Hepatitis Viruses

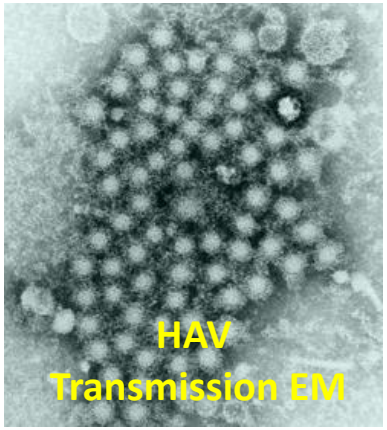
Virus	Transmission Route	Disease	Incubation Time(days)
Hepatitis A Virus	Water/ Poor Sanitation	Acute	15–45
Hepatitis B Virus	Blood	Acute / Chronic	45–160
Hepatitis C Virus	Blood	Acute / Chronic	15–150
Hepatitis D Virus	Blood	Chronic	30–60
Hepatitis E Virus	Water/ Poor Sanitation	Acute / Epidemic	15–60

Hepatitis Viruses

Virus	Virus Family	Genome
Hepatitis A Virus	Picornavirus	(+) ssRNA
Hepatitis B Virus	Hepadnavirus	dsDNA
Hepatitis C Virus	Flavivirus	(+) ssRNA
Hepatitis D Virus	Deltavirus	ssRNA (Viroid-like)
Hepatitis E Virus	Hepevirus	(+) ssRNA

Hepatitis A Virus

- Historical references to a transmissible (non-blood borne) hepatitis
- 1940s-50s Faecal-oral transmission – distinguished HAV from "homologous serum jaundice" (i.e. HBV)
- 1973 EM of faecal material from infected human volunteers (who had ingested faecal extracts from suspected HAV cases)
- 1979 Cell culture production of HAV
- Genome Identified and cloned in early-mid 1980s
- 1987 RNA transcripts used to produce HAV in cell culture
- 1990s cell culture derived HAV used to make an effective vaccine
- HAV classified in the Hepatovirus genus of Picorna viridae



Hepatitis A Virus: Transmission

Mainly by the faecal-oral route:

- **Contamination of food or water**
  - **Poor hand washing – faecal residues transferred to the food.**

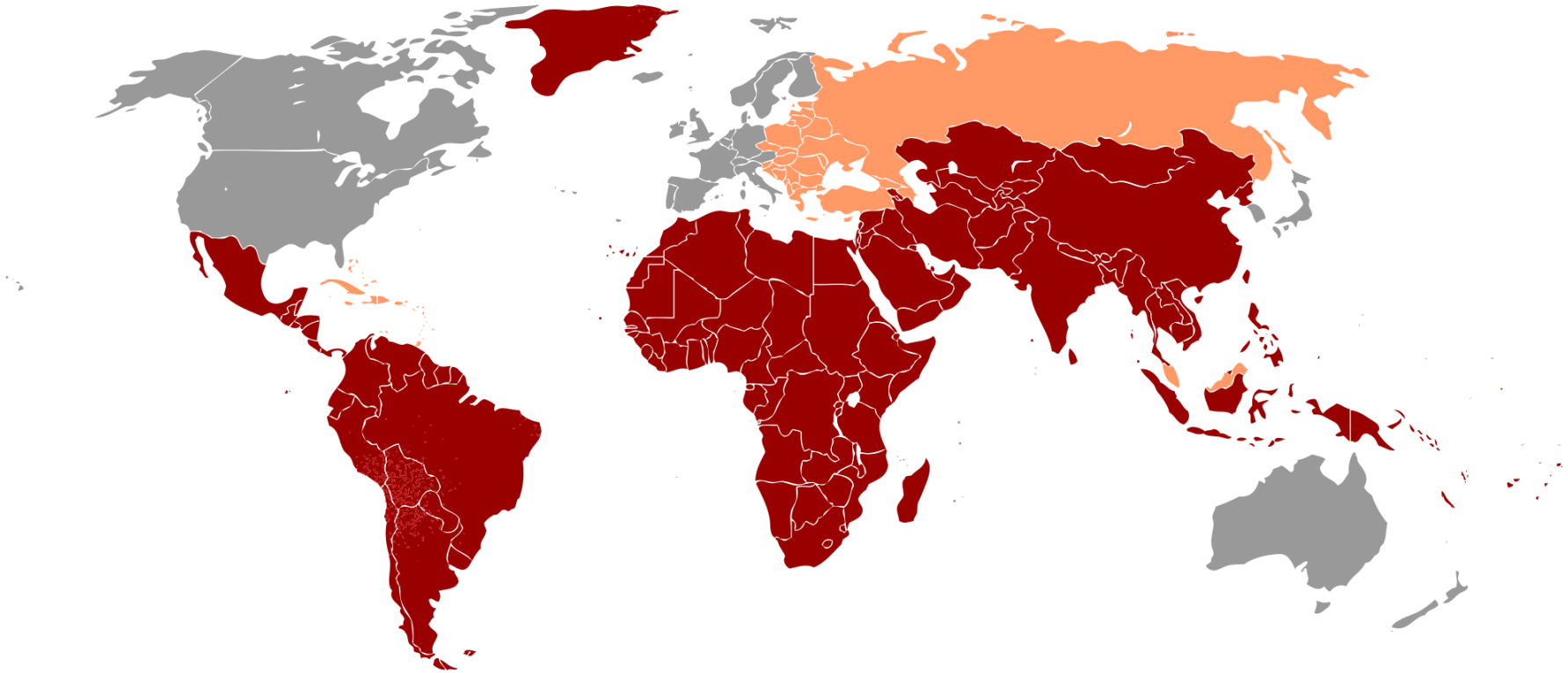
  - **Sewage → Shellfish**

- **Close person-to-person contact**
- **Sexual oral-anal contact**

Less commonly:

- **In body fluids e.g. blood and saliva**

Geographic distribution of Hepatitis A prevalence (Anti-HAV-Antibody), 2005



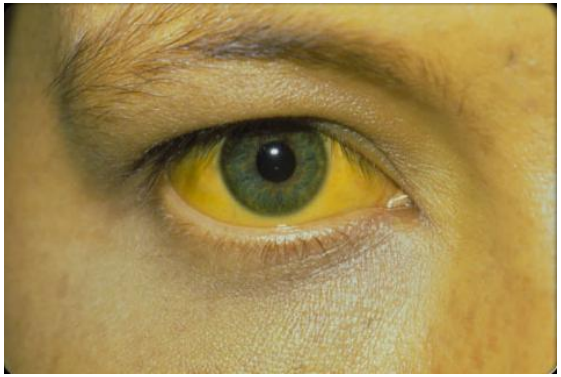
High: Greater than 8%
Intermediate: Between 2-8%
Low: Less than 2%

Hepatitis A Virus: Transmission

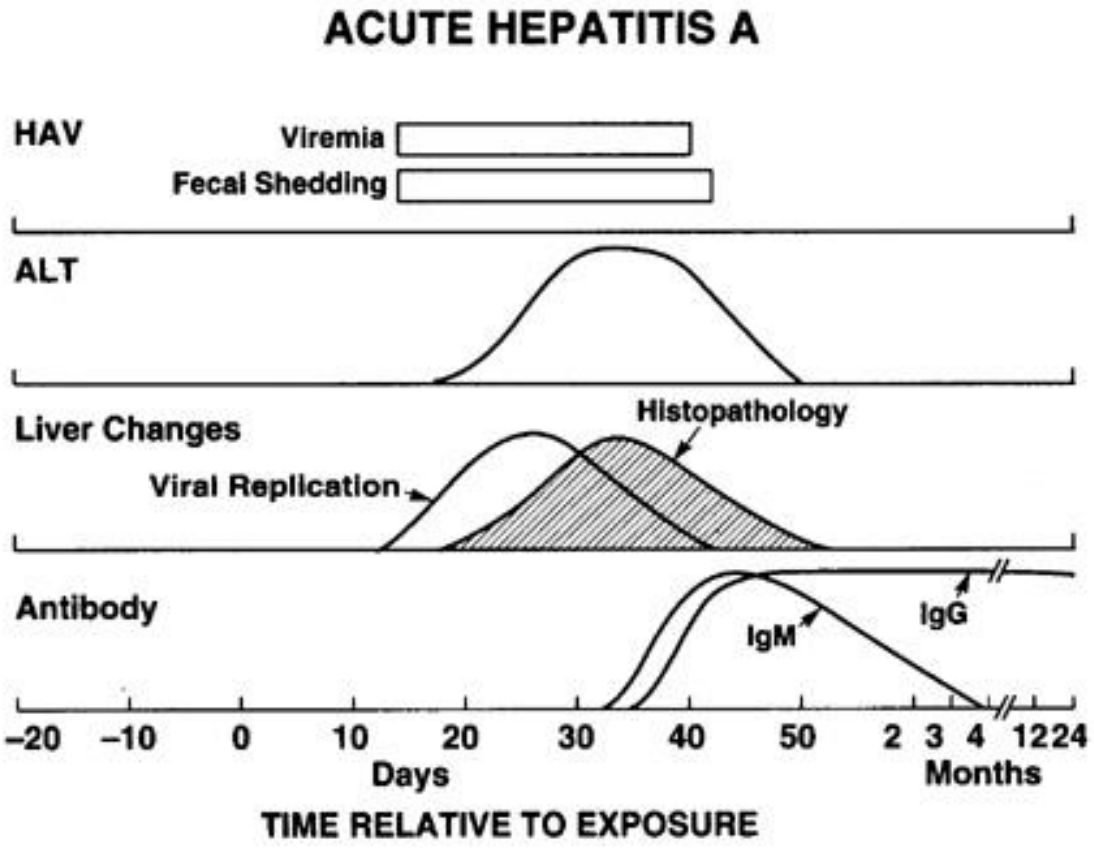
- **Extensive shedding of virus in faeces during 3-6 week incubation period and early days of illness**
- **Causes high prevalence when low levels of hygiene are present**
- **HAV is very stable at ambient temperature and low pH increasing its longevity in contaminated food and water**
- **Resistant to acid and detergents – can pass through the stomach on entry and leave via the biliary tract on exit**
- **Secreted from hepatocytes through biliary system into intestine → faeces**

Hepatitis A Virus: Symptoms

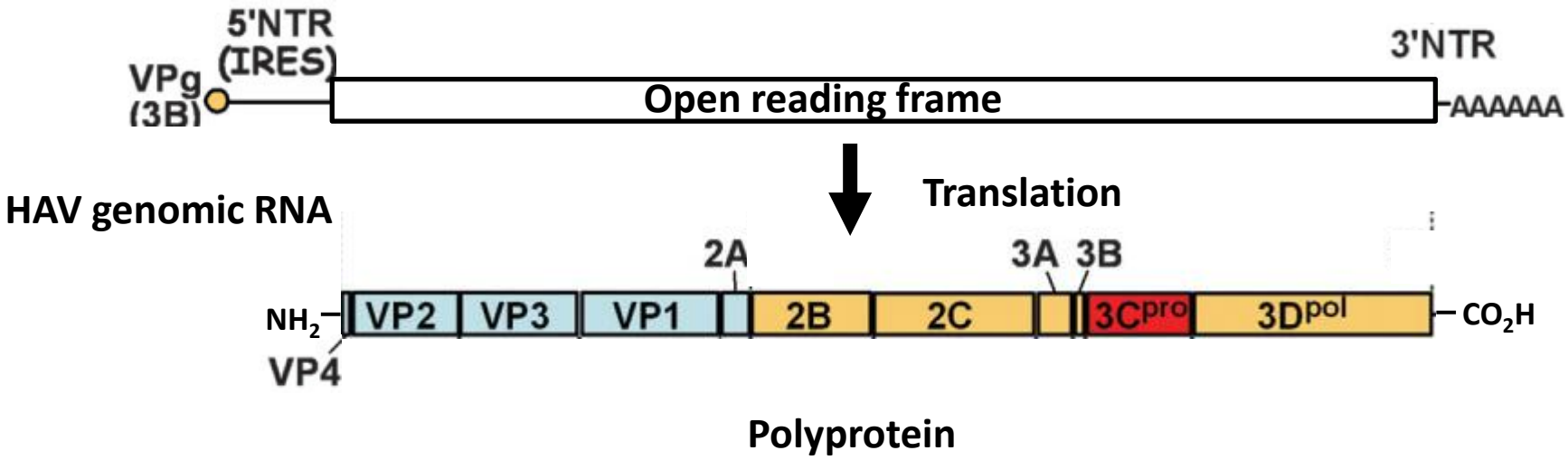
- Fatigue,
- Nausea,
- Poor appetite,
- Stomach pain,
- Mild fever, or
- Yellow skin or eyes (jaundice.)



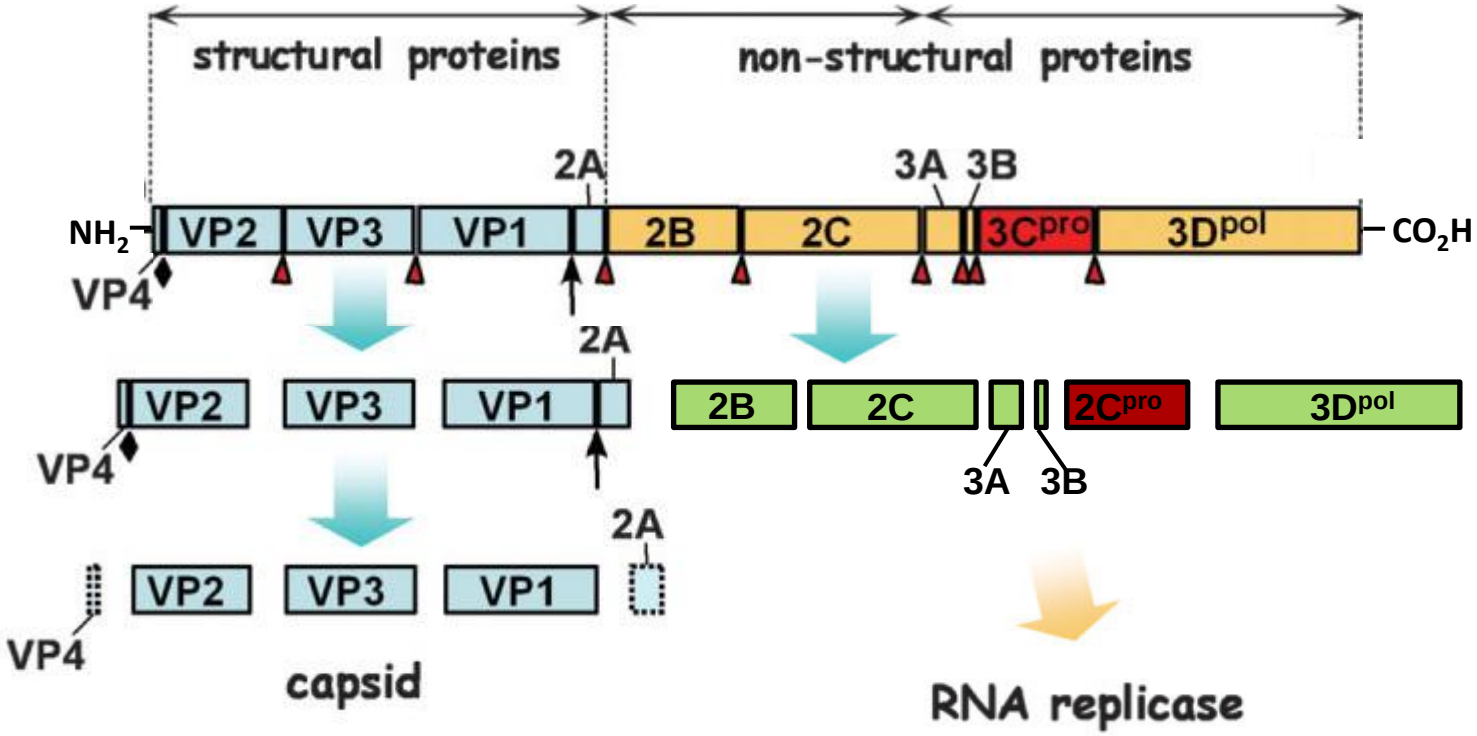
Hepatitis A Virus: Pathogenesis



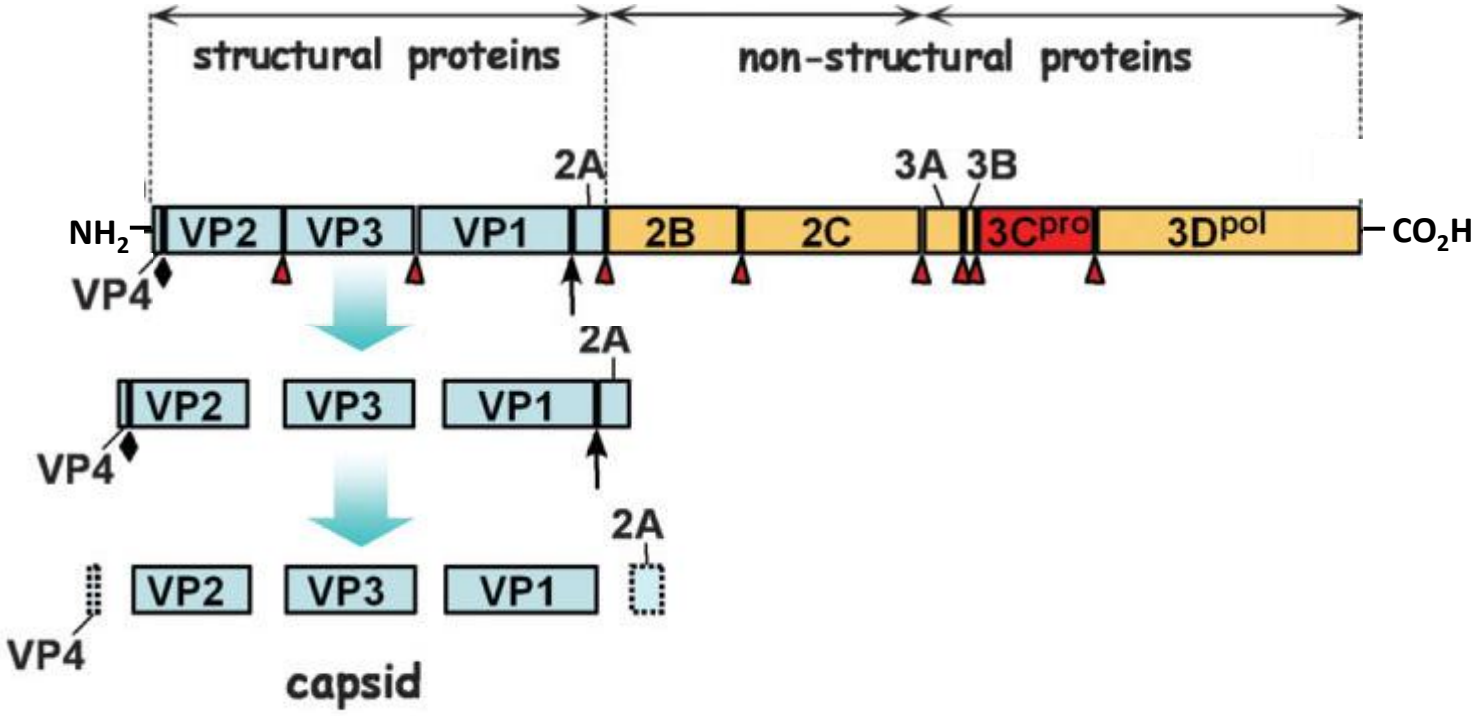
Hepatitis A Virus Genome



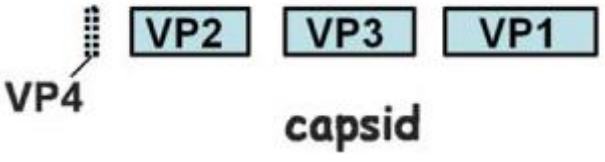
Hepatitis A Virus: Polyprotein Processing



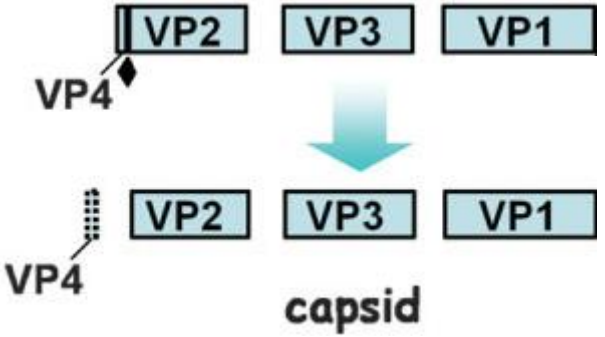
Hepatitis A Virus: Virus Assembly



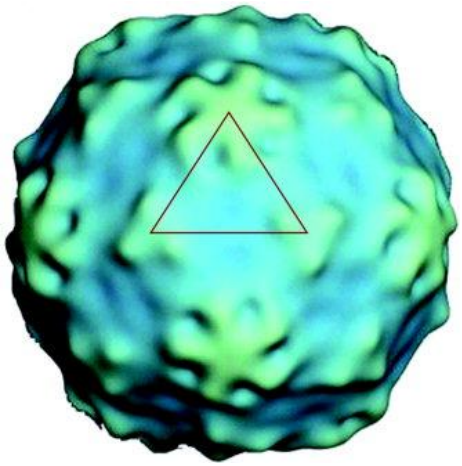
Hepatitis A Virus Particle



60 copies of each protein

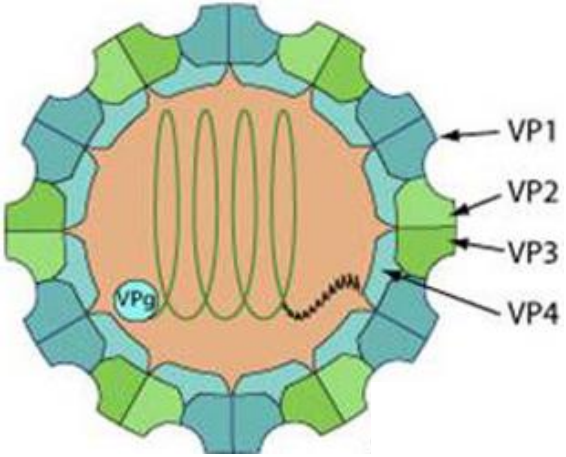


Cleavage between VP2 and VP4 after genome encapsidation



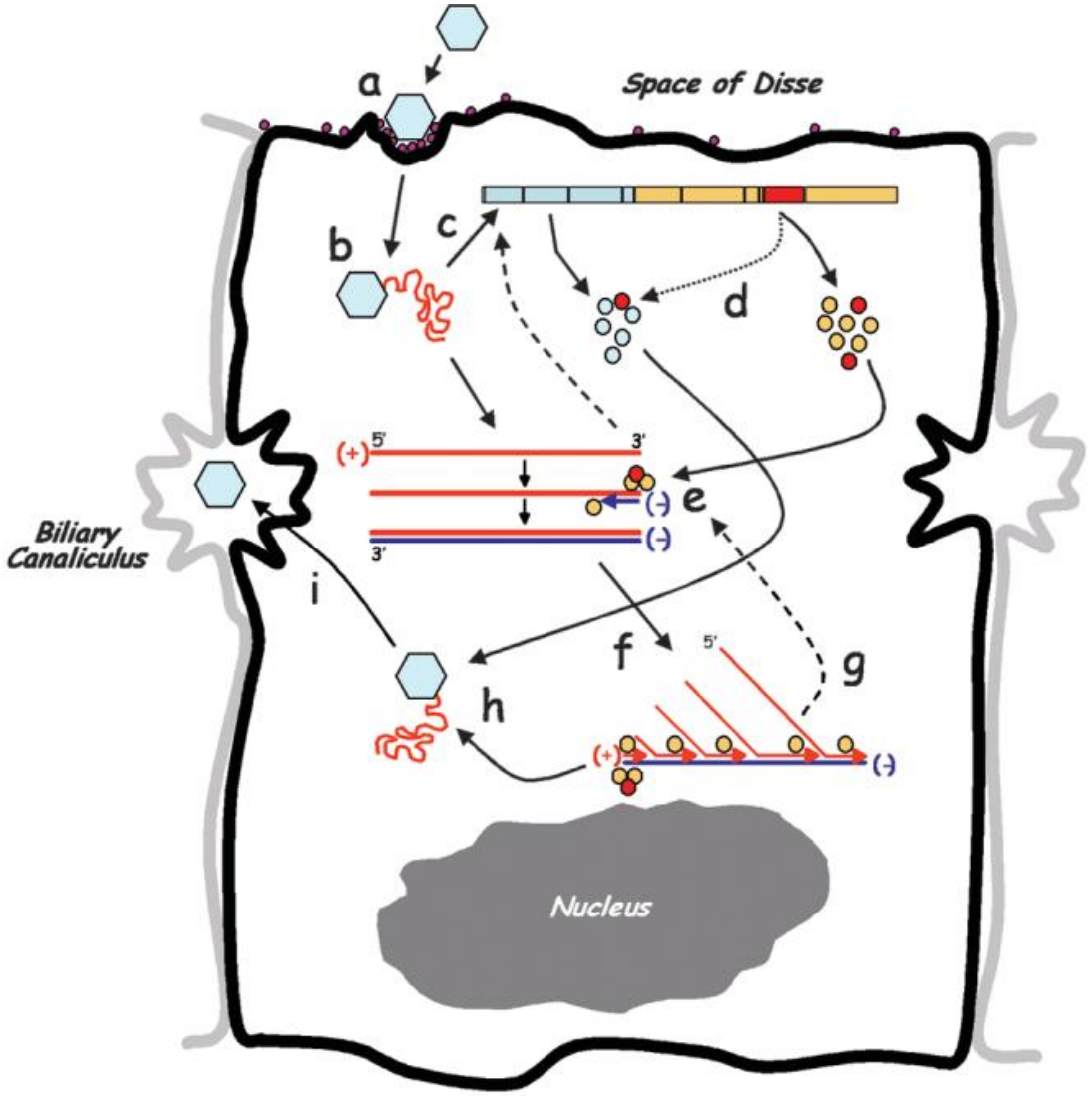
HAV structure (Cryo-EM)

HAV structure Diagrammatic



HAV structure Cross-section

Hepatitis A Virus Replication



(a) Virus entry as HAV-IgA complexes

(b) Uncoating and genome release

(c) cap-independent translation.

(d) post-translational proteolytic by viral protease, 3Cpro.

(e) Negative RNA synthesis.

(f) Positive RNA synthesis.

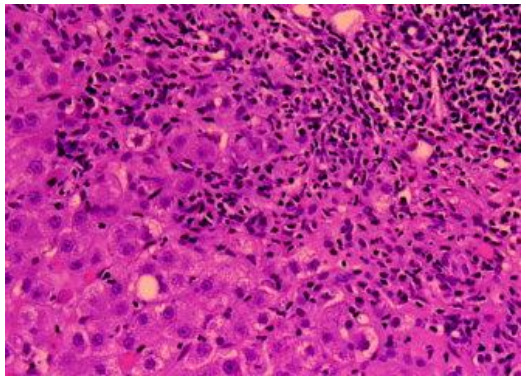
(g) Some newly synthesized positive-sense RNA is recycled for further RNA synthesis or translation (dashed lines).

(h) Positive-strand RNA molecules are packaged into new viral particles.

(i) Newly assembled HAV particles are secreted by the cell across the apical membrane of the hepatocyte into the biliary canaliculus, from which they are passed into the bile and small intestine.

Hepatitis A Virus: Host Responses

- Not cytopathic in cell culture and in vivo
- HAV blocks TLR3 and RIG-I signals reducing type1 IFN protection
- Injury due to immunopathic effects
- Cytotoxic $CD8^+$T cells recovered from liver
- $CD8^+$T cells secrete IFNγ – stimulates recruitment of inflammatory cells to site of HAV replication
- Anti-HAV IgM produced initially then protective IgG



Liver section from acute HAV patient
Shows lymphocyte invasion
and heptatocyte ballonning

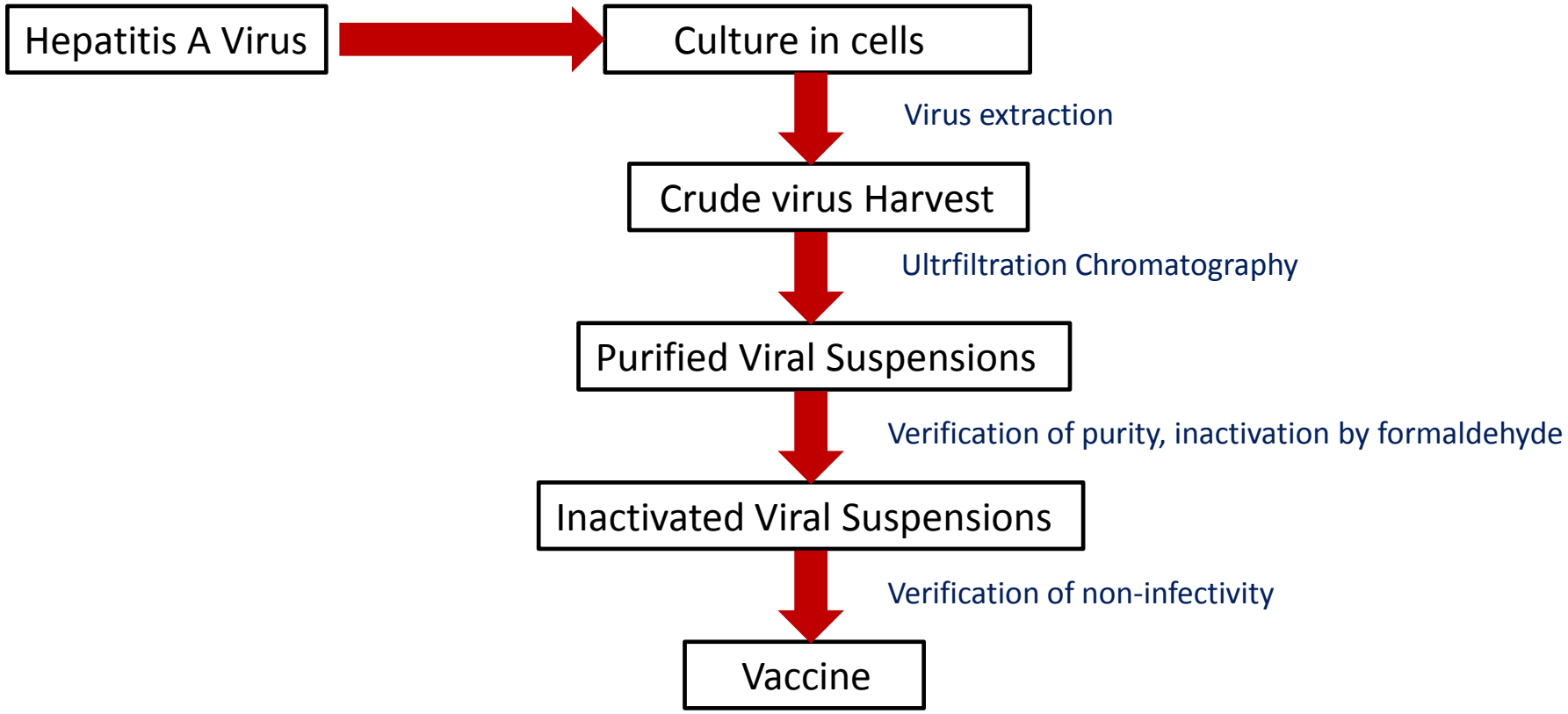
Prevention of Hepatitis A

- Improvement in water supply, sanitation and hygiene
- Isolation of infected individuals
- Passive immunization (IgG)
- Active immunization (vaccination)

Inactivated Vaccine

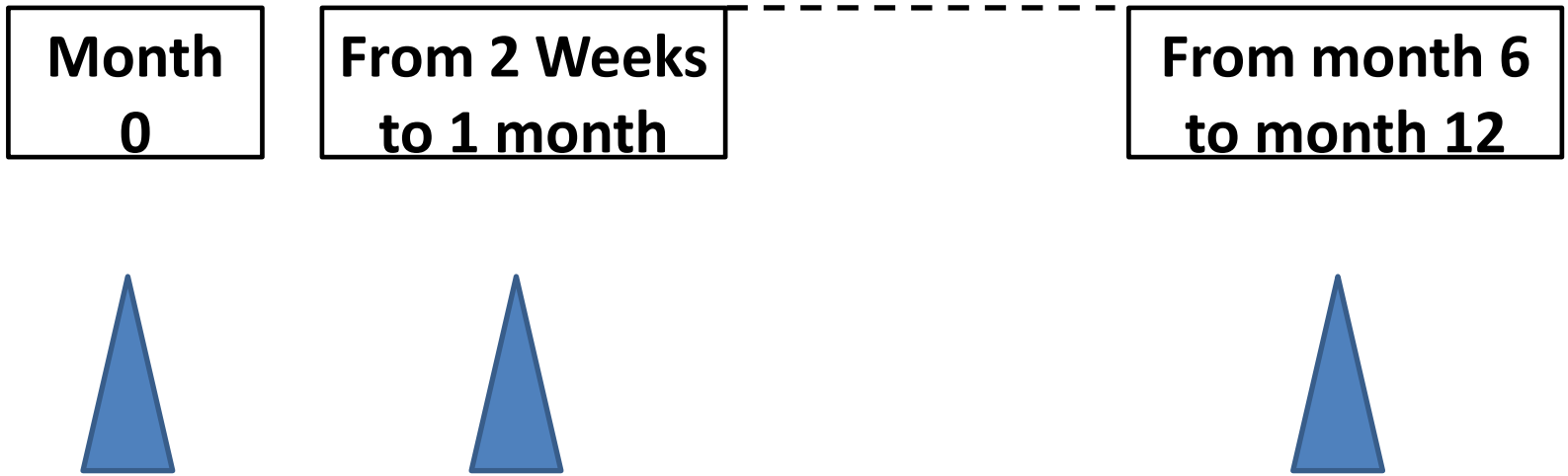
- **Killed virus – incapable of causing active infection**
- **Killed virus – possesses the antigens which stimulate the production of anti-HAV**
- **Developed using proven technology (polio, Salk)**

Production Process for Inactivated Hepatitis A Vaccine



Vaccination Schedule

Primary course **Booster dose**



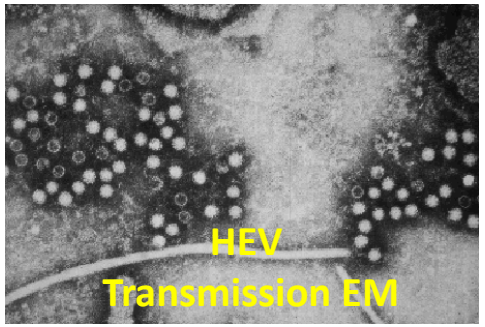
- **Highly effective - seroconversion rate 99.9 – 100%**

Hepatitis A Vaccine Recipients

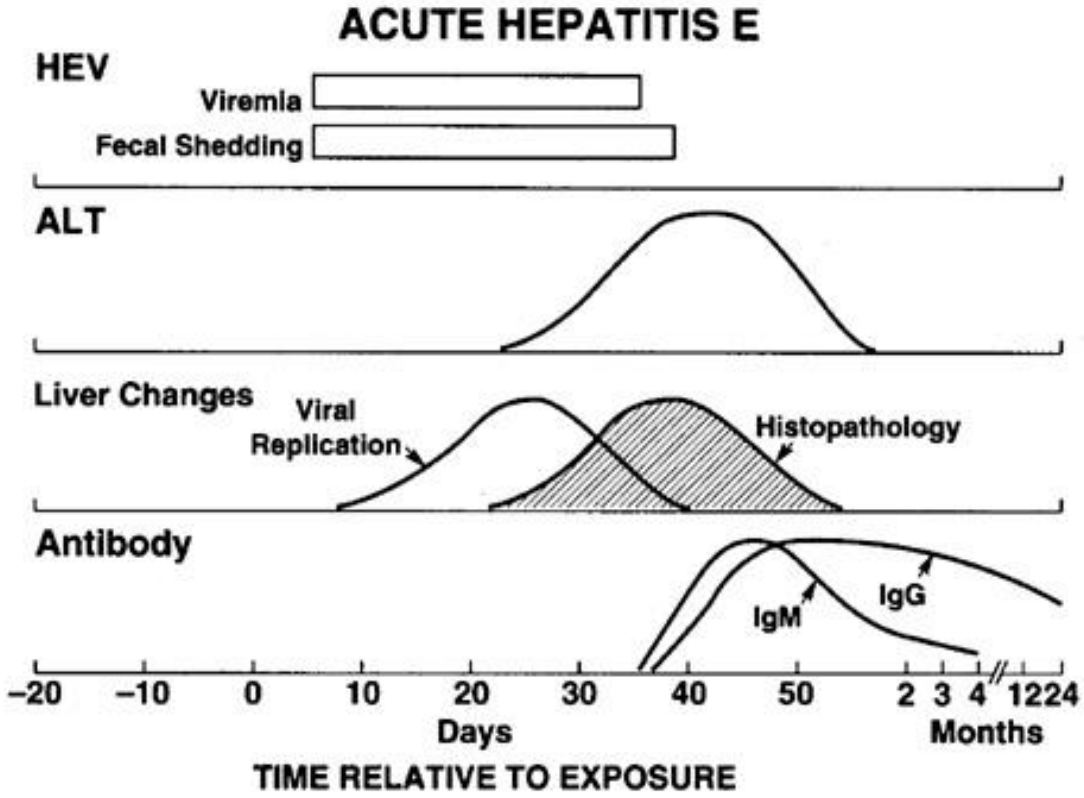
- Travelers to areas with increased rates of hepatitis
- Men who have sex with men
- Injecting and non-injecting drug users
- Persons with clotting-factor disorders (e.g. haemophilia)
- Persons with chronic liver disease
- Military personnel
- Day care centre personnel

Hepatitis E Virus

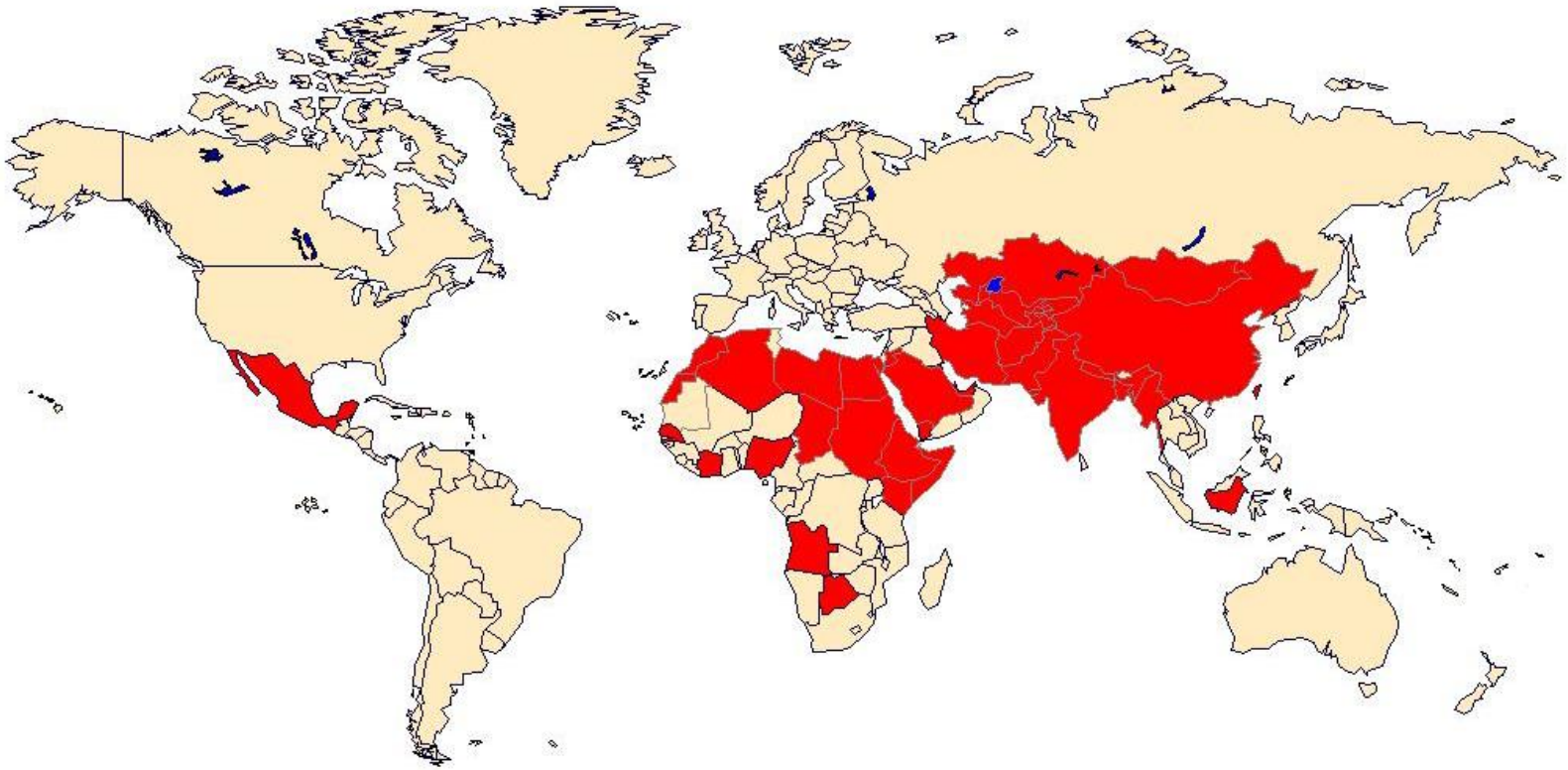
- 1980 first recognised as a new disease in epidemics of HAV negative viral hepatitis transmitted by faecal-oral route
- 1983 EM of faecal material from infected virologist Mikhail Balayan (ingested faecal extracts from HEV cases)
- Most oral-faecal transmitted hepatitis virus in developing countries due to HEV not HAV
- 1990-1 genome identified and cloned
- Four genotypes – in different geographical locations
- HEV may be zoonotic – found in mammals (e.g.pigs, deer, rodent) and birds
- Cell culture system recently developed
- HEV classified in the *Hepevirus* genus of *Hepeviridae*



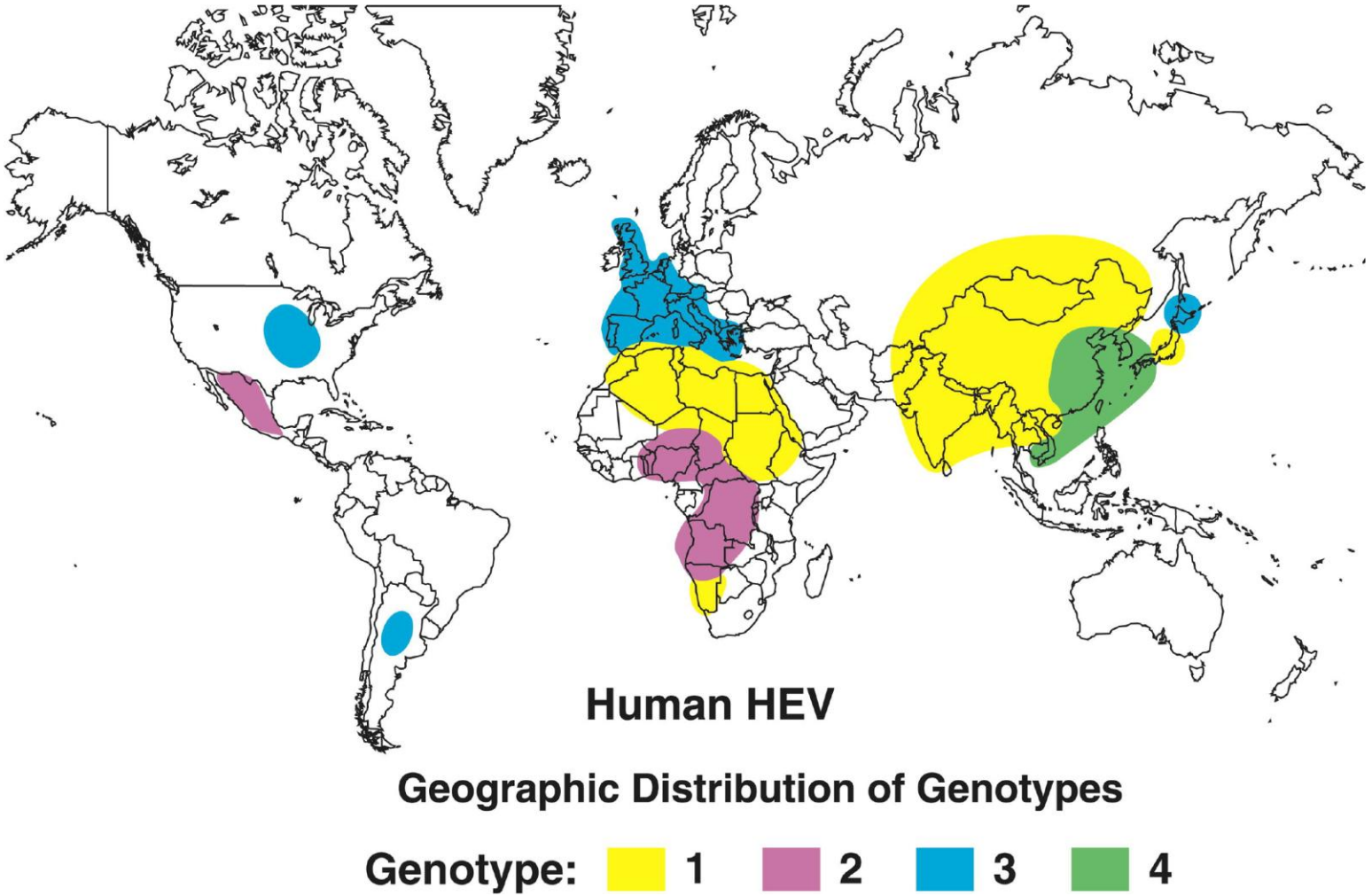
Hepatitis E Virus



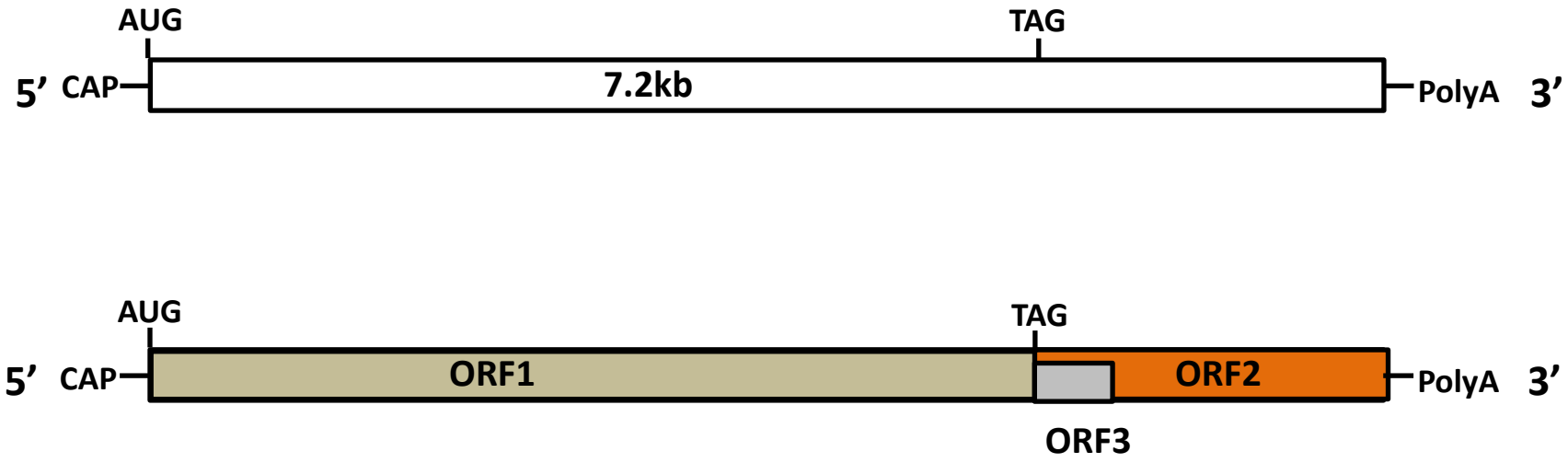
Regions with High HEV Prevalence



Geographic Dstribution of HEV Genotypes

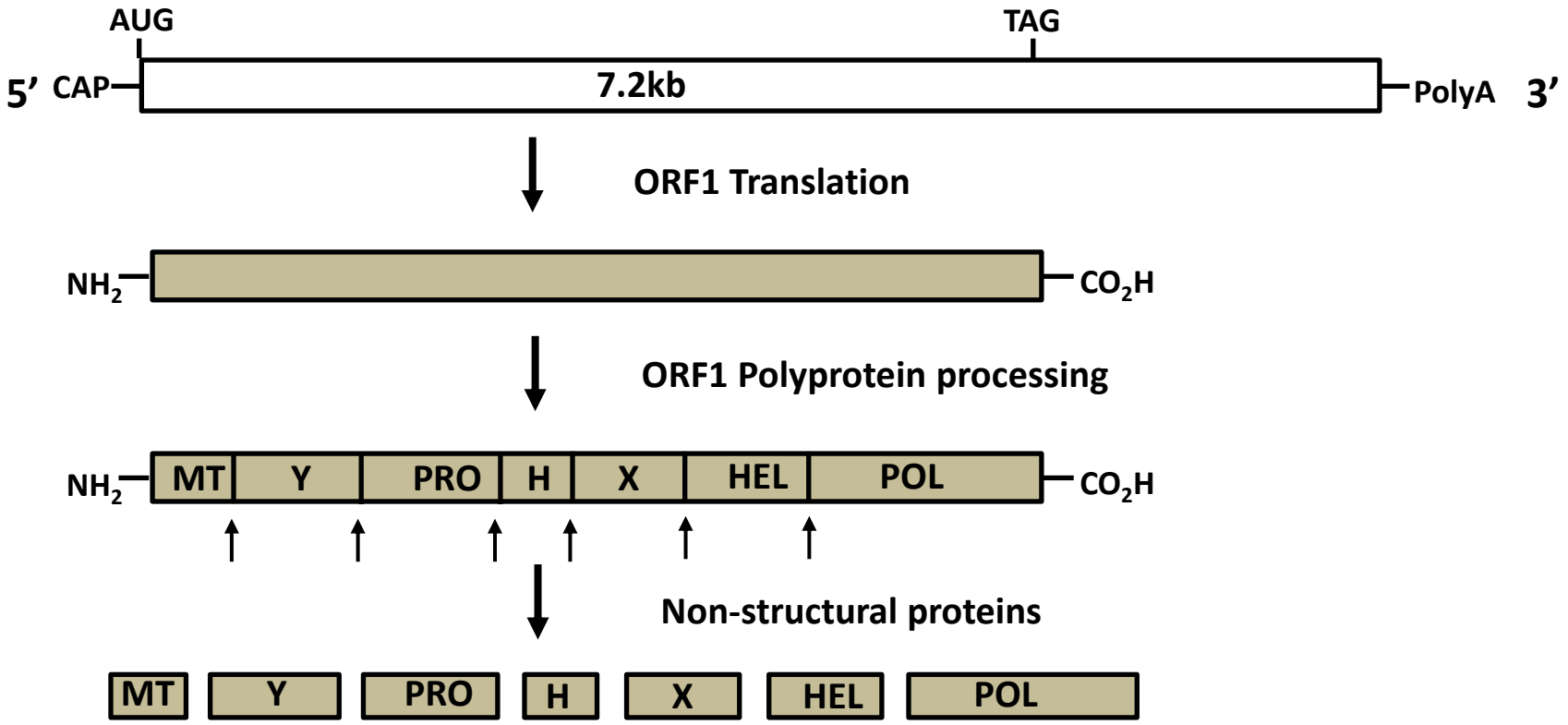


HEV Genome



- Genomic RNA 7.2kb in length
- Positive sense (i.e. can be directly translated)
- Contains 3 open reading frames (ORFs)
- Only ORF1 is translated from genomic RNA
- ORFs 2 and 3 are translated from sub genomic mRNAs

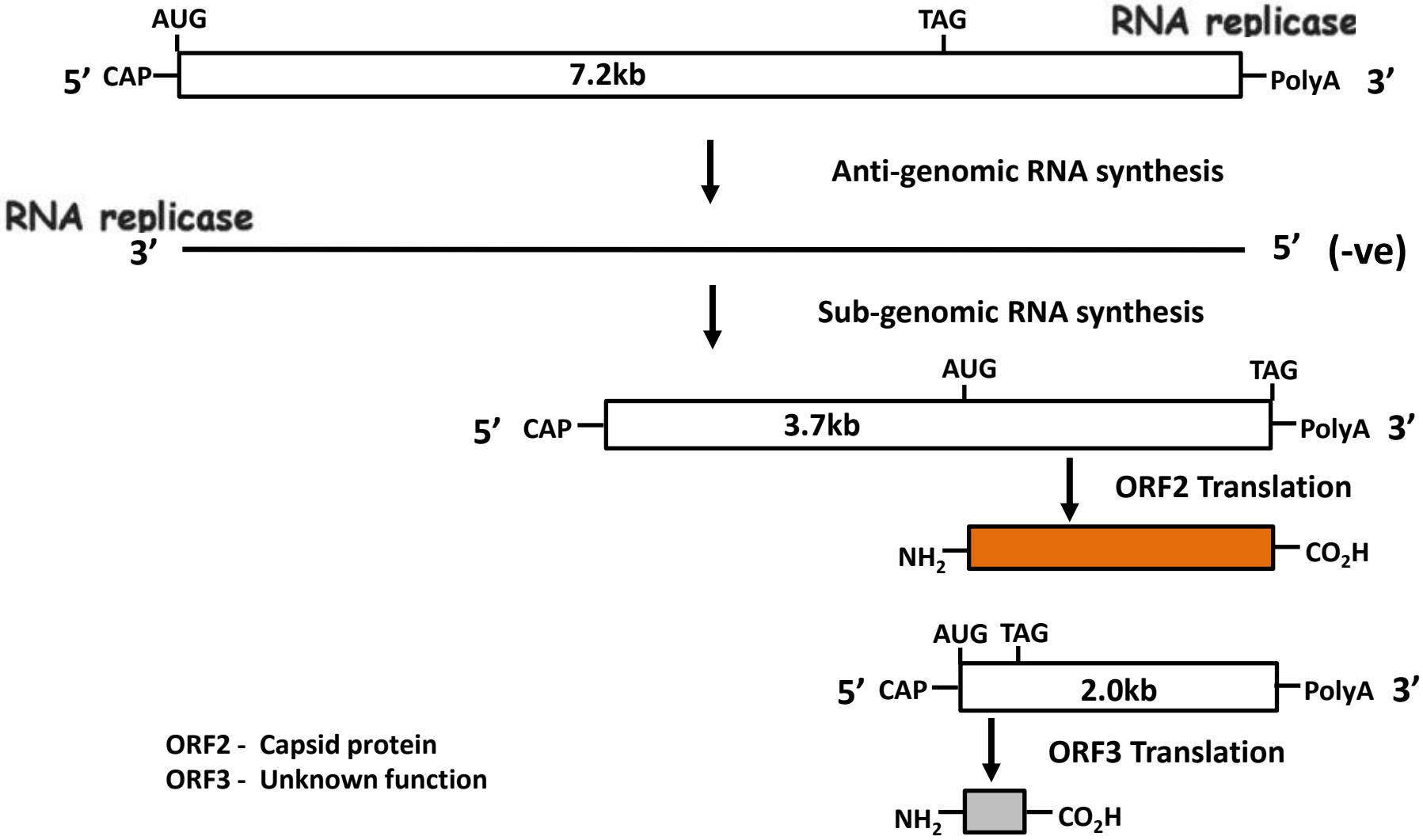
HEV ORF1 Translation and Processing



MT – methlytransferase
PRO – protease
HEL – RNA helicase
POL – Polymerase
Y, X, H – unknown functions

RNA replicase

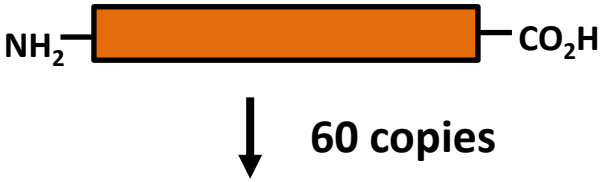
HEV Genome Replication and ORF2 & 3 Expression



ORF2 - Capsid protein
ORF3 - Unknown function

Hepatitis E Virus Particle

ORF2 - Capsid protein



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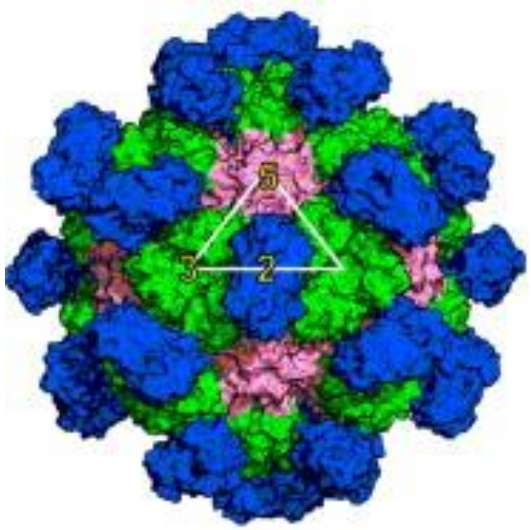
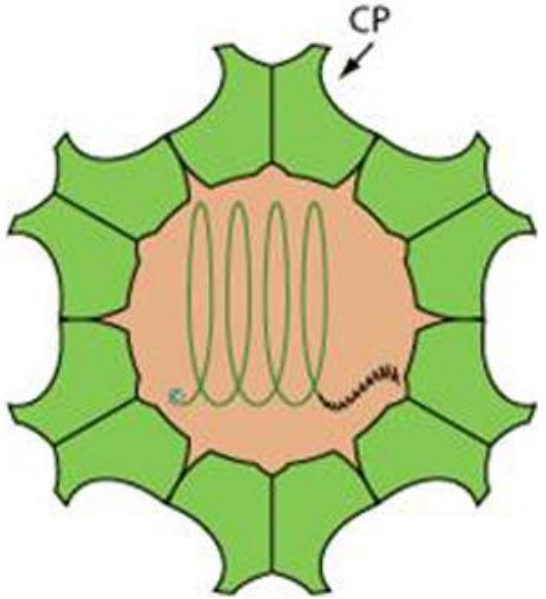


HEV structure (Cryo-EM)

HEV structure Diagrammatic



HEV structure Cross-section

HEV Replication

- Similar to HAV
- Virus binds to receptor(s)
- Entry into cytoplasm
- Genomic RNA released
- Translation of ORF1 and processing to form non-structural proteins
- RNA replicase formation
- Antigenomic RNA synthesis
- Genomic RNA synthesis and subgenomic RNA synthesis
- Formation of virus particle
- Release of new viruses from hepatocytes.

Hepatitis E Pathogensis

- **HEV is an epidemic virus**
- **Mainly in under developed countries**
- **May be zoonotic (i.e. Animal reservoirs)**
- **Mortality greater than HAV but may not be age dependent**
- **Mortality in pregnant women – 20%**

Prevention and Control Measures for Travellers to HEV-Endemic Regions

- Avoid drinking water (and beverages with ice) of unknown purity, uncooked shellfish, and uncooked fruit/vegetables not peeled or prepared by traveller
- Immunoglobulin prepared from donors in Developed countries does not prevent infection
- Unknown efficacy of Ig prepared from donors in endemic areas
- Vaccine?

Comparison 1 of HAV and HEV

	HAV	HEV
Size (nm)	28	32–34
Genome	Positive sense, single-stranded RNA	Positive sense, single-stranded RNA
Genome size	7.5kb	7.2kb
5′ non-coding region	Complex, IRES	Simple, capped
Open reading frames	1 (polyprotein)	3 (different reading frames)
3′ non-coding region	Poly A tail	Poly A tail
Growth in cell culture	Poor	Poor
Stability of viruses	Very stable	Less stable (?)
Infectious titer in faeces	10^6–10^9	10^4–10^7
Host range	Primates	Primates, pigs, rats, chickens, cattle, sheep, etc.
Naturally attenuated strains	No (?)	Yes (?)

Comparison 2 of HAV and HEV

	HAV	HEV
Incubation period	~30 days	~40 days
Dose-dependent severity	No	Yes
Mortality	0.1–2%	1–4%
Mortality in pregnancy	No difference	Up to 20%
Bimodal disease	Common	Rare
Chronicity	(No)	(No)
In developed regions	Epidemic, endemic	Antibody, but rare disease
In developing regions	Antibody, but rare disease	Epidemic, endemic
Age	Older children, younger adults	Older children, younger adults
Sex	No difference	No difference (except in pregnancy)

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