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This edition of *Viral Hepatitis* is based on material presented at the Viral Hepatitis Prevention Board meeting on **Prevention of viral hepatitis in the Netherlands: Lessons learnt and the way forward**, Rotterdam, the Netherlands, November 13-14, 2008.

Editorial

This issue of *Viral Hepatitis* reviews topics covered at the Viral Hepatitis Prevention Board (VHPB)'s autumn meeting on the *Prevention of viral hepatitis in the Netherlands: Lessons learnt and the way forward*, held on November 13-14, 2008 in Rotterdam, the Netherlands.

This *country* meeting focused on the current state of the art on viral hepatitis prevention in the Netherlands. Presentations and discussions provided an overview of surveillance systems for infectious diseases, an update of the epidemiology of viral hepatitis as well as the evaluation and possible implementation of prevention and control measures on viral hepatitis. The meeting concluded with the identification of successes, problems and barriers to overcome, as well as the way forward.

Today, viral hepatitis prevention at global level is affected by the complexity of changing epidemiological patterns and behaviour. Increased global travelling and migration contribute to the changing epidemiology of infectious diseases, such as viral hepatitis. Also, new forms of high risk behaviour, such as new sexual practices, piercing and tattooing, lead to new forms of exposure which have to be taken into account when implementing prevention strategies. Moreover, thanks to vaccination and successful antiviral therapy, hepatitis B and C became preventable and treatable diseases.

VHPB meetings represent a unique platform where such issues can be elucidated and where different perceptions can be discussed between public health experts, epidemiologists, microbiologists, hepatologists and other clinicians. In this context, this *VHPB* country meeting in the Netherlands was particularly timely since the Dutch Ministry of Health was re-evaluating the possible introduction of universal hepatitis B vaccination into the National Immunization Programme by the end of 2008.

From the discussions it appeared that the Netherlands has high standards of surveillance within a well-organized healthcare system and a national vaccination programme with high coverage rates.

Several databases and documentation systems linked to the population register are operational at national level in the Netherlands, such as *Osiris*, yielding useful information on infectious diseases for epidemiologists, and *Praeventis*, used to monitor vaccination coverage for infant vaccines. As such, very high standards of measurement are obtained and a wealth of good documented data has been collected, representing a level of information that is not usually available in other European countries. This allows an appropriate response to problems identified.

Other meeting highlights revealed specificities of epidemiology in the country with low endemicity for viral hepatitis, together with the initiatives taken at the level of prevention, control and treatment in order to avoid end-stage liver disease.

With regards to hepatitis B immunization programmes, the discussion focused on universal versus risk group vaccination strategies. Information related to the impact of adding new vaccinations to an existing programme was shared from countries with such experience. The complex logistics, high costs and limited effectiveness of risk group vaccination were also discussed, particularly in the context of competing disease priorities. In the light of these arguments and even after the lively discussions the question remained whether or not the Netherlands will consider prevention of hepatitis B as a priority in 2009.

Harry Janssen and Koen Van Herck
on behalf of the Viral Hepatitis Prevention Board

Breaking News

The Dutch Health Council revised their Hepatitis B vaccination advice. (March 2009)

After an evaluation of the current high-risk group approach in the Netherlands and a cost-effectiveness analysis, the Health Council recommended at the end of March 2009 to expand the current vaccination programme with routine vaccination against hepatitis B. Both general vaccination scenarios (infants/ adolescents) meet the assessment criteria for the National Vaccination Programme. However, the Committee would prefer a programme that includes general vaccination of infants. The Committee recommends that a catch-up campaign will be organised for twelve-year-olds, when general vaccination of infants is being implemented. This ensures that, every year, a cohort of twelve-year-olds also receives protection against hepatitis B.

More information is available from the Health Council's website.
http://www.gezondheidsraad.nl/samenvatting.php?ID=1825

Prevention of viral hepatitis in the Netherlands: Lessons learnt and the way forward Rotterdam, the Netherlands, November 13-14, 2008

The healthcare system in the Netherlands: National Immunization Programme (NIP) and viral hepatitis immunization policies

The National Immunization Programme (NIP) is one of the most visible public health tools in the Netherlands, run in a very "programmatic" way since 1957, with several extensions made over the years, in particular the inclusion in 1989 of HBV vaccination of infants born from HBsAg-positive mothers screened during pregnancy; in 2003, HBV vaccination of children with one or two parents originating from intermediate/high endemicity countries; and in 2006 addition of a birth dose for infants born from HBsAg-positive mothers. Of note, >1-year-old siblings of infants born from HBsAg-positive mothers are not included in the programme although they may be vaccinated through other channels.
Recently, two further additions were made to the programme, including infant vaccination against pneumococcal disease in 2006 and adolescent girl vaccination against human papilloma virus (HPV) to be started in September 2009 (see slide below).

GROWTH OF NIP IN THE NETHERLANDS

Disease	Year of introduction
Diphtheria	1957
Pertussis	1957
Tetanus	1957
Polio	1957
Rubella	1974
Measles	1976
Mumps	1987
Hepatitis B – mother HBsAg+	1989
Haemophilus influenzae type b	1993
Meningococcal C infections	2002
Hepatitis B – children at risk	2003
Pneumococcal disease	2006
Cervical cancer	2009

Specificities of the Dutch vaccination schedule are illustrated in table below.
The Dutch Childhood Vaccination Schedule as on 16 December 2006 is still current and is adopted from http://www.euvac.net/graphics/euvac/vaccination/netherlands.html

The Dutch Childhood Vaccination Schedule

	DTaP	IPV	Hib	MMR	dT	HepB	PCV7	MenC
At birth						Yes[1]		
2 months	Yes	Yes	Yes			Yes[2]	Yes	
3 months	Yes	Yes	Yes			Yes[2]	Yes	
4 months	Yes	Yes	Yes			Yes[2]	Yes	
11 months	Yes	Yes	Yes			Yes[2]	Yes	
14 months				Yes				Yes
4 years	Yes	Yes						
9 years		Yes		Yes	Yes			

Abbreviations:
D: Diphtheria vaccine (normal dose); d: Low dose diphtheria vaccine (booster; dose); T: Tetanus vaccine (normal dose); aP: Acellular pertussis vaccine (normal dose); Hib: Haemophilus influenzae type b vaccine; IPV: Inactivated polio vaccine; MenC: Meningococcal meningitis C conjugate vaccine; MMR: Measles, Mumps and Rubella vaccine; PCV7: Pneumococcal heptavalent conjugate vaccine.
[1] Only for children born to HBsAg-positive mothers.
[2] Only children of whom at least one parent was born in a country where hepatitis B is moderately or highly endemic and children of HBsAg-positive mothers.

Planned changes in 2009 include the introduction of the HPV vaccine for 12 year-old girls in September 2009, including a catch-up vaccination programme, starting in the first half of 2009, for girls between the ages of 13 and 16.

As many as 23 more candidate vaccinations were identified; among those, the following are either currently under examination or can be considered as serious candidates for potential future inclusion in the NIPs:

- Universal HBV vaccination;
- Infant vaccination against rotavirus;
- Elderly vaccination against shingles;
- Children vaccination against chickenpox;
- Older children and adult vaccination against pertussis;
- Children vaccination against influenza.

Further candidates that could be considered include vaccination against hepatitis A, invasive meningococcal B infection, cytomegalovirus infection (CMV), respiratory syncytial virus (RSV), Herpes simplex type 2 infection (HSV-2), invasive pneumococcal infection in the elderly, gastrointestinal ulcers and stomach cancer triggered by Helicobacter pylori, pelvic inflammatory disease attributable to Chlamydia trachomatis, gonorrhoea, HIV infection and AIDS, hepatitis C, Group A and Group B Hemolytic streptococcus (GAHS, GBHS), Lyme, etc.

The NIP is traditionally targeted to children and, as such, is part of a more general context of infant and youth welfare and healthcare check-ups and visits. It is publicly funded and free of charge, and despite its voluntary basis, very high participation rates (>95%) are observed. The NIP is linked to population registers which are very useful to identify children to be vaccinated and allow for active invitations, recalls and outreaching activities.

The organization of the NIP is articulated around the:

- **Dutch National Institute for Public Health and the Environment (RIVM, Rijksinstituut voor Volksgezondheid en Milieu)** which runs the programme in collaboration with infant clinics and school health services, and is also responsible for the continuous education of the public and professionals, as well as the evaluation of vaccine safety and effectiveness;
- **Vaccine Institute of the Netherlands (NVI, Nederlands Vaccin Instituut)** which produces and buys the vaccines;
- **Health Council (GR, Gezondheidsraad)** which provides independent, scientific advice on the content of the programme via peer-reviewed public reports from multidisciplinary committees covering scientific, ethical and legal aspects. Committee members are appointed on a personal basis, including advisors from the Ministry of Health (MOH), RIVM and Medicines Evaluation Board (MEB), and deliberate confidentially in order to exclude conflicts of interest and favour free discussions. Committee hearings are hold with social organizations and industry.

On the basis of advice provided by the Review Committee of the Health Council, taking into account scientific evidence, surveillance data, ethical and legal aspects, communication science and organizational aspects, the Minister of Health takes evidence based decisions.

Two vaccines, against meningococcal C and pneumococcal disease, became available for inclusion into the NIP. On this occasion, the Health Council was faced with a decision to be made, balancing health priorities. This situation revealed the need for an independent and transparent assessment framework which was then put in place, in accordance with the principle that the NIP *should include a moderate range of vaccinations that are judged to be important, effective and safe* (Health Council, 2001).

The objectives of the NIP to protect individuals and society against serious infectious disease by means of vaccination was also made explicit at that time, through specific targets:

- eradication and elimination of disease as gold milestone, supported by more pragmatic approaches;
- to reach and maintain herd immunity; and, at the least
- protecting as many individuals as possible.

The growing number of vaccines becoming available reinforced the need for independent and transparent assessment, considering the importance of a disease in terms of public health priorities, the availability, cost and acceptability of vaccination to the public, as well as its potential side effects. Based on the two ethical objectives of protecting the population at large and in the best possible way, and distributing protection fairly among those groups who most need vaccination, a set of seven ethical principles for collective vaccination programmes were developed and published in 2007 [1, 2].

Following criteria with the aim of assessing inclusion of candidate vaccination into the NIP, were published in the Health Council advisory report on the future of the National Immnunisation Programme of March 2007 [2]:

Disease burden

1. The infectious disease is serious for individuals and has the potential to affect a large number of people

Effectiveness

2. Vaccination is effective for the prevention of disease or the reduction of symptoms
3. Adverse effects are not sufficient to substantially diminish the public health benefit

Acceptability

4. The inconvenience or discomfort of vaccination is not disproportionate to the health benefit
5. The inconvenience or discomfort of the vaccination programme **as a whole** is not disproportionate to the health benefit

Efficiency

6. The cost-effectiveness ratio compares favourable with other means of prevention

Urgency/priority

7. Provision of vaccination serves a (potentially) urgent public health need

These criteria usually only allow for qualified answers, i.e. a vaccine is never 100% safe, efficacious or cost-effective, but they support a systematic checklist to discuss all relevant aspects and help the Health Council providing independent advice to the Minister

of Health who will make the final decision. Also, it is important to maintain the programme acceptable as a whole.

In the same report produced by the Health Council in 2007 [2], the NIP was evaluated retrospectively using these criteria. Current vaccinations included in the NIP all met the seven criteria while none of the 23 candidate vaccinations received an unqualified positive recommendation, but four deserved more careful assessment, such as:

- HPV, which received a subsequent positive recommendation in March 2008;
- chickenpox/shingles, for which a preliminary negative advice was received due to perception of chickenpox as mild childhood disease versus potential increased risk of shingles in the elderly;
- rotavirus infection, for which advice should be provided in 2009;
- and HBV universal vaccination, for which a scientific advisory board report was issued in March 2009 [3].

With regards to HBV, on the basis of low prevalence and incidence, as in other Northwestern European countries including Denmark, Finland, Iceland, Norway, Sweden and the United Kingdom, the Netherlands has currently opted for a targeted approach as preferred option.

As a result from an assessment performed by the Health Council in 2007, using criteria previously discussed in this report, the country has decided to pursue with a risk group HBV vaccination approach, as illustrated below.

Assessment of HBV universal vaccination in the Netherlands (2007):

- Hepatitis B is serious, but uncommon in Northwestern Europe, mostly limited to specific risk groups (Criterion 1)
- Vaccines: are safe and effective with some uncertainty about duration of protection (Criteria 2-3)
- Vaccination is not beneficial for most people, so it is only acceptable from public perspective if targeted approaches do not reach risk groups sufficiently (Criteria 4-5)
- Initial unfavourable cost effectiveness ratios: 25,000-57,000 EURO/life year gained (l.y.g) [4], although not confirmed by later analyses (Criterion 6)
- So far, targeted approaches were preferred (Criterion 7)

Importantly, since the inclusion of horizontal transmission in cost-effectiveness analyses performed at the RIVM, thus taking into account transmission patterns among migrant populations which mirror patterns from high endemicity countries, cost-effectiveness ratios have become acceptable: 9,500-26,500 EURO/l.y.g [5], all the more so since vaccine price has come down since 2003.

However, the question whether to introduce universal HBV vaccination in the Netherlands should be carefully assessed against current targeted programmes, whose effectiveness should, in turn, be continuously assessed and improved.

An advisory report from the Health Council was expected December 2008, to be mainly based on the results of modeling comparisons. Those currently performed at the RIVM between targeted and universal vaccination approaches, using a dynamic model and screening of pregnant women as baseline data, indicate that universal approaches are more effective than targeted ones [6] while other ongoing modeling exercise from the United Kingdom rather suggests that universal approaches may be effective but at a very high price, thus not proving cost-effective [7]. Differences between analyses may be due to different models used, as well as different parameters, i.e. the Markov model used in the UK analysis is less sophisticated than the Dutch dynamic model, and mainly, UK policy making takes solely provider costs into account while, in the Netherlands, societal costs are also included.

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Based on a presentation by H. Houweling,
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Viral hepatitis surveillance in the Netherlands

Infectious disease surveillance in the Netherlands

In the Netherlands, infectious disease surveillance is one of the core tasks of the Centre for Infectious Disease Control, established in 2003 at the National Institute for Public Health and the Environment (RIVM). Surveillance is focused on diseases of public health importance at national level. RIVM also contributes to international surveillance networks coordinated by ECDC, WHO Regional Office for Europe and WHO Headquarter.

The main objectives of the epidemiology and surveillance unit are to trigger alert signals in case of acute changes in disease incidence, thus securing early warnings for outbreaks; detect slower changes

that require public health interventions; as well as the evaluation and adjustment of disease control policies. Surveillance of vaccine preventable diseases includes monitoring of disease incidence, vaccination coverage, sero-epidemiology, molecular surveillance, and reporting of adverse events following immunization.

Notification of infectious diseases

The first law on notification of infectious diseases dates from 1865 in the Netherlands. While hepatitis A, B and C are all notifiable today, some differences exist in modalities, i.e. importance of epidemiologically linked cases for HAV surveillance, HBV notification includes chronic infections since 1999; and since 2003, HCV notification is restricted to cases probably acquired less than 1 year before.
Notification is coordinated by RIVM, using *Osiris*, a web-based application which is in place since 2002, allowing reports to be produced, yielding very useful information for notifiers, as well as epidemiologists.

In order to comply with 2005 International Health Regulations initiated by WHO, a new Public Health law was passed in the Netherlands on 1 December 2008, replacing three previously existing laws on infectious diseases. In accordance with this new law, the responsibility of infectious disease control remains with municipalities except for polio, smallpox, SARS or any other health problem for which WHO has advised management at national level by the Ministry of Health. With this law, the number of notifiable diseases has increased to 42, with compulsory notification by clinicians, laboratories and heads of institutions.

Vaccination coverage

Monitoring of HBV vaccination coverage of infants born to HBsAg-positive mothers and children from immigrant parent(s) under the NIP relies on a web-based national register called *Praeventis*, which is linked to municipal population registers and includes all immunizations received by infants since birth. Yearly vaccination coverage is extracted from this *Praeventis* database, the annual report can be consulted on the RIVM website (http://www.rivm.nl/bibliotheek/#rapp).

In terms of HBV vaccination coverage among behavioral risk groups, as in other countries, no targeted population register is available in the Netherlands. However, as part of the national risk group HBV vaccination programme, data are collected from a national vaccination database where administered vaccine doses are documented, together with characteristics of vaccinated individuals, and their sero-status at first visit. Such data already represent a level of information that is not usually available in other European countries, even if it only allows for the estimation of vaccine coverage ranges, due to the lack of denominators in this population.

With regards to occupational HBV vaccination coverage, no specific surveillance system is available in the Netherlands.

Sero-epidemiological surveillance

Several data sources are used to provide insight on hepatitis sero-epidemiology in the Netherlands, including HCV sero-epidemiological data available from blood banks, yielding information within the lowest risk group in society and allowing to measure the risk for blood product recipients. HBV antenatal screening also provides data which can be considered as more representative although limited to pregnant women. Additional data is also obtained via testing of at risk individuals prior to HBV vaccination.

In addition to these data sources with complimentary but limited scope, sero-epidemiological data is mainly obtained at national level via the *Pienter* project, with the first one conducted in 1996 [1] and a second one in 2007. For the latter, laboratory test and analysis are still ongoing. A total of 48 municipalities participated in this second *Pienter* project, involving 7,395 data from individuals out of 20,000 invited (www.rivm.nl/preventie/vaccinatie/PIENTER), thus showing a relatively low response rate of ~ 35%. Importantly, in this 2007 study there was over-sampling of migrants in order to produce better HBV prevalence estimates than the 1996 study.

Molecular epidemiological surveillance

Systematic molecular typing is performed for HBV in the Netherlands, with all acute cases of HBV infections typed for a specific part of the genome in the pre-S2 and S-region since January 2003, as part of a collaborative project between RIVM, the Public Health Laboratory in Amsterdam and Erasmus Medical Centre in Rotterdam. Molecular typing of chronic HBV infections and HCV are only done as part of research projects to date.

Adverse event reports following immunization

Adverse events reported post-immunization represent a passive reporting system but it does not provide information on potential association of vaccination with onset of auto-immune or chronic diseases, addressing concerns such as those raised by the association of HBV vaccination with multiple sclerosis. Such information could only be obtained via epidemiological studies linking information between immunization and general practitioner visits or auto-immune/chronic disease databases. However, the use of such data has to be carefully weighed against ethical concerns relating to privacy.

Overall outputs from HAV, HBV and HCV surveillance are used in Dutch journals such as the '*Nederlands Tijdschrift voor de Geneeskunde*' and the *Infectious Diseases Bulletin*. Data are also presented to the Health Council for their use as advice and recommendations on vaccination policies. In the case of HBV, surveillance data is also published annually as part of NIP reports (RVP) on the internet and as part of an annual STI-HIV report (http://www.rivm.nl/bibliotheek/#rapp).

Limitations and future developments of viral hepatitis surveillance in the Netherlands can be summarized as follows:

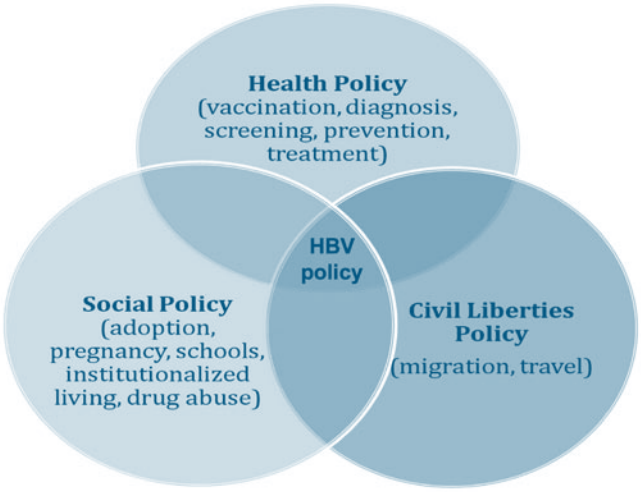
- **HAV** vaccine coverage is currently not recorded, hence specific national programmes targeted at children from migrant parents post-travelling to their home countries cannot be properly assessed in spite of positive observations in terms of reduced incidence and disease burden.
- **HBV** is a complex disease to accurately monitor because most infections are asymptomatic, mainly in children, and therefore not detected. Further factors make HBV surveillance data incomplete, such as vaccination coverage data not including occupational risk groups (data are only available from fragmented healthcare databases that could be

centralized); seroprevalence data collected from *Pienter* project not covering high risk groups (this also applies to HCV); HBV-related mortality not easily attributable to a particular form of infection/disease, and molecular surveillance of chronic infections not being representative today.

- **HCV** surveillance does not capture asymptomatic infections although they represent the majority of new infections. Molecular typing and other new diagnostic tools are needed to better analyse the data and provide more relevant insight in the dynamics of the disease. The notifiable disease system could be adapted for a better monitoring and prevention of (new) HCV infection.
- Specific developments desirable for **HBV and HCV** surveillance include continued molecular surveillance, to be complemented with the implementation of new tools in areas of research, such as surveillance of antiviral resistance, access to treatment (and monitoring of potential inequities), new phylogenetics methods (such as coalescence analyses), and behavioural surveillance.

Need for chronic viral hepatitis monitoring system

The need for a national strategy for the management of HBV and HCV was presented and should target monitoring, prevention, early diagnosis and access to care, involving national leadership, public health networks, and advocacy groups. However, a national policy for HBV and HCV is hampered by the complexity of distinct policy areas involved, as illustrated below.



The main factors contributing to suboptimal management of viral hepatitis - which are not specific to the Dutch situation- include a poor management of prevention, diagnosis and treatment of HBV/HCV patients by physicians combined with a global lack of awareness of disease burden and infectiousness, resulting in deprioritization, lack of resources and funding on the part of budget holders, policy makers, and governments.

Monitoring of viral hepatitis is needed in the Netherlands in order to better assess the magnitude of the problem and convince policy makers of the severity of disease too often obscured by the many routes of transmission for both diseases, as well as the fact that HBV and HCV are "silent killers", with many patients diagnosed for the first time with cirrhosis or hepatocellular carcinoma while they acquired infection 30-50 years earlier.

A better understanding of HBV and HCV disease mechanisms and a better monitoring of patients would in turn provide better insight into mortality statistics related to hepatic failure. Also, measuring the effect of current immigration and traveling would support better vaccination policies, such as routine HBV immunization, to be assessed more adequately, offering protection to immigrant as well as Dutch populations. Eventually, improved patient monitoring would also allow assessing the effect of treatment. Unlike 20 years ago, treatment is effective nowadays and has the potential to significantly reduce disease burden, should the number of treated patients be increased. Monitoring of patients is also essential to assess drug resistance which has already started to develop, particularly in the case of HBV.

Strengthened surveillance leading to reinforced detection, prevention and control of HBV and HCV in the Netherlands requires financial support for monitoring of patients and treatment at national level. Practically, monitoring and data acquisition could be linked to the existing system in place for HIV although only partially since HBV and HCV patients are essentially managed by gastroenterologists and hepatologists rather than infectious disease doctors. Numbers of chronic HBV and HCV patients and the related mortality data from this monitoring system could in turn be disseminated for the purpose of timely public health interventions at national and European level.

Ongoing initiatives include a successful network of chronic HCV patients registered within a collaborative research project in the Netherlands, which could be extended at national level. A proposal was also made for a European register (up to 170,000 patients included) to ensure enhanced funding. Successful experience was also reported from a funded programme in Greece since 2003 -with funding secured until 2011- to register HBV and HCV patients and follow-up every 6 months. However, no new patients have been added since 2008 because the database has already reached its full capacity with current funding available in order to continue follow-up of registered patients.

Viral hepatitis surveillance performed by the National Hepatitis Center (NHC)

The National Hepatitis Center (NHC) is an independent foundation working in cooperation with the government, patient associations, academic hospitals, public health organizations (GGD's) and the RIVM. The centre aims at drawing attention on viral hepatitis and its effects on individuals and society, focusing on the following activities: collection and dissemination of scientific knowledge and information; counseling and prevention; promotion of professionalism; and coordination and support of research studies and projects [2]. Daily access by phone and to the website offers all concerned up to date information about viral hepatitis.

NHC is currently involved in pilot HCV surveillance projects, supporting Health Council advice:

- 2007: *Hept.test Project*: anonymous online HCV self-testing
- 2007: Information to the general population/risk groups and general practitioner training on HCV
- 2007: Prevalence studies in pregnant women, STI-clinics, tattoo shops, and immigrants
- 2009: HCV part of the 2nd *Pienter* project study

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Based on presentations by

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Epidemiology of viral hepatitis in the Netherlands

HAV epidemiology in the Netherlands

Although HAV is not considered a serious public health problem in the Netherlands, as less than one fatal case/ year has been reported over the last years, the disease has implications for public health. Two major distinct transmission patterns have been identified in the Netherlands: transmission among MSM and importation from high endemic countries. Seasonal fluctuations related to Turkish and Moroccan children visiting their home countries have been observed, while an important number of infections remain of unknown source, potentially attributable to food borne transmission.

Data collected in 1993-2002 on reported HAV cases in the Netherlands show that the average age of reported infections is increasing, with more risk of complications since morbidity and mortality are more frequent in adults and adolescents. The prevalence of anti-HAV antibodies, assessed in the Dutch nationwide serum sample (N = 7367), collected in 1995-1996 for the population-based *Pienter* project, showed that overall, 33.8% of the Dutch population had anti-HAV antibodies [1]. Another study conducted in 2004 estimated the anti-HAV seroprevalence in the overall Amsterdam population aged >18 years old to be 57.0% [2]. For those born before 1945, 77% were anti-HAV antibody-positive but this was less than 10% in individuals born after 1960. Being born before 1960 and being of non-Western origin, appeared to be strongly associated with the prevalence of anti-HAV due to greater prior exposure to HAV. For those aged 15-49 years, HAV seroprevalence among Turkish (90.9%) and Moroccan (95.8%) was higher than among autochthonous Dutch (20.2%) and those originating from other Western countries (25.0%) [1]. Autochthonous Dutch and other Westerners born after World War II were less frequently exposed to HAV during childhood than older birth cohorts. Thus, more susceptibility is likely in the coming decades with greater risk of outbreaks in future years in age groups where the impact of infection is greater.

The impact of migration on HAV epidemiology in the Netherlands is discussed below in the section on migration and viral hepatitis.

MSM

In several studies transmission among MSM was described as one of the major HAV transmission routes in the Netherlands. However, in Amsterdam in 2004, no differences were found when the prevalence of anti-HAV in MSM was compared with the overall Amsterdam population. In the same study, the higher HAV prevalence among women having sex with women could not be statistically explained due to too low numbers [2].

HAV strains isolated from Dutch MSM living in Amsterdam were of genotype 1A, with few different strains identified, which were transmitted on a continuous basis among MSM for several years [3]. The reason for the HAV source and contact tracing approach by Municipal Health Service (MHS) not being effective among Amsterdam MSM is due to the fact that many MSM contacts are anonymous (dark room practices).

It was suggested that the use of a combined HAV/HBV vaccine for Dutch MSM could be considered the best option to address the transmission problem in this population, with little extra cost compared to the free of charge HBV target vaccination programme for MSM, but no cost-effectiveness data are available.

HAV infection of unknown source

For approximately 20% of notified HAV cases the source of infection is unknown and it could not be confirmed if these cases were food borne or related to another source. The currently ongoing national molecular epidemiologic surveillance conducted by all MHS and laboratories coordinated by the Centre for Infectious Disease Control at the RIVM on food-specimens collected since August 2008 should provide further clarification on this group of transmission.

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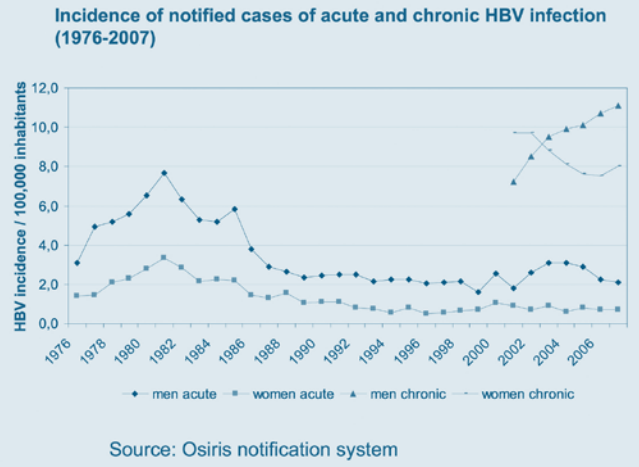
Based on presentations by J. van Steenbergen, Centre for Infectious Disease Control (RIVM), Bilthoven, the Netherlands.

HBV epidemiology in the Netherlands

According to the 2008 ECDC report [1], 7500 new HBV cases were diagnosed annually in Europe, with HBsAg prevalence varying widely. HBV mostly affects the 25-44 years age group, followed by those aged 15-24 years and men are 2.4 times more affected than women. HBV infection is clustered to several risk groups: injecting drug users (IDUs), immigrants from high endemic regions, sex workers, MSM, prisoners, healthcare workers (~300,000 in the Netherlands), HIV patients, and other high risk patients (haemodialysis or haemophilia patients, mentally ill or patients with Down syndrome; for a total of ~50,000 in the Netherlands).

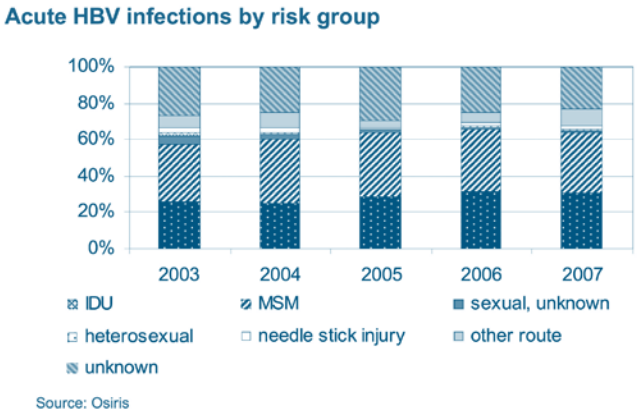
Data resulting from the Dutch national notification system *Osiris*, of acute and chronic HBV infections, show a peak in acute HBV incidence in the early 80's followed by a decrease to a constant rate over the last 15 years with a higher incidence in males than in females (see Figure below). The overall incidence of chronic HBV infections (notifiable since 1999) has been stable over the last 5 years. Thus, despite the targeted HBV vaccination strategy, the absolute annual number of newly notified HBV cases over the period 2003-2007 did not decline but remained quite constant over the last years, with a considerably higher number of chronic cases (1400-1600 cases) than acute cases (200-300 cases).



Women get infected at an earlier age (peak age category 20-24 years) whereas the peak incidence in men occurs at 35-44 years. Geographical distribution shows that incidence is highest in large, urban centres, such as Amsterdam and Rotterdam (up to >4 cases/100.000 inhabitants) whereas in rural areas the incidence is as low as <1/100.000 [2]. The overall average incidence for the country is estimated ~2/100.000 inhabitants, representing 300 officially notified acute cases per year with a male versus female ratio of 5:1.

In general, the notification systems for clinically diagnosed HBV infections suffer from important underreporting due to the asymptomatic character of the disease and related undiagnosed cases, and possible omissions in the notification of reported cases. For instance in the UK, it is estimated that 75% of symptomatic cases are reported. In the Netherlands the percentage of underreporting is unknown.

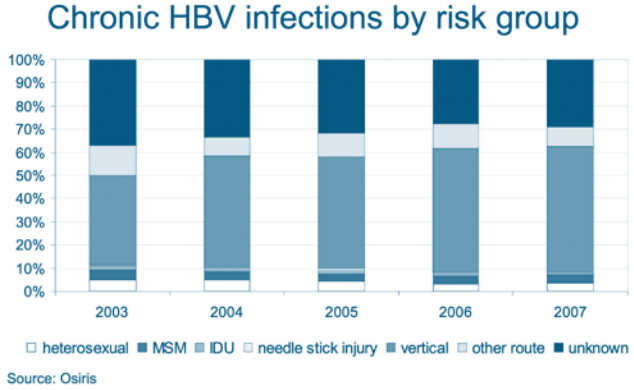
When considering acute HBV incidence by different risk groups (see Figure below), sexual contact is clearly the most important risk factor (65% in 2007), with an equal proportion of MSM and heterosexual contact among acute cases. In 2007, 10% of acute infections occurred through other routes and for an important proportion (23%) the source of infection was unknown. The proportion of acute cases due to healthcare occupational exposure (e.g. needlestick injury) (1%) or due to IDU (0.9%) was low. Of all acute cases 19% occurred in first generation immigrants with 17% infected abroad.



The large proportion of unknown sources of HBV infection is probably due to sexual transmission, horizontal transmission plays a minor role in the Netherlands. The few cases notified (in 0 to 4 years old) all had an immigrant background with 30-40% originating from Africa, but it was not possible to identify whether transmission occurred in their home country before moving to the Netherlands.

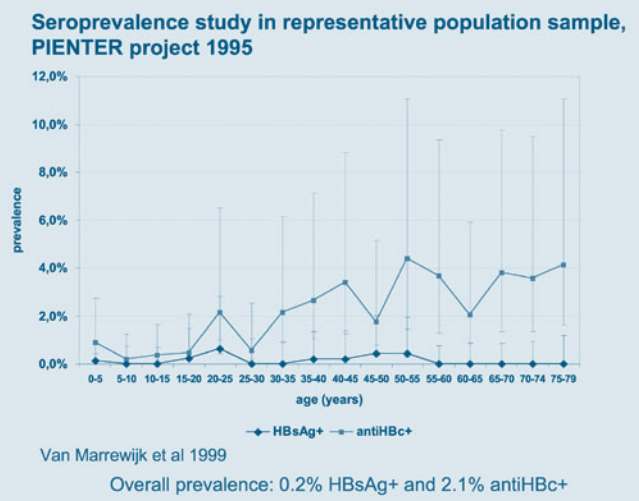
The distribution over the different risk groups is different for chronic cases where in 2007 54% of all cases are probably due to perinatal transmission and only a minority is due to sexual contact (7%) (see Figure). Few chronic cases are reported to be due to healthcare occupational exposure (0.6% needlestick injury) or IDU (0.6%), while in 29% the route of infection is unknown and 8% are caused by another source.

The high proportion of chronic HBV among first generation migrants is explained by the fact that they have become infected at birth or during their childhood in their country. The very low incidence of chronic HBV in IDUs (unlike high chronic HCV in IDU, see below) can be explained by the fact that injecting starts at adulthood when the probability of becoming chronic carrier is much lower than in childhood.
A much higher proportion of chronic HBV cases than acute case are notified in first generation immigrants and 73% of these cases were infected abroad.



The role of immigration in the HBV epidemiology is discussed later in this report.

The *Pienter* project conducted in 1995-1996 can be considered the most important nationwide seroprevalence study (n=7373) for the Netherlands. The Figure below shows the age-dependent prevalence for chronic cases (HBsAg positive) and of cases who ever had HBV (anti-HBc antibody positive) [3]. The overall seroprevalence rates for the Dutch population were 0.2% for HBsAg and 2.1% for anti-HBc antibodies. However, these figures are underestimated because risk groups were not included in a representative way. A second *Pienter* seroprevalence study with over-sampling of migrant populations to have more reliable estimates was conducted in 2007; with analyses ongoing in 2008, and 2009.



More insights in HBV transmission dynamics were gained from mathematical modelling. Model estimates revealed important differences in HBV transmission dynamics between the heterosexual and the MSM population. In MSM, HBV infection was found to persist with long transmission chains of specific clusters while import of newly infected persons has little impact on the epidemiology of the disease within the group [4]. In contrast, in the overall heterosexual population, transmission chains were short and non-persistent with few secondary cases but with a substantial effect of the import of infected persons.

An IDU-specific cluster nearly disappeared after 1998 [5], which might be an effect of the targeted vaccination program but could also be due to the decline in injecting practices.
No clear link between HBV genotype and severity (symptomatic versus asymptomatic character) was noted. Genotype A (64%) and genotype D (22%) were the most common genotypes in acute HBV cases. Within the genotype A cluster, the fraction of MSM decreased from 61% in 2004 to 47% in 2007, which is possibly a result of the targeted vaccination program. Genotype C (3% of cases), typically circulating in South-East Asia, was only observed in Dutch males and is possibly spread via sex workers. Surprisingly, in 4% of Dutch isolates genotype F was found (with a higher incidence of 24% in samples collected in the region of Friesland), while this strain was thought to be only circulating in South America and no transmission source for these genotype F cases could be identified.

The spread of antigen variants and HBV mutants with antiviral resistance appeared to be limited. Data on occult HBV infection are not currently available for the Netherlands but HBV DNA testing should be started as of end November 2008.
As a recommendation on the basis of the HBV epidemiology data presented and considering the number of HBV cases that could be prevented by vaccination, HBV disease would rank as a priority on the list of vaccine preventable diseases in the Netherlands.

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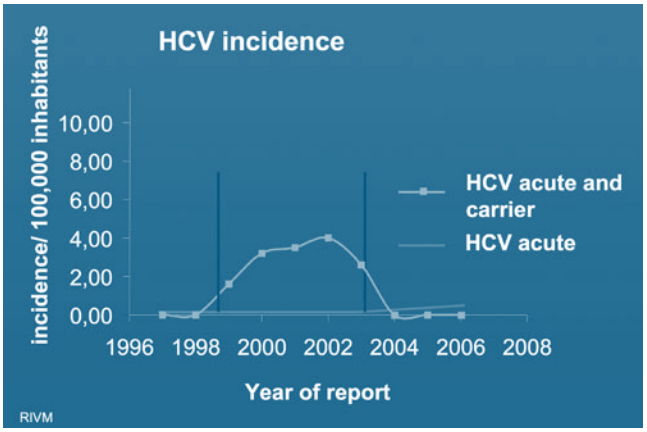
HCV epidemiology in the Netherlands

In Europe, 27,000 to 29,000 HCV cases are newly diagnosed per year. A high variability in HCV prevalence is noted across the member states ranging from low prevalence (≤0.5%) in the Netherlands to high prevalence (≥3%) in some other European countries. The age group 25-44 years is mostly affected by HCV, followed by the younger age group 15-24 years. Men are 1.9 times more affected than women. Groups at risk for HCV infection are IDUs as well as non-injecting drug users, HIV positive individuals, prisoners, immigrants from high endemic regions, healthcare workers with exposure to blood or blood products, patients with transplantation or transfusion of blood products before 1992, and individuals with tattoo or piercing. In contrast to HBV, heterosexual contact is no common transmission route for HCV. Recently, an important increase in HCV spread among MSM has been noted.

As of 1999 HCV is a notifiable disease in the Netherlands. Since then, 600-700 HCV cases were notified annually, of which 3% was acute and at least 85% chronic. Since 2003, a new case definition for HCV reporting was used whereby only HCV cases probably acquired less than 1 year before were to be notified, which explains

the decrease in the incidence data (see Figure below). Comparison of the data and interpretation of trends before 2003 are therefore difficult.



There is no reliable overall country estimate for the HCV prevalence in the Dutch general population. However, it is clear that since 2003, the number of acute HCV cases in the Netherlands tends to increase. As for HBV, the incidence of HCV is highest in large urban centres, including some peripheral regions of cities, with up to >20 cases/100.000 inhabitants reported by the Municipal Health Authority in 1999-2001. Prevalence rate estimates for the Dutch general population surveys are variable (from 0.08% to 0.66%) [1],[2],[3], most probably due to biased choice of population in these studies (see Table below).

General population – HCV prevalence

- Estimated HCV prevalence (0.1-0.4%)

Population	Year	Nr screened	Prevalence	Author
Dutch population	1995	7373	0.08%	*Veldhuijzen*
Amsterdam pregnant*	2003	5146	0.31%	*Urbanus*
Amsterdam population	2005	1355	0.66%	*Baaten*
Arnhem/Nijmegen	2006	2200	0.18%	*Slavenburg*

* Testing still ongoing

The anti-HCV prevalence as reported by the Dutch Health Council in 1997 ranges between 0.1% and 0.4%. On a total of 16 million inhabitants, this makes 16,000-65,000 anti-HCV positive individuals and 11,000-46,000 HCV-RNA positives. Due to the asymptomatic character of the disease it is estimated that 75% of HCV patients in the Netherlands are not diagnosed. Genotype 1a/b is most frequently isolated (50% of cases) followed by genotype 3a (30%), while genotypes 2a/b and 4a/d circulate less frequently in the Netherlands (each 10%).

Blood donors

Since 1991, blood donors in the Netherlands are screened for HCV at each donation using anti-HCV ELISA and since 1999 also with nucleid acid testing (NAT). HCV prevalence observed among Dutch blood donors ranges between 0.1-0.3% in new donors and is approximately 10-fold lower in repeat donors [4]. Because blood donation is unpaid in the Netherlands, blood donors probably represent a selected population at low risk, and therefore their prevalence rate is not representative for the general population.

HCV prevalence and incidence rates among Dutch donors were extremely low with a negligible estimated residual risk of transmitting HCV of approximately 1 in 30 million donations in 2000-2002. The genotypic pattern of HCV isolates in donors mainly depends on geographic origin, route of transmission and year of infection. The majority of the donors were infected with IDU-related subtypes 1a and 3a, whereas subtype 1b was traced back through previous contaminated blood transfusions or various other nosocomial modes of transmission. The presence of genotype 4 and other rare subtypes could be associated with infections acquired in endemic countries [5] and IDU.

HCV prevalence in risk groups

IDU

IDUs are at high risk for HCV infection through the sharing of needles and injection equipment. The Netherlands counts approximately 30,000 IDUs. An important decline in HCV prevalence from 86% in 1986 to 44-64% in 2005 was observed among IDUs in a large Amsterdam cohort study [6]. In this study, HCV prevalence in non-injecting drug users was clearly lower (6.5%) compared to IDUs (44-64%), but still higher than in the general population and blood donors. Both the unpopularity of injecting drug use and the success of prevention campaigns such as needle exchange programs and methadone use, are likely responsible for the decline in HCV seroprevalence. The higher HCV prevalence among IDU in other cities (up to 79% in Rotterdam) is associated with a high proportion of HIV infection. Treatment, in combination with the continuation of prevention programs, might further decrease HCV transmission. HCV genotypes la and 3a are most prevalent among drug users in Amsterdam, but a genotypic shift towards difficult to treat genotypes (1 and 4) is observed.

Some studies found an alarming high frequency of HCV reinfection and HCV persistence within IDUs, which suggest the absence of protective immunity. This may imply limited possibilities of successful development of a vaccine against HCV disease.

MSM

Between 2000 and 2003, a 10-fold increase in HCV incidence, up to 0.87/100 person years, was observed among MSM in the Amsterdam cohort study, with HCV infection almost exclusively found in HIV positive MSM (97%) with high risk behaviour [7]. Similar increasing HCV incidences were noted among MSM in other European countries (with the same MSM specific strains emerging), Australia and the United States of America, suggesting a large international transmission network, with distinct, sexually transmitted HCV strains clearly phylogenetically different from IDU strains.

The unexpected, rapid spread of HCV among HIV positive MSM starting in the late 90's was related to several potential factors. These included increased sexual risk behaviour following the introduction of HAART and altered sexual networking due to better communication networks such as the Internet. Sexual techniques potentially leading to mucosal damage, concomitant STIs and drug use seem facilitating factors for spread. The role of HIV in the spread of HCV among MSM remains unclear, but increased susceptibility (lower immunity), high HCV infectivity and high HIV viral load, as well as HIV serosorting may play a role.

Haemodialysis and haemophilia patients and blood transfusion recipients

Risk factors for HCV infection in haemodialysis patients were haemodialysis before 1992, kidney transplantation before 1994, and birth or dialysis in a foreign country [8].

The high prevalence of HCV among haemophiliacs (54% with current HCV infection and 15% with past infection, who cleared the virus) is explained by the fact that before 1992 donor blood was not screened [9].

The prevalence among individuals receiving transfusion before 1992 was 0.17%. Individuals with blood products received before 1992 were not actively identified in the Netherlands until recently. A campaign with TV spots has only recently been started in the Netherlands, while similar campaigns were already implemented earlier in other European countries.

Perinatal transmission

Approximately 20% of babies acquire HCV through perinatal transmission when mothers are HCV/HIV co-infected. This higher % of perinatal transmission in HIV+ mothers (20% vs 4% in HIV negative) might be explained by several hypotheses, such as immuno-suppression in HIV positives, higher viral load in co-infected individuals or higher virulence of the virus.

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HEV epidemiology in the Netherlands

Until recently, HEV was thought to be only travel-related and in the Netherlands no HEV diagnosis was requested in unexplained acute hepatitis patients without travel history. Recent figures on HEV seroprevalence (confirmed by Western Blot or PCR) are not very different from the situation 15 years ago: ~5% of acute hepatitis cases reported between 2002 and 2005 were due to HEV and seroprevalence among blood donors was 2-6% [1]. These figures show that HEV prevalence in the Netherlands is not very different from the situation in other European countries. As for most Western European countries, HEV infections in the Netherlands are due to genotype 3 (US/Swine genotype). Possible transmission routes for HEV genotype 3 are fecal-oral, waterborne, zoonotic, food born zoonotic and blood transfusion and organ transplantation. Due to high quality sanitation, waterborne and fecal/oral routes are not expected to occur frequently in the Netherlands. No large outbreaks are observed and person-to-person transmission is rare, but HEV is circulating in the environment (river water, ditch water).

In Dutch swine herds, PCR-based prevalence of HEV is approximately 50%. Possible zoonotic transmission from domestic swine to humans was suggested after the discovery of porcine HEV strains that showed extensive similarity to human HEV strains. Direct contact with swine was suggested to be a risk factor for HEV seroconversion among veterinarians and swine farm-workers compared to control individuals, when using a Bayesian approach. This could however not be confirmed when a validated diagnostic algorithm was applied [2]. In patient cohorts, being a swine worker was not found to be a risk factor.

Although there is no proof that HEV transmission occurs through porcine meat, the possibility can not be ruled out. A small HEV outbreak with a presumed common source of uncooked pig meat consumption was recently reported in the Northern part of the country. Possible food borne transmission was studied by quantifying the presence and infectivity of HEV in Dutch porcine meat, but the implications for human are currently unknown.

For many HEV cases in the Netherlands, the source of infection is unknown, with some having a history of blood transfusion [3]. Data from other countries indicate that HEV indeed can be transmitted through blood transfusion or organ transplantation.

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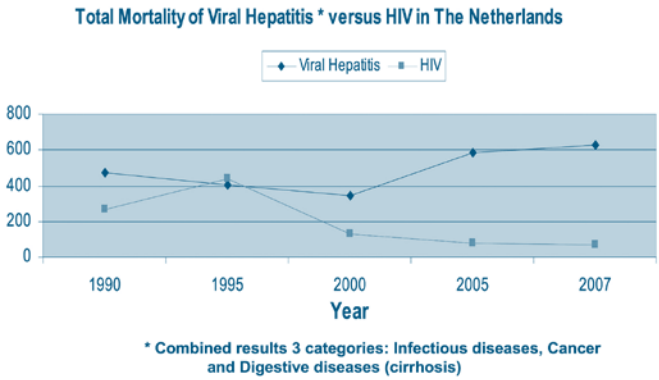
Mortality due to chronic viral hepatitis

Based on the Dutch national reference databases for disease burden (www.rivm.nl/vtv/ and statline.cbs.nl/), an average of 26 persons per year died from HBV over the years 2000-2006 in the Netherlands, with the large majority due to chronic HBV. No data for fatal HCV are available in the national databases. Of important notice, these official mortality rates for HBV ignore mortality due to cirrhosis and HCC. Estimates of the contributions of chronic HBV and HCV infections to mortality from cirrhosis and liver cancer had been lacking. Therefore, prevalence rates of serologic HBV and HCV markers among patients diagnosed with cirrhosis or hepatocellular carcinoma (HCC) of published reports were used to estimate attributable fractions of cirrhosis and HCC [1].

When applying these estimated HBV and HCV contributions on Dutch figures for 2007 (statline.cbs.nl/), the estimated mortality rate due to HCC comes to ~250 cases/year attributable to HCV and a smaller proportion of ~100 annual deaths is estimated related to HBV. For cirrhosis, >350 deaths/year were registered in 2007 and of these ~50% are estimated attributable to HBV or HCV.

The annual mortality of viral hepatitis as registered in the 3 categories Infectious Diseases, Cancer and Digestive diseases/cirrhosis in the Dutch database (statline.cbs.nl/) versus HIV is shown in the Figure below. Mortality due to HIV clearly declined after 1995 due to HAART, but the estimated mortality from chronic HBV and HCV became more important after 2000 in the Netherlands and is now several times higher than the reported HIV mortality and is rising despite introduction of antiviral therapy and the availability of a vaccine against HBV.



This trend was confirmed by mathematic modelling of the natural history of chronic HBV disease. According to this model, the liver related mortality over a 20-year period (2005-2025) in the hypothetical Dutch cohort with chronic HBV was estimated to be 200-400 annual deaths. Furthermore, the model predicted that 20% of chronic HBV patients without cirrhosis and 74% of those with cirrhosis will have died after 20 years.

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Based on a presentation by
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Migration and viral hepatitis

Of the 16 million total population in the Netherlands, 10% are first generation migrants and 10% are second generation migrants. Main countries of origin of first generation migrants are Turkey (12.0%), Suriname (11.4%), Morocco (10.3%) and Indonesia (7.6%). There is no screening for viral hepatitis of immigrants entering the Netherlands.

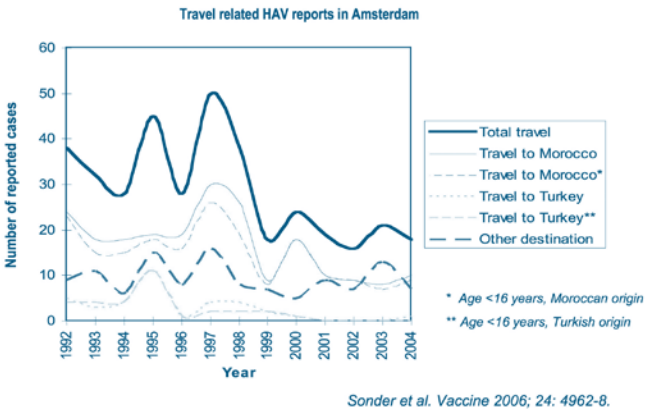
Impact of migration on HAV in the Netherlands

Although the Netherlands is a country considered with overall low endemicity for HAV, data are available showing that more prevention efforts in urban regions with higher endemicity are warranted. For instance in Amsterdam, HAV seroprevalence among first-generation Turkish and Moroccan immigrants (98.6% and 97.1%) was significantly higher than among Dutch residents (45.6%) and second generation immigrants (37.4%) (2004 data), indicating that second generation immigrants are comparable to the Dutch population in terms of HAV susceptibility [1]. Prevalence rates reported in Rotterdam in the age group 5-7 years old were even lower, only 2-10% of Turkish and Morrocan immigrant children were anti HAV positive. Thus, the majority of young Turkish and Moroccan children in Rotterdam are not protected against HAV, while they have a high risk of becoming infected when visiting their native country [2].

Another study conducted to investigate origin and travel history of registered HAV cases shows that not only young individuals originating from countries with high HAV endemicity who had been travelling are at risk for HAV but also their siblings who had not been travelling [3]. The potential disease burden caused by the high number of HAV cases among immigrant children should not be underestimated in the light of the recent epidemiological changes observed in South America where a rise of fulminant cases among children is noted [4].

Clusters of HAV strains circulating among persons from Moroccan origin (mainly genotype 1B) were identified, with import of many different new strains but limited transmission (only seen among siblings and in schools) [5]. Therefore, the Municipal Health Service (MHS) approach with case based source and contact tracing approach seems to work well for the immigrant population, as confirmed by low transmission risk and no tertiary cases observed in HAV outbreaks [6].

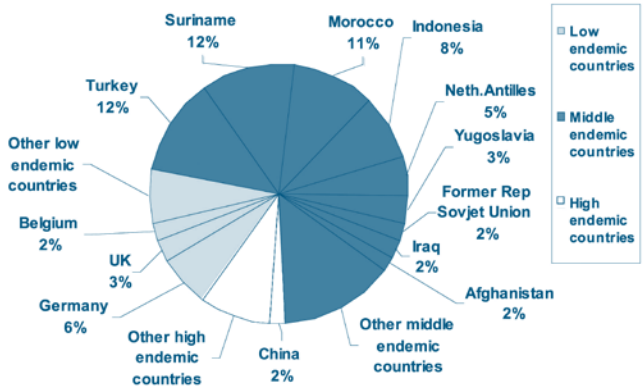
A decrease in the number of travel related HAV notifications in the Netherlands was observed after introduction of the HAV vaccine in 1997 (see Figure below for Amsterdam), but this also coincides with the decreasing HAV incidence in the endemic source country [7].



Impact of migration on HBV in the Netherlands

As shown in the following Figure, the majority (71%) of first generation migrants originate from intermediate HBsAg endemicity countries and 11% are born in high-endemic countries.

First generation migrants: Main countries of origin and HBsAg-prevalence levels



Of all HBV chronically infected individuals in the Netherlands, 58-72% are first generation migrants infected in an HBV endemic area.

The population of migrants was under-represented in the national *Pienter* project (1995 - 1996), which led to an underestimation of the true HBsAg prevalence [8]. The adjusted prevalence estimate for the Dutch population, when taking into account 3.77% HBsAg as estimate for the prevalence in first generation migrants [9], was calculated between 0.32 and 0.51%.

A difference in HBV transmission route between Dutch and immigrant populations was noted. In the Dutch population, sexual transmission accounted for the largest proportion of infections whereas perinatal transmission was reported to be higher in the group of non-Dutch origin [10],[11]. The low rate of HBV transmission from immigrants to Dutch population and absence of imported circulated strains, in spite of more than 50 years of immigration may be explained by the high proportion of subclinical infections not being detected.

When the effect of increasing infant HBV vaccination coverage in high and intermediate endemic countries becomes apparent in the coming years, migration is expected to have less effect on prevalence of chronic HBV infections in low endemic countries, including the Netherlands.

Impact of migration on HCV in the Netherlands

The estimated overall HCV prevalence among first generation immigrants in the Netherlands is 2.2%, with HCV positive immigrants mainly originating from Turkey (1.5-2.9% are HCV positive), Suriname (1.0-5.5%), Morocco (1.1-2.9%) and Indonesia (2.1-2.9%) [12].

Of all HCV infections in the Netherlands, 56% occur in first generation migrants [13] and among HCV infected voluntary Dutch blood donors, 12% were born in HCV endemic countries. Long-time residence abroad (>5 years) was also identified as a risk factor for HCV transmission [14].

Migrants and their close contacts are a very important target group in the Netherlands for hepatitis screening and prevention programmes as well as for treatment programmes for chronic HBV and HCV.

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Based on presentations by
J. van Steenbergen, Centre for Infectious Disease Control (RIVM), Bilthoven, the Netherlands
and T. Wörmann, Department of Public Health Medicine, School of Public Health, University of Bielefeld, Germany;
S. Slavenburg, Radboud University Medical Centre, Nijmegen, the Netherlands.

HIV and viral hepatitis co-infection in the Netherlands

Liver related disease has become the second cause of death in HIV-infected patients, after AIDS. In the Netherlands, there were approximately 12,000 HIV infected patients in follow-up in 2007.

HIV/HCV co-infected patients

Not all Dutch HIV-positive individuals have been tested for HCV. Among the 7424 HIV-patients tested, ~10% are HCV co-infected, and this is lower than in other European countries where the average HCV co-infection prevalence among HIV-positives is 33%. In the Netherlands, 94% of co-infections are attributable to IDU. Due to prevention strategies, this proportion is declining and a shift to an increasing category of MSM, currently accounting for 3% of the coinfected individuals, is observed. HCV genotype 1 is most prevalent in HIV/HCV coinfection, followed by genotype 3.

HCV is a slowly progressing disease compared to HIV: 25% of HCV infected patients will develop liver fibrosis after 25 years, whereas 90% of HIV infected patients develop AIDS after 15 years if not treated with HAART. HIV co-infection not only results in more HCV patients to develop liver cirrhosis but also the mean time to cirrhosis development is much shorter. HCV patients also have an increased risk of dying of liver disease when they are co-infected with HIV. When looking at the etiology of liver cirrhosis in the HIV infected population, the majority of cases (~80%) are due to HCV. Furthermore, treatment of HCV is known to be much more difficult in HIV/HCV co-infected patients than in HCV mono-infected patients, with a less favorable clinical outcome, this is related to higher HCV viral load, higher BMI (due to lipodistrophy), and faster progression to liver fibrosis.

HCV co-infection has a profound influence on the health outcome of HIV patients. Therefore, screening of HIV-infected patients for HCV on a yearly basis is recommended, in addition to more frequent liver enzyme testing.

HIV/HBV co-infected patients

HIV is known to negatively affect HBV infection, resulting in:

- Increased carriage (HBeAg) rates and decreased seroconversion rates
- Higher levels of HBV viremia
- More rapid decline of anti-HBs antibody titres after HBV vaccination
- More reactivation episodes (flares)
- Faster progression to cirrhosis
- Liver cell carcinoma occurs at younger age and is more aggressive
- Lower CD4+ cell counts associated with increased risk for HCC
- Possibly increased mortality (but conflicting data in literature)

Among the Dutch HIV infected patients tested, 7% have an active HBV infection. In the Netherlands, all HIV infected patients are offered HBV vaccination.

The treatment algorithm to start HBV antiviral therapy in the Netherlands takes into account the level of HBV viral load, liver function tests and status of liver fibrosis. Although many antiviral drugs are available, drug choice requires careful consideration since some cause HIV virus drug resistance. Combination antiviral therapy in HIV/HBV co-infected patients not only results in treatment success in terms of HBV viral load (most patients achieve undetectable viral load) but also results in slower progression of liver disease. HBV infection has no impact on response to HAART.

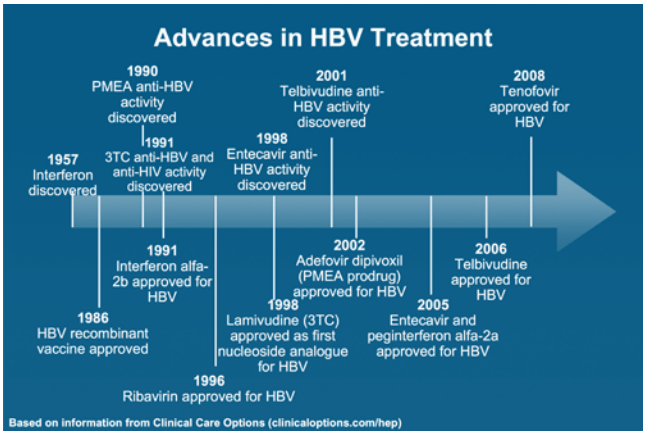
Based on a presentation by
Andy I.M. Hoepelman, University Medical Centre, Utrecht, the Netherlands.

Viral hepatitis prevention and control in the Netherlands

This session discusses current measures for prevention and control of viral hepatitis in the Netherlands, including HBV/HCV screening and treatment. Both prevention and treatment of viral hepatitis could well be optimised in the Netherlands. HAV and HBV vaccination strategies are extensively discussed in the next session *Vaccination programmes in the Netherlands*.

Need for chronic viral hepatitis monitoring system

Both chronic HBV and HCV infections are silent killers. Many infected individuals do not experience any complaints until they develop liver cirrhosis or liver cancer 20-30 years post-infection. When patients are identified, effective treatments are available (see slide beside). Several studies have shown that antiviral therapy may lead to virus suppression in 90% of chronic HBV patients and



cure in 30%. In the case of chronic HCV, approximately 60% of cases may be cured, thus confirming that treatment strategies have significantly evolved during the last decades [1-8].

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Based on a presentation by
H.L.A. Janssen, Erasmus University Medical Centre,
Rotterdam, the Netherlands;
and related meeting discussions.

Prevention and treatment approaches in HCV risk groups

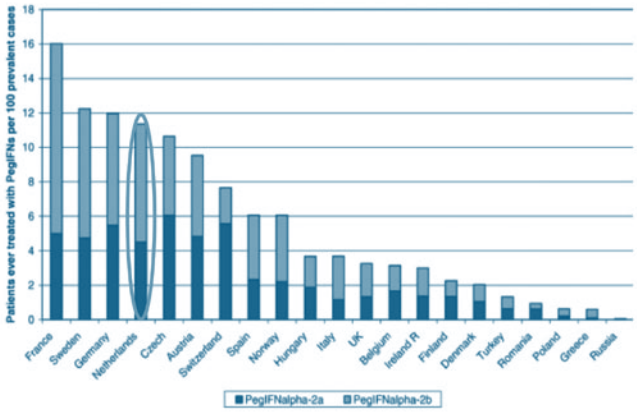
As in other countries, IDUs represent the main risk group for HCV infection (60% of all cases) in the Netherlands. Therefore, some study projects were started with screening programmes mainly focusing on individuals enrolled in methadone maintenance treatment (MMT) programmes and imprisoned individuals.

While methadone use reduces transmission and infection risk, MMT programmes additionally contribute to HCV prevention by recommending screening of all patients and providing an ideal setting for risk reduction counselling and additional health interventions. A specific screening programme called *Active Testing* was initiated in 2007, in collaboration with public health services, but results are not available yet.

Comparable projects in other countries of IDUs entering an MMT programme show similar cure rates, with sustained virological response (SVR) rates around 50% [1,2]. Also, DUTCH-C study (Drug Users Treatment for Chronic HCV) of Health Service in Amsterdam shows very good interim results when IDUs are treated in a multidisciplinary setting.

As IDUs continue to drive the HCV spread, it is obvious that its control must include systematic programmes in this risk group. Several studies have shown that MMT programmes, combined with syringe exchange programmes, directly observed therapy (whereby patients come to the healthcare centre for each treatment to be administered), and a multidisciplinary approach, are essential in the management of HCV-infected IDUs. In the Netherlands there are very good examples of successful full harm reduction approaches in which needle exchange has been combined with methadone treatment, resulting in a significant decline of HCV incidence [3].

The need for enhanced HCV control measures is confirmed by the percentage of treated patients with peginterferon reported for the Netherlands in 2008 [4], which is still as low as 12% (see graph below), while early detection and treatment offers the opportunity of gaining years of life.



In the context of alarming continued transmission of HCV among HIV-positive MSM, systematic HCV screening of this population is therefore recommended. Early diagnosis is important since early treatment is more beneficial and risk reduction counselling can prevent new cases. Targeted education and prevention strategies are also needed to raise awareness of HCV risk among HIV-positive MSM. Meanwhile, HIV-negative MSM should be monitored.

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Based on presentations by
R. de Knegt, Erasmus Medical Centre, Rotterdam, the Netherlands;
H. Reesink, Academic Medical Centre, Amsterdam, the Netherlands;
and T. van de Laar, Public Health Service Amsterdam,
Amsterdam, the Netherlands;
and related meeting discussions.

Modelled impact of treatment on the control of chronic HBV

Early identification of chronic HBV infection is essential to prevent transmission, as well as to ensure that infected individuals receive necessary care, preventing or delaying onset of liver diseases. Initiating medical evaluation and treatment at an early stage, before symptoms occur, thus potentially results in gaining years of life.

Thanks to the availability of many approved medications for the treatment of adults with chronic HBV infections and recent advances in the detection of liver cancer, the identification of HBV infected individuals permits implementation of effective intervention strategies that have the potential to reduce morbidity and mortality caused by chronic HBV infection.
The issued recommendations for the identification of chronic HBV infections and treatment guidelines can help the public health management of this infection [1-2], however knowing the long-term outcome of the available antiviral therapy in terms of reduction in morbidity and mortality, and especially the impact of antiviral resistance, would be beneficial for public health decision making.

The results from a study, which assessed the potential impact of antiviral therapy and antiviral resistance on chronic HBV burden of disease, within a median follow-up of 20 years, using a mathematical model, should become available shortly [3]. Main findings indicate that if all patients from the active chronic HBV cohort included in the model would be fully treated, liver-related mortality would be reduced by almost 80% with a low resistance profile drug (i.e. drugs unlikely to cause resistance). Beneficial effects of antiviral therapy were observed both in reduced development of cirrhosis, as well as reduced complications of cirrhosis. Importantly, the use of high resistance profile drugs (i.e. drugs likely to cause resistance) may reduce the clinical benefits of antiviral therapy by almost 50%, if antiviral resistance remains unaddressed.
In terms of public health strategy, results from this study indicate that long-term antiviral therapy with low resistance profile drugs may have a substantial preventive impact on reduced mortality and morbidity related to chronic HBV.

Such findings support the need to increase detection and monitoring of HBsAg-positive individuals and to optimize current referral in the Netherlands. The current proportion of 10% treated HBsAg-positive patients could also be raised to 30%, while 60% HBsAg-positive patients are inactive carriers kept under observation by GP as there is usually no disease progression for 10-15 years unless cirrhosis develops.

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Based on a presentation by
J.H. Richardus, Erasmus Medical Centre,
Rotterdam, the Netherlands;
and related meeting discussions.

Healthcare-associated viral hepatitis

Transmission from infected personnel to patients: management of HBV-infected personnel

In 1999, the so-called *Veghel incident* happened in the Netherlands, whereby a surgeon infected 8 operated patients with proven identical HBV sequence, probably infected 2 more, and possibly 20 additional cases [1]. On this occasion, a *Committee for the prevention of iatrogenic HBV* was established in the Netherlands in 2000, which produced legally binding guidelines on the management of HBV-positive personnel issued in 2002. These guidelines were subsequently revised in 2007 in a document published by the RIVM [2]. Per guideline, HBV-infected healthcare personnel is excluded from performance of exposure prone procedures (EPP) according to a viral load threshold, expressed in HBV-DNA copies/ml.

Several Western countries have written guidelines for HBV, which differ on exclusion thresholds, thereby showing the critical absence of consensus: $>10^3$ copies/ml in the UK and Australia; $>10^4$ copies/ml as per European guideline; and $>10^5$ copies/ml in the Netherlands; whereas in the USA, Canada, New Zealand, Germany and France, local expert committees decide on exclusion, based on variable, case by case, analysis.

The number and nature of HBV-infected healthcare workers reported to the *Committee for the prevention of iatrogenic HBV* was reviewed over the period 2000-2008. It revealed a yearly decreasing number of cases from 12 in 2000 to 2 in 2008, with a total of 99 cases, among whom 50 individuals performing EPPs. These were mainly distributed among medical interns (11), dentists (9), anaesthesiologists (5), surgeons (5) and gynaecologists (4). Out of these 50 cases, 25 had low viral load and were therefore allowed to continue performing EPPs under HBV-DNA monitoring while 11 were initially excluded from EPPs due to high viral load. Among these 11 cases, five of them have resumed work to date, thanks to antiviral therapy. The remaining 14 cases stopped working, moved abroad, died, or changed profession [4].

Transmission from infected personnel to patients: management of HCV-infected personnel

There is currently no guideline for the management of HCV-infected personnel in the Netherlands. Only a few Eurpean countries have guidelines but without any standardization. In the UK, HCV-infected healthcare workers have to self-assess their level of exposure, decide to get tested, and are subsequently excluded from

EPPs if they are HCV-RNA-positive. Similarly, HCV-RNA-positive healthcare workers are excluded from EPPs in Australia and Italy, regardless of viral load level. On the other hand, a very low viral load threshold (10^3 copies/ml) is implemented in Germany, as well as acute infection, as criterion for exclusion from EPPs.
HCV-prevalence among EPP performing healthcare workers is unknown in the Netherlands. This has hampered the development of a guideline. However, the recent self-reporting of a surgeon with acute HCV infection may prompt the development of a guideline. EPP performers could be offered yearly HCV-RNA screening. Considering that higher cure rates can be achieved when HCV infection is detected at early stage, that EPP performers are at risk of infection from their patients, and that the risk of iatrogenic infection is real, yearly screening of all EPP performers seems justified, especially for thoraco-cardial and gynaecological surgeons. More generally, the need was underlined for the management of HCV-infected healthcare workers to be addressed at European level, focusing on promoting referral and treatment.

Transmission from infected patients to healthcare workers

There are several guidelines relating to the risk of occupational injuries in the Netherlands, including a guideline on needle stick injuries published in April 2007 by the RIVM [3]. The number and nature of occupational injuries reported to the Academic Medical Centre from Amsterdam was reviewed over the period 2003-2007, revealing a fairly constant number of yearly reported accidents, amounting to 927 over 5 years. Critical findings from this study have shown that the main cause of accident was needle stick injury (69 %); accidents happened most commonly with healthcare workers in training (33%) and most frequently during cleaning up after medical procedure. In 8.7% of cases, the source was HBV (1.7%)- or HCV (2.8%)- or HIV (4.2%)-positive and 5% of personnel was not immune for hepatitis B virus.
Findings from this study led to the implementation of prevention measures, including the introduction of safety devices and reinforcement of awareness programmes, particularly among personnel in training. However, the small number of transmissions actually occurring makes the impact of preventive measures difficult to be assessed.

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Based on a presentation by
H. Zaaijer, Academic Medical Centre, Amsterdam, the Netherlands.

Screening of migrants

HBV screening of migrants in the Netherlands is warranted since individuals born in HBV endemic countries represent an important risk group for HBV-related liver disease in the country. This group could be targeted for screening and benefit from the opportunity of currently available improved treatment options that would otherwise be missed since chronic HBV is mostly asymptomatic.
Although screening has been in place for various risk groups targeted by HBV vaccination programmes (pregnant women, MSM, drug users, and contacts of HBV patients), no screening programme has been initiated in the specific risk group of migrants.
Therefore, two projects were started aiming at promotion of HBV screening in the Turkish and Chinese populations of Rotterdam.

HBV screening in the Turkish population

The project was started in 2007 as part of a health promotion programme, with a view to identify behavioural and socio-cultural determinant factors of intention to be screened among the Turkish population in Rotterdam. A postal survey was conducted among Turkish-Dutch migrants aged 16-40 years, with the intention to be screened as outcome measure. In a second step, the project aims at screening 1,000 first generation Turkish migrants, representing 10% of the target population.
From analyses performed on survey results, it can be concluded that a higher level of satisfaction with the Dutch healthcare services has a positive effect on the intention to be screened. A positive attitude and perceived social norm regarding screening are also related to a stronger intention to be screened. However, a stronger perception of the link between HBV testing and sexual behaviour has a negative effect on the attitude and therefore on the intention to be screened. A positive social norm regarding screening is predicted by the perception of close family ties.
Next steps of the project will involve the development of a culturally tailored internet intervention. All first generation Turkish migrants in Rotterdam will receive an invitation to visit a website where HBV testing at a local laboratory will be offered. Follow-up will be performed according to current practice and, eventually the effect of the intervention will be assessed.

HBV screening in the Chinese population

A pilot project was started at the end of 2008 to inform and stimulate HBV testing and treatment or vaccination, as appropriate, among 500-1000 Chinese migrants living in Rotterdam, with HBV screening offered for at least three months. Post-campaign, screening data will be analyzed in terms of coverage and test results, disease awareness will be re-assessed, and there will be a process evaluation with project partners, eventually leading to a report.

Screening opportunities: systematic versus opportunistic approaches

Screening of migrants can be done via proactive approaches, either as *outreach* like the project in the Chinese population of Rotterdam or *systematic* like the project in the Turkish population of Rotterdam. Another option is an opportunistic approach, where screening is offered to individuals on the occasion of health service use, such as a visit to the GP. Because opportunistic programmes reach only the part of the population seeking health care, and active participation of the health care provider is required, coverage may be poor.
In terms of proactive approaches, outreach strategies-which are the

only available option to target illegal migrants- have been reported to be labor intensive and costly, as well as yielding low coverages (0.5%) [1]. No data are available yet on ongoing systematic approaches.
HBV screening coupled with treatment and subsequent vaccination of close contacts of persons found to be infected has been reported to be cost-effective among Asian and Pacific Islander adults in the USA, even with a prevalence as low as 1% [2], but no comparable data are currently available in the Netherlands. Therefore, a pilot study will be started at national level in order to assess the feasibility of HBV screening.

A mathematical model will be used to assess the cost-effectiveness of HBV screening targeted at first generation migrants from HBV endemic countries. Assumptions regarding the HBV prevalence in the target population, participation in the screening programme, the proportion of successful referral, and treatment compliance will be made based on the literature where available. To assess the impact of the assumptions on the cost-effectiveness estimates, sensitivity analysis will be performed, taking the low and high ranges for the assumptions.

While it was felt that costly migrant HBV screening programmes would benefit from funding at governmental level, the inclusion of HCV was discussed but eventually discarded due to the difficulty of conveying simultaneous messages on the importance of two diseases, and the related risk of confusing messages.

More generally, the importance of adequately targeting migrants and their close contacts in screening programmes was underlined, as well as providing them with HAV and HBV vaccination, and treatment of chronic HBV and HCV. Screening of all new entering migrants (with vaccination as appropriate) was considered to potentially help avoiding new cases while information materials on diagnosis, clinical course of the disease, treatment and prevention in foreign languages should be provided to support adequate care for migrants.

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Based on a presentation by
I. Veldhuijzen, Municipal Public Health Service Rotterdam-Rijnmond, Rotterdam, the Netherlands;
and related meeting discussions.

Pregnancy and viral hepatitis

Since 1989 pregnant women are routinely screened for HBV in the Netherlands, and the children from the HBsAg-positive mothers receive human immunoglobulins and a birth dose of HBV vaccine. In 2008, a project was started, focusing on follow-up of HBsAg-positive pregnant women.

Among ~200,000 annual deliveries in the Netherlands, 700 mothers (0.35%) are HBsAg-positive, including 25% of newly found carriers. Most women are immigrants, as appears from 2006 data from Amsterdam showing 41% of women coming from Africa and 35% from Asia, against only 15% from Europe.

Before the implementation of the postnatal vaccination programme in the Netherlands, 30% of infants born from HBsAg-postive mothers were perinatally infected, with 10-30% risk if mother was HBeAg-negative and 90% risk if mother was HBeAg-positive.
After the introduction of the postnatal vaccination programme, perinatal HBV transmission was reduced to $\leq$ 1%. This residual transmission is probably due to in utero transmission, or breakthrough infection, explaining vaccine failure.

Before 2008, several guidelines applied in the Netherlands for the care of newborns from HBsAg-positive mothers but none of them specifically addressed the pregnant women. Therefore, a multidisciplinary committee was established to revise these guidelines in order to ensure referral of HBsAg-positive pregnant women to specialists. In particular, a new guideline targeting midwives was designed while the general guideline for GPs and for HBV treatment both entail a specific paragraph relating to HBV and pregnancy. Main changes focus on the responsibility of the obstetrician (midwife/gynaecologist) to ensure that pregnant women are tested for HBeAg in the case of HBsAg-positivity and that HBeAg-positive pregnant women are referred to a specialist who will decide on the appropriate treatment approach, while pregnancy can be monitored by the obstetrician.

For HBeAg-positive pregnant women Lamivudine is the recommended treatment after 32 weeks of pregnancy in the current guideline. This decision is motivated by the fact that Lamivudine has been used, even in higher doses, in HIV-positive pregnant women, as well as in HBV-infected pregnant women with high viral load. There is no experience with Adefovir-dipivoxil, Entecavir and Telbivudine. Safety data on the use of Lamivudine and Tenofovir are derived from the antiretroviral pregnancy registry. Both drugs are also used in HIV-infected patients. For hepatitis B and treatment during pregnancy, most experience is established with Lamivudine, which is 'unofficially safe' during pregnancy.

Administration of Lamivudine during pregnancy increases the risk of HBV flare-up post-delivery to 60-65% instead of 45% risk observed without treatment. Finally, Lamivudine should be used with caution in the case of breast-feeding and it is recommended to wait for 48 hours to breast-feed after Lamivudine administration.

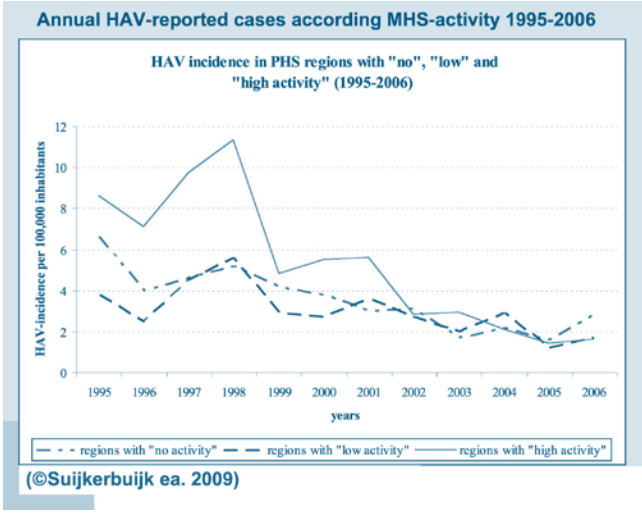
More generally, revised guidelines recommend enhanced communication between obstetricians, physicians, gynaecologists, midwives, specialists and infectiologists, as well as enhanced and improved communication with HBV-infected pregnant women who are most commonly immigrants from Africa and Asia.

Based on a presentation by
G.J. Boland, National Hepatitis Centre, Amersfoort, the Netherlands;
and related meeting discussions.

Vaccination programmes in the Netherlands

HAV vaccination in the Netherlands

A pre-travel HAV vaccination programme was set up to address the frequent import of HAV through travelling of Dutch migrants to their home country. Certain municipal health services organize specific HAV vaccination sessions for immigrant children, before travelling to their home country, but the vaccine uptake is low, e.g. <40% in Amsterdam. The effect of the pre-travel programmes was recently investigated among municipal health services with different level of pre-travel activity, going from no activity, over low activity (e.g. leaflet distribution), to high activity with active vaccination sessions [1]. As shown in the Figure below, the most important decline in HAV incidence was seen in regions where municipal health services had most active pre-travel vaccination programmes.



Interestingly, vaccinating Turkish and Moroccan children at pre-travel had a decreasing effect on the number of HAV infections with source in the Netherlands. The decline in overall HAV incidence was mainly due to a decrease among Turkish and Moroccan children aged less than 16 years.

In this study it remains inconclusive to what extend the vaccination programmes led to a decline in HAV notification. However, since HAV is still endemic in many countries it is important to avoid import of HAV by travellers to endemic countries. The vaccination coverage of immigrant children should therefore be maximized. A HAV vaccination programme targeting all immigrant children in Amsterdam was said not to be cost saving, but may have a favourable cost-effectiveness [2]. There is a HBV vaccination program in place that administers HBV vaccine to all children born with one or both parents originating from areas of medium or high endemicity. Implementing a combined HAV/HBV vaccination programme was considered as a solution, but it would be difficult to implement in infants since the combined vaccine can not be administered below the age of 1 year.

Although logistically, universal vaccination would be the best solution to reduce HAV burden, some felt the low number of annual cases in the Netherlands would not justify inclusion of HAV vaccination in the infant programme. As an alternative solution, funding vaccination of all children in Morocco and Turkey was proposed. Indeed, these countries are undergoing an epidemiological transition towards intermediate endemicity and therefore are expected to face epidemics with outbreaks in the future.
For the Netherlands, similar to flu vaccination strategies, a later-in-life HAV vaccination could be considered to protect Dutch elderly travellers.

HAV vaccination to address transmission among MSM is performed on a voluntary basis in the Netherlands. MSM have the possibility to be vaccinated against HAV at the municipal health service in the context of the HBV vaccination programme, through the use of a combined HAV/HBV vaccine at an additional cost. Coverage data of HAV/HBV vaccination among MSM are not directly available. Also, the cost-effectiveness of including the combined HAV/HBV vaccine into the programme for MSM was not studied.
HAV vaccine is also effectively used in case of food borne outbreaks in the Netherlands but was said to be costly.

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Based on a presentation by
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and related meeting discussions.

HBV vaccination in the Netherlands: Risk group approach

In the Netherlands, there are about 1,800 cases of HBV-infected individuals notified each year; the majority concerns individuals chronically infected prior to immigration to the Netherlands. The incidence of acute infection is very low in the Netherlands. This has in the past been one of the arguments why the Dutch Health Council has recommended a HBV high risk group vaccination strategy.

The HBV risk group vaccination programme in the Netherlands targets three main risk groups, discussed below: infants from HBsAg-positive mothers, infants from immigrants and behavioural risk groups. In addition, the programme targets a total of ~50,000 patients, including patients on hemodialysis, hemophiliacs and other patients regularly in need of blood products, as well as individuals institutionalized for mental illness and individuals with Down syndrome. Professionally at-risk individuals represent a further risk group amounting to 300,000 individuals.

Infants of HBsAg- positive mothers

Prevention of perinatal transmission is one of the primary aims of targeted vaccination, as infants infected at birth are at high risk of chronic infection. The number of home deliveries is high in the Netherlands. When the mother is HBsAg-positive, the birth dose of HBV vaccine and hepatitis B immunoglobulin is administered by the midwife.

Good vaccine coverage rates are obtained in newborns from carrier mothers: from 90.4% in 2003 to 97.4% of the birth cohort in 2005 [1]. Importantly, coverage is high across all regions of the country (>90%). The very high coverage reached in the Netherlands among infants of carrier mothers may be explained by a better, direct follow-up by one dedicated person, causing few dropouts. The incidence of breakthrough infections in the Netherlands is low: 0.7% for those who completed the vaccination series [2].

Infants of immigrants

Since 2003, all children with at least one parent born in an endemic country (HBsAg prevalence of at least 2%) receive free HBV vaccination in their first year of age (administered by nurses in infant health clinics as part of immunizations delivered through the NIP). However, children who are older than one year, e.g. siblings of targeted infants, are not included in the programme which targeted about 15% of the national birth cohort since 2003 (representing ~30,000 infants), but with large variation across the country (up to 50% of newborns in cities like Amsterdam).

Despite the fact that coverage is somewhat lower than for other vaccines and region-dependent, with half of the regions reaching a vaccine uptake >90%, the overall vaccine coverage rate among immigrant infants was rather good, 87-90% in 2003-2005 [1].

The impact of the immigrant infant vaccination strategy on HBV incidence is difficult to monitor because to date only children up to the age of 4 years have been immunized, and the incidence in this groups was already very low prior to introduction of the programme. In addition, most HBV infections in children are asymptomatic.

Although the targeted strategy for immigrant infants is important, the approach has some limitations. Parents as well as older children who also frequently travel to their home country often do not get vaccinated. The incidence of acute HBV among immigrants is nearly 3 times higher than in persons born in the Netherlands.

Behavioural risk groups

The risk group policy in the Netherlands was enhanced since 2002 by implementing a national vaccination programme to reduce transmission among behavioural high risk groups. Estimated HBV vaccine coverage for the different behavioural risk groups was 39% among drug users and 25% among sex workers (see Table below). Estimated vaccination coverage among MSM was only 6% and of these, 75% were fully compliant. Most probably the 6% is underestimated because the fraction is calculated using a denominator for all Dutch MSM, while not all MSM contribute to transmission. Practical experience indeed reveals higher coverage rates, especially among the core group responsible for transmission.

HBV vaccination coverage, October 1998 - December 2007

Risk group	Estimated total population	Vaccination coverage (range)
MSM	278,000-392,000	6% (4-7)
Drug users	24,000-46,000	39% (17-60)
Sex workers	20,000-25,000	25% (19-30)
Heterosexuals at high risk	195,000	17% (13-21)
Total	517,000-658,000	12% (8-15)

van Houdt et al, 2009 [3]

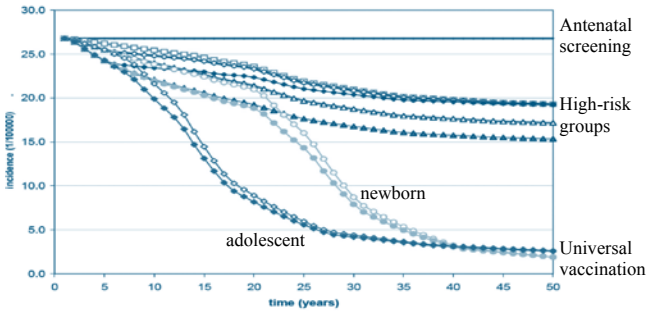
A decrease in the number of acute infections was noted for all targeted behavioural risk groups (see Table below), despite possibly increasing risk behaviour. However, in non-targeted subgroups with other mode of transmission or in those with unknown source of infection, a similar decrease in notifications is seen.

Most probable mode of HBV transmission	Number of reported acute HBV infections per year				
	2003	2004	2005	2006	2007
Homosexual	104	105	106	83	78
Heterosexual	84	74	89	75	69
Sexual	13	7	4	4	2
IDU	7	3	0	1	2
Other	30	33	13	15	18
Unknown	88	74	90	64	51
Total	**326**	**296**	**302**	**242**	**220**

Molecular typing data show that the typical MSM strain was found with decreasing frequency over the years 2004-2007, while the proportion of heterosexual transmission was increasing. The need to better target MSM at younger age was expressed, but it was also questioned whether intensification of the programme will be able to reach sufficient coverage (at least 70%) among younger MSM. Mathematical modelling predicting the impact of targeted vaccination among MSM in Amsterdam [4], concluded that even with modest coverage (2% each year), the targeted approach can almost eliminate HBV transmission among MSM, but only after a longer period and with a small incidence decrease in the initial phase.

Free vaccination of heterosexuals with high rate partner change was stopped in 2007 despite an important proportion of transmission occurring through heterosexual contacts (31%) and unknown sources (23%). This decision was justified by that fact that in these groups most infections are acquired from importations rather than sustained transmission within the Netherlands. When looking at travellers, Dutch pre-travel advice only recommends HBV vaccination for persons, particularly children, who stay for at least 6 weeks in countries with HBV prevalence >2% under primitive conditions. Countries such as Spain and Turkey are not on the list. In 2007, 17% of all acute HBV infections reported in the Netherlands were acquired abroad.

Mathematical modelling was also done to predict the impact of different approaches (only prenatal screening without vaccination, targeted risk group vaccination, universal vaccination) over 50 years (see Figure below; [5]). According to this model, using antenatal screening as baseline, universal HBV vaccination has the potential to decrease HBV incidence to significantly lower levels than what can be achieved with a high risk programme. Universal vaccination of adolescents is predicted to have a substantially faster effect because with infant universal vaccination, the most important incidence decline is only seen after 20 years (at onset of high risk behaviour).



Kretzschmar et al, 2009 [5]

Some participants to the meeting felt there is no real evidence that the Dutch targeted vaccination approach can protect the whole population, and they perceived the policy as not very effective. The majority of persons reported with acute HBV in the Netherlands do not belong to a risk group. Doubt was raised whether the costly risk-based approach, requiring a lot of effort, is the best approach in a globalizing world with increasing numbers of immigrants and intensified travel. However, recent economic evaluations have found that the targeted approach is cost-effective. Even when universal vaccination would be introduced, the selective programme would need to be continued for at least 20 years. In Norway, an expert recommendation was given to the government to include HBV vaccine in the NIP, because the only alternative would be to extend the current risk group approach (e.g. inclusion of sexual partners to IDUs and prisoners), but this further intensification would make it a very complex and more expensive strategy.

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Based on presentations by
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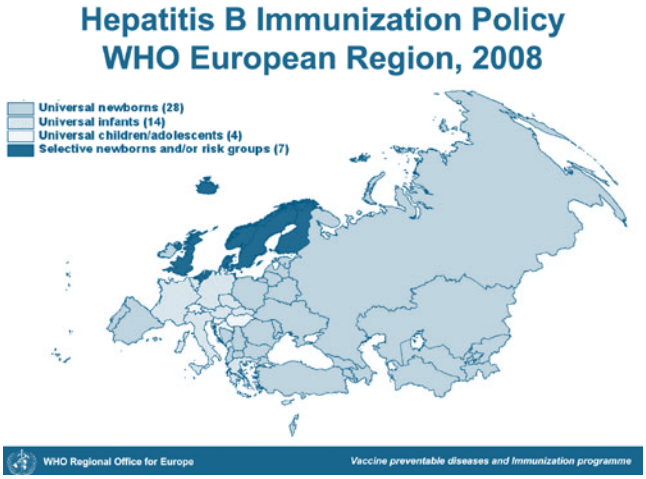
HBV vaccination in the Netherlands: universal approach?

Major reasons for implementing universal HBV vaccination were discussed during the meeting. The WHO European position, which strongly recommends HBV routine infant/childhood vaccination to all countries, was re-emphasized. These WHO relevant recommendations, outlined below, aim to decrease carrier rate in immunized cohorts, reduce HBV mortality and reduce the incidence of acute HBV infections worldwide.

Recommendations from WHO Hepatitis Position Paper 2004 [1]:

- Routine vaccination of all infants against HBV infection;
- High coverage of infant vaccination has the greatest overall impact on prevalence of chronic HBV infection and should be the highest HBV-related priority;
- Catch-up strategies targeted at older age groups or risk groups should be considered as a supplement to routine infant vaccination in countries of intermediate or low HBV endemicity.

As a result, successful HBV universal immunization is implemented in 46 out of the 53 countries of the WHO European region (see Figure below), with the exception of 7 countries with low endemicity, including Denmark, Finland, Iceland, Norway, Sweden, the Netherlands and the United Kingdom which have opted for a risk group approach.



In 2007, 95% coverage was reached in 28 countries implementing universal immunization (and reporting data to the WHO Regional Office for Europe), compared to 82% in 2003. Also, recent data reported from Italy confirm the impact of HBV universal vaccination with acute HBV cases reduced from 11/100,000 in 1987 to 1.6/100,000 in 2006; an emerging generation of young adults (all ages up to 27-year-old) with almost no HBV markers; and in South Italy, 20 years after implementation of vaccination, HBsAg rate dropped from 13.4% pre-vaccination era to 0.9%, while anti-HBc dropped from 66.9% to 7.6% in the same population.

In 1995, the Netherlands were seriously considering implementation of a universal HBV vaccination strategy. More than 10 years later, all countries considering universal strategy at that time moved forward to implementation (with most recently Ireland in September 2008 through the use of hexavalent vaccine) while this is still not the case for the Netherlands, the UK and the Scandinavian countries. Given the high level of immigration within the EU, the European Parliament (EP) stated in 2007 that the lack of uni-

Major achievements of the WHO Regional Office for Europe:	Challenges remaining for the WHO Regional Office for Europe:
• HBV universal vaccination introduced in most countries, even the poorest ones with GAVI support; • All countries with high endemicity provide first vaccine dose at birth; • HBV vaccine successfully combined with existing programmes; • The impact of universal childhood vaccination demonstrated on HBV-related disease burden; • HBV vaccine introduction used as a model for introduction of other underutilized and new vaccines.	• Seven countries not implementing universal HBV vaccination; • Timeliness and validity of reported birth dose coverage in high endemicity countries; • Discrepancies between reported and survey data relating to high coverage for 3-dose HBV schedule; • National data revealing under-performing districts and collection of data at sub-national data can be poor.

formity in vaccination policy threatens the potential for EU-wide strategies to contain the spread of HBV. The EP therefore recommends a uniform policy of vaccination across the EU, in line with WHO recommendations, and encourages a cohesive policy of all infants and adolescents as well as temporary vaccination of populations at risk. Meanwhile, in the UK, despite a strong call from the British Medical Association to introduce HBV vaccine in the national childhood schedule, no follow-up was given by the government. In the Netherlands, pro-vaccination pressure groups from the medical profession, advocating for better care of HBV patients, also questioned the Dutch government about intentions regarding implementation of routine HBV vaccination.

It was not assessed whether including HBV vaccine would reduce the NIP programme efficacy in the Netherlands, but concern of potentially losing coverage was expressed. However, at global level, from WHO experience, no impact is seen. Evidence from other countries (Belgium, Italy) shows indeed that introduction of a new vaccine to a well-functioning infant immunization programme can even increase coverage. Possible negative impact of the hexavalent vaccine on the immunogenicity and effectiveness of the *Haemophilus influenzae* type b (Hib) component was brought up during the meeting. However, Belgian and Italian experience shows there is no evidence of reduced Hib vaccination efficacy, since the number of Hib cases has substantially declined in the last years, especially in the younger age groups involved in routine vaccination with hexavalent vaccine [2].

In terms of safety, based on the billions of doses administered, the HBV vaccine has an excellent safety profile with only minor adverse events, as reported by the Global Advisory Committee on Vaccine Safety (www.who.int/vaccine_safety/en/). It was recommended to use these extensive global safety data and worldwide high compliance with HBV vaccination rather than re-starting the debate and investigations in the Netherlands. The presumed association of HBV vaccine with multiple sclerosis is still a problem of negative perception although plenty of studies and statements from health authorities and organizations (including WHO and CDC) show no scientific evidence [3-5]. Of note, both the US and Italian association of patients affected by multiple sclerosis immediately reacted in 1998 to the allegation occurring in France, stating there was no demonstration of a link between HBV vaccine administration and multiple sclerosis, and therefore there was no reason to suspend an important public health programme.

Another argument supporting implementation of universal HBV vaccination without further delay is that the vaccine can be easily integrated into the Dutch NIP with a high coverage guaranteed at relatively low cost (incremental costs of hexavalent vaccine over pentavalent vaccine). Universal vaccination is logistically easier, although it should be coupled with continued intensified risk group approach for a limited period of time. Nevertheless, the high risk group approach was said to be cost-effective in the Netherlands, despite being demanding in effort and logistics, but this was subject to debate. The cost of the behavioural high risk group strategy in the Netherlands was said to amount to 2 million euro per year. However, this excludes the targeted infant programmes as well as the costly HBsAg screening. A cost-effectiveness study directly comparing targeted risk group vaccination only versus universal vaccination was recommended, taking into account the potential for negotiating lower HBV vaccine price in the case of routine vaccination.

In addition to economic analyses, the forum recommended to consider routine infant vaccination as a philosophy of prevention and control because it offers protection to the entire next generation before risk behaviour starts, without discriminating between country of birth or sexual preference. Importantly, prevention of early childhood infection will decrease the number of persons entering unnoticed the large pool of chronic HBV carriers. Protecting the whole population against an oncogenic virus should be seen as an ethical duty of each country.

Following the above arguments in favour of universal vaccination, questions were raised about priorities, affordability and competition with other candidate vaccines for introduction of HBV vaccine into the Dutch NIP. It was emphasized that the decision whether low endemic northern European countries should introduce universal HBV childhood vaccination should be based on a balanced public health assessment. In response to this question, the forum recommended that benefits of routine HBV vaccination be considered at a global level, taking into account current changing behaviours rather than focusing on "a too low endemicity to benefit" approach.

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Based on presentations by
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Conclusions

Organization of the National Immunization Programme (NIP) in the Netherlands

The Dutch National Institute for Public Health and the Environment (RIVM) runs the NIP in collaboration with infant clinics and school health services. RIVM is also responsible for the continuous dissemination, education and evaluation of vaccine safety and effectiveness. The Netherlands Vaccine Institute (NVI) produces and/or buys the vaccines whereas the Dutch Health Council provides independent, scientific advice on the content of the NIP. Committee members include advisors from the Ministry of Health (MOH), RIVM and Medicines Evaluation Board (MEB).

The Dutch NIP is a strong programme with high participation rates and its content is continuously reviewed. This is done on the basis of an assessment framework, allowing informed decision-making, using seven explicit criteria for inclusion of a vaccine in a public programme. All vaccines currently included in the NIP meet these criteria. When applying them to 23 candidate vaccines, none of them resulted in an unqualified positive recommendation: four require additional analysis, including universal vaccination against HBV. A scientific advisory report on universal HBV vaccination was due end December 2008 and has been published in March 2009.

Viral Hepatitis surveillance systems in the Netherlands

Surveillance of infectious diseases is the task of the RIVM, supported by a well-developed and performing web-based notification system.
As of December 2008, surveillance falls under the scope of a new Public Health law, with a total of 42 diseases now notifiable, including HAV, HBV and HCV (if acquired less than one year before). Reporting is mandatory for clinicians, laboratories and heads of institutions. It is expected that this new Public Health Law will strengthen data reporting and collection.
Several databases and documentation systems linked to the population register are operational at national level in the Netherlands, such as *Osiris* (infectious diseases), and *Praeventis* (all infant vaccines). Information is also available from occupational health databases, as well as from different cohort studies. A national serum bank was established through the population-based *Pienter* studies (1995 - 1996 and 2007) to facilitate sero-epidemiology studies for HBV and HCV.
Some pilot projects on surveillance of HCV infection (targeting specific groups, such as pregnant women and STI clinics) are coordinated by the National Hepatitis Centre (NHC).
Very high standards of measurement and documentation, as well as special committees and guidelines exist in the Netherlands. However, discrepancies are still observed between reported and actual data relating to seroprevalence and disease incidence, as well as vaccine coverage rates.

Epidemiology of HAV in the Netherlands

Although HAV is not considered as a serious public health problem in the Netherlands, the disease has important implications. Seasonal fluctuations related to Turkish and Moroccan children visiting their home countries have been observed.
A decrease in the number of HAV notifications was observed after introduction of the targeted HAV vaccination programme for children of immigrant families, as well as effective source and contact tracing. This decline

also coincides with the decreasing HAV incidence in the endemic source country. Many different HAV strains are imported in the Netherlands but only a few are circulating in Dutch migrants. Implementing vaccination with a combined HAV/HBV vaccine in the existing HBV programme for children with one or both parents from areas of medium of high endemicity was considered as a solution. However, it would be difficult to implement in infants since the combined vaccine can not be administered below the age of 1 year.
In contrast to the immigrant population, continuing HAV transmission chains were identified among MSM. Contact tracing is far from evident because of anonymous sexual contacts. Adding the combined HAV/HBV vaccine to the HBV vaccine programme was considered as an option to address the transmission problem for the MSM population.
An ongoing nation-wide epidemiological surveillance study with collaboration at European level, including sequencing and phylogenetic analyses of HAV isolates, may further help identifying sources of food-borne HAV infections.

Epidemiology of HBV in the Netherlands

The adjusted HBsAg seroprevalence rate for the Dutch general population was 0.32-0.51% (*Pienter* project 1995-1996). Although the national prevalence rate is low, it can hide areas of higher endemicity in the country, such as large, urban centres.
Migrants also largely contribute to the chronic HBV infection burden in the country. Each year, ~700 pregnant women, mostly immigrants, are found positive for HBsAg. Despite the intensified targeted HBV vaccination programme, no decrease in HBV incidence was observed in the Netherlands over the last years.
Infection dynamics among different risk groups and the effectiveness of the targeted vaccination programme were investigated through molecular typing of HBV strain. The decrease in genotype A circulation among MSM could possibly be a vaccination effect. Furthermore, spread of HBV antigenic variants, immune escape or resistant mutants was limited.

Mortality statistics for HBV do not include mortality due to cirrhosis and hepatocellular carcinoma (HCC). When these are included, HBV mortality is several times higher than HIV mortality and is rising despite introduction of antiviral therapy. This trend was confirmed by mathematic modelling of the natural history of chronic HBV disease.

Epidemiology of HCV in the Netherlands

HCV prevalence in the Netherlands is ≤0.5%, which is at the lower end of the WHO European Region range. The Health Council reports 11,000-46,000 individuals affected by HCV, but due to the predominantly asymptomatic course of HCV infection, it is estimated that 75-80% of cases are not diagnosed. There is no reliable overall country estimate but different population surveys report 0.08-0.6% seroprevalence; differences being probably due to biased choice of populations studied.

Main groups at risk of HCV infection are injecting drug users (but with declining incidence), recipients of unscreened blood (in Europe before 1987), haemophilia and haemodialysis patients, first generation immigrants, and MSM, with an unexpected and rapid spread of HCV in HIV-positive MSM.

Epidemiology of HEV in the Netherlands

HEV is not a notifiable disease in the Netherlands. The anti-HEV seroprevalence among blood donors is about 2-6%. In acute hepatitis patients, 6% is HEV PCR confirmed. As in most other Western European countries, HEV infections in the Netherlands are due to genotype 3. The virus is found in surface water and in pigs, which form a huge reservoir, with 50% seroprevalence, but the role in human infections is still not clear. Until recently, HEV was thought to be related to travel. However, after a recent study of 19 HEV cases in the Netherlands, non-travel risks including older age, underlying disease, consumption of pig meat more than once a week, as well as receipt of blood transfusion, were identified and need further investigation.

Migration and viral hepatitis

Of the Netherlands' 16 million population, 10% are first generation migrants and 10% are second generation migrants. Most migrants originate from countries with historically intermediate prevalence rates of HBV and HCV, ranging between 1% and 5%, such as Turkey, Morocco, Suriname, and Indonesia. Among first generation migrants, HCV prevalence is estimated to be 2.2% and this population is responsible for 56% of HCV infections (besides IDU and transfusion recipients). Residents who were abroad for more than 5 years may also be at risk for HCV infection.

In low-endemic countries without a universal HBV vaccine programme, increasing travel and immigration contribute to increased prevalence of chronic infections and risk of HBV infection. In terms of impact of immigration on HBV epidemiology in the Netherlands, about 60-70% of all chronic HBV patients were born abroad in high-endemic countries. Furthermore, in 60% of heterosexually transmitted cases, the source was a partner from a HBV endemic region.

Prevention, treatment and control of viral hepatitis in the Netherlands

There is a general need for an integrated approach regarding prevention and control measures, including vaccination, against viral hepatitis. When deciding on viral hepatitis prevention strategies, changing epidemiological patterns should be taken into account, such as:

- HBV and HCV which have now become preventable (HBV) and treatable (HBV and HCV);
- HIV has become a chronic and manageable disease, requiring adapted prevention strategies and messages.

The full economic burden of HBV and HCV, including treatment and management of chronic liver disease and cirrhosis, should be established.

Behaviours can also change or can be changed (e.g. refrain from injecting drugs) but, to some extent only. Unsafe sex in travellers and increasing HCV levels in HIV-positive MSM remain behaviour-related issues.

Detection and monitoring systems for chronic HBV and HCV patients should be further developed in the future. Good antiviral treatments are available (including combination therapy in HIV/HBV patients) and early treatment is valuable but concerns about liver toxicity and resistance remain. Treatment of chronic HBV is a successful public health measure, but clinical benefits may be reduced by 50% if drug resistance is not addressed. There is a continued need for molecular testing, including surveillance of antiviral resistance, and access to treatment should be improved. Also, the impact of HBV treatment on perinatal transmission, and general practitioners' concerns or lack of knowledge about treatment in pregnancy, remain to be addressed.

Dutch guidelines for prevention of occupational HBV infections have power of law in the Netherlands. Their threshold for exclusion of infected healthcare workers is even stricter than the European recommendation. However, data collection and protection of healthcare workers is not seen as a high priority. Some personnel is still unimmunized but programmes to raise awareness among healthcare workers are being introduced. Like in most European countries there are no guidelines for HCV-infected healthcare workers. Although HCV prevalence among healthcare workers performing exposure prone procedures (EPP) is unknown, guidelines are currently in preparation, which possibly include recommendations for annual HCV screening of those performing EPP, especially for thoraco-cardial and gynaecological surgeons. The need was expressed to address the management of infected healthcare workers at European level.

Targeted screening of migrants and their close contacts will contribute to increased access to treatment of HBV and HCV.
Dutch guidelines on the management of HBsAg positive mothers have been updated to include monitoring and treatment (with Lamivudine) and this resulted in an increase of referred HBV-positive women seen by a specialist.

Immunization programmes in the Netherlands

New vaccines are being introduced in many European countries, with introduction of HBV vaccine functioning as a model for other, new vaccines. In WHO Regional Office for Europe, 46 out of 53 countries introduced successful universal HBV immunization for their infants and/or adolescents (in addition to their risk group policy), while 7 countries, including the Netherlands, opted for a risk group approach only.
HBV vaccination for newborns from carrier mothers was first introduced in the Netherlands in 1989. Subsequently, the immunization programme for at risk occupation and specific patient groups was intensified; in 2001 for healthcare workers and, in 2002, for behavioural risk groups. Since 2003, children with at least one parent from a country with high or intermediate endemicity are also included in the programme. In 2006, the birth dose of HBV vaccine for infants born from HBsAg-positive mothers was added. The current Dutch policy of continuing targeted HBV vaccination is in disagreement with the WHO recommendations of implementing routine HBV vaccination. In addition to the WHO, the European Parliament and British Medical Association have also called for universal immunization of infants against HBV, with supplementary targeted programmes.

In the Netherlands, high rates of HBV vaccination coverage are reached in newborns of HBsAg-positive mothers, combined with an effective perinatal transmission prevention programme. Sharing methods with other coun-

tries, e.g. one dedicated person overseeing immunization and follow-up of infants from HBsAg-positive mothers, helps increasing vaccine coverage rates.

High vaccination coverage is also achieved in immigrant infants. However, their parents as well as older siblings, who also frequently travel to their home country, are not included in the immunization programme. Based on the coverage rates, it was concluded that reaching target groups is feasible, although there is room for improvement and the actual impact remains difficult to assess. Occupational HBV vaccine coverage data are available from fragmented healthcare databases only. The interrupted HBV transmission among injecting drug users is both attributable to the HBV vaccine programme and to the decline in injecting practices.

The impact of HBV vaccination among MSM remains difficult to assess and, overall, the focus on MSM was considered not to be very effective. The official 6% HBV vaccine coverage among MSM is probably an underestimate.

The risk group programme was said to be cost-effective, however, it could also be seen as stigmatizing and not reaching all those at risk. HBV vaccine is offered free for MSM but not for heterosexuals at risk despite an important proportion of transmission (>50%) occurring through heterosexual contacts and unknown sources.

Outreach to groups at risk is complex, costly and of limited effectiveness: more than 30% of individuals with acute HBV have no identifiable risk factors and are therefore missed by any risk group approach. An up-to-date economic analysis of different vaccination approaches remains to be conducted. Strong arguments in favour of universal vaccination combined with risk group approach, being more effective and feasible were expressed while others vigorously defended the exclusive vaccination of risk groups. Questions were raised about the safety of HBV vaccines and the priorities and competition with other candidate vaccines for introduction into the NIP (such as human papillomavirus vaccine).

The meeting was concluded with lessons learnt and challenges identified during presentations and discussions:

Lessons learnt and challenges

Surveillance and epidemiology

- HAV, HBV and HCV are notifiable in the Netherlands (HEV is not).
- The public health sector in the Netherlands benefits from a very high standard of measurement, documentation and data collection. But similar to other low endemic countries, there is still a lot of variation in the reported data in the Netherlands.
- The new Public Health Law, effective since 1 December 2008, should streamline and enhance reporting of diseases and data gathering, while building on existing tools such as the population register, and the *Osiris* and *Praeventis* databases for infectious disease notifications and infant vaccination, respectively. The usefulness of this law still needs to be assessed.
- Mortality statistics in the Netherlands seriously understate the burden of HBV disease because deaths due to cirrhosis and liver cancer are excluded.
- Screening strategies require more attention. For instance, about 60-70% of all chronic HBV patients were born abroad in high-endemic countries, therefore routine screening of all new migrants would be preferable in order to manage prevention and control, but feasibility and stigmatization remain an issue.

Prevention and Control

- Lack of knowledge about viral hepatitis persists in the Netherlands among the general population and professionals. Therefore, providing good information is essential to overcome prejudice and barriers of ignorance, as well as to counter anti-vaccine lobbying.
- There is a continuing need for advocacy of themes such as:
  - HBV and HCV being “silent killers”;
  - HBV vaccine being promoted as an anticancer vaccine.
- Detection and monitoring systems for chronic HBV and HCV patients should be further developed, as good antiviral treatments are available and early treatment is valuable.
- The current immunization programme in place in the Netherlands (NIP) retains public confidence, confirmed by high coverage rates. It is a strong programme and Dutch health authorities want to protect it. However, evidence from other countries, such as Italy and Belgium, shows that introduction of a new vaccine does not undermine, but can even increase vaccination coverage.
- An approach of viral hepatitis surveillance and prevention at a global level (European Union, WHO region) would be more beneficial.
- In the European region of WHO, 46 countries of 53 implemented universal HBV immunization, with most recently Ireland starting the universal approach. Of the low endemic countries in Europe, only the Netherlands, UK and the Nordic countries choose to provide vaccine only to well-defined groups at risk.
- Targeted HBV vaccination programmes in the Netherlands are very successful in reaching newborns whose mothers are HBV infected (HBsAg-positive) and children with at least one parent from a country where

HBV is prevalent. However, risk behaviour is very difficult to predict and more than 30% of individuals with acute HBV have no identifiable risk, hence they will be missed by any risk group approach. Models suggest that continued reliance on vaccination of at risk individuals and targeted campaigns will reduce HBV incidence by 30% over 50 years.

- Universal vaccination is the best alternative to increasing the number and complexity of targeted HBV vaccination programmes, not reaching all those at risk.
- Prevention programmes should not only be cost-effective but also affordable. Economic evaluations in low endemicity countries, using realistic vaccine cost, have shown that addition of the HBV antigen in the existing universal programmes is economically attractive.
- Arguments to add universal vaccination programme in addition to the risk group approach in the Netherlands include: international recommendations, proven effectiveness, ease of integration into the Dutch immunization programme, the likely consequent decrease in morbidity and mortality, and protection of the whole future generation before risk behaviour start.
- The WHO Regional Office for Europe regrets the present Dutch policy of exclusive vaccination of risk groups. It recognizes that the programme to prevent perinatal transmission is highly effective, but recommends giving a high priority to the inclusion of the HBV antigen in the universal programme: it is a global and regional strategy to prevent future generations to contract HBV.

Based on a presentation by D. FitzSimons, WHO

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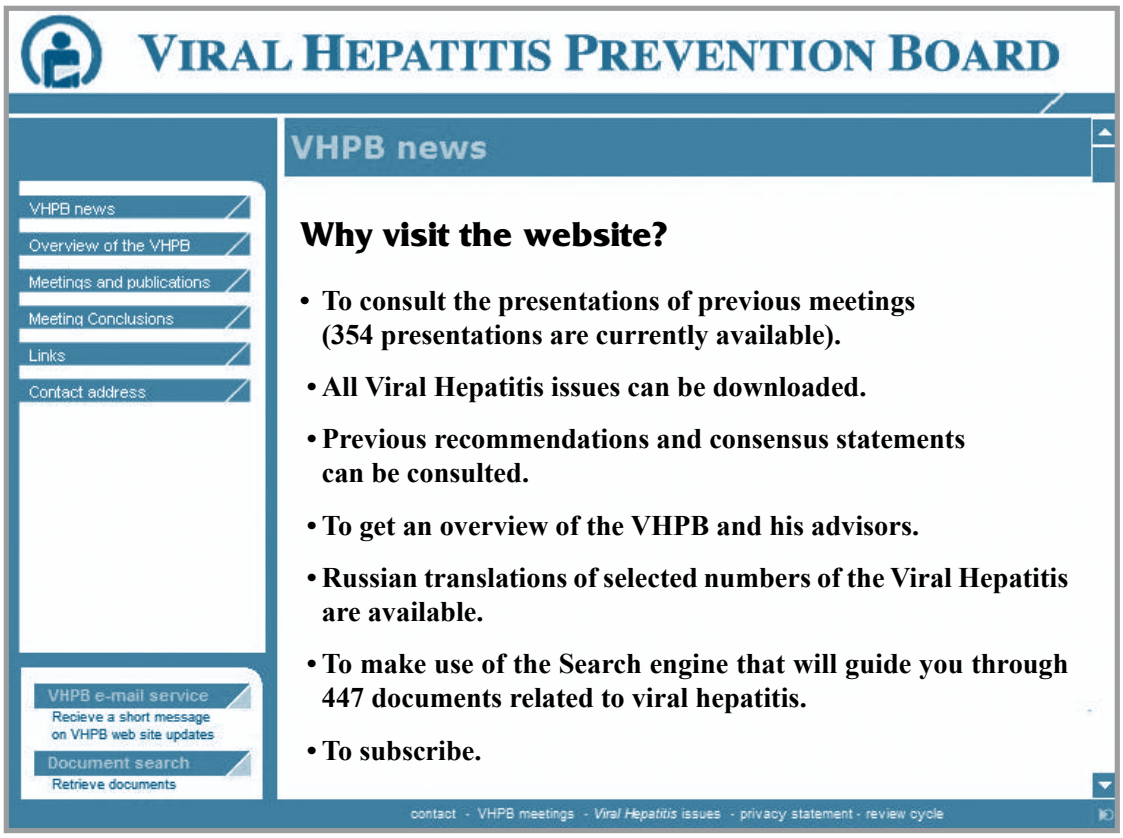

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