

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

Anzahl übermittelter Erkrankungen

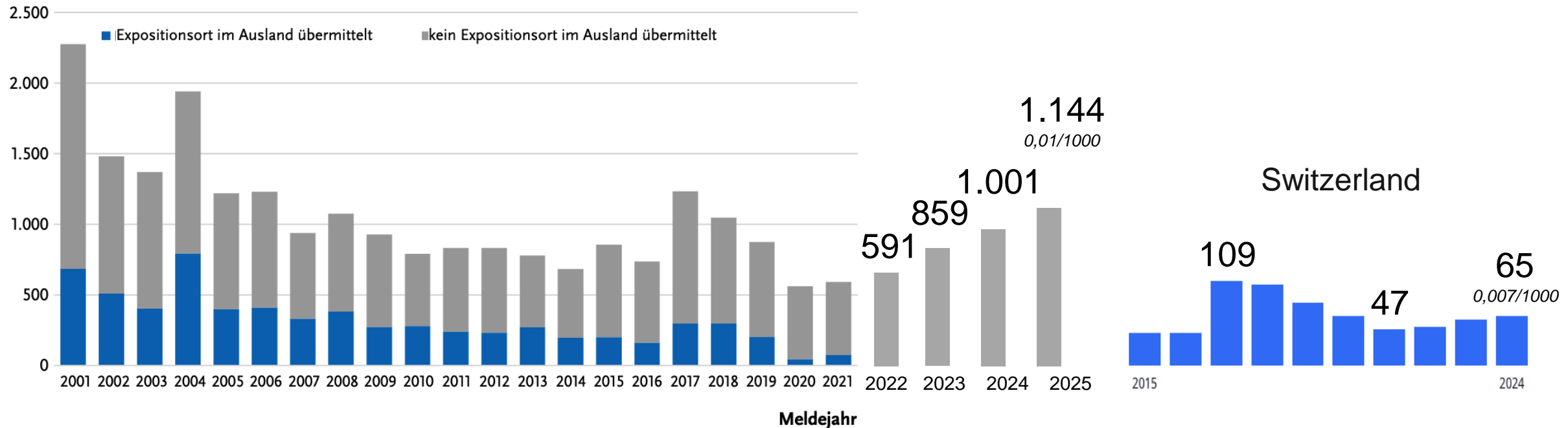


Abb. 2 | Hepatitis A in Deutschland 2001–2021, Meldedaten gemäß Infektionsschutzgesetz (IfSG)

- 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

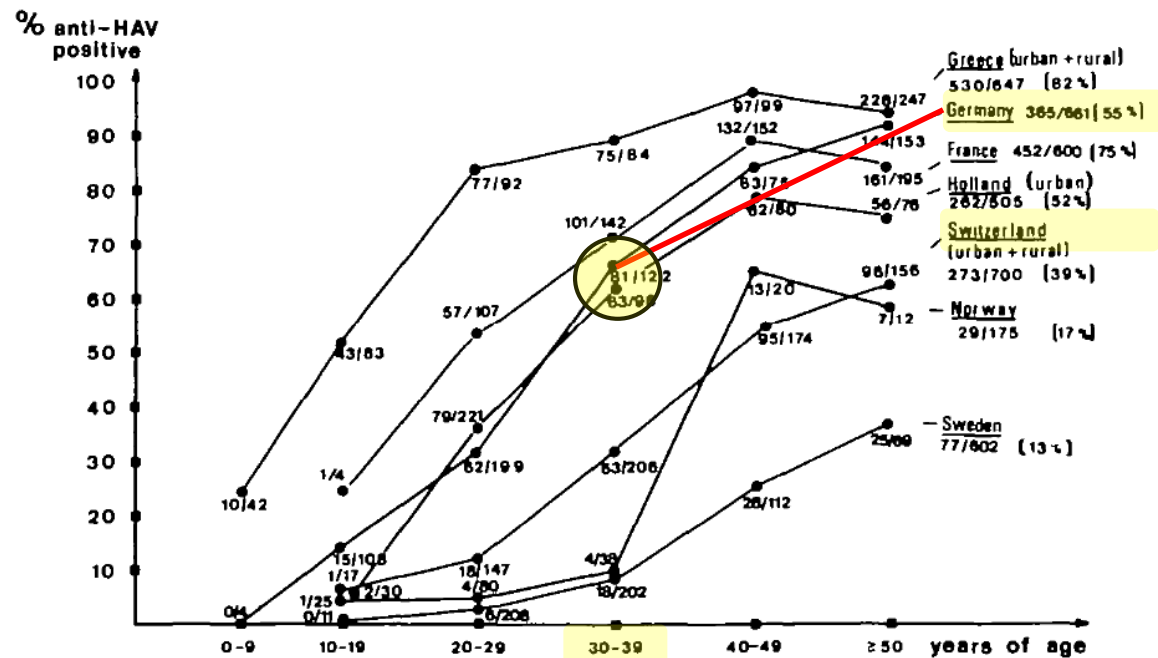
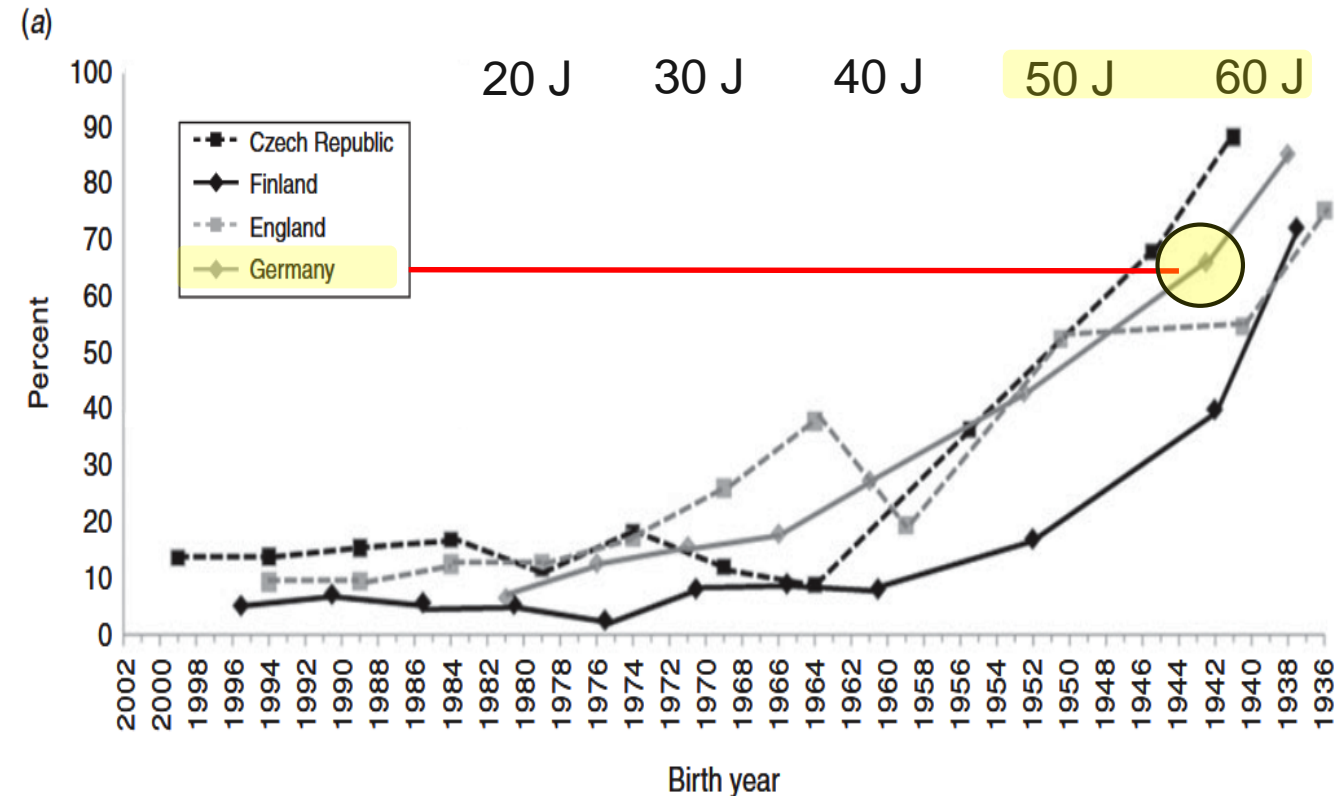


FIGURE 1. Prevalence of anti-HAV in different age groups in seven European countries.

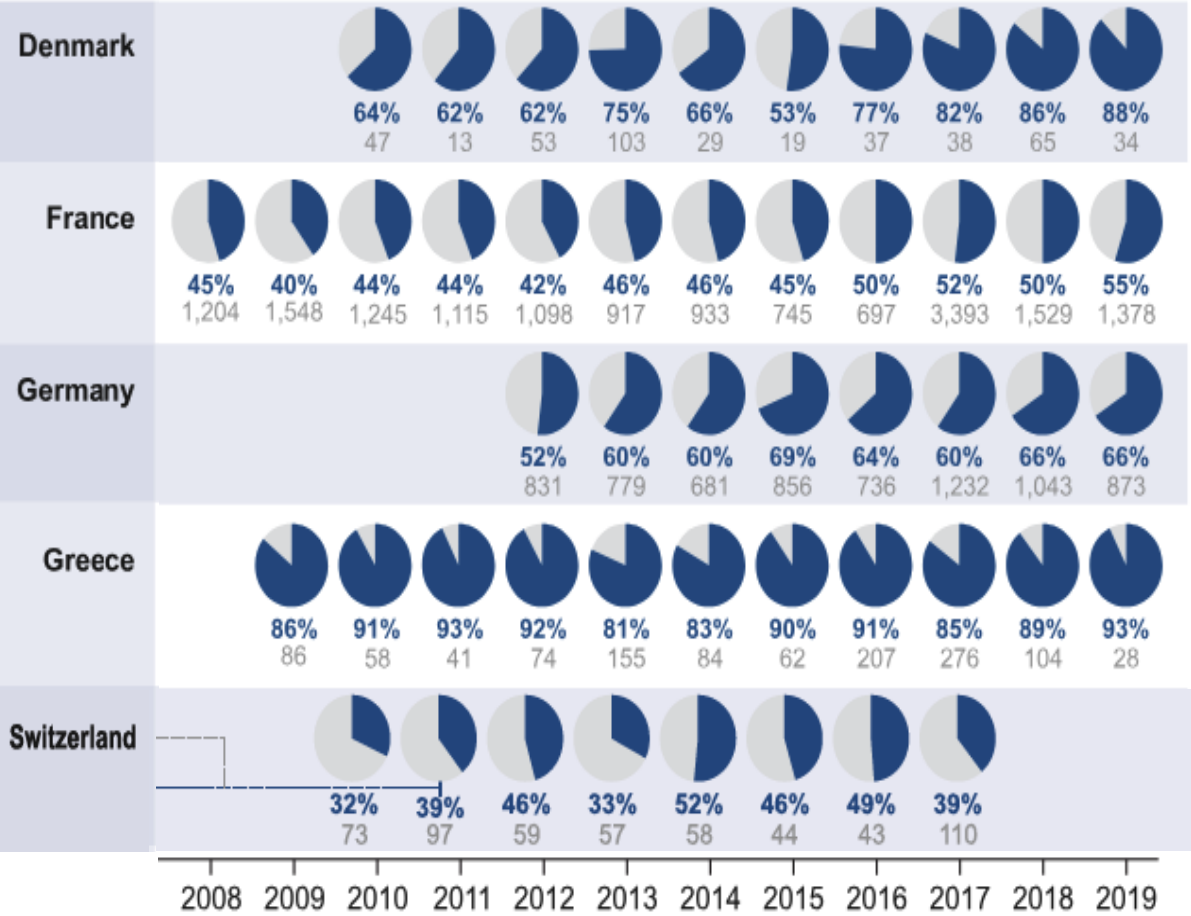
1996-2004



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 PEH since end of 2025; gaps in 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

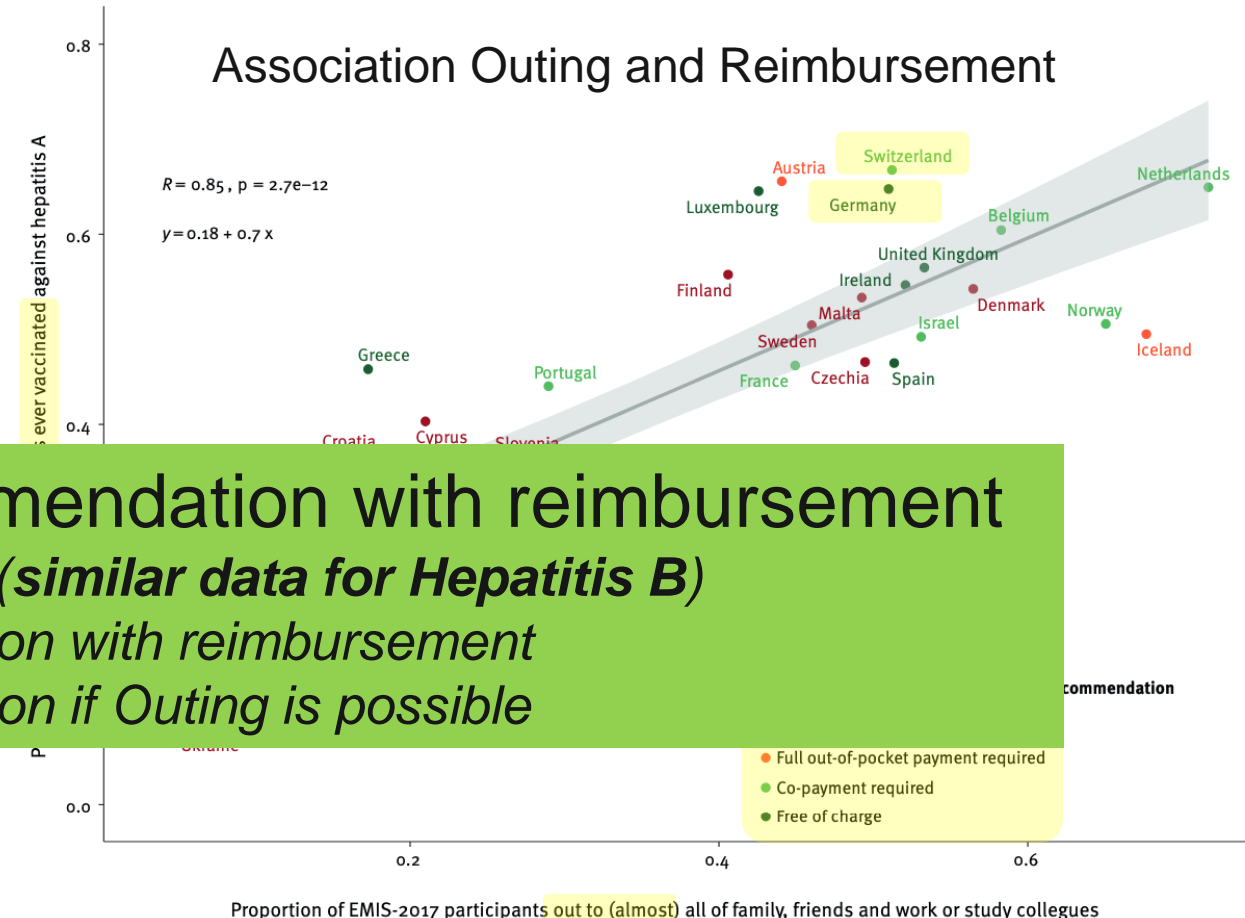
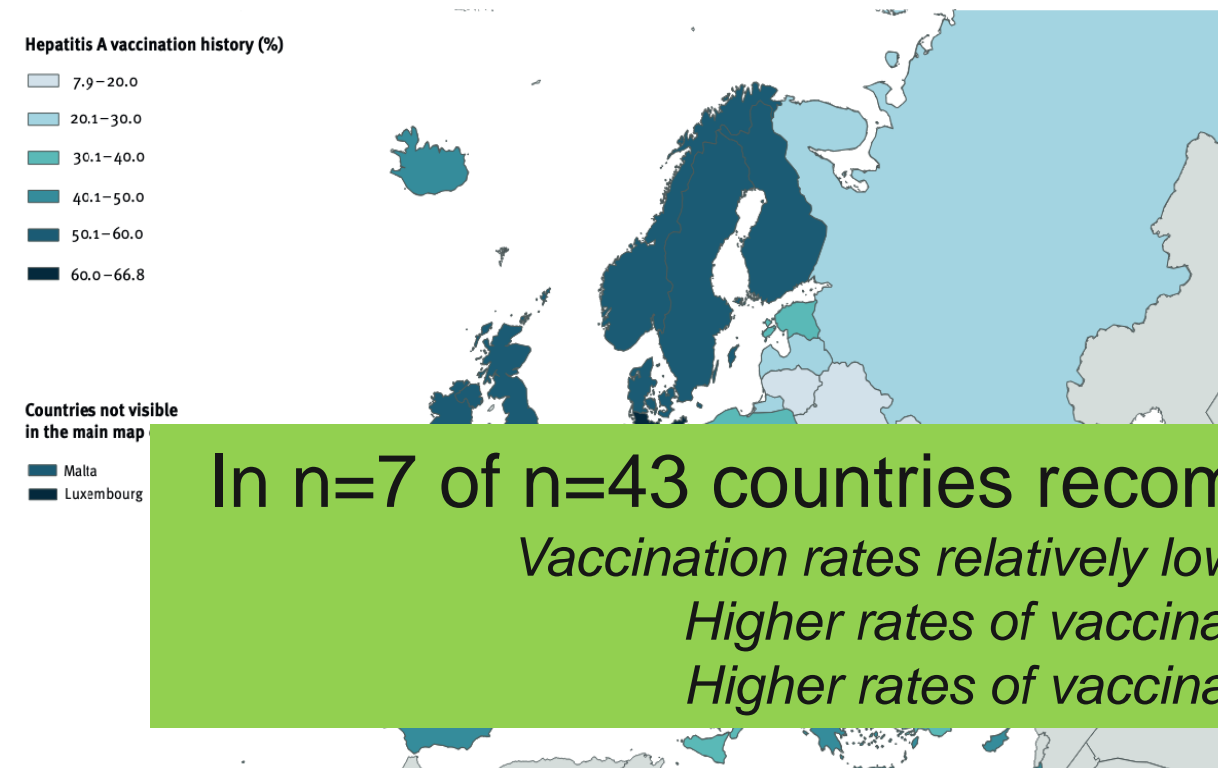
Europe: mainly for people at risk only
(Traveling, Profession, Sexual behavior, Liver disease, ...)

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 outing 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:

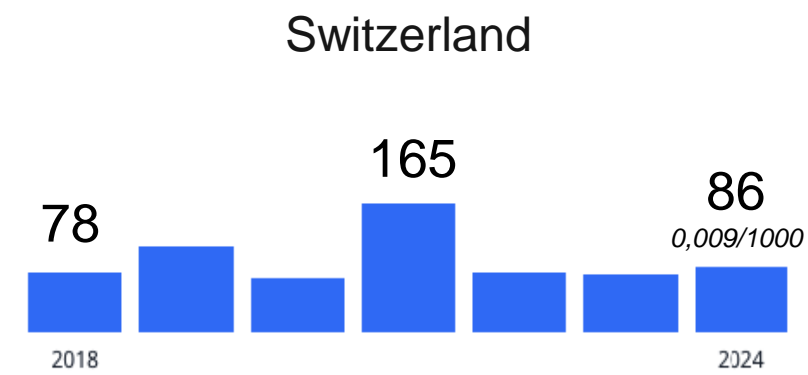
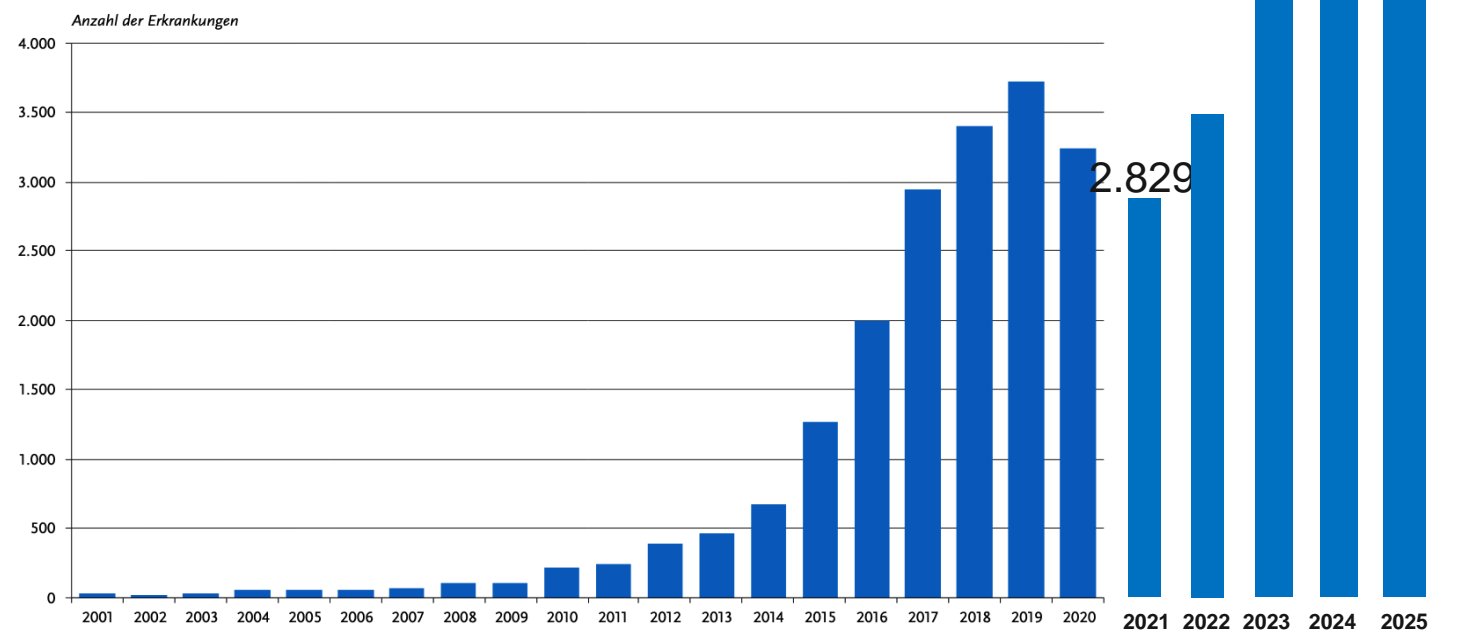
- vaccination before diagnosis of chronic liver disease unknown
- type of chronic liver disease unknown in 60%
- no exclusion of persons with past HAV infection

- **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

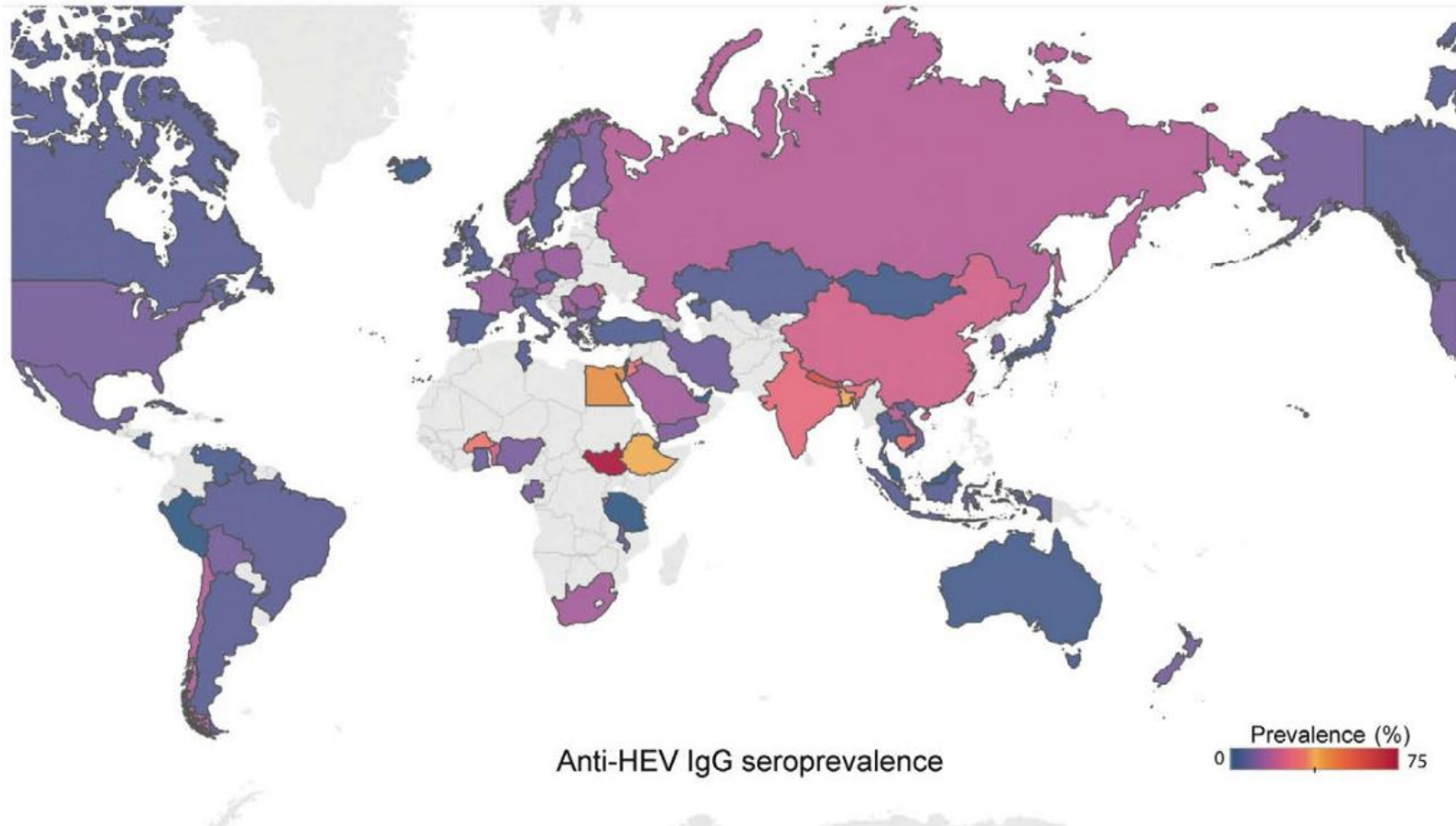
Hepatitis E

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

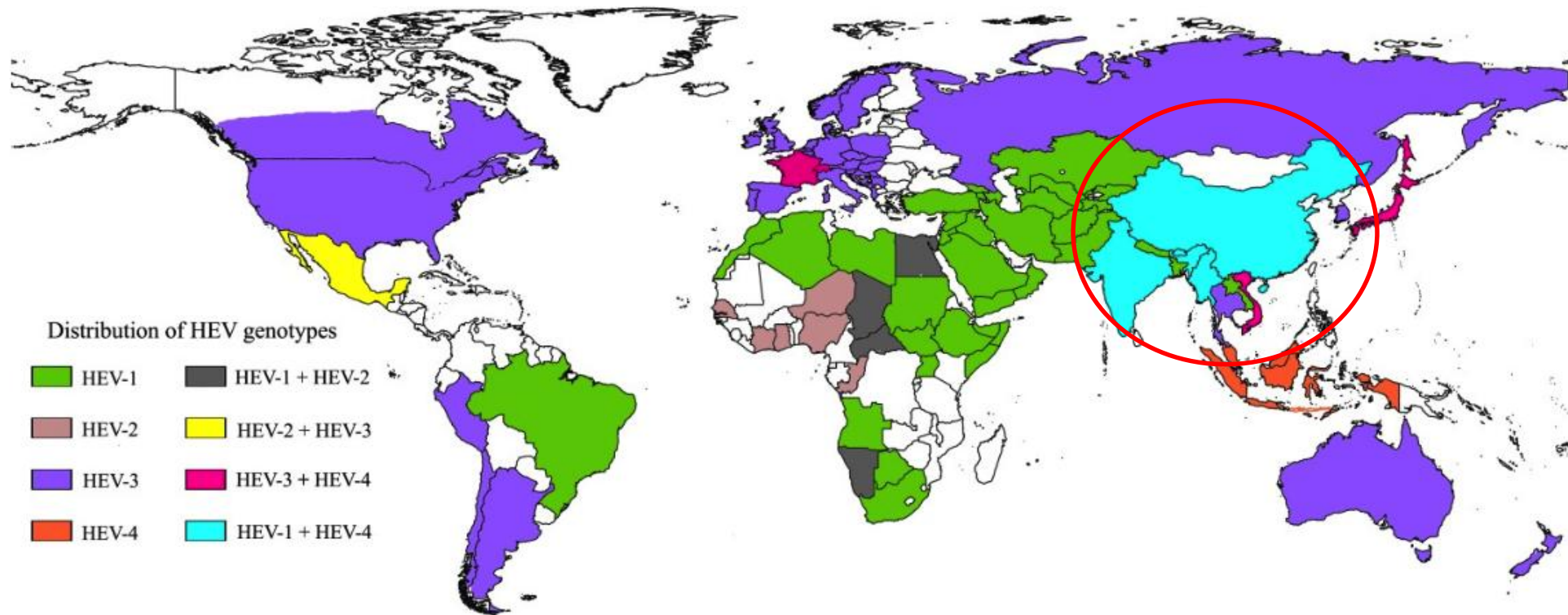


Figure 2. Global HEV genotype distribution. Different colors on the map indicate the distribution of HEV genotypes (HEV-1 through -4) across the globe. The figure was created using SimpleMapper,

Hepatitis E – Vaccination

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

(HEV-239 Hecolin™ Vaccination Months 0, 1, 6, n=112 60)

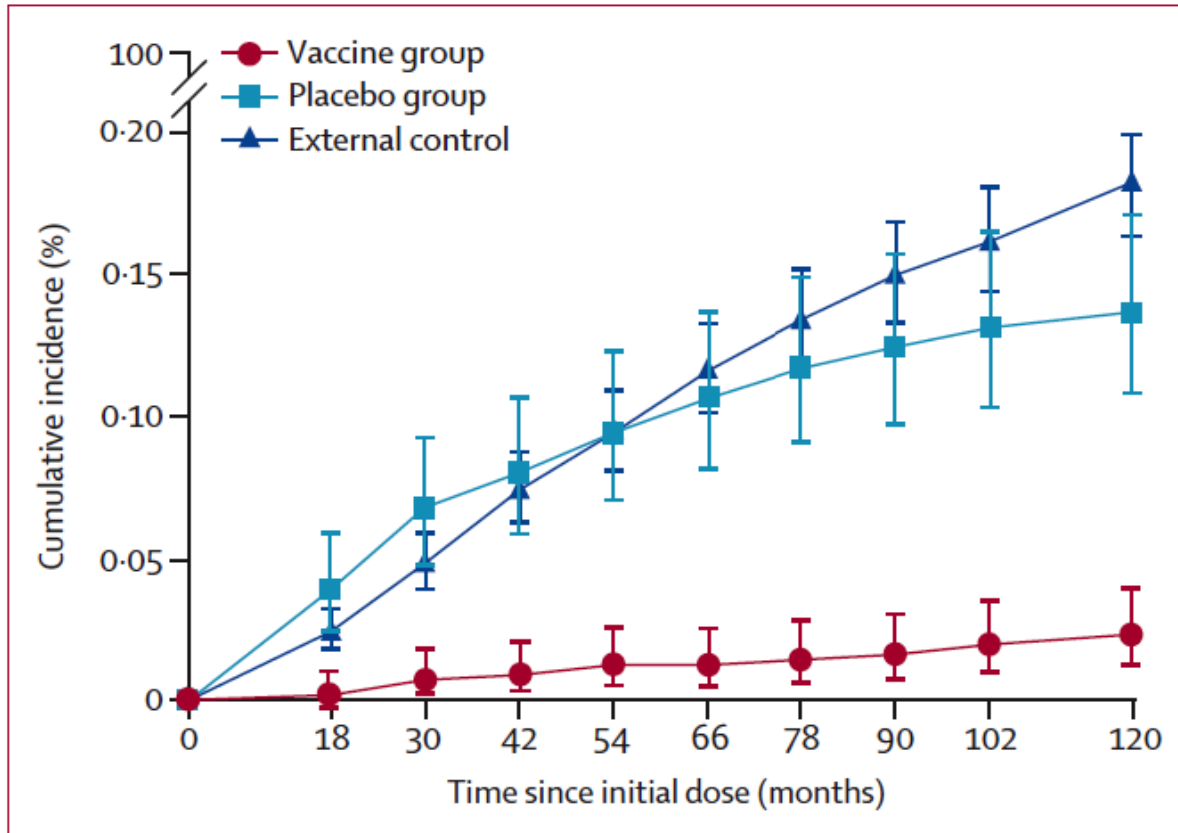
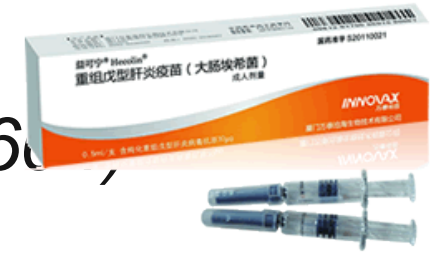


Figure 4: Cumulative incidence of hepatitis E in participants who received at least one dose of the vaccine or placebo

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 10⁴ 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 × 0 µg	1	28	<10	<2	1.8	5	+
		29	<10	<2	4.6	6	+
		30	<10	<2	0.8	4	+
[B] 2 × 0 µg	4	34	<10	<2	0.9	1	+
		35	<10	<2	1.1	4	+
							+
[C] 2							—
[D] 2							—
[E] 2 × 20 µg	1	11	01800	1949	1.7	0	—
		12	43200	960	0.7	0	—
		22	44300	1377	1.8	0	—
		23	61400	3314	1.6	0	—
[F] 2 × 10 µg	4	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)

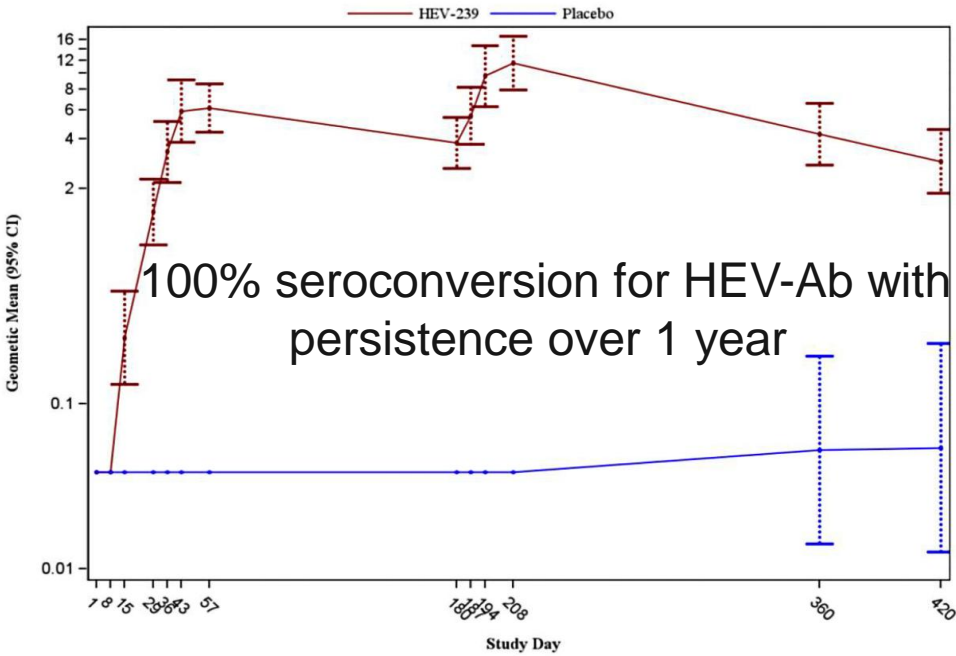
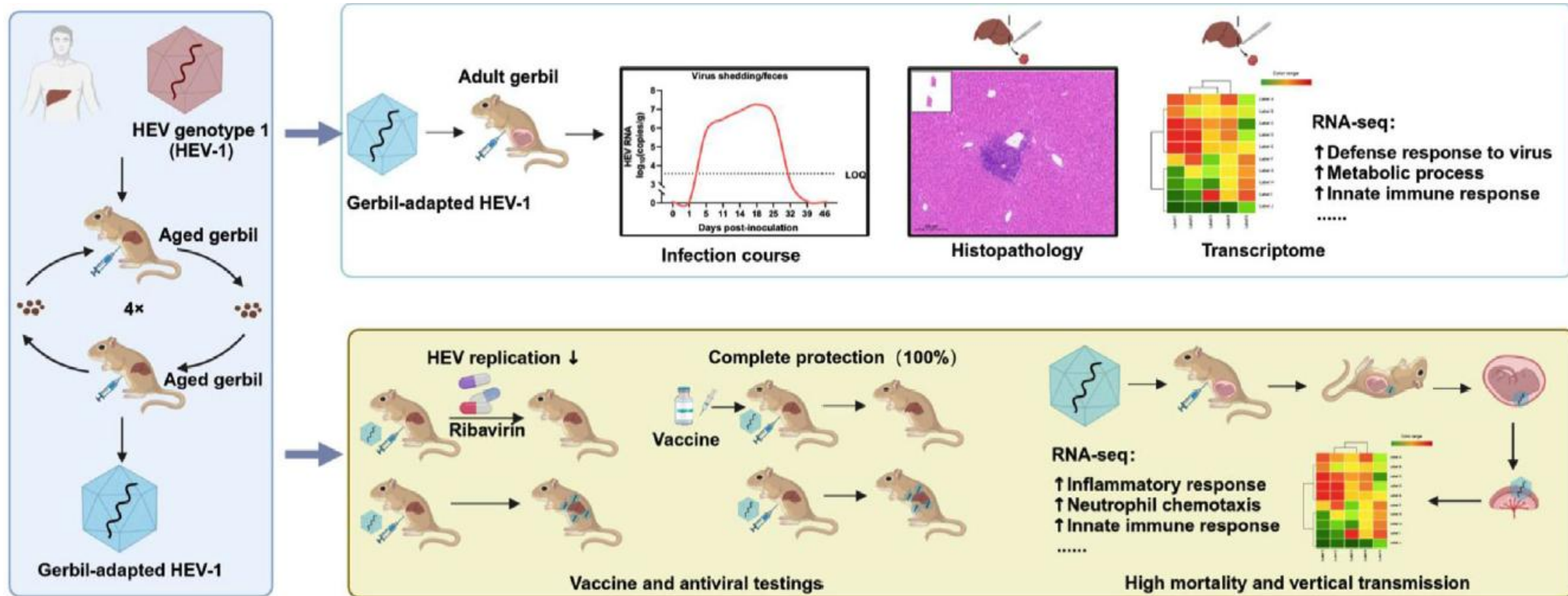


Figure 3. Immunogenicity of HEV-239 versus placebo; immunoglobulin G (IgG) geometric mean concentration, modified intention-to-treat population.

- 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)*

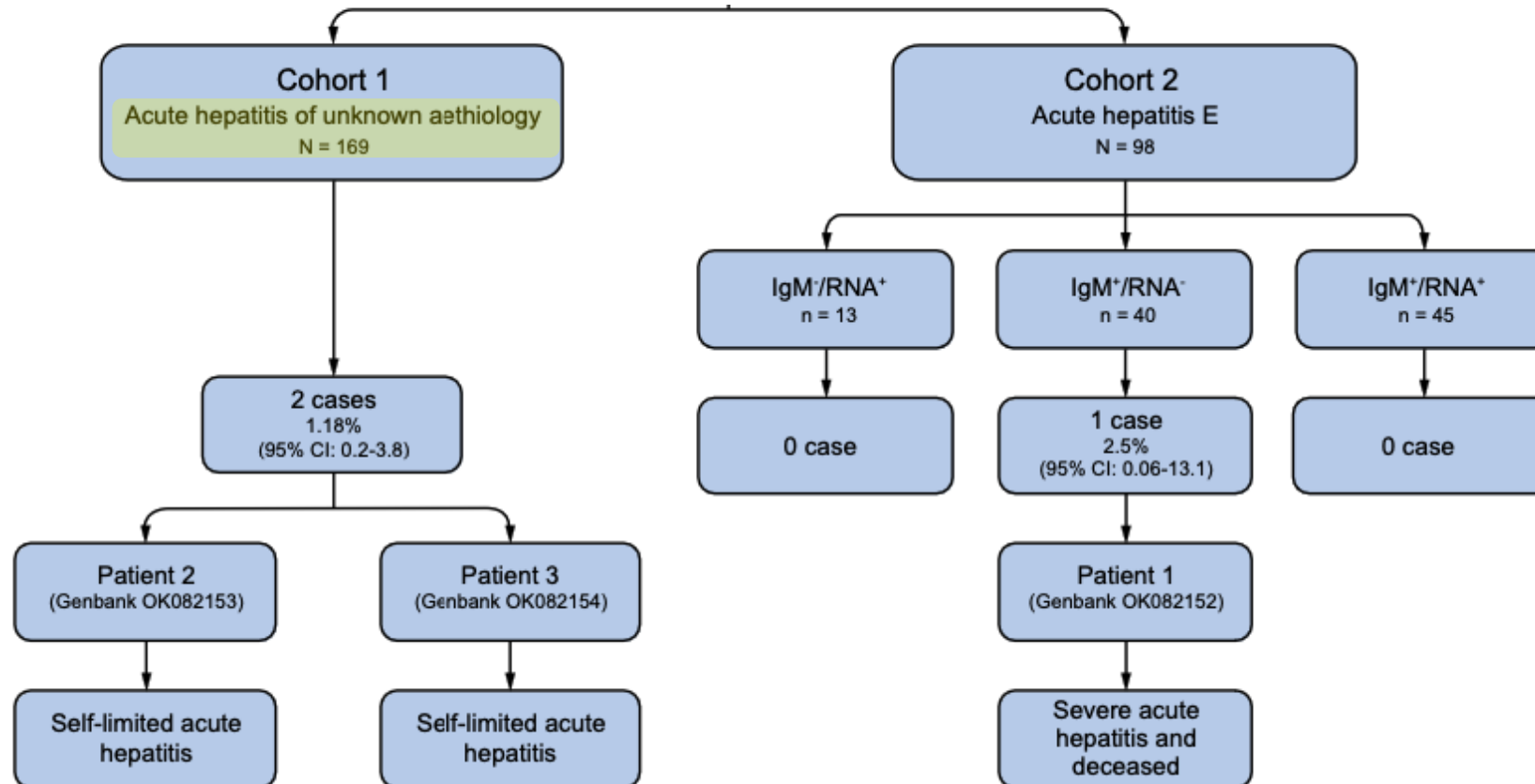


- Adaptation HEV-GT-1 to Gerbil Mice by serial intestinal passage (finally weak oral re-infection)
- Establishment of full replication cycle with high mortality of HEV infection in pregnant mice
- Chronic infection on tacrolimus – recovery with Ribavirin – protection with HEV-239 vaccine
- **Recovery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

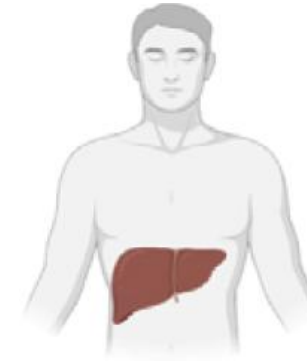
Testing



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

Derivation

n = 103

17.5% (n = 18)

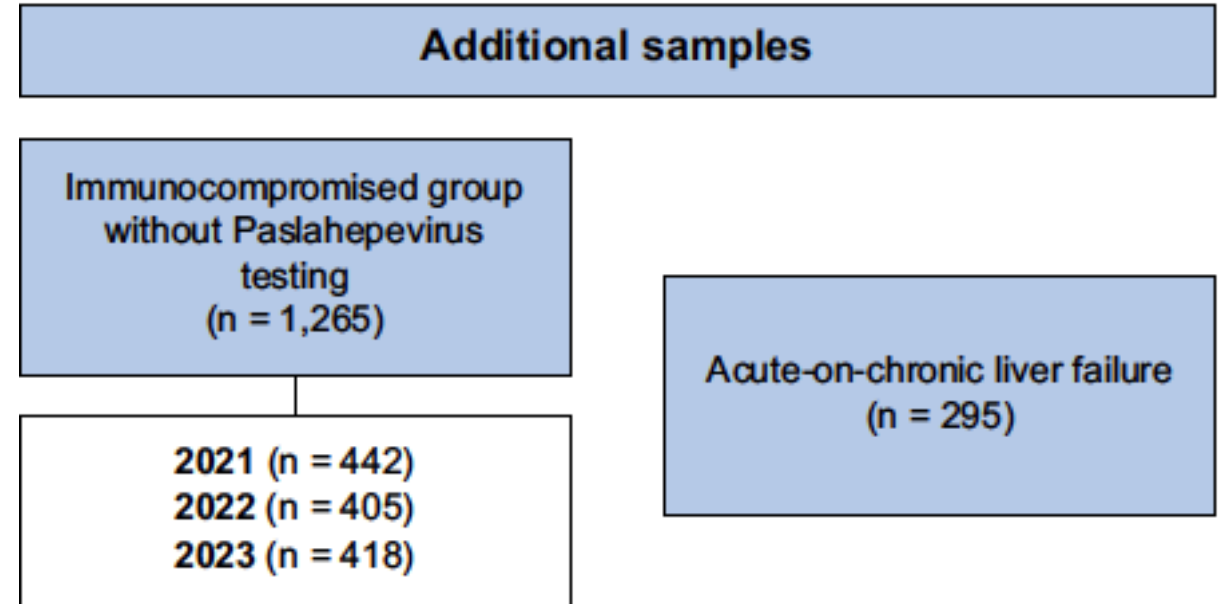
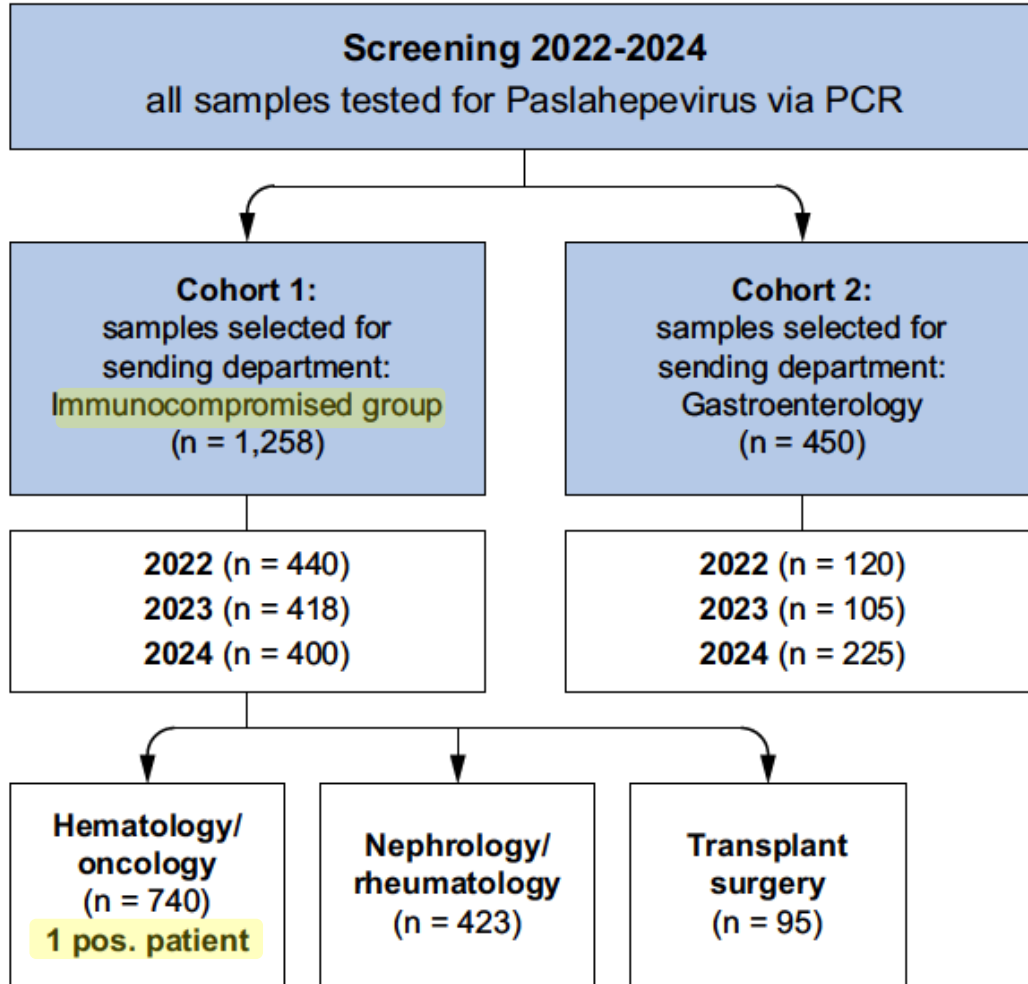


Proposed testing algorithm

- 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

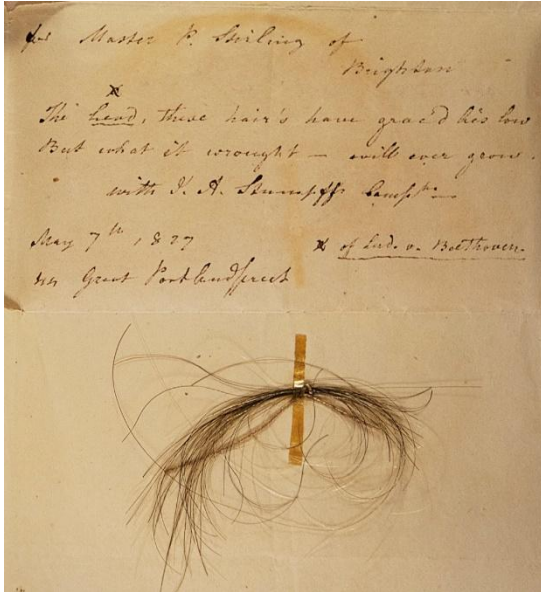
➤ *n=3.194 anti-HEV IgG positive versus n=3.838 anti-HEV IgG negative*

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

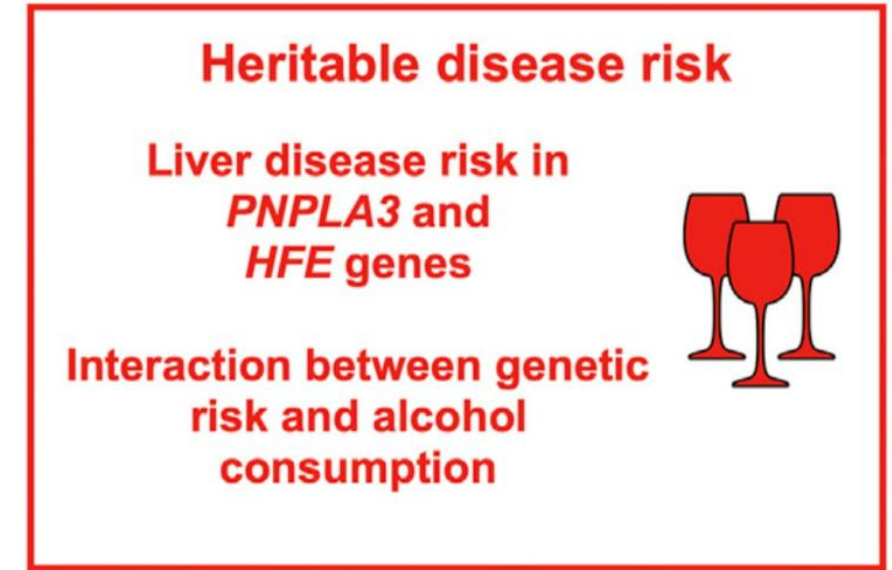
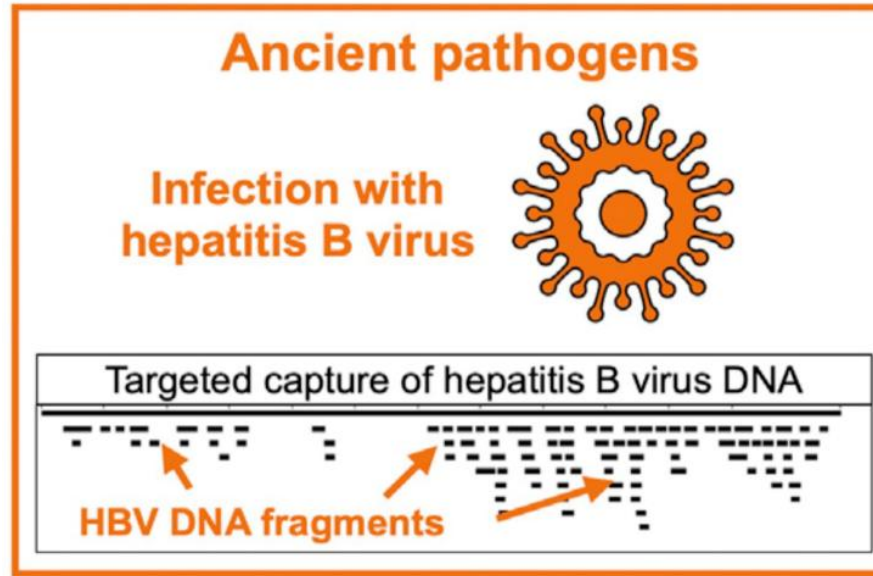
Period	Seropositive group (N=3194)		Seronegative group (N=3838)		Crude protection	
	No. of cases	Incidence (/10000 p-yr)	No. of cases	Incidence (/10000 p-yr)	% (95% CI)	P value
Hepatitis E						
0-18m	1	2.1	3	5.2	59.9 (-285.1,95.8)	0.4282
0-30m	1	1.3	4	4.2	70.0 (-168.7,96.6)	0.2820
0-66m	2	1.1	6	2.8	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

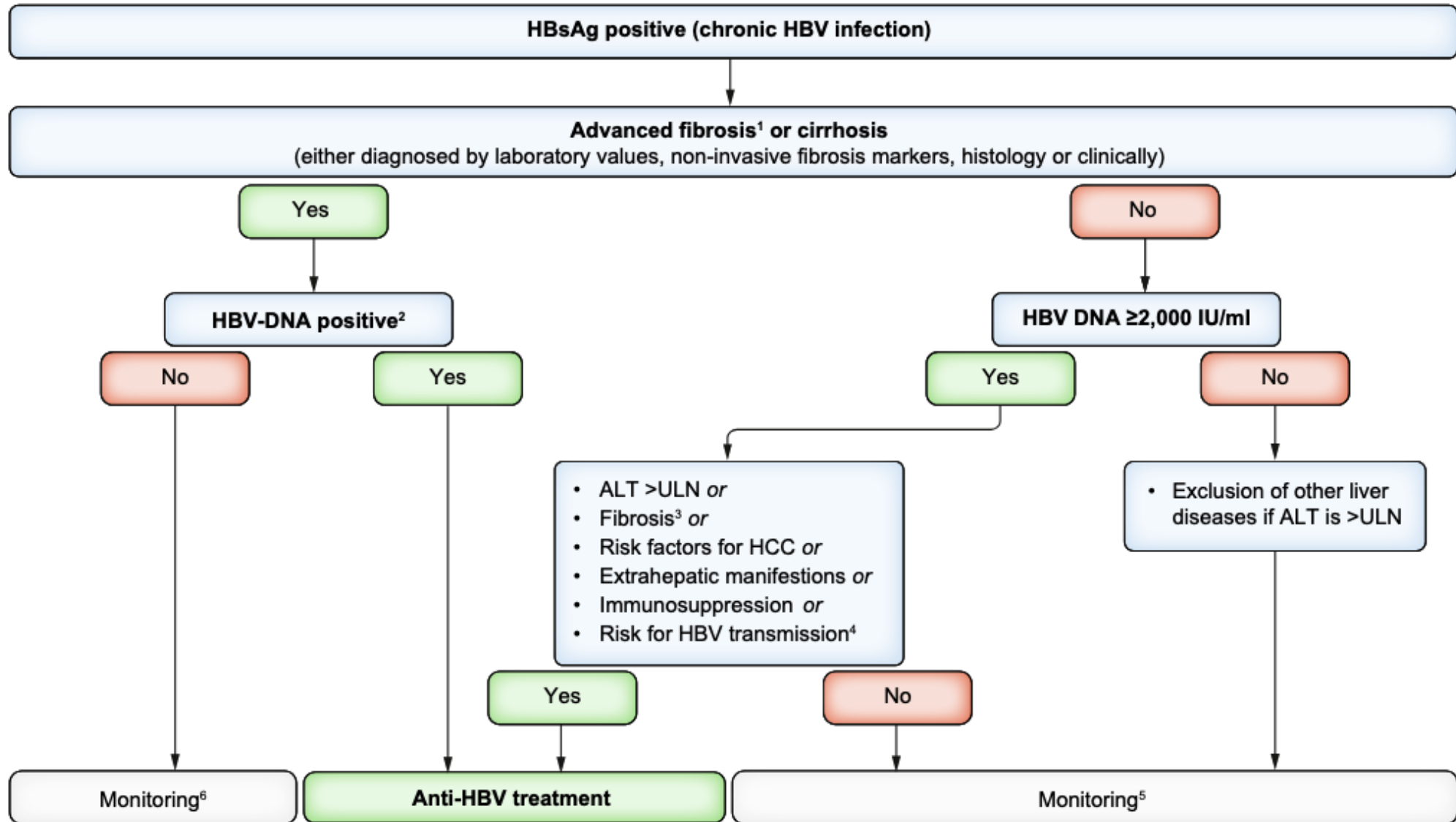


Locks of Hair from 8 Museums



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	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

Outcomes

HCC (n = 37)

Cirrhosis (n = 13)

Hepatic decompensation (n = 10)

0 0.25 0.5 0.75 1 1.25 1.5 1.75 2

Annual incidence rate (%)

Annual incidence rate

0.32% (0.21-0.48%)

0.67% (0.30-1.49%)

0.34% (0.17-0.69%)

- **Study population:** 41% had moderate to severe inflammation; 40% had F3, 7% had F4
- **Risk faktors 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

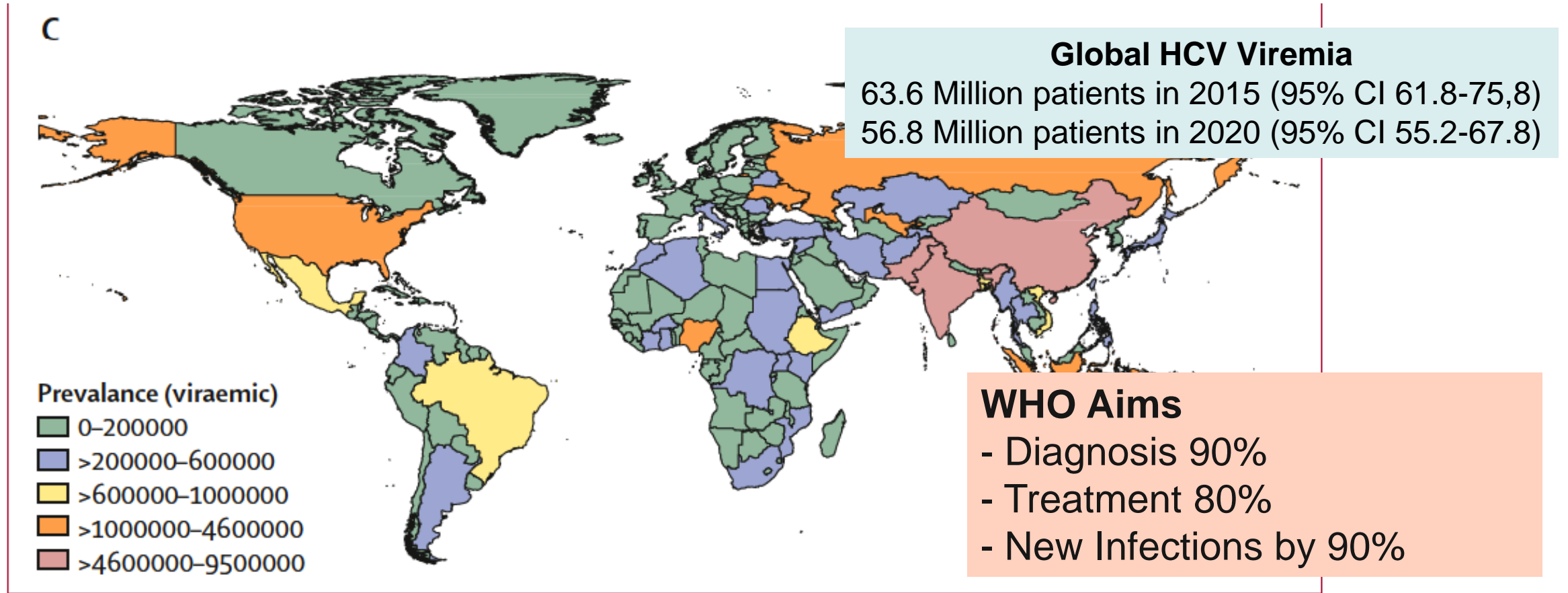


Figure 1: Country-level and territory-level HCV prevalence estimates (beginning of 2020)

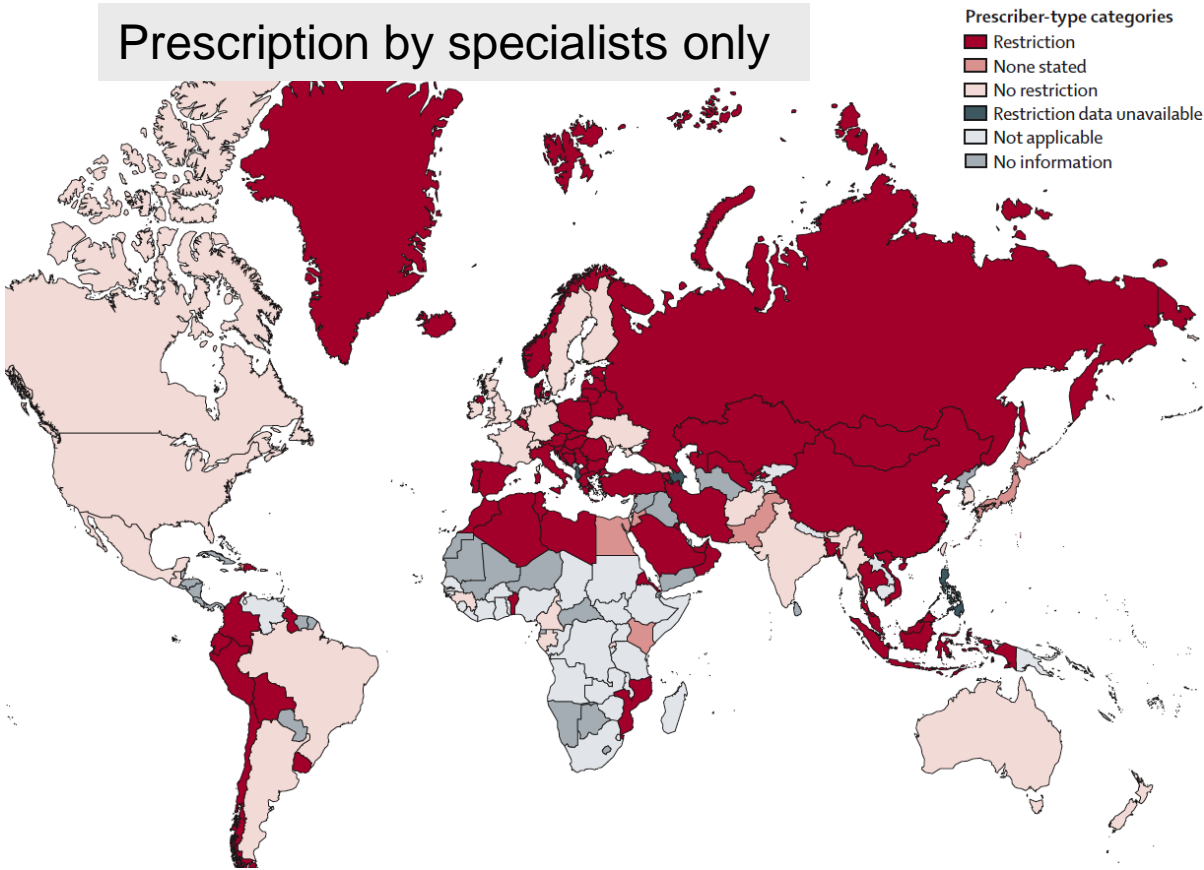
(A) Viraemic HCV infection prevalence among countries and territories with approved or estimated models.

(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

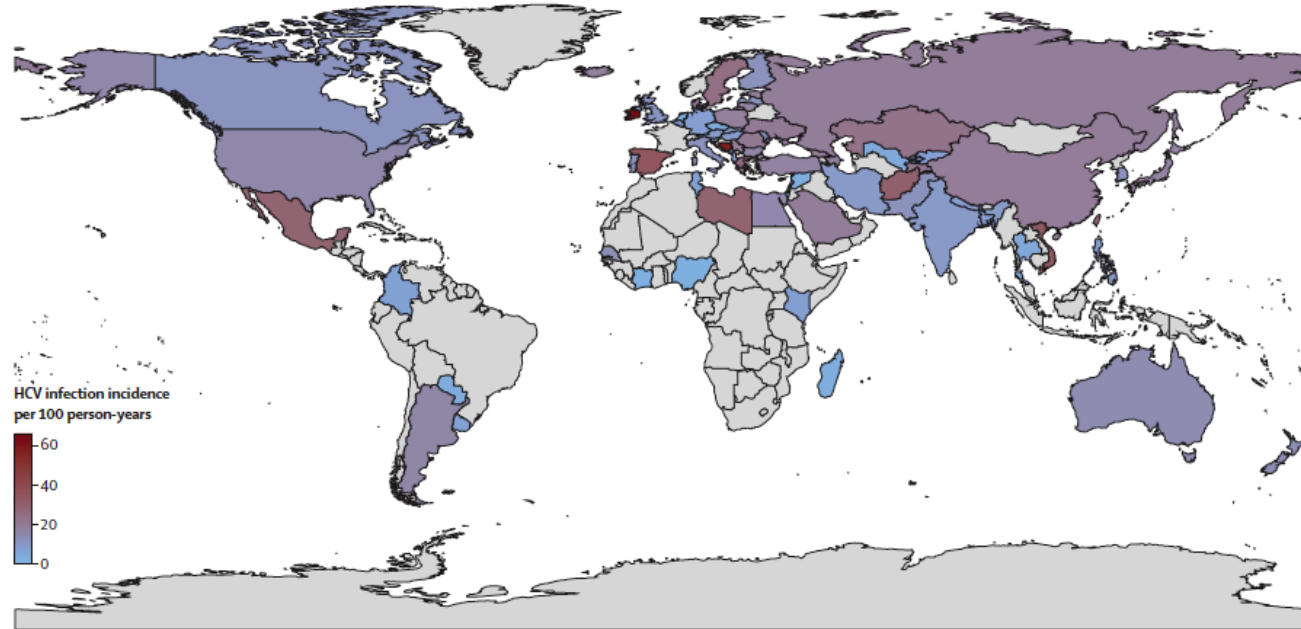
	✓ Registered × Not registered	Sofosbuvir- velpatasvir	Sofosbuvir- velpatasvir- voxilaprevir	Glecaprevir- pibrentasvir	Sofosbuvir- daclatasvir	Sofosbuvir
Austria	Reimbursed	✓	✓	✓	Not reimbursed	Not reimbursed
Belgium	Reimbursed	✓	✓	✓	Not reimbursed	Reimbursed
Denmark	Reimbursed	✓	✓	✓	Not reimbursed	Reimbursed
England	Reimbursed	✓	✓	✓	Not reimbursed	Reimbursed
Finland	Reimbursed	✓	✓	✓	Not reimbursed	Reimbursed
France	Reimbursed	✓	✓	✓	Not reimbursed	Reimbursed
Germany	Reimbursed	✓	✓	✓	Not reimbursed	Reimbursed
Greece	Reimbursed	✓	✓	✓	Not reimbursed	Reimbursed
Greenland	Reimbursed	✓	✓	✓	Not reimbursed	Reimbursed
Iceland	Reimbursed	✓	✓	Not registered	Not reimbursed	Reimbursed
Ireland	Reimbursed	✓	✓	✓	Not reimbursed	Reimbursed
Italy	Reimbursed	✓	✓	✓	Not reimbursed	Reimbursed



- 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

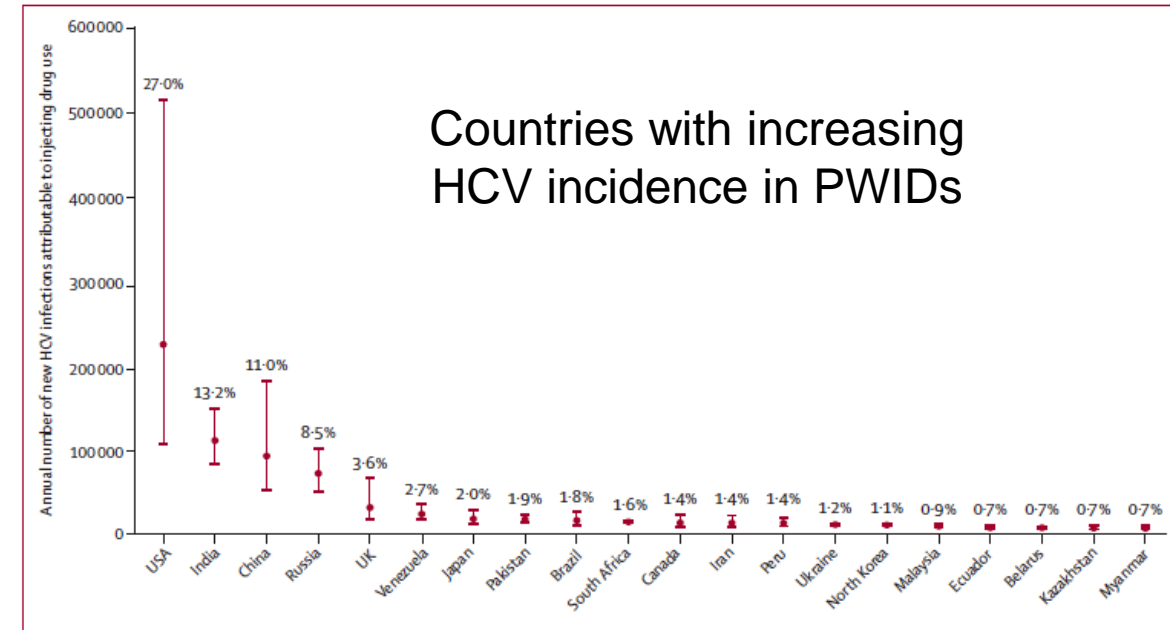
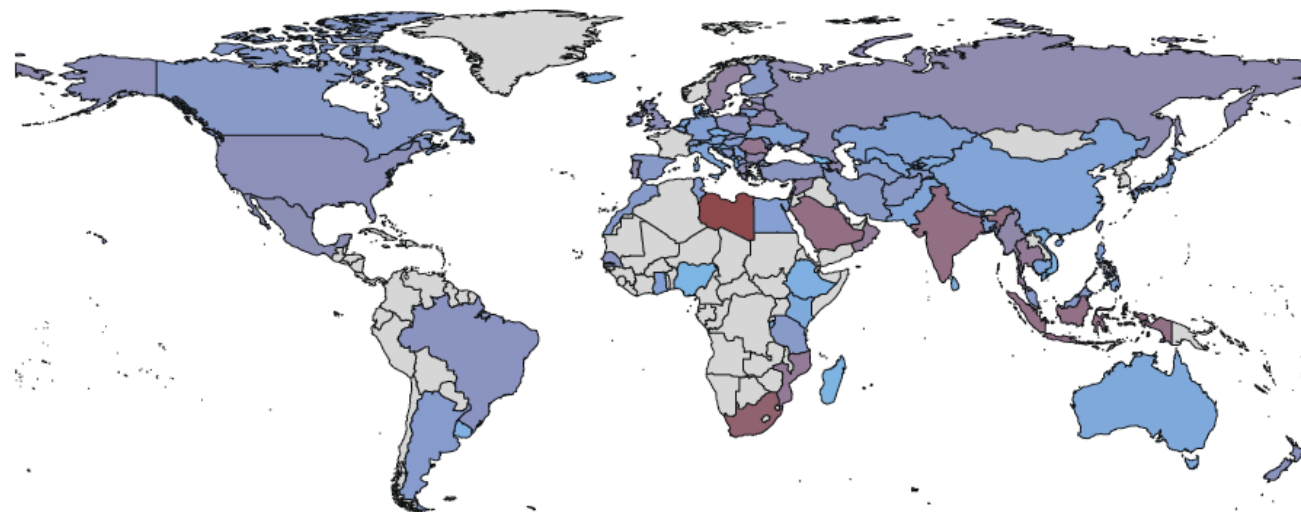
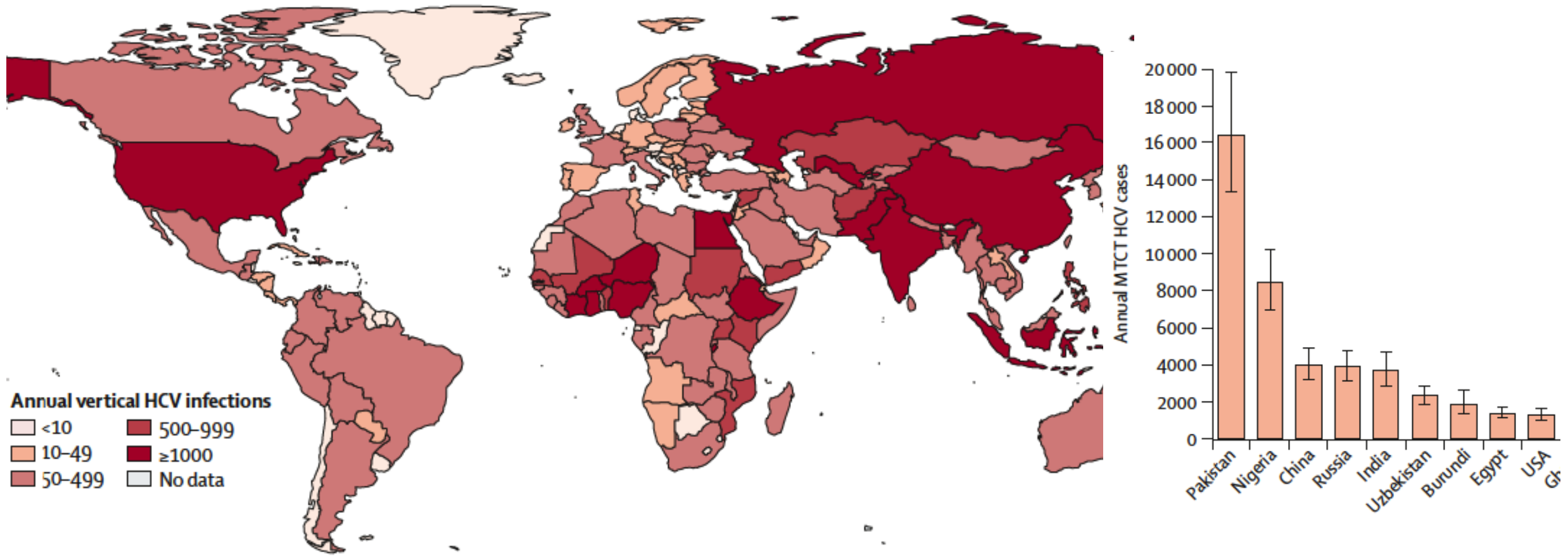


Figure 4: Number of new HCV infections attributable to injecting drug use annually for the 20 countries with the highest values. Estimates are based on 2015–21 HCV incidence data. Circles represent point estimates of the number of new HCV infections attributable to injecting drug use, and vertical error 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,

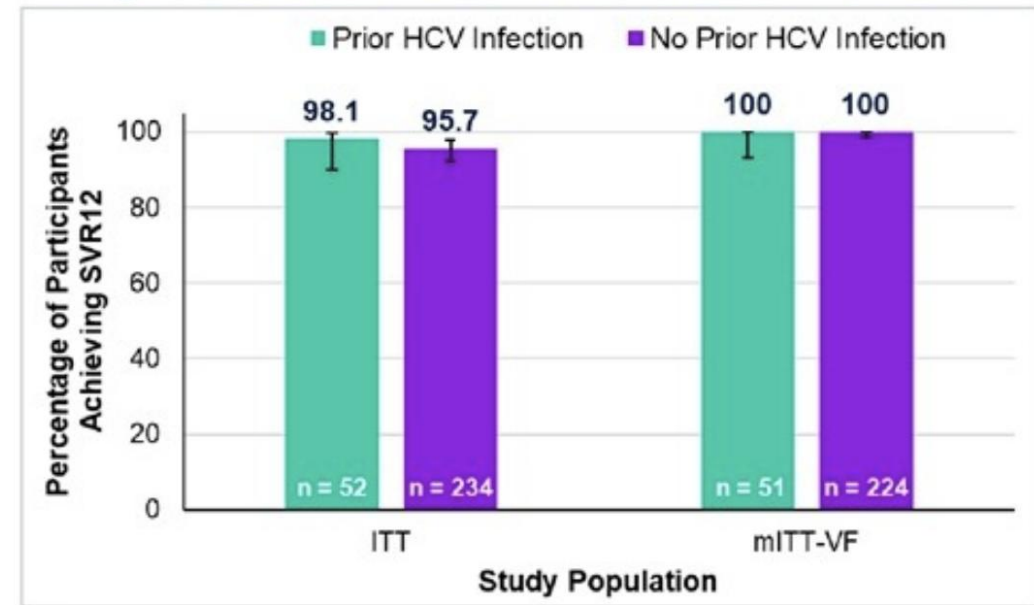
Definition of acute Hepatitis C (approx. 80% diagnosed within first 3 months):

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

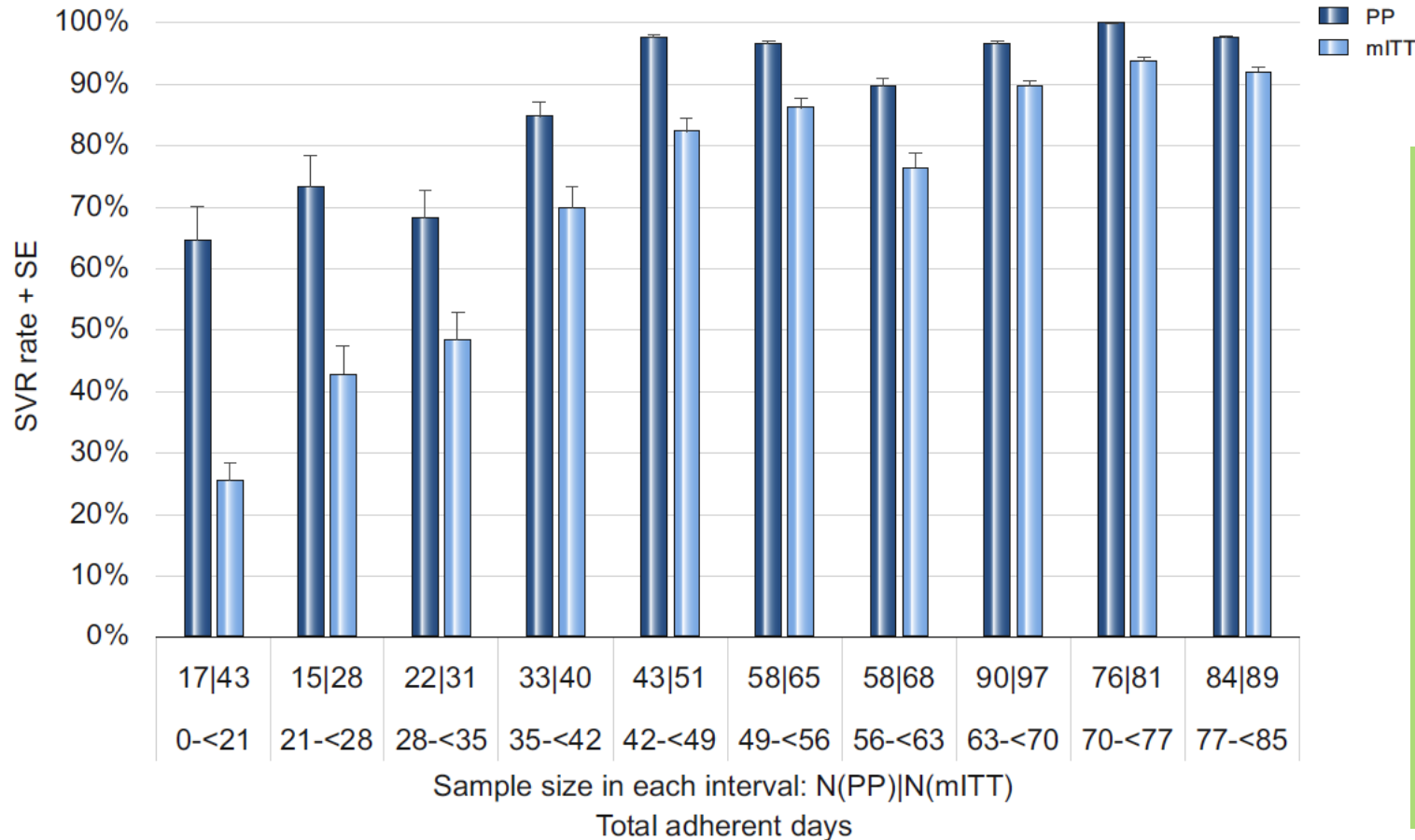


ITT, intention-to-treat; mITT-VF, ITT set excluding participants who did not achieve SVR12 for reasons other than virologic failure; SVR12, sustained virologic response at 12 weeks post treatment.

- 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)

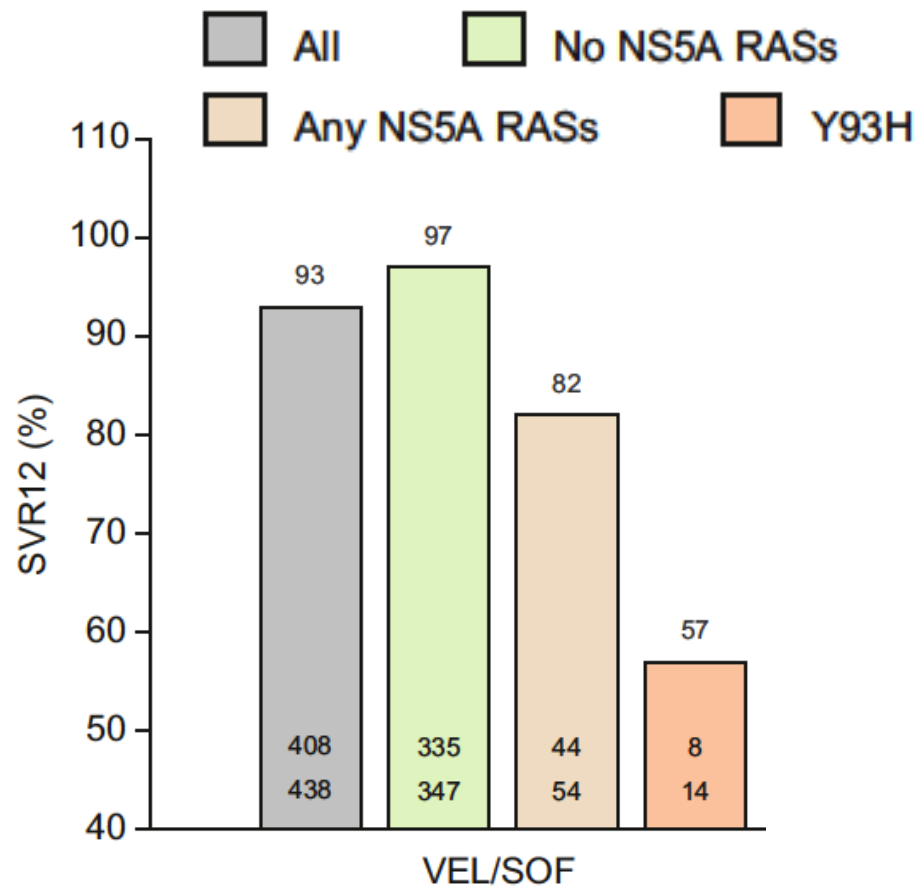
n=755 PWIDs with SOF/VEL for 12 wks., national study USA (HERO-Study) – adherence via electr. blister



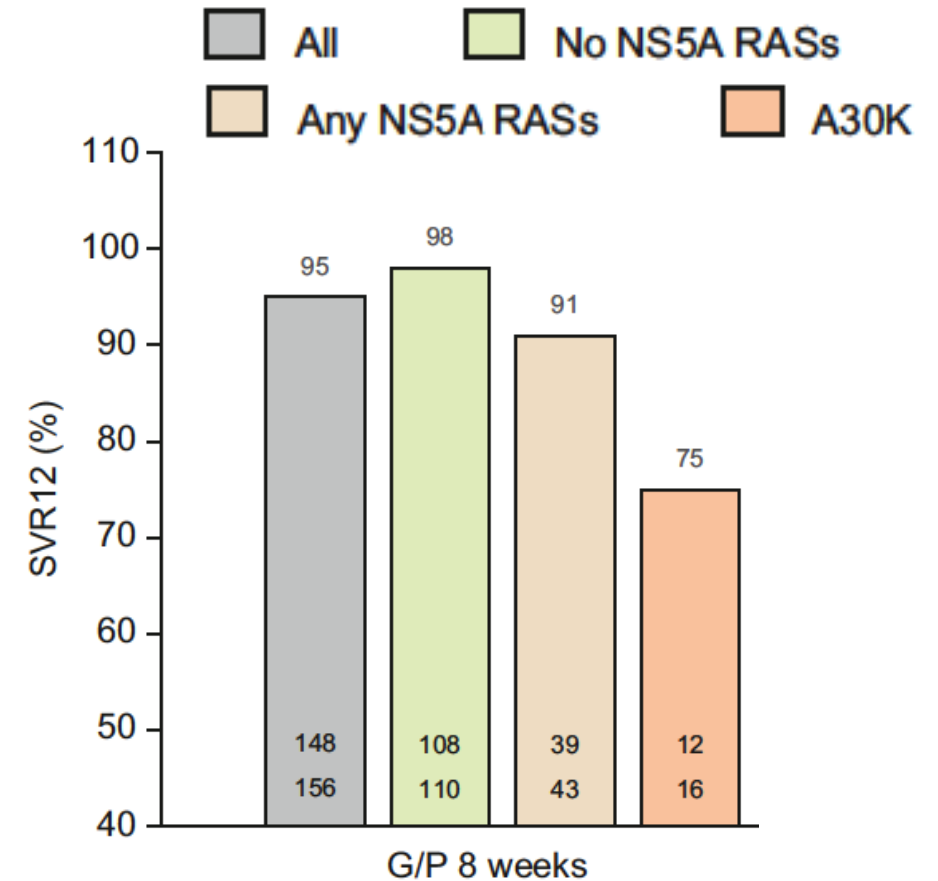
- SVR 92.7%
- Median adherence 75%
- Less than 26 missed days: >90% SVR
- With lower adherence than 50% SVR rates decline significantly
- Pausing of ≥ 2 weeks: 85% SVR
- Discontinuation within first months of treatment: 25% SVR

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

SOF/VEL in GT3 with cirrhosis

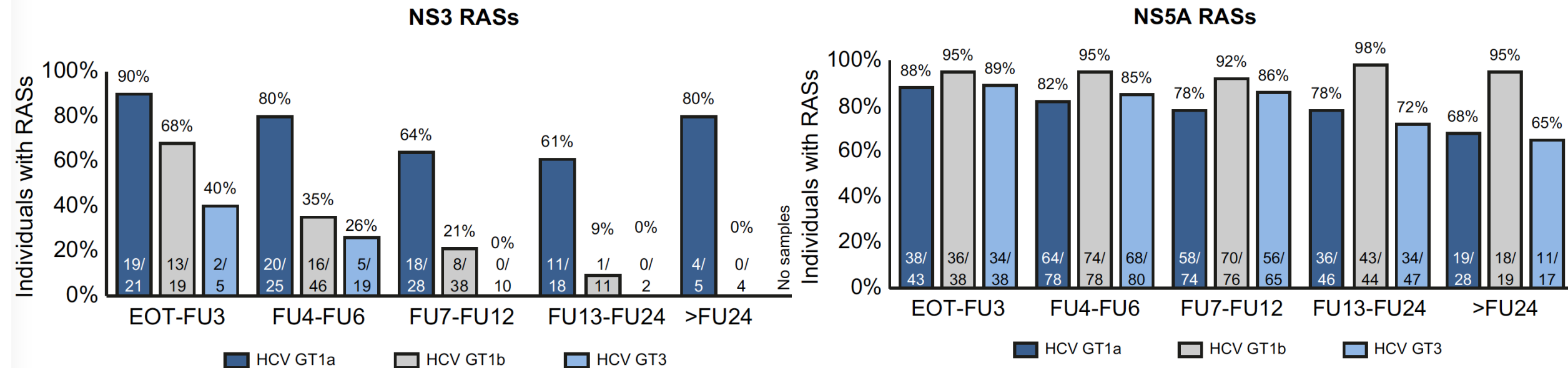


G/P in TN GT3 without cirrhosis



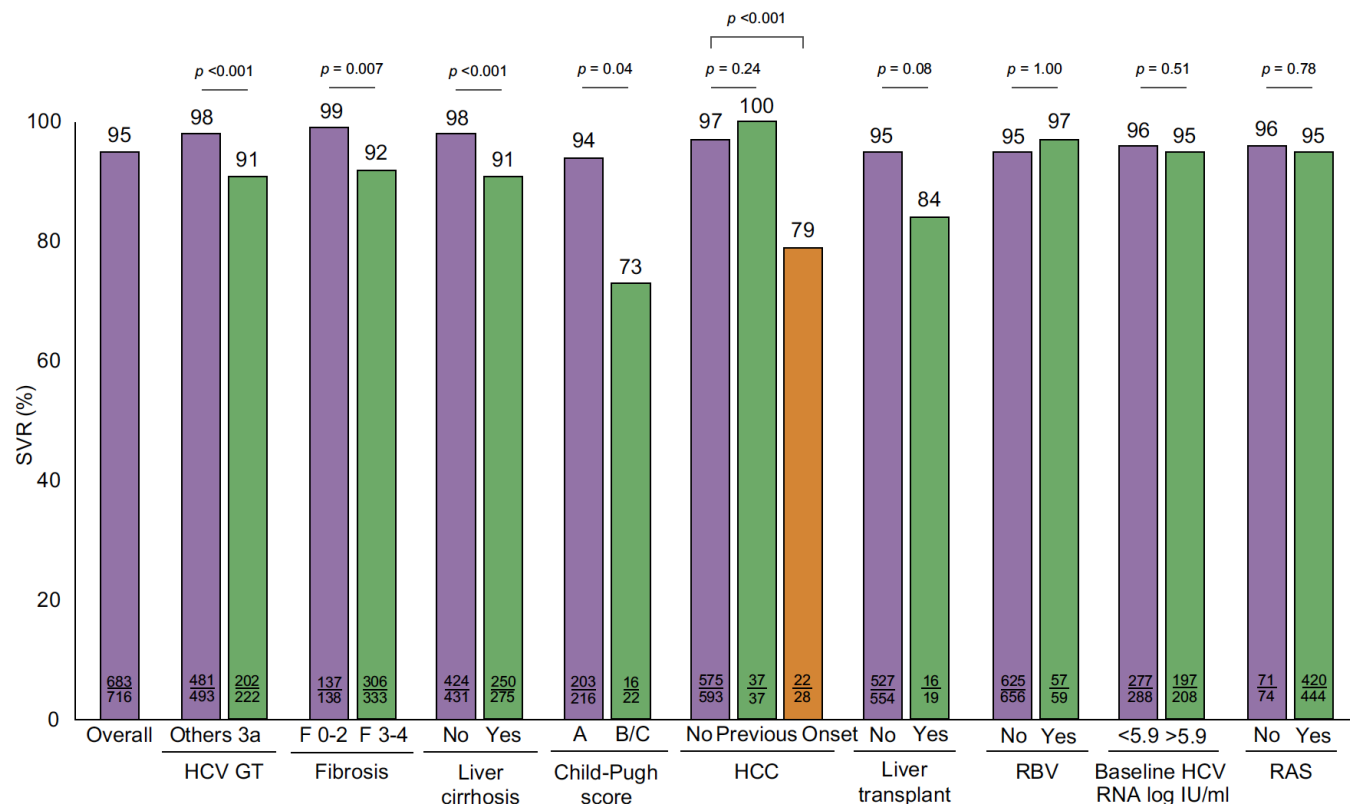
Persistence of resistance after failure to DAA regimens

European HCV Resistance Databank, Frankfurt
n=678 patients with failure to DAA regimens followed for up to 2 years without re-treatment

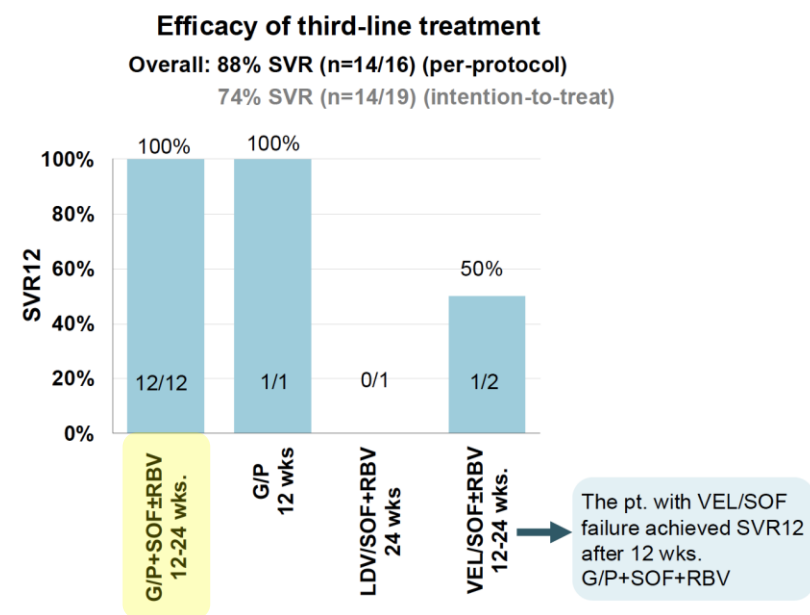


Re-treatment of DAA failure patients: Real World Data

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



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



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

- Recommendation:
G/P+SOF+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