How to improve access to therapy for HBV patients

Michael Manns

Dept. of Gastroenterology, Hepatology and Endocrinology, Medical School Hannover, Germany

Helmholtz Center for Infection Research (HZI), Braunschweig, Germany

Hannover Medical School

10th Paris Hepatology Conference, 31 January 2017

How to improve access to management (prophylaxis and therapy) for HBV patients

Michael Manns

Dept. of Gastroenterology, Hepatology and Endocrinology, Medical School Hannover, Germany

Helmholtz Center for Infection Research (HZI), Braunschweig, Germany

Hannover Medical School

10th Paris Hepatology Conference, 31 January 2017

Conflict of interest

Michael Manns has received financial compensation for consultancy and/or lecture activities from Abbvie, Boehringer Ingelheim, Bristol Myers Squibb, Idenix, Gilead, GlaxoSmithKline, Janssen Therapeutics, Merck, Novartis, Roche and research grants from Abbvie, Boehringer Ingelheim, Bristol Myers Squibb, Gilead, Janssen Therapeutics, Merck, Novartis and Roche.

Acknowledgements

- Jennifer Debarry, Hannover
- Markus Cornberg, Hannover

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

Status quo
Management of HBV

Management of HBV requires

1. Awareness and Prevention
2. Surveillance
3. Screening
4. Detection and Diagnosis
5. Treatment

Status quo
Management of HBV

Awareness and Prevention

HBV vaccine

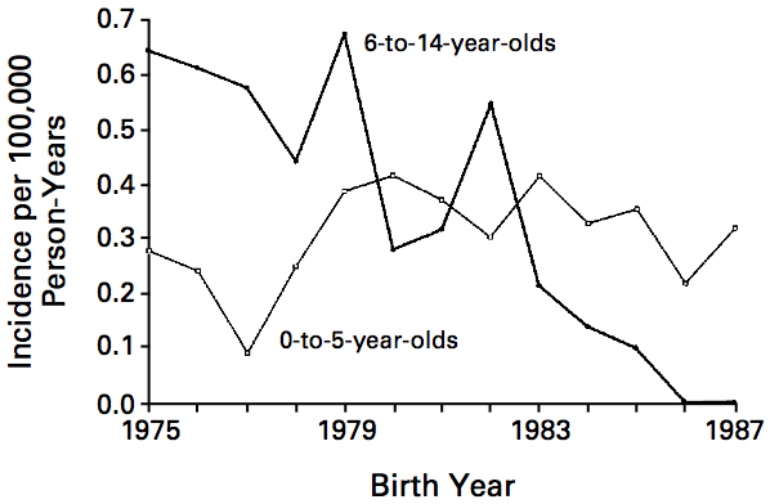
- available since the 1980’
- universal infant vaccination reduces HBV1

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

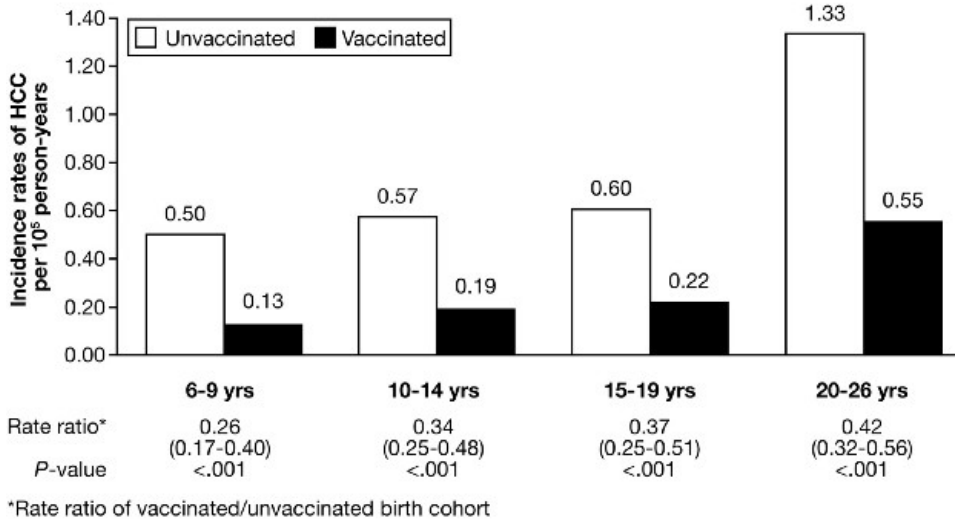
HBV vaccine reduced the incidence of HCC

HBV vaccination program was launched in Taiwan in July 1984

Comparison of the incidence of liver cancer in children 6 to 14 and 0 to 5 years of age, According to birth cohort.
Analysis 1997



Comparison of the incidence rates of liver cancer by age for birth cohorts born before vs after the start of the universal HBV vaccination program.
Analysis 2016



Chang MH et al., N Engl J Med. 1997 Jun 26;336(26):1855-9.
Chang MH et al., Gastroenterology. 2016 Sep;151(3):472-480

Status quo
Management of HBV

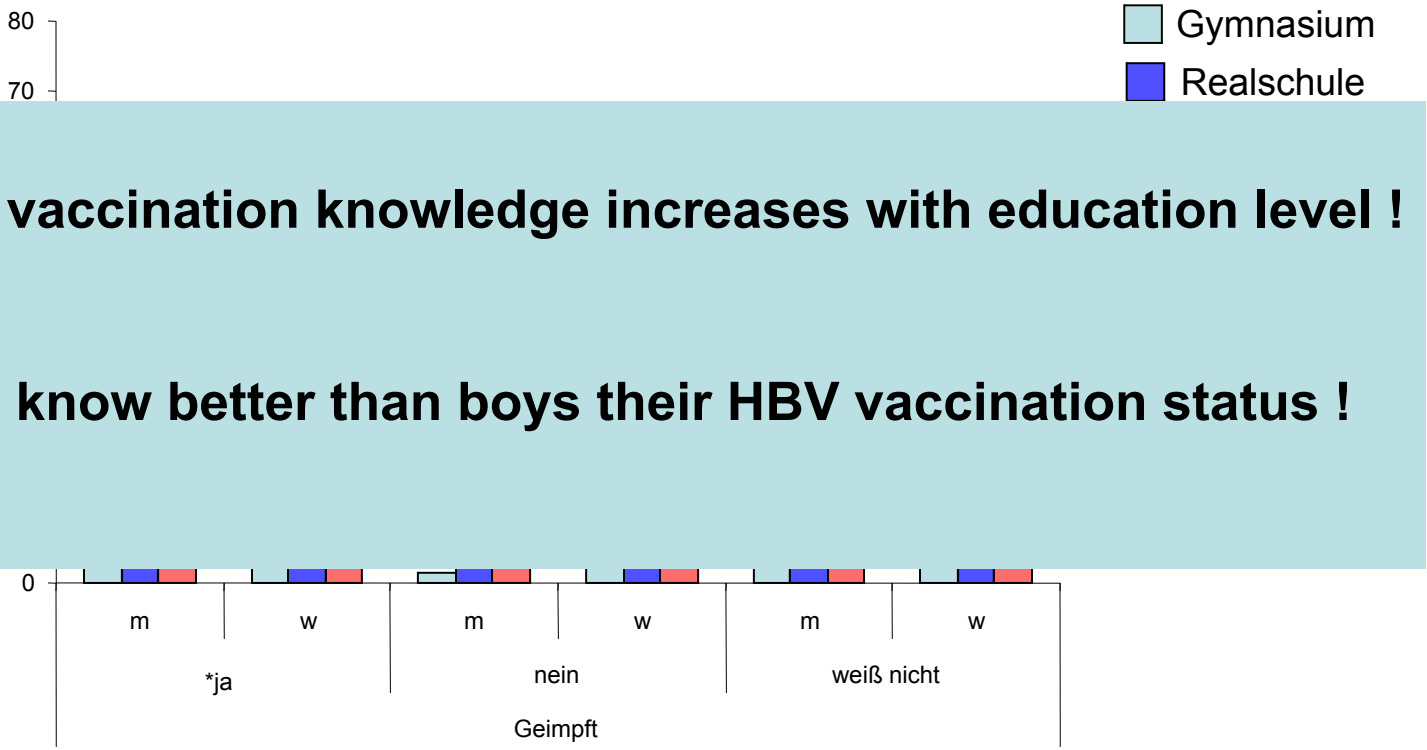
Awareness and Prevention

HBV vaccine

- available since the 1980' *
- universal infant vaccination reduces HBV1

***in Germany since 1995**

Answer of pupils to the question: „Have you been vaccinated against hepatitis B ?“



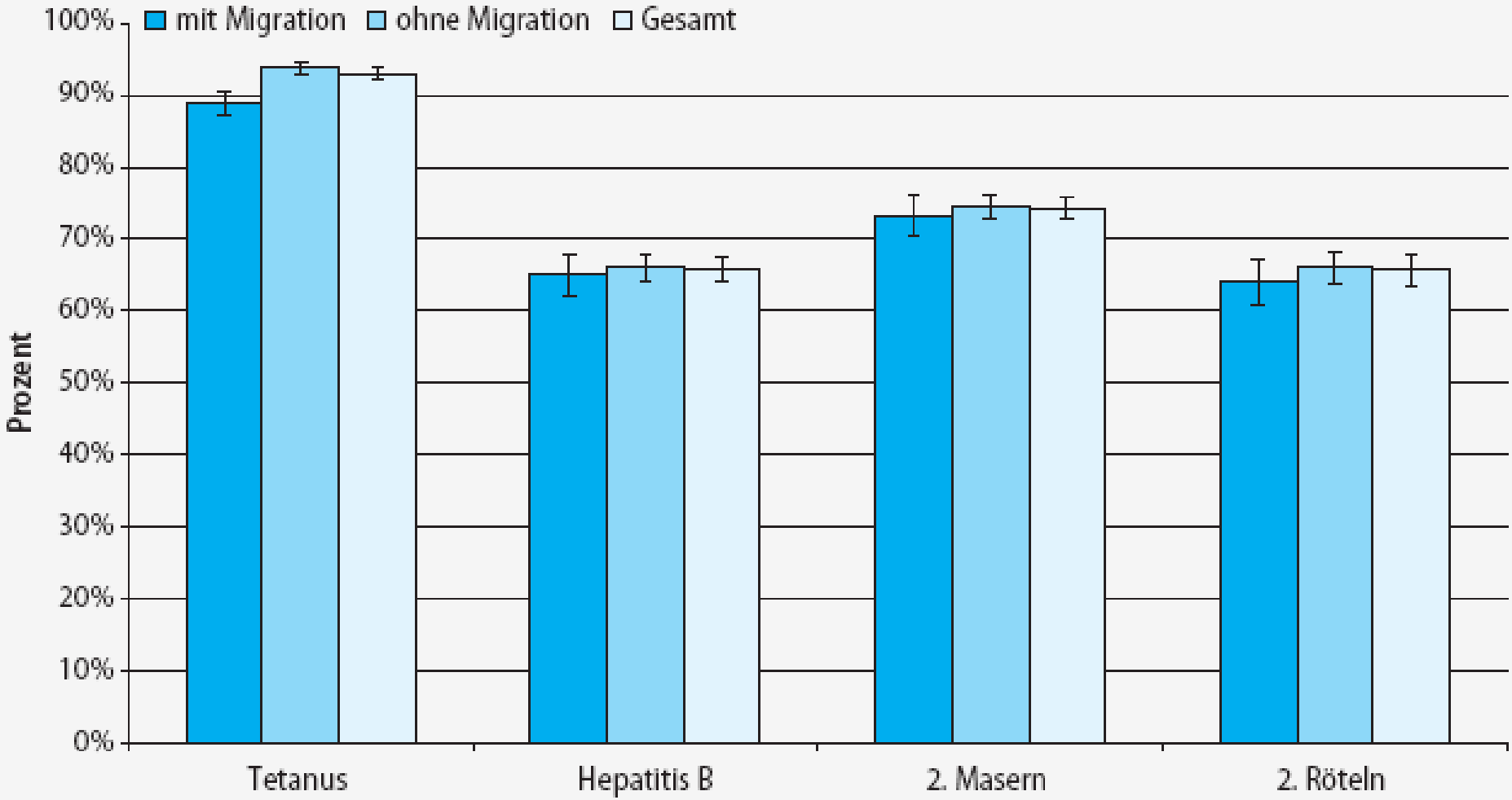
HBV vaccination knowledge increases with education level !

Girls know better than boys their HBV vaccination status !

Mädchen kannten ihren Impfstatus signifikant häufiger als Jungen ($p<0.001$).
*Der Unterschiede zwischen Hautschülern und Gymnasiasten/Realschülern war hoch signifikant ($p<0.001$)

Proportion of children vaccinated

according to KiGGS (2003 – 2006)



Status quo
Management of HBV

Awareness and Prevention

HBV vaccine

- available since the 1980'
- universal infant vaccination reduces HBV1

Treatment

HBV treatment options include

- alpha interferons
- nucleoside and nucleotide analogues

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

High virological response and low viral resistence in long term use of ETV or TDF

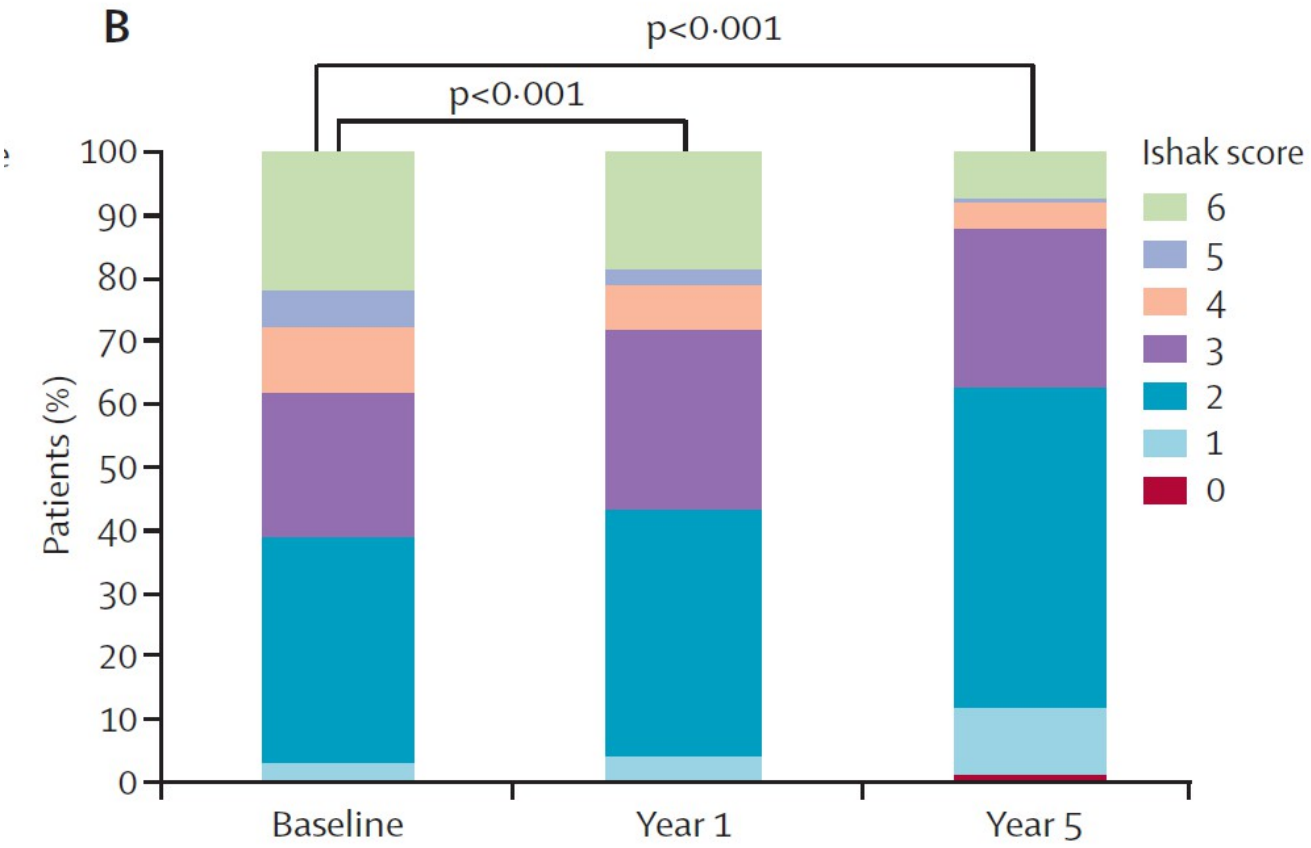
Response	ETV		TDF	
	HBeAg+ Patients Year 51	HBeAg- Patients Year 32,a	HBeAg+ Patients Year 63	HBeAg- Patients Year 63
HBV DNA undetectableb	**94%** (88/94)	**95%** (54/57)	**99%** (167/169)	**99.6%** (283/284)
Resistance	**1% (n=1)**	NR	**0%**	**0%**

aETV re-treatment (relapsed <6 months post-treatment in ETV-027 study)
bTDF: HBV DNA <400 copies/mL; ETV HBV DNA <300 copies/mL

1Chang TT et al. Hepatology 2010;51:422–430; 2Shouval D et al. Hepatology 2008; Abstract 927;
3Marcellin P et al. AASLD 2012; Abstract 374.

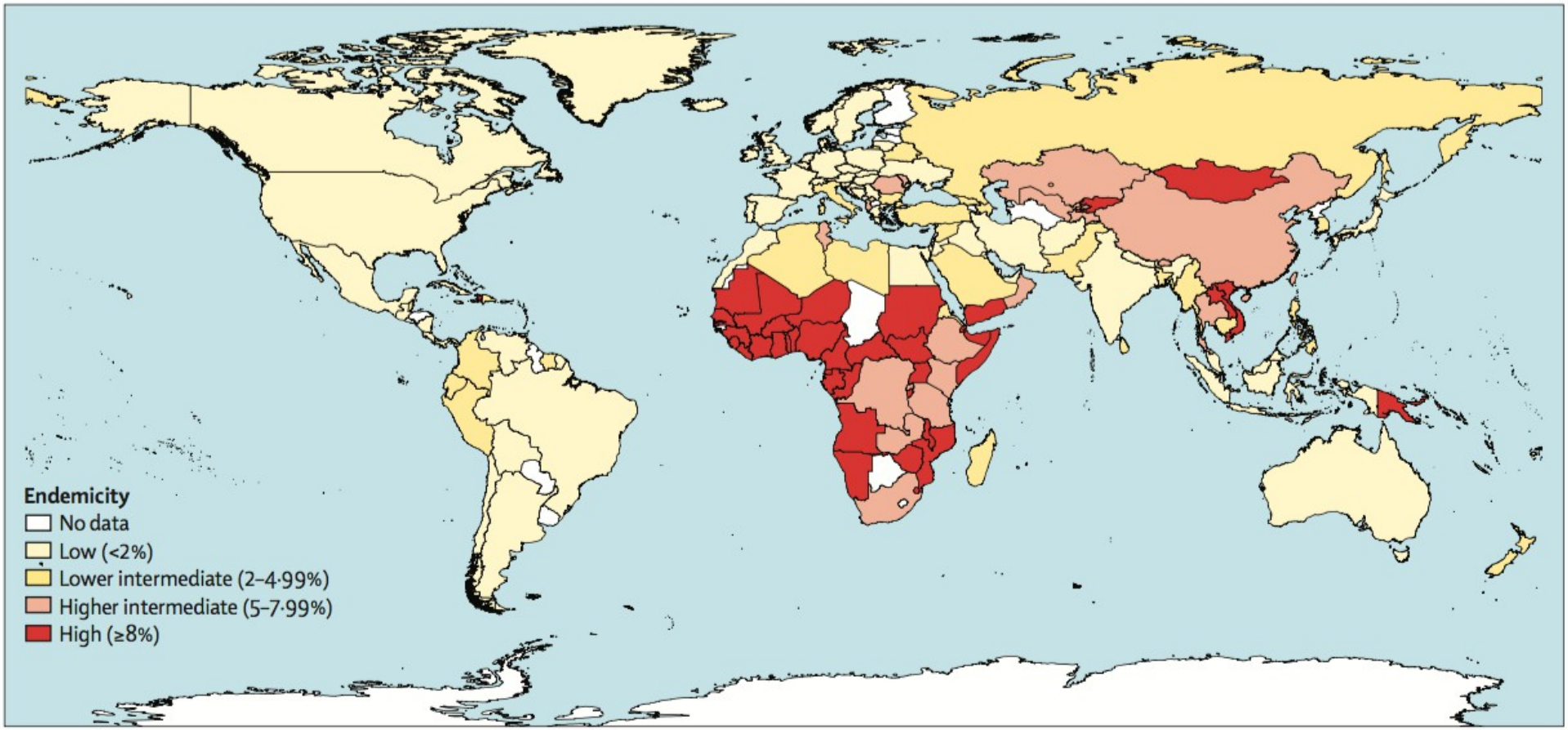
Improvement of histology after 5 years of **Tenofovir** therapy

Marcellin et al., Lancet 2013; 381: 468-75



Status quo
Prevalence of HBV

Endemicity levels (HBsAg positive patients) varies widely



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

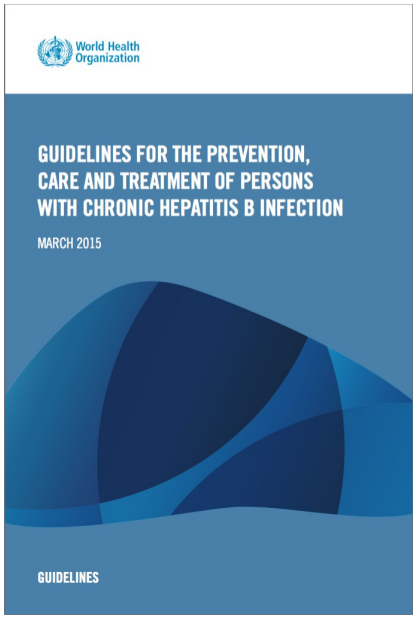
Access to vaccination and treatment in high-prevalence regions

Highly-prevalent regions are mostly developing countries with low- to middle - income.

- cost and allocation of resources is a major issue

→ **NEEDED:** development of national policies and country-specific guidelines to scale-up prevention, care and treatment of hepatitis B

WHO released guidelines targeting especially those resource-poor settings.



Access to vaccination and treatment in high-prevalence regions

1 Awareness and Prevention

- **awareness campaign** can help reducing the risk of in-hospital infection

Use of non-sterile equipment needs to be eliminated

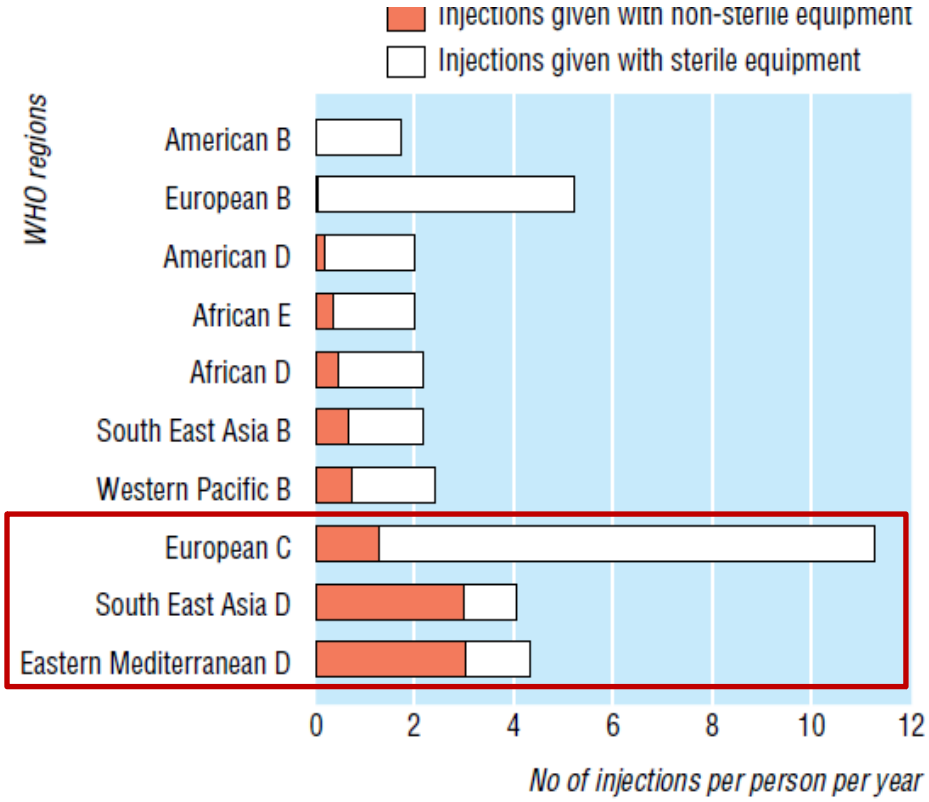


Fig 2 Number of injections per person and per year and proportion of these administered with injection equipment reused in the absence of sterilisation, by region, 2000

Fig 1 Injection equipment soaked in tepid water before reuse in the absence of sterilisation, Africa, 2000. Note the plastic syringes rinsed in the tepid water and the multidose medication vials

Hutin YJ, Hauri AM, Armstrong GL. Use of injections in healthcare settings worldwide, 2000: literature review and regional estimates. BMJ 2003;327:1075.

Access to vaccination and treatment in high-prevalence regions

1 Awareness and Prevention

- **awareness campaign** can help reducing the risk of in-hospital infection
- **vaccination** of all **health-care workers** has to be priority
- **vaccination** of all **infants within 24 hours of birth** should be implemented to reduce perinatal HBV transmission
- **safety of blood and blood products** is crucial to lower the risk of iatrogenic transmission but requires better and affordable assays

The blood supply in low and middle income countries needs to be safe

- 25 countries still report collecting paid donations in 2012
- In low income countries, 65% of blood transfusion are given to children under 5 years of age
- In high income countries, 76% of all blood transfusions are given to adults older than 65 years old
- 25 countries are not able to screen all donated blood for HIV, HBV or HCV

	HIV	HBV	HCV
High-income countries	0.002%	0.02%	0.02%
	(0.0004%-0.02%)	(0.008% - 0.24%)	(0.004% - 0.22%)
Middle-income countries	0.12%	0.64%	0.37%
	(0.03% - 0.2%)	(0.19% - 2.33%)	(0.13% - 0.71%)
Low-income countries	0.85%	3.59%	1.07%
	(0.48% - 2.0%)	(2.01% - 6.08%)	(0.63% - 1.96%)

WHO Fact Sheet No 279, updated June 2014

Access to vaccination and treatment in high-prevalence regions

2 Surveillance

- **surveillance data** for hepatitis B will help **directing preventive measures** and **control their impact**

3 Screening

- scaling-up screening activities will help to **reduce disease burden by identifying asymptomatic carriers** spreading the disease
- **HBsAg positive mothers** to be identified, with high viral load **should be treated**

Access to vaccination and treatment in high-prevalence regions

4 Detection and Diagnosis

- alternative **diagnostic tests**, which are **more readily available and less expensive**, need to be established

5 Treatment

- is **limited** by **lack of available infrastructure** and **high costs**
- BUT recent **screen-and-treat programs** showed **feasibility** with an **acceptability rate of 60-80%** and **link to care of 40-80%**1

1 Lemoine et al. *Lancet Glob Health.* 2016;4:e559-e567.

Access to vaccination and treatment in high-prevalence regions

Key challenges	Key measures
Lack of knowledge and awareness	• Education of the public and targeted awareness campaign for high-risk groups
Safety of blood	• Implement policies on safety of blood and blood products
Limited screening and linkage to care	• Foster implementation of national policies on HBV screening • Easy-to-use and low-cost diagnostic assays • Point of care screening
Lack of vaccination	• Prioritized vaccination of high risk groups and healthcare workers • HBsAg testing in mothers to prioritize active (and ideally also passive) immunization of the newborn
Limited treatment	• Increase accessibility of drugs by innovative cost models

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

Prevalence in Europe is generally considered to be low to intermediate, BUT

- there are regional differences with prevalence increasing eastwards1
- studies indicate high prevalence in certain groups and communities2,3

→ **NEEDED:** development of national policies and programs that take into account the dynamics of HBV transmission and country-specific health-care policies

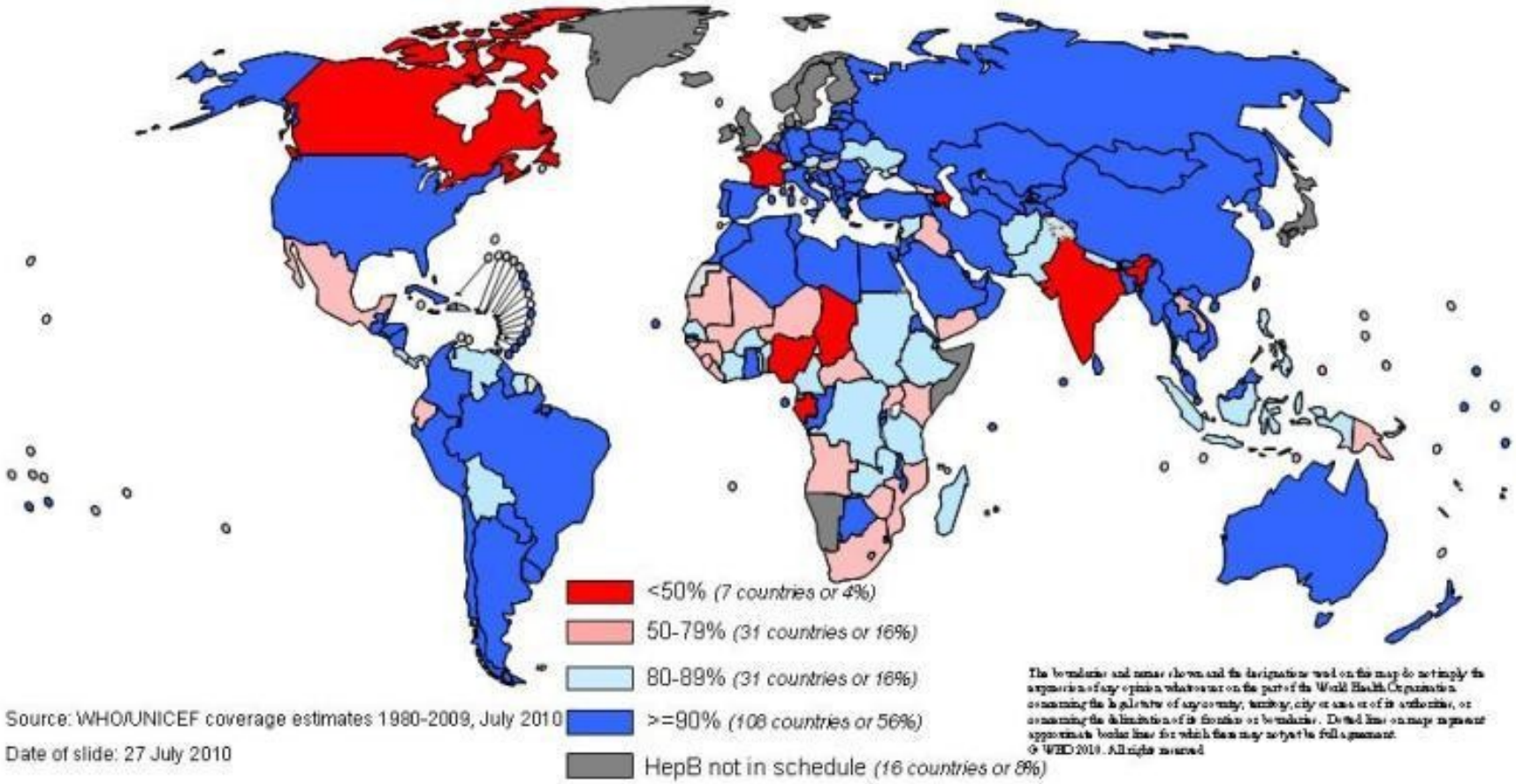
1 Schweitzer et al. *Lancet.* 2015;386:1546-1555.
2 Lavanchy, D. J Viral Hepatology 2004; 11 (2): 97-107
3 Falla et al. *Eur J Public Health*. 2016; DOI 10.1093/eurpub/ckw100

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

1 Awareness and Prevention

- **Awareness campaign** will help increasing prevention and treatment coverage as **prejudice against risk groups is a significant barrier** in many Western and European countries
- Adjustment of **national vaccination programs** is needed to **increase vaccination uniformity** and thereby hindering **spread of the disease**

Immunization coverage with 3rd dose of HepB vaccines in infants, 2009



Source: WHO/UNICEF coverage estimates 1980-2009, July 2010

Date of slide: 27 July 2010

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

2 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)
- Southern European countries have to expect an increase in HBV-related liver diseases as the **unvaccinated population comes of age**1
- **unmask local clusters of high endemicity and infection**

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

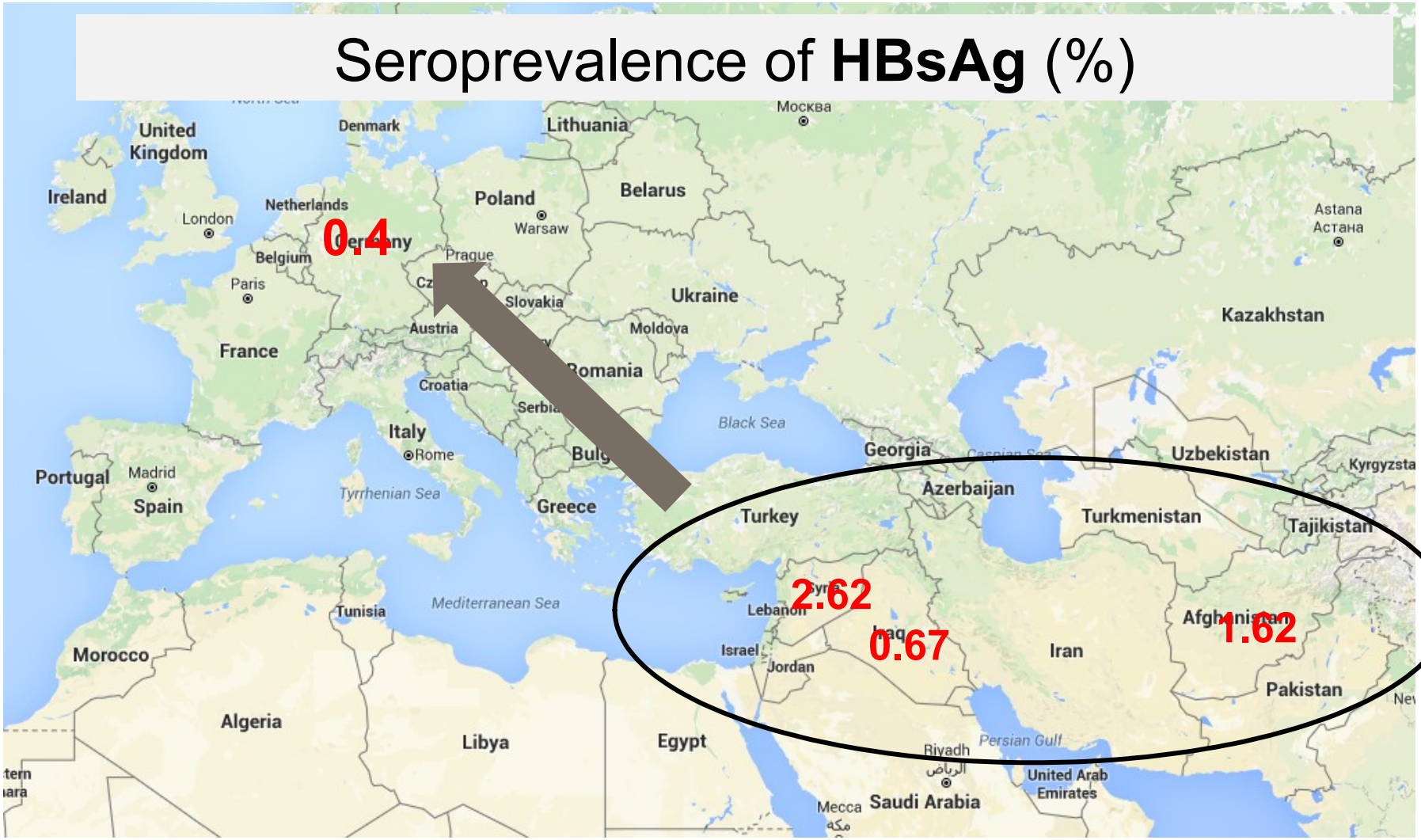
Access to vaccination and treatment in intermediate- to low-prevalence regions (example Europe)

3 Screening

- To **reach certain sub-populations** with higher prevalence but limited access to treatment, *e.g.* refugees, people without health insurance, people who inject drugs (PWID) or abuse alcohol, **HBV management programs need to be adopted**1,2
- Current **challenge in Europe** created by arrival of **large numbers of refugees**, prevalence must be evaluated in those populations and appropriate control strategies must be adopted

1 Falla et al. *Eur J Public Health*. 2016; DOI 10.1093/eurpub/ckw100
2 Hampel et al. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz*. 2016;59:578-583.

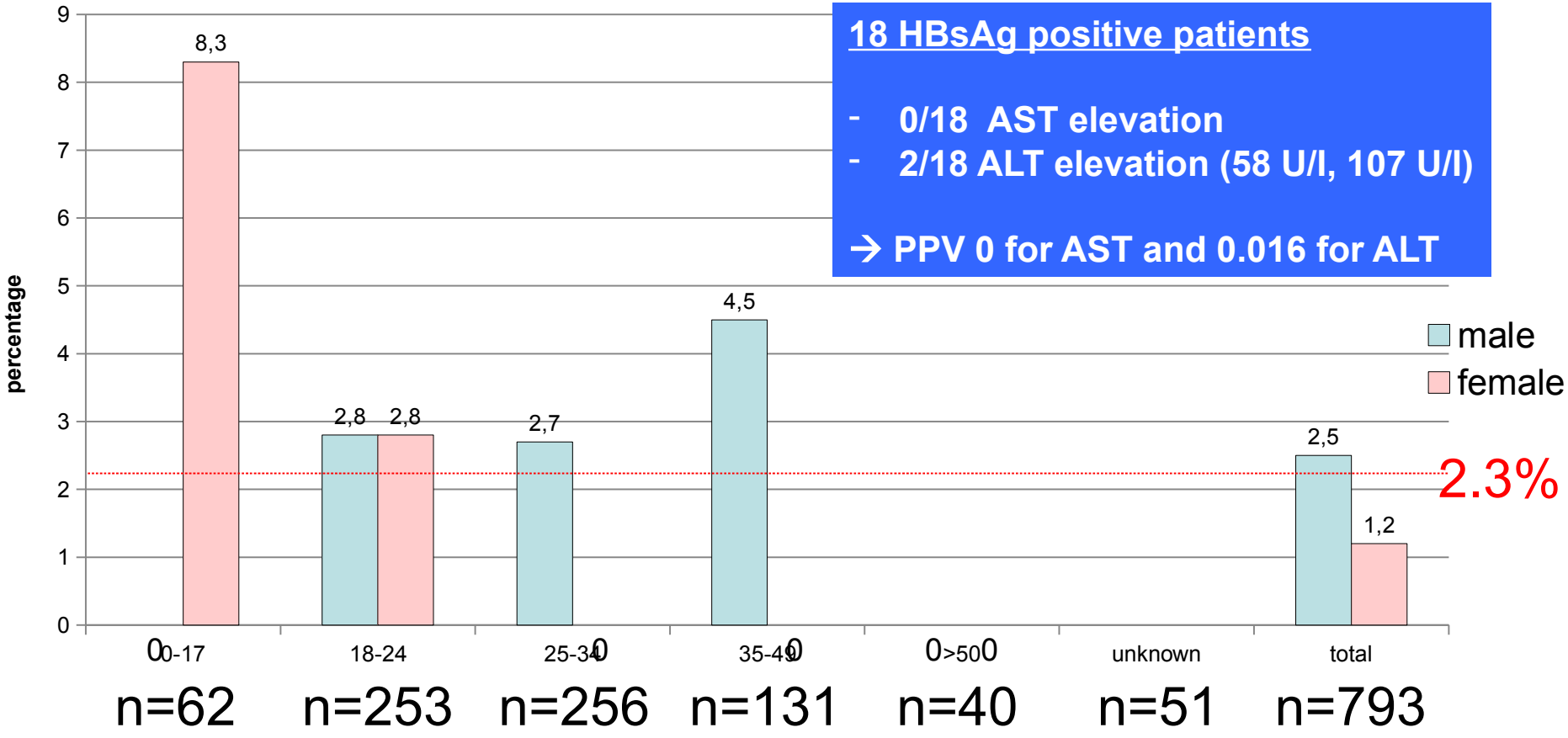
Increase of HBV prevalence in Germany through refugees ?



Schweitzer A et al. LANCET 2015

HBsAg prevalence in 793 refugees

2.3% (18/793)



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

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

3 Screening

- Example Germany
  - **Refugees have a higher HBsAg prevalence** than the German population 2.3% vs. 0.4%
  - 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**

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.

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

4 Detection and Diagnosis

- **Enhance low diagnosis rate** by increasing **awareness of risk scenarios in primary care setting**
  - a recent **screening study** in Germany including >20,000 patients **revealed 85% previously unknown infections**1
  - Misperception in primary care that elevated ALT levels are mainly associated with alcohol abuse2

1 Wolffram, Wiegand et al. *J Hepatol*. 2015;62:1256-1264.
2 Vu et al. *BMJ Open Gastroenterol*. 2015;2:e000060.

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

5 Treatment

- **awareness campaigns** will help to **reduce barriers to access** in many western countries
- **declining resources and economic constraints** reduced sustainable investments in HBV management2
- → **investments will be needed to increase proportion of HBV-infected individuals that receive treatment**

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

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

Key challenges	Key measures
Lack of knowledge and awareness	• evidence-based knowledge to create an appreciation of the impact of the disease
Limited screening and linkage to care	• Screening of risk groups (according to guidelines) to increase treatment uptake • Screening of pregnant women
Lack of vaccination	• Implementation of universal infant vaccination
Limited treatment	• Better training of physicians: improve screening, optimal treatment based on guidelines, prevent reactivation
Social stigma and discrimination	• Increase knowledge in the general population

Access to vaccination and treatment in special populations: pregnant woman

Vertical transmission from mothers to their newborns

- is the **most common route in high prevalence regions**
- is the **route with highest rate of chronicity**

Prevention of vertical transmission can be reached by **active and passive immunisation** of the infant within 24 hours after birth1,2, **BUT**

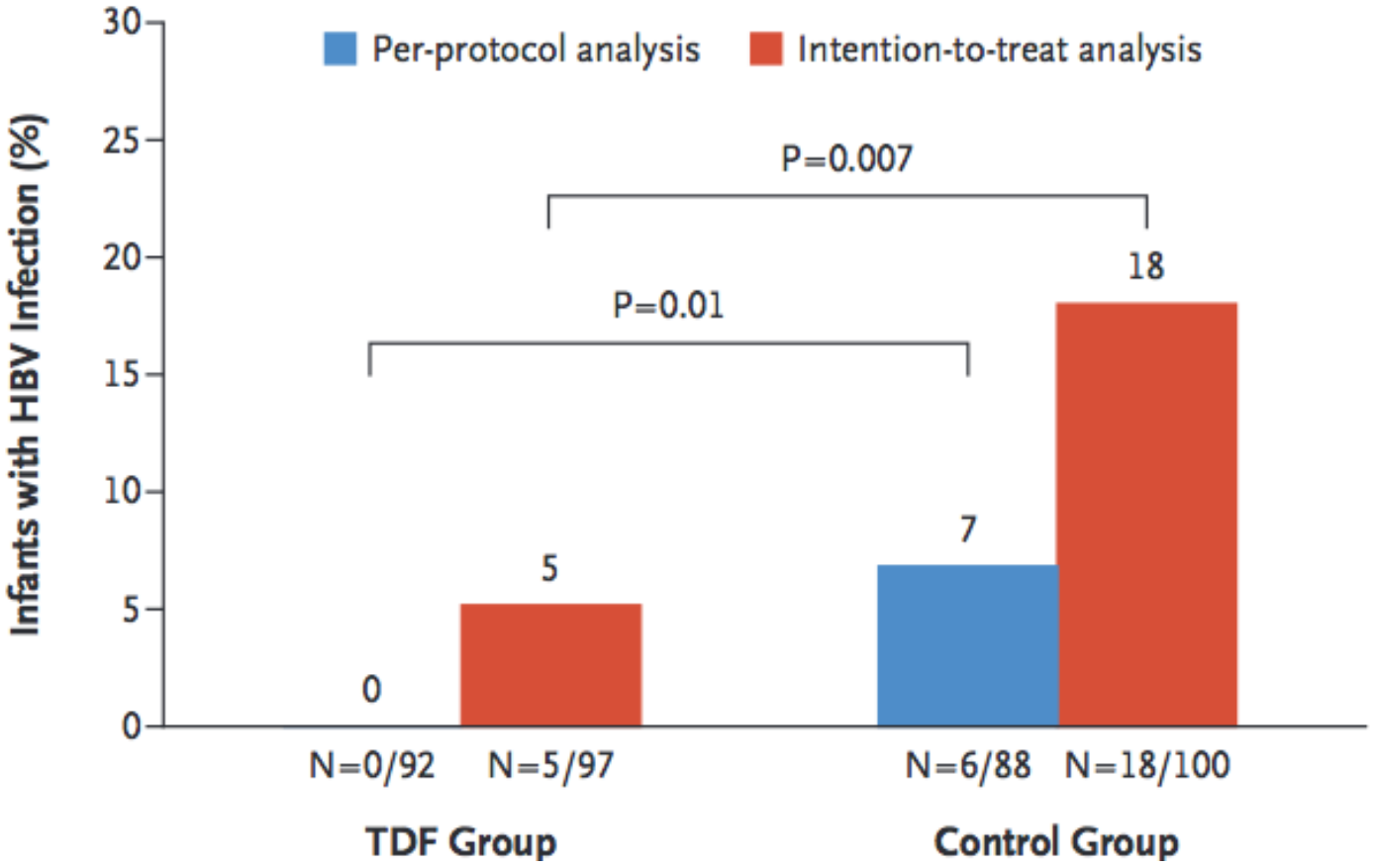
- often **no access to HBIg**
- **failure of vaccination** in infants born from mothers with very high viral loads3

→ **NEEDED:** additional antiviral therapy with NUCs in pregnant women with very high viral loads 4,5

1 Aspinall et al. *Occup Med (Lond).* 2011;61:531-540. | 2 Visvanathan et a. *Gut.* 2016;65:340-350.
3 Chang et al. *Clin Canc Re.* 2005;11:7953-7957. | 4 Pan et al. *N Engl J Med.* 2016;374:2324-2334.
5 Brown et al. *Hepatology.* 2016;63:319-333.

Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load.

HBsAg positive mothers with HBV-DNA levels >200,000 IU/mL



Access to vaccination and treatment in special populations: pregnant woman

Proposed scenario

- HBsAg screening of pregnant women in the first trimester
- starting antiviral therapy at 28-32 weeks of gestation if HBV DNA is above 200,000 IU/mL

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.

1 Komatsu. *World J Gastroenterol.* 2014;20:8998-9016.

Access to vaccination and treatment in special populations: immunosuppressive therapy

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

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

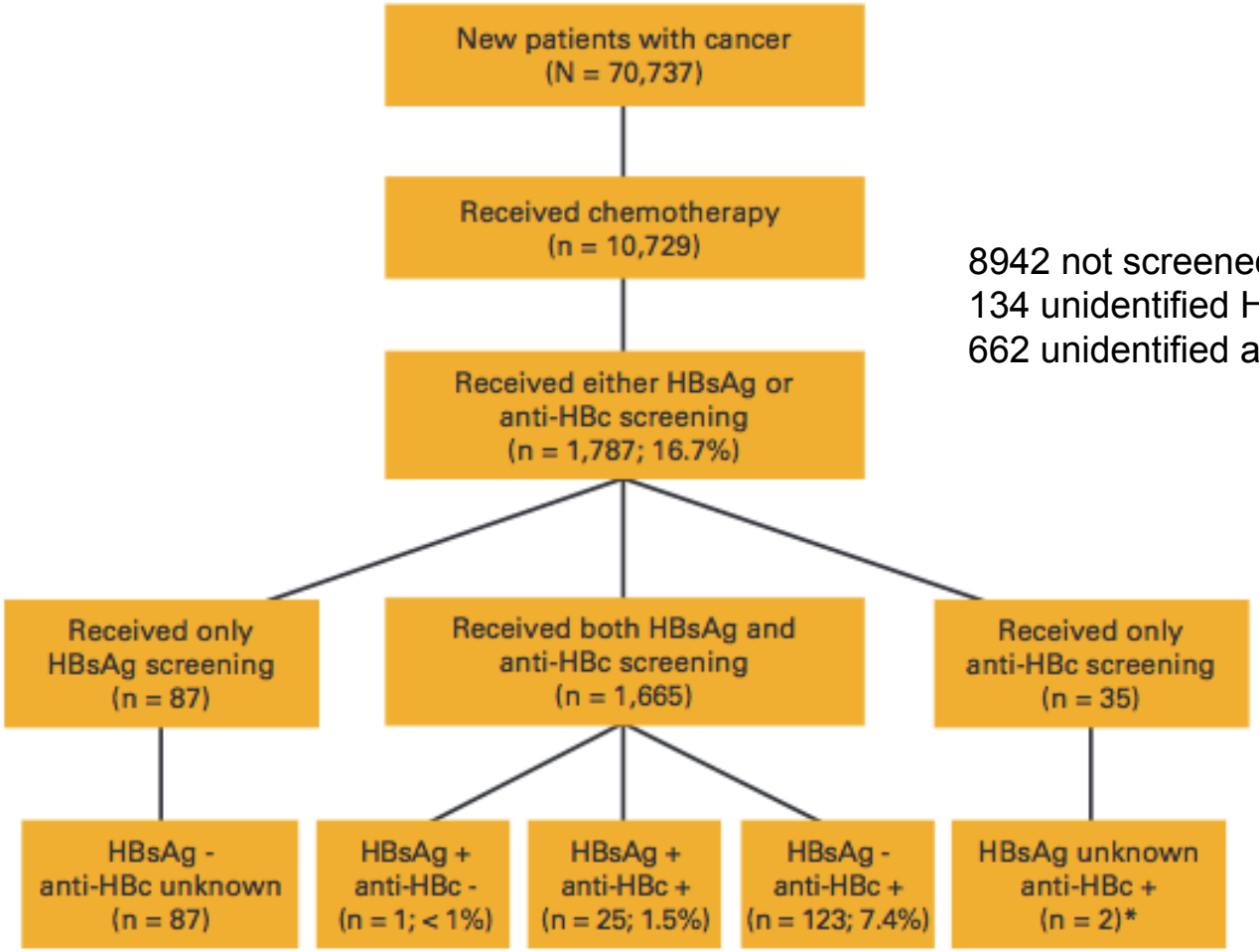
Prophylactic antiviral therapy is highly effective and current guidelines recommend screening everyone undergoing immunosuppressive treatment2, **BUT**

- screening rate is low, even among specialists3-5

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

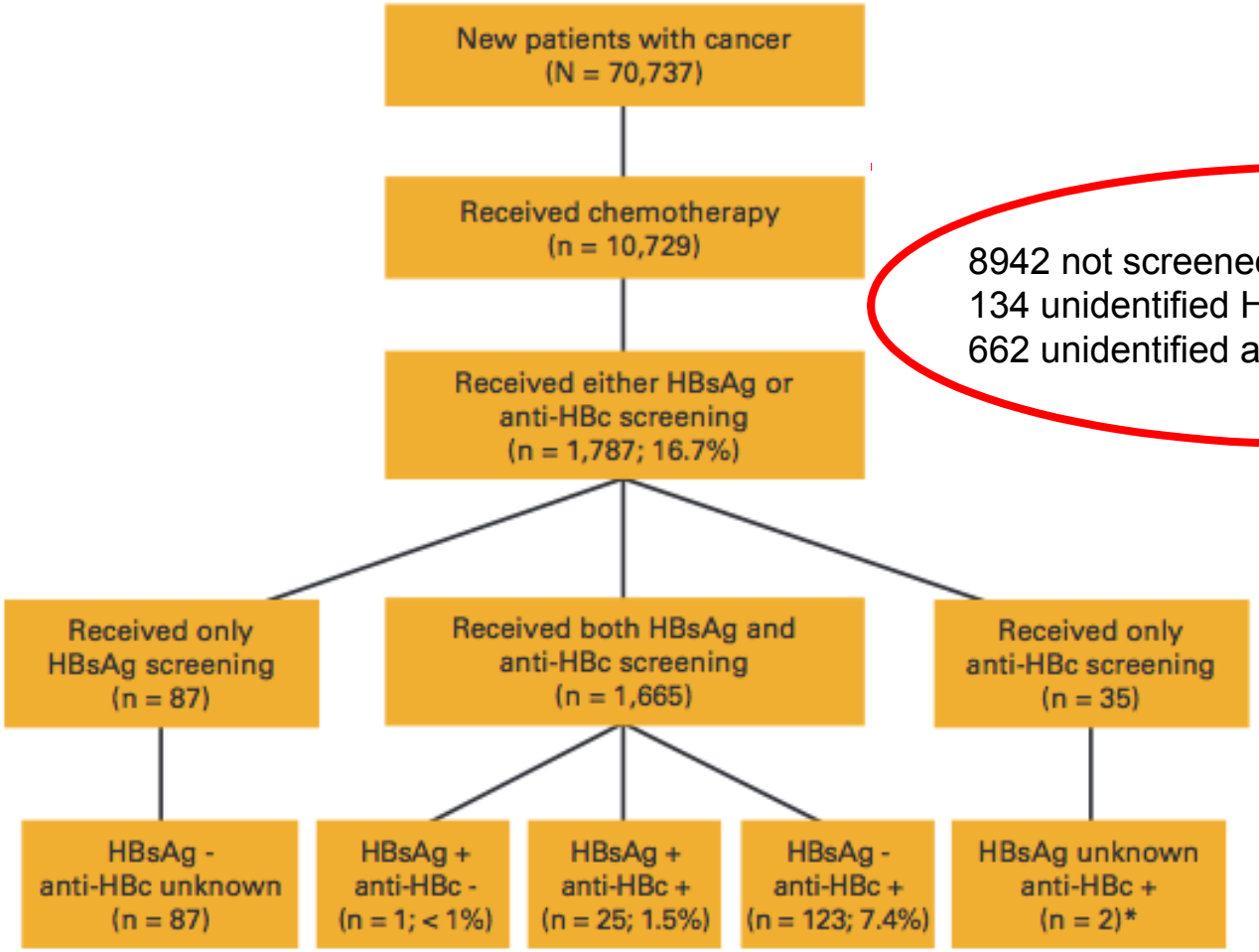
1 EASL clinical practice guidelines. *J Hepatol*. 2012;57:167-185. | 2 Weinbaum et al. *MMWR Recomm Rep.* 2008;57:1-20.
3 Leonard et al. *Ann Hematol*. 2016;95:27-33. | 4 Paul et al. *Dig Dis Sci.* 2016;61:2236-2241.
5 Hwang et al. *J Viral Hepat.* 2015;22:346-352.

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%)?

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%)?

Ultimate goal: eradicating HBV

Key points

- Management of viral hepatitis should become a global health priority

- Sustainable funding will be needed to reach the ultimate goal of globally eradicating HBV

THANKS FOR YOUR ATTENTON !!