Challenges in warranting access to prophylaxis and therapy for hepatitis B virus infection

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Status quo
HBV infection

Chronic hepatitis B virus infection

- remains a major global health burden
- is one of the top 20 causes of mortality worldwide[1]

HBV-related end stage liver disease and hepatocellular carcinoma (HCC)

- cause up to 1 million death per year
- are responsible for up to 10% of liver transplantations[2]

1 Global Burden of Disease Study 2013. *Lancet*. 2015, 385:117-171.
2 Fattovich et al. *Gastroenterology*. 2004;127(5 Suppl 1):S35-S50.

Status quo
HBV infection

Worldwide more than 240 million people suffer from chronic HBV infection

- only estimated 10% are diagnosed and estimated 1% actually treated

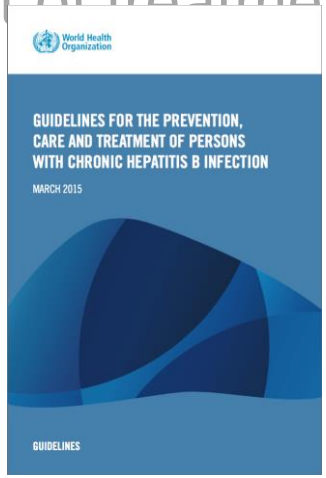
- Prevalence unchanged in the last decade despite vaccination and effective treatment options available

WHO Global Hepatitis Report 2017
Debarry et al. Liv Int 2017

Challenges differ by ressources and prevalence of infection

Low- middle income countries

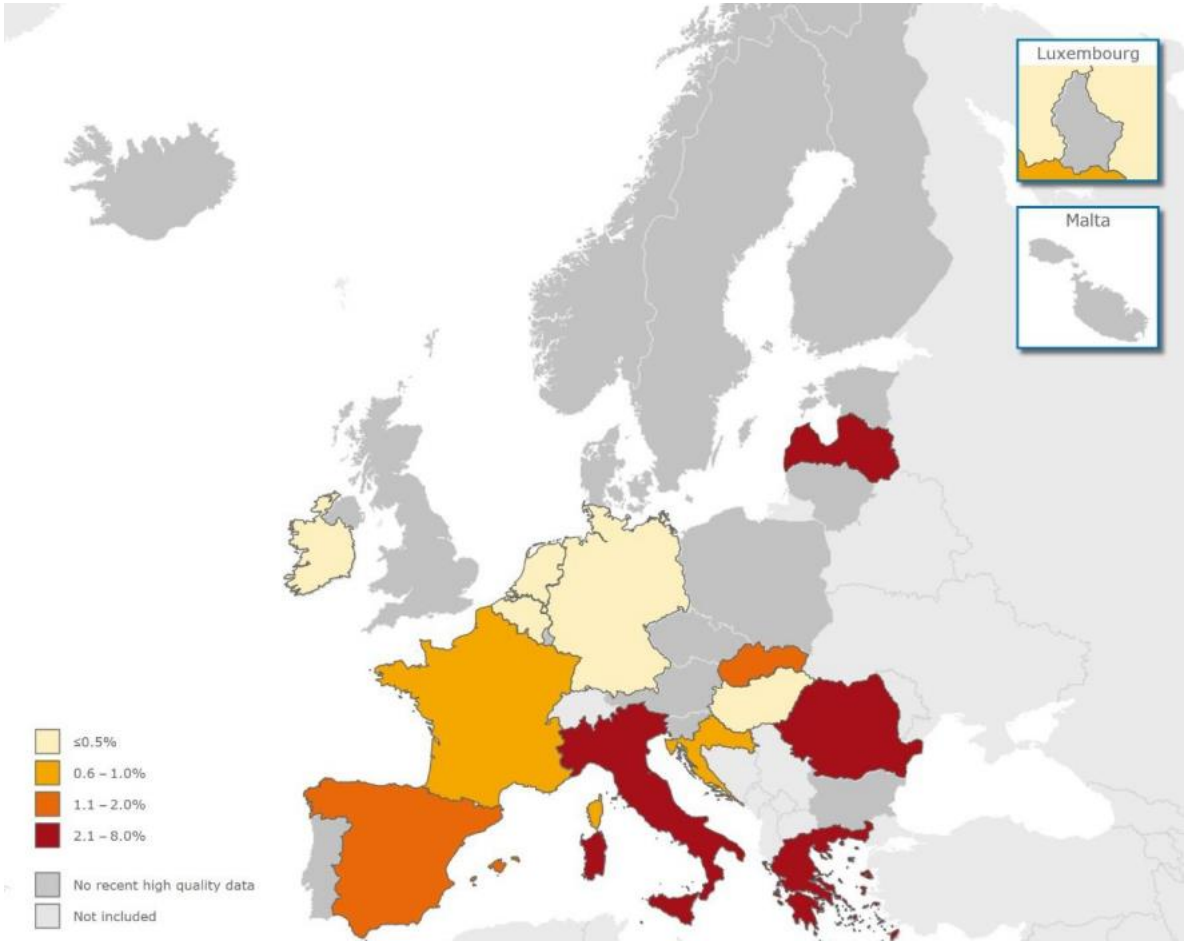
- High prevalence
- Lack of availability of treatment
- Cost of treatment



Middle – high income countries

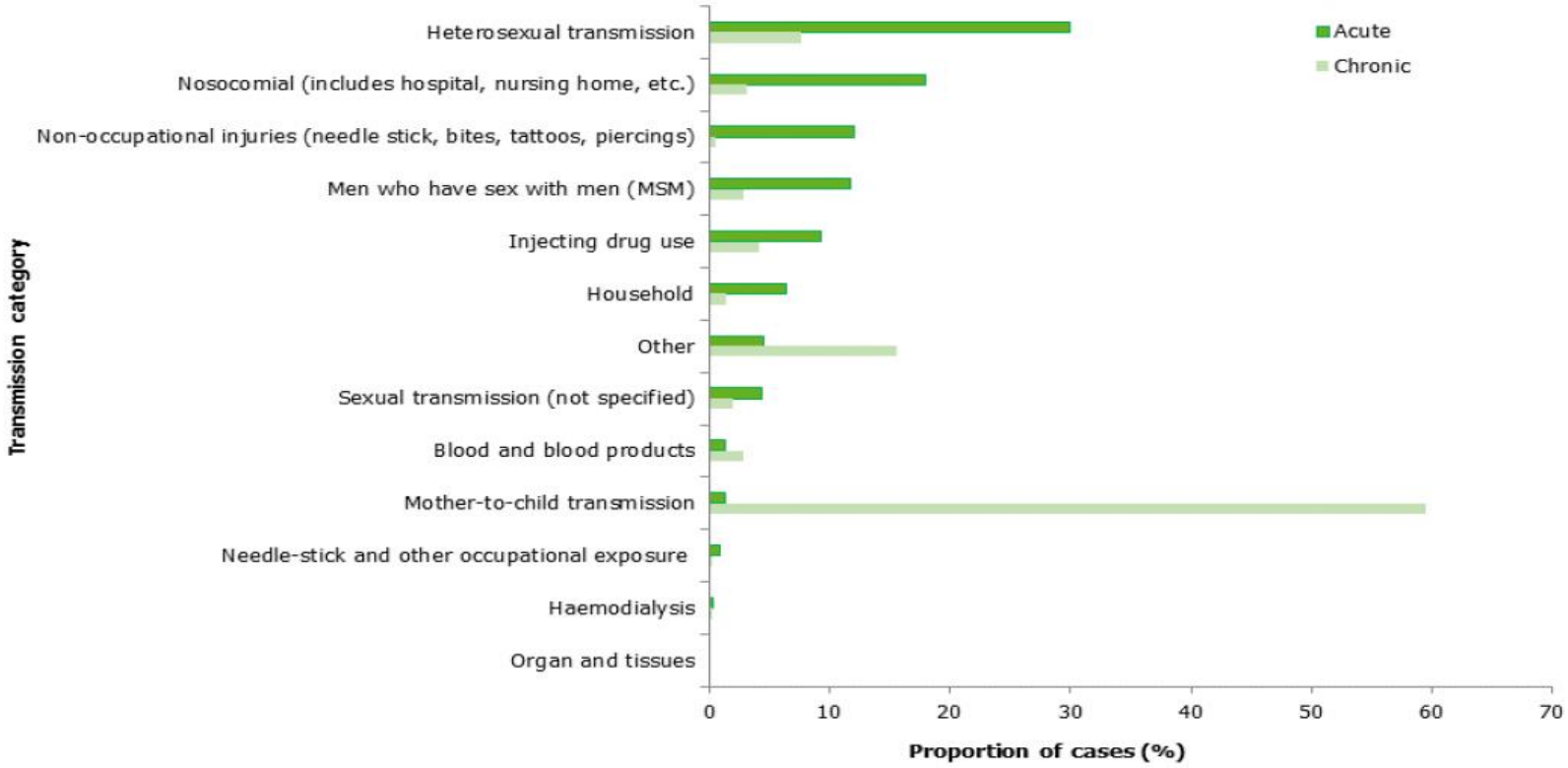
- Low prevalence
- Low screening rates
- Lack of awareness
- Social stigma
- discrimination

HBV distribution in EU/EEA



About 5 million chronically infected patients, prevalence about 0.9%

Routes of infection in EU/EEA



Source: Country reports from Austria, Denmark, Estonia, Finland, France, Germany, Hungary, Ireland, Italy, Latvia, Lithuania, Malta, the Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Sweden, and the United Kingdom**.
* Among cases where transmission status is known
** UK data exclude Scotland

The most affected age group for both acute and chronic infections was the group of 25–34 year olds accounting for 33.8% of cases

Prevention of HBV

Awareness and Prevention

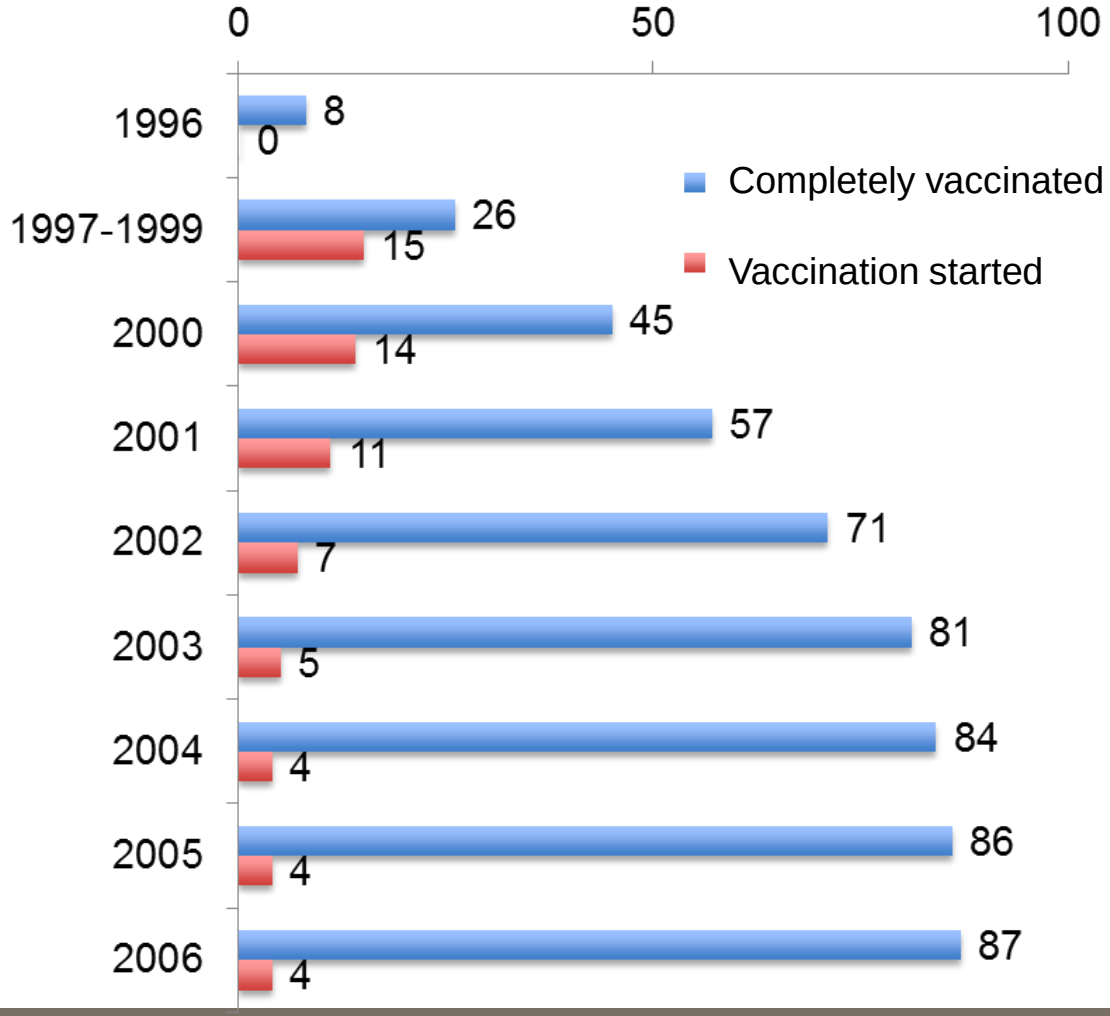
HBV vaccine

- available since the 1980' *
- universal infant vaccination reduces HBV[1]

***in Germany since 1995**

1 Chang et al. *N Engl J Med.* 1997;336:1855-1859.

Percentage (%) of children vaccinated against HBV when entering school



Access to vaccination and treatment in intermediate- to low-prevalence regions (example Germany)

Access to vaccination

Tabelle 1: Impfkalender (Standardimpfungen) für Säuglinge, Kinder, Jugendliche und Erwachsene

Recommendation for vaccination

age in months

age in years

Impfung	Alter in Wochen											
	6	2	3	4	11–14	15–23	2–4	5–6	9–14	15–17	ab 18	ab 60
Tetanus		G1	G2	G3	G4	N	N	A1	A2		A (ggf. N) [e]	
Diphtherie		G1	G2	G3	G4	N	N	A1	A2		A (ggf. N) [e]	
Pertussis		G1	G2	G3	G4	N	N	A1	A2		A (ggf. N) [e]	
Hib *H. influenzae* Typ b		G1	G2 [c]	G3	G4	N	N					
Poliomyelitis		G1	G2 [c]	G3	G4	N	N		A1		ggf. N	
Hepatitis B		G1	G2 [c]	G3	G4	N	N					
Pneumokokken [a]		G1		G2	G3	N						S [g]
Rotaviren	G1 [b]	G2	(G3)									
Meningokokken C					G1 (ab 12 Monaten)		N					
Masern					G1	G2	N				S [f]	
Mumps, Röteln					G1	G2	N					
Varizellen					G1	G2	N					
Influenza												S (jährlich)
HPV Humane Papillomviren									G1 [d]	G2 [d]	N [d]	

Access to vaccination and treatment in intermediate- to low-prevalence regions (example Germany)

Access to vaccination

- Example Germany
  - **Refugees have a higher HBsAg prevalence** than the German population 2.3% vs. 0.7%
  - Especially in young age HBV **immunization status is poor** →„every vaccination counts“
  - Social welfare covers treatment only if life is being threatened → **new transmission dynamics have to be expected**
  - To **reach certain sub-populations** with higher prevalence but limited access to treatment, *e.g.* refugees, people without health insurance, people who inject drugs or abuse alcohol, **HBV management programs need to be adopted**[1,2]

Schweitzer et al. *Lancet.* 2015; 386(10003):1546-55 | 2 Chu et al. *Eur J Public Health* 2013; 23: 642-647, Burgazli et al. *Eur Rev Med Pharmacol Sci* 2014 | Heidrich et al. *Eur J Gastroenterol Hepatol*. 2014 Hampel et al. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz.* 2016;59:578-583. Falla et al. *Eur J Public Health*. 2016; DOI 10.1093/eurpub/ckw100

Access to vaccination and treatment in special populations: pregnant woman

Proposed scenario

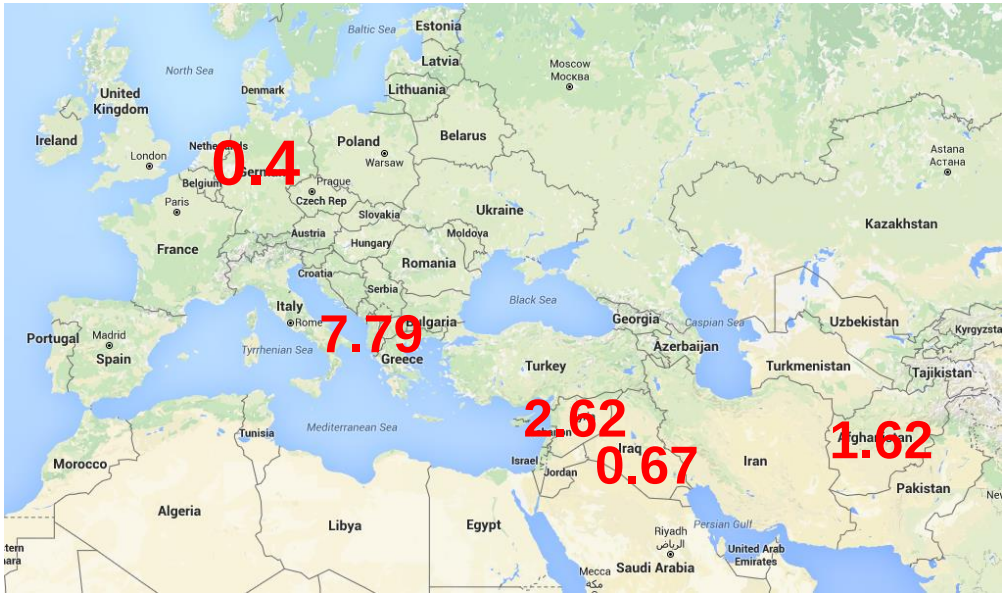
- Screening of pregnant woman in the first trimester
- starting antiviral therapy at 28-32 weeks of gestation if HBV DNA is above 200,000 IU/mL
- Vaccination at birth

In **high-income countries time-point of screening will need to be adapted**, *e.g.* in Germany mothers are currently screened only in week 32 of gestation.

Awareness of clusters

Surveillance

- Example Germany



In Germany: 19% history of migration

Top 3 countries of origin

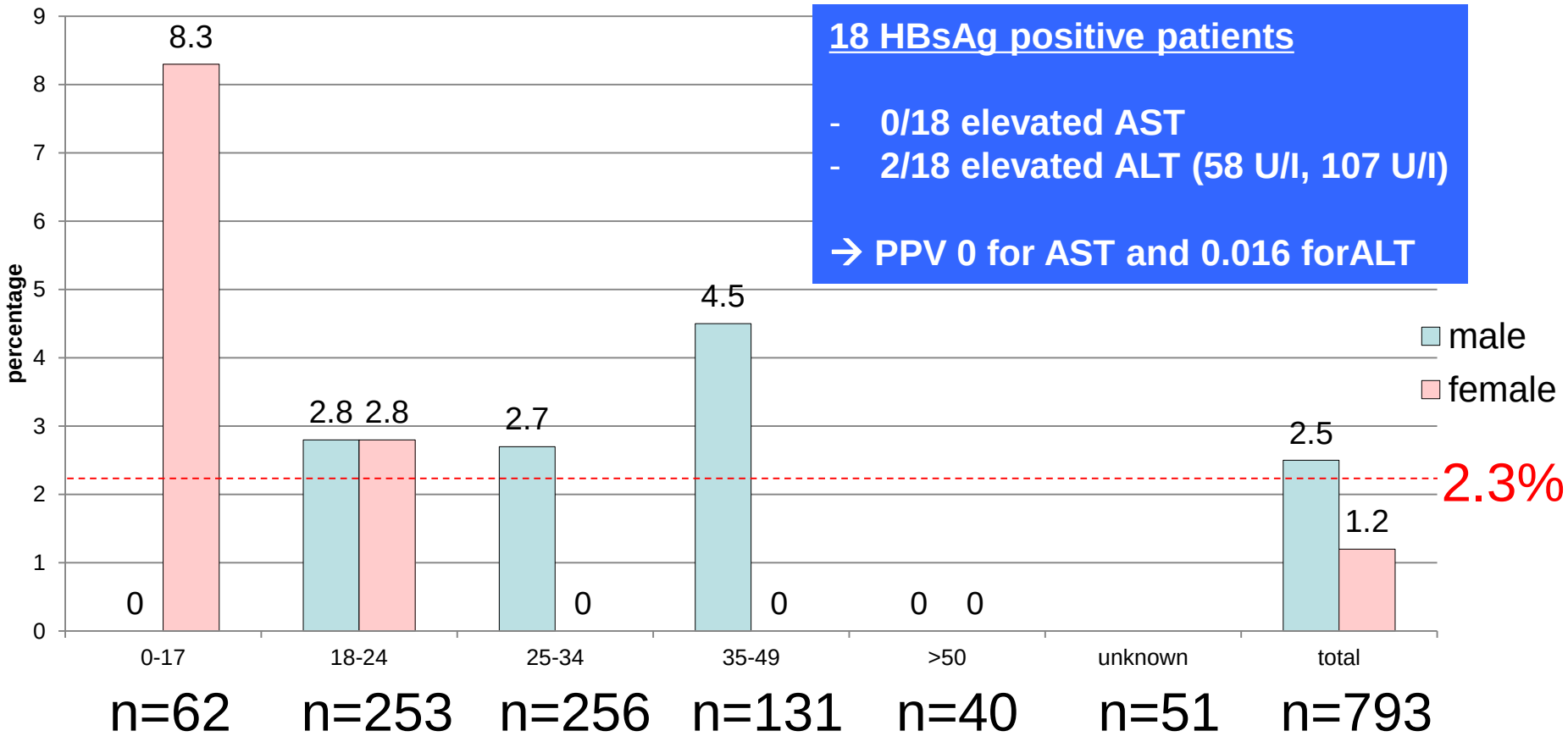
1. Turkey	HBsAg: **4.0%**
2. Italy	HBsAg: **2.52%**
3. Former Yugoslavia	HBsAg: **0.48%**

increased HBsAg seroprevalence among immigrants

1 Schweitzer et al. *Lancet.* 2015; 386(10003):1546-55 | 2 Chu et al. *Eur J Public Health* 2013; 23: 642-647
3 Burgazli et al. *Eur Rev Med Pharmacol Sci* 2014 | 4 Heidrich et al. *Eur J Gastroenterol Hepatol*. 2014
5 Hampel et al. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz.* 2016;59:578-583.

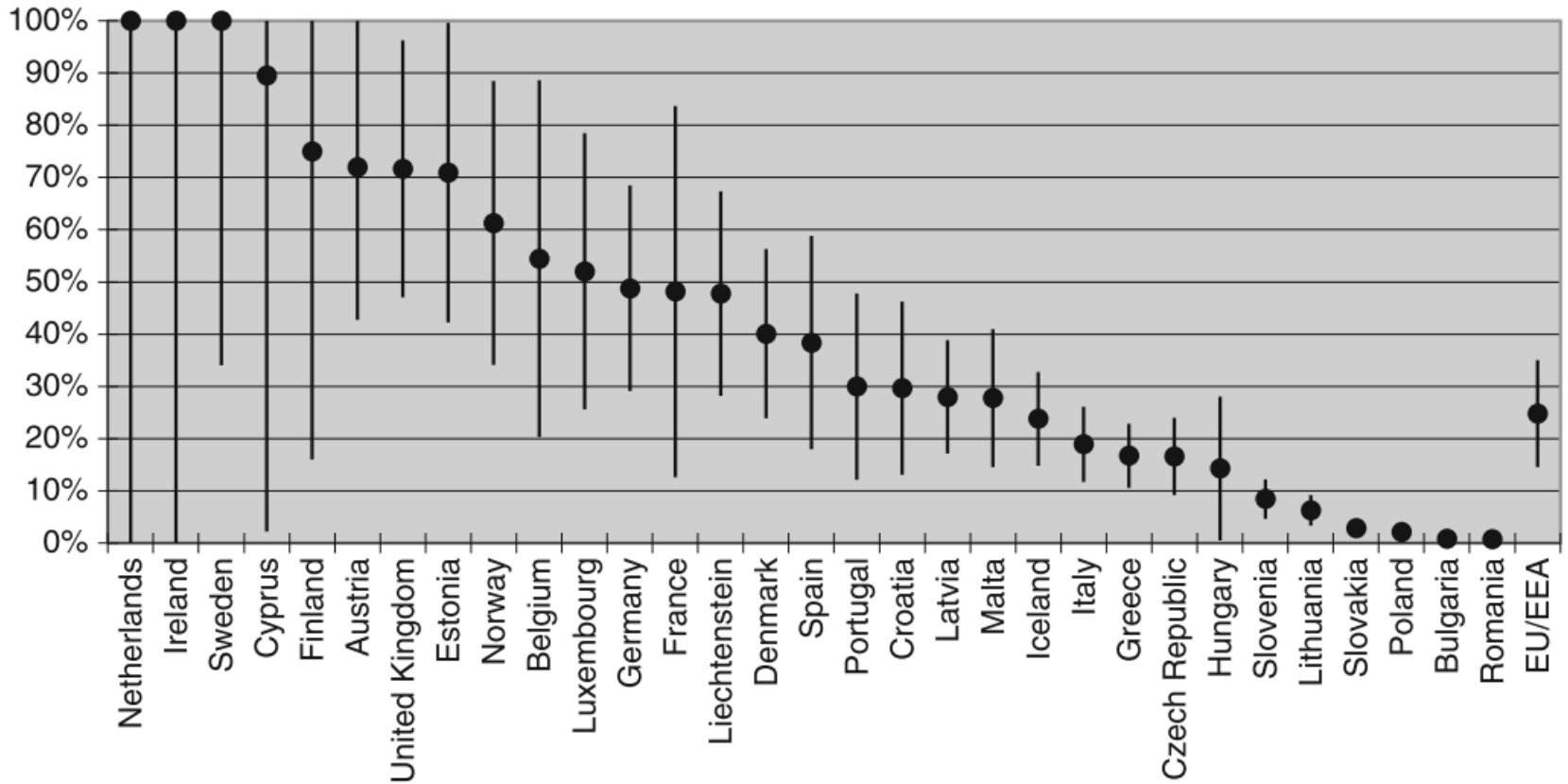
HBsAg prevalence in refuges

2.3% (18/793)



Hampel, Solbach, Cornberg et al., Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2016 May;59(5):578-83.

Relative contribution of migrants to the total number of CHB cases per EU/EEA country



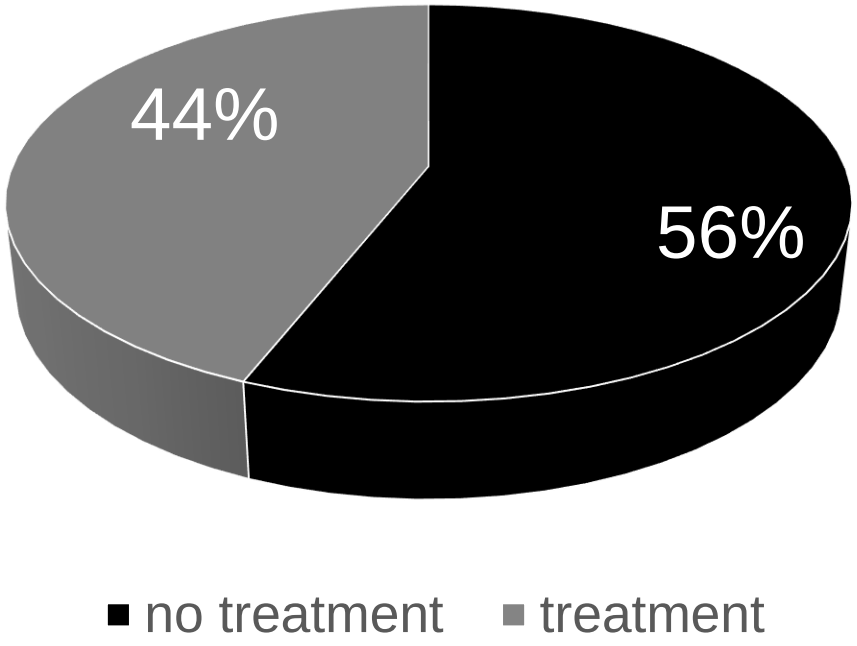
Access to vaccination and treatment in intermediate- to low-prevalence regions (example Europe)

Surveillance

- Surveillance data will help **adjusting national programs** to respond **to new dynamics of HBV infections** (*e.g.* HBV genotype, HBeAg status, mode of transmission)
- **Pointed analysis of HBV endemicity** needed as general picture of low endemicity may **mask local clusters of high endemicity and infection**

1 Schweitzer et al. *Lancet.* 2015;386:1546-1555.

Antiviral treatment of treatment-eligible patients



Meta analysis of 13 studies (6 US, 7 non-US) including 31342 patients

Lack of awareness in clinical practice (Example: Germany)

Clinicans, GPs:

Elevated ALT = alcohol abuse

Normal ALT = no need to screen for viral hepatitis

Vu et al. BMJ Open Gastroenterol. 2015;2:e000060.
Wolfram et al. J Hepatol. 2015;62:1256–1264.

Lack of awareness in clinical practice (Example: Chinese population in England)

Clinicans, GPs:

" I am not sure that any GP is going to have a **sufficient population** of Chinese to know that this is a major risk factor …"

"I'm hoping that there will be **more ethnic training**"

" put down some **hepatitis B results** in front of any of us … I suspect we would probably have to go and **have a little read** on the internet or in the books."

"Because most of us trained more than **ten years ago**, there's a perception that well there' s no point in treating hepatitis."

Lack of awareness in clinical practice (Example: Chinese population in England)

Patients:

" [We] really **know nothing** about this (disease). "

" **What' s the point** of taking all the blood tests, and (getting) no treatment? "

" …HBV is easily transmitted through social contacts, so HBV carriers are … a public nuisance… are expected to …. **keep their distance** "

What if other people see me going into a sexual health clinic (for a hepatitis B test)? **What will they think about me?**

Lack of awareness in clinical practice (Example: Chinese population in England)

Community:

"The community takes on … new entrants and support them in a way that means **they are not as visible"**

"So if there ' s a **different language** (involved) you know you definitely have to make sure that what you' ve said is being understood."

"Maybe they have **no understanding of** the NHS **system**. Maybe they are new to this country."

" Well I do believe we need the help from the (Chinese) population to push their own cause ….. Then it is more **difficult to argue against** I think. "

Access to vaccination and treatment in intermediate- to low-prevalence regions (example Europe)

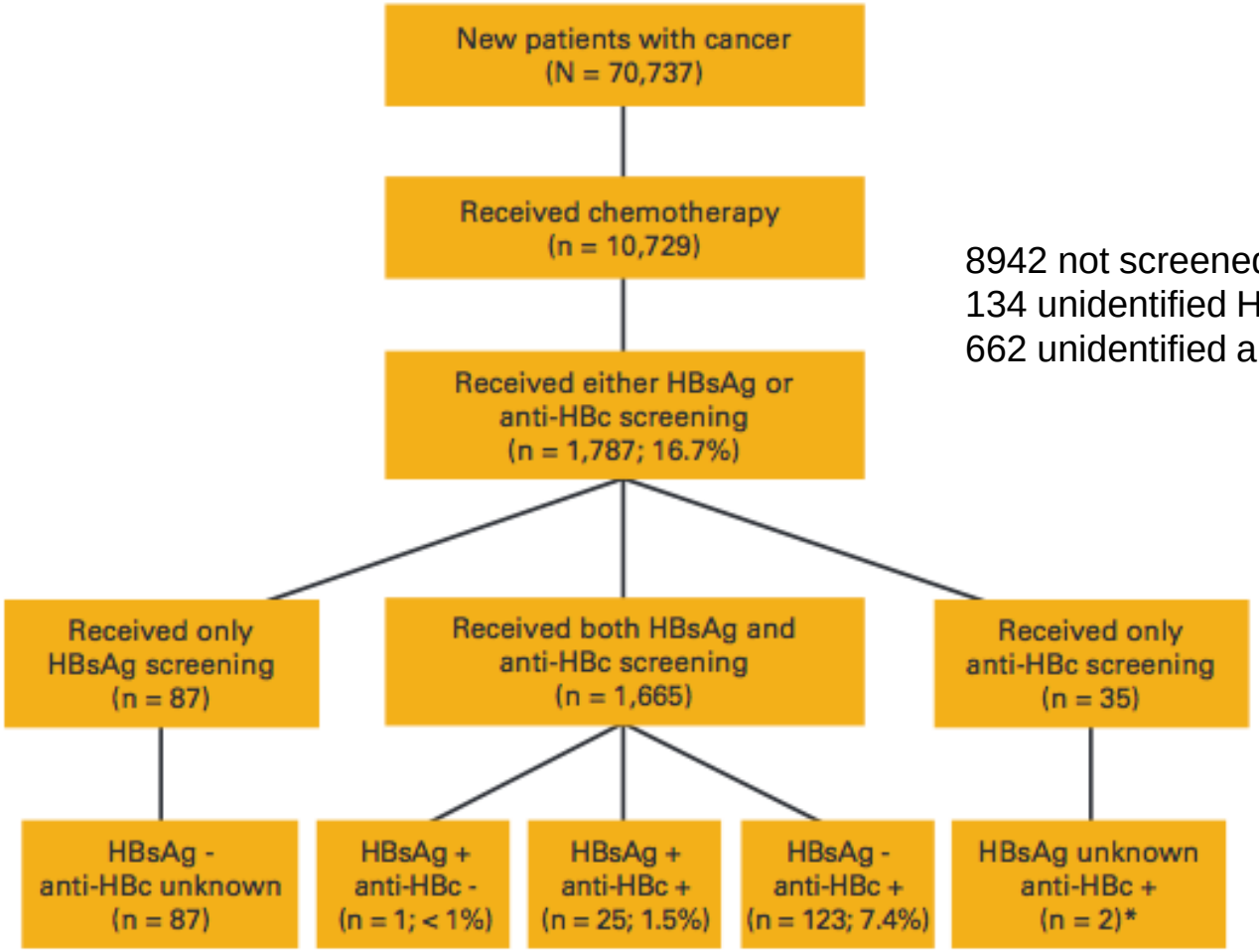
Treatment

- **awareness campaigns** will help to **reduce barriers to access** in many western countries
  - due to **lack of awareness, social stigma and discrimination**
  - due to **suboptimal transition from diagnosis to care** by lack of evidence-based knowledge of HBV preventing appropriate patient management[1]

- → **invests will be needed to increase proportion of HBV-infected individuals that receive treatment**[2]

1 Vu et al. *BMJ Open Gastroenterol*. 2015;2:e000060.
2 Papatheodoridis et al. *J Viral Hepat.* 2016;23(Suppl 1):1-12-

Low rates of hepatitis B virus screening at the onset of chemotherapy.



8942 not screened:
134 unidentified HBsAg positive (1.5%)?
662 unidentified anti-HBc positive (7.4%)?

Access to vaccination and treatment in special populations: patients with immunosuppressive therapy

HBsAg pos and HBsAg neg, anti HBc positive patients undergoing **immunosuppressive therapy** are at high risk

- of **HBV reactivation**
- and subsequent **liver failure and death**[1]

Prophylactic antiviral therapy is highly effective and current guidelines recommend screening everyone undergoing immunosuppressive treatment[2], **BUT**

- screening rate is low, even among specialists[3-5]

→ **NEEDED:** efforts to improve screening and treatment as mortality to HBV reactivation can be prevented.

1 EASL clinical practice guidelines. *J Hepatol*. 2012;57:167-185. | 2 Weinbaum et al. *MMWR Recomm Rep.* 2008;57:1-20.
3 Leonard et al. *Ann Hematol.* 2016;95:27-33. | 4 Paul et al. *Dig Dis Sci.* 2016;61:2236-2241.
5 Hwang et al. *J Viral Hepat.* 2015;22:346-352.

Conclusion – an invisible disease in an invisible population

Policymakers
- Understand the medical need and the consequences of untreated infection
- Clarify roles and responsibilities for special populations (migrants, IV drug users, prisoners,……)
- Recognise community diversity and tailor responses to local needs and context
- Ensure adequate ressources for prevention, screening, surveillance and treatment measures
- Look to make services sustainable and accessible
- Explore collaboration with other agencies and the voluntary sector

Community-level
- Improve knowledge and awareness of the disease in at-risk groups (consequences of untreated infection)
- Raise awareness of the asymptomatic nature of disease
- Tackle misperceptions
- Provide health system navigators and clarify entitlements to health services
- Integrate family to influence testing and longer term compliance

Healthcare practitioners and services
- Improve healthcare practitioners ’ knowledge of the disease, and raise their awareness of risk groups
- Provide language support
- Make greater use of informational aids and tools such as patient alerts in electronic health records

Lee et al. BMC Public Health (2017) 17:747,
Debarry et al. Liv Int 2017,
Subic et al. Liv Int 2018