Congresso Nazionale
AGGIORNAMENTI INFETTIVOLOGICI:
HIV, EPATITI & .....
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Lo scenario italiano dell'infezione da HBV: i dati della coorte PITER

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No Disclosures

Coordinamento dello studio:
Lo studio è coordinato dall'Istituto Superiore di Sanità (ISS), dall'Associazione Italiana Studio Fegato (AISF) e della Società Italiana di Malattie Infettive e Tropicali (SIMIT) attraverso un Comitato esecutivo

Comitato esecutivo: E. Villa, S. Vella, T. Santantonio, G. Raimondo, M. Puoti, A. Marzano, P. Lampertico, L. Kondili, GB Gaeta, C. Ferrari, V. Di Marco, B. Coco and MR Brunetto
AISF: Vincenza Calvaruso SIMIT: Roberto Parrella

PITER HBV/HDV si propone come uno *studio prospettico multicentrico nazionale* mirato a valutare complessivamente l'epidemiologia clinica dell'infezione e malattia HBV/HDV correlata in Italia

Disegno dello studio: arruolamento *consecutivo di soggetti con infezione cronica da HBV /HDV con o senza malattia, indipendentemente dallo stato di terapia antivirale*.
Ciascun centro partecipante potrà arruolare i pazienti osservati nell'arco temporale di un anno. I pazienti arruolati saranno seguiti con frequenza annuale per un *periodo di 5 anni*.

Criteri di inclusione:
- Infezione cronica da HBV documentata da HBsAg pos da almeno 6 mesi con o senza coinfezione da HDV, HCV ed HIV

Criteri di esclusione:
- Soggetti con infezione da HBV pregressa ma HBsAg negativo al momento dell'arruolamento
- Pazienti con epatite da HBV acuta

59 centri progressivamente attivati da Nov 2019
5.494 soggetti HBsAg pos arruolati

Main baseline characteristics of the PITER HBV-HDV cohort

4729 HBsAg carriers enrolled from Oct 2019 to Dec 2021

analysis on 4583 HBsAg positive carriers

		Subjetcs evaluated (n)	% (n) or median (range)
Age	years	4583	58.8 (16 – 95)
Gender	M	4583	62.2 (2850)
Origin	Italian Non-Italian native	4372	78.2 (3419) 21.8 (953)
Genotype	D non-D	625	77.0 (481) 23.0 (144)
HBeAg	Positive	3817	**7.1 (322)**
Phase of infection	HBe Ag pos infection HBeAg pos CH HBe Ag neg infection HBeAg neg CH	3689	0.3 (11) 5.8 (214) 22.1 (815) 71.8 (2649)
Coinfections	HDV HCV HIV	3566 3491 3305	**9.2 (314)** 4.5 (169) 1.5 (51)
Cirrhosis		4181	24.1 (1107)
HCC		4131	4.6 (210)
Treatment status	Treatment on going	4171	**66.5** (3043)

		% (n)
Familiar exposure	Parents Other family members Partner Community unknown	13.7 (574) 14.9 (624) 2.4 (99) 0.2 (9) 42.5 (1778)
Sexual exposure		5.3 (82)
IV Drug use		1.9 (70)
Alcohol	Absent On going Previous	65.3 (2540) 24.0 (929) 10.8 (420)
Cofactors of liver disease	Steatosis NASH Cholangiopaties AIH other	26.9 (198) 1.6 (69) 0.1 (4) 0.2 (8) 0.1 (5)
Comorbidities	Diabetes Dyslipidemia CV disease Onco-hematologic diseases Tumors	9.4 (385) 8.8 (367) 25.0 (1044) 6.3 (262) 8.6 (360)

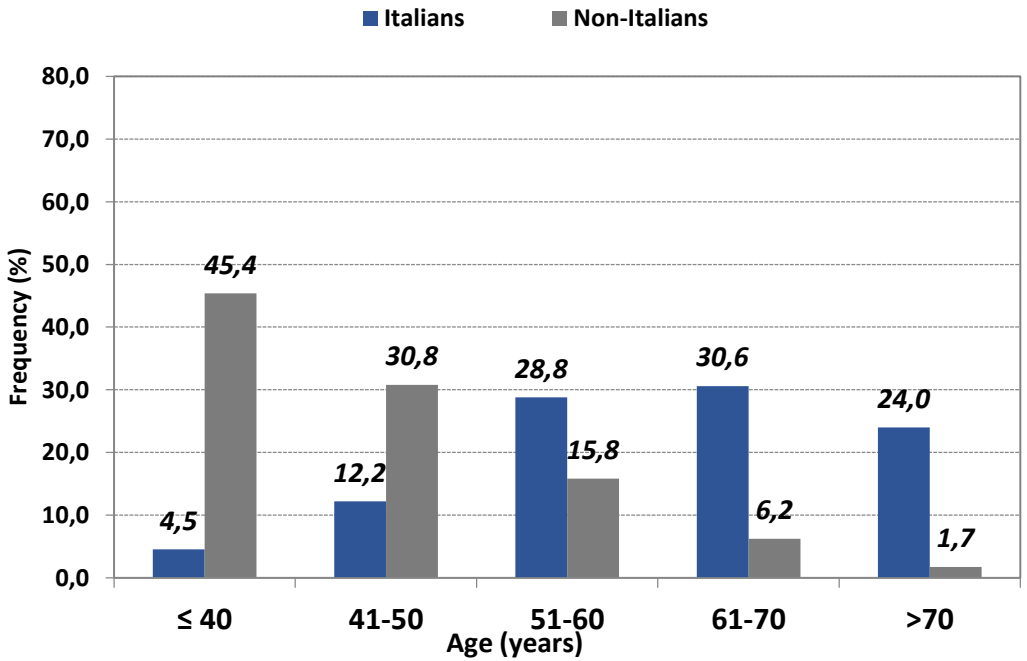
G. Brancaccio, B.Coco and PITER investigators, Int J Infec Dis, 2023

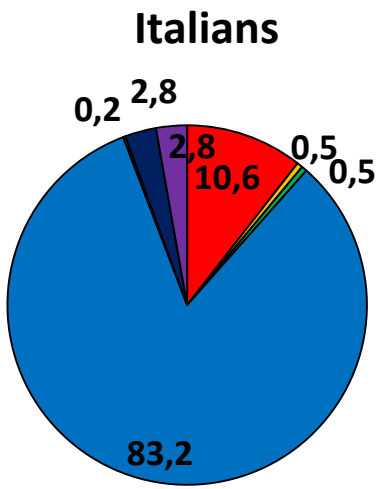
Age and genotype distribution in Italian and non-Italian native HBsAg subjects overall PITER HBV-HDV study cohort

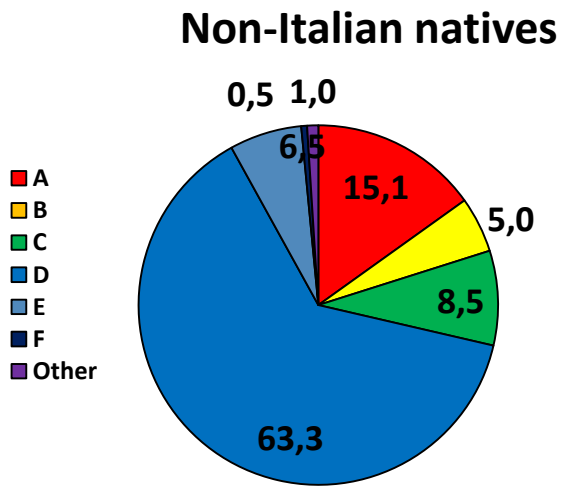
21.8% (953) subjects were non Italian natives

Countries of birth	%
Italy	78,2
East Europe	12.5
Africa	3,7
Asia	5,0
America	0,5

Living in Italy from
<10 aa :**28%**
10-19 aa: **33%**
>= 20 aa: **39%**



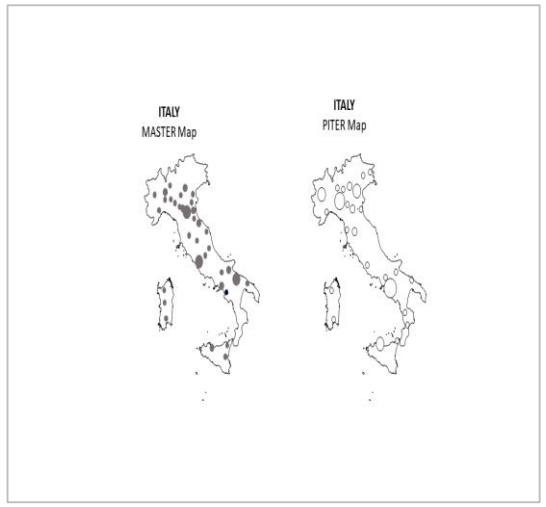




G. Brancaccio, B.Coco and PITER investigators, Int J Infec Dis, 2023

Main characteristics in Italian and *non-Italian natives* HBsAg subjects overall PITER HBV study cohort

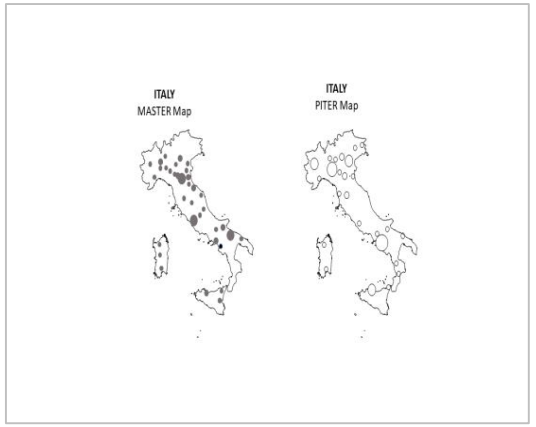
		Italian % (n)	*non- Italian natives* % (n)	p
Age	years	**62** (16-95)	***42*** *(19 – 84)*	<0.001
Gender	F M	**34.7** (1125) 65.3 (2112)	***47.2*** *(417)* *52.8 (467)*	<0.001
Genotype	D non-D	**83.2** (352) 16.8 (71)	*63.3 (126)* *36.7 (73)*	<0.001
HBeAg	Pos Neg	4.4 (128) 95.6 (2798)	***11.9*** *(100)* *88.1 (743)*	<0.001
Phase of infection	HBe Ag pos infection HBeAg pos CH HBe Ag neg infection HBeAg neg CH	**0.1** (3) **4.0** (114) **19.2** (540) **76.7** (2161)	***1.0*** *(8)* *11.9 (98)* ***32.3*** *(267)* ***54.8*** *(453)*	<0.001
Coinfections	HDV	7.9 (205)	***12.2*** *(94)*	<0.001
Alcohol	On going In the past	24.0 (716) 10.5 (315)	*24.2 (204)* *12.1 (102)*	0.395
Cofactors of liver damage	Steatosis NASH	26.8 (167) 1.7 (56)	*28.0 (30)* *1.5 (13)*	0.537 0.595
Comordities	Diabetes Dyslipidemia CV disease	**11.0** (357) **9.9** (321) **29.8** (965)	*3.9 (35)* *4.7 (42)* *7.9 (70)*	<0.001 <0.001 <0.001
Cirrhosis		**26.1** (896)	***14.8*** *(141)*	<0.001
HCC		**5.06** (171)	***1.2*** *(12)*	<0.001
Treatment status	Treatment on going	**70.3** (2397)	***52.5*** *(501)*	<0.001



	MASTER B *2012- 2015* n = 2920 % (n)	PITER HBV/HDV *2019 - 2022* n = 4583 % (n)	p
Age (median;years)	49.8	**58.8**	0.0001
Gender (male)	68,6 (2003)	**62.2 (2850)**	0.0001
Origin Italian naive East Europe Africa Asia South Central America Central Western Europe	73.2 (2136) 13.2 (386) 5.9 (173) 6.6 (194) 0.5 (15) 0.4 (12)	**78.2 (3419)** **12.5 (547)** **3.7 (162)** **5.0 (221)** **0.3 (13)** **0.2 (10)**	0.0001
Alchol use	31.1 (783)	**34.2 (1408)**	0.009
HBeAg pos	**12.3 (323)**	7.17 (322)	0.0001
Cirrhosis	24.7 (722)	24.1 (1107)	0.55
Anti HDV	8.3 (161)	9.2 (314)	0.23
On going therapy	34.2 (1000)	**66.6 (3043)**	0.0001

- 5.6% in the PITER cohort with HBV DNA > 20,000 IU/mL were *not* under treatment and 35.9% in the MASTER cohort

G. Brancaccio, B.Coco and PITER investigators, Int J Infec Dis, 2023



	MASTER *Cirrhosis* n=722 (24.7%)	PITER *Cirrhosis* n=1107 (24.1%)	*p*-value
Age (Years)	57.2	**63.6**	<0.0001
Gender (Males)	79.9 (577)	73.9 (816)	0.0032
BMI >/= 30	25.5 15.3 (127)	25.5 15.1 (92)	0.90
HBV DNA (pos)	**56.5 (392)**	24.6 (257)	<0.0001
Origin Italian natives East Europe Asia Africa America Central Western Europe	 80.6 (578) 7.7 (56) 5.9 (43) 5.8 (42) 0.42 (3) 0 (0)	 **86.4 (896)** 8.5 (89) 2.9 (31) 1.8 (19) 0.1 (1) 0.1 (1)	 <0.0001
Alcohol use (Yes)	29.7 (187)	37.1 (366)	0.0023
HBeAg (Positive)	**12.6 (81)**	4.9 (54)	<0.0001
Anti-HDV (Positive)	17.5 (88)	**24.8 (213)**	0.0017
HCC (Present)	14.0 (99)	16.6 (183)	0.1408
Ongoing therapy (Yes)	50.5 (365)	**91.5 (1012)**	<0.0001

HDV coinfection was the strong factor associated to cirrhosis (OR 10.08; C.I. 7.63-13.43) together with *age, gender, BMI and non Italian origin*

G. Brancaccio, B.Coco and PITER investigators, Int J Infec Dis, 2023

In 2016, the **WHO Global Health Sector Strategy (GHSS) on viral hepatitis endorsed the** *elimination of viral hepatitis as a public health problem by 2030* and provided the initial targets to reach it:

- diagnosing 90% of people HBsAg infected
- treatment 80% of elegible population
- reduction in new infections by 95%
- reduction in HBV prevalence among children age 5 under 0.1% and less
- reduction in mortality by 65%

Quantifying the national, regional and global prevalence of HBsAg carriers and monitoring changes in disease burden are critical steps to prioritize health-resource allocation and advocate for action or investment by stakeholders and governements

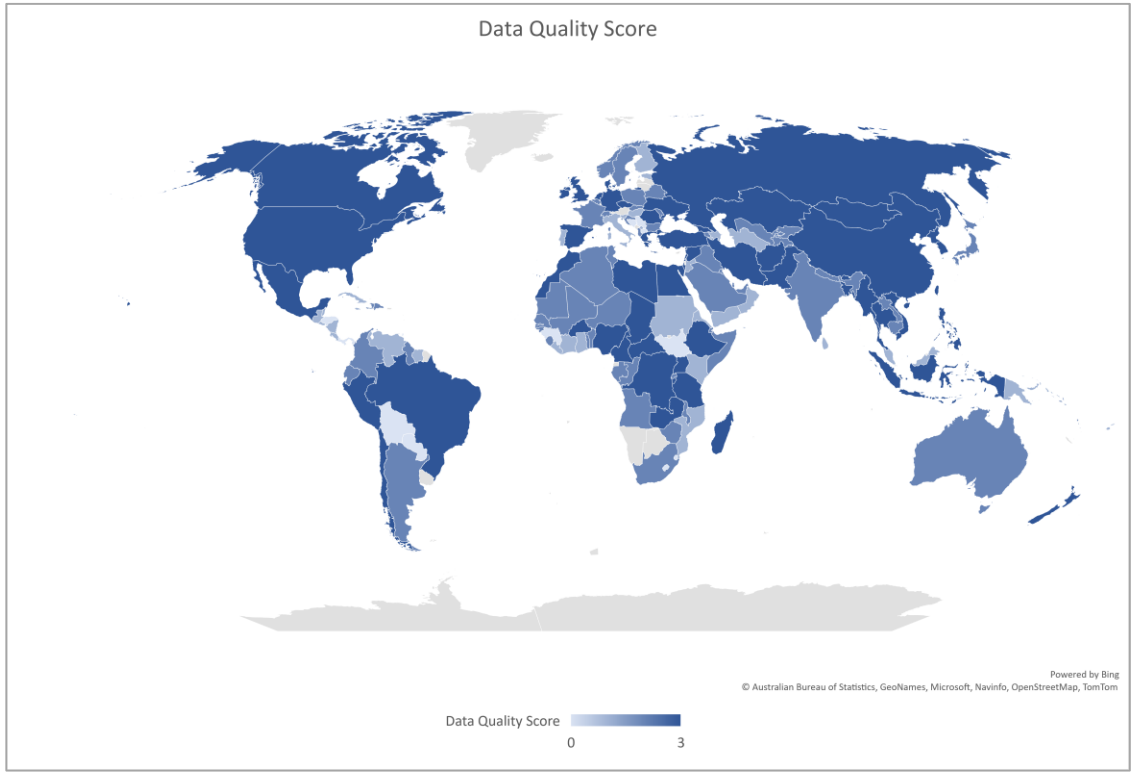
Global prevalence, cascade of care, and prophylaxis coverage of hepatitis B in 2022: a modelling study by Polaris Observatory

Methods:

A Delphi process with data from literature reviews and interviews with country experts was used to quantify the prevalence, diagnosis, treatment, and prevention measures for HBV infection.

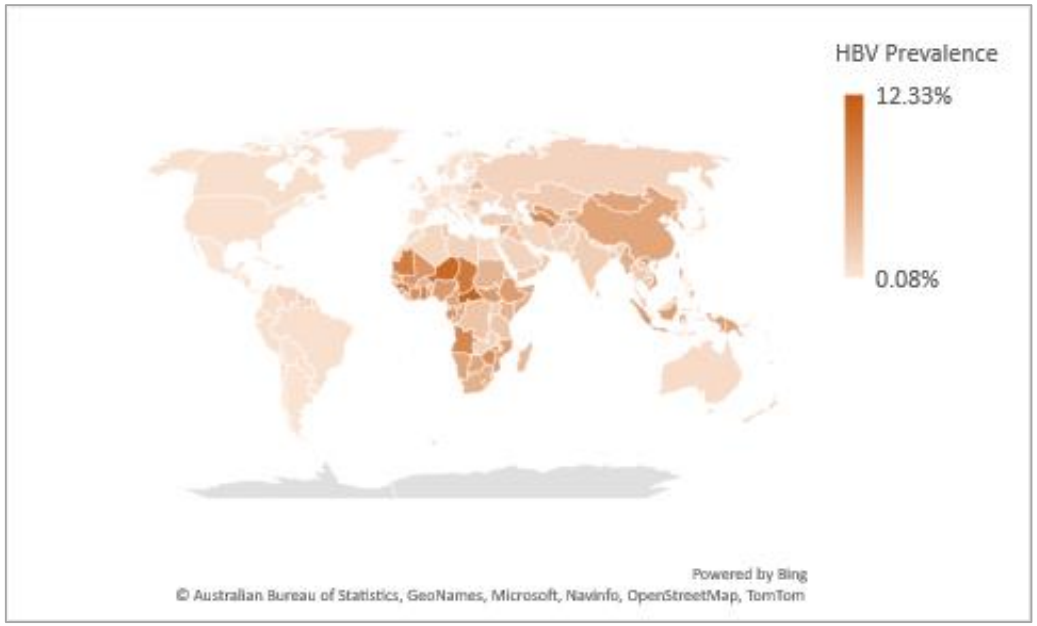
The PRoGReSs Model, a dynamic Markov model, was used to estimate the country, regional, and global prevalence of HBV infection in 2022, and the effects of treatment and prevention on disease burden.

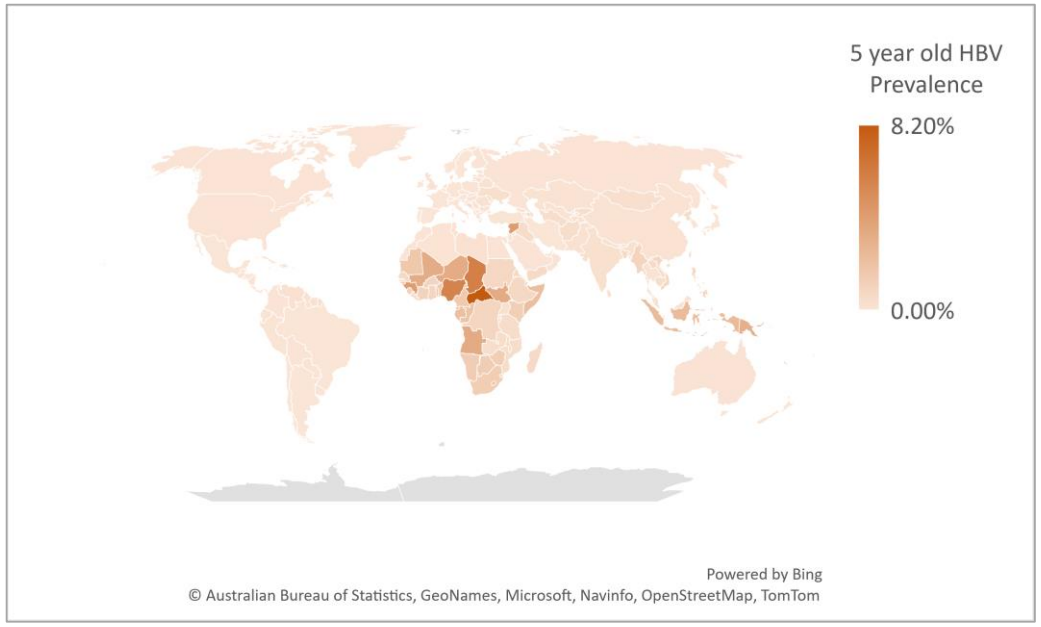
The future incidence of morbidity and mortality in the absence of additional interventions was also estimated at the global level.



Polaris Observatory Collaborators, Lancet Gastroenterol Hepatol 2023

Global prevalence, cascade of care, and prophylaxis coverage of hepatitis B in 2022: a modelling study by Polaris Observatory





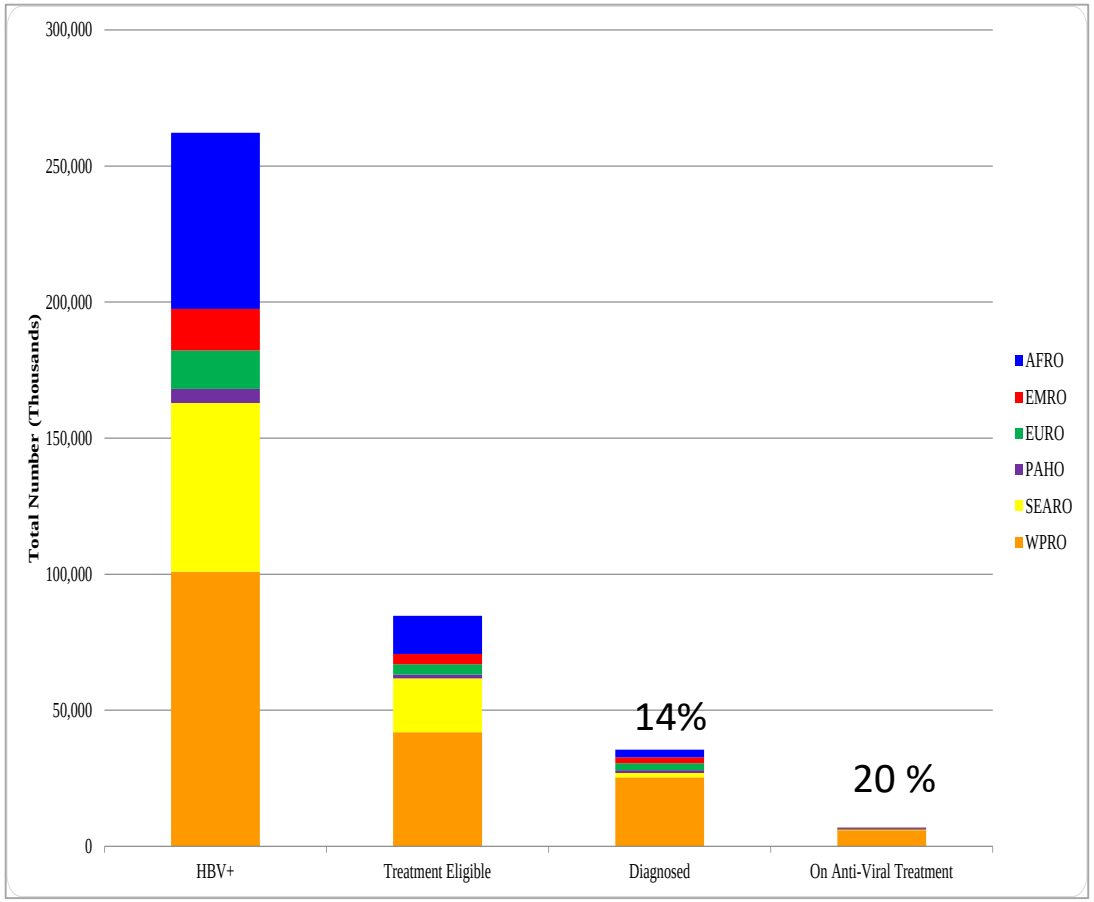
3.2% estimated global prevalence of HBV infection
257.5 million HBsAg carriers

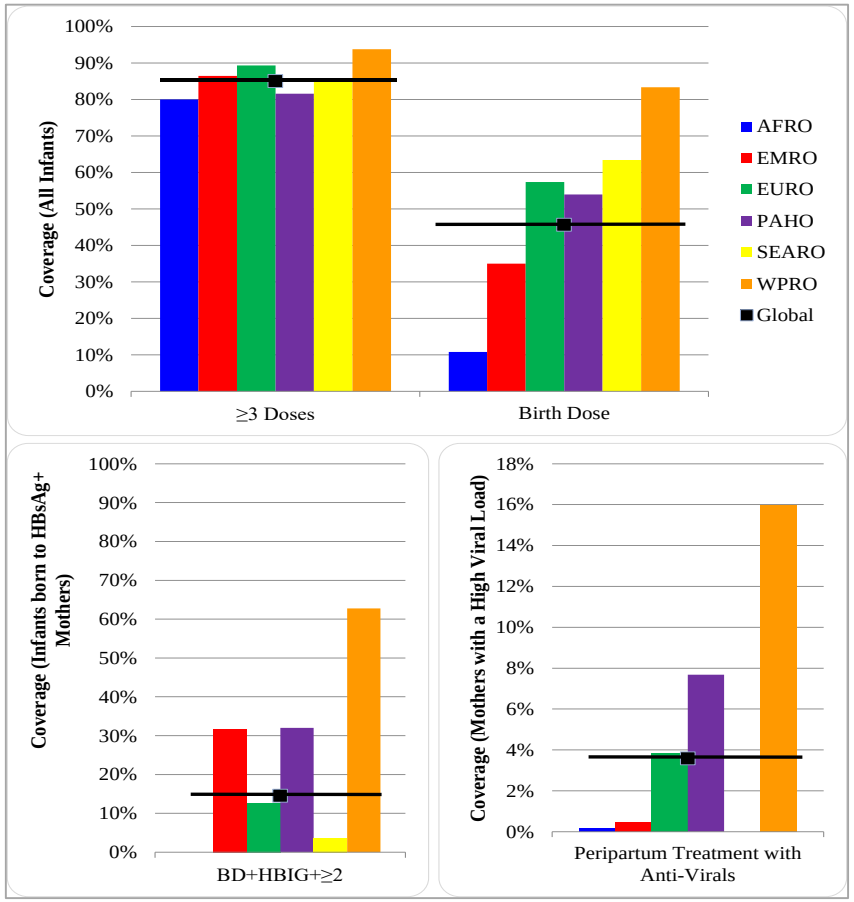
0.7% estimated prevalence among children 5 years or younger
5.6 million children with HBV infection

- ✓ Mainland China, India, Indonesia, Nigeria and Ethiopia account for over 57% of all HBsAg infections, respectively
- ✓ Nigeria, Indonesia, India, Niger and Angola account for over 57% estimated infections among children younger than 5 years old

Polaris Observatory Collaborators, Lancet Gastroenterol Hepatol 2023

Global prevalence, cascade of care, and prophylaxis coverage of hepatitis B in 2022: a modelling study by Polaris Observatory





Polaris Observatory Collaborators, Lancet Gastroenterol Hepatol 2023

Global prevalence, cascade of care, and prophylaxis coverage of hepatitis B in 2022: a modelling study by Polaris Observatory

HBV scenario in ITALY in 2021 by modelling

HBV prevalence: 0.5% (0.4-0.6%)
HBV population: 308.000 (246-369.000)
Treatment elegible: 92.400 pts

Diagnosed: 30%
Treated of total elegible: 45%

HBV prevalence among 5 years old: <0.1%

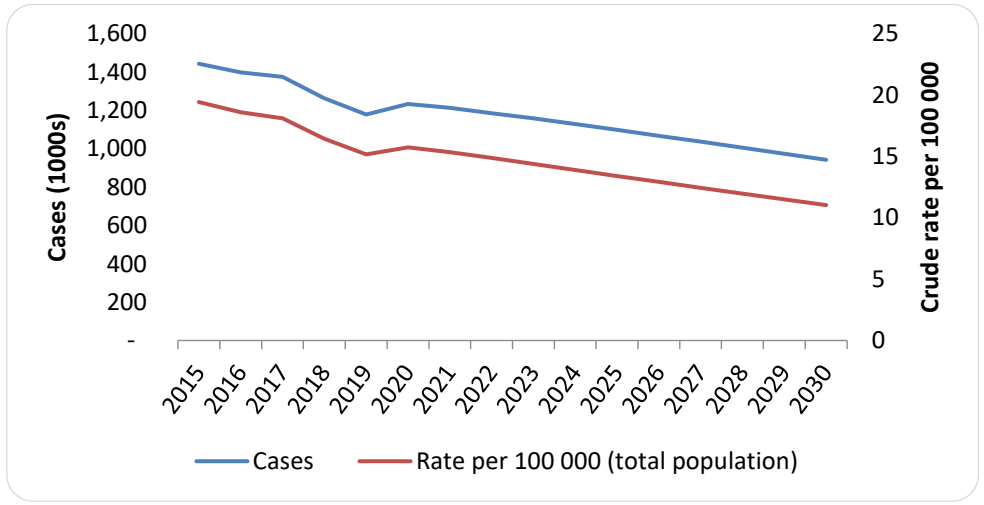
Profilaxis:

- 3D vaccine 94%
- BD vaccine < 1%
- HBIG + 2D vaccine 100%
- Antiviral therapy of mothers: 10%

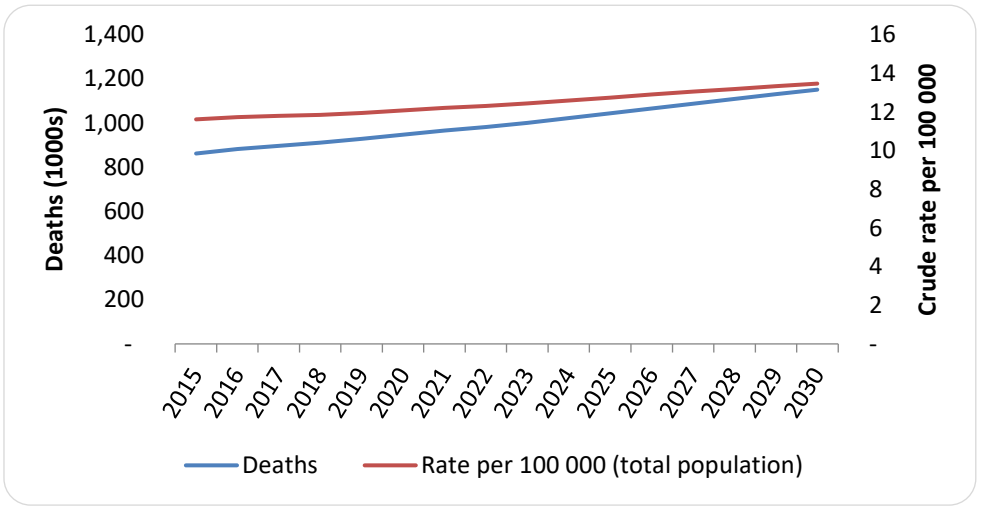
Polaris Observatory Collaborators, Lancet Gastroenterol Hepatol 2023

HBV DISEASE BURDEN PROJECTIONS, 2015 - 2030

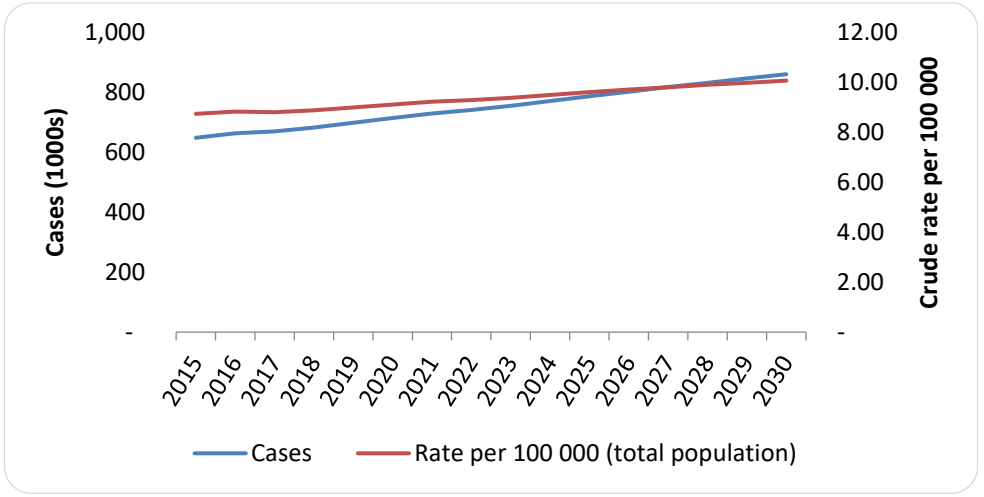
Global Incidence of HBV



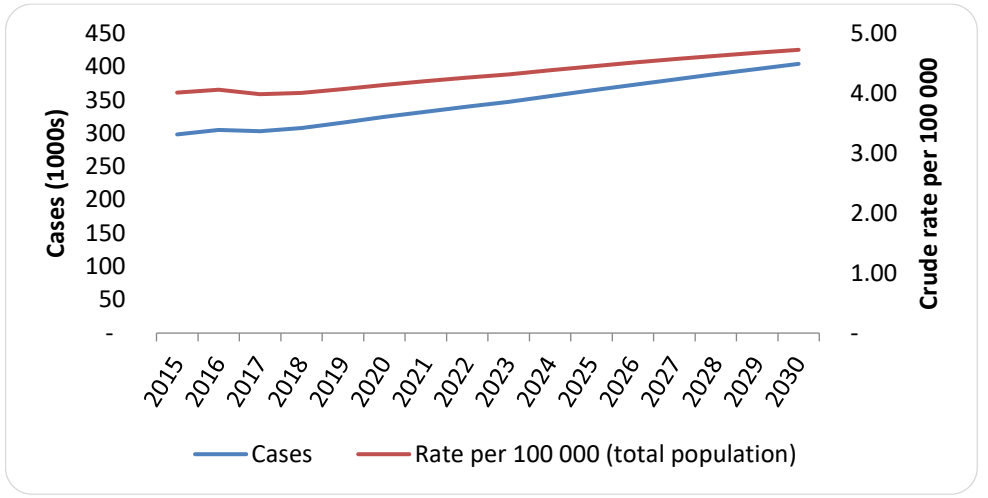
Global Incident Cases of HBV Deaths



Global Incident Cases of HCC



Global Incident Cases of Decompensated Cirrhosis



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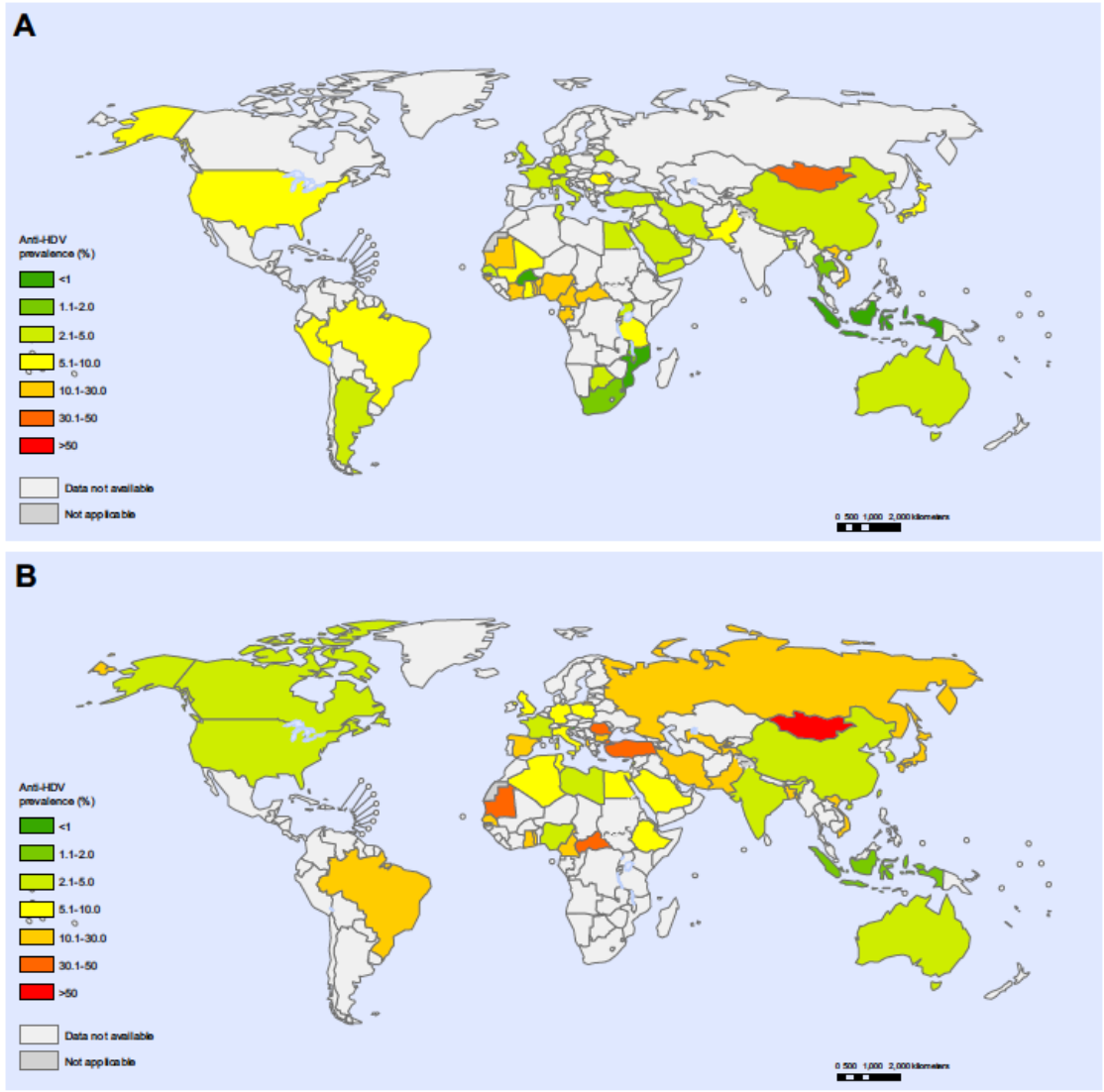
HDV Epidemiology

HBsAg positive general population



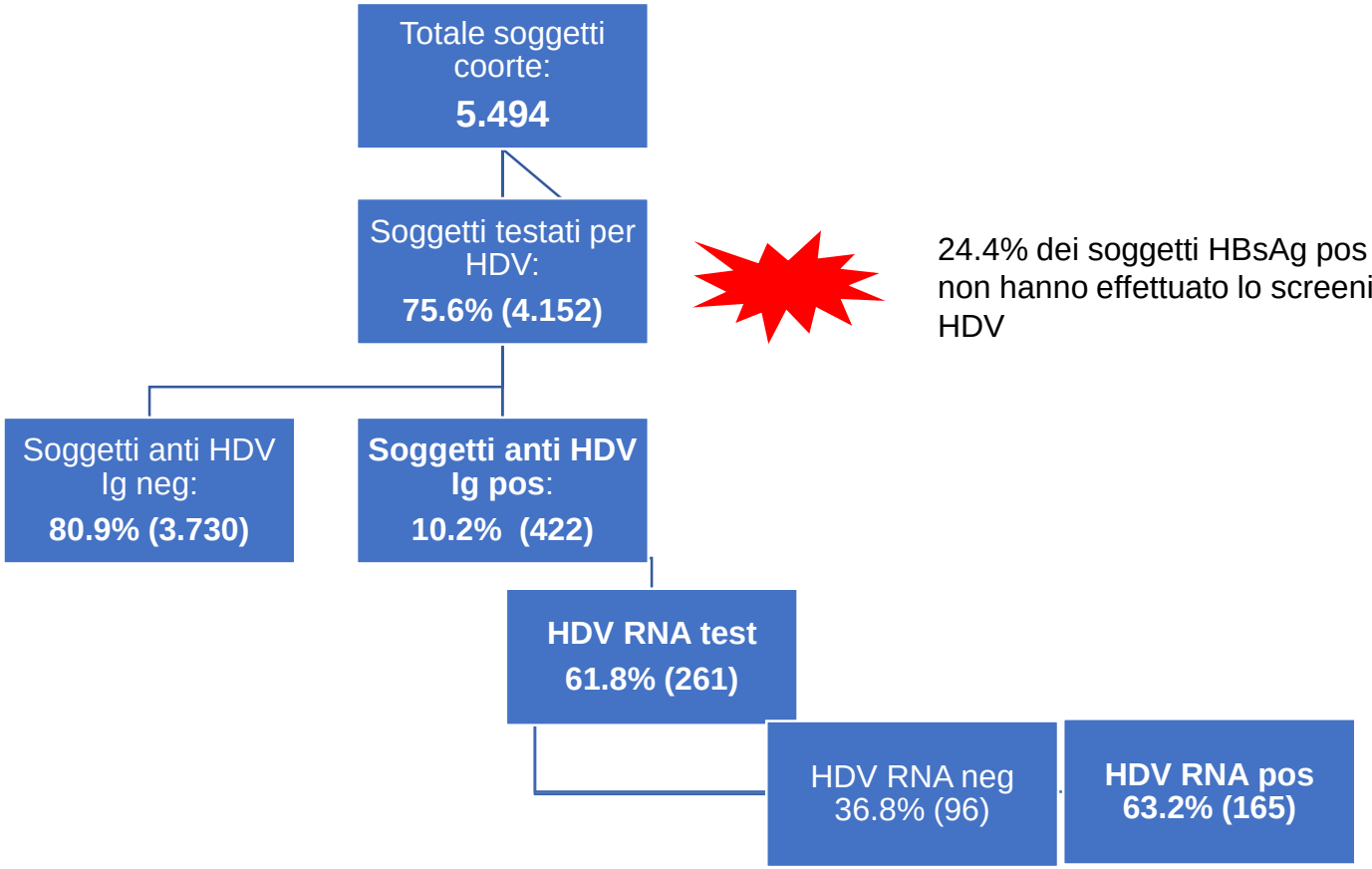
HBsAg positive Hepatology clinic population

- **15-20 million people** are estimated to **be infected by HDV**, but the global prevalence is not known and recent report suggests up to **62-72 million** infected individuals.
- Globally the estimate of **anti-HDV prevalence among HBsAg positive i**ndividuals is **4.5%** (95% CI 3.6-5.7); 0.16% in the total population.
- The **geographic distribution** of HDV infection is **heterogeneous** with higher prevalences in Mongolia, republic of Moldova, Western and Middle Africa Countries
- Several **population groups** (PWID, haemodialysed patients, CSWs and MSM, patients with HCV and HIV infections) show an association with **higher anti-HD prevalences**
- Methodological issues limit the consistency of the available data and contribute to the heterogeneity ot HDV prevalence, however variation of local risk factors and the occurrence of localized defined foci of transmission could contribute to the findings
- **Among HBsAg chronic carriers the prevalence of HDV infection is higher in patients with more advanced liver disease**

Koh C et al, Gastroenterology 2019; Chen HY et al, Gut 2018 Stockdale AJ et al J Hep 2020

Soggetti con coinfezione HBV/HDV arruolati della coorte PITER

5.494 soggetti HBsAg positivi arruolati da Dic 2019 a Feb 2023

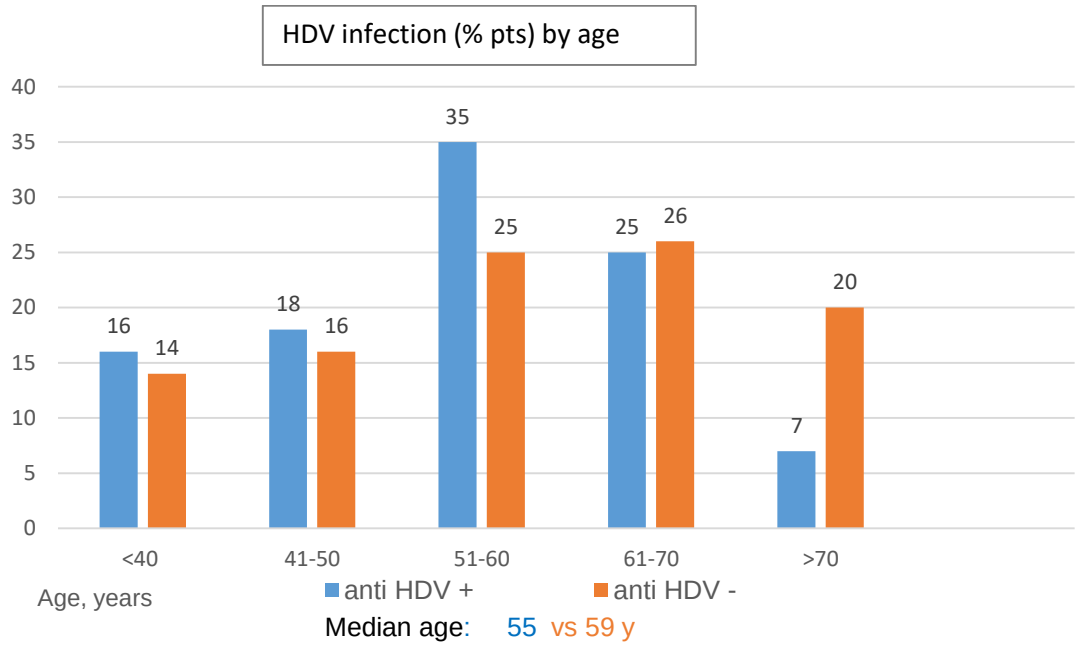


Kondili L and PITER collaboratos, submitted

Main baseline characteristics of the PITER HDV cohort

422 anti HDV positive carriers enrolled from Dec 2019 to Feb 2023:
165 out of 261 subjetcs who were tested had HDV RNA positive

	anti-HDV positive N° = 422	anti-HDV negative N° = 3730	p-value
Age median (Q1, Q3)	**55 (**46, 62)	59 (48, 68)	<0.001
Males	253 (60.0)	2335 (62.6)	0.287
Non-Italian natives	**142 (33.6)**	850 (22.8)	<0.001
Injection drug use	**35 (10.0)**	55 (1.7)	<0.001
ALT > 35 IU/L	**243 (59.4)**	566 (15.3)	<0.001
GGT >50 IU/L	**121 (36.3)**	344 (11.1)	<0.001
HBeAg positive	25 (6.1)	253 (6.8)	0.582
Cirrhosis	**299 (70.8)**	892 (23.9)	<0.001
HCC	**42 (10.2)**	106 (2.9)	<0.001
HBV DNA positive	115 (29.1)	1330 (36.5)	0.004
HDV RNA positive (261 tested)	**165 (63.2)**	---	---
Previous IFN	142 (33.6)	580 (15.5)	<0.001
Potential disease co-factors			
Ongoing alcohol use	775 (22.6)	412 (12.0)	0.130
Past use	65 (18.7)	51 (14.7)	
Diabetes	29 (6.9)	375 (10.0)	0.037
BMI 25-30	32 (7.6)	384 (10.3)	0.004
BMI ≥30	109 (25.8)	1.173 (31.4)	
anti-HCV positive	**39 (10.4)**	126 (3.6)	<0.001
anti-HIV positive	**17 (4.8)**	35 (1.1)	<0.001
Ongoing therapy (>95% NUCs)	**323 (76.5)**	2529 (67.8)	<0.001



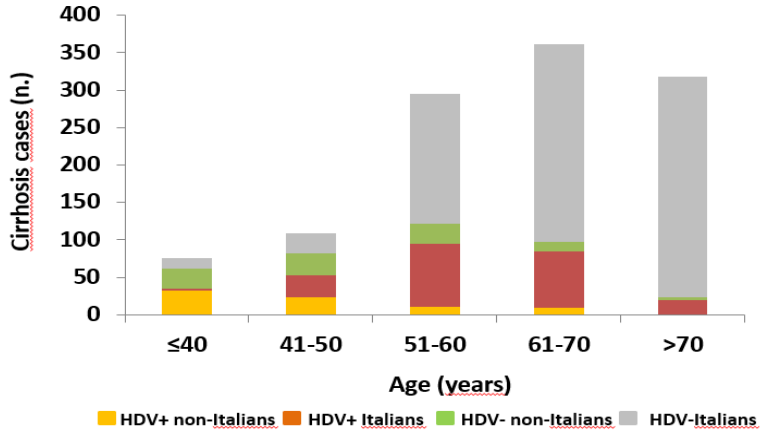
Kondili L and PITER collaboratos, submitted

Main baseline characteristics of the PITER HDV cohort

422 anti HDV positive patients enrolled from Dec 2019 to Feb 2023:

***299 (70.8%)** anti HDV + pts have cirrhosis:*
251 (84.0) Child A
41 (13.7) Child B
7 (2.3) Child C

Cirrhosis by age, presence of anti-HDV antibodies and patients' origin

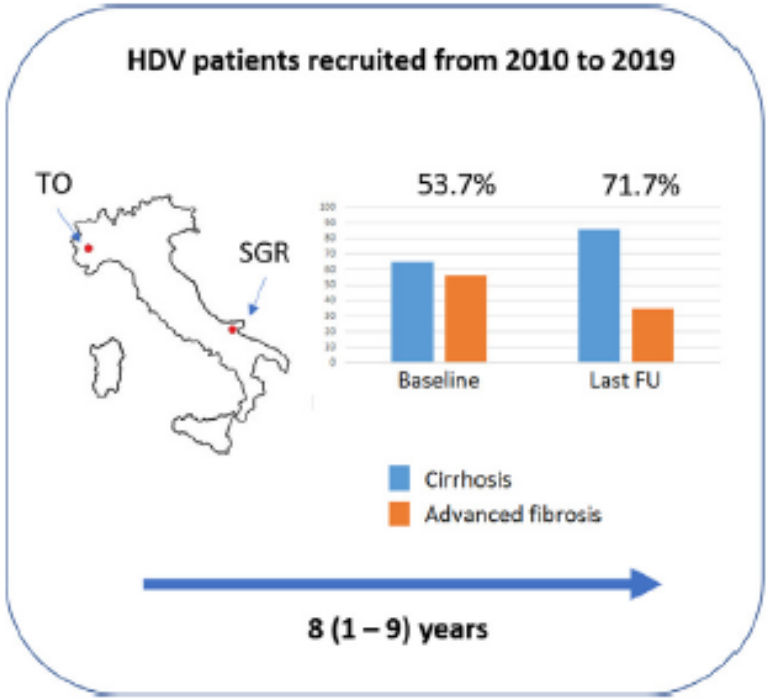


- 47.4% of patients with HDV infection had one or more comorbidities: younger (< 55 y) had higher frequency of psychiatric disorders whereas older patients had higher prevalence of overweight/obesity, autoimmune disorders and digestive disease

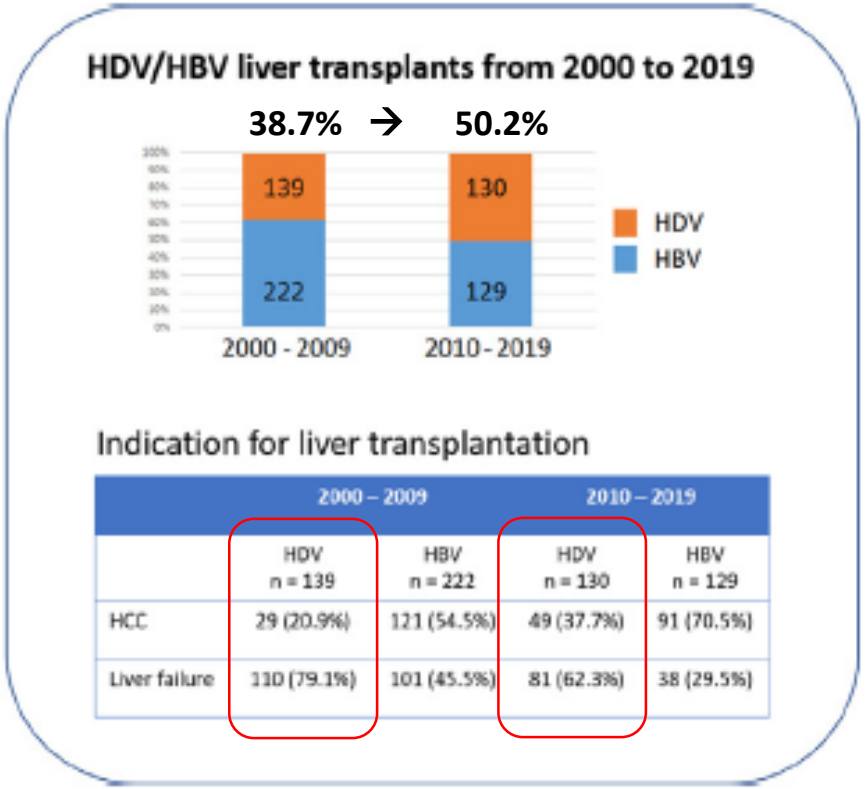
- 46.7% (77) of HDV RNA + patients were elegible to peg-IFN; 40.6% (67) and 12.7% (21) had absolute or relative controindication

Kondili L and PITER collaboratos, submitted

The hepatitis D virus in Italy. A vanishing infection, not yet a vanished disease



- ✓ **121** of 193 (**62.7%**) HBsAg/anti-HD positive patients, who were followed up from 2010 to 2019 at Turin and San Giovanni Rotondo, were **Italian natives**
- ✓ At the last observation:
  - the their **median age** was **58 years**
  - median liver stiffness values were 12.0 kPa (95% CI 11.2-17.4)
  - **86** (**71.1%**) had **cirrhosis**



Indication for liver transplantation

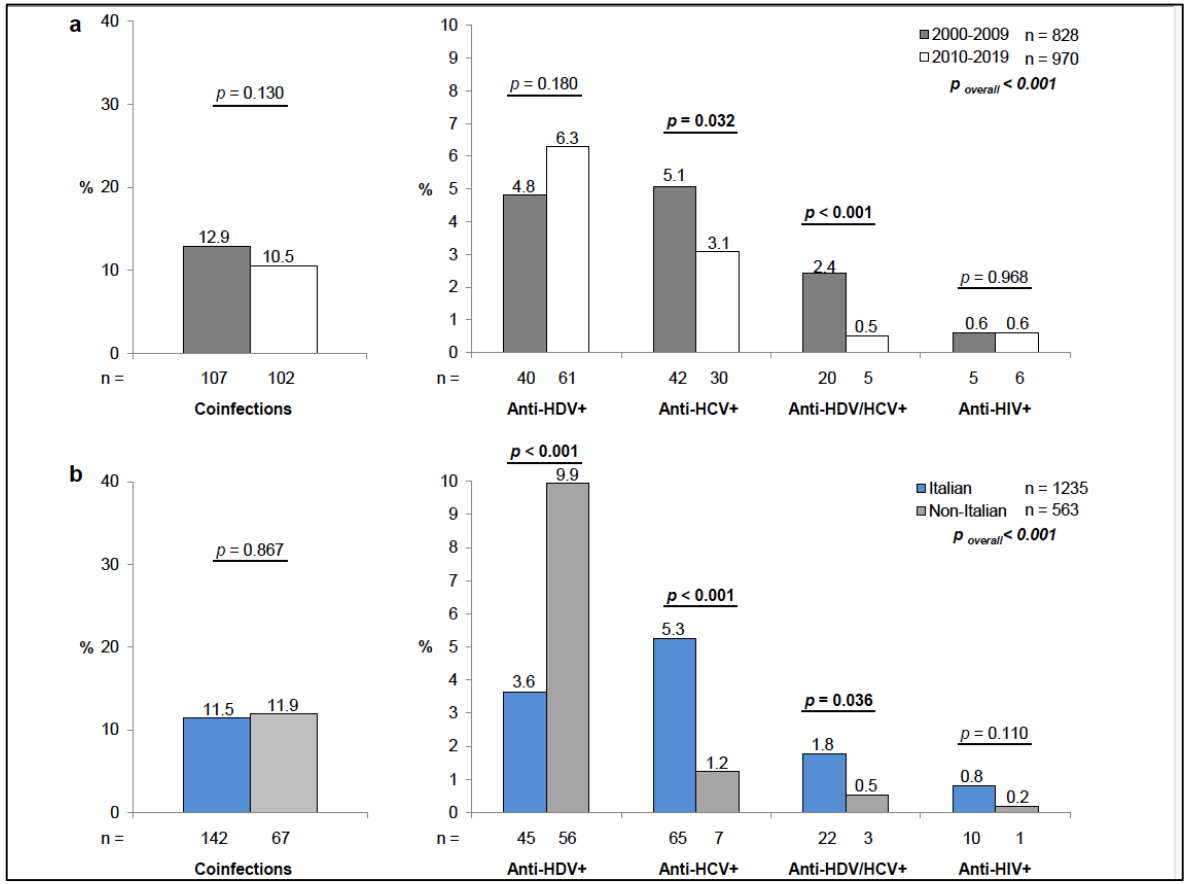
	2000 – 2009		2010 – 2019	
	HDV n = 139	HBV n = 222	HDV n = 130	HBV n = 129
HCC	29 (20.9%)	121 (54.5%)	49 (37.7%)	91 (70.5%)
Liver failure	110 (79.1%)	101 (45.5%)	81 (62.3%)	38 (29.5%)

Though HDV is vanishing in Italy, a legacy of ageing native-Italian patients with advanced HDV liver disease still represents an important medical issue and maintains an impact on liver transplantation.

Caviglia GP et al J Adv Res 2021

Highly dynamic changes of regional HBV epidemiology across two decades: a single center cohort study

1878 subjects with HBV chronic infection were observed from 2000 to 2019
1589 (88.4%) HBV had mono-infection and **209 coinfection**:
101 (5.6%) anti-HDV; 72 (4.0%) anti-HCV; 25 (1.4%) anti-HDV/anti-HCV; 11 (0.6%) anti-HIV positive

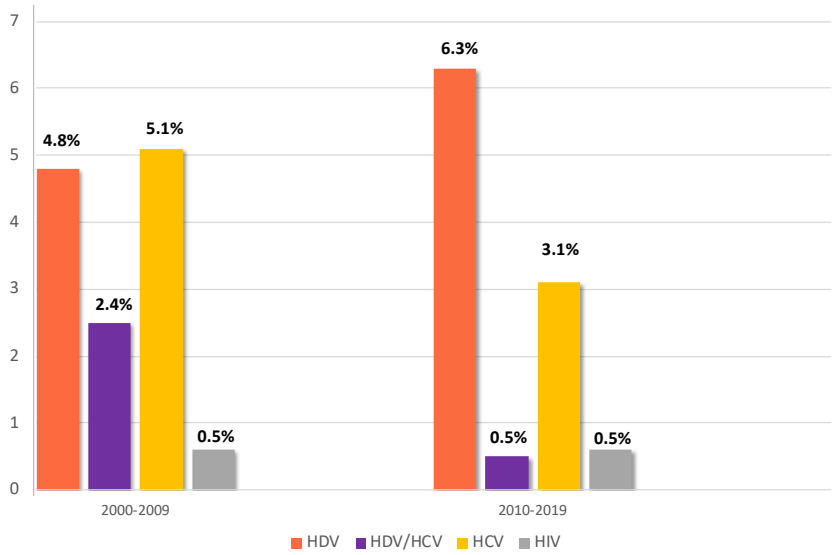


The co-infection prevalence differed across the decades and by origin

Ricco G , Dig Liver Disease 2022

HDV coinfection over a 20 year observation period

1798 chronic HBsAg positive individuals (828 first decade, 970 second decade)



- 126 (**7%**) patients were **anti-HDV positive**, of whom 25 were also anti-HCV positive.
- **46.8%** of the **HBV/HDV** coinfected patients were **non-Italian natives,** their **prevalence** increased significantly in the second decade, from **31.7% to 60.6% (**P=0.002)
- **Non-Italian natives** were **younger** (34.6 vs 50.8 years, P<0.001) and with a **higher prevalence of female gender** (49.2% vs 26.9%, P=0.017)
- **13.5%** of anti-HDV patients were **HDV-RNA negative** (35.3% previous or ongoing IFN treatment).
- **76.1%** and **71.2% of Italian** and **non-Italian** HBV/HDV coinfected patients **had cirrhosis** (P=0.671).
- **Non-Italian** HBV/HDV **cirrhotic** patients were **younger** than Italian HBV/HDV cirrhotics [37.8 *vs* 51.8 years (P<0.001)].
- **HCC** at admission was present in Italian natives only

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- The **combined effect** of **vaccination policies** and increasing **flows of immigrants** from HBV highly endemic areas were responsible for the highly dynamic changes of HBV epidemiology in Italy
- Non Italian native HBsAg carriers significantly increased across the last decades
- **Antiviral therapy mitigated** the long lasting infections in **aging Italians with CHB,** as suggested by the stable/slight reduction of cirrhotic patients in the last decade in spite of the older age of the patients

- **CHD** is the **most severe form of viral he**patitis with an estimaded **risk of cirrhosis** and **HCC development 3** and **2 fold increased** as compared to chronic **hepatitis B** and **C**
- Currently Italian epidemiological data suggest that there are **2 distinct subsets of CHD patients**: *older Italian patients* with long lasting history of HDV infection with an indolent, but still **slowly progressive course**, and *younger immigrants* with **active and rapidly progressive disease**

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Comitato Esecutivo e i centri partecipanti disponibili in:
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INNOVATIVE MODEL OF
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