

Clinical management of viral hepatitis in 2026

16th Challenges in Viral Hepatitis and Liver Disease; Lausanne, 29.01.2026

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COI

- Research / Clinical Studies: Abbvie, Boehringer, Falk, Genkyotex, Inventiva, Mirum
- Speaker / Advisor: Abbvie, MSD/Merck, Gilead, Falk, Roche, Shionogi, Sobi, Takeda

Hepatitis A

Annual cases Hepatitis A – Germany and Switzerland

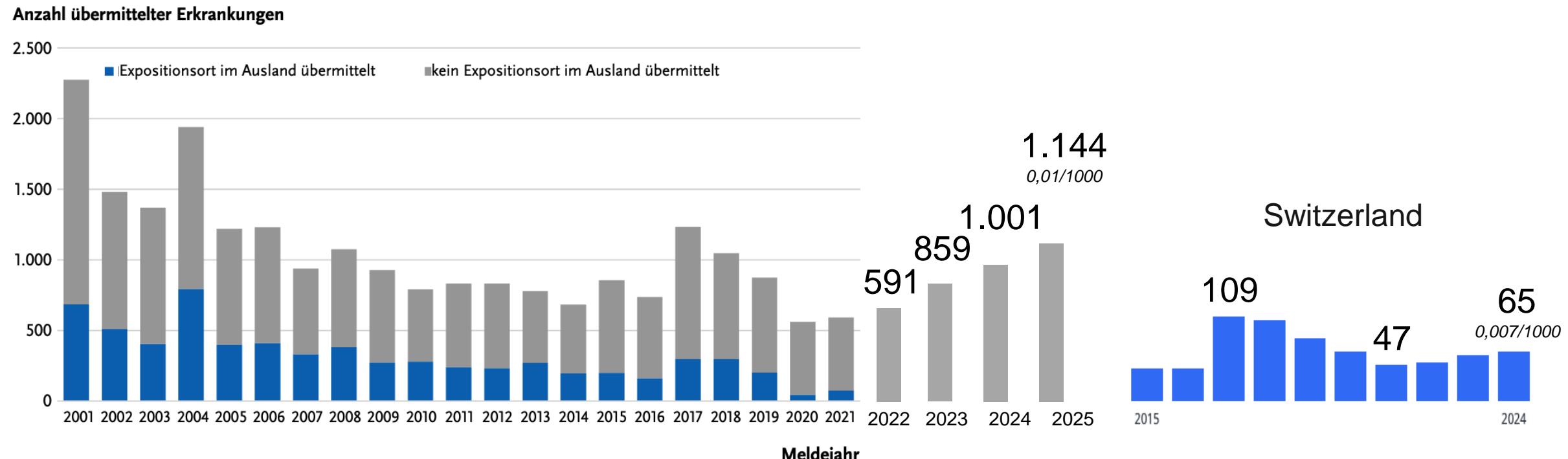


Abb. 2 | Hepatitis A in Deutschland 2001–2021, Meldedaten gemäß Infektionsschutzgesetz (IfSG)

- Increasing global HAV incidence with approx. 150 Million annual cases and approx. 39.000 deaths
- European and other high income countries with low incidence

Hepatitis A Virus Antibody Prevalence

Changes in HAV antibody prevalence in European Countries

1975

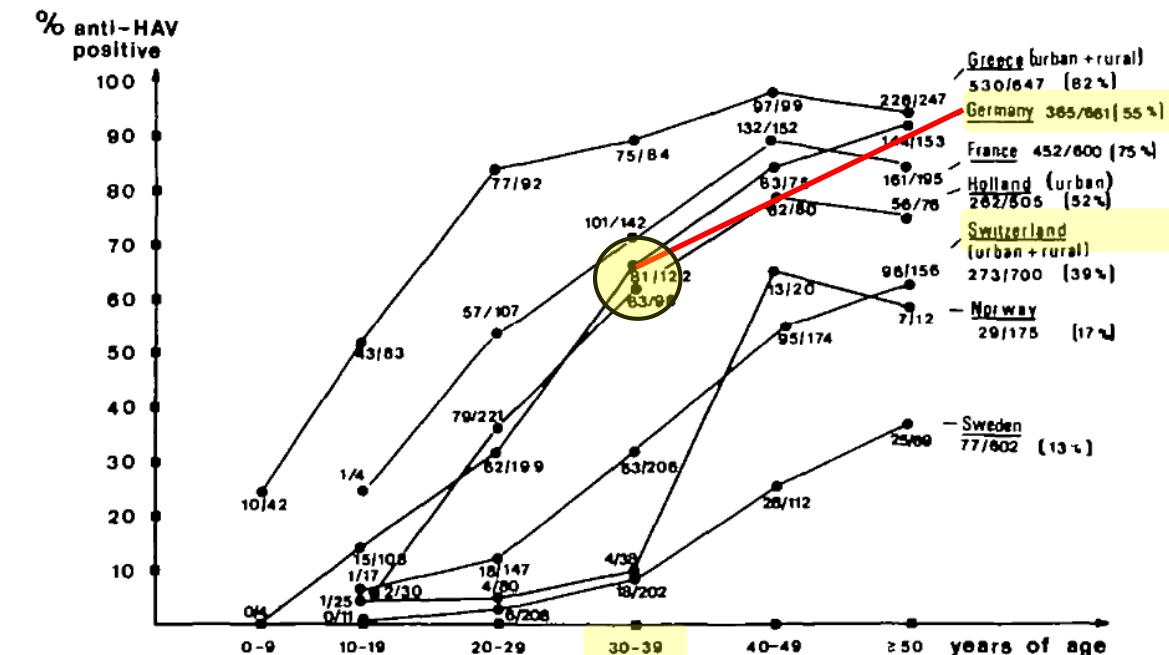
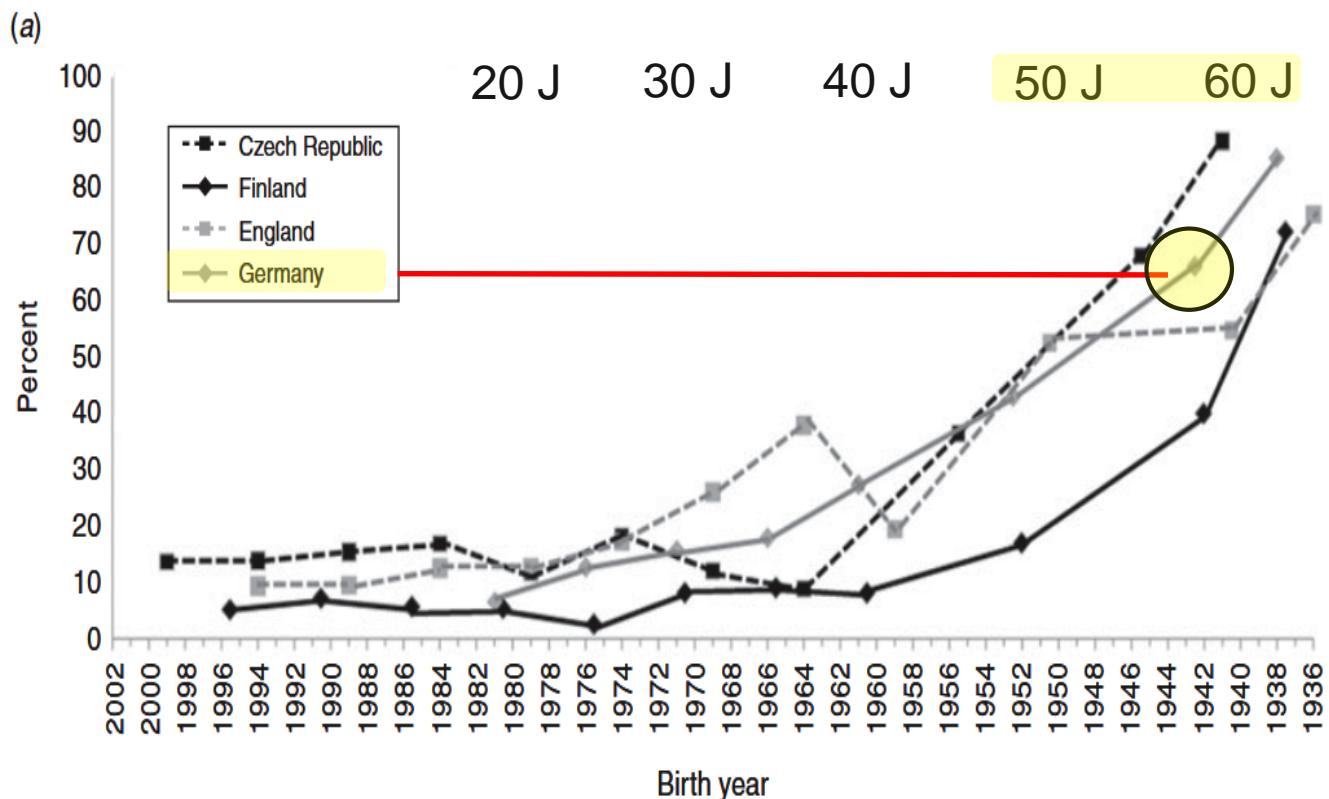


FIGURE 1. Prevalence of anti-HAV in different age groups in seven European countries.

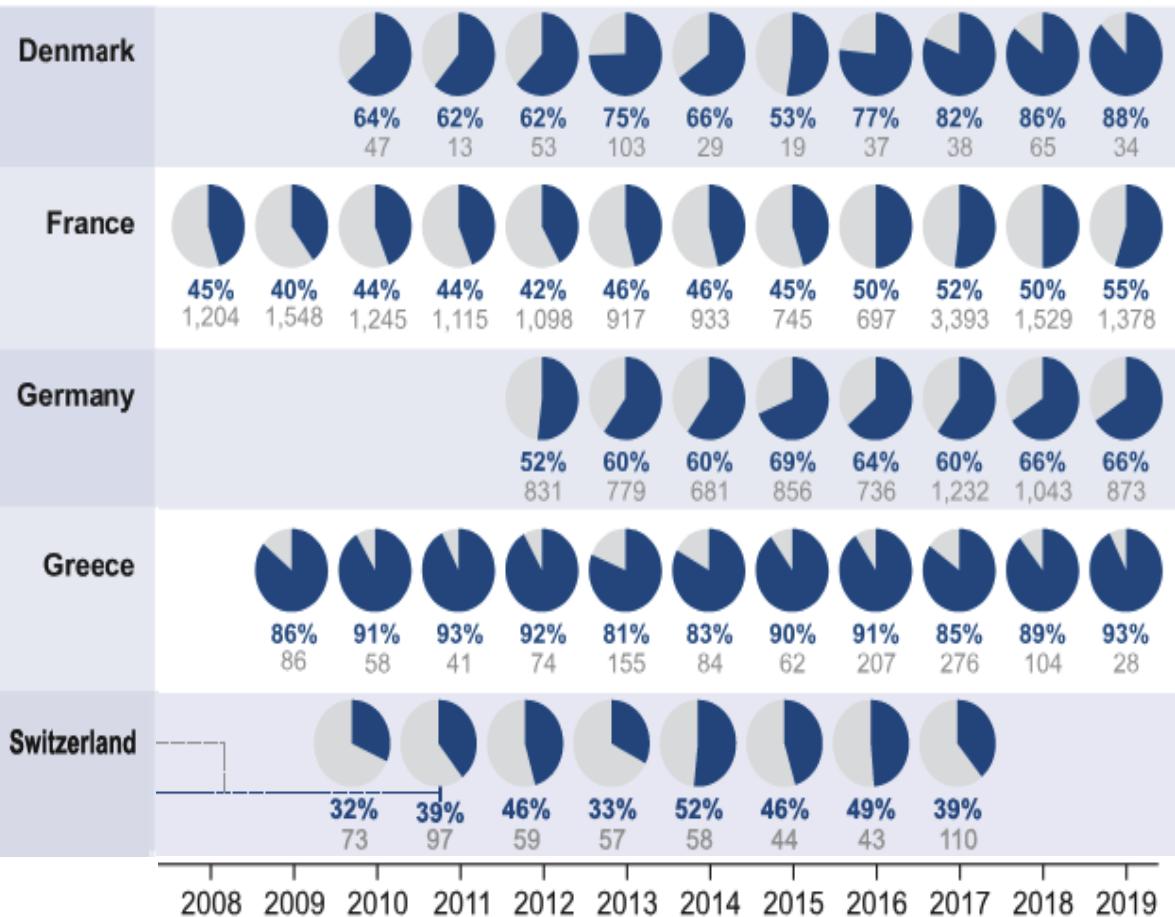
1996-2004



Epidemiology of Hepatitis A

Increasing risk for (severe) HAV-infection due to declining HAV-antibody prevalence

Annual rates of hospitalization



Number and rates of death 1988-2019

TABLE 1 | Case fatality rates due to HAV infection in 11 European countries.

Country	Number of deaths	Case fatality rate
Denmark [17, 73–76, 119–121]	2	0.15%
France [17, 59]	No data on deaths	—
Germany [17, 80]	32	0.15%
Greece [17, 70]	0	—
Hungary [17]	7	0.11%
Italy [20]	5	0.03%
The Netherlands [17]	0	—
Spain [17, 71, 72]	52 ^a	0.26%
Sweden [17, 60–65]	No data on deaths	—
Switzerland [66, 67]	No data on deaths	—
United Kingdom [17, 68, 69]	No data on deaths	—

- Severe cases in 0.1-20% of reports
- n=8 cases with liver transplantation
- Mortality: 69% >60 years, 43% comorbidities (liver disease, HBV, HCV, HIV, NI, Diabetes, PWID...)

Vaccine Strategies

Targeted (travelers, men who have sex with men, PEH)	National Health Service covers high-risk groups	Limited adult awareness	Johnson <i>et al</i> [46], United Kingdom
Recommended (travelers, men who have sex with men, laboratory staff)	Reimbursed by insurance	Stable low incidence; high cost limits universal rollout	Szucs[47], Germany
Universal since 2003 in several regions	Government-funded	Decline in hepatitis A virus cases; regional autonomy causes inconsistency	Bechini <i>et al</i> [48], Italy
Targeted vaccination	Regional funding	Good outbreak response; inequity across regions	Urbiztondo <i>et al</i> [49], Spain
Routine childhood vaccination; targeted adult vaccination (VFC program)	Free under VFC; OOP for adults without insurance	Outbreaks in PE adult uptake	Nelson <i>et al</i> [41], United States
Universal single-dose schedule	Government-funded	Successful herd immunity; sustained low incidence	Flichman <i>et al</i> [45], Argentina

Position paper Europ Soc Clin Microbiol and Inf Dis 2026

Recommendation for global universal childhood, outbreak and high risk group vaccination

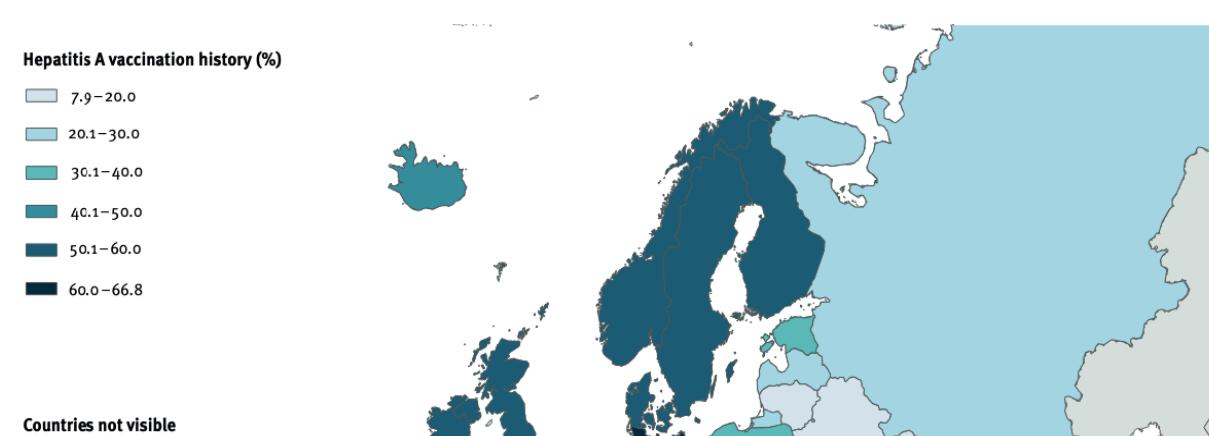
Aim: Global eradication of Hepatitis A

Europe: mainly for people at risk only
(Traveling, Profession, Sexual behavior, Liver disease, ...)

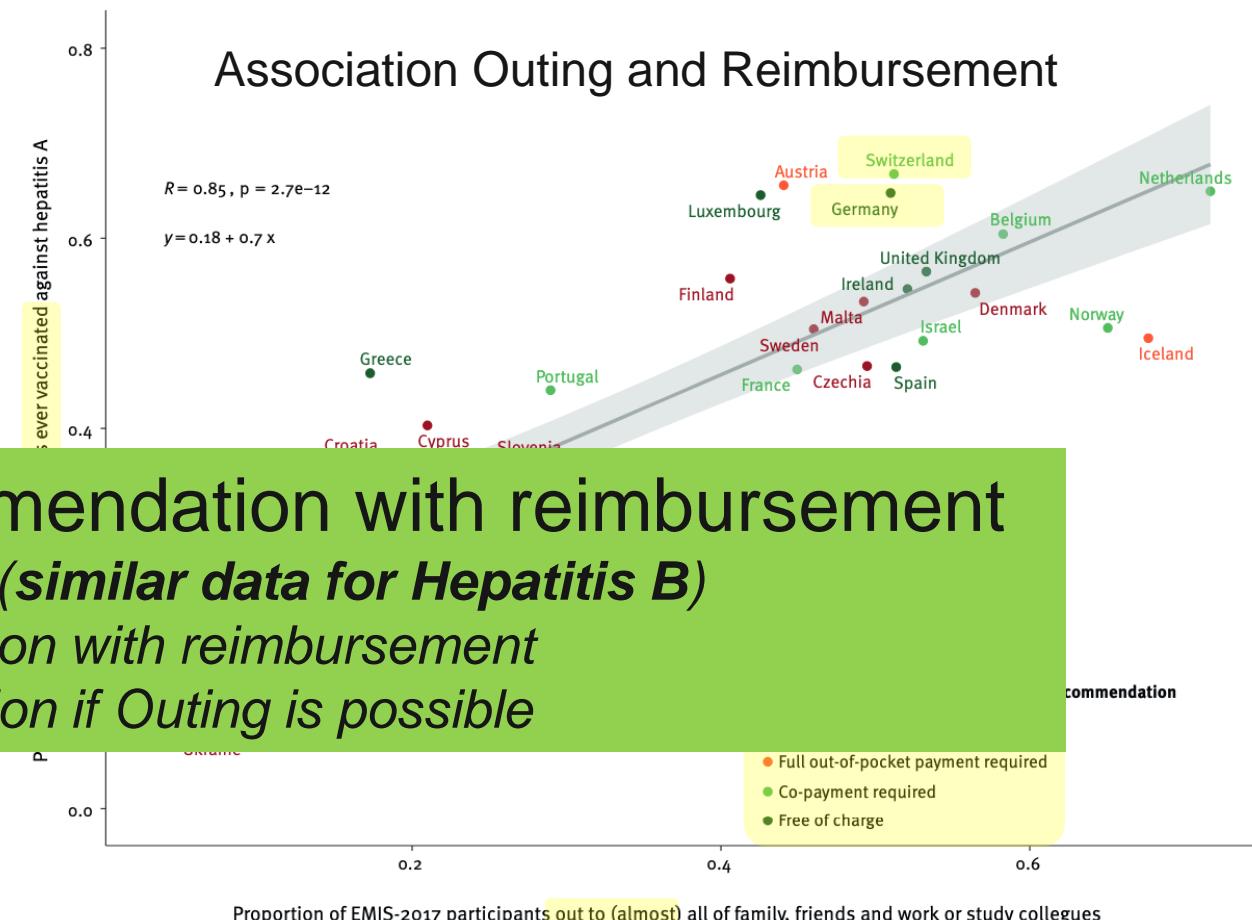
Hepatitis A Virus Antibody Prevalence: Risk MSM

HAV-Vaccination (self reported) n=113 884 MSM, median age 36 years, n=43 Europ. countries, EMIS 2017

Proportion of participants who ever received a hepatitis A vaccination by country of residency in 43 WHO European Region countries, EMIS-2017 (n=105,255)



Correlation between outness and hepatitis A vaccination history, including MSM-specific hepatitis A vaccination recommendation, 43 WHO European Region countries, EMIS-2017



In n=7 of n=43 countries recommendation with reimbursement

Vaccination rates relatively low (similar data for Hepatitis B)

Higher rates of vaccination with reimbursement

Higher rates of vaccination if Outing is possible

Hepatitis A Vaccination: Risk Liver Disease

HAV-Vaccination recommended adults with chronic liver disease, England 2012-2022, Gen Pract Res Centre
➤ Retrospective cohort study on vaccination coverage and mortality, n=625 079 chronic liver disease

	Overall (n=625 079)	Unvaccinated (n=611 204)	Vaccinated (n=13 875)	p value
Age, years			2,2%	
18-38	121 148 (19.4%)	116 631 (19.1%)	4517 (32.6%)	<0.0001
39-49	120 876 (19.3%)	117 368 (19.2%)	3508 (25.3%)	..
50-57	115 703 (18.5%)	113 045 (18.5%)	2658 (19.2%)	..
58-68	136 445 (21.8%)	134 013 (21.9%)	2432 (17.5%)	..
≥69	130 907 (20.9%)	130 147 (21.3%)	760 (5.5%)	..
Ethnicity				
White	492 040 (78.7%)	484 351 (79.2%)	7689 (55.4%)	<0.0001
Death	101 797 (16.3%)	101 065 (16.5%)	732 (5.3%)	..

Limitations:

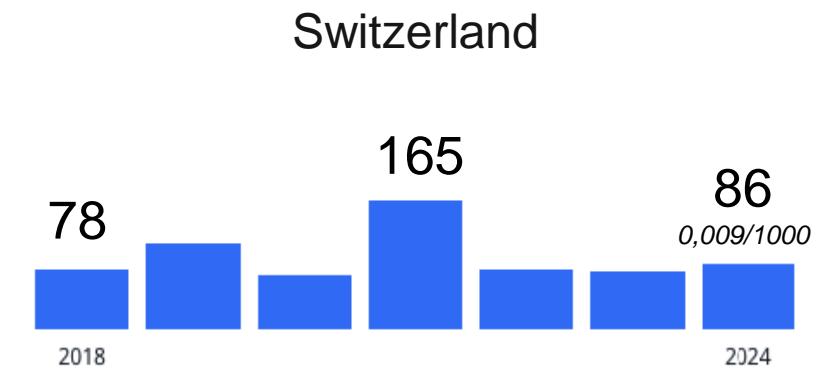
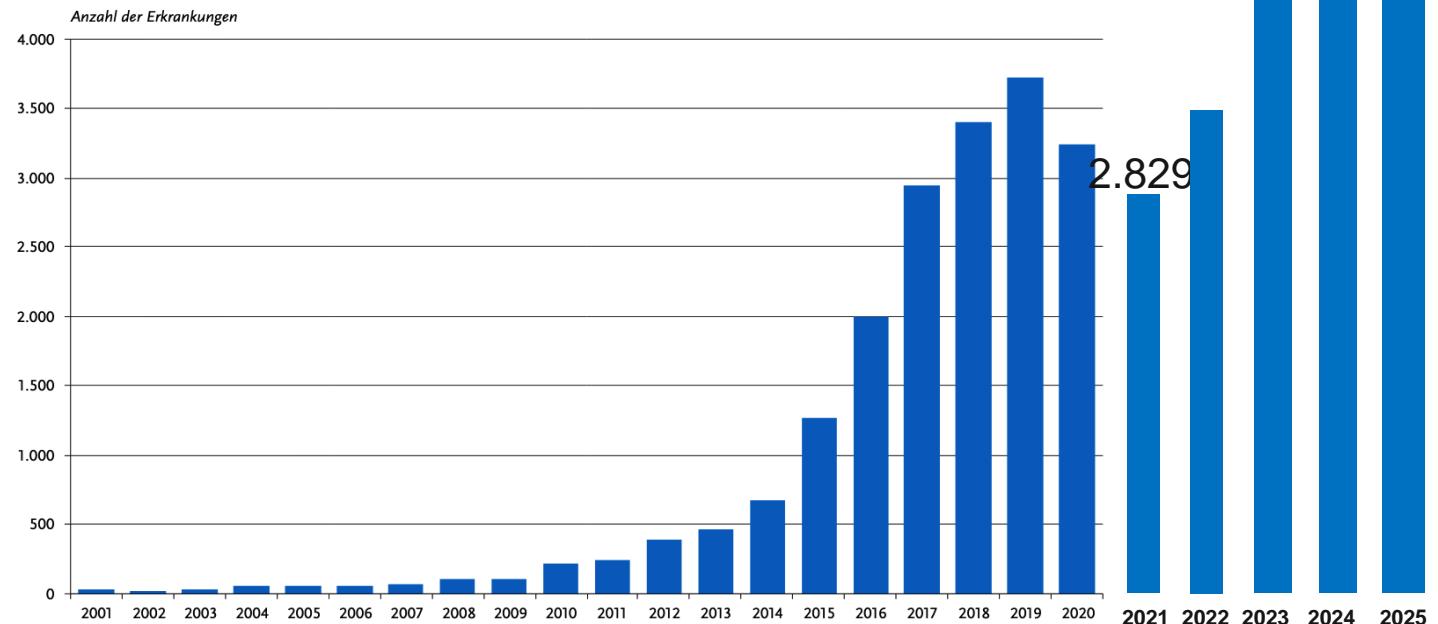
- vaccination before diagnosis of chronic liver disease unknown
- type of chronic liver disease unknown in 60%
- no exclusion of persons with past HAV infection

- **Parameters associated with vaccination:**
younger age, non-smokers, urban areas, higher socioec. status, MASLD
- **Parameters associated against vaccination:**
alcohol, type 1 diabetes, kidney disease, mental disorders

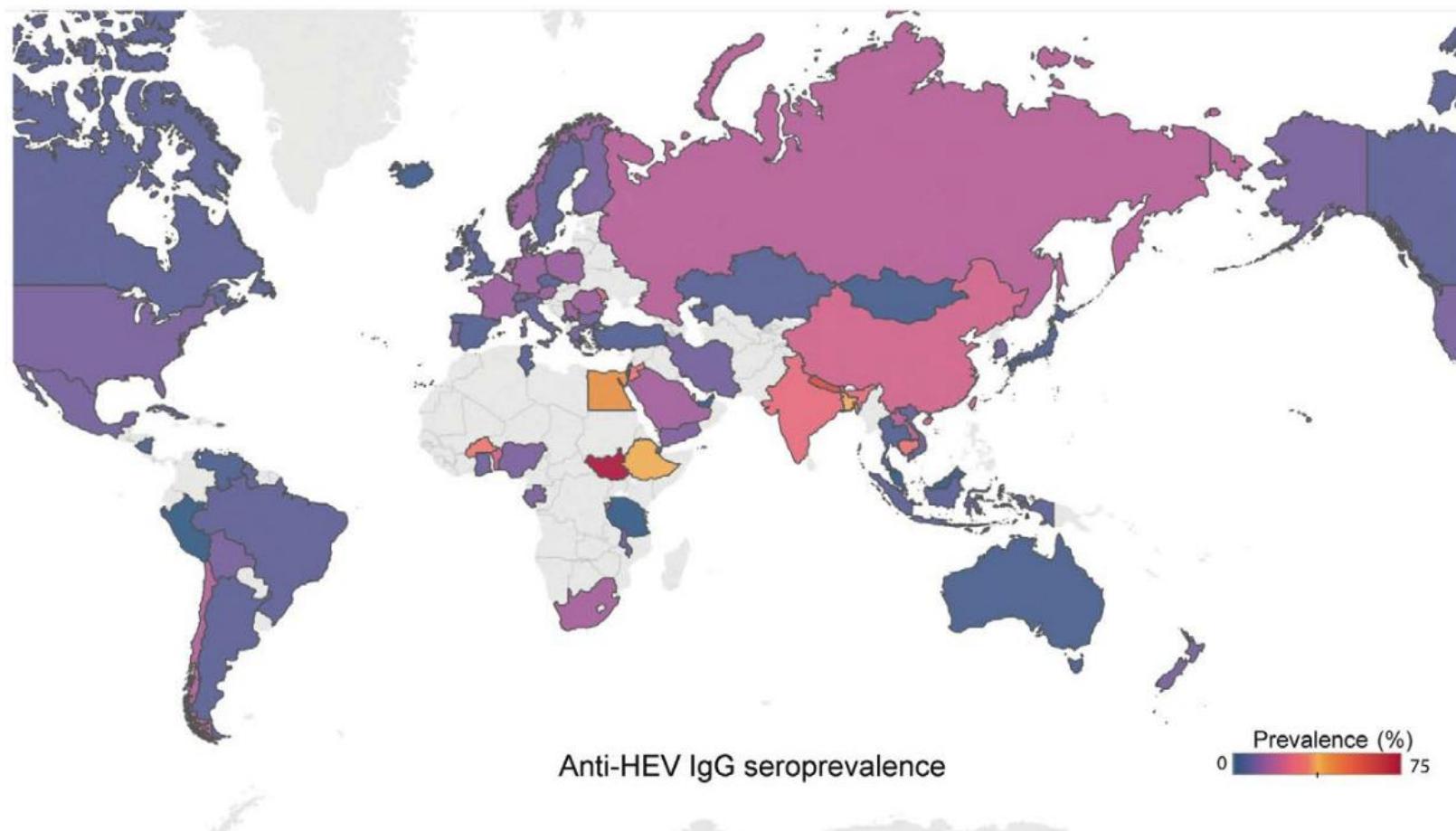
Hepatitis E

Annual cases Hepatitis E – Germany and Switzerland

Abb. 6.27.1:
Übermittelte Hepatitis-E-Erkrankungen nach Meldejahr, Deutschland, 2001 bis 2020



Hepatitis E - Epidemiology



- typical male patients between 50-79 years
- Europe: Genotype 3 (4),
- undercooked animal meat (swine, wild boar, goat, deer...)
- Inactivation: $>70^\circ$ for 5-20min

✿ Globally approx. 20 Mill. infections

✿ Globally approx. 3.3 Mill. symptomatic cases

✿ Globally approx. 44 000 fatal cases

✿ Globally approx. 3 000 stillbirths

Hepatitis E - Epidemiology

Switch from Genotype 1 to Genotype 4 in China since the year 2000

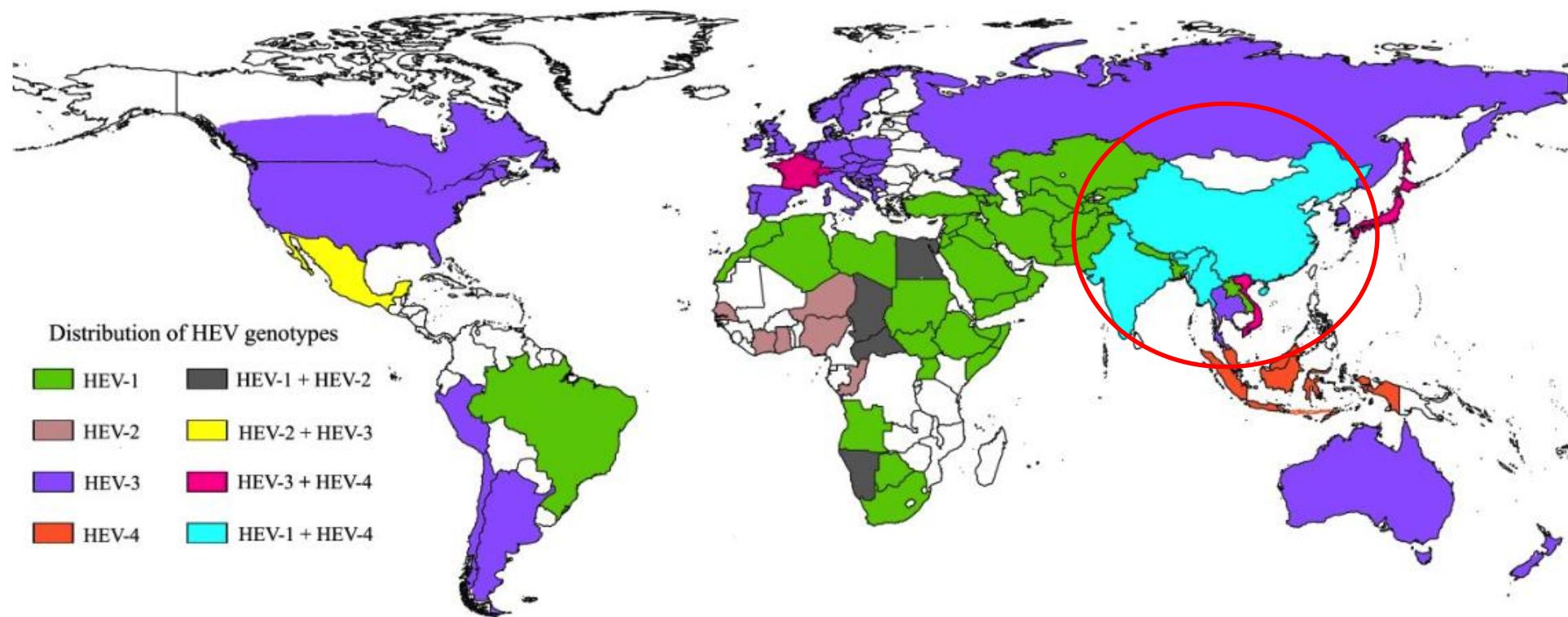
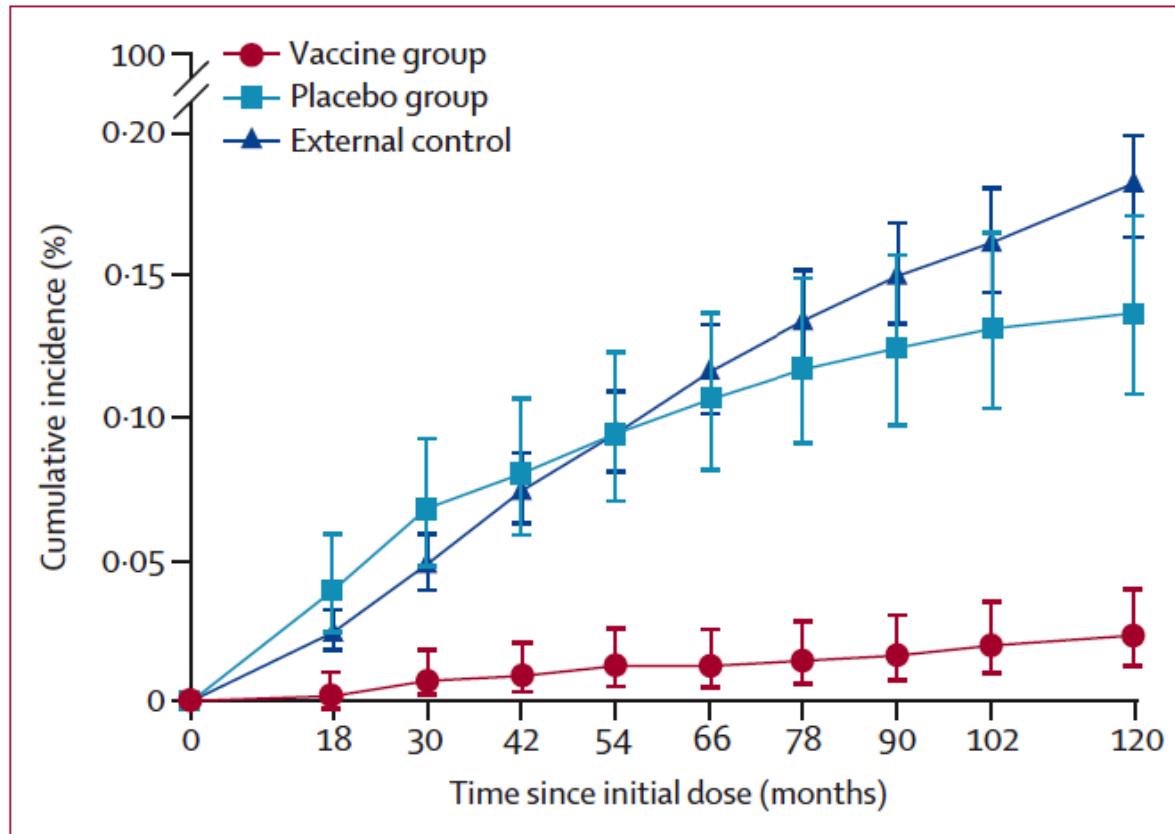


Figure 2. Global HEV genotype distribution. Different colors on the map indicate the distribution of HEV genotypes (HEV-1 through -4) across the globe. The figure was created using SimpleMappr,

Hepatitis E – Vaccination

Hepatitis E Genotype 1 Vaccine approved since 2011 (China and Pakistan)

/HEV1-230 Hecolin™ Vaccination Months 0, 1, 6, n=112 60



Long term follow-up 10 years (07-17):

- ✿ Vaccine Efficacy: 83.1% (87.3% PP)
 - ✿ for Genotype 1: 82.1%
 - ✿ for Genotype 4: 87.9-92.9%
- ✿ HEV infections: mainly genotype 4
- ✿ No specific side effects
 - Efficacy in Genotype 2+3?

HEV-Vaccination: Development HEV-239 & Study USA

Double blinded, randomised phase 1 study (4:1), n=25, age 18-45 years, interim after 12 months

Table 4

HEV 239 vaccine protects rhesus monkeys against challenge with 10^4 genomic dose of genotype 1 or 4 HEV

[Groups]	vaccine	Virus genotype	Monkey code	Anti-HEV (pre-infection)		ALT (peak/pre)	Virus shedding (w)	Ab resp.
				1/titer	IU			
[A] 2 x 0 µg	1	28	<10	<2	1.8	5	+	
		29	<10	<2	4.6	6	+	
		30	<10	<2	0.8	4	+	
[B] 2 x 0 µg	4	34	<10	<2	0.9	1	+	
		35	<10	<2	1.1	4	+	
[C] 2								
[D] 2								
[E] 2 x 20 µg	1	11	61800	1242	1.7	0	—	
		12	43200	960	0.7	0	—	
		22	44300	1377	1.8	0	—	
[F] 2 x 10 µg	4	23	61400	3314	1.6	0	—	
		24	84300	2498	1.5	0	—	
		16	41900	1012	1.8	0	—	
		17	59700	2520	0.8	0	—	
		18	66500	316	1.5	0	—	

Development of HEV-239 in rhesus-monkeys
With efficacy in HEV GT1 and GT4
(all HEV genotypes have same serotype)

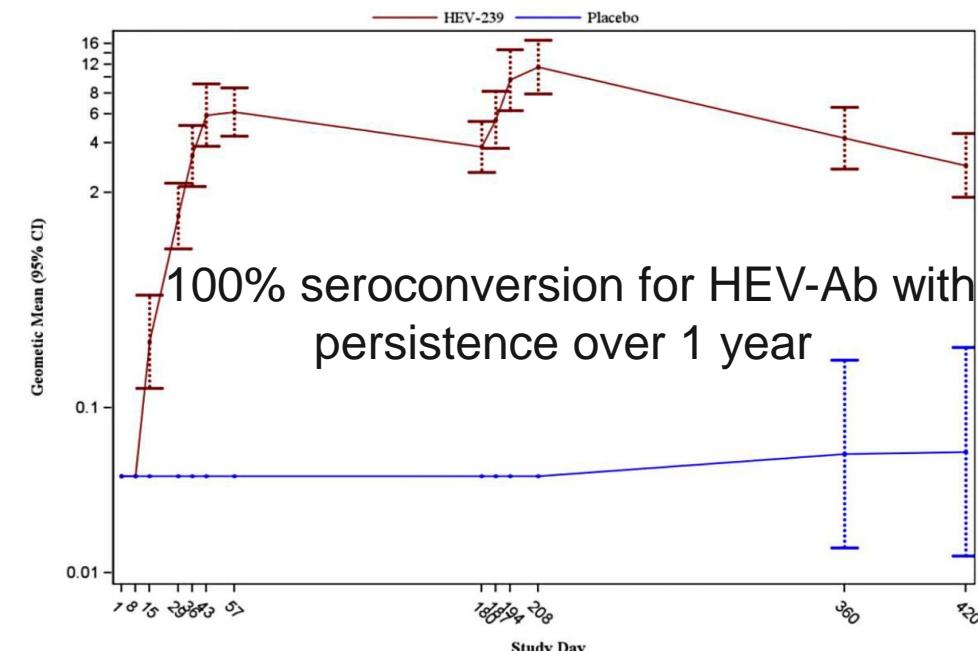
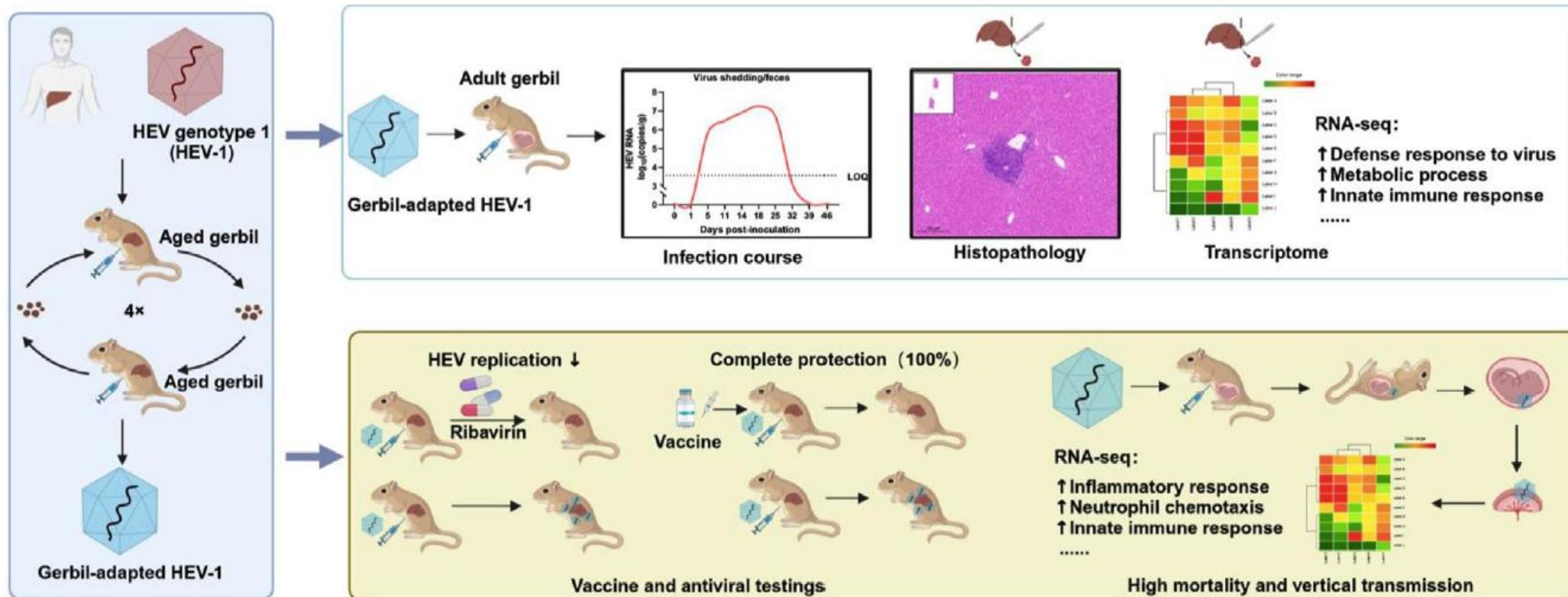


Figure 3. Immunogenicity of HEV-239 versus placebo; immunoglobulin G (IgG) geometric mean concentration, modified intention-to-treat population.

Position paper Eur. Soc. of Clin. Microbiol. & Infectious Dis. Viral Hepatitis Study Group:

- Four HEV vaccine candidates. Only HEV-239 approved against genotype 1 ORF2-capsid (China)
- High probability of efficacy not only in genotype 1+4 but also genotype 2+3
- Vaccination programs espec. in at risk groups (Pregnancy, liver disease, immunosuppr./transplant.)

Replication Model for HEV Infection: *Gerbil Mice (immune competent)*

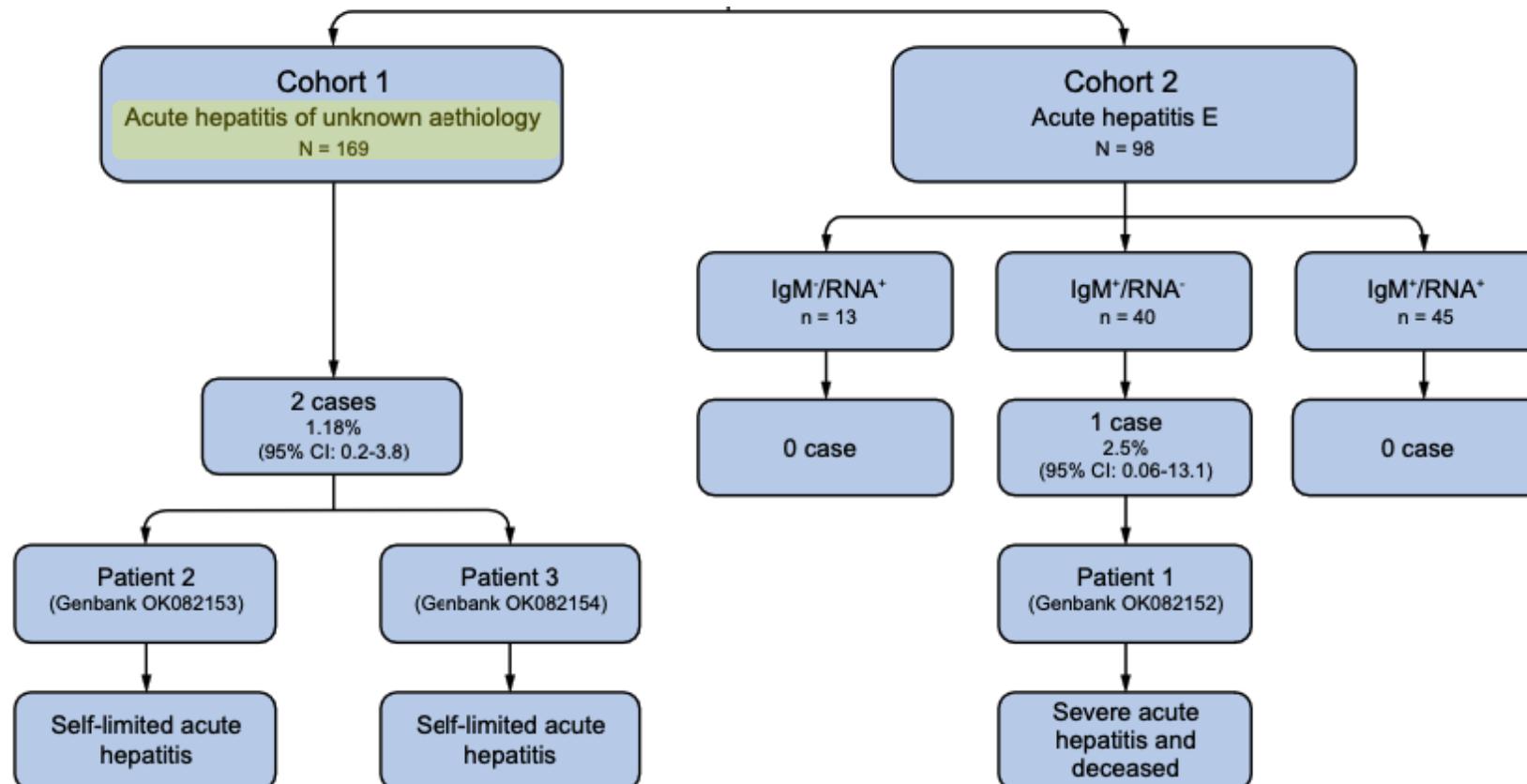


- Adaptation HEV-GT-1 to Gerbil Mice by serial intestinal passage (finally weak oral re-infection)
- Establishment of full replication cycle with high mortality of HEV infection in pregnant mice
- Chronic infection on tacrolimus – recovery with Ribavirin – protection with HEV-239 vaccine
- **Recovery after HEV-GT-1 infection showed prevention for HEV-GT-3 infection**



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 Reina⁵, Ana Fuentes-Lopez^{2,6,7}, Carolina Freyre-Carrillo⁸,
Encarnación Ramirez-Arellano⁹, Juan Carlos Alados¹⁰, Antonio Rivero^{1,2}, For the HEPAVIR and
GEHEP-014 Study Groups



Rat Hepatitis E Virus (rHEV)

Rare cause of acute/chronic viral hepatitis with few cases from Hong Kong, Spain, France, Canada
➤ Establishment of diagnostic algorithm and estimation of frequency

Diagnostic algorithm established

Testing



→ 12 PCRs



n = 50

Derivation

n = 103

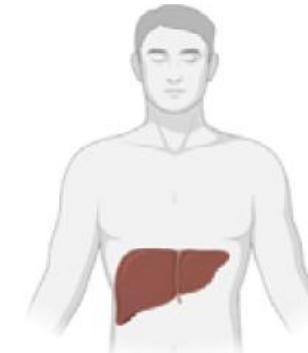


17.5% (n = 18)



Clinical validation

N = 562



↓
1.4% (n = 8)

Acute hepatitis of unknown origin (3 years)

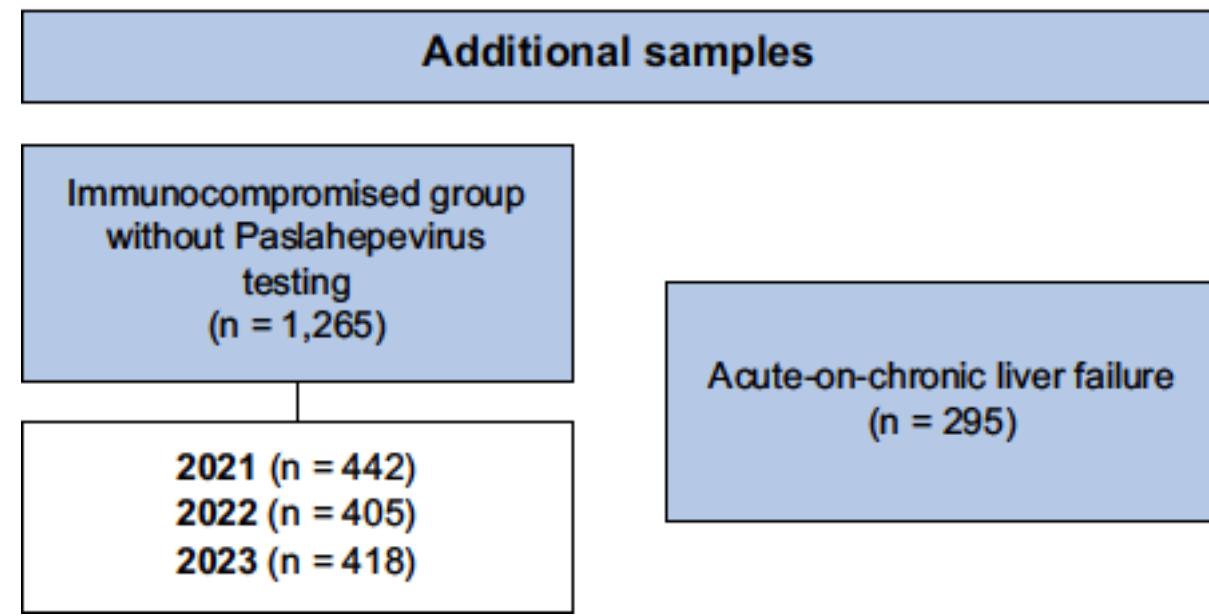
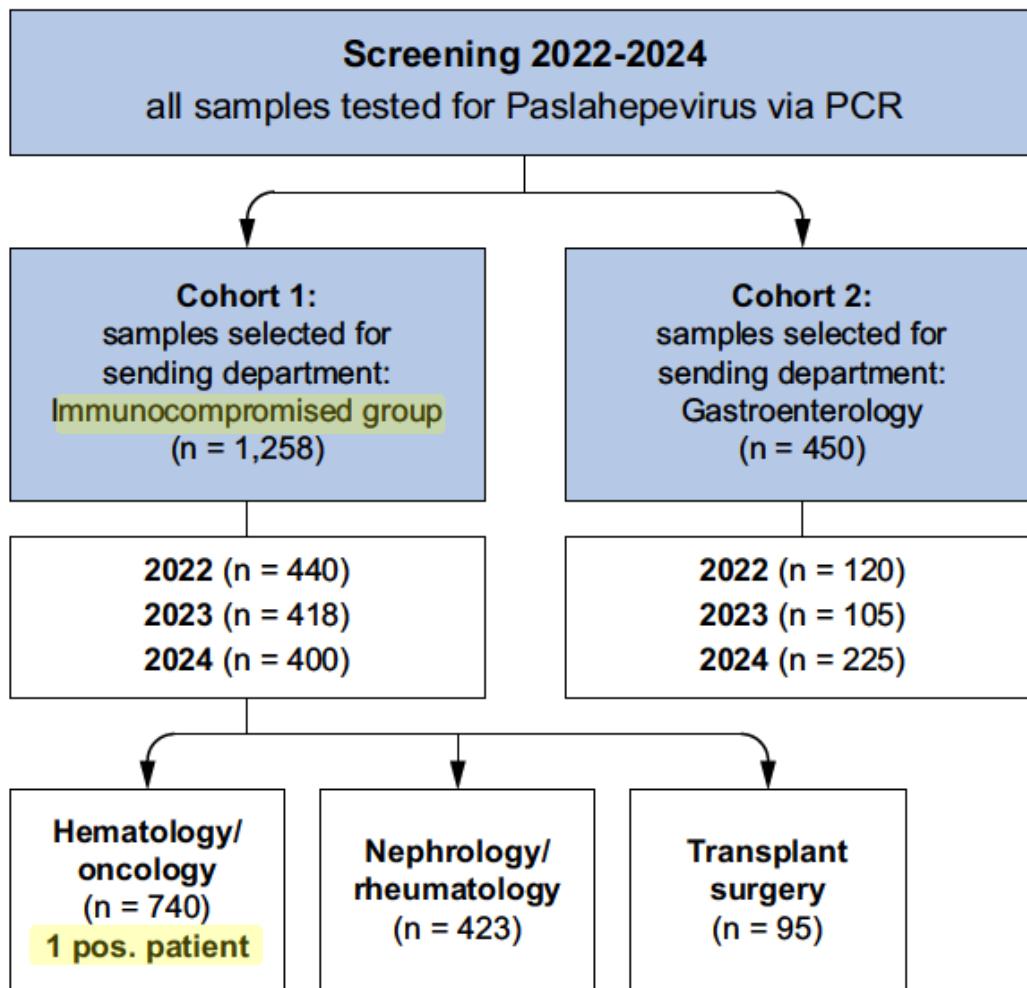
- n=4 male
- n=7 HEV-IgG pos., n=3 HEV-IgM pos.
- n=4 hospitalization, n=1 severe course (cirrhotic), n=1 death

Proposed testing algorithm

- Screening: qPCR-1 and qPCR-4 in parallel: if positive →
- Sequencing: seqPCR-1 and, if negative, seqPCR-3 or seqPCR-5

Rat Hepatitis E Virus (rHEV)

Samples for viral hepatitis testing (Berlin, Charité) and additional samples from immunocompromised & acute on chronic liver failure patients (Berlin, Frankfurt, Munich)



- n=1 patient Rocahepevirus (rHEV) positive (male, 50-60 years, hematologic malignancy, ALT 132, spontaneous resolution, serology?)

Immunity against HEV re-infection?

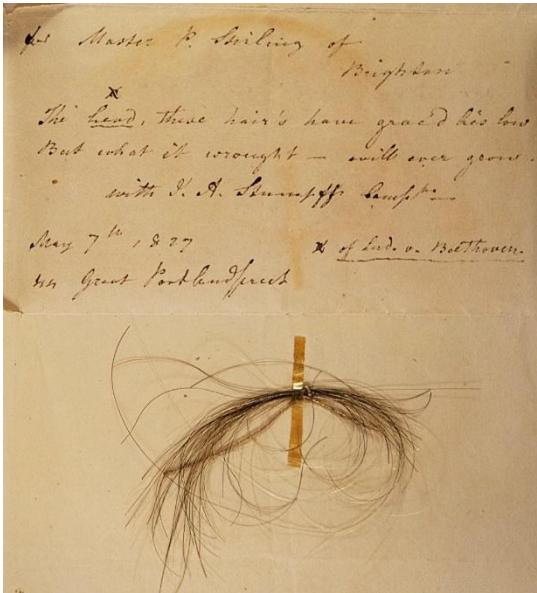
Anti-HEV antibodies decline after HEV infection – protection against re-infection is unclear
Phase 3 HEV vaccine approval study, China, n=7,032 persons from placebo arm, 8.5 years FU
➤ n=3,194 anti-HEV IgG positive versus n=3,838 anti-HEV IgG negative

Table 2 | Protection of pre-existing antibodies against Hepatitis E cases and hospitalization cases

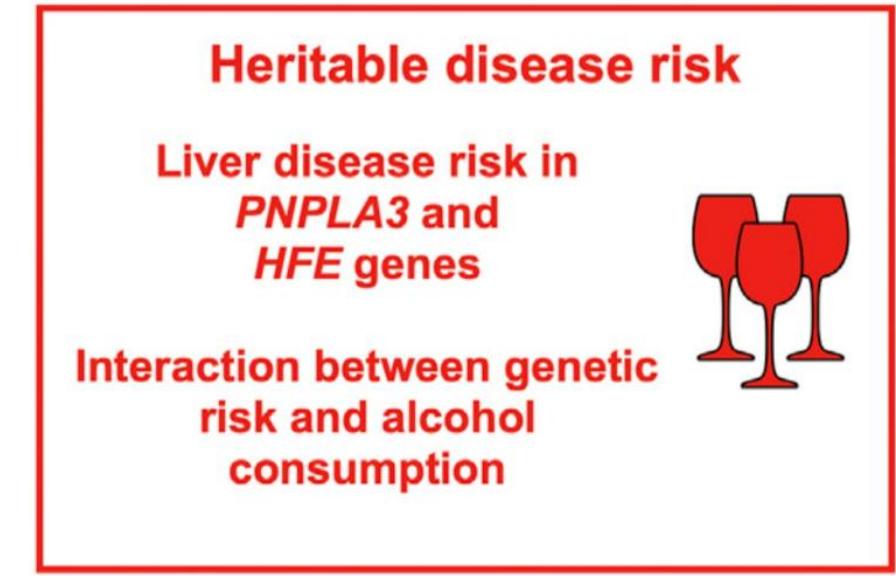
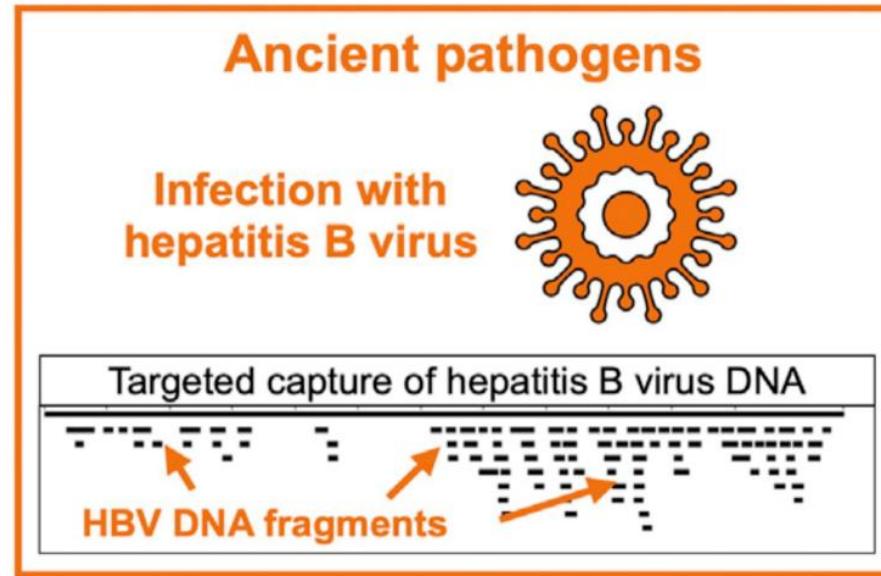
Period	Seropositive group (N=3194)		Seronegative group (N=3838)		Crude protection	
	No. of cases	Incidence (/10000 p-yr)	No. of cases	Incidence (/10000 p-yr)	% (95% CI)	P value
Hepatitis E						
0-18m	1	2.1	3	5.2	59.9 (-285.1,95.8)	0.4282
0-30m	1	1.3	4	4.2	70.0 (-168.7,96.6)	0.2820
0-66m	2	1.1	6	2.8	60.0 (-98.3,91.9)	0.2622
0-90m	2	0.8	7	2.4	65.7 (-65.1,92.9)	0.1821
0-120m	2	0.6	8	2.1	70.0 (-41.3,93.6)	0.1279
Hepatitis E with hospitalization						
0-18m	0	0.0	2	3.5	100.0 (-317.2,100.0)	0.2979
0-30m	0	0.0	3	3.1	100.0 (-106.0,100.0)	0.1626
0-66m	0	0.0	5	2.4	100.0 (1.5,100.0)	0.0484
0-90m	0	0.0	6	2.1	100.0 (22.2,100.0)	0.0264
0-120m	0	0.0	6	1.6	100.0 (22.3,100.0)	0.0264

Hepatitis B

Ludwig van Beethoven 1770-1827 – died from liver cirrhosis

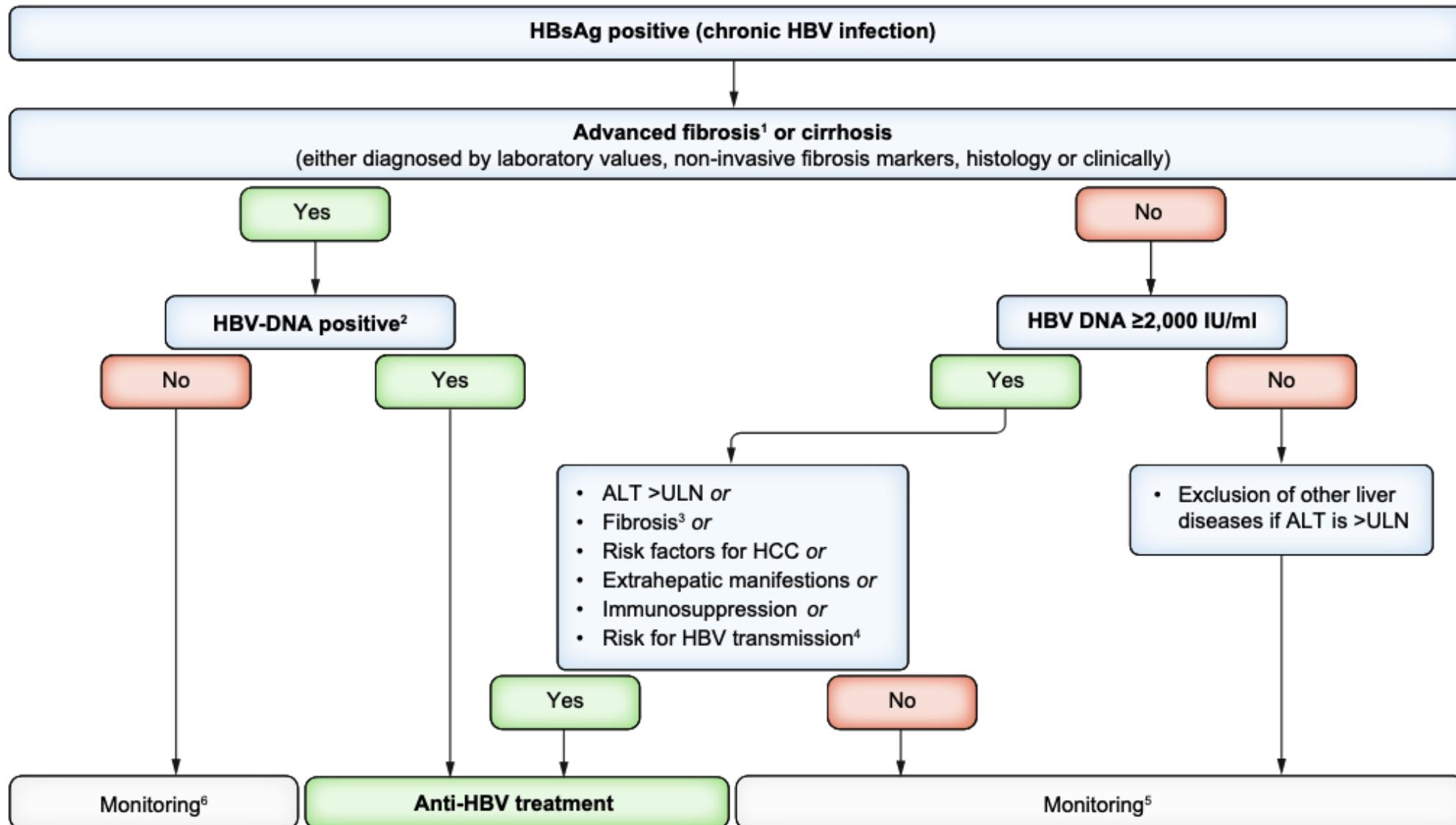


Locks of Hair from 8
Museums



Prove of HBV infection almost 200 years after his death and high genetic risk for development of liver cirrhosis

Indication for Antiviral Treatment – EASL



Indication for antiviral therapy: viral load +/- liver enzymes +/- age?

n=734 HBeAg pos/neg., n=22 centers Taiwan/South Korea, median age 53 y., interim analysis 17.7 mo. HBV-DNA 4-8 log + ALT <70/50 ♂♀, prosp. rand. TAF vs. Observation; Endpoints: Decomp., HCC, OLT, Death

Tenofovir alafenamide group (n=369)	Observation group (n=365)	Hazard ratio (97.5% CI)	p value
Composite primary endpoint			
Number (%)	2 (1%)	9 (2%)	0.21 (0.04 to 1.20) 0.027
Incidence rate per 100 person-years	0.33	1.57	..
Secondary endpoints			
Hepatocellular carcinoma	2 (1%)	7 (2%)	0.27 (0.04 to 1.62) 0.079
Hepatic decompensation	0	1 (<1%)	NE 0.31
Death	0	1 (<1%)	NE 0.29
Liver transplantation	0	0	NE

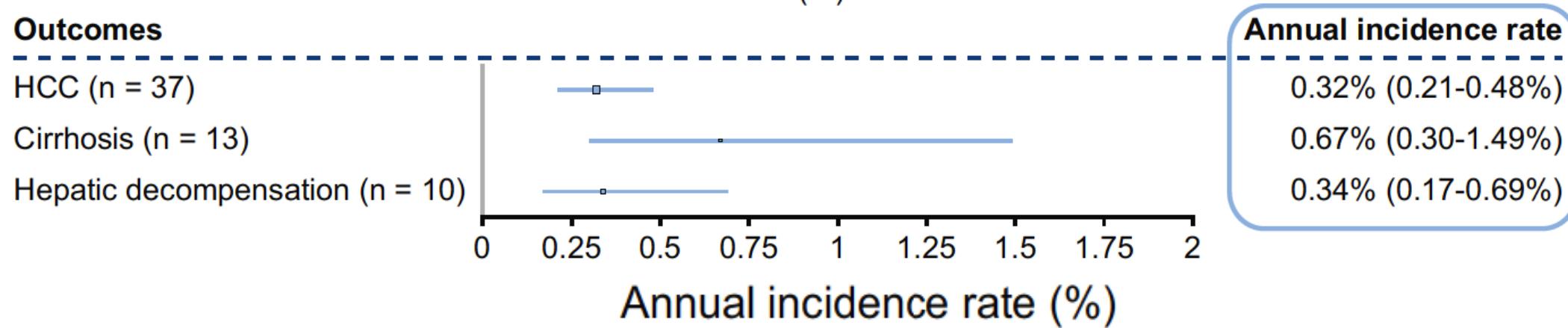
- Even in patients with normal ALT antiviral therapy with NUCs is significantly better than observation (0 versus 4 pts. with endpoint, $p=0.044$)
- Indication for antiviral therapy if viral load is elevated ($>2\ 000$?) and (in older pts.) also if liver enzymes are normal?

Indeterminate Phase of chr. Hepatitis B: Meta-Analysis

HBeAg neg./pos.: HBV-DNA >2.000/10 Mill but normal ALT – HBV-DNA <2.000/10.000 but elevated ALT (EASL)

103 studies on chronic hepatitis B
in the indeterminate phase

34,017 patients included



- **Study population:** 41% had moderate to severe inflammation; 40% had F3, 7% had F4
- **Risk factors for HCC, cirrhosis, hepatic decompensation:** no antiviral therapy, older age, male, HBeAg +
- **Limitations:** Mainly retrospective studies, no close follow-up of ALT/HBV-DNA, mainly studies from Asia

Hepatitis C

SVR (viral eradication) is achieved in practically all cases with mainly use of pangenotypic DAA regimens:

VEL/SOF for 12 weeks or
G/P for (mainly) 8 weeks

No or minor side effects and rescue treatment for rare cases of treatment failure

Follow-up of patients after treatment

Hepatitis C – Epidemiology and Elimination Goals

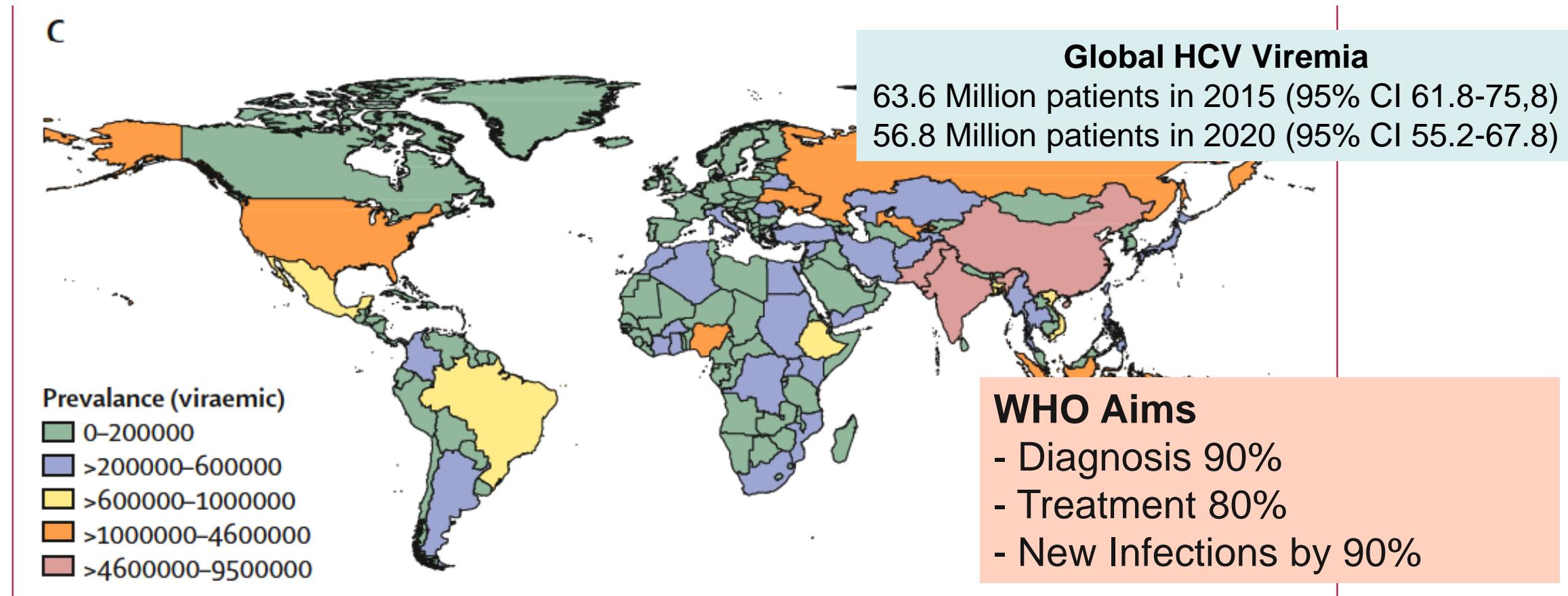


Figure 1: Country-level and territory-level HCV prevalence estimates (beginning of 2020)

- (A) Viraemic HCV infection prevalence among countries and territories with approved or estimated models.
- (B) Viraemic HCV infection prevalence for all countries and territories, including those with extrapolated prevalence.
- (C) Number of viraemic HCV infections for all countries and territories. HCV=hepatitis C virus.

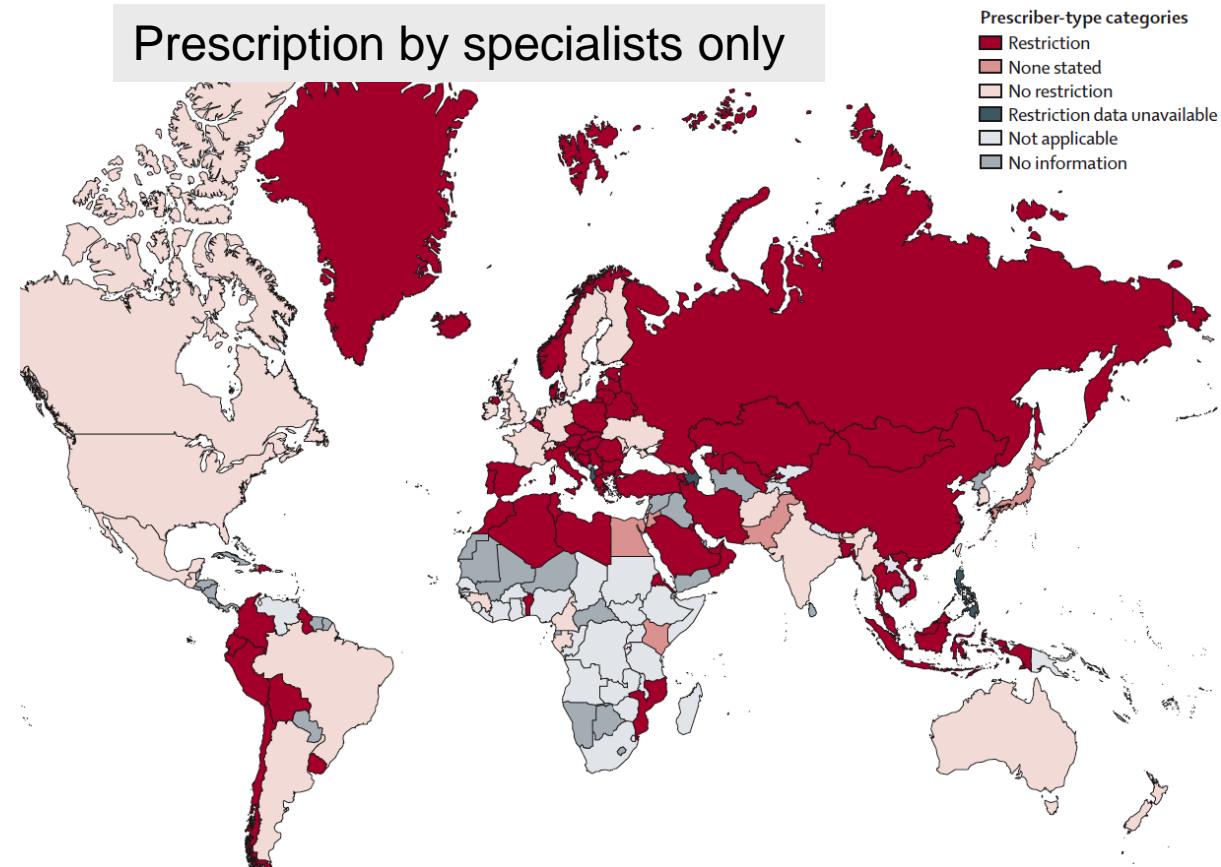
Global Situation of DAA therapy: Reimbursement and Conditions

Reimbursed
 Not reimbursed
 Reimbursement status unknown

✓ Registered
✗ Not registered

	Sofosbuvir-velpatasvir	Sofosbuvir-velpatasvir-voxilaprevir	Glecaprevir-pibrentasvir	Sofosbuvir-daclatasvir	Sofosbuvir
Austria	✓	✓	✓	✓	✓
Belgium	✓	✓	✓	✗	✓
Denmark	✓	✓	✓	✗	✓
England	✓	✓	✓	✗	✓
Finland	✓	✓	✓	✗	✓
France	✓	✓	✓	✗	✓
Germany	✓	✓	✓	✓	✓
Greece	✓	✓	✓	✗	✓
Greenland	✓	✓	✓	✗	✓
Iceland	✓	✓	✗	✗	✓
Ireland	✓	✓	✓	✗	✓
Italy	✓	✓	✓	✗	✓

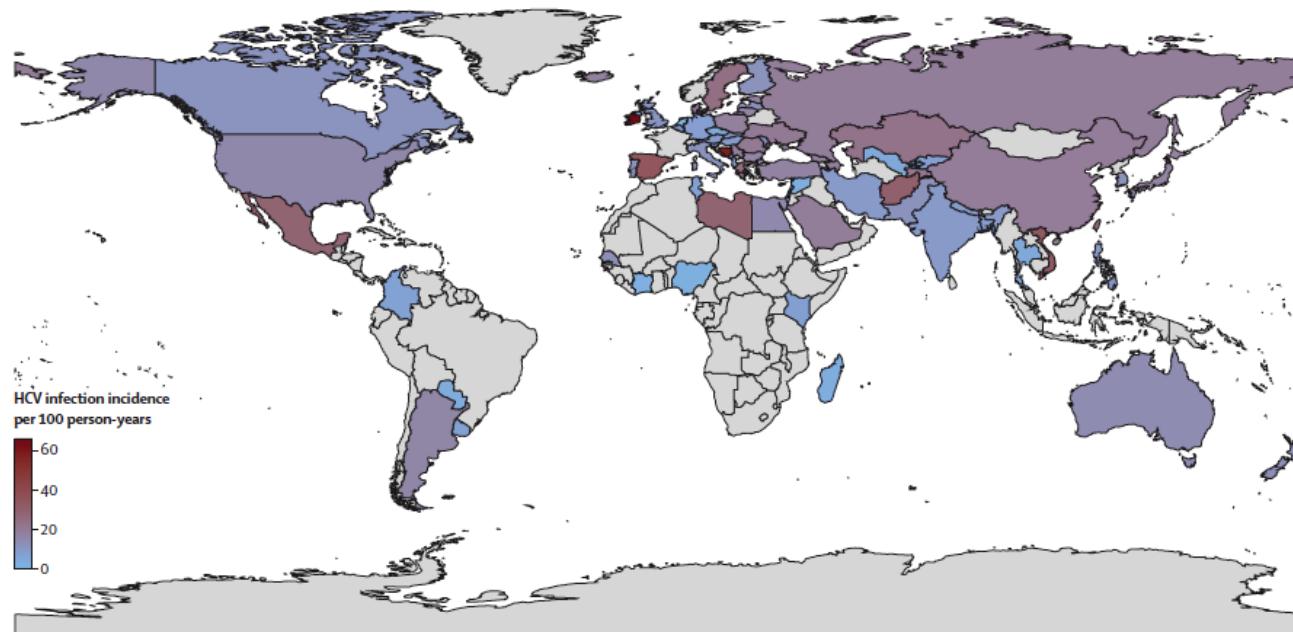
Prescription by specialists only



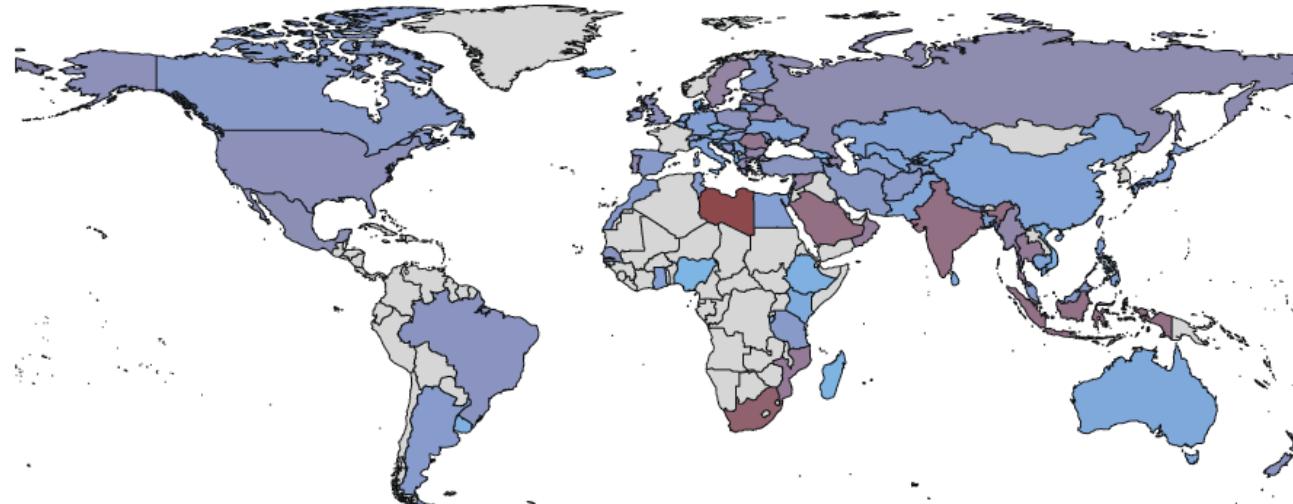
- 91% of countries with at least one DAA regimen approved (VEL/SOF, VVS, G/P, DAC/SOF, SOF)
- 68% of countries with reimbursement of at least one DAA regimen
- 61% of countries globally require prescription by a specialist

Epidemiology of HCV Infection in PWIDs

A Pre-2015 period



B 2015-21 period



Countries with increasing HCV incidence in PWIDs

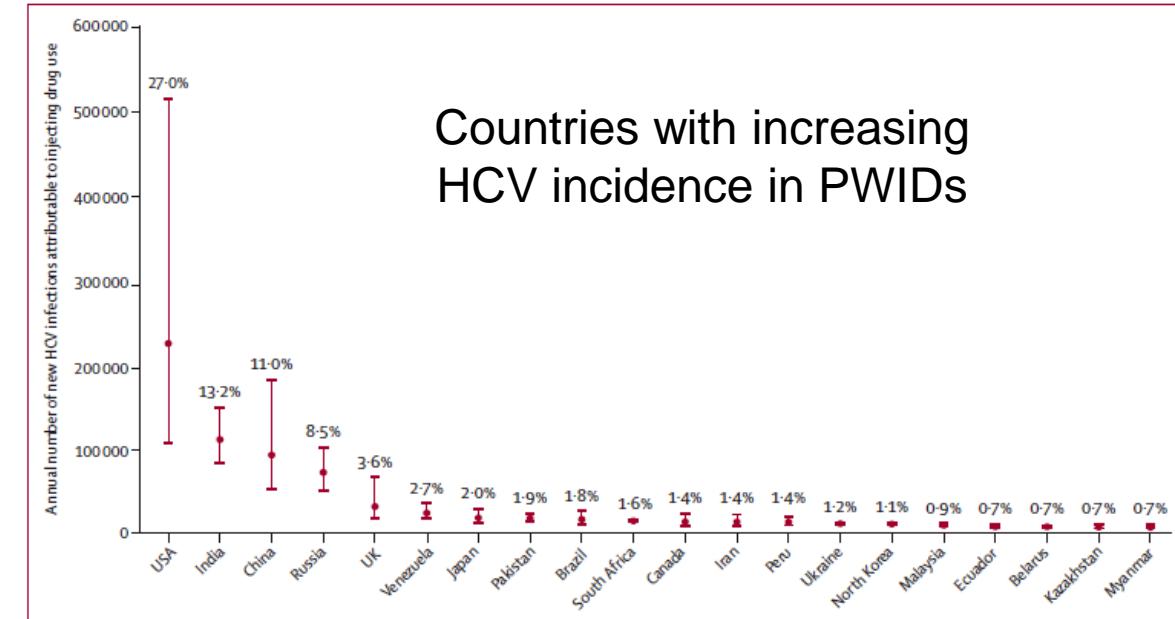
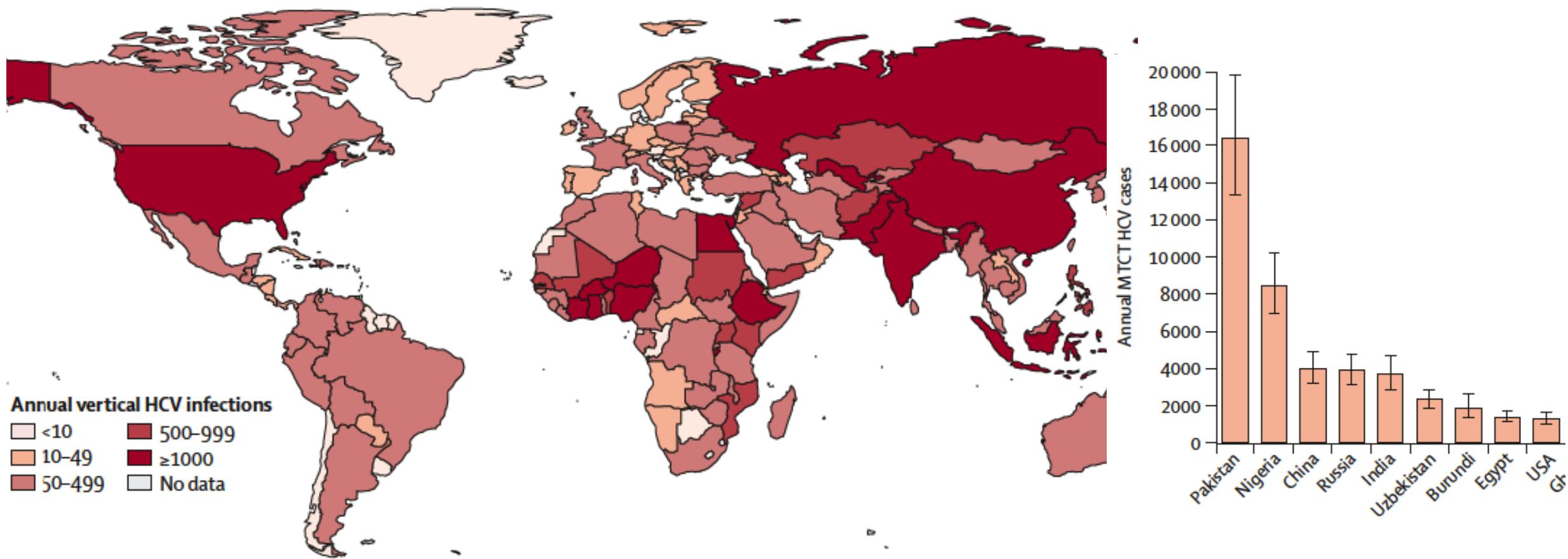


Figure 4: Number of new HCV infections attributable to injecting drug use annually for the 20 countries with the highest values
Estimates are based on 2015-21 HCV incidence data. Circles represent point estimates of the number of new HCV infections attributable to injecting drug use, and vertical error bars indicate 95% uncertainty intervals. Percentages shown above error bars are the proportion of global infections attributed to each country, based on their median values (appendix pp 47-49). HCV=hepatitis C virus.

- Global decline of HCV incidence in PWIDs from Pre-2015 (13.9 100PY) to 2015-2021 (8.6 100PY)
- However, significant increase in USA, India, China, UK, Russia, Japan...

Global Vertical Transmission of HCV: Data Synthesis Study



- Vertical transmission 7 (without HIV) and 12% (with HIV)
- Annual vertical transmissions globally: approx. 70.000 (at age of 5 years approx. 20.000)
- Recommendation of HCV screening during pregnancy (and DAA treatment)

Phase 3 Study acute Hepatitis C with 8 Weeks G/P

n=286 (n=234 first infection), prospective, multicentre phase 3 study,

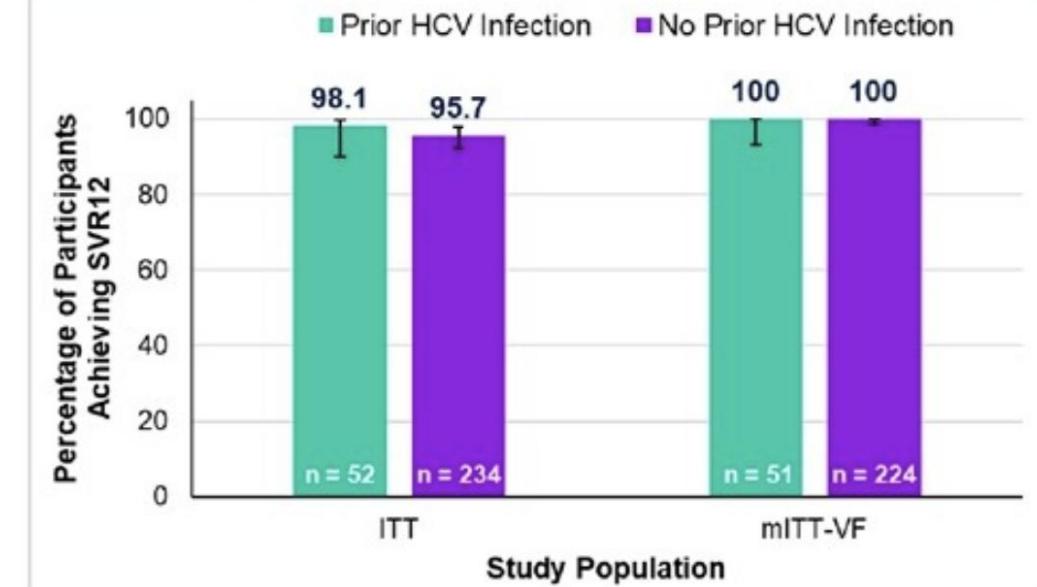
Definition of acute Hepatitis C (approx. 80% diagnosed within first 3 months):

Conversion HCV-Ab within 11 mo or HCV-RNA / coreAg within 8 mo

Constellation of acute hepatitis C with high liver enzymes and pos. HCV-RNA / coreAg + risk factor

	Prior HCV Infection (N = 52)	No Prior HCV Infection (N = 234)
Age (Years), Median (IQR)	48.0 (41.5, 56.0)	41.5 (34.0, 49.0)
Male	50 (96.2)	205 (87.6)
HCV Genotype*		
1	32 (68.1)	133 (63.3)
2	2 (4.3)	9 (4.3)
3	4 (8.5)	29 (13.8)
4	9 (19.1)	39 (18.6)
Missing	5	24
Non-Cirrhotic	50 (96.2)	228 (97.4)
HCV RNA (\log_{10} IU/mL), Median (IQR)	5.47 (3.11, 6.16)	5.36 (4.19, 6.15)
HIV-1 Coinfection	48 (92.3)	94 (40.2)
PWID Status		
Current	4 (7.7)	10 (4.3)
Recent	8 (15.4)	19 (8.1)
Former	3 (5.8)	4 (1.7)
Non-PWID	37 (71.2)	201 (85.9)

Figure 1. SVR12 in the ITT and mITT-VF Sets

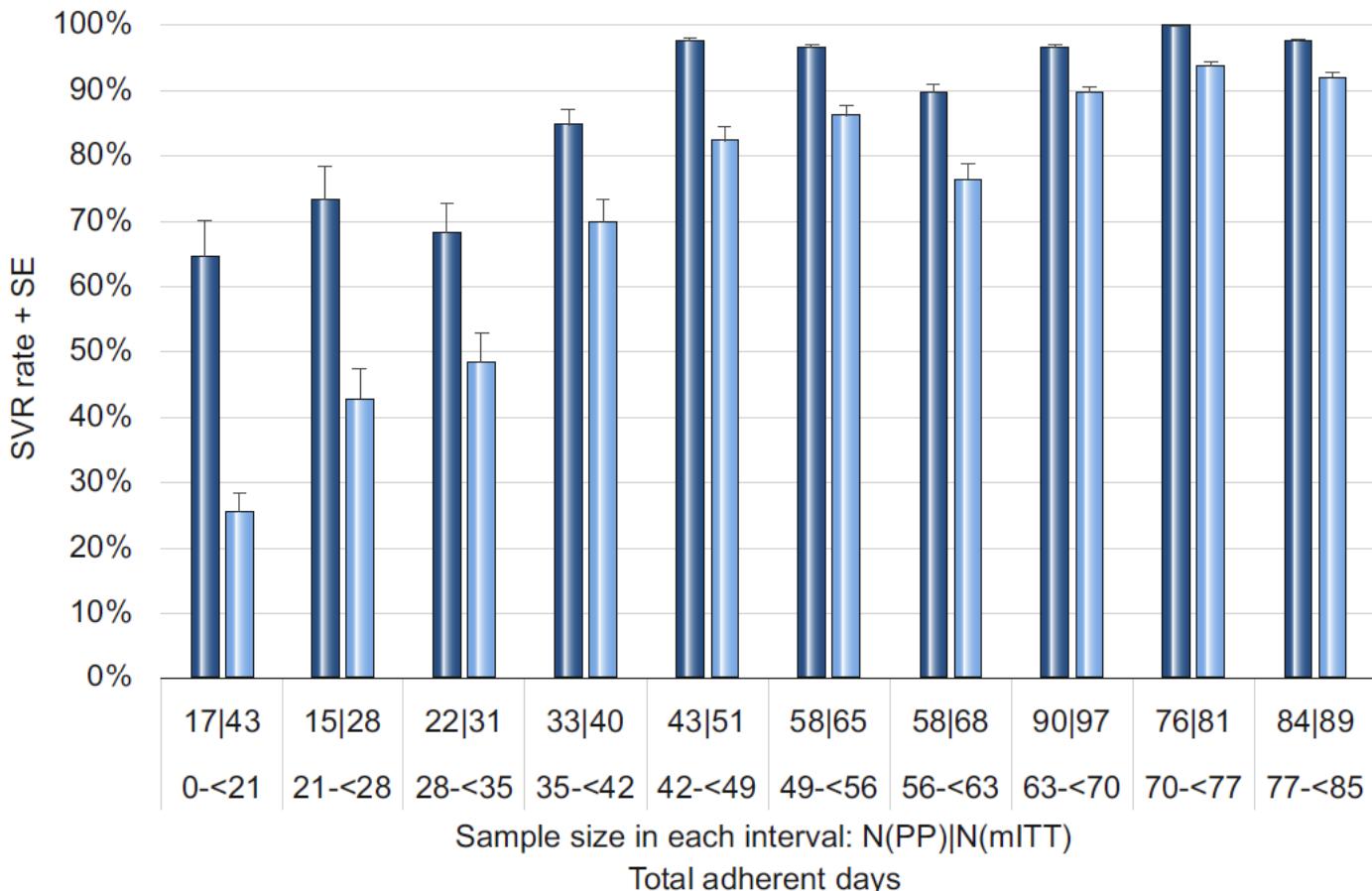


ITT, intention-to-treat; mITT-VF, ITT set excluding participants who did not achieve SVR12 for reasons other than virologic failure; SVR12, sustained virologic response at 12 weeks post treatment.

- High SVR rates with improvement of liver enzymes
- SVR rates independ. of re-infection / re-treatment
- **Approval of G/P for acute Hepatitis C expected**

Therapy of patients who inject drugs (PWID)

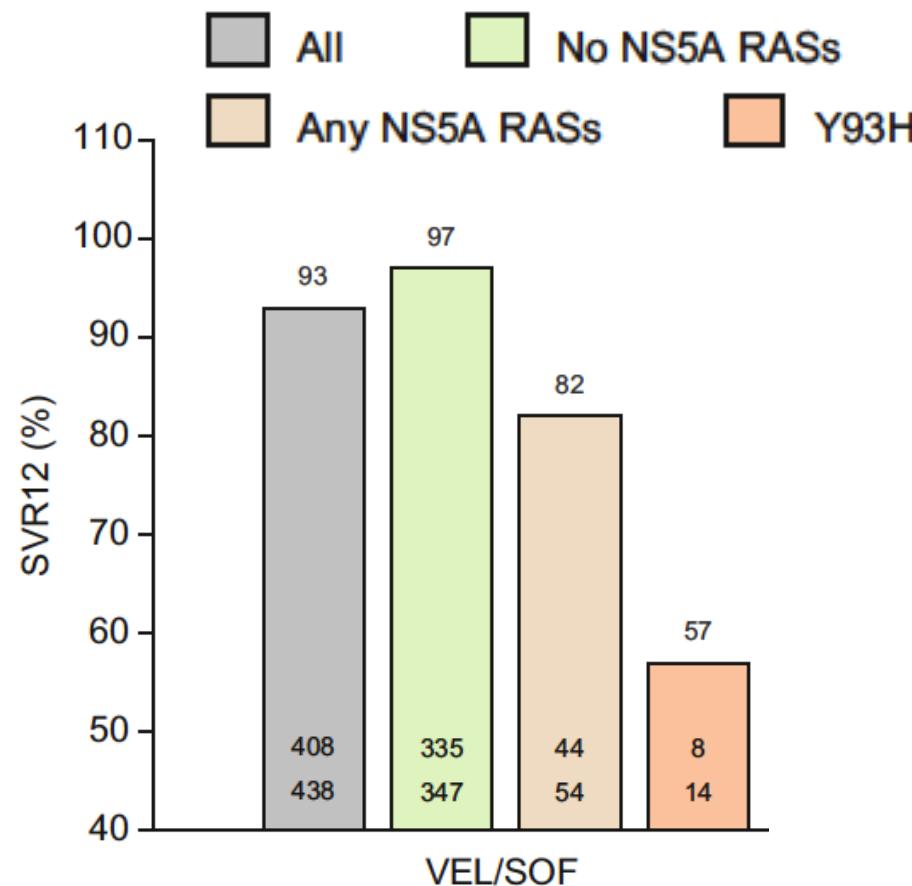
n=755 PWIDs with SOF/VEL for 12 wks., national study USA (HERO-Study) – adherence via electr. blister



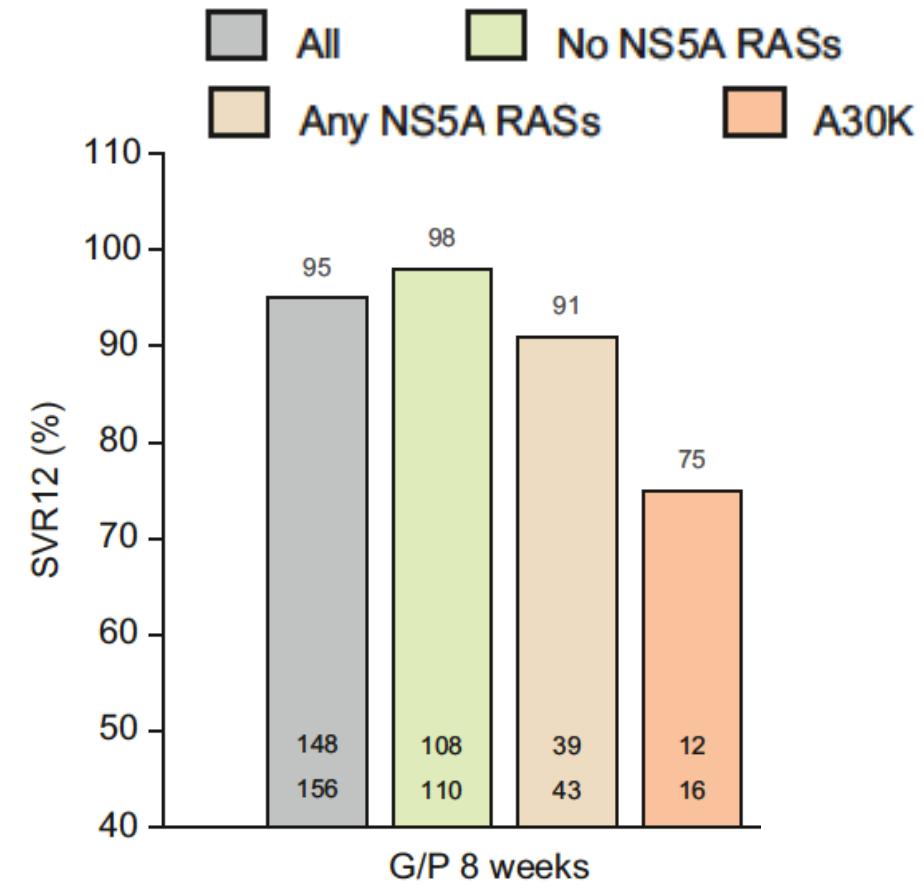
- SVR 92.7%
- Median adherence 75%
- Less than 26 missed days: >90% SVR
- With lower adherence than 50% SVR rates decline significantly
- Pausing of ≥ 2 weeks: 85% SVR
- Discontinuation within first months of treatment: 25% SVR

Virological failure to pangenotypic DAA treatments: Importance of baseline resistance in specific subgroups

SOF/VEL in GT3 with cirrhosis



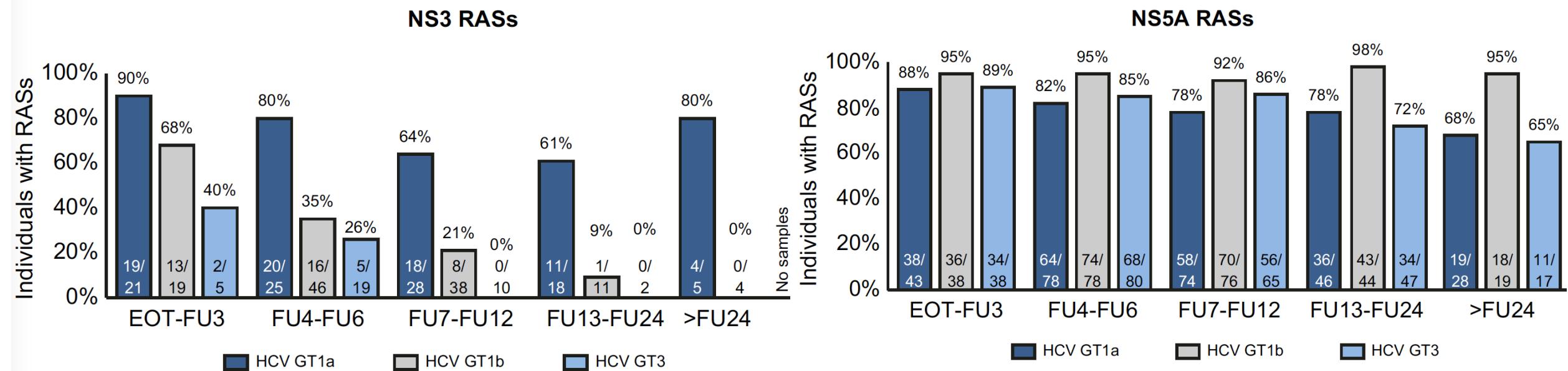
G/P in TN GT3 without cirrhosis



Persistence of resistance after failure to DAA regimens

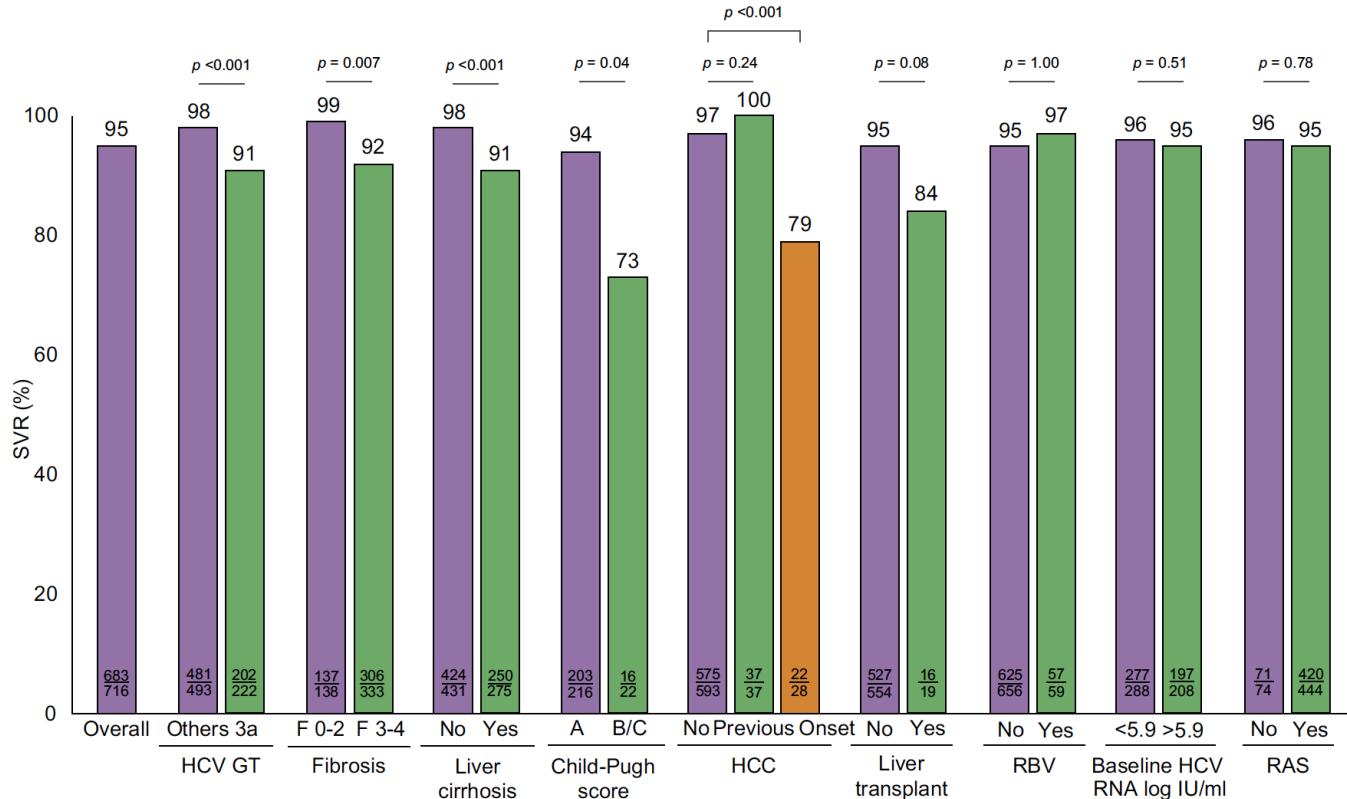
European HCV Resistance Databank, Frankfurt

n=678 patients with failure to DAA regimens followed for up to 2 years without re-treatment



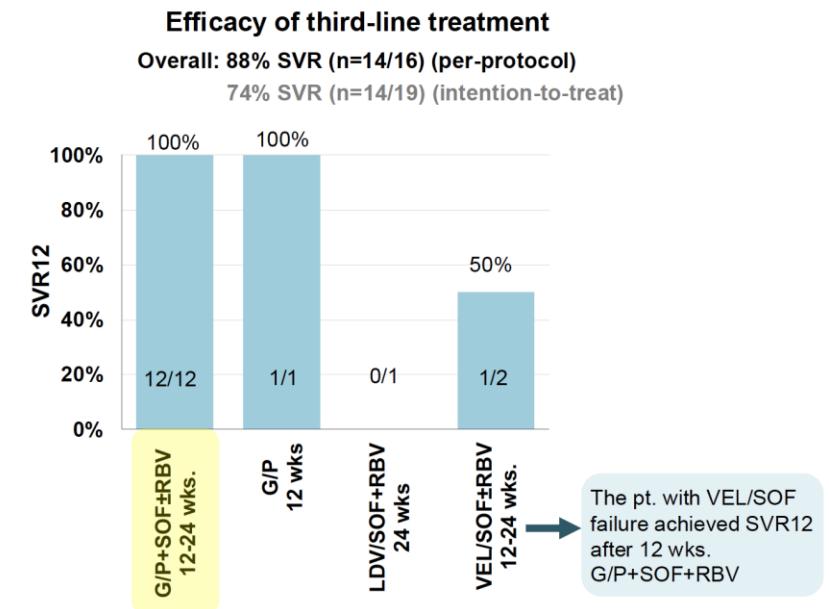
Re-treatment of DAA failure patients: Real World Data

VOX/VEL/SOF+/- RBV for 12 weeks (n=746)
Data from the European HCV Resistance Group, Frankfurt



- SVR rate 95%
- Independent neg. correlation with GT3, Child B/C & HCC

Frankfurt HCV Resistance Group:
n=1 420 DAA-Failures, 2014-2025
➤ n=31 with VOX/VEL/SOF failure



- Recommendation: G/P+SO+F+RBV for 12-24 wks
- If not available: RAS analysis

Summary

➤ Hepatitis A and E

- Hepatitis A: declining herd immunity – more severe cases / hospitalization
- Vaccination of at-risk groups versus general vaccination?

➤ Hepatitis E

- Chinese Hepatitis E Vaccine also active in GT3?
- Importance of ratHEV
- Immunity against HEV re-infection for 10 years at 70-100%

➤ Hepatitis B

- HBV infection detectable in Beethoven's hair almost 200 years after his death
- Current recommendations for treatment challenged by grey zone hepatitis B?

➤ Hepatitis C

- Highly effective DAAs with high forgiveness – soon also for acute Hep C
- Baseline RASs relevant for pangenotypic DAA regimens in GT3 but rare
- Second and third line re-treatment is highly effective irrespective of RASs