhage

Fetus:

- Miscarriage
- Stillbirth
- Premature delivery
- Neonatal jaundice

Maternal response to infection

Vertically transmitted infection



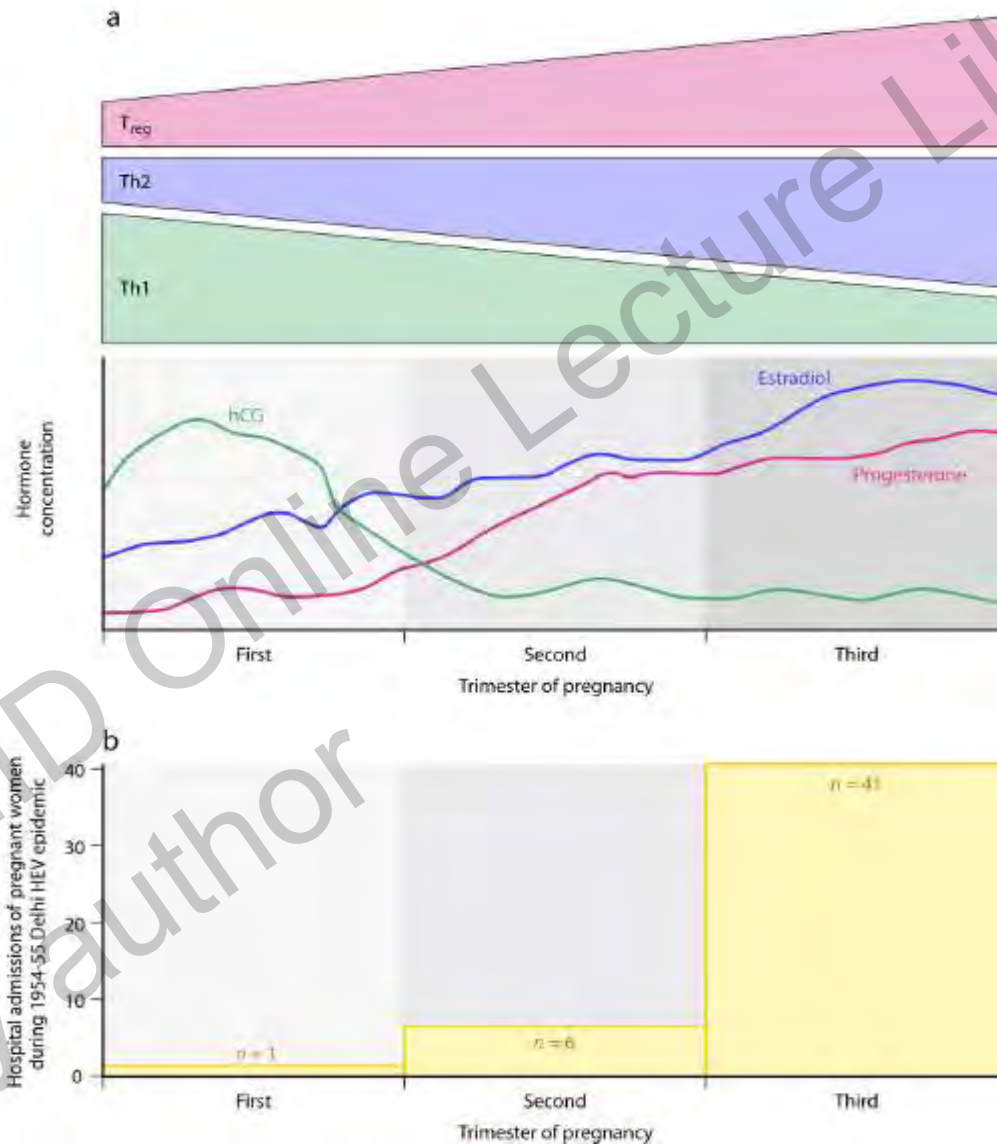
HEV in pregnancy

Vertically transmitted HEV infection, morbidity and mortality in live-born infants of mothers with laboratory confirmed antenatal HEV infection

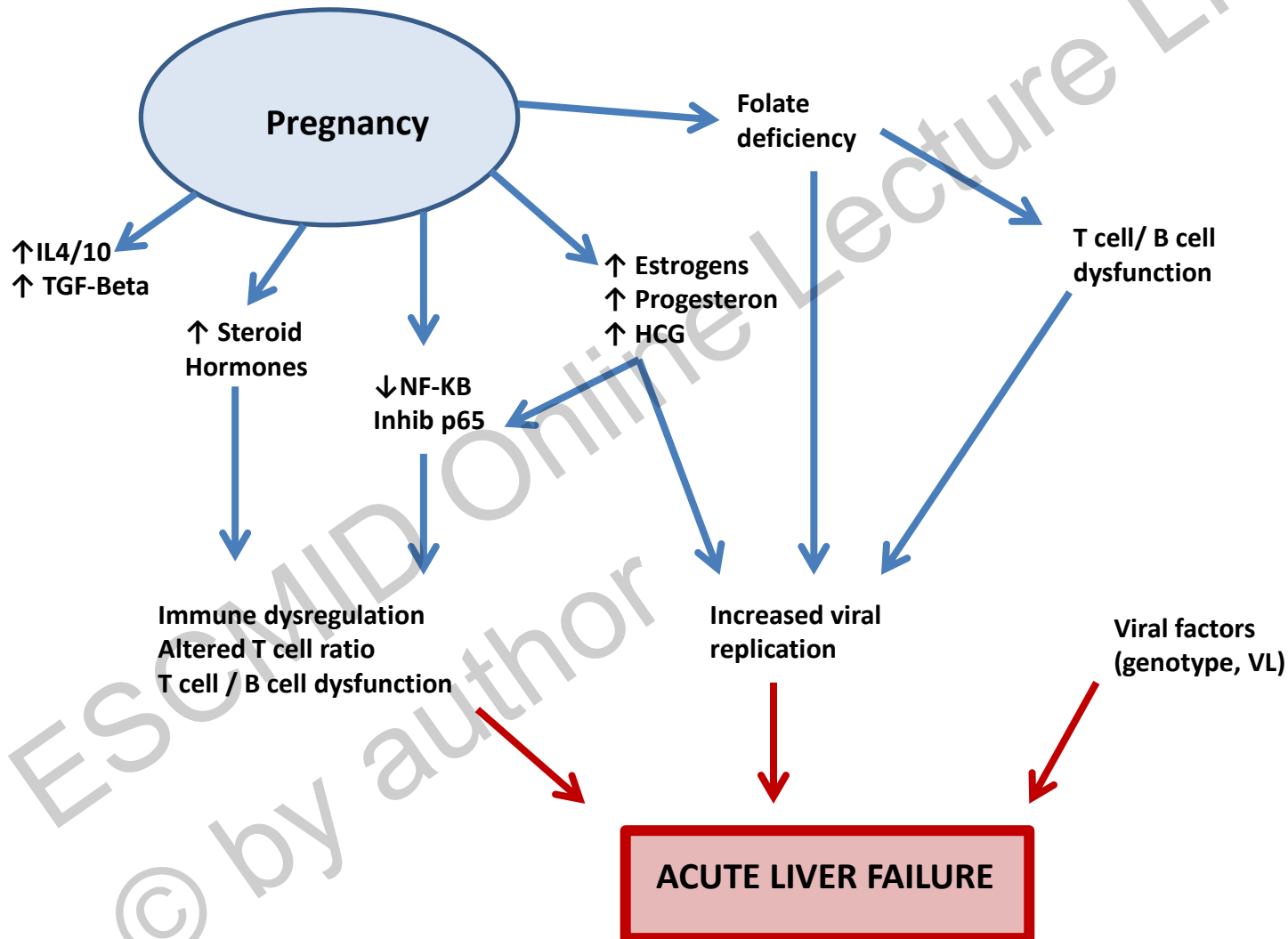
Location	Mothers with AVH/FHF	Live births	HEV infections in neonates (% of live births)	HEV cases in neonates (% of live births)	Icteric HEV cases in neonates (% of live births)	Neonatal deaths (% of live births)
India ¹	20/16	33	22 (67%)	22 (67%)	20 (61%)	11 (33%)
India ^{2,3}	19/9	18	6 (33%)	No data	No data	No data
India ⁴	8/14	6	3 (50%)	1 (17%)	1 (17%)	0 (0%)
Ghana ⁵	1/2	1	1 (100%)	1 (100%)	1 (100%)	0 (0%)

¹ Khuroo et al, JK Pract 2006; ² Kumar et al, Int J Gynaecol Obstet 2004; ³ Dahiya et al, Indian Gastroenterol 2005; ⁴ Singh et al, Indian J Pediatr 2003; ⁵ Bonney et al, BMC Res Notes 2012

Pregnancy: an unique immunological situation



Pregnancy: an unique immunological situation



HEV in pregnancy: coagulopathy

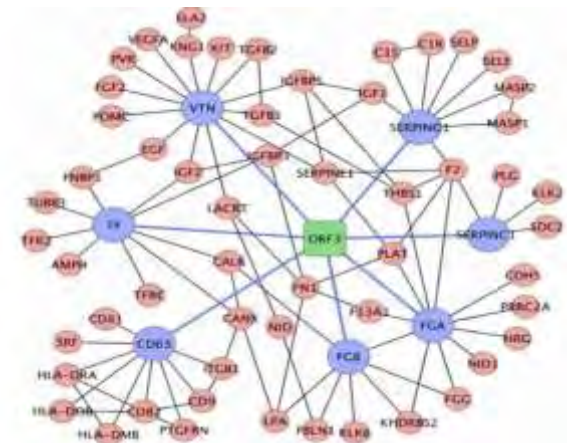
Post-partum haemorrhage (PPH) is the leading proximal cause of maternal death in developing countries

Variable	HEV-Infected Women (n = 132), n/n (%)	Non-HEV-Infected Women (n = 88), n/n (%)	Relative Risk (95% CI)	P Value
Maternal mortality rate				
Overall	54/132 (41)	6/88 (7)	6.0 (2.7–13.3)	<0.001
Patients with fulminant hepatic failure	54/73 (74)	6/18 (33)	2.2 (1.1–4.3)	0.001
Second trimester	18/27 (66)	0/7 (0)	–	0.002
Third trimester	36/46 (78)	6/11 (54)	1.4 (0.8–2.5)	0.11
Patients without fulminant hepatic failure	0/59 (0)	0/70 (0)	–	1.00
Medical complications				
Coagulation defect†	104/132 (79)	32/88 (36)	2.2 (1.6–2.9)	<0.001
Nasal or gastrointestinal hemorrhage	25/132 (19)	4/88 (4)	4.2 (1.5–11.6)	0.002
Leukocyte count $\geq 11 \times 10^9$ cells/L	86/132 (65)	31/88 (35)	1.8 (1.4–2.5)	<0.001
Serum creatinine concentration $\geq 34 \mu\text{mol/L}$ ($\geq 2 \text{ mg/dL}$)	39/132 (30)	4/88 (4)	6.5 (2.4–17.5)	<0.001
Ascites	33/132 (25)	5/88 (6)	4.4 (1.8–10.8)	<0.001
Clinical signs of increased intracranial tension	27/132 (20)	1/88 (1)	18.0 (2.5–130.1)	<0.001

Patra S, *Ann Int Med* 2007

Puri M, *Obstet Med* 2011

HEV-ORF3 may interact with several clotting related pathways:



HEV in pregnancy: Key questions

Can maternal vaccination prevent vertical transmission of HEV?

Does vertical transmission occur during labor?

Can breastfeeding contribute to neonatal infection?

What risks do early in pregnancy maternal HEV infections pose to fetal health?

Are some delivery-associated PPH related to not diagnosed HEV infection?

How to treat in order to avoid maternal, fetal and neonatal morbidity and mortality?



Evaluate the effectiveness and safety of vaccines

Additional investigation of HEV pathogenesis in pregnant women

Population-based serologic surveillance in pregnancy and follow-up of neonatal outcomes are needed to address these issues