The impact of vaccination against viral hepatitis: advances towards elimination and remaining challenges

ESCMID Postgraduate course
Elimination of viral hepatitis: are we ready?
Ljubljana, Slovenia: 27-18 September 2019
Hepatitis A: 6 challenges

Fig. 1. (Top) Organisation of the ~7.5 kb HAV genome. The ORF is shown as a box, flanked by the 5’ and 3’ UTRs. The 5’UTR is covalently linked to a small viral protein, VPg (or 3B), the protein primer for RNA synthesis is at its 5’ end, and contains an IRES that directs translation of the downstream ORF. The 3’UTR terminates in a 3’ poly(A) tail. Individual viral proteins are processed from the polyprotein as described in the text. Except for the VP0 (VP4-VP2) maturation cleavage and VP1-pX cleavage, all are mediated by 3C Pro, a cysteine protease and the only protease expressed by the virus. (Bottom) Transmission electron micrographs of eHAV and naked HAV particles found in the supernatant media of infected cell cultures (Reproduced with permission from Feng et al.) eHAV, quasi-enveloped hepatitis A virus; ORF, open reading frame.
Challenge 1: reach the target!

**Type A viral hepatitis: A summary and update on the molecular virology, epidemiology, pathogenesis and prevention**

Stanley M. Lemon¹, Jórdis J. Olt⁴,³,³, Pierre Van Damme⁴,¹, Daniel Shouval⁵,¹

**Summary**

Although epidemic jaundice was well known to physicians of antiquity, it is only in recent years that medical science has begun to unravel the origins of hepatitis A virus (HAV) and the unique pathobiology underlying acute hepatitis A in humans. Improvements in sanitation and the successful development of highly efficacious vaccines have markedly reduced the worldwide occurrence of this enterically-transmitted infection over the past quarter century, yet the virus persists in vulnerable populations and those without HAV immunity and remains a common cause of food-borne disease outbreaks in economically-

![Graph showing age distribution of reported deaths and cases of hepatitis A](image_url)

**Fig. 5.** Age distribution of reported deaths from (n = 689, upper panel) and reported cases of (n = 235 153, lower panel) hepatitis A within the US, 1983–1991 (2). Bars represent reported deaths or cases (left ordinate), lines represent incidence rates (right ordinate). Reprinted with permission from.⁹⁰
Challenge 2: changing hepatitis A epidemiology in the European Union
ref: Gossner et al, Eurosurveillance 2015; 20 (16)

- Increasing number of susceptibles
- Notification 1997 to 2011:
  - fallen from 10.0 to 2.5/100,000 population
  - 2011: 21/28 countries reported rate $\leq 1/100,000$
  - Peak in reported cases in September/October
- 2005-2012: reported proportion of cases contracted abroad: Sweden (49-80%), France (36%), Germany (37%)
- Increasing number of outbreaks (in MSM in EU, 2016-2019)
The hepatitis A paradox

- Improved socio-economic conditions
- Childhood exposure to virus
- Proportion of susceptibles among older children and adults
- Proportion of symptomatic disease increase with age
- Risk for clinically significant outbreaks — disease becomes more visible

Challenge 3: how long does the vaccine protect?  
- anti-HAV GMCs in 2 Studies Over 20 Years

- Anti-HAV antibody GMCs peaked 1 month post-dose 2 in both studies
- GMCs decline sharply over first year after primary vaccination
- Thereafter, low rate of decay in antibody levels
- 20 years post-primary vaccination anti-HAV GMCs persist at 317.3 mIU/ml (Study A) and 311.8 mIU/ml (Study B)

GMC, Geometric mean concentrations; HAV, hepatitis A virus.  
*Time-points corrected to count from the last vaccine dose  
Van Damme P, et al. NECTM 2014 and Personal Communication

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Long-term immunogenicity after 2-3 doses in different age groups

<table>
<thead>
<tr>
<th>Age groups</th>
<th>Follow up period</th>
<th>Vaccine</th>
<th>Schedule</th>
<th>SC rate</th>
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</thead>
<tbody>
<tr>
<td><strong>Children</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lopez et al</td>
<td>14-15y</td>
<td>Avaxim</td>
<td>0-6</td>
<td>100%</td>
</tr>
<tr>
<td>Plumb et al/ Mosites et al</td>
<td>20y</td>
<td>Havrix 360</td>
<td>0-1-6</td>
<td>94%</td>
</tr>
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<td></td>
<td>20y</td>
<td>Havrix 360</td>
<td>0-1-12</td>
<td>94%</td>
</tr>
<tr>
<td>Sintusek et al</td>
<td>13-18y</td>
<td>Havrix 720</td>
<td>0-6</td>
<td>97.5%</td>
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<tr>
<td><strong>Adolescents</strong></td>
<td></td>
<td></td>
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<td>Beran</td>
<td>15y</td>
<td>Twinrix</td>
<td>0-6</td>
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<td></td>
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<td>Twinrix jun</td>
<td>1-1-6</td>
<td>100%</td>
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<tr>
<td><strong>Adults</strong></td>
<td></td>
<td></td>
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<tr>
<td>Chapuis</td>
<td>20y</td>
<td>Epaxal</td>
<td>0-12</td>
<td>100%</td>
</tr>
<tr>
<td>Theeten</td>
<td>20y</td>
<td>Havrix</td>
<td>0-6/0-12</td>
<td>94%/98.8%</td>
</tr>
<tr>
<td>Van Damme</td>
<td>20y</td>
<td>Twinrix</td>
<td>0-1-6</td>
<td>96-100%</td>
</tr>
</tbody>
</table>
Challenge 4: which strategies to choose?

• Immunization strategies
  – targeted immunization
    • high-risk individuals
  – universal immunization
    • children
      – main reservoir of infection
    • adolescents

• Outbreak control
  – immune globulin or vaccine
    • pre-school children at day-care centres, their parents and siblings
    • day-care centre employees
    • individuals in close contact with infected people

• WER 2012, 87th year, 87, 261–276 http://www.who.int/wer - WHO position paper;
• MMWR1999 p.25; ACIP october 2005
### Table 3: Example of risk groups for HAV vaccination

- Travelers from non-endemic to HAV endemic countries
- Family members and close contacts of an individual with acute hepatitis A
- Men who have sex with men (MSM)
- Patients with chronic liver disease
- Day care center staff
- Laboratory and sewage workers with potential risk
- Immune suppressed patients living in areas of intermediate HAV endemicity
- Users of illicit intra-venous drugs
- Food handlers
- Recipients of frequent blood products
- Military personnel from non-endemic countries deployed overseas
- Care takers of non-human primates

Fig. 7. Incidence of acute hepatitis A in Israel between January 1992 and December 2016. UMV was started in 1999 with administration of an inactivated HAV vaccine at 18 and 24 months of age. Data collected through passive surveillance of the Israeli Ministry of Health (MOH). (Received by courtesy of Dr E. Anis, MOH, Israel). HAV, hepatitis A virus; UMV, universal mass vaccination.
Challenge 5: longterm effectiveness of a 1-dose schedule?

Fig. 8. Impact of the single-dose immunisation strategy against hepatitis A in Argentina. (Reproduced with permission from177).
Challenge 6: hepatitis A vaccine shortage!

Hepatitis A outbreaks in the EU/EEA mostly affecting men who have sex with men

Second update, 19 May 2017

Hepatitis A vaccine availability in the EU

As reported by some of the affected EU/EEA Member States (e.g. Austria, Italy, Portugal and Spain), vaccine availability in the EU is currently limited, with some countries facing shortages. Other countries like the Czech Republic, Denmark, Estonia, Finland, Ireland, Slovenia and Sweden reported no shortages.

Supply information was obtained from three major hepatitis A vaccine marketing authorisation holders (MAH) in the EU/EEA. The information received confirmed observations made at the national levels. The supply of HAV vaccine, whether in single antigen presentation or as part of a combination vaccine with other antigens, is stretched at the global level, owing to a combination of past and ongoing production issues in MAH which resulted in reduced production along with an increased demand exceeding existing stocks. For some manufacturers, the situation is not expected to return to normal before the end of 2018.
Hepatitis B virus
• Despite the availability of safe and effective HBV vaccines since more than 30 years
• Global burden of disease is still substantial:
  • About 2000 million (2 billion) have been infected
  • 240 - 350 million chronically HBV infected,
  • ~600,000 deaths/yr as a result of HBV infection
  • 57% of cirrhosis was attributable to either HBV or HCV
    – 30% of cirrhosis was attributable to HBV
  • 78% of HCC was attributable to HBV or HCV
    – 53% of HCC was attributable to HBV

Estimations of worldwide prevalence of chronic hepatitis B virus infection: a systematic review of data published between 1965 and 2013

Aparna Schweitzer, Johannes Horn, Rafael T Mikolajczyk, Gérad Krause, Jördis J Ott

Summary

Background The quantification of the burden of disease attributable to hepatitis B virus (HBV) infection and the adaptation of prevention and control measures requires knowledge on its prevalence in the general population. For most countries such data are not routinely available. We estimated the national, regional, and global prevalence of chronic HBV infection.

Methods For this systematic review and pooled analyses, we searched for data on prevalence of chronic HBV infection published between Jan 1, 1965, and Oct 23, 2013, in the databases Medline, Embase, CAB Abstracts (Global health), Popline, and Web of Science. We included studies reporting the hepatitis B surface antigen (HBsAg) serological marker of chronic HBV infection in non-high-risk groups and extracted data into a customised database. For each country, we calculated HBsAg prevalence estimates and 95% CIs weighted by study size. We extrapolated prevalence estimates to population sizes in 2010 to obtain the number of individuals with chronic HBV infection.

Findings Of the 17 029 records screened, 1800 report on the prevalence of HBsAg covering 161 countries were included. HBsAg seroprevalence was 3·61% (95% CI 3·61–3·61) worldwide with highest endemi city in countries of the African region (total 8·83%, 8·82–8·83) and Western Pacific region (total 5·26%, 5·26–5·26). Within WHO regions, prevalence ranged from 0·20% (0·19–0·21; Mexico) to 13·55% (9·00–19·89; Haiti) in the Americas, to 0·48% (0·12–1·90; the Seychelles) to 22·38% (20·10–24·83; South Sudan) in the African region. We estimated that in 2010, globally, about 248 million individuals were HBsAg positive.

Interpretation This first global assessment of country-level population prevalence of chronic HBV infection found a wide variation between countries and highlights the need for continued prevention and control strategies and the collection of reliable epidemiologic data using standardised methodology.
STATUS OF HEPATITIS B, 2015

Cumulated incidence of chronic infection:
Prevalence of HBV infection in children under 5 reduced from 4.7% to 1.3% (immunization)

Prevalence:
257 million people living with HBV
68% in Africa/Western Pacific

* Work in progress to understand differences between PAHO and WHO estimates

Source – WHO (LSHTM)
Transmission through blood

- Transmitted by percutaneous or mucosal exposure to infectious blood or body fluids (such as semen and vaginal fluids) of an infected person
  - perinatal transmission
  - close contact in early childhood
  - sexual contact
  - blood transfusions
  - contaminated needles/syringes (health care setting, IDU, tattooing…)
- Same mode of transmission as HIV, but 50 to 100 times more infectious

Outcome of HBV Infection According to Age at Time of Infection

Proportion becoming carriers vs Age at infection (yr)
Perinatal transmission: most efficient!

HBsAg-positive Mother

HBeAg-positive

Transmission Rate 70-90%

Neonate Evolution to Carrier: 90%

HBeAg-negative

Transmission Rate 10%

Neonate Evolution to Carrier: 10-15%
Relation between saliva and serum for HBV-DNA

![Graph showing the relationship between log HBV DNA in serum and log HBV DNA in saliva. The graph includes a lowess line and a quadratic line.](image-url)
challenge 1: Non-response to conventional vaccination against HBV

Protective efficacy of yeast derived HBV vaccines: 95-100% in young-healthy recipients decreasing to 60-75% in individuals > 60y old*

*Leroux-Roels G. 2015;204:69-78
Fishman DN et al.2002;35:1368
The Unmet Need: High-Risk Populations of Non-Responders & Low Responders to Conventional HBV Vaccination

**SEROPROTECTION RATES:**

- Cancer patients (children) ~57%
- Patients with chronic liver disease ~50%
- Chronic renal failure & dialysis 34-81%
- Acute lymphocytic leukemia ~10%
- Bone marrow /stem cell transplant recipients 15-68%
- Pre-transplantation candidates 28-36%
- Post-transplantation patients ~10%
- HIV (children & adolescents) ~30%
- Miscellaneous (i.e. older healthcare workers engaged in exposure prone procedures; genetically determined non-responders, celiac disease, IBD)
The hepatitis B vaccine

- Three generations of hepatitis B vaccine
  - Plasma-derived vaccines (HBsAg) introduced in 1982 – no longer in use
  - DNA recombinant vaccines synthesized in yeast, since 1986. Most widely used vaccines in the world.
  - Third generation vaccines: mammalian cell derived recombinant vaccines (HBsAg/ S, preS1, preS2 antigens), with enhanced immunogenicity. Possible indication for non-responders at risk. So far access limited to a few countries (France, Israel, some East Asian countries).
- Hepatitis B vaccines are available as monovalent vaccine or in combination with other vaccines
Three generations of HBV vaccines

Plasma derived Vaccines 1980-1986

rDNA Yeast derived vaccines 1986-2017

rDNA Mammalian cell derived vaccines 2000-

Enhancement of Immunogenicity of HBV Vaccines

• New adjuvants*:
  – Fendrix GSK™ (MPL /A&QS21)
  – Heplisav, DynavaxR (CpG ODNs TLR 9)
  – MF 59 (oil in water)
  – AgB/RC 529 (MPL ,Corixa, Berna Biotech)
  – Cytokines (GM-CSF, IL-2, IL-4, IL-12, IFN α, TLR 9 ag)
  – Miscellaneous (Cationic lipid, Virosomes ,HBcAg)

• Double or Triple antigen vaccines(Pre-\(S_1\)/Pre-\(S_2\)/\(S\) (with alum hydroxide))**: 
  – GenHevac B™ - France (Discontinued)
  – Hepagene™ - UK (Discontinued)
  – BioHep B/ HepImmune/ Sci B VacR (licensed in Israel)

*Leroux-roels G 2015; Med Microbiol Immunol 204;69
Wen Y et al. Emerging Microbes and Inf 2016, 5,e25
**Shouval D et al. Med Microbiol Immunol. 2015;204:57
Immunogenicity of an hepatitis B vaccine with a Toll-like receptor 9 hepatitis B *agonist adjuvant (HBsAg-1018) compared to a licensed vaccine in healthy adults 40–70 years of age.
Challenge 2: How long does hepB vaccine-induced protection last?
Overall description of proportions of anti-HBs $\geq 10$ mIU/ml 5 to 20 years for children vaccinated with hepatitis B vaccine in infancy. Schönberger et al PIDJ 2013
Antibody Levels and Protection After Hepatitis B Vaccine: Results of a 30-Year Follow-up Study and Response to a Booster Dose

Michael G. Bruce,¹ Dana Bruden,¹ Debby Hurlburt,¹ Carolyn Zanis,¹ Gail Thompson,¹ Lisa Rea,¹ Michele Toomey,¹ Lisa Townshend-Bulson,² Karen Rudolph,¹ Lisa Bulkow,¹ Philip R. Spradling,³ Richard Baum,¹ Thomas Hennessy,¹ and Brian J. McMahon¹,²

Figure 2. Levels of antibody to hepatitis B surface antigen (anti-HBs) decline over 30 years among 3 groups in Alaska. Group 1 comprised persons who responded to a booster dose with anti-HBs levels >10 mIU/mL at 1 month.
Persistence of immunity up to 20 years after HBV vaccination

Results from multiple long-term clinical trials

Five independent long-term follow-up clinical trials have assessed the antibody persistence and the response to a challenge dose 5 to 20 years after a 3-dose vaccination course of Engerix-B.

Circulating anti-HBs antibodies decline over time (orange bars).

In contrast, the ability to mount an anamnestic response upon receipt of a challenge dose (blue bars) remains >95% even 20 years after vaccination, demonstrating the persistence of immune memory beyond the presence of circulating antibodies.

Challenge 3: can we prevent perinatal transmission?

No

Can we prevent perinatal HBV infection?

Yes
Outcome of infants born to women infected with hepatitis B, US, 2007-2013

Schillie et al. Pediatrics 2015

- HBIG and HBV vaccine administered within 12h
  Combined efficacy: 94%

- Failure of the immunoprophylaxis was related to
  - HBeAg+
  - high viral load,
  - < 3 hepB vaccine doses in infants
Challenge: timely birth dose!
BCG & Hep B Vaccine within 24 hours of birth:
N=526 infants participated (2015-2016)

<table>
<thead>
<tr>
<th>BCG vaccine</th>
<th>Freq</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 24 hours after birth</td>
<td>234</td>
</tr>
<tr>
<td>2 – 7 days</td>
<td>136</td>
</tr>
<tr>
<td>&gt;7 days</td>
<td>149</td>
</tr>
<tr>
<td>Not given</td>
<td>7</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>526</strong></td>
</tr>
</tbody>
</table>
WHO recommendations

Hepatitis B vaccines
WHO recommendations October 2009

- All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours.

- The birth dose is crucial in areas of high hepatitis B endemicity, but important even in intermediate and low endemicity areas.

- To complete the primary series the birth dose should be followed by 2 doses, spaced by ≥ 4 weeks, e.g. at the time of the first and third doses of DTP vaccine, or, if programmatic more convenient, by 3 doses coinciding with DTP or other routine infant vaccines.

- There is no evidence to support the need for a booster dose following 3 (or 4) doses of hepatitis B vaccine in routine immunization programmes.
Challenge 4: what is the impact of hepatitis B immunization?
## Impact of Immunization

<table>
<thead>
<tr>
<th>Country</th>
<th>HBsAg prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alaska (Harpaz)</td>
<td>18</td>
</tr>
<tr>
<td>China, rural (Xu)</td>
<td>16</td>
</tr>
<tr>
<td>FSM (Mahoney)</td>
<td>14</td>
</tr>
<tr>
<td>The Gambia (Viviani)</td>
<td>12</td>
</tr>
<tr>
<td>Indonesia (Ruff)</td>
<td>10</td>
</tr>
<tr>
<td>Mongolia (Chongsrisawat)</td>
<td>8</td>
</tr>
<tr>
<td>Samoa (Mahoney)</td>
<td>6</td>
</tr>
<tr>
<td>Saudi Arabia (Al-Faleh)</td>
<td>4</td>
</tr>
<tr>
<td>Saudi Arabia (Abdo)</td>
<td>3</td>
</tr>
<tr>
<td>Shanghai, China (Kol)</td>
<td>2</td>
</tr>
<tr>
<td>Taiwan (Chen)</td>
<td>2</td>
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<tr>
<td>Taiwan (Shi)</td>
<td>2</td>
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<tr>
<td>Taiwan (Tsou)</td>
<td>2</td>
</tr>
<tr>
<td>Thailand (Chongsrisawat)</td>
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<td>Thailand (Pattarasri)</td>
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<tr>
<td>USA, Hawaii (Perz)</td>
<td>2</td>
</tr>
<tr>
<td>Uzbekistan (Avazova)</td>
<td>2</td>
</tr>
</tbody>
</table>

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CONTROL OF HBV INFECTION THROUGH VACCINATION INCLUDING TIMELY BIRTH DOSE, CHINA, 1962-2013 BIRTH COHORTS

Source – Cui, EID, 2017
CUMULATIVE NUMBER OF IMMUNIZED WITH HBV VACCINE NEWBORNS AND HEPATITIS B INCIDENCE (PER 100 000) IN CHILDREN 0-14 AND 15-19 YEARS OF AGE IN BULGARIA, 1983 – 2010

- Cumulative number immunized newborns
- Incidence per 100,000 in age group 0-14 yrs
- Incidence per 100,000 in age group 15-19 yrs

Selective Immunization
Universal Immunization

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China, Qidong, cross sectional surveys in 1996-2000 and 2008-2012:
Incidence of PLC and mortality of end stage liver disease significantly lower in vaccinees versus controls

Chunfeng Qu, PLOS Medicine, 2014
Challenge 5: raise the global hepB infant coverage

Number of countries having introduced Hepatitis B vaccine and global infant coverage for Hepatitis B 3rd dose (HepB3), 1989-2017

'91 global advisory group
EPI sets 1997 as target for integrating HBV in national immunisation programmes.

'92 adherence by WHO and WHA
(resolution 45.27)

In 2010, MS re-iterated the 1992 resolution and adopted resolution 63.18, which called WHO to draft a comprehensive viral hepatitis prevention and control strategy.

2012: introduced in 181 countries
2013: introduced in 183 countries
2014: introduced in 184 countries
2017: excluding 3 countries where HepB administered for adolescents

HEPATITIS B BIRTH DOSE: 39% COVERAGE: IMPACT ON CHRONIC LIVER DISEASES

Source: WHO AND UNICEF
Tremendous progress since 1990!

- But ....

- A number of challenges:
  - Guarantee high coverage in neonates and infants
  - Guarantee timely birth dose administration
  - Reach the target groups (“access”)
  - Address the non-responders
  - Understand longterm protection & boostability
  - Integrate hepB vaccination in a control and elimination plan with therapy
  - Political will is needed!
World Hepatitis Day – July 28

Over 90% of new hepatitis B infections occur through mother-to-child transmission and during early childhood. But other groups are also at higher risk of both hepatitis B and C, including people who inject drugs; men who have sex with men; people who have had tattoos or acupuncture; partners of people living with hepatitis B; and health care workers.
Website and social media:

- Newsletters
- Renewed membership of Vaccine Safety Network
- Twitter

Questions ... www.vhpbp.org

Viral Hepatitis Prevention Board

Highlighting underserved groups for screening, prevention and
treatment of viral hepatitis B and C in Europe

In the 28 Member States of the European Region of the World Health Organization (WHO), an estimated 15 million people live with hepatitis C. Generally, data on HCV infection, however, are scarce and not easily comparable.

Several diverse, hard-to-reach and underserved populations in Europe remain at risk of severe high prevalence rates of chronic hepatitis B and C virus infection or disease. These groups include people who inject drugs (PWID), prisoners, migrants, homeless, and those who use meth (MIV), sex workers and other vulnerable populations.

On March 2016, the Viral Hepatitis Prevention Board organized a meeting in Liège (Belgium) for European experts and organizations to review issues surrounding screening, prevention, treatment and access to care for these people.

Underserved groups

PWID. In Europe, PWID probably form the main group at risk for HCV infection and disease. They may number up to one million people, but data are lacking. Important exceptions include PWID in Eastern Europe, the FSU and the Balkans.

MIV. In Europe there may be up to 2 million MIV, mainly drug users, but some HIV-positive drug users may also be involved in injecting drugs.

Hepatitis B virus (HBV). HBV affects many people in Europe and has a high incidence of chronic disease and liver cirrhosis. In Europe, the incidence of HBV is highest in the Mediterranean region.

Hepatitis C virus (HCV). In Europe, the incidence of HCV is highest in the Mediterranean region.

Prevention and control of Viral Hepatitis in Belgium and Luxembourg: lessons learnt and the way forward.

The latest country meeting of the Viral Hepatitis Prevention Board (VHPB) held in Brussels on 7-8 November 2017 focused on Belgium and Luxembourg.

The meeting concluded that both countries are well on their way to support WHO's viral hepatitis control milestones and targets to be achieved by 2020 (see page two of the meeting conclusions). Recommendations to strengthen current efforts in prevention and treatment were made. The highlights:

- Maintain the high hepatitis B vaccination coverage rate in both countries.
- Increase screening of hepatitis B and C in pregnant women to level-up screening coverage (in Belgium currently less than 50% reported and documented).
- Strive towards an enhanced availability of hepatitis B and C prevalence data (e.g. - via linked central registries) to improve case finding, follow-up, access to and quality of treatment.

Browse the meeting presentations online.

Meeting conclusions, including more recommendations, can be downloaded here.