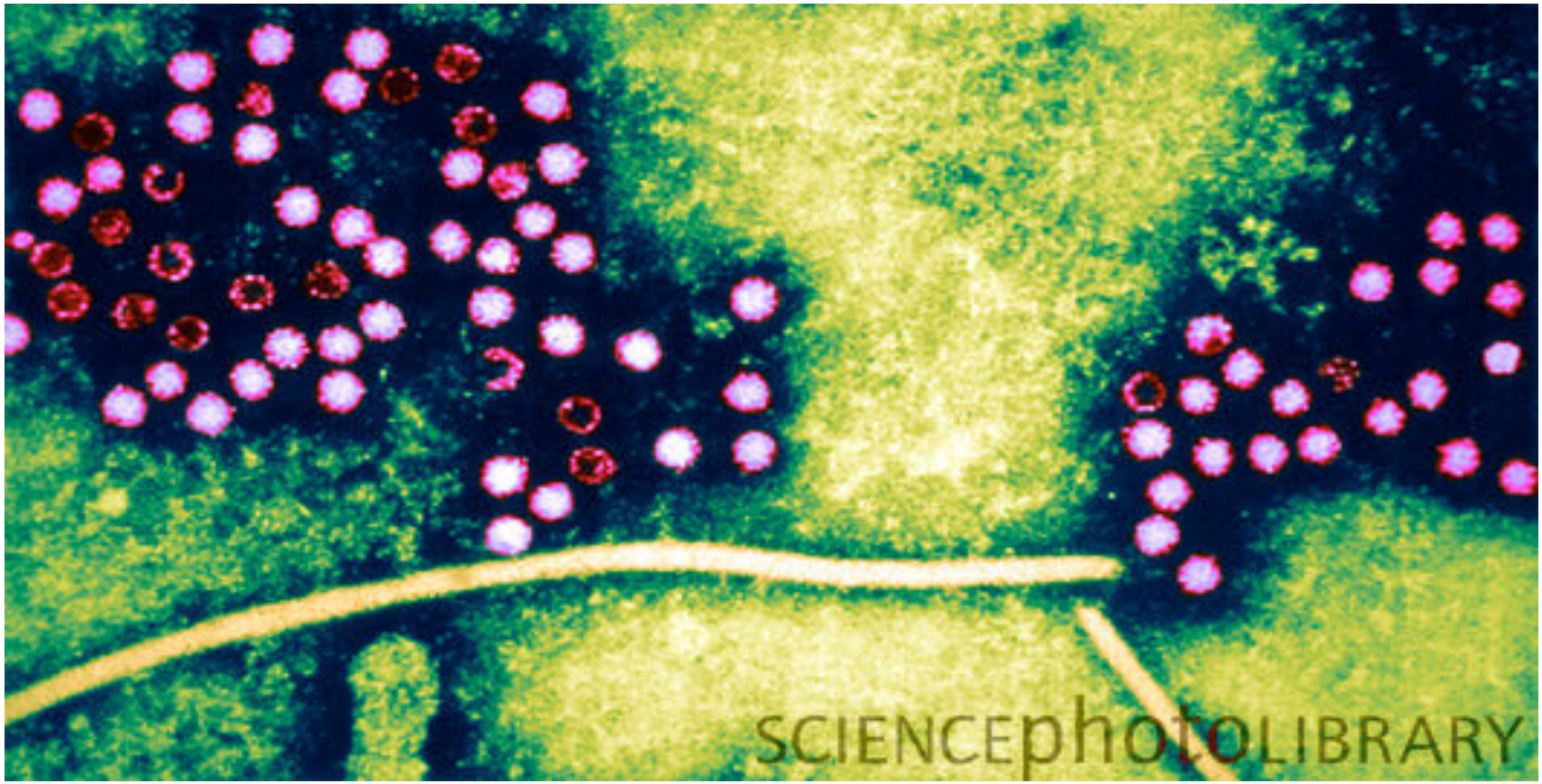
Update on Hepatitis Virus Vaccines

Monique Andersson
University of Stellenbosch
AAVC
13th November 2014

Overview

- Hepatitis E
- Hepatitis C
- Hepatitis B



HEV

Hepatitis E virus

- Infects 20 million people annually

•Cause of acute hepatitis in 3.5 million

•Responsible for 70,000 deaths annually

•Endemic areas 1-3% mortality

- 30% pregnant women
- 70% chronic liver disease

•Member of the new *Hepeviridae* family

• Non-enveloped, spherical particle, approx 30-34nm in diameter

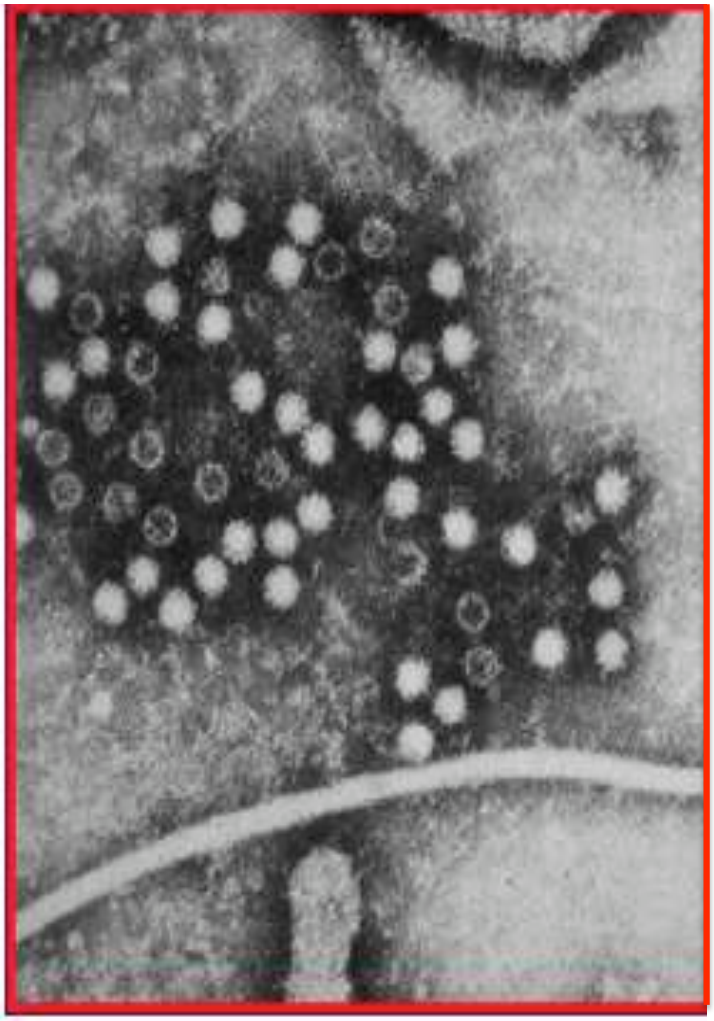
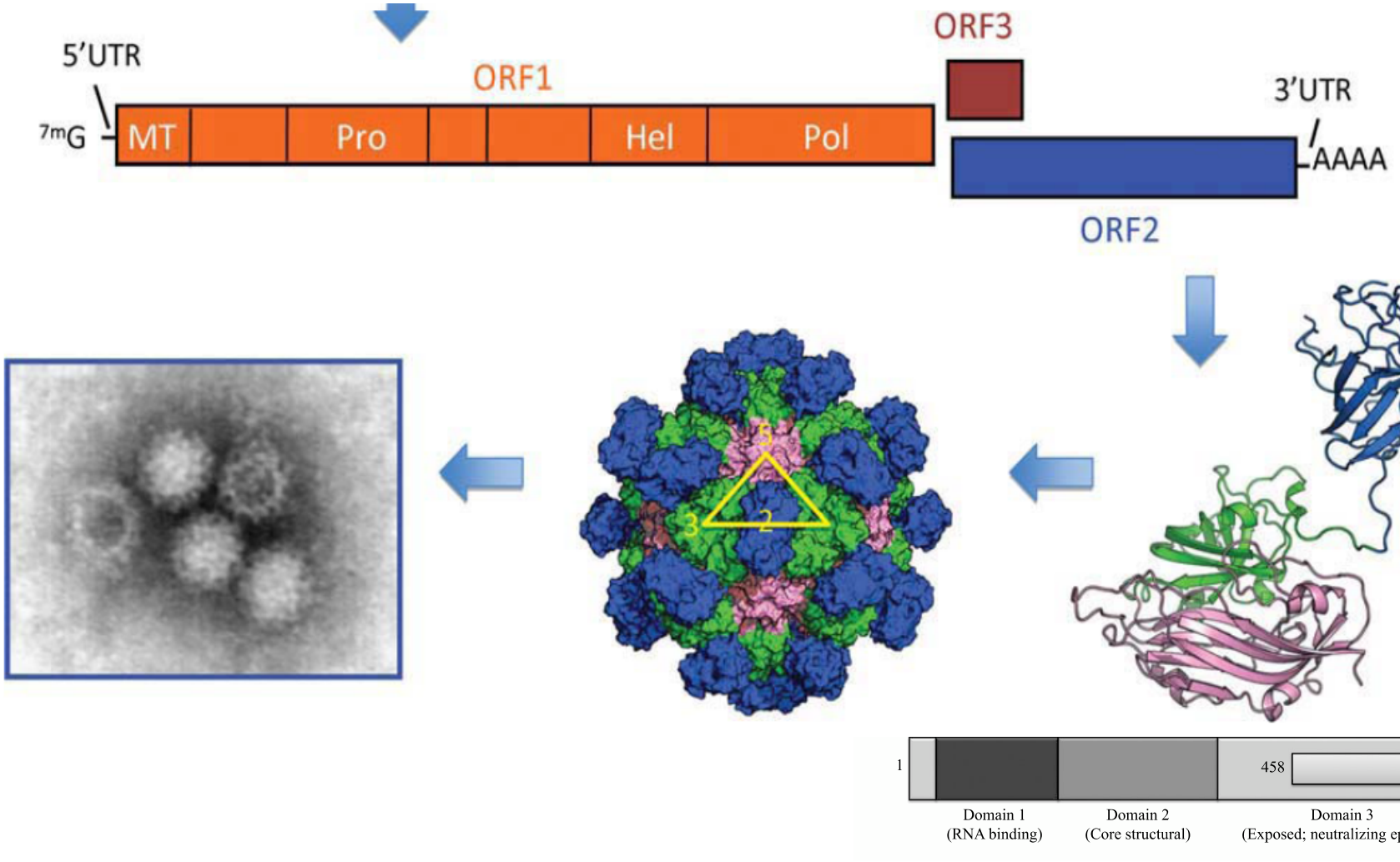


Table 2. Clinical Manifestations of Hepatitis E

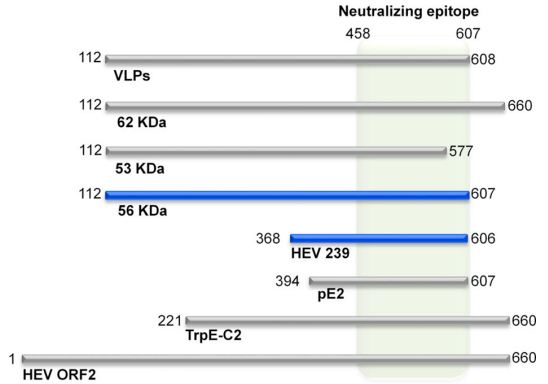
Hepatic manifestations
Icteric hepatitis (similar to other forms of viral hepatitis)
Severe hepatitis leading to fulminant hepatic failure
Anicteric hepatitis (biochemical abnormalities but no jaundice)
Inapparent or asymptomatic infection
Acute-on-chronic liver disease
Rare extrahepatic manifestations
Acute pancreatitis
Hematological manifestations: thrombocytopenia, hemolysis
Autoimmune phenomena: Membranous glomerulonephritis, Henoch-Schonlein purpura
Neurological syndromes
Guillian-Barre syndrome
Meningoencephalitis
Pseudotumor cerebri
Cranial nerve palsies
Bilateral pyramidal syndrome
Peripheral neuropathy

Type of Hepatitis

	A	B	C	D	E
Source of virus	faeces	blood/ blood-derived body fluids	blood/ blood-derived body fluids	blood/ blood-derived body fluids	faeces/ zoonosis
Route of transmission	faecal-oral	percutaneous permucosal	percutaneous permucosal	percutaneous permucosal	fecal-oral
Chronic infection	no	yes	yes	yes	possible
Prevention	pre/post-exposure immunization	pre/post-exposure immunization	blood donor screening; risk behavior modification	pre/post-exposure immunization; risk behavior modification	ensure safe drinking Water, vaccine

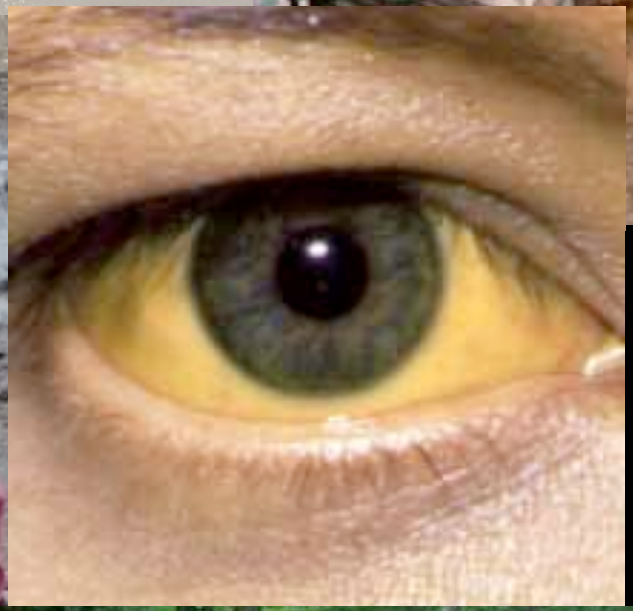


- Linear, positive sense RNA virus
- 7·2 kb genome
- Three open reading frames (ORFs)
- Capsid protein encoded by ORF 2 (72kDa)
- Neutralisation epitope aa 458-607



Hepatitis E

- One serotype, four genotypes
- TWO FACES……



Genotype 1 and 2

- Epidemic in RLS
- Associated with contaminated water
- Person-to-person described
- Infection restricted to humans
- HEV geno 1 Asia, HEV geno 2 Africa,Mexico
- 0.2% to 4% mortality
- Pregnant women and <2yrs greatest risk
- Risk of symptoms – men 4-5x
- Asymptomatic 2-4x symptomatic cases

Published Date: 2014-09-26 17:06:52
Subject: PRO/EDR> Hepatitis E - Sudan (02): displaced persons
Archive Number: 20140926.2808725
HEPATITIS E - SUDAN (02): DISPLACED PERSONS
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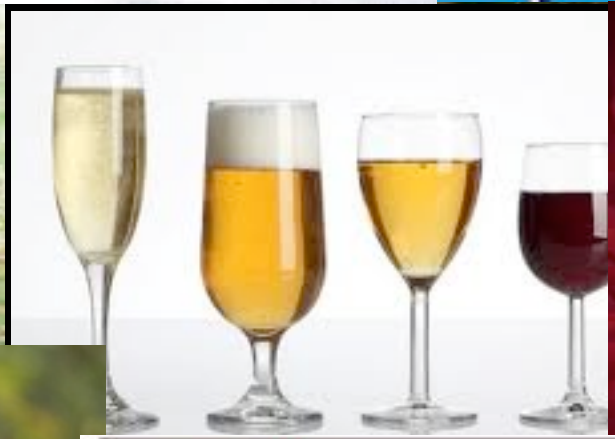
The number of hepatitis E cases in South Darfur and Blue Nile states of Sudan has risen to more than 700 confirmed cases. Almost half of the reported cases were identified in South Darfur's Kalma camp for the displaced. In Blue Nile state, more than 80 cases have been reported, the UN Office for the Coordination of Humanitarian Affairs (OCHA) in Sudan reports in its latest weekly bulletin released today, 25 Sep 2014.

According to the WHO, as of 17 Sep 2014, a total of 84 hepatitis E cases, with 3 deaths, have been reported in the area of Madina 10, Geissan locality, Blue Nile state. The actual number of people infected with the hepatitis virus may be much higher, as this is an area with a large population and most of the cases go unreported as people make use of traditional treatments.




HUMAN
ORGAN
FOR TRANSPLANT


NDC 0093-7227-58
RIBAVIRIN Capsules
200 mg
For combination use with INTRON® A* (interferon alfa-2b, recombinant) Injection
ATTENTION PHARMACIST: Each patient is required to receive a Medication Guide.
*INTRON® A is a registered trademark of Schering Corporation.
℞ only
84 CAPSULES
TEVA
AVOID PREGNANCY WHILE TAKING THIS MEDICATION
READ THE MEDICATION GUIDE FOR IMPORTANT INFORMATION
KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN
0093-7227-58

Genotypes 3 and 4

- Zoonosis
- Mild disease - 98% asymptomatic
- Associated eating pork, deer, mussels
- Clinical older men, HBV co-infected
- Background prevalence <5% in rrs
- No increased mortality in pregnant women
- Genotype 3 associated with chronic infection

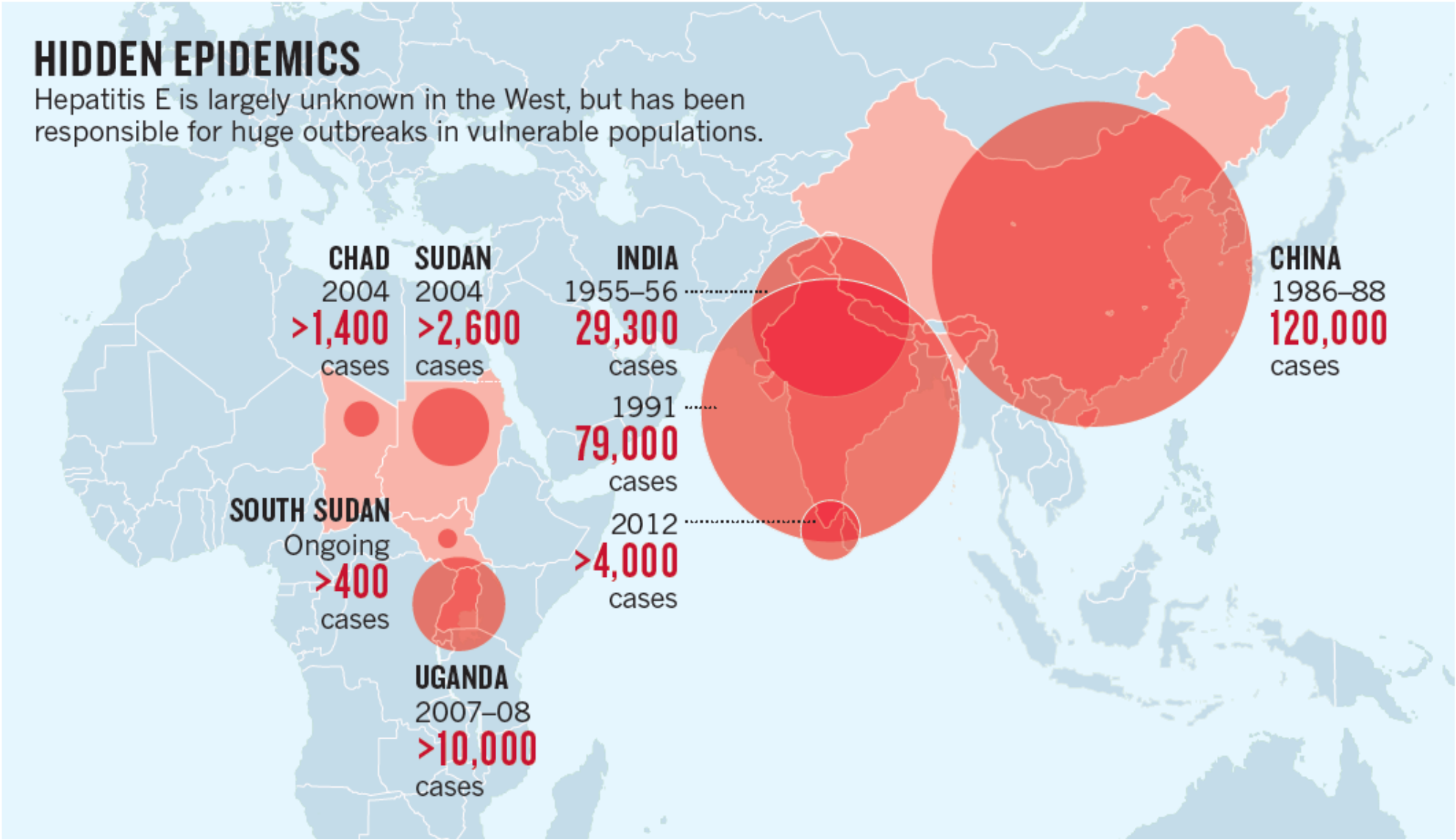
Chronic HEV

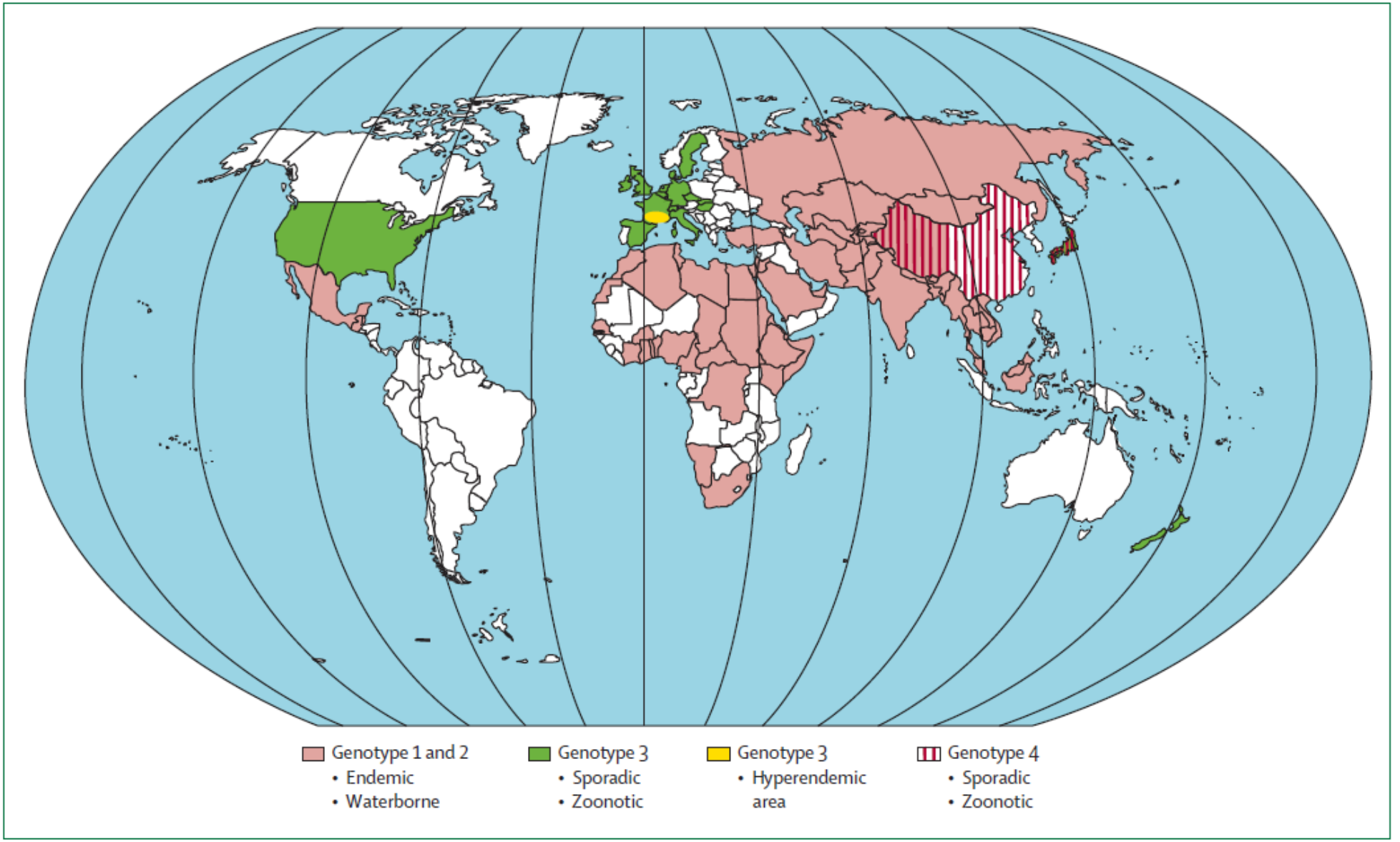
- ONLY GENOTYPE 3 (so far described)
- Diagnosis by HEV PCR

- Outcomes: 60% rapid progression to liver fibrosis, 10% cirrhosis[1]

- Ribavirin 3 months therapy of choice

1 Kamar et al. Gastroenterology 2011


HIDDEN EPIDEMICS
Hepatitis E is largely unknown in the West, but has been responsible for huge outbreaks in vulnerable populations.
CHAD
2004
>1,400
cases
SUDAN
2004
>2,600
cases
INDIA
1955–56
29,300
cases
1991
79,000
cases
2012
>4,000
cases
CHINA
1986–88
120,000
cases
SOUTH SUDAN
Ongoing
>400
cases
UGANDA
2007–08
>10,000
cases


Genotype 1 and 2
• Endemic
• Waterborne
Genotype 3
• Sporadic
• Zoonotic
Genotype 3
• Hyperendemic area
Genotype 4
• Sporadic
• Zoonotic

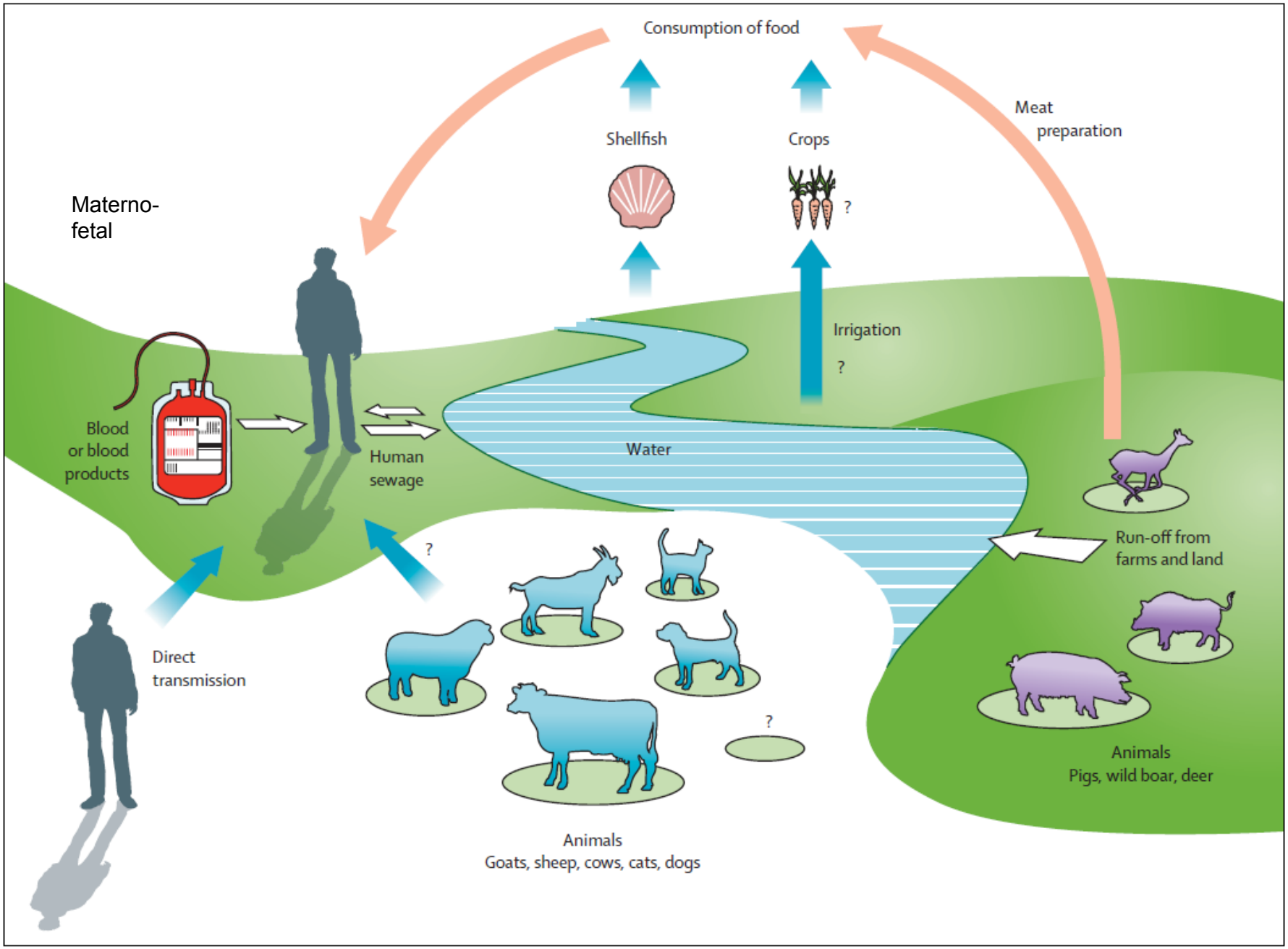
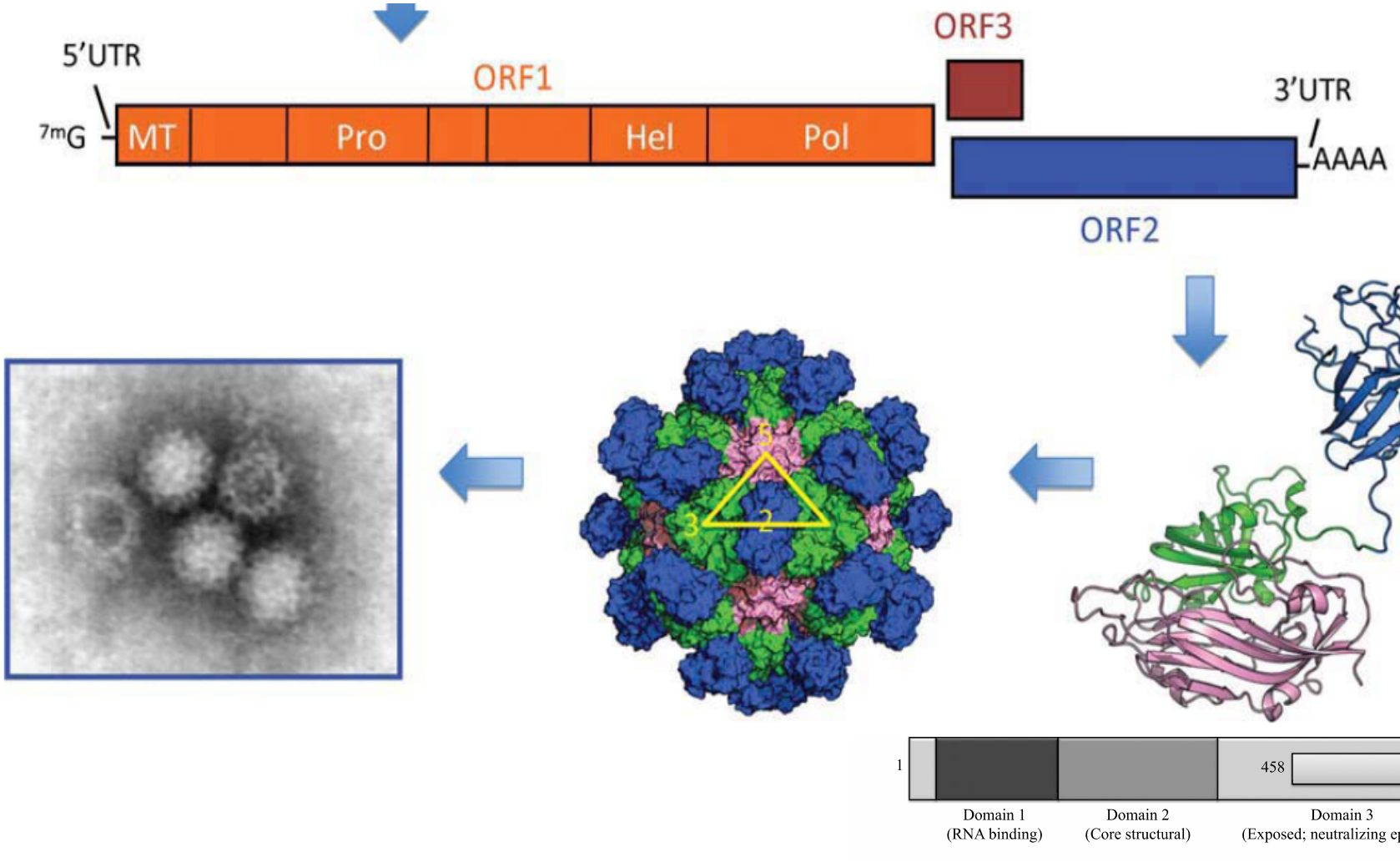


***Figure 3*: Source and route of HEV1–4 infection**
HEV1 and HEV2 are waterborne only, with possible human-to-human transmission, including vertical transmission.

Prevention of HEV infection

- Reduce exposure – Sanitation
  - Food hygiene
  - Blood product screening?

- Vaccination – Subunit vaccine (Hecolin - not commercially available outside of China)



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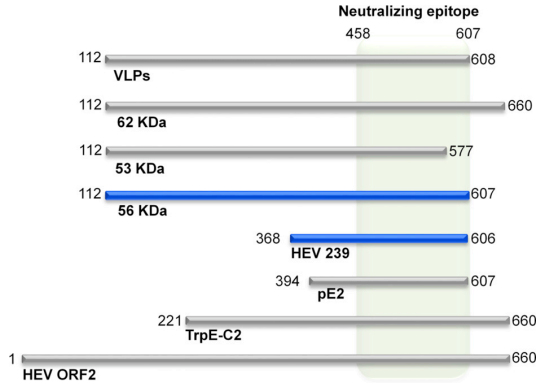


HEV Vaccine

- Two vaccines have been through Phase I/ II
- Currently only one vaccine ‘available’

- rHEV NIH developed
- Baculovirus expressed 56kDa protein
- Nepalese Phase II study
- HEV 7.4% vs 0.3%
- No further progress reported

HEV 239

- Phase III RDBPC study 112,604 adults China (Placebo HBV)
- 23nm VLPs encompassing 368-606aa of ORF2 of HEV genotype 1
- Incidence of adverse events low
- After third dose 100% developed antibodies
- None of vaccinated had hepatitis episode (placebo 15 cases)
- Genotype 4 protection using geno 1
- Produced by Hecolin, Xiamen, China

Zhu et al. Lancet 2010

Who would benefit?

- Endemic countries
- Outbreak control
- Food workers
- Chronic liver disease
- Immunosuppressed

Who would profit?

Chronic Viral Hepatitis: a problem?

- Major infectious disease killers –

HIV, TB, malaria

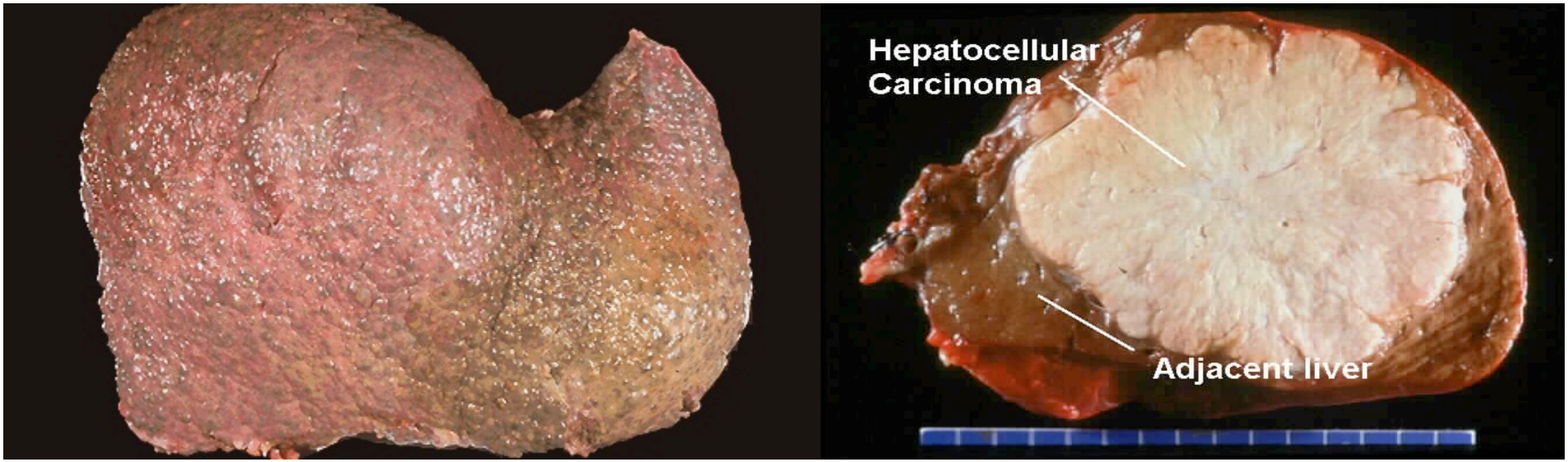
Chronic Viral Hepatitis: a problem?

According to Global Burden of Disease Study

- 1.47million deaths from HIV
- 1.2 million deaths from TB infection
- 1.24 million deaths from malaria infection

1.3 million die from chronic viral hepatitis infection each year

Lozano et al. Lancet 2012:380;9859



HCV

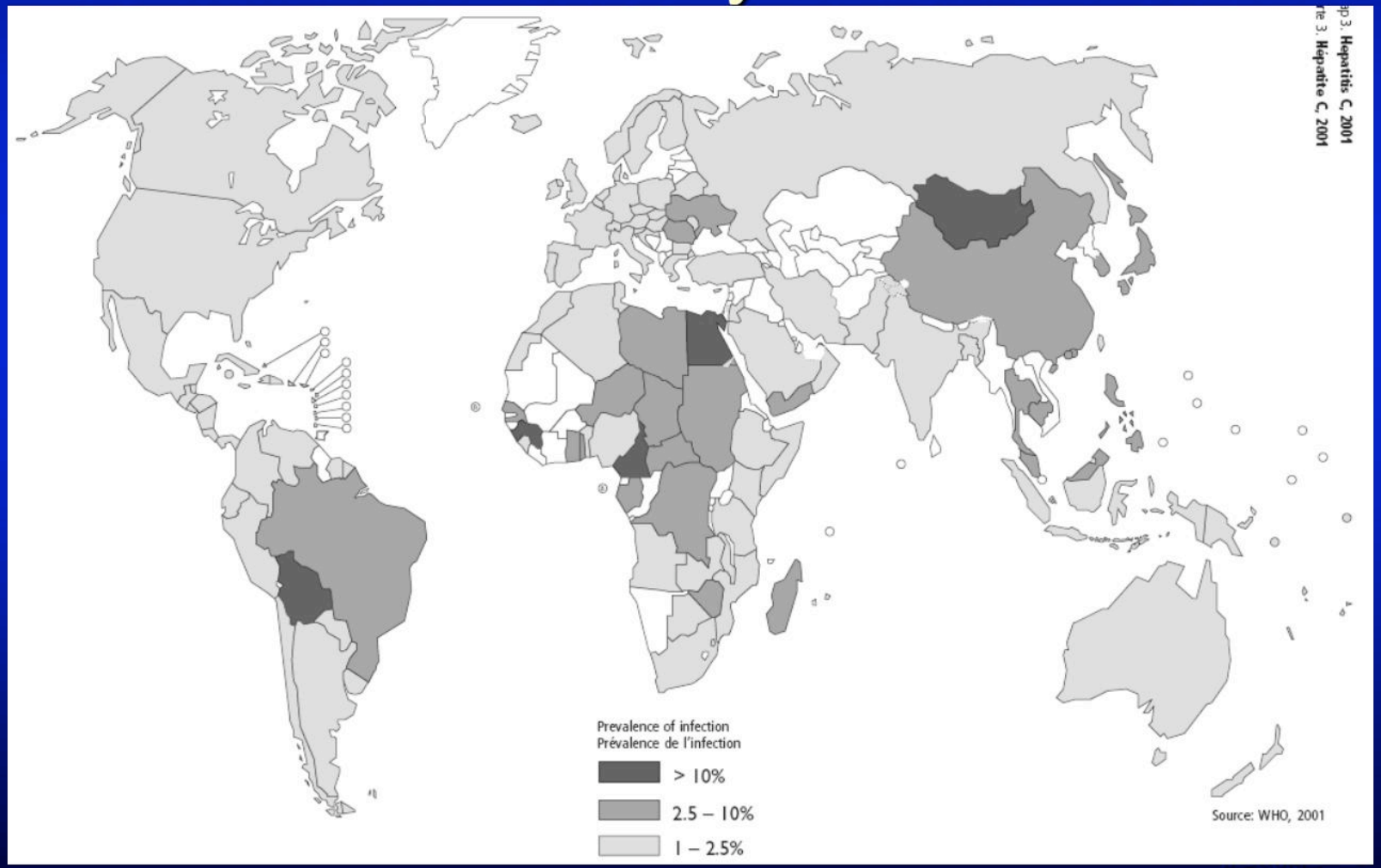
WHO region	Total population (millions)	HCV rate (%)	Infected population (millions)
Africa	602	5·3	31·9
Americas	785	1·7	13·1
Eastern Mediterranean	466	4·6	21·3
Europe	858	1·0	8·9
Southeast Asia	1500	2·0	32·3
Western Pacific	1600	3·9	62·2
Total	5811	3·1	169·7

Source: WHO Weekly Epidemiological Record, No. 49, December 1999

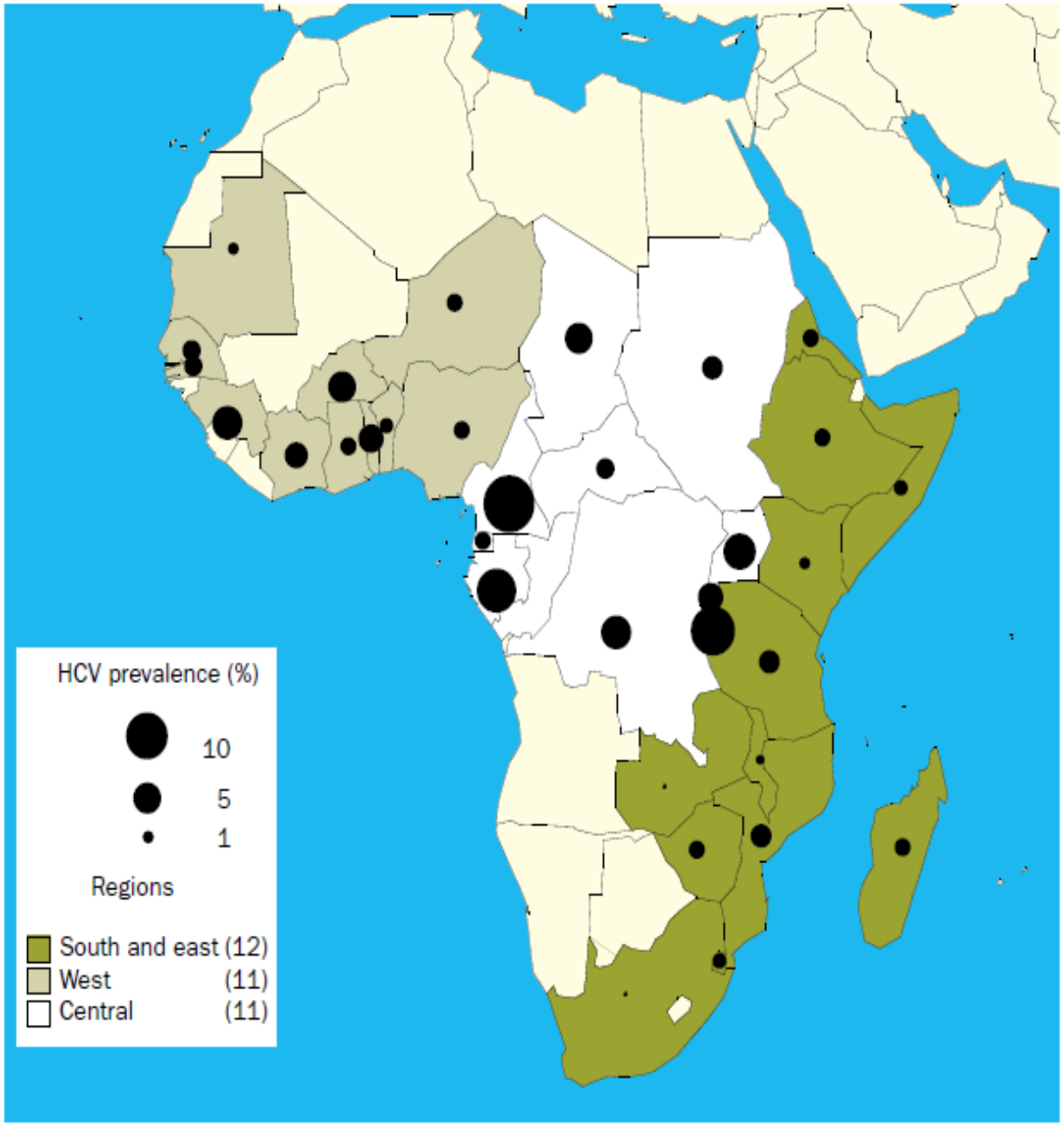
Lancet Infect Dis 2002; **2:** 293–302

HCV Epidemiology

~180 million chronically infected worldwide

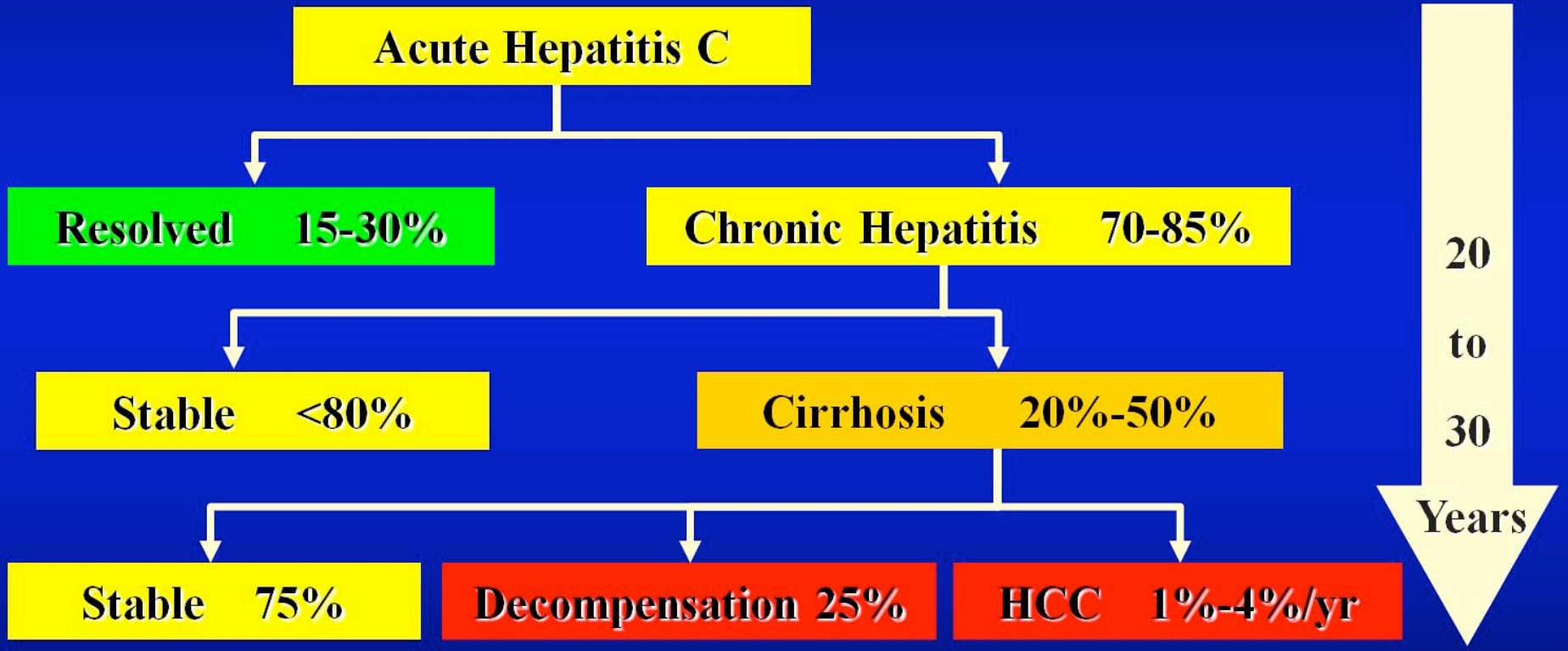


WHO Data



Lancet Infect Dis 2002; **2:** 293–302

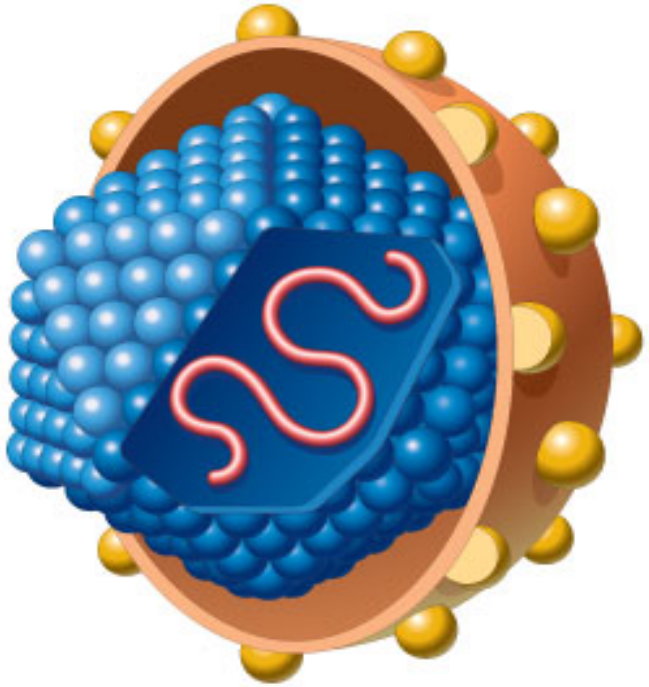
HCV: Natural History



Natural History

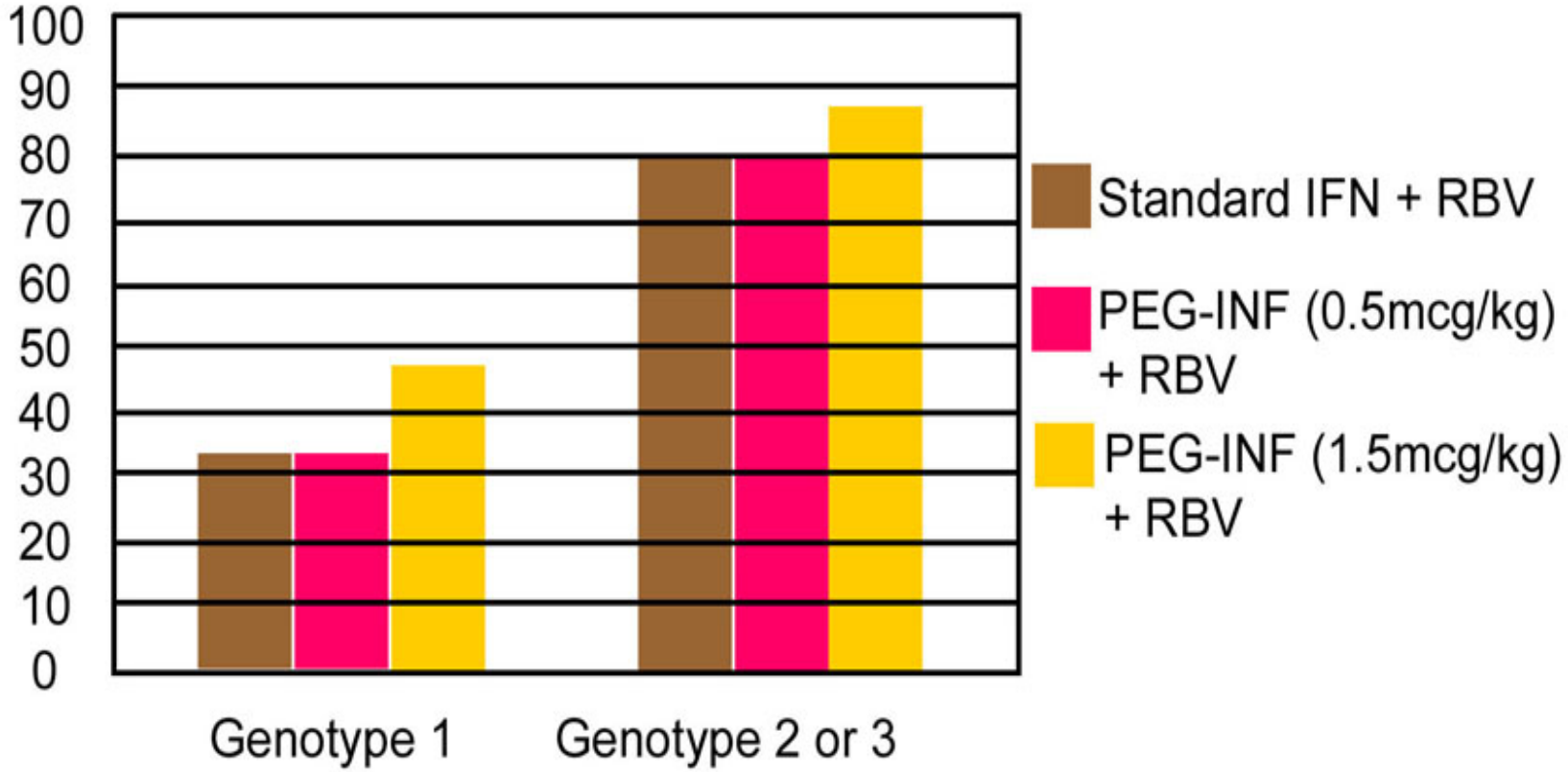
- 25% eliminate spontaneously
- 70-80% persistently infected
- 25% of cirrhosis and HCC worldwide
- 2 million new infections every year

Hepatitis C

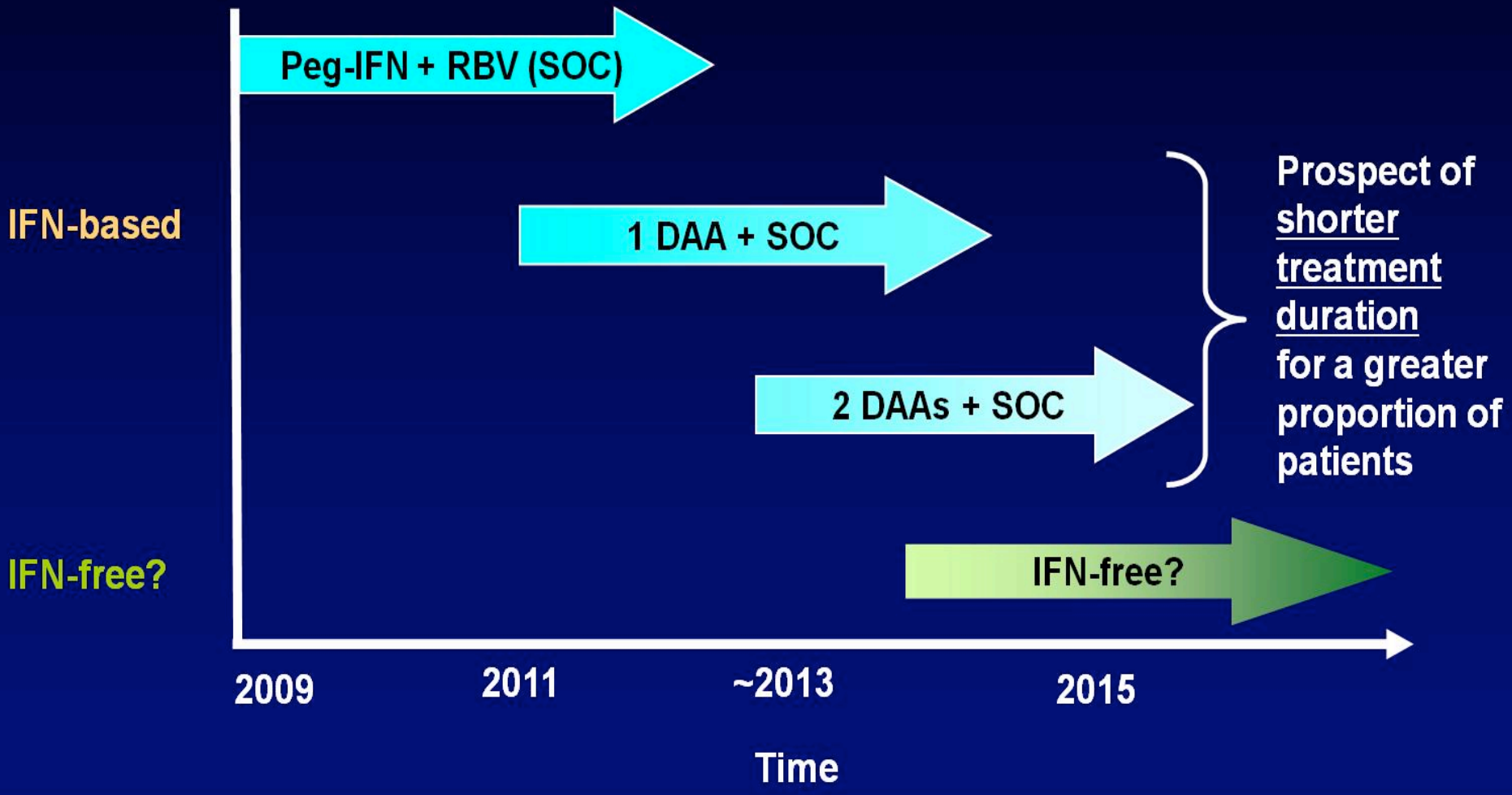


- Enveloped
- Single stranded RNA virus
  (+ssRNA) 9.6kb
- *Flaviviridae* family
- Subdivided into 7 major genotypes

Peg-interferon Alfa-2b + Ribavirin
Virologic Response by Genotype
RBV Dose >10.6 mg/kg

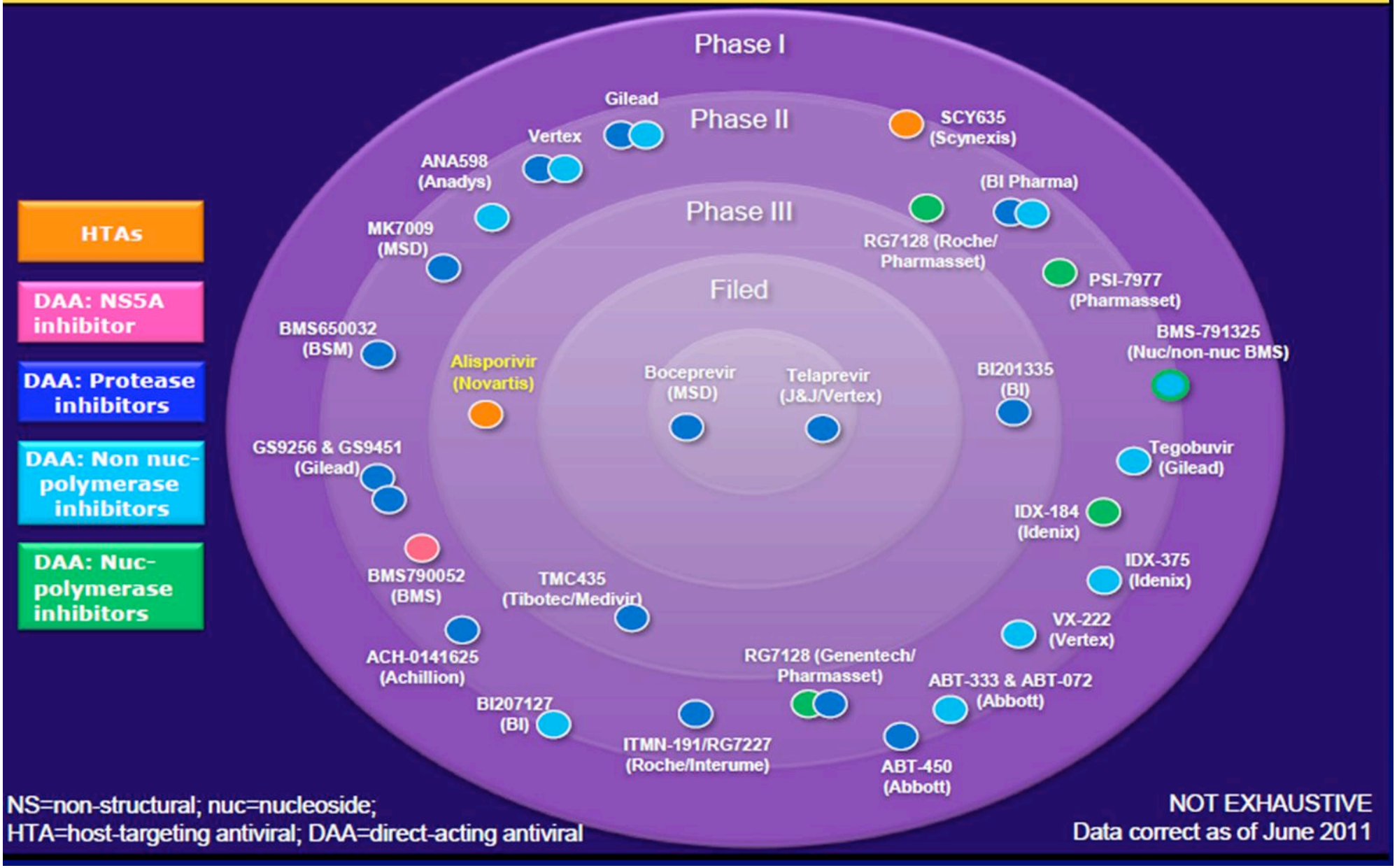


DAAs as Components of New Treatment Paradigm for Hepatitis C



DAA=direct-acting antiviral; SOC=standard of care (Peg-IFN + RBV)

Treatment options for HCV will increase dramatically in the coming years



NS=non-structural; nuc=nucleoside;
HTA=host-targeting antiviral; DAA=direct-acting antiviral

NOT EXHAUSTIVE
Data correct as of June 2011

Topline Summary of Sofosbuvir Trials

Trial	Patient Population	n	Regimen	Duration, Wks	SVR12, %
NEUTRINO[1]	Tx-naive GT 1	292	SOF + P/R	12	89
	Tx-naive GT 4	28	SOF + P/R	12	96
	Tx-naive GT 5/6	7	SOF + P/R	12	100
FISSION[2]	Tx-naive GT 2	70	SOF + RBV	12	97
	Tx-naive GT 3	183	SOF + RBV	12	56
FUSION[3]	Tx-experienced GT 2	36	SOF + RBV	12	86
	Tx-experienced GT 3	64	SOF + RBV	12	30
	Tx-experienced GT 2	32	SOF + RBV	16	94
	Tx-experienced GT 3	63	SOF + RBV	16	62
POSITRON[4]	IFN-UII GT 2	109	SOF + RBV	12	93
	IFN-UII GT 3	98	SOF + RBV	12	61

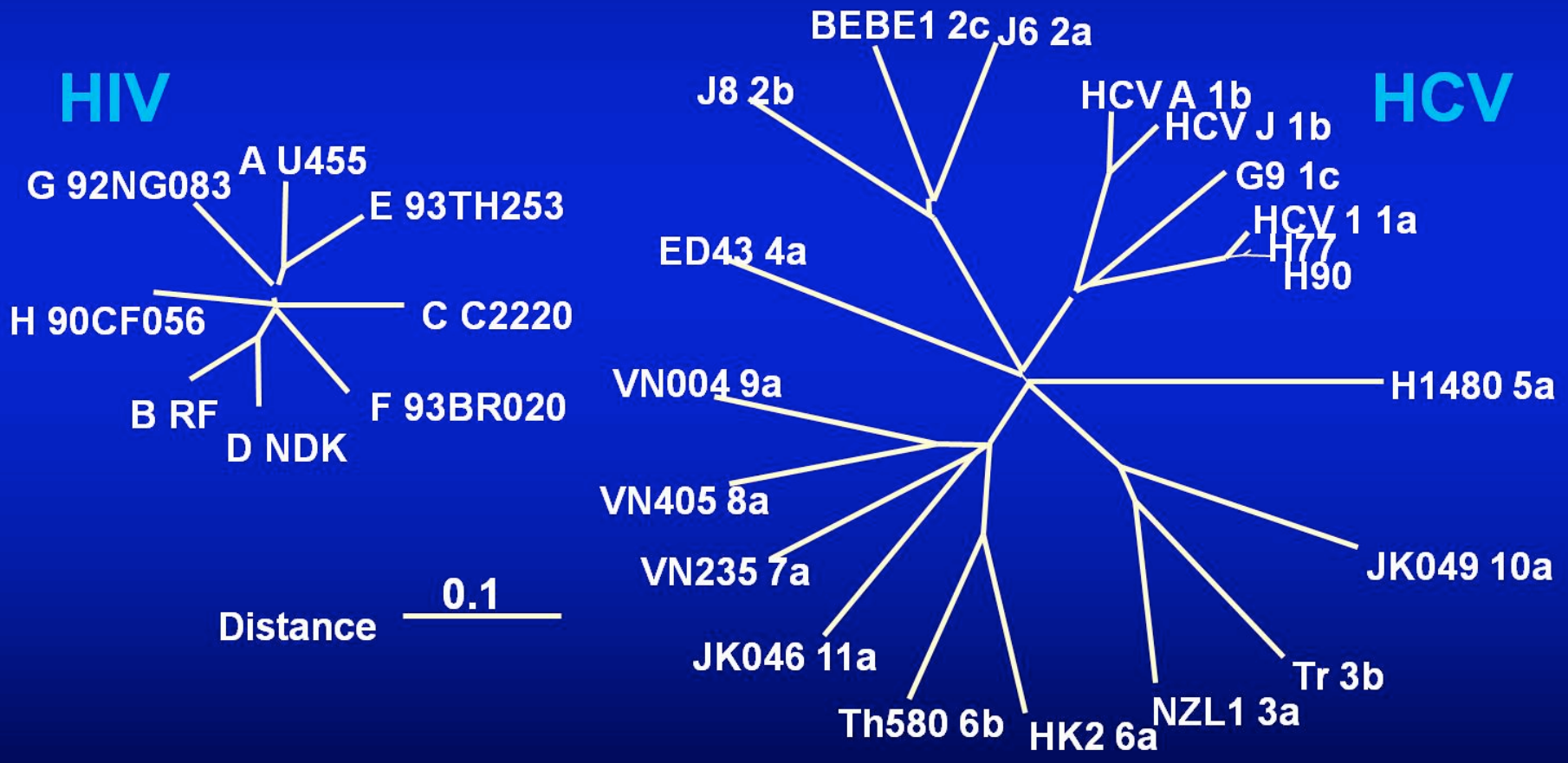
1. Lawitz E, et al. EASL 2013. Abstract 1411. 2. Gane E, et al. EASL 2013. Abstract 5.
3. Nelson D, et al. EASL 2013. Abstract 6. 4. Jacobson I, et al. EASL 2013. Abstract 61.

Hurdles to HCV vaccine development

- Immense sequence variation
- Few in vitro cell lines which supports viral replication
- Humans and chimpanzees only species susceptible to HCV –Chimp research now limited
- Correlates of immunity not well understood

Viral Genetic Diversity

- Influenza



Source: S Ray

Hurdles to HCV vaccine development

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HCV Vaccine Approaches

3 major approaches:

- Recombinant envelope protein to induce nAbs

Vaccination with recombinant E1/E2 proteins – cross reactive nAbs providing protective immunity

- VLPs that express HCV structural proteins induce cellular and humoral reponses

But rechallenging chimps failed – infected

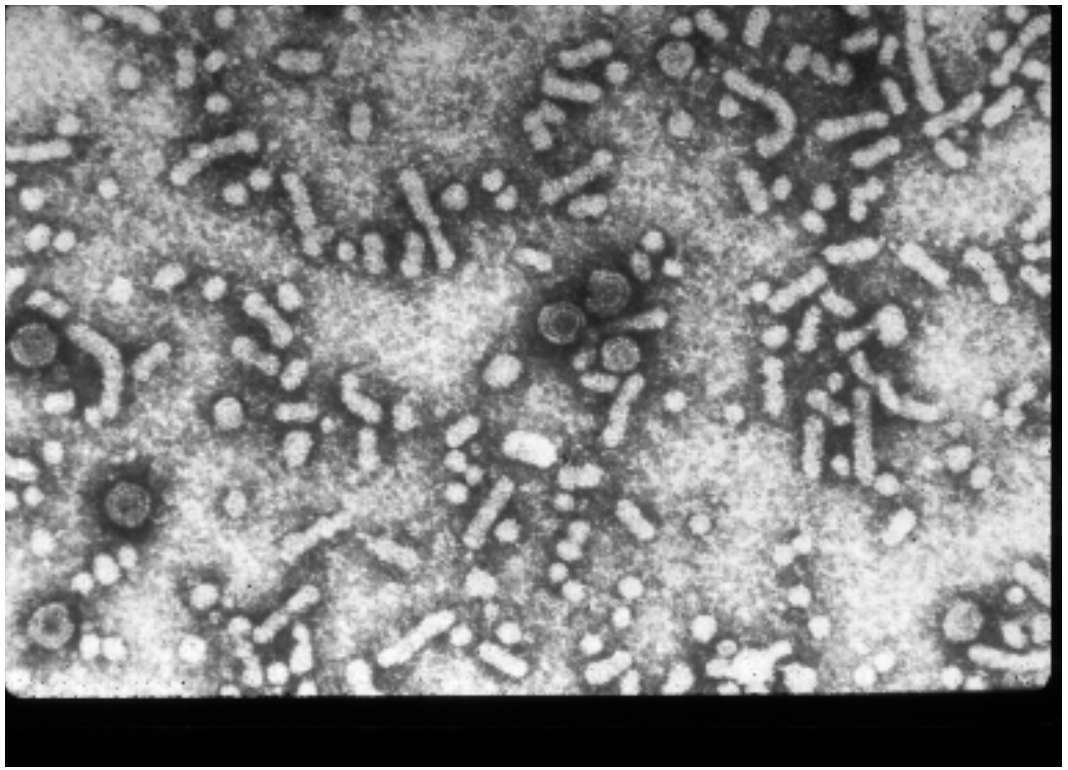
- Viral vector prime and DNA or recombinant protein boost

Sci Transl Med. 2014 Nov 5;6(261): 261

A human vaccine strategy based on chimpanzee adenoviral and MVA vectors that primes, boosts, and sustains functional HCV-specific T cell memory.

Swadling L, Capone S, Antrobus RD, Brown A, Richardson R, Newell EW, Halliday J, Kelly C, Bowen D, Fergusson J, Kurioka A, Ammendola V2, Del Sorbo M, Grazioli F, Esposito ML, Siani L, Traboni C, Hill A, Colloca S, Davis M, Nicosia A, Cortese R, Folgori A, Klenerman P, Barnes E.

A replicative defective simian adenoviral vector (ChAd3) and modified vaccinia Ankara (MVA) vector



HBV

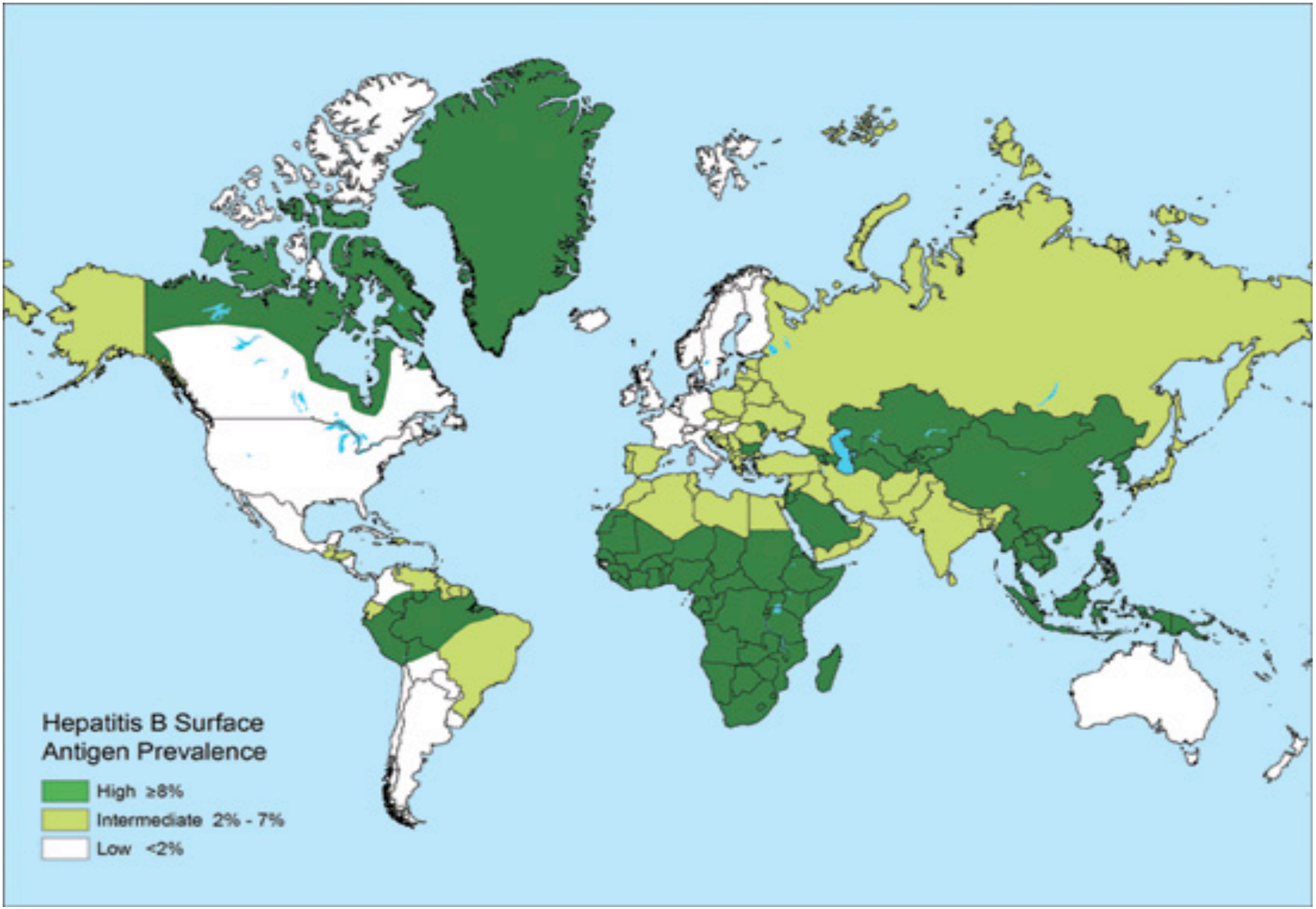
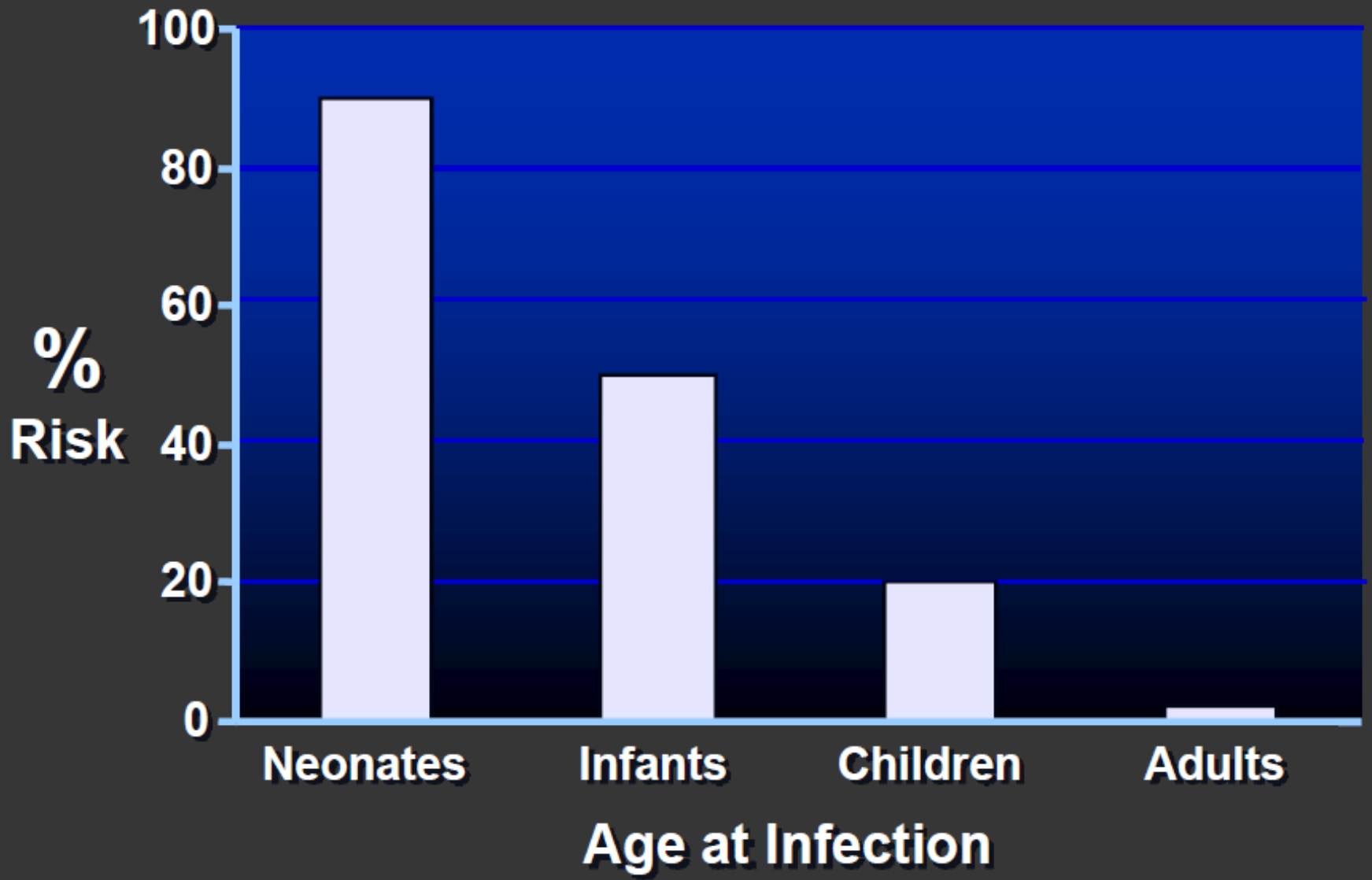


Figure 1.8 Geographic Distribution of Chronic HBV Infection
(Source: Centre for Disease Control, Atlanta)

Risk of Chronic Infection

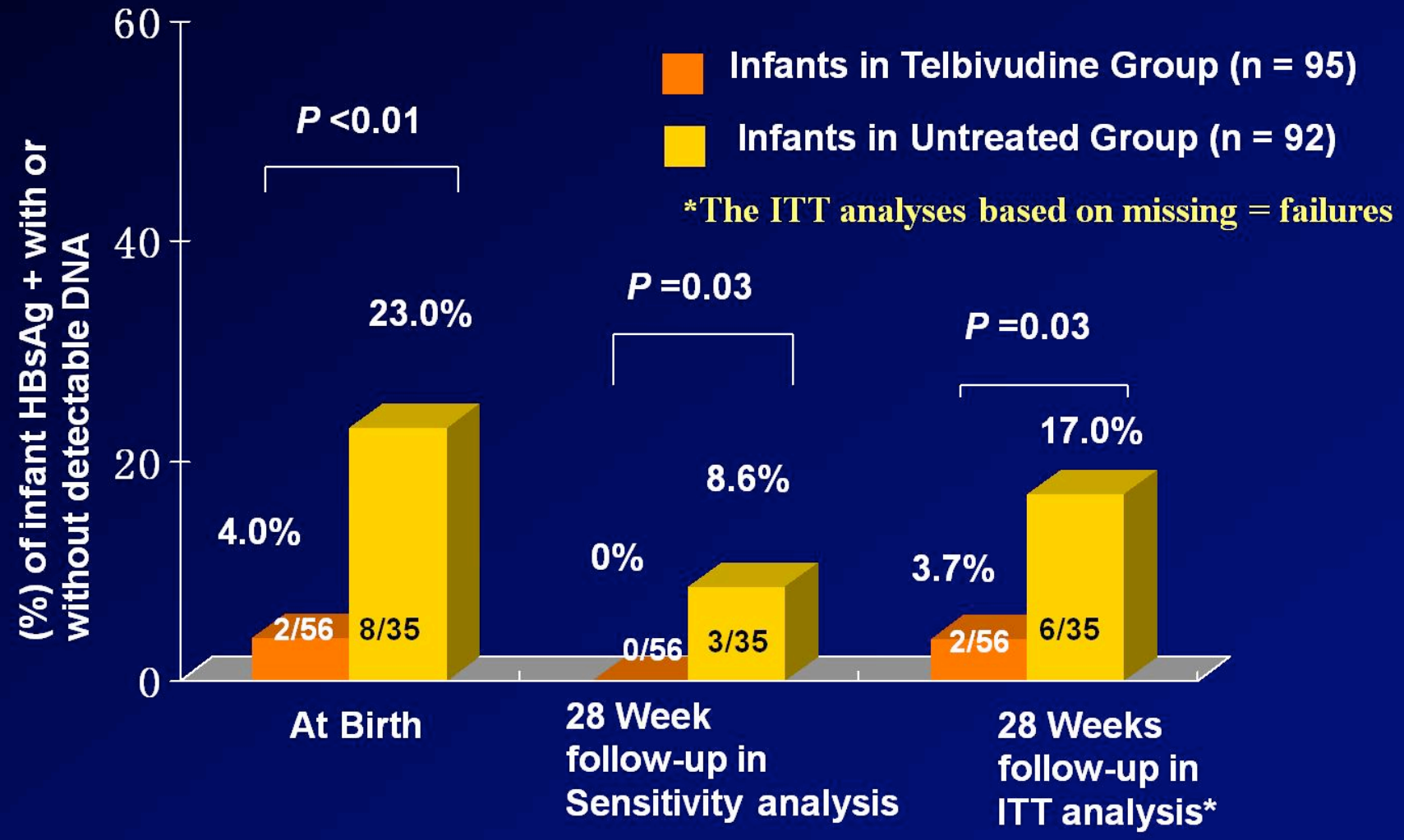


Maternal HBV Status and Outcome of HBV Infection in Infants

Mother		Infant	
HBeAg	HBsAg	No Vaccination	With Immunoprophylaxis
+	+	>90% chronic HBV	Vaccine + HBIG: 10% to 15% chronic HBV
-	+	<5% chronic HBV Risk of fulminant hepatitis, acute hepatitis	<1% chronic HBV and risk of fulminant hepatitis Reduced risk of acute hepatitis

Telbivudine Prevents Vertical Transmission from Women With CHB

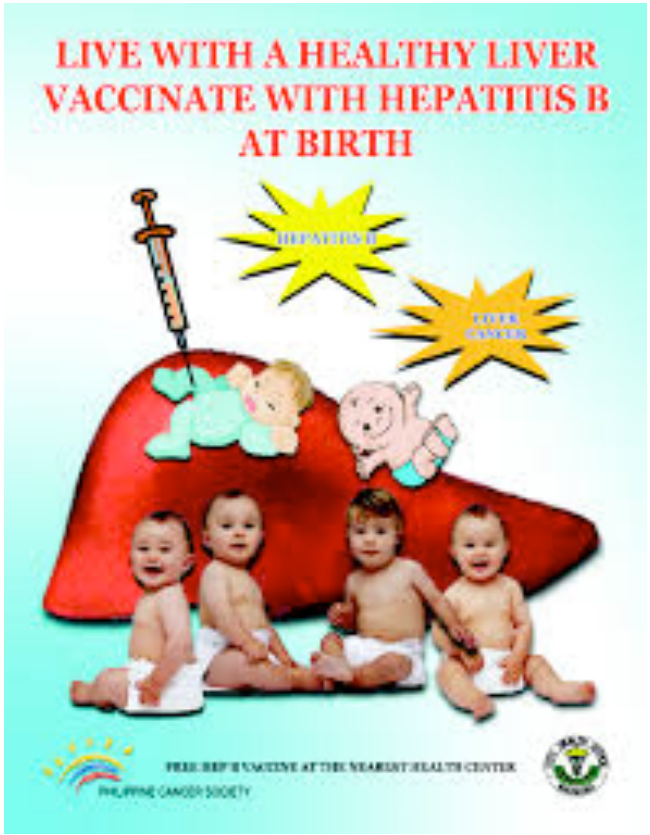
Open-label prospective study (n=88). Infants received standard HBV prophylaxis
Treated-groups(n=53,telbivudine started at week 20-32). Control (n=35, no treatment)

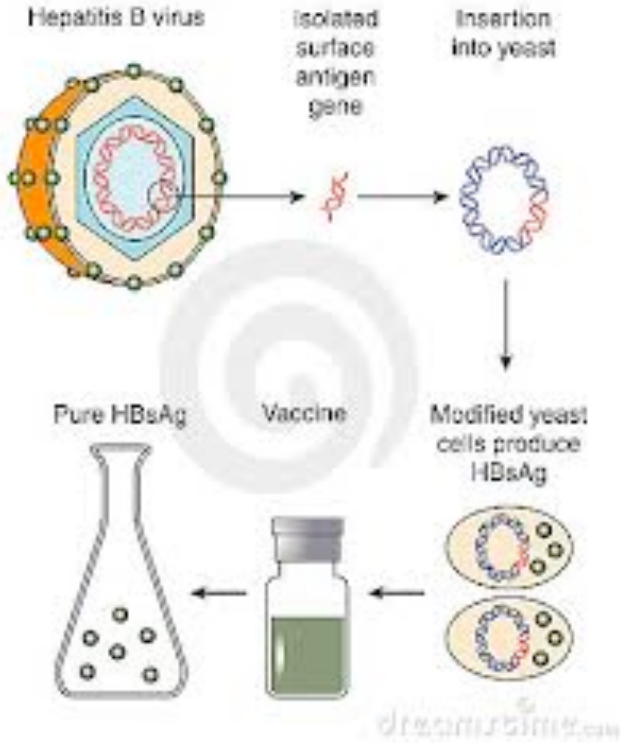


Pan CQ, et al. Clin Gastroenterol Hepatol, Feb. 2012. (Epub ahead of print)

HBV Vaccination

- The cornerstone of HBV prevention is HBV vaccination





Prevention of HBV infection in infants

- WHO guideline advises vacciantion within 24 hours of delivery
- South Africa introduced the vaccine against HBV into EPI in April 1995
- HBV Vaccine is administered at **6, 10 and 14** weeks
- The timing of vaccination is predicated on pre-HIV data that HBV transmission occurs predominantly horizontally after birth [1,2]

1. Whittle Lancet 1983;8335:1203-6
2. Botha et al. Lancet 1984;8388:1210

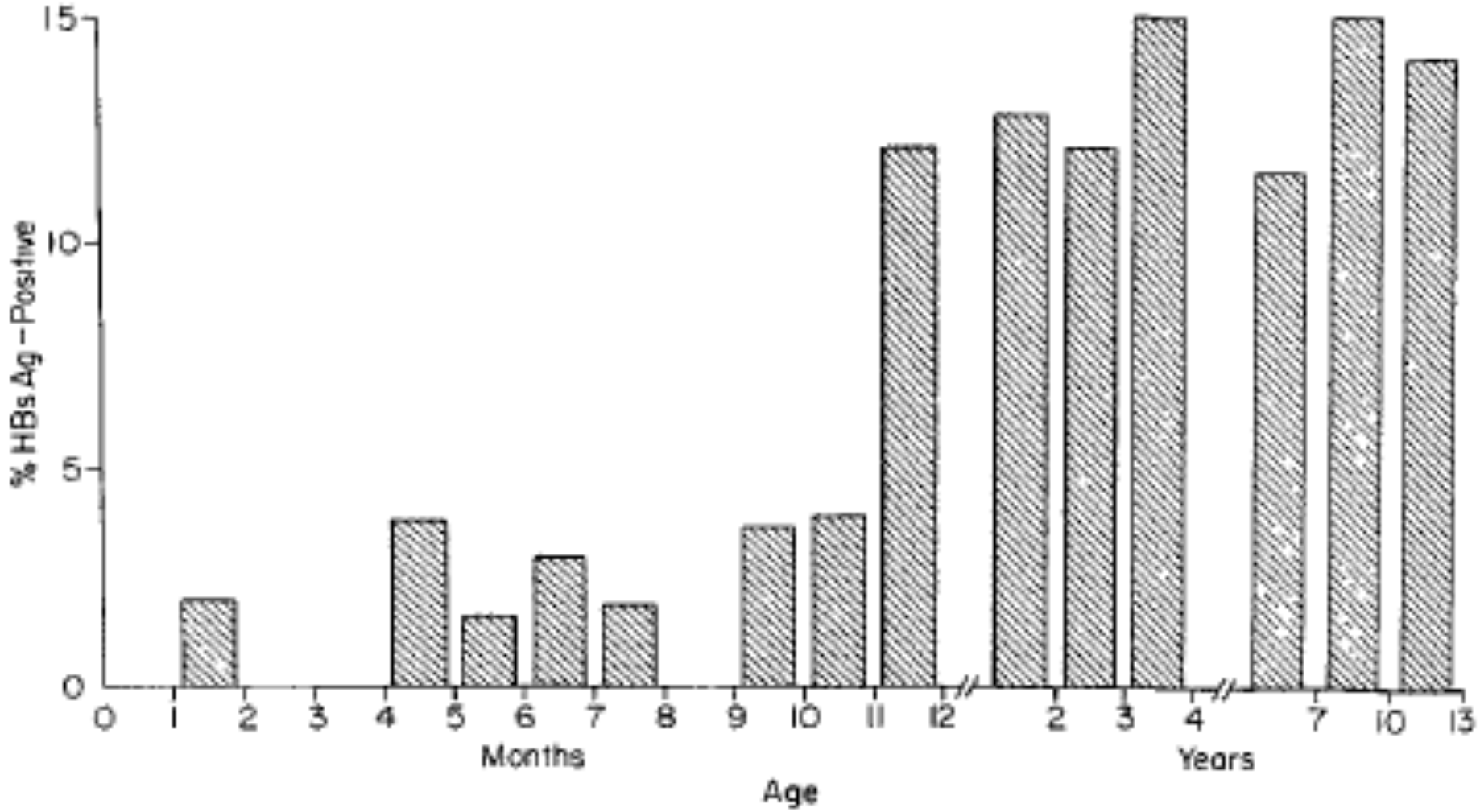


Fig 1—Prevalence of HBsAg in children between birth and 13 years.

Botha et al. Lancet 1984

HBeAg status of pregnant women

- HBeAg prevalence was once thought to be very low. This is associated with low risk of vertical transmission.

- Durban in HIV infected women showed a HBeAg prevalence of 37.5% (Thumbiran et al 2014),
- A Soweto study found 6/14 women were HBeAg positive (Hoffmann et al 2014).
- Our data showed 18.9% of HIV infected women and 17.1% of HIV-uninfected women were HBeAg positive (Andersson et al 2013).
- A smaller cohort of HIV infected pregnant women we showed 5 of 12 HBsAg positive women were HBeAg positive (Andersson et al 2012).
- The Malawi studies showed a HBeAg prevlance of 38.2% in HIV infected women (Chasela et al 2013)

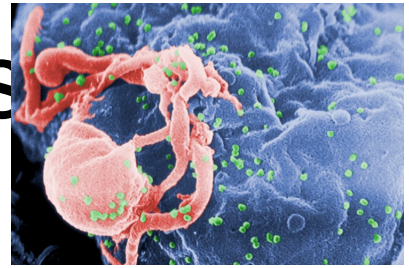
HBV Infant infection

- South African study of HBV in children has reported a 4.9% prevalence of antiHBc or HBsAg in HBV-exposed HIV-infected children, with HBsAg prevalence of 1.2% (Simani et al. 2009).
- A study carried out in 2001 showed that of 598 none were infected with HBV. (only one mother HBeAg positive) (Tsebe et al 2001).
- A study from Soweto showed that 4/14 HIV infected women transmitted HBV to their infants (Hoffmann et al 2014).

HBV Infant Infection

- WC study 4/1000 HIV-exposed infants were HBV infected (unpublished)
- 851 HIV exposed infants from Johannesburg, Durban and Cape Town and found 5 HBV infected infants
- Northern Namibia showed the prevalence of HBV to be 8.7% in 1057 HIV-infected children 0-17 years of age. (Brandt et al 2011 unpublished)

HBV Vaccine Responses in HIV exposed



- Simani et al.[1] Cohort of 303 clinic patients
  Trend towards a difference in seroprotection in HIV infected vs HIV uninfected

- Abramczuk et al.[2] Cohort 165 infants
  Results showed that 6.7% of the HIV-exposed 3.6% of the HIV-unexposed infants were nonresponders

- Thaitkumyanon et al.[3] Cohort 76 patients
  71.4% HIV exposed vs 91.9% HIV unexposed seroconversion ($p<0.05$)
  More rapid decline in antibody ($p<0.001$)

- Rutstein et al.[4] 41 HIV exposed or infected22/24 (92%) HIV exposed antibody response, 6/17 HIV infected ($p<0.0005$)

1. Simani et al. Vaccine 2009
2. Abramczuk et al. Clin Vacc Imm 2011
3. Thaithumyanon et al. J Med Assoc Thai 2002
4. Rutstein et al. AIDS 1994

Cost-effectiveness analysis of an additional birth dose of Hepatitis B vaccine to prevent perinatal transmission in a medical setting in Mozambique

Corinna Klingler[a,*], Andrea I. Thoumi[a,b], Vinod S. Mrithinjayam[a]

[a] *London School of Economics and Political Science, Houghton Street, London WC2A 2AE, United Kingdom*
[b] *London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, United Kingdom*

Method: A Markov model was constructed to analyse the costs and effects

The comparator intervention is the existing vaccination schedule administered at 6–10–14 weeks.

Main outcome measure was disability-adjusted life years (DALYs) averted.

Results: Incremental cost-effectiveness ratio (ICER) for the additional birth dose of 250.95 US$ per DALY averted.

(Assuming a willingness-to-pay threshold of 441 US$, which was the GDP per capita for Mozambique in 2008, the findings show the additional birth dose to be highly cost-effective.)

Advantages of HBV Birth Dose Vaccine

- Prevent MTCT (in context of other interventions)
  - Important in areas of high HBsAg prevalence in mothers
  - Eradication of HBV MTCT?
- Compliance
- Protection against other early exposures
- ? Importance of HIV-exposed poor responses

Prevention of MTCT

- Identify those women at risk of HBV transmission with rapid test
- Commence antiviral therapy in those who need it
- Birth dose vaccine
- Follow up mother and infant

Advantages of HBV Birth Dose Vaccine

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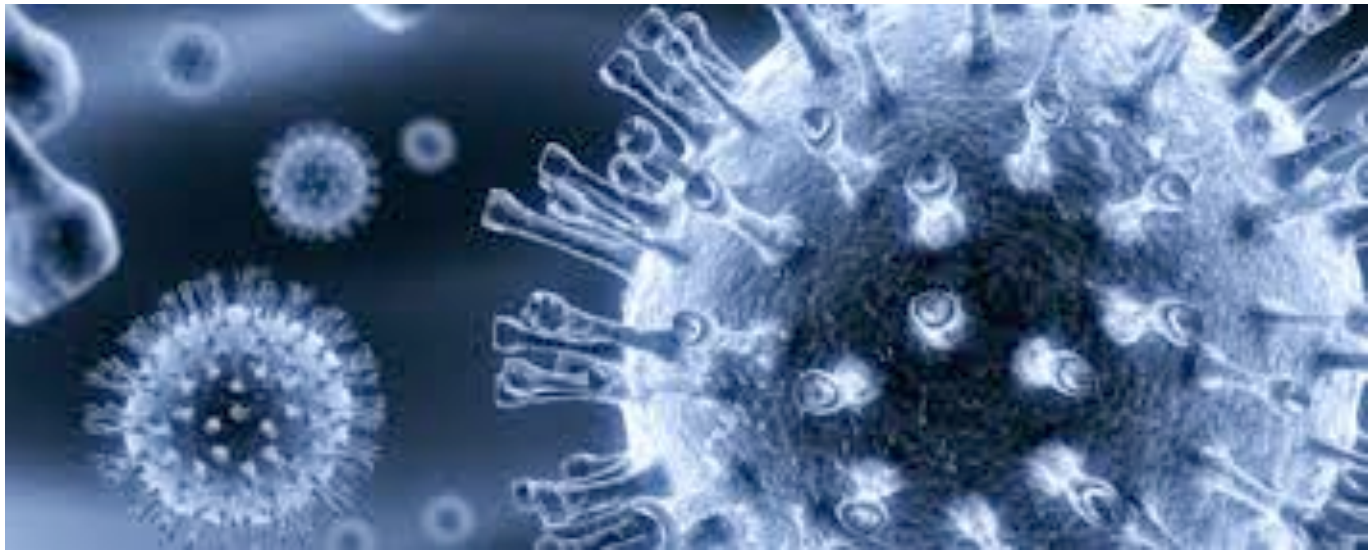
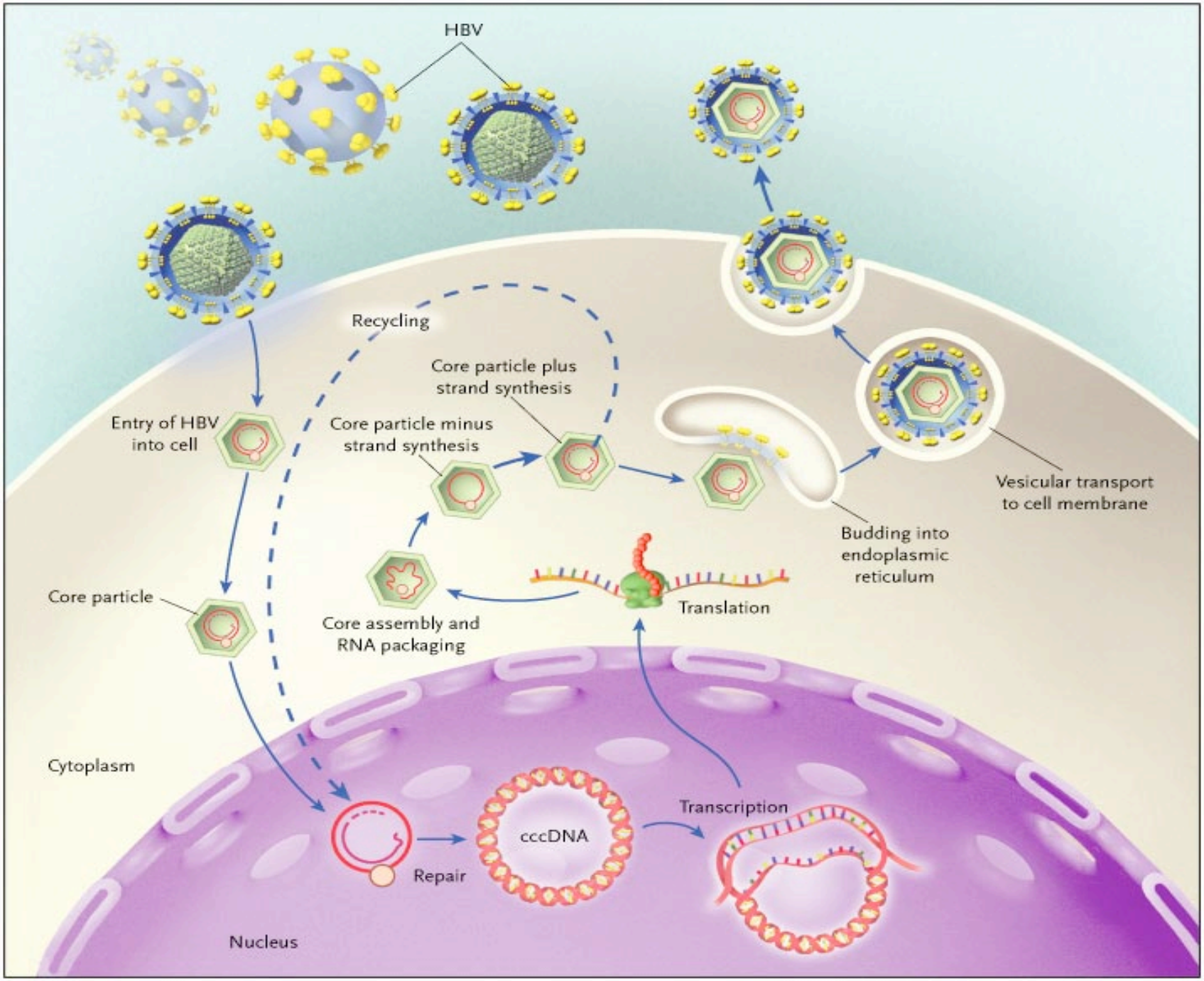
HBV Therapeutic Vaccine

- HBV CURE?

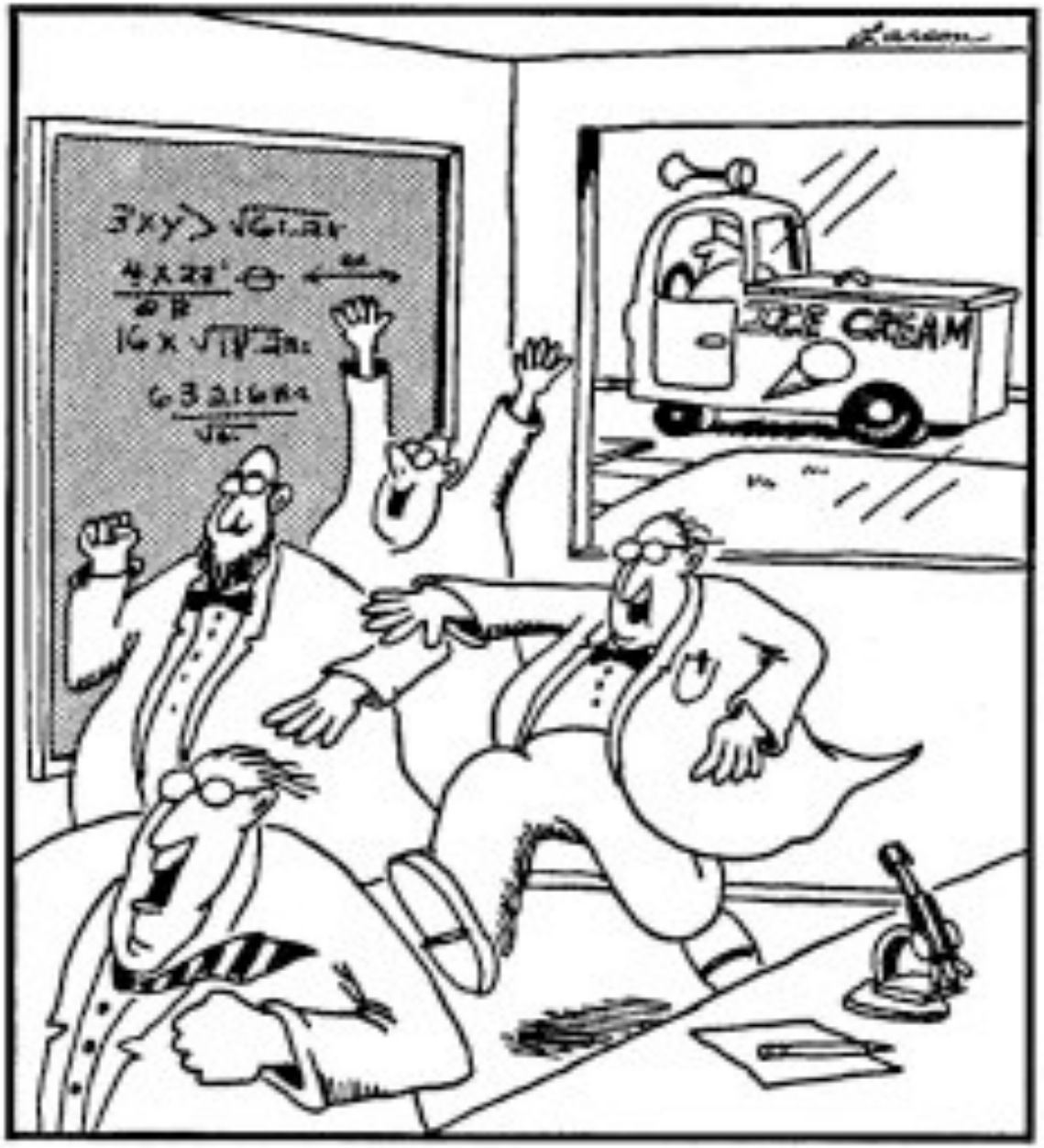
- HBV T-cell exhaustion major reason for HBV persistence
- cccDNA




HBV
Recycling
Core particle plus strand synthesis
Core particle minus strand synthesis
Entry of HBV into cell
Vesicular transport to cell membrane
Budding into endoplasmic reticulum
Core particle
Core assembly and RNA packaging
Translation
Cytoplasm
Transcription
cccDNA
Repair
Nucleus

HBV Therapeutic Vaccine

- Combination approach:
  - ➢ Antiviral therapy to reduce viral load
  - ➢ Therapeutic vaccination: recombinant HBV proteins, naked DNA combined with viral vector
  - ➢ Addition of immune modulator eg. PD-1 and PD-L1 blockade
- Watch this space….


ICE CREAM

"I've got it, too, Omar … a strange feeling
like we've just been going in circles."

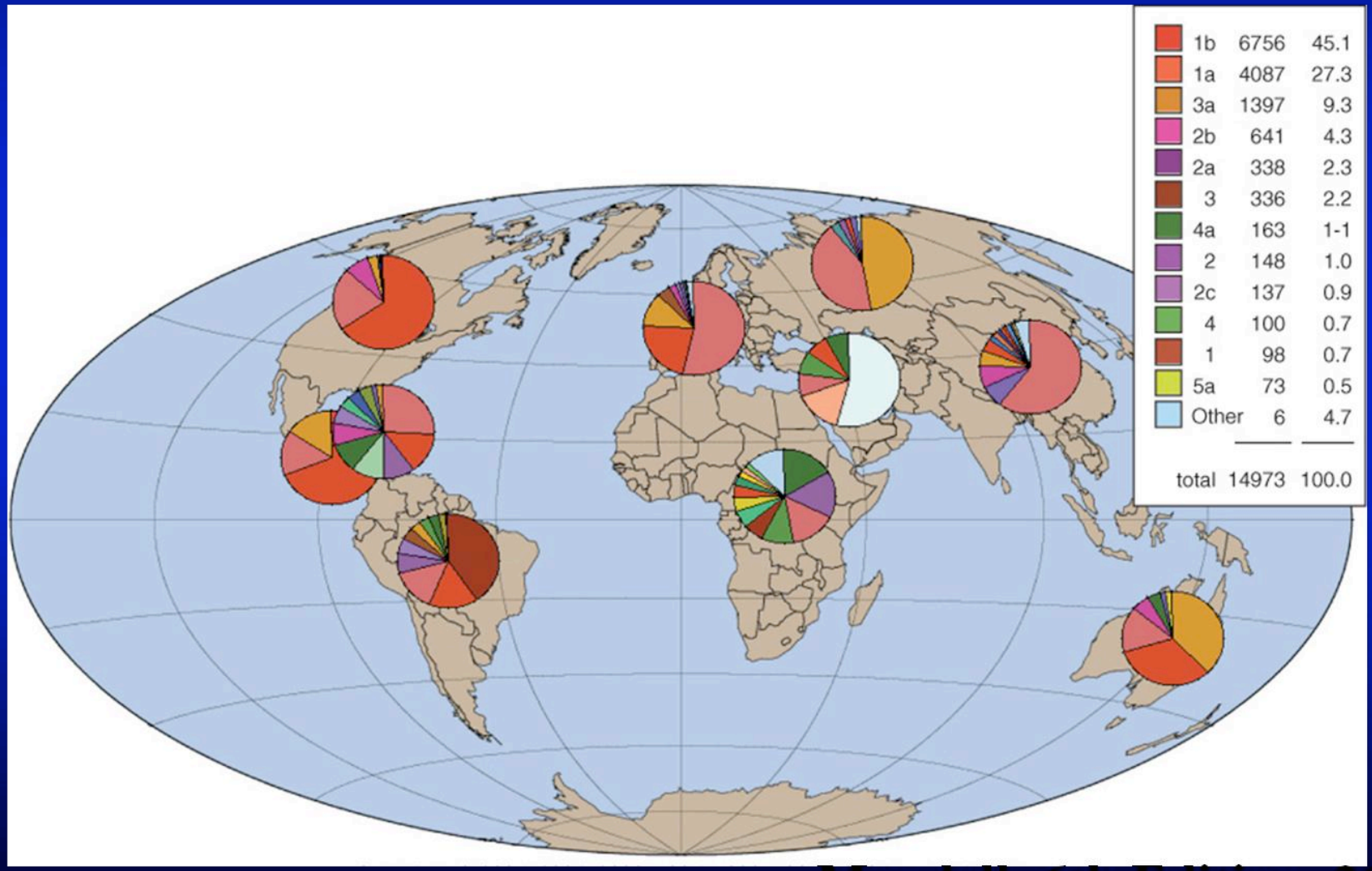

TELL US, IN LAYMAN'S TERMS, WHAT YOUR BREAKTHROUGH MEANS.
CERTAINLY.
$K-\frac{4\pi^3}{7}\sqrt{P}...4\cdot\frac{\Sigma L}{5T}$
$K-\frac{4\pi^3}{7}\sqrt{P}...4\cdot\frac{\Sigma L}{5T}$
S. Harris

Slowly he would cruise the neighborhood, waiting for that occasional careless child who confused him with another vendor.

"Look, just shut up about the caravan will you — it's too late to go back for it now.....!"

- The study evaluated and compared the prevalence of anti-HBs and exposure to hepatitis B virus (HBV) in vaccinated South African babies aged between 5 and 24 months from the Expanded Programme on Immunisation clinic [EPI group] and paediatric outpatient clinic [OPD group], and results were stratified by HIV status. A total of 303 (243 EPI group and 60 OPD group) babies were studied. All sera were tested for anti-HBs, HBsAg and anti-HBc, while IgM anti-HBc and HBV DNA were only tested in samples positive for HBsAg and/or anti-HBc. Overall, there was a gross difference in the prevalence of anti-HBs marker between the EPI and OPD groups. The EPI group demonstrated higher levels of seroconversion (89.3% vs. 81.7%; p=0.105) and seroprotection rates (86.0% vs. 75.0%; p=0.038), compared to the OPD babies. When the overall results were stratified by HIV status, seroprotection was 85.7% for the HIV-negatives and 78.1% for the HIV-positives, although this was not statistically significant (p=0.125). The seroprotection rates were almost comparable between the HIV-positives (84.3%; n=51) and the HIV-negatives (86.5%; n=192) (p=0.695) in the EPI group. In contrast, reduced seroprotection rates were observed between the HIV-positives (63.6%; n=22) and HIV-negatives (81.6%; n=38) in the OPD group, although this was not statistically significant (p=0.123). Interestingly, no HBsAg or anti-HBc marker was detected in the OPD group, compared to total exposure rate of 4.9% (HBsAg carriage was 1.2%) in the EPI group.

HCV Subtype Distribution: A Mosaic of Overlapping Sub-Epidemics



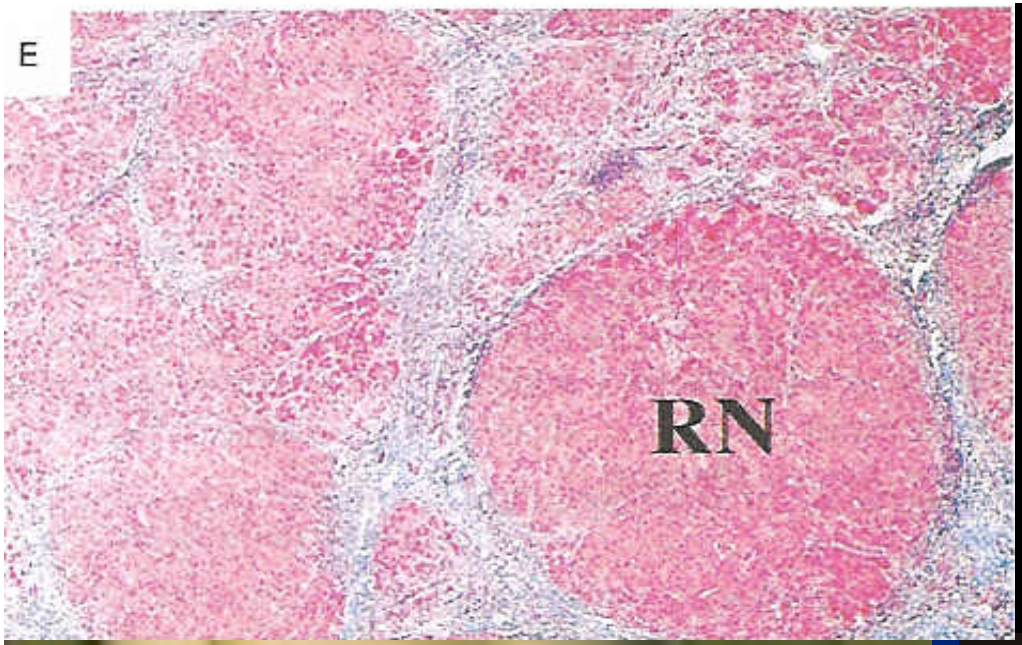
Mandell, 6th Edition, 2005

A human vaccine strategy based on chimpanzee adenoviral and MVA vectors that primes, boosts, and sustains functional HCV-specific T cell memory.

Swadling L1, Capone S2, Antrobus RD3, Brown A1, Richardson R1, Newell EW4, Halliday J5, Kelly C5, Bowen D1, Fergusson J1, Kurioka A1, Ammendola V2, Del Sorbo M2, Grazioli F2, Esposito ML2, Siani L2, Traboni C2, Hill A3, Colloca S2, Davis M6, Nicosia A7, Cortese R8, Folgori A2, Klenerman P5, Barnes E9.

- A protective vaccine against hepatitis C virus (HCV) remains an unmet clinical need. HCV infects millions of people worldwide and hepatocellular cancer. Animal challenge experiments, immunogenetics studies, and assessment of host immunity during acute infection highlight the critical role that effective T cell immunity plays in viral control.
- In this **first-in-man study**, we have induced antiviral immunity with functional characteristics analogous to those associated with viral control in natural infection, and improved upon a vaccine based on adenoviral vectors alone. We assessed a heterologous prime-boost vaccination strategy based on a replicative defective simian adenoviral vector (ChAd3) and modified vaccinia Ankara (MVA) vector encoding the NS3, NS4, NS5A, and NS5B proteins of HCV genotype 1b. Analysis used single-cell mass cytometry and human leukocyte antigen class I peptide tetramer technology in healthy human volunteers. We show that HCV-specific T cells induced by ChAd3 are optimally boosted with MVA, and generate very high levels of both CD8(+) and CD4(+) HCV-specific T cells targeting multiple HCV antigens. Sustained memory and effector T cell populations are generated, and T cell memory evolved over time with improvement of quality (proliferation and polyfunctionality) after heterologous MVA boost.
- We have developed an HCV vaccine strategy, with durable, broad, sustained, and balanced T cell responses, characteristic of those associated with viral control, paving the way for the first efficacy studies of a prophylactic HCV vaccine.

Sci Transl Med. 2014 Nov 5;6(261):261


E
RN