

HAV and HBV vaccination in drug users.

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Potential conflict of interest

- A. Vorsters and G. Hendrickx have no conflict of interest
- P. Van Damme has been principal investigator of vaccine trials for several vaccine manufacturers, for which the University of Antwerp receives research grants.

Content

- Increased risk of HBV, HAV infection and complications
- International guidelines for vaccination of drug users (DU)
- Coverage and outcome of HAV and HBV vaccination
- Challenges and possible solutions
- Conclusions

Substance users are at increased risk of HAV, HBV infection and complications

- IDU are more often exposed to these infections; however improved and more complete epidemiological data are required¹.
- Infections may lead to increased morbidity and mortality because of pre-existing chronic liver disease/HIV infection in this population
 - Fatality rate of HAV infection in patients with chronic liver disease (HCV/HBV) was 23-58 folds higher^{2,3}

1 Nelson et al. Global epidemiology of hepatitis B and C in people who inject drugs: results of systematic reviews. The Lancet, 2011

2 Vento et al. NEJM, 1998; 3 Pramoolsinsap et al. Ann Trop Med Parasitol, 1999

International guidelines for HBV vaccination of DU

- Hep B vaccine was already recommended for high risk populations in 1982, 29 years ago!
- WHO Hepatitis B vaccines: WHO position paper. WER 2009; 84: 405-420
- A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the US. ACIP recommendations on Immunization of adults. CDC MMWR 2006; 5:RR-16
- And even more important WHO recommends since 1992 that all countries introduce universal HBV.

International guidelines for HAV vaccination of DU

- Hep A vaccine was recommended for high risk populations by WHO in 2000¹.
- CDC² HAV vaccination recommendations for adults covering DU
 - Medical indication: chronic liver disease
 - Behavioral indication: persons who use illegal drug

1 Hepatitis A vaccines. WHO position paper. Wkly Epidemiol Rec 2000; 75 (5):38-44

2 CDC Recommended Adult Immunization Schedule, US 2009, MMWR 2009; 57: N°53

Implementation of guidelines

- EUROHEPNET project showed that only 9 of 22 EU countries reported HAV vaccination for drug users¹.
- The EUROHEPNET survey and the ECDC survey report that respectively 15 of 20 EU and 18 of 29 EU/EEA countries have a risk group HBV vaccination programme for injecting drug users².

1 Eurohep.net (2004) Surveillance and Prevention of Vaccine Preventable Hepatitis. Available at <http://www.eurohep.net/default.asp?p=93&l=0604>

2 Control. ECDC (2010) Surveillance and prevention of hepatitis B and C in Europe. . Stockholm: ECDC

Coverage and outcome of HAV and HBV vaccination

Reference	Population (Country, City)	Year	HBV vac coverage	HBV Prevalence	HAV vac cov	Comments
Removille et al. BMC Public Health 2011	Problem drug users in out-treatment and prison centers (Luxemburg)	2011	Not reported	29,1% (all markers i.e. acute/chronic or past cured)		Only 56% of outpatients collected serology results
Schreuder et al. Harm Reduct 2010	Opioid drug users at annual voluntary screening. (Netherlands, Amsterdam)	2004-2008	92%	33% (anti-HBc)		
	(Netherlands, Heerlen)	2003-2009	45%	48% (anti-HBc)		
Rivas et al. Drug Alcohol Depend 2010	IDU admitted to detoxification (Spain, Barcelona)	1987-1991	3.7%	9.3% (HBsAg) 81.1% (any marker)		
		2002-2006	19.9%	1,8% (HBsAg) 51.2% (any marker)		
Mossner et al. J Med Virol 2010	Drug users attending treatment centers. (Denmark, Island of Funen)	1996	0.7%	9.8% (HBsAg) 70% (anti-HBc)		
		2007	24%	0.9% (HBsAg) 50.2% (anti-HBc)		
Day et al. Drug Alcohol Depend 2010	Participants recruited through primary health care, drug treatment service and street press. (Australia, Sydney)	2010	27% serology 43% recalled being vaccinated	5% (HBsAg) 45% (anti-HBc)		

Coverage and outcome of HAV and HBV vaccination

Reference	Population (Country, City)	Year	HBV vac coverage	HBV Prevalence	HAV vac coverage	Comments
Ferreira et al. J Med Virol 2009	Non-injecting drug users (Brazil, Central-West region)	2009	8%	0.1% (HBsAg) 14.0% (any marker)		HBV infection in blood donors 10.7%
Roy et al. Scott Med J 2008	IDU (Scotland, Glasgow)	1993	1.8%	52.3% (markers previous infection)		32.1% susceptible
		2001	13.2%	24.3% (markers previous infection) 2-3% (current infection)		Susceptibles increased to 41%
Lum et al. J Viral Hepat 2008	Street-recruited IDU < 30 years (USA, San Francisco)	2008	22%	21% (any marker past or current infection)		
Amesty et al. J Community Health	Heroin, crack and cocaine users (USA, New York City) 18<25 years	2008	30%	20% (evidence of infection)		50% susceptible for HBV
	25 years or older		10.6%	30.2% (evidence of infection)		59,2% susceptible of HBV
Van Houdt et al. Vaccine 2007	DU (The Netherlands, Amsterdam)	2003	9%	24-74% (anti-HBc)		Vaccination had limited influence

Coverage and outcome of HAV and HBV vaccination

Reference	Population (Country, City)	Year	HBV vac coverage	HBV Prevalence	HAV vac coverage	Comments
Gerlich et al. Eur J Epidemiol 2006	Patients entering heroin-assisted treatment. (Switzerland)	1994-1996		73.2%		In Switzerland HAV/HBV vaccination is recommended and these patients were in drug treatment
		1998	8%	68%		
		2000-2002	15.6%	53.3%	10.3%	31.1% susceptible for HBV, of which 73% targeted for HBV vaccination of which 20% refused HBV vaccination.
Christensen et al. Eur J Epidemiol 2006	Post-mortem samples from drug related deaths (Denmark)	2004	16%	35%		
Hope et al. J of Viral Hepat 2007	IDU recruited at different settings (England)	1998	27%			Self reported vaccine uptake.
		2004	59%			38% of IDU reported being vaccinated in prison

HAV prevalence/coverage

- Less data is available
 - Transmission route not necessarily the same as for HCV and HBV – hygienic living situation!
- Increased prevalence in DU, frequent outbreaks

Vaccination coverage data in DU

- Vaccination coverage data: Serological evidence of vaccine-conferred immunity was not detected among 50-73% of IDU who reported being vaccinated. Self-reported histories should not be used. (Topp et al Drug Alcohol Rev. 2009)
 - “Don’t ask, vaccinate” policy (Kuo et al Clin Infect Dis 2004)
- Vaccination coverage: serology (anti-HBsAg only) can underestimate vaccine coverage. Without prevaccination bloodsampling and testing, a vaccinated person with a resolved infection can not be distinguished from unvaccinated persons with a resolved infection. In addition more than 10% do not generate an immunological response to a full course of vaccine; even more to an incomplete course.

Challenges to obtain a good vaccination coverage (full scheduled) and protection

- IDUs are hard to reach and difficult to engage in a vaccination program
- IDUs have often already been exposed to HAV or HBV before being reached for vaccination (requesting screening procedures)
- The quality of prevention and care services are often not tailored to IDUs
 - Low number of HCW with required training and experience
 - HCW may have negative attitudes towards DU
- Issues of reduced vaccine immunogenicity have been reported
- Accelerated immunization schedules, in order to increase the completion of the vaccination schedules, may not provide adequate protection.

Vaccine immunogenicity in IDU¹

- There is a tendency towards decreased anti-HBs response, but no conclusive evidence of decrease in clinical protection¹
 - robust anamnestic immune responses have been demonstrated in vaccinated individuals without detectable anti-HBs levels²
 - one prospective cohort study in It over 15 years. 258 DU vaccinated, 71,9% had protective anti-HBs-levels, two seroconverted to anti-HBc. Of 45 who refused vaccination 13 seroconverted. $P < 0,001$ ³
 - Need to include IDU population in future vaccine trials¹
- Similar findings are reported for HAV vaccination. Decreased anti-body response but a one dose vaccination seems to be sufficient to end HAV outbreaks¹

1 Baral et al. Vaccine immunogenicity in injecting drug users: a systematic review. The Lancet 2007; 7: 667-674

2 European consensus group on Hepatitis B Immunity. Are boosters immunisations needed for lifelong hepatitis B immunity? Lancet 2000; 355: 561-65

3 Lugoboni et al. Progressive decrease of hepatitis B in a cohort of drug users followed over a period of 15 years: the impact of anti-HBV vaccination. Scan J Infect Dis 2004; 36: 131-33.

Do we need to know the serological outcome before vaccinating in a screening program for chronic viral hepatitis?

- Pre-vaccination testing is cost effective when the cost of serological testing is less or equal to the cost of vaccinating persons who are already immune¹.
 - But in populations that are difficult to access serological testing should not be a barrier to vaccination.
- Results of an (US) economic evaluation of delivering hepatitis B vaccine to IDU².
 - Give everyone first dose at screening
 - Administer under accelerated schedule
 - Obtain highly discounted vaccine from local health departments
- Offering HBV screening in the absence of vaccination is economically inappropriate².

¹CDC Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the US. MMWR 2006; 55: RR-16

²Hu et al. Economic evaluation of delivering hepatitis B vaccine to injection drug users. Am J Prev Med. 2008; 35:25-32.

Post-vaccination testing ^{1, 2}

- Post-vaccination testing in routine vaccination of adults is not necessary
- It is recommended for persons whose clinical management depends on the knowledge of their immune status.
 - HIV infected persons
 - Sex or needle-sharing partners of HBsAg-positive persons

1 CDC Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the US. MMWR 2006; 55: RR-16

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Schedules for hepatitis B vaccination of risk groups: balancing immunogenicity and compliance¹.

- Super accelerated schedules have lead to increased compliance.
- In healthy vaccinees protective anti-HBs are reached more rapidly with accelerated schedules (0, 1, 2, 12 months or 0, 7, 21, 360 days)
- As the long-term protection of accelerated schedules has not been established the fourth dose at 12 months is required
- Alternatively 1, 2, 4 months may be considered
- Accelerated schedules should be restricted for those where protection as early as possible is preferable or for those where compliance is an issue.
- *As need for accelerated schedules also indicates increased risk and continued risk, providing robust long-term protection is important.*

1 Van Herck et al. Schedule for hepatitis B vaccination of risk groups : balancing immunogenicity and compliance. Sexually Transmitted Infections 2007; 83:426-432

Combination HAV-HBV vaccine

- Advantages:
 - Simplifies implementation of the program
 - Less injections and reduced number of visits
 - May improve coverage
 - Reduces cost of immunization program
 - May induce higher Ab-titres.
- Dose of hep A component is lower than in the single-antigen hep A vaccine, allowing it to be administered in a 3-4 dose schedule: 0, 1, 6 months or 0, 7, 21-30, 360 days.

Other factors for compliance

- Feasibility study for hepatitis B vaccination among heroin users; 9 public centers for drug users (PCDU); 1175 DU enrolled; vaccination schedules 0, 1, 6 months or 0, 1, 2 months¹.
 - 88% completed the vaccination series, 77% had protective anti-HBs response.
 - Completion of vaccination not influenced by schedule or by still under drug abuse treatment at the end of the series. It was strongly related to number of patients enrolled at PCDU. => importance of setting
 - Lack of sero-conversion associated with older age, 2 month vaccination schedule, HCV sero-positivity and HIV sero-positivity

1 Quaglio et al. Compliance with hepatitis B vaccination in 1175 heroin users and risk factors associated with lack of vaccine response. *Addiction* 2002; 97:985-992

Components of a successful adult hepatitis B vaccination program¹

- Institutional commitment to the program
- Trained and knowledgeable staff who promote the program
- Patients who are informed about hepatitis B and the health benefits of hepatitis B vaccination.
- Integrated delivery of vaccination and other services
- Protocols and standing orders
- Protected patient confidentiality
- Infrastructure that ensures vaccine administration is accessible, convenient, and flexible for patients
- Funding for vaccine

1 A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the US. ACIP recommendations on Immunization of adults. CDC MMWR 2006; 5:RR-16

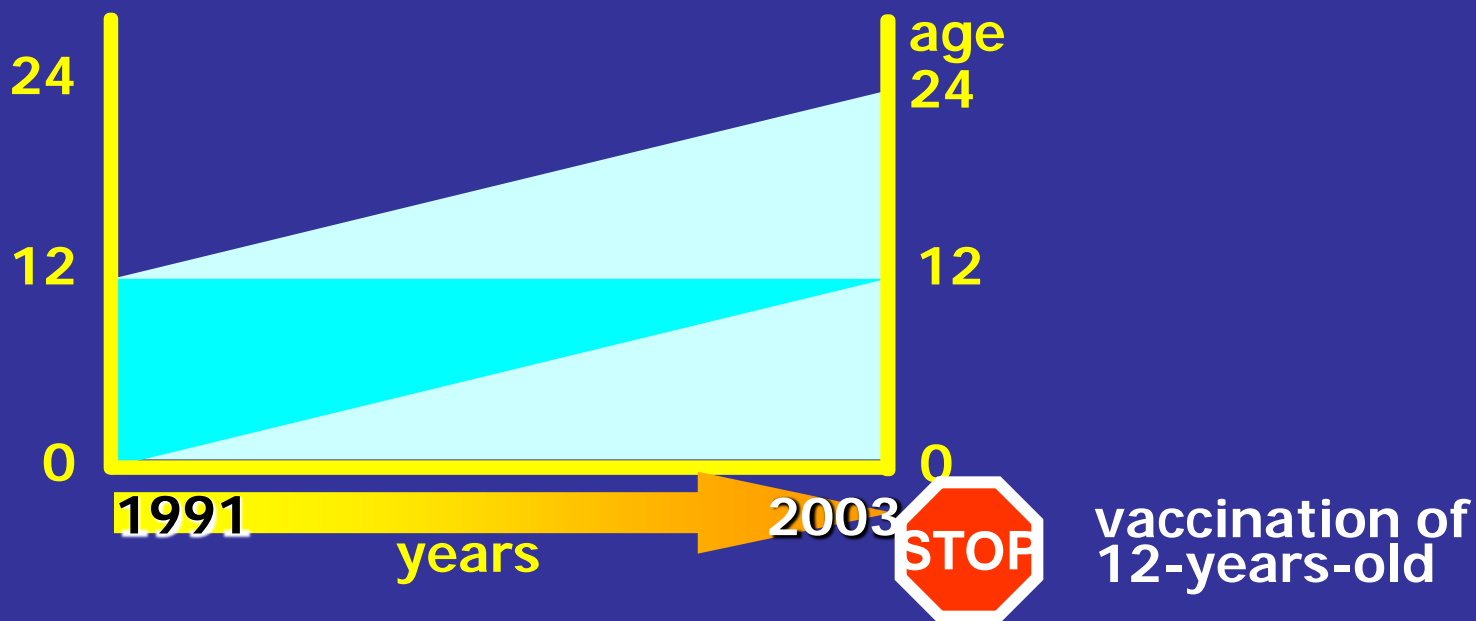
Settings in which HBV vaccination is recommended for all adults¹.

- Sexually transmitted infections treatment facilities
- HIV testing and treatment
- Facilities providing drug-abuse treatment and prevention services
- Health-care settings targeting services to injection-drug users
- Correctional facilities
- Health-care settings targeting services to MSM
- Chronic-hemodialysis facilities and end-stage renal disease programs
- Institutions and nonresidential day care facilities for developmentally disabled persons.

1 A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the US. ACIP recommendations on Immunization of adults. CDC MMWR 2006; 5:RR-16

HBV vaccination in Italy

- ✓ By the end of 2003, the first infant cohort vaccinated in 1991 reached the age (12 years) when adolescent's vaccination takes place. Thus vaccination of adolescents was stopped



- ✓ Italy's priorities for the future include the maintenance of vaccination of infants, and catch-up immunization of unvaccinated adolescents
- ✓ As a result of this policy of vaccination, 32 age classes (1-32 years) are at present immunized against hepatitis B. => 95% coverage including the high-risk groups/

Conclusions

- Despite clear international guidelines for HAV/HBV vaccination of adults, national implementation is sometimes lacking and vaccination coverage in DU remains in general low.
- There is a need for better HAV/HBV prevalence data in drug users.
- There is few data on the impact of vaccination in this population. Including DU in vaccine trials may be considered.
- 29 years after having an HBV vaccine many DU are still unprotected or have been infected with HBV. If countries would have started with universal vaccination 29 years ago.....
- Improving vaccination coverage in DU is multifaceted, efforts and commitments are required at all levels.
- Adapted (accelerated) schedules are helpful to increase the number of protected persons – but centre plays clearly a role too.

For HBV the most efficient approach still is universal childhood vaccination with an adolescent catch-up program.

Put a safety belt before you drive not while you are driving.