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CONTENTS

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Editorial

This issue of Viral Hepatitis reviews topics covered at the VHPB's spring meeting held on March 18-19, 2010 in Budapest, Hungary. After an overview of existing screening programmes and new developments in the treatment of hepatitis B and C, the meeting evaluated the extent to which the criteria for screening elaborated 40 years ago by Wilson and Jungner are applicable to current screening programmes for chronic hepatitis. Reports of health technology assessments of such programmes were presented, and participants weighed the benefits of screening against costs and potential harm that may ensue. Further discussions covered the conditions for screening, the strengths and weaknesses of the approach and its public health and social implications, including screening's impact on individuals. The meeting concluded with a review of lessons learnt, challenges, needs and proposed steps forward.

Several organizations have recently taken the initiative to promote screening and the identification of persons with chronic hepatitis. Because the implementation of screening programmes can have a tremendous impact on a country's health care system and its citizens, the VHPB advisors were convinced that it was important to discuss these different policies during the VHPB meeting.

There are approximately 600,000 deaths each year worldwide as a result of hepatitis B (HBV) and 350,000 due to hepatitis C (HCV). Around 500 million people worldwide are chronically infected with HBV or HCV, and most of them are not aware of it. Currently there is no clear evidence that screening, prevention and control strategies in the general population and even in risk groups are effective. In this meeting the gaps, and needs for policy makers to make decisions on the implementation of new prevention and control strategies, were discussed.

Therefore the VHPB considered it important to take stock of current surveillance and screening of chronic diseases and the lessons learnt. At present, surveillance data are insufficient and too heterogeneous, only in some areas is the quality of the data sufficient to form the basis of informed policy decisions. The collection of data at national and regional levels is in response to different needs and requests. The surveillance data lack validation, are based on inconsistent case definitions and are in most cases not intercomparable. Although there are a substantial amount of data available, mostly this does not provide the reliable information required. Strong coordination of surveillance, collection of data and analysis are required for progress to happen.

The criteria for screening that were published by Wilson and Jungner in 1968 are still valid 40 years later. To make them more applicable to current situations they have had to be adapted to take into account changes in medical practice, including defined objectives and target population, proven effectiveness of screening methods, equity of access, minimization of harm and evaluation. The suitability of these adapted criteria with respect to chronic hepatitis was evaluated during the meeting.

Population screening is a strategy used to detect a disease in asymptomatic individuals, enabling earlier interventions and management to reduce morbidity and mortality. However screening has a considerable financial cost. Furthermore, there is a potential for causing harm, and this needs to be balanced with the potential benefits of a screening programme. The effectiveness of treatments needs to be taken into account in this equation.

It is unlikely that screening the general population for HBV or HCV would be cost-effective, and it would become even less cost-effective as the prevalence is decreasing. Screening high risk groups seems a better strategy, but here also there is a lack of strong evidence. There are difficulties identifying these groups, persuading them of the benefits of screening, and providing treatment for people once identified.

Current initiatives in eight different countries have been recorded and are presented in order to learn about the advantages and disadvantages of different strategies for case finding. It is clear that screening programmes should be linked to primary health care and other 'easy access' programmes. There is a need to reduce the number of top-down decisions and mechanisms, in favour of patient-based organizations and community led programmes. There is no 'one solution fits all' but programmes need to be tailored to local needs, infrastructures and circumstances.

Screening is much more than installing a diagnostic test. Necessary resources must be allocated to develop effective screening programmes. If screening programmes are implemented, there must also be guaranteed assignment of responsibility, setting of priorities, adequate funding, medical resources to provide follow-up and treatment for suitable candidates, as well as monitoring and evaluation.

David Goldberg and Francoise Roudot-Thoraval,
on behalf of the Viral Hepatitis Prevention Board

Identification and Management of Persons with Chronic Viral Hepatitis in Europe, Budapest, Hungary, March 18-19 2010

Screening for persons with underlying chronic disease

In 1968, the World Health Organization (WHO) commissioned a report on screening for disease [1]. In the report, entitled, 'Principles and practice of screening for disease' - which has since become a public health gold standard - the authors JMG Wilson and G Jungner listed ten criteria that can be used to decide whether or not to introduce screening (see figure).

Wilson and Jungner classic screening criteria[1]

1. The condition sought should be an important health problem.
2. There should be an accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8. There should be an agreed policy on whom to treat as patients.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process and not a "once and for all" project.

However, over the past 40 years, a growing number of approaches to screening policy-making have been introduced. Most of them were variations of the original set, but new, additional criteria reflect emerging trends and changing medical practices such as non-paternalism, evidence-based decision making, and results-based management [2]. The figure below summarises proposed screening criteria which have emerged in the meantime:

Synthesis of emerging screening criteria proposed over the past 40 years

- The screening programme should respond to a recognized need.
- The objectives of screening should be defined at the outset.
- There should be a defined target population.
- There should be scientific evidence of screening programme effectiveness.
- The programme should integrate education, testing, clinical services and programme management.
- There should be quality assurance, with mechanisms to minimize potential risks of screening.
- The programme should ensure informed choice, confidentiality and respect for autonomy.
- The programme should promote equity and access to screening for the entire target population.
- Programme evaluation should be planned from the outset.
- The overall benefits of screening should outweigh the harm.

Perennial challenges in policy making for screening

Mainly due to changing patterns in epidemiology, knowledge of natural history of the disease, and innovations in diagnosis and treatment and other clinical developments, policy making on screening is an iterative process rather than a static one, and involves a range of issues including ethical considerations, individual and population perspectives, and a need

for multiple types of evidence. Ultimately, certain value judgements must be made and decisions will depend upon health systems and political contexts.

Screening policy-making raises many complex questions:
- Does screening provide an added benefit?
- Do the benefits outweigh the harms?
- Can the benefits be realized in this context?
- Is screening worth the opportunity costs?
- Which perspectives are used to decide?
- What evidence is needed to decide?

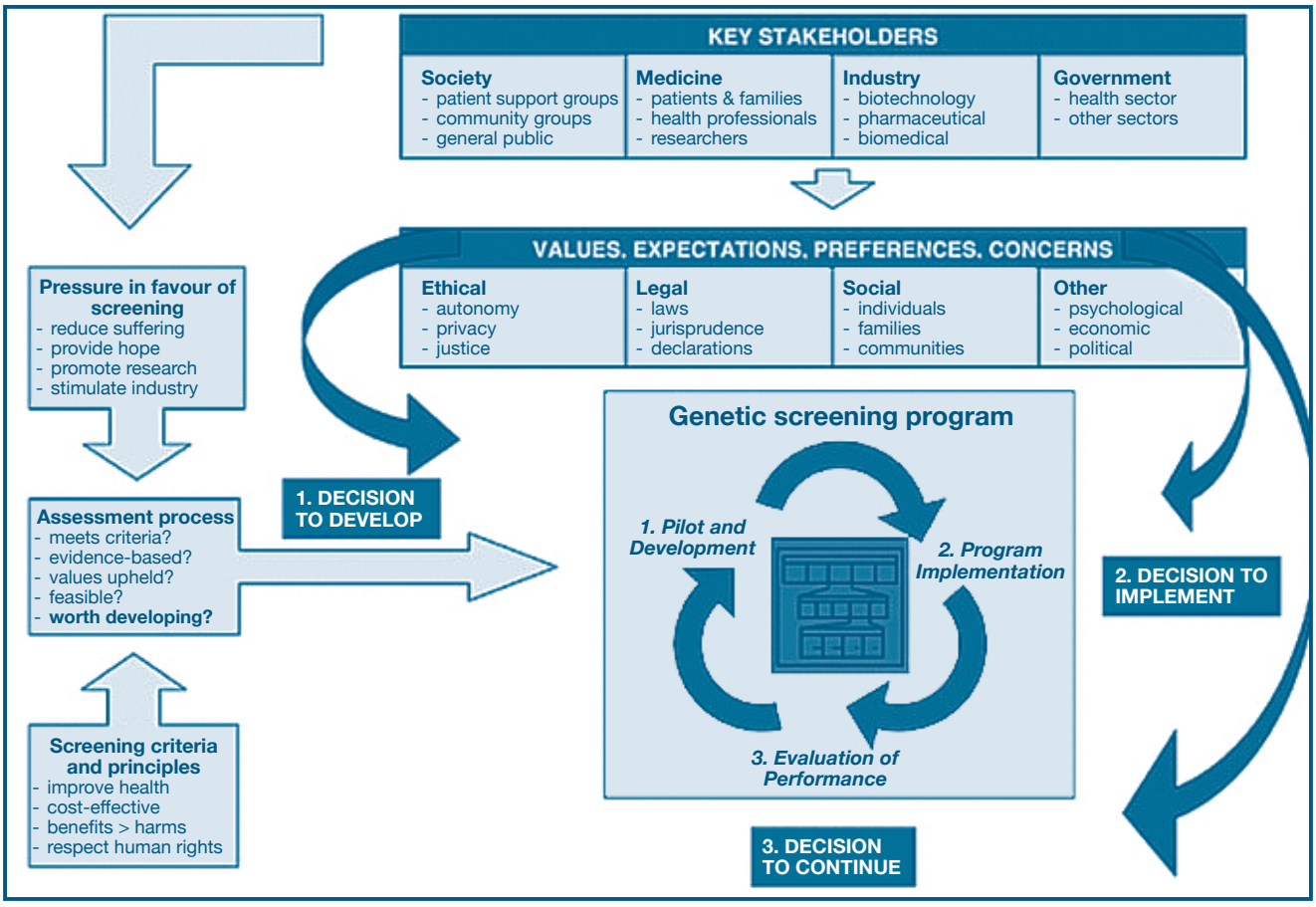
The obvious benefits of screening are early diagnosis and treatment that may lead to reductions in morbidity and mortality. Other, sometimes controversial, potential benefits might include more informed family planning, and a simpler pathway from diagnosis to treatment. However, it must be demonstrated that screening truly provides an added value compared to the status quo (e.g., routine clinical care), other screening strategies (e.g., targeting other conditions) and non-screening alternatives (e.g., primary prevention). It is not always easy to decide whether the benefits of screening are outweighed by the possible harms. A screening programme involves people who are 'well', who may then be exposed to harm through the investigations or treatment. The harms could be psychological, for example the anxiety resulting from false negative/positive test results, or where a result leads to groups or individuals being stigmatised; or there could be direct physical risks to the patient from the use of non-benign interventions. Overestimation of benefits and especially underestimation of the harms should be avoided. Policy makers should always take into account that screening is not the only strategy that can be used to reduce the burden of disease, and the impact of other public health initiatives should be evaluated.

No screening should be performed outside a screening programme, which should be coordinated at three levels:
- programme management (e.g., supervision, resource management, monitoring outcomes);
- clinical services (education, recruitment, obtaining informed consent, offer of screening, non-directive counselling, offer of intervention, follow-up, etc.); and
- laboratory testing (analytical validity, clinical validity, quality assurance, data storage, confidentiality, etc.).

The implications of screening can vary widely depending on the target disease, the test(s) used, the timing of testing, the intervention(s), the target population, the screening programme and the implementation context.

The decision on whether to screen ultimately involves a value judgement which must take into account the best evidence and local contextual factors, as well as balancing the different needs and perspectives of individuals and families at risk, the target population and society at large. Evidence that needs to be considered includes data on expected benefits, potential harms and opportunity costs. This requires critical appraisal of research, as well as consultations with the target population and experts in the field, and possibly a wider public debate, as presented in the Figure below [3].

Public debate on whether to screen



Hepatitis screening recommendations

Two examples of decision making in HBV screening were presented during the meeting.

1. The evidence-based screening recommendations made by the US Preventive Services Task Force in 2004 strongly supported screening for HBV in pregnant women. Routine screening of chronic HBV in the general asymptomatic population was however, not recommended because the introduction of universal vaccination had made prevalence of HBV very low; also important was the fact that the majority of those infected do not develop chronic disease, and evidence for the effectiveness of therapeutic interventions is limited [4, 5]. There is no evidence that screening the general population improves outcomes for cirrhosis, hepatocellular carcinoma (HCC) or mortality. Based on results from studies in hyper-endemic areas, it is recognised that universal screening and immunization reduces chronic carrier state and new infection rates in children and adolescents, however this may not be generalizable.
2. The Morbidity and Mortality Weekly Report (MMWR) screening recommendations were formulated in 2008 [6]. Before this recommendation, serologic testing for HBV surface antigen (HBsAg) was recommended for the following groups: pregnant women; infants born to HBsAg+ mothers; household contacts and sex partners of HBV-infected persons; persons who are the source of blood or body fluid exposures that might warrant post-exposure prophylaxis (e.g., needlestick injury to health worker or assault); persons born in countries with HBsAg prevalence of >8%; and persons infected with HIV. From the perspective of infectious disease control, the function of screening high-risk groups is to prevent further transmission. The 2008 recommendations focused on this aim, and added some new high-risk groups. Routine testing for HBsAg became recommended for injecting drug users (IDU); men who have sex with men (MSM); and those born in regions with HBsAg prevalence of >2% (including intermediate and high endemicity countries). The rationale for these 2008 recommendations was based on the availability of effective interventions, the need to prevent further transmission, and high risk groups meeting screening criteria (e.g., increased likelihood of a serious health disorder, the possibility of diagnosis before symptoms occur, existence of minimally invasive test, years of life gain if intervention is initiated early, and acceptable cost of screening).

Decision guide for population screening

A decision guide for population screening has been published [7]. Although it was developed for the purpose of genetic screening it can also be seen as a conceptual framework for the development of a decision guide for screening for infectious or other chronic diseases. This guide can be used to make explicit the many advantages and disadvantages of screening, as well as the potential opportunity costs. It would also make ultimate political decisions more transparent and allow decisions to be revisited as the knowledge base evolves.

Working through the large amount of evidence required to address each of the criteria, it becomes apparent that screening decisions are tremendously complex. The process of evaluating all this evidence can allow different stakeholder groups to come to a shared understanding.

Discussions during the meeting pointed out that, in addition to the effectiveness of testing and treatment, the effectiveness of the recommendation should also be considered. In order to assess the uptake of a measure in terms of reduced morbidity and mortality, specific target populations have to be identified; screening programmes must be properly managed and the level of implementation and outcome of guidelines need to be monitored and evaluated.

Furthermore, it was emphasized that a balance should be maintained between the benefits and the possible negative effects of screening such as anxiety (especially with respect to false positives/negatives), invasive procedures, difficulty in testing the appropriate target population at risk, starting treatment too early (with the risk of contributing to drug resistance), treatment for high viral load, and a lack of evidence for the benefits of treatment of mild and moderate diseases in terms of reduced mortality.

Some of the challenges identified in developing screening recommendations for hepatitis include the variable availability of surveillance data on the prevalence of disease in different countries, the rapidly changing landscape of available treatments, the limited number of well-designed long-term trials evaluating the effectiveness of screening for hepatitis (i.e., demonstrating that early diagnosis and intervention provides an added benefit compared to standard clinical care), and the long latency between time of infection and the endpoints to be averted, including developing cirrhosis and HCC, and possibly death.

Policymakers therefore need to take into account that it takes time to develop a well-designed screening programme that maximizes the benefits while minimizing the harms. While opportunistic initiatives by clinicians in various fields are often the trigger for public health actions, pilot screening projects need to be properly assessed and suitably tailored to the proposed implementation context prior to large scale expansion at a population level.

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Based on a presentation by
A. Andermann, Woodrow Wilson School of Public and International Affairs, Princeton University, Princeton, USA.

Lessons learnt from other screening programmes

For years, experiences have been built up through screening for other (chronic) diseases such as human immunodeficiency virus (HIV), breast cancer, and chronic kidney disease. During the meeting lessons learnt from a number of these programmes were discussed.

The case of HIV screening

In the US, HIV testing recommendations have changed frequently since the beginning of the epidemic: to improve screening of donated blood (1985); to test pregnant women (1995 and 2001, 2003); and to test individuals in health care (2001, 2003). In 2006, revised CDC recommendations proposed the expansion of HIV testing in health care settings [1]; now opt-out HIV screening is recommended as a part of routine clinical care for patients aged 13-64 years. In addition, all persons likely to be at risk of acquiring HIV (MSM, IDU, etc.) should be tested at least annually. Barriers to implementing these recommendations have included: conflict with state laws or agencies; the persistent stigma associated with HIV infection; fears of discrimination; the perception that risk-based testing is more cost effective; the identification of at risk people and the need for re-imbursement for testing [2].

Likewise, in France and the UK, new HIV screening strategies and recommendations are currently under evaluation with a view to expanding HIV screening among the general population and performing routine screening among high-risk populations [3]. There are also initiatives under way by the British HIV Association, the British Association of Sexual Health and HIV, the British Infection Society, and the Health Protection Agency.

Different rationale supported the changes in HIV screening, for example the awareness that better HIV screening can reduce HIV transmission and improve disease prognosis. Persons unaware of their HIV+ status are more likely to cause new infections. Antiretroviral therapy (ART), by reducing HIV viral load, reduces the infectiousness of treated individuals by 50-99%. The prevalence of undiagnosed HIV infection remains high (21-33% of cases in USA and 25-30% in the UK.) In the US, the proportion comprising ~25% who are unaware of their HIV+ status accounts for ~54% of new infections, indicating that HIV transmission can be limited substantially by increasing the number of HIV+ persons who are aware of their status [4].

It has recently been suggested that instead of considering prevention as a secondary benefit of ART, it should be considered as the primary purpose [5]. There is also potential to improve the prognosis in HIV disease. Despite the widespread availability of screening, a substantial proportion of people are diagnosed late for HIV in USA, UK and France. These 'late testers' are presenting with advanced disease and hence a worse prognosis and more costly treatment.

Rapid HIV tests have recently become available that can be performed without special equipment, require only saliva or a drop of blood, and provide quick results with a very high sensitivity and specificity. The cost-effectiveness of 'one-time' routine HIV screening in the US population ranges from less than $50,000/Quality Adjusted Life Years (QALY) to $60,700/QALY [6, 7]. A recent collaborative study, conducted to assess the cost-effectiveness of routine HIV screening in France, found that a similar approach was acceptable by French standards and, at a cost of 95,000 Euros/QALY, it compared favourably with current practices [8].

Uptake of screening is more difficult to measure than uptake of vaccination. Although the use of a rapid HIV test facilitates screening, dedicated personnel and funding are required [7]. The 'test and treat strategy' could reduce transmission, but it is unlikely that it will eliminate HIV in hyper-endemic settings. The effect of new strategies on health outcomes needs to be assessed.

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Based on a presentation by
C. Semaille, Département des Maladies Infectieuses, Institut de Veille Sanitaire, Saint Maurice Cedex, France.

Screening for chronic kidney disease in Europe

In Europe, chronic kidney disease is found in about 10% of the general population. Annual costs related to renal dialysis are estimated to amount to approximately €50,000/patient.

The criteria used in European screening programmes to identify chronic kidney disease are often limited to the estimated glomerular filtration rate (eGFR), thereby only providing data on advanced chronic kidney disease (stage 3 and higher). It was proposed that screening should also include data on microalbuminuria, because this allows early identification of chronic kidney disease, which is important since the risk for cardiovascular (CV) events in the earlier stages is equal to that in more advanced stages.

Studies have shown that assessing the albuminuria level appeared to be more useful than the glomerular filtration rate (GFR) in predicting both renal and CV prognosis [1]. Not only does albuminuria allow early identification of a patient at increased risk, lowering albuminuria by means of treatment can prevent CV events in microalbuminuretic patients [2].

Costs of screening programmes in the general population are said to be high, and cost-effective only for preventing end-stage renal disease when they are targeting selected high-risk groups, for example patients with diabetes, or hypertension, and the elderly. Limiting screening to patients over the age of 50 makes screening even more cost-effective. However, in evaluating cost-effectiveness, the benefits of preventing CV events should also be taken into account, as it has indeed been shown that screening for albuminuria is cost-effective in preventing CV events [3].

As an alternative to targeted screening for chronic kidney disease, pre-selection among the general population has been proposed based on albuminuria testing or a simple dipstick test for proteinuria. Presently, in the Netherlands this testing is still limited to subjects with diabetes or hypertension, or in patients with prior CV event. Persons testing positive can undergo further investigations to have more detailed information on renal and CV risk factors and to receive specific treatment as needed [4].

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Based on a presentation by
P.E. de Jong, University Medical Center, Groningen, The Netherlands.

ECDC reviewed the effectiveness of screening, surveillance and prevention of HBV and HCV in Europe

The European Centre for Disease Prevention and Control (ECDC) commissioned a review of the literature on the effectiveness of screening for HBV and HCV in the European Economic Area (EEA). The aim was to gain an insight into the prevalence of chronic HBV and HCV, the burden of disease and national screening policies and their effectiveness. This literature study was conducted by Irene Veldhuijzen (Municipal Public Health Service Rotterdam-Rijnmond, the Netherlands) and Susan Hahné (National Institute of Public Health and the Environment, Bilthoven, the Netherlands).

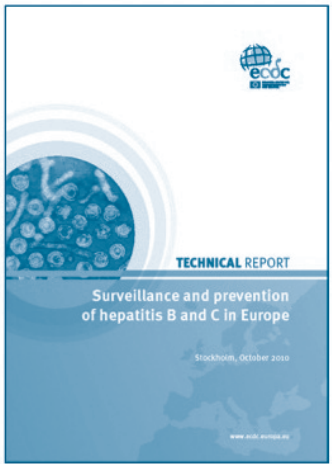
Meanwhile ECDC also commissioned an analysis of a survey carried out at the end of 2009, to map existing national surveillance systems and prevention programmes for HBV and HCV in EU/EEA. The latter was conducted by the VHPB secretary. Both projects received a preliminary presentation at the VHPB Budapest meeting, but as the final reports are now published on the ECDC website we opted to include here the abstracts and the references of both finalized reports.

HBV and HCV in the EU neighbourhood: prevalence, burden of disease and screening policies

(http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=560) (asccessed on 10 dec 2010)

This literature review answers a series of questions on the prevalence of chronic HBV and HCV infection in the general EU population, the numbers of individuals with chronic HBV or HCV infection, and current national practices for screening for chronic HBV and HCV infection, all with the overarching goal of promoting national and European policies on the secondary prevention of these two diseases.

Surveillance and prevention of HBV and HCV in Europe



(http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=567) (asccessed on 10 dec 2010)

This report on HBV and HCV presents the results of a survey in all EU/EEA countries. Twenty-two of the surveyed countries have already implemented universal vaccination programmes on HBV for infants and adolescents, and half of the surveyed countries conduct screening programmes for HCV, primarily for injecting drug users and prison inmates. Data on HBV and HCV screening policies, both for the general population and high-risk groups, remain sparse.

The reports caution that predicting disease trends for viral hepatitis is extremely difficult as disease surveillance systems in Europe differ considerably. In addition, the asymptomatic nature of HCV further complicates data interpretation.

Long-term effectiveness and cost-effectiveness of screening for HCV infection

The above mentioned WHO guidelines and principles of screening are still as applicable as they were in 1968 and are used today. However, in the last decade, agencies such as the UK's National Institute for Health and Clinical Excellence (NICE), and Germany's Institute for Quality and Efficiency in Health Care (IQWiG) require formal incremental cost-effectiveness as one of the decision criteria, not just benefit and overall monetary budget impact. Therefore, the term 'cost-effectiveness' has been added to Wilson and Jungner's principles 8 and 9, which now read:

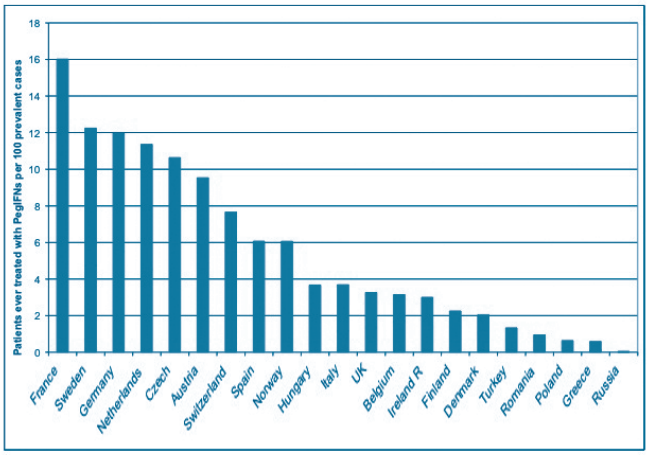
8. There should be an agreed cost-effective policy on who to treat.
9. The total cost and cost-effectiveness of finding a case should be economically balanced in relation to medical expenditure as a whole.

The cost-effectiveness of treatment with the currently available antiviral therapies (AVT) has been demonstrated in several single economic evaluations, as well as in two reviews of the long-term cost-effectiveness of antiviral treatment in chronic HCV [1, 2]. However it is not enough for a cost-effective treatment to exist, patients must also have access to it. In fact there are many more issues to consider with respect to the cost-effectiveness of screening for HCV, including considerations at the logistic and programmatic levels, screening costs, validity of tests, access to the target group, and so on.

Therefore, two studies, respectively addressing the burden of HCV disease and market access to drugs for treatment of HCV in different European countries, were conducted and published [3, 4]. In the first study, country-specific HCV prevalence and burden-of-disease data were collected. In the second study, sales data were converted into country-specific numbers of HCV patients treated. From the two studies, administration of prevalence-adjusted PegInterferon (PegIFN, the state-of-the-art treatment) was compared across countries and inequalities of access to optimised therapy were assessed.

Market uptake of PegIFN and relative treatment rates differed considerably across Europe (see Figure below), suggesting unequal access to optimised therapy. Interestingly, the countries with higher prevalence, such as Romania, have less access to treatment compared to other countries. Reasons for unequal access include budget restrictions and different treatment policies; but also differences regarding policies for case finding and screening across these countries.

Prevalence-adjusted cumulative PegIFN treatment rates until end 2005



Source: Calculated from IMS Health data and HCV prevalence rates derived from national sources

In the light of these results, a systematic literature review including health technology assessment reports, systematic reviews, long-term clinical trials, full economic studies and decision analytic modelling studies, was conducted on whether screening should be performed and for which populations [5]. The objectives of this review on screening were to systematically review the long-term effectiveness and cost-effectiveness of screening for HCV. Emphasis was placed on the influence that HCV prevalence has on the cost-effectiveness of screening.

The results of this review showed that long-term effectiveness, in terms of QALYs gained varied considerably. Compared with no screening and standard care, HCV screening and early treatment lengthened a patient's life by between 0.15 and 24 days; or a gain of 0.0001-0.072 QALYs. Screening in populations with higher HCV prevalence (32%-68%) was more effective than screening in populations with low/average prevalence (1%-16%). However, the incremental cost-effectiveness ratio of HCV screening combined with PegIFN treatment did not

appear to increase with increasing HCV prevalence and this unexpected lack of linear relationship has not been explained.

Screening is not always cost-effective because not all HCV-infected patients progress to severe liver disease during their lifetime (only 20%); and AVT is not effective in all patients (only 60%); and most of them would also be detected in time for treatment without screening. It has been noted also that limitations of the cost-effectiveness model include not taking into account that up to 75% of HCV patients are not eligible for treatment and up to 80% of those treated drop out.

Results from this review showed that HCV screening and early treatment have the potential to slightly increase average life expectancy, but should focus on populations with elevated HCV prevalence in order to be cost-effective. High prevalence target groups could be selected based on risk factor profiles, for example, history of blood transfusion, elevated alanine aminotransferase (ALT), IDU status, age, attendance at hepatology wards/emergency departments. Cost-effectiveness may not be the only decision criterion for the implementation of HCV screening. In view of the multitude of iatrogenic infections, aspects like fairness might be considered as well. Currently, many European countries plan to introduce national screening programmes, but the question of whom to screen and how to screen needs to be resolved.

Some questions to be answered include:
- How many people are infected?
- How many infected people have not yet been detected?
- How many of those need immediate treatment?
- How many would be detected too late for AVT without screening?
- What is the appropriate target group for screening?

Further research

Further research is necessary on the long term health economic impact of HCV screening, when combined with appropriate monitoring and treatment strategies in different European health care systems. Cost-effectiveness studies of HCV screening with different monitoring strategies in populations with low or moderate HCV prevalence should be performed. The optimal target groups and settings for cost-effective screening strategies should be evaluated. A Pan-European HCV screening model is required, which can be adapted to the context of the different health care systems and countries within Europe.

It has been suggested that liver function data collected in other programmes, such as lowering blood pressure or cholesterol, should be used in chronic hepatitis screening programmes. As standards of care may change in the future (e.g., if vitamin D is found to have a role in the success of HCV treatment), cost-effectiveness may need to be recalculated accordingly.

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Based on a presentation by
G. Sroczynski, Medical Decision Making and Health Technology Assessment (HTA), Department of Public Health, Austria.

Screening of migrants

Around the world migration of populations is increasing, yet the health implications of this mobility have until recently been largely ignored.

HBV and HCV prevalence in the EU is increasing at such a rapid rate as to constitute a major public health concern. Much of the reported and suspected increases result from rapidly growing migration within and into the EU. The UK Hepatitis B Foundation estimates that people arriving from high prevalence countries in Africa, Asia, Eastern Europe and new EU States may constitute up to 50% of the UK's new hepatitis cases.

The UN reports that migrants number about 300 million worldwide, a figure that does not include world urban migrants, refugees, asylum seekers, people moving for relatively short periods of time, or regular clandestine migrants - meaning that the total number of migrants in the world is probably closer to 1,000 million. In Europe, there are about 20 million migrants from just about every part of the world. Most of them are co-ming from countries with a higher prevalence of both HBV, and HCV, than the countries to which they are moving. In doing so, migration is helping to create new patterns of HBV and HCV distribution and new health challenges for which many countries are ill prepared.

Migrants are a heterogeneous group with different personal experiences and different levels of risk exposure to HBV and HCV. They differ not only in the ease with which they can be identified and accessed by health agencies but also in their capacities to understand the implications of HBV and HCV and how to prevent and respond to the diseases. The growing numbers of irregular migrants, who largely remain invisible to local health authorities, present a special problem. Identifying and following up with migrants of all kinds, but especially irregular ones, and offering voluntary counselling and testing for HBV and HCV is essential, as is providing HBV vaccination in culturally sensitive ways. Screening always carries with it major legal, ethical and logistical implications.

Given that migrants are moving between regions with variable levels of HBV and HCV prevalence (or with unknown levels), should we propose that everyone be screened, or should we screen based on known risk factors like country of origin and country of destination? Or should we focus more on people migrating on long term contracts, or intending to settle, rather than those who are staying for short periods, such as seasonal workers? Conversely, a much broader brush approach that makes no assumptions about the prospective length of stay might be more effective from an international public health perspective. Although more costly, this latter approach offers the opportunity of cutting the cycle of transmission at a more global level.

The timing of screening presents another dilemma. Some countries have implemented pre-migration screening for people with diseases such as TB and HIV. Such programmes have not been very effective in long term predictive value, but they do offer an opportunity to identify and follow up migrants once they enter the country. Other countries have decided, in the cases of HIV and TB, to screen on entry and then refer to treatment, if necessary. Although this approach offers better follow-up opportunities than pre-migration screening, it has implications for ensuring compliance with treatment. Because migrants often move into populations in which risk factors are high, periodic monitoring may be necessary. All these approaches raise logistical issues.

Whatever the approach, screening must be based on better risk data than we currently have available in the area of migration and health. The approach needs to be based on screening concepts that are robust and tested. Methods should be evidence based with regards to timing of screening, for example, single or a multiple time approach. The ethical principles and practices of migrants should be respected - targeted population screening could be considered discriminatory in some countries. Screening policies should be both helpful to the population already in the country and to anyone moving into the country. However, more data are needed, especially on risk evaluation, before such policies can be written and recommended.

Based on a presentation by
R. Cody, International Centre for Migration and Health, Geneva, Switzerland.

The global burden of disease of viral hepatitis

An estimated 2.7% of all deaths are due to liver cancer and cirrhosis resulting from HBV and HCV infections, and the percentage is increasing over time. An estimated 57% of liver cirrhosis cases and 78% of primary liver cancer cases are due to HBV or HCV infection. About 2 billion people have been infected with HBV worldwide, over 350 million are chronically infected with HBV and there are approximately 600,000 deaths each year as a result of HBV infection. Approximately 130-170 million people are chronically infected with HCV, and there are over 350,000 deaths each year as a result of HCV infection. Around 500 million people around the world are currently infected with chronic HBV or HCV.

In 2008, the World Hepatitis Alliance (www.worldhepatitis-alliance.org) launched a global awareness raising campaign, “Am I Number 12?”, designed to communicate the fact that worldwide one in 12 people is living with either HBV or HCV. Its aim is to encourage people to get tested. The campaign has been very successful and continues to be used by patient groups around the world.

The WHO Immunization Department’s model estimates that the annual number of HBV-related deaths worldwide is 600,000 (500,000-700,000). The US CDC’s model estimates that the number of HBV-related deaths in 2000 was 620,000. Commonly used maps showing the prevalence of viral hepatitis (WHO and US CDC) are not well referenced and the information provided is not dated, making it impossible to check the accuracy of the data. Furthermore, the global burden of disease estimates produced by WHO on cirrhosis and liver cancer are not linked to the specific type of viral hepatitis. It was suggested during the meeting that it might be in the public health interest if such a link could be permitted when generating future estimates.

The WHO Global Burden of Disease (GBD) 2004 update [1] estimated the burden of death and disability from HBV and HCV infections. From their figures, and by including the contribution made by HBV/HCV infection to HCC and cirrhosis, it is possible to estimate the total global burden from HBV and HCV infection as follows.

According to the CDC model’s estimates, out of the 620,000 HBV-related deaths (ranging from 12,000 in the Americas to over 300,000 in the Western Pacific), Southeast Asia and the Western Pacific together accounted for the majority (75%) of these deaths. Of the deaths, 94% resulted from the sequelae of chronic infection. Acute HBV only accounted for 6% of deaths.

Without vaccination the CDC model estimated 64.8 million new HBV infections, 9.7 million chronic infections, and 1.4 million HBV-related deaths (acute and chronic) in the year 2000 birth cohort over their lifetime [2].

The heaviest components of the HBV/HCV burden are cirrhosis and HCC. The prevalence of serologic markers of HBV and HCV among patients diagnosed with cirrhosis or HCC obtained from representative samples of published reports [3] shows that: 57% of cirrhosis was attributable to either HBV or HCV (30% attributable to HBV and 27% to HCV); and 78% of HCC was attributable to HBV or HCV (53% due to HBV and 25% to HCV).

Applying these HBV/HCV fractions [3] to the 2004 WHO estimates of total HBV burden results in the following figures [1].

Total HBV and HCV burden

	WHO GBD (2004 Estimate)	Attributable to HBV (Perz, 2006)	Attributable to HCV (Perz, 2006)
Deaths (% of total)			
HCC	610,000 (1.0%)	* 0.53 = 323,300	* 0.25 = 152,500
Cirrhosis	772,000 (1.3%)	* 0.30 = 231,600	* 0.27 = 208,440
Other hepatitis-related deaths			
- HBV	105,000 (0.2%)	105,000	
- HCV	54,000 (0.1%)		54,000
Total deaths		***659,900***	***414,940***
DALYs‡ (% of total)			
HCC	6,712,000 (0.4 %)	* 0.53 = 3,557,360	* 0.25 = 1,678,000
Cirrhosis	13,640,000 (0.9 %)	* 0.30 = 4,092,000	* 0.27 = 3,682,800
Other hepatitis-related DALYs			
- HBV	2,068,000 (0.1%)	2,068,000	
- HCV	955,000 (0.1%)		955,000
Total DALYs		***9,717,360***	***6,315,800***

‡ *Disability-adjusted life years*

The WHO Global Burden of Disease II report is due to be published in 2010/2011. During Phase I a systematic review of the literature was conducted on hepatitis A (HAV, complete), HBV and HCV (search complete, abstracting and meta-analysis in progress), hepatitis E (HEV, nearly complete), and unsafe injections (work in progress). Phase II will consist of disease modelling on HAV, HBV (both complete), HCV and HEV (both in progress). Modelling of unsafe injection data remains to be done. Phase III will include the final validation and generation of mortality and DALY estimates. This part will be completed by the Institute of Health Metrics and Evaluation at the University of Washington.

The following initial data are needed for estimating GBD:

- HAV
  - Anti-HAV marker of past infection that is commonly available;
  - Cohort-specific HAV vaccine coverage used as protective factor.
- HBV
  - Anti-HBc marker of past infection;
  - HBsAg marker of current or chronic infection, since acute infection is rare this is used as proxy for chronic infection;
  - HBV early antigen (HBeAg) marker for highly infectious persons and prevalence in women of child bearing age used to estimate perinatal HBV transmission;
  - Cohort-specific HBV vaccine coverage used as protective factor.
- HCV
  - Prevalence of anti-HCV.
- HEV
  - Past infection can be determined by anti-HEV.
- Unsafe injection
  - Prevalence of unsafe injections.

There is a gap between registry data and mortality estimates, hampering the calculation of the burden of disease data. WHO is currently looking into different ways of modelling viral hepatitis infection data in order to estimate the burdens of disease of HAV, HBV, HCV and HEV.

For this burden of disease exercise WHO plans the publication of:

- A systematic literature review (which is already available for HAV) [4];
- Models for burden of disease estimates;
- A revision of prevalence and risks maps; and
- Country specific estimates after country consultations.

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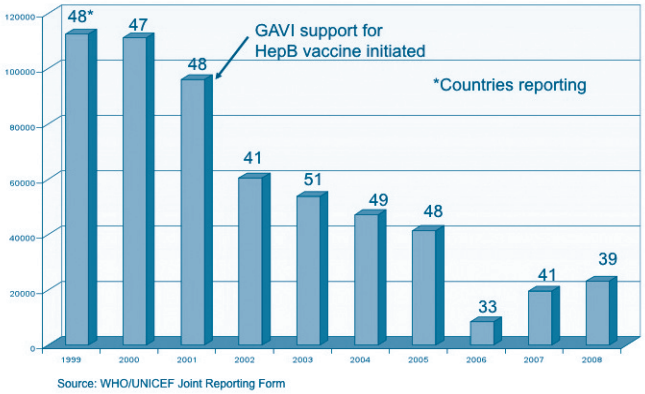
Based on a presentation by S. Wiersma, WHO, Geneva, Switzerland.

HBV/HCV case definitions and surveillance in the WHO European region

HBV

The number of acute HBV cases in the WHO European region decreased significantly from 1996 to 2006 mainly due to the introduction of immunization. However, the number of cases started to rise again in 2007 and 2008 (see Figures page 11) [1].

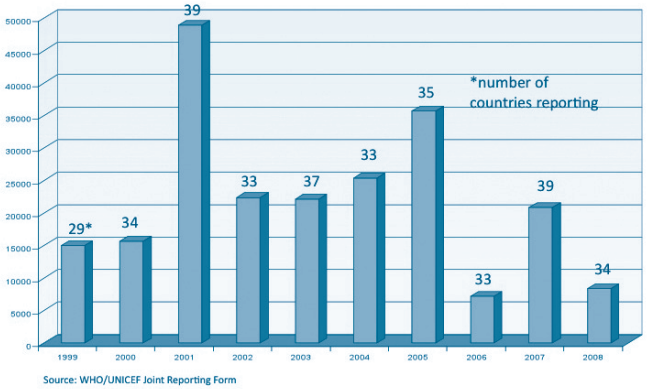
Reported acute HBV cases, WHO European region, 1999 to 2008



HCV

The trend observed for HBV is not visible in the number of reported cases of acute HCV in the European region; only in recent years has it decreased (see figures below).

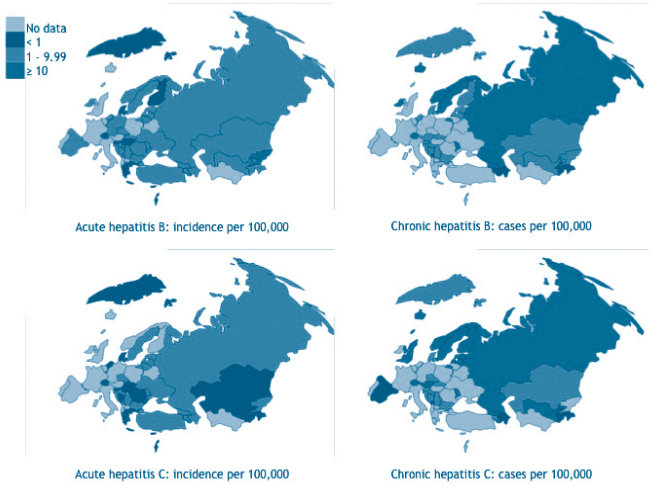
Reported acute HCV cases in the European region, 1999 to 2008



HBV and HCV surveillance

At present, there is a lack of information on the incidence of HBV and HCV at sub-national level and in risk groups (apart from in HIV-infected populations). WHO does not provide guidance to Member States on how to collect data on chronic cases, apart from the use of International Classification of Disease (ICD) codes and the recommendation to only collect data on newly diagnosed cases. Therefore, prevalence of chronic HBV and HCV is unknown. Member States' compliance reporting data on chronic HBV and HCV cases to WHO needs to be improved.

Chronic and acute infection with HBV and HCV in the WHO European region, 2008 [1]



Source: WHO/UNICEF Joint Reporting Form

Due to the fact that there are no standard surveillance guidelines or protocols, and clear case definitions are missing, the collected data are not comparable between countries. The establishment of an expert advisory group would be useful to implement improvements to surveillance. To improve the hepatitis surveillance system, collaboration with the ECDC should be encouraged.

Guidelines for reporting of acute infections, chronic carriage and risk factors should be established. These should take into account ethical and practical factors, such as linking testing and counselling with other surveillance programs (e.g., HIV, STI and TB) as well as treatment and response options.

Reference

[1] Derived from official reports by countries through the WHO/UNICEF Joint Reporting Form.

Based on a presentation by
D. Mercer, Communicable Disease Unit, WHO Regional Office for Europe, Copenhagen, Denmark.

Ongoing activities to raise awareness and gather information about chronic viral hepatitis and organizations' vision on screening

The Institute of Medicine, IOM

The Institute of Medicine (IOM) is an independent non-profit organization in the US that provides unbiased and authoritative advice on health issues and disparities to decision makers and the public. Despite federal state and local public health efforts to prevent and control HBV and HCV, the diseases remain a serious health problem. In response to the demands of several public health organizations the IOM formed a multidisciplinary committee to develop evidence based recommendations to:

- Determine ways to reduce new HBV and HCV infections and the morbidity and mortality related to chronic viral hepatitis;
- Assess current prevention and control activities and identify priorities for research, policy, and action; and
- Highlight issues that warrant further investigations and opportunities for collaboration between private and public sectors.

The committee considered strategies to prevent new HBV and HCV infections and to reduce morbidity and mortality from chronic HBV and HCV; they assessed the type and quality of data needed from state and local viral hepatitis surveillance systems to guide and evaluate prevention services; and they looked at health disparities between specific subpopulations at high risk, such as Asian Americans, African Americans, persons born in HBV-endemic countries, IDU, MSM, and young people. As a result of this project, a report was written entitled 'Hepatitis and Liver Cancer - A National Strategy for Prevention and Control of Hepatitis B and C' [1] and this was presented to government agencies and to Congress in January 2010.

HBV, HCV and HIV: prevalence, awareness, associated deaths and prevention funding

Virus	Prevalence	% of infected population unaware of their status	Deaths in 2006 related to infection	Prevention funding by NCHHSTP*
HBV	800,000-1.4 million	About 65%	3,000	~$17.6 million (2% of NCHHSTP budget)
HCV	2.7-3.9 million	About 75%	12,000	
HIV	1.1 million	About 21%	14,016	~$640 million(69% of NCHHSTP budget)

CDC; Lin et al, 2007 [2]; Hagan et al, 2006 [3]
** funding by National Center for HIV/AIDS, Viral Hepatitis, Sexually Transmitted Disease, and Tuberculosis Prevention (NCHHSTP)*

Findings and recommendations of the IOM committee
In the USA, the majority of those infected with HBV and HCV are unaware of their status until they have symptoms of cirrhosis or HCC many years later. There is a lack of detection and awareness programmes for HBV and HCV. The Table above shows that more people die from HBV and HCV, than from HIV.

In 2008, the National Centre for HIV/AIDS, Viral Hepatitis, Sexually Transmitted Disease (STI) and TB Prevention (NCHHSTP) had a budget of $1 billion. Although viral hepatitis infections are 3-5 times more frequent than HIV in the US, only 2% of this budget is spent on viral hepatitis, while 69% is spent on HIV.

Enhanced by the disparity of funding there is a lack of public and care-provider awareness, as well as a lack of resources. People at risk often do not know how to prevent hepatitis infection, have no access to the services for prevention, are not screened and do not know that they are infected. There is inadequate access to management, and often care providers do not know how to manage the infections. Surveillance systems for HBV and HCV are inadequate in the USA. To address these consequences the committee proposed recommendations in four main areas:

1. Improved disease surveillance
Due to underfunding of the Division of Viral Hepatitis, only one person is responsible for surveillance in each State. In at least a third of the States it is not a requirement to report chronic HBV. The viral hepatitis surveillance system in the US is highly fragmented and poorly developed – as a result, surveillance data are lacking.

CDC should evaluate the health surveillance system for HBV and HCV and update the guidelines for surveillance, including an assessment of the ideal surveillance system in the US.

CDC should develop specific cooperative agreements between all state and territorial health departments to support core surveillance for acute and chronic HBV and HCV. The feasibility of reporting chronic cases should be linked to the feasibility of follow up, implementing American Association for the Study of Liver Diseases (AASLD) and European Association for the Study of the Liver (EASL) evidence-based guidelines, e.g., for HBV currently pregnant women are only identified for the purpose of newborn follow up, while there is no medical management of identified HBsAg+ pregnant women.

Targeted active surveillance in specific geographic regions and populations, including appropriate serologic testing and monitoring of HBV and HCV incidence and prevalence in populations not fully captured by core surveillance (such as prisoners, the homeless and ethnic groups) should be provided by CDC.

2. Knowledge and awareness
Health care providers and social care providers were found to have very limited knowledge about HBV and HCV prevalence or incidence, risk factors, appropriate screening tests, vaccination policies, or about the stigma that is associated with testing positive in some population groups. Following testing, many providers were not aware of how to interpret the test results, or how to refer these patients for management. Sometimes treatment is inappropriate, for example, when treatment is started too early, or in the case of immune-tolerant patients. In addition, there is also a need for education of the general population because of the low awareness of HBV and HCV and the stigma associated with the diseases.

To increase provider and community knowledge and awareness, the report recommended that CDC works with key stakeholders including other federal agencies, state and local governments, professional organizations, health care organizations and educational institutions to improve education programmes for health care providers and social services providers; and should work with the community to develop, coordinate and evaluate innovative outreach and educational programmes for HBV and HCV.

The report recommended that health insurance programmes, federal programmes, and even private programmes should incorporate guidelines for screening and referral for patients with HBV and HCV. There should be adequate resources for

federally funded health care communities to develop comprehensive programmes. This could all change if a universal health care system is introduced in the USA.

3. Viral hepatitis service

Health services related to viral hepatitis prevention, risk-factor screening, serologic testing and medical management are both sparse and fragmented at all levels. The committee believes that a coordinated approach is necessary to reduce hepatitis infection. The report recommended the establishment of a number of viral hepatitis services including:

- Community outreach via community and care-provider awareness programmes;
- Prevention via vaccination, harm reduction, needle-exchange programmes, drug and alcohol treatment services, and vaccination of HBV-susceptible contacts;
- Identification of infected persons using risk factor screening, and laboratory testing;
- Social and peer support via positive prevention services and education and referral to other related services and care; and
- Medical management via assessment for, and provision of, long-term monitoring for viral hepatitis; selection of appropriate persons for treatment (in accordance with AASLD guidelines); psychiatric and other mental health care, and adherence support.

4. Immunization

In spite of the longstanding availability of effective HBV vaccination, and the possibility of eliminating new infections, 1,000 newborns are infected each year. To avoid these new infections the committee recommended that all newborns from HBsAg+ mothers, with a birth weight of at least 2,000g, should receive single antigen HBV vaccine and hepatitis B immune globulin in the delivery room as soon as they are stable.

Avoiding perinatal transmission is the main priority but, in addition, HBV vaccination coverage in adolescents, adults and health care workers needs to be improved:

- All States should mandate that HBV vaccine series be completed or be in progress as a requirement for school attendance;
- Additional resources should be devoted to increase HBV vaccination of at-risk adults and to expand immunization information for adolescents and adults;
- Federal government should work to ensure an adequate, accessible and sustainable HBV vaccine supply; and
- Support research to speed the development of HCV vaccine.

Screening-specific recommendations

Populations at risk of acquiring HBV and HCV are known, but are not necessarily being screened systematically and effectively. Most chronically infected individuals are unaware of their status. Populations and settings of special interest to be screened include pregnant women, foreign-born individuals, IDU, incarcerated populations, and high impact settings (STI and HIV clinics, homeless shelters, mobile health units).

The reasons for identifying infected persons are: to prevent transmission to contacts, to implement prevention measures (e.g., HBV vaccination); to prevent development of disease, and to start follow up and treatment of patients, if appropriate.

1. Pregnant women

While the screening programmes for pregnant women are efficient, and the infants of infected mothers are taken care of, identified pregnant women are not being systematically referred for management as most programmes are understaffed. Therefore it was recommended that the CDC should provide additional resources and guidance to the perinatal HBV prevention programme. Although more antiviral suppression medication became available recently, very little research has been conducted into its impact during the last trimester of pregnancy in women with high viral load and with high risk of perinatal transmission. Accordingly, the committee also recommended that the National Institutes for Health (NIH) support a randomized controlled trial to investigate the use of AVT in the third trimester of pregnancy.

2. Foreign-born populations

There are over 37 million foreign-born residents in the USA, which constitutes 12% of the national population [1]. Half of the US foreign-born population originated from HBV-endemic countries. One of the explanations for the difficulty of screening foreign-born individuals is linked to cultural stigma. There are some culturally tailored community-based or faith-based awareness and screening programmes, such as those involving Asian and Pacific Islander populations, but there are only a few programmes that are designed for other high risk foreign-born populations from HBV endemic countries.

The committee recommended that CDC - in conjunction with other federal and state agencies - expand community-based HBV screening, and testing of foreign-born individuals for HBsAg and anti-HBc. Those that test negative should be vaccinated for HBV and those that are HBsAg+ should be put into a management programme together with their household contacts and sexual contacts

3. IDU

The prevalence of HCV in IDU is highly variable and typically between 35-70% in the US. The committee found that there are limited HCV services within IDU facilities. Although most clinics educated patients about HCV testing, only 7% of the clinics tested all IDU for HCV and 22% did not test at all.

The committee recommended that federal, state, and local agencies should expand programmes to reduce the risk of HCV infection through injected drug use by providing comprehensive HCV prevention programmes for IDU as well as for non-injecting drug users. In addition to providing sterile syringes and drug preparation material, IDU outreach should include education, HBV testing and vaccination and post-test counselling.

4. Incarcerated populations

The prevalence of HBsAg in US prisons is 1-4% and the HCV infection rate is 12-35%. HBV and HCV screening and prevention programmes should be implemented in the prison setting, which calls for partnership between the Department of Justice and the Health Department. All susceptible incarcerated people should be offered HBV vaccine, which has been found to be very cost-effective [4]. Screening all incarcerated people for risk factors can identify those who need a blood test.

Following a positive test, patients should be treated and, if they leave prison before the end of the treatment, there should be community programmes to continue their management.

5. High impact settings

The rates of chronic HBV in HIV-infected people are about 6-14% and the rates for chronic HCV are about 33%. Approximately 30% of those diagnosed with acute HBV have previously been treated for an STI. Most of these high risk groups may not have access to care through traditional heath care venues. Therefore an HBV and HCV viral hepatitis service, including screening, prevention and awareness, should be integrated into existing settings that are already known by high risk populations. Examples include STI clinics, sites for HIV services and care, homeless shelters and mobile health units.

Desired outcomes

With the recommendations the committee hopes to create advancements in the major areas:

- Improve knowledge and awareness on viral hepatitis among health care and social service providers, general public and policy makers;
- Expand targeted viral hepatitis services including more targeted prevention programmes; and
- Increase resources and efforts for more research on effective vaccination and treatment options.

Overall the committee would like to realize a reduction both in transmission and in the incidence of new viral hepatitis infections; fewer deaths and medical complications of the liver caused by viral infection; an improvement in the quality of life of an infected person and, ultimately, a reduction in the cost of healthcare.

The IOM report was well received by the media. However, the implementation of these recommendations will involve a considerable cost, requiring a change in the strategic plan and budget priorities of the US Department of Health and Human Services (HHS), NIH and CDC.

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Based on a presentation by
B. McMahon, Alaska Native Medical Center, Liver Disease and Hepatitis, Anchorage, Alaska.

The European Association for the Study of the Liver, EASL

The European Association for the Study of the Liver (EASL) was founded in 1966 and is based in Geneva, Switzerland. Currently there are over 2000 members from more than 100 countries worldwide, including hepatologists and gastroenterologists, but also infectious disease physicians, surgeons, internal medicine specialists and others. The most common interest and area of expertise of all members is viral hepatitis, involving not only disease prevention but also focusing on treatment and follow up of liver disease. The Journal of Hepatology published by EASL monthly and with a readership of 40,000 was given an impact factor of 7.1 in 2009.

The role of EASL is to:

- Promote research concerning the liver;
- Promote state of the art education of physicians and cientists;
- Act as an advisor to European health authorities;
- Foster public awareness of liver diseases and their management;
- Support the participation of young investigators at EASL meetings and educational events; and
- Facilitate scientific exchange and foster European multicentre controlled trials.

One of the important activities of EASL is the organization of their yearly International Liver Congress. The last meeting on 14-15 April 2010 in Vienna attracted more than 7,000 participants and 1,200 abstracts were accepted. Viral hepatitis is the primary focus of this meeting, in addition to HCV drug development, for which this meeting is the primary forum worldwide. The meetings also include non-industry-sponsored educational symposia. Patient groups are involved in symposia organised by the European Liver Patients Association (ELPA) and the World Hepatitis Alliance. EASL also organizes monothematic and special conferences, and postgraduate courses; and endorses meetings that take place throughout the year.

Since 2009 EASL has been issuing clinical practice guidelines. The first were on management of chronic HBV infection [1]. Clinical practice guidelines for HCV are planned for 2010. EASL is also planning to have common guidelines with AASLD. By means of its different fellowships EASL supports research in liver pathology and pathophysiology, the main aim being to actively promote scientific exchange by supporting enhanced mobility of the young investigators within different European institutes.

EASL believes that the EU has a key role to play in raising awareness of liver disease in Europe, increasing funding for research, and setting standards for the prevention, diagnosis and care of liver disease. Together with ELPA, EASL is therefore organizing advocacy activities in the EU policy-making area, and supports the resolution proposed by Brazil on viral hepatitis at the World Health Assembly meeting in May 2010, i.e., that viral hepatitis be considered a primary health burden worldwide.

The web site of EASL (www.easl.eu) is open to new members and can be used to promote research or educational activities in this field. EASL webcast programmes are used as a tool to create public awareness and to educate physicians and scientists.

Reference

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Based on a presentation by H. Wedemeyer, EASL, Geneva, Switzerland.

The European Liver Patients Association, ELPA

ELPA was formed during the 2005 EASL meeting and now represents 21 member patient organizations from 17 countries. ELPA's aim is to create awareness and promote education about viral hepatitis among the general public, specific risk groups, and health care professionals. For HBV, in theory, worldwide eradication could be possible, thanks to reliable vaccination programmes. In addition to vaccination, promotion of education about viral hepatitis is important to avoid further transmission of the disease and to improve quality of life for infected persons.

The publication, 'Europe's hepatitis challenge: defusing the viral bomb' published in the Journal of Hepatology in 2009 [1], describes ELPA's vision on screening and their awareness-building activities. Nine out of 10 chronic hepatitis carriers are not aware of their infection and many patients remain undiagnosed for years, even decades. In the time interval before diagnosis patients can develop serious conditions, such as liver cirrhosis and liver cancer.

The main aim of ELPA has been to save hepatitis carriers from having to wait a long time before diagnosis, so that infected individuals can be counseled and treated sooner and they can take precautions to prevent further transmission. Hence, ELPA advocates screening and organizes frequent screening promotion and lobbying campaigns involving EU and national policy makers, liver specialist organizations and public health experts.

Screening of the general population would not be (cost-) effective in most European countries and ELPA is doubtful whether the public would respond positively to such a general request. A more promising approach, in ELPA's view, is to have targeted screening programmes in well-defined HBV and HCV risk groups (see below). Some of the HCV categories are also valid for HBV. Because the risk groups are diverse and difficult to reach, tailored approaches are needed for each group. These approaches should raise awareness, educate about risks of transmission, and offer information on the possible consequences of not getting tested and treated.

It is essential that health care professionals, particularly those in primary care, encourage testing for people that might have been at risk of contracting viral hepatitis. ELPA also proposes awareness campaigns aimed at primary care professionals because unfortunately they have a low awareness of hepatitis and of liver disease in general.

Generally policy makers are also poorly informed about issues relating to viral hepatitis. ELPA has turned to the EU for political guidance on how to improve efforts in detecting, identifying and treating hepatitis patients. ELPA's long term goal is the adoption of the European Council's recommendation on HBV and HCV screening, which is not legally binding, but should be signed by all 27 health ministers of the EU and would represent an important political commitment. A precedent for such a disease-specific council recommendation is the cancer screening recommendation, adopted in 2003 [2]. Although half of the EU Members have not fully implemented it, Health Ministers have reaffirmed that full compliance with the recommendation will happen in the near future.

ELPA has secured the support of the European Parliament. In its written declaration on HCV, made in March 2007, the European Parliament called upon the European Commission and the European Council to draft and adopt Council recommendations on hepatitis screening programmes. Since then, the European Parliament has hosted high level events on the occasion of World Hepatitis Day in 2007 and 2008. Before the EU

High risk groups for hepatitis B include:

- Persons with elevated liver enzymes and/or clinical sign of hepatitis
- Patients with liver cirrhosis or fibrosis
- Patients with hepatocellular carcinoma
- People who share or have ever shared needles (injecting drug users)
- People with long-term imprisonment history
- People who are undergoing or have undertaken hemodialysis
- Men who have sex with men or heterosexual persons with multiple sex partners
- People with HIV or HCV infection
- Families and household members or sexual partners of persons infected with HBV
- Patients and staff in psychiatric institutions or residents of welfare institutions for mentally disabled persons
- Pregnant women and newborns of HBV-infected mothers
- Recipients of organ transplants and blood products
- Blood and organ donors
- Patients before or during immunosuppressive treatment or chemotherapy
- Migrants from countries with high prevalence of hepatitis B
- Unvaccinated healthcare workers and public safety workers who undertake exposure-prone procedures.

High risk groups for hepatitis C include:

- Persons with elevated liver enzymes and/or symptoms of hepatitis
- Patients with liver cirrhosis or fibrosis
- People who share or have ever shared needles (injecting drug users)
- People with long-term imprisonment history
- People who are undergoing or have undertaken haemodialysis
- People who have received repeated percutaneous injections
- People who have had invasive medical and paramedical or dental work in countries with high prevalence or poor sterilization procedures, such as use of multidose vials
- People who received blood transfusions or other blood derived products outside the EU or before 1992 in the EU
- People who received organs and tissue transplants outside the EU or before 1992 in the EU
- Haemophiliacs who received concentrated coagulation factors before 1987
- People with HIV infection
- People who have used intra-nasal cocaine
- People with body piercings if being performed in non-hygienic environments
- Children of HCV-infected mothers
- Healthcare workers and public safety workers who undertake exposure-prone procedures

will take any action on hepatitis, there needs to be reliable and comparable data to demonstrate the burden of disease. Therefore ELPA supported the ECDC decision to include viral hepatitis in their annual plan as of 2008.

In the US, the IOM have recommended risk group specific testing in order to curb the hepatitis burden [3] (see previous section on IOM in this report). ELPA believes that such a recommendation is as pertinent for Europe, given its proximity to endemic countries.

Together with EASL, ELPA has published expert recommendations on screening for hepatitis with the help of the French health minister and health authorities. The recommendations were launched in 2009 at an event in the European Parliament and they have now been disseminated to the national health ministries and parliamentary health committees.

Cancer has occupied a prominent place in the new public health agenda over the last two years. The European Commission formally established the European Partnership on Action Against Cancer in 2009 and one important focus of this partnership is cancer prevention. Since becoming a member of the partnership, ELPA's goal is to secure recognition that liver cancer is one of the few cancers on the rise in Europe. Primary and secondary prevention measures for hepatitis will be important in any plan to prevent liver cancer.

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Based on a presentation by
N. Piorkowsky, ELPA, Meckenheim, Germany.

The State of the Art (SOTA) summit conference on HBV and HCV

The 2010 SOTA summit conference on HBV and HCV (October 14-15, 2010 Brussels, Belgium) brought together EU policy makers, stakeholders and experts to analyze new and existing information and engage in targeted discussions to devise public policies in response to the epidemic of HBV and HCV in Europe. Also, scientific data and other evidence were presented to encourage the formulation of a comprehensive Europe-wide public health strategy on the prevention and management of viral hepatitis as a health care priority.

A steering group comprising key European, international and national associations, leading national experts from the Member States, and an advisory board including representatives of ECDC and VHPB, helped develop the summit programme with the aim of promoting, and giving direction to, a uniquely consolidated and coordinated response to the problem of viral hepatitis in the 27 Member States of the EU. The summit has been supported by the European Commission, WHO, ECDC, VHPB, EASL, ELPA and by the Belgian government and was part of the official programme of the Belgian presidency of the EU Council of Ministers during the second part of 2010. The conference programme and more background information are available on the meeting website [1].

Results of work currently undertaken by ECDC, and fast track research commissioned by the SOTA steering group, were presented at the summit:

- Prevalence and burden of disease related to HBV and HCV in the 27 EU Member States (research undertaken by ECDC);
- Cost effectiveness of HBV and HCV screening and timing of referral for treatment;
- Migration and HBV/HCV in Europe - barriers to prevention and treatment (an ELPA-commissioned study produced by the International Centre for Migration and Health, on the effects of migration on the spread of HBV and HCV); and
- Good practice relating to patient self help, which can contribute positively to the public health system of a country in the EU Member States, at regional or national level.

New research and the compilation of existing research for the October summit, and the discussions which took place there, delivered a compelling evidence-based 'call for action' from the major stake holders across Europe. It is hoped that this action will include recommendations in the following areas: awareness and prevention issues; enhancing surveillance for HBV and HCV; screening/case findings for HBV/HCV and related diseases where co-infection is common; universal access to early treatment in line with evidence-based guidelines; and expansion of research resources.

Reference

[1] The 2010 SOTA summit conference on HBV and HCV (October 14-15, 2010 Brussels, Belgium) meeting website, available at http://hepsummit2010.org/

Based on a presentation by
N. Piorkowsky, ELPA, Meckenheim, Germany.

World Health Organization, WHO

Recently different viral hepatitis initiatives were taken by WHO on a number of levels: the Regional Committee, the WHO Executive Board (WHO EB) and, last summer, the World Health Assembly discussed and adapted the viral hepatitis resolution.

The WHO EB has recognized that viral hepatitis prevention and control efforts by WHO are successful, but improvements are still needed as the control and prevention of viral hepatitis is fragmented and without any comprehensive strategy. There is no specific department at WHO for viral hepatitis, and there is no formal way to coordinate the scattered activities.

WHO viral hepatitis initiatives

Regional

EMR (RC56) Resolution: the Eastern Mediterranean region (EMRO) adopted a regional committee resolution for HBV and HCV including improved screening, treatment and surveillance. The regional target for HBV control is to reduce the prevalence of chronic HBV to less than 1% among children below 5 years of age by 2015. Comprehensive national strategies for viral hepatitis control, including improved screening, treatment and surveillance need to be drafted. The WHO is requested to provide increased technical support to the countries in the region, to support national studies and surveillance activities; and to facilitate technology transfer and increased access to lower priced medicines.

Executive board (EB)

The January 2010 WHO EB meeting called for setting a clear direction, priorities and allocation of resources for a WHO programme of work (see below). The WHO EB drafted text for consideration by the World Health Assembly (May, 2010) [1].

Excerpts of this text urge Member States:

- to implement and/or improve epidemiological surveillance systems and to strengthen laboratory capacity, where necessary, in order to generate reliable information for guiding prevention and control measures;
- to incorporate in their specific contexts the policies, strategies and tools recommended by WHO in order to define and implement preventive actions, diagnostic measures and the provision of assistance to the population affected by viral hepatitis including migrant and vulnerable populations; and
- to strengthen national health systems in order to address prevention and control of viral hepatitis effectively through the provision of health promotion and national surveillance, including tools for prevention, diagnosis and treatment of viral hepatitis, vaccination, information, communication and injection safety.

There is a strong call for a WHO position on HCV treatment for individuals co-infected with HIV.

WHO viral hepatitis ongoing screening and awareness activities

HBV treatment consultation

During a milestone consultation on the 'Treatment of HBV for Resource-constrained Settings' in February 2009, the WHO engagement in providing advocacy, leadership and coordination on the global issue of chronic HBV treatment was discussed. Currently available drugs for HBV can be used to treat chronic HBV even in the developing world, largely due to the presence of HIV/STI infrastructure. Liver biopsy and DNA tests probably would not be available in these settings, but serology for hepatitis markers, liver enzymes and common chemistry tests can be used to identify candidates for treatment, as well as guiding treatment. Additional affordable and standardised laboratory tools need to be developed and made available.

In terms of screening and treatment in resource-limited settings, screening for HBsAg is considered an appropriate tool. Target populations to be treated need to be defined better, and linkages to other existing programmes should be investigated. All HIV+ individuals should be screened for HBV and, conversely, all HBV+ individuals should be screened for HIV. HBsAg+ individuals should be referred for management including patient education, contact follow up, further diagnostic measures, and/or treatment.

Recommendation for chronic HBV treatment consultation in resource-limited settings:

- Prioritise treatment of persons with cirrhosis (decompensated or compensated cirrhosis) and certain persons with HIV/HBV co-infection;
- HBV DNA assays should be robust, reliable, sensitive, quantified, standardised, regularly quality-controlled, affordable and available to guide management;
- Liver biopsy may be useful, if available, provided it can be performed safely and interpreted appropriately; and
- Alternatively, non-invasive tests of liver fibrosis may be considered when available.

Research recommendations related to chronic HBV treatment in resource-limited settings :

- Burden of disease data, especially through disease and death registries;
- HBV prevalence in HIV-infected persons;
- HBsAg carriage in persons with cirrhosis and HCC;
- HBV prevalence, treatment and outcomes in regions of Africa and Asia;
- Effectiveness of screening programmes;
- Liver-related mortality including HCC;
- Best practices for surveillance of HBV outcome;
- Laboratory quality control panels for testing HBV DNA; and
- Replacement for liver biopsy.

Guidelines for initiation of anti-retroviral therapy (ART)

Guidelines on ART for HBV/HIV co-infected adolescents and adults were proposed by WHO in October 2009. For HBV/HIV co-infected patients with active chronic HBV it was strongly recommended to start ART irrespective of the CD4 count. Therefore there was a call for increased HBV screening of HIV+ individuals. A clear case definition of active chronic HBV was drafted:

A proposed case definition for active chronic HBV is as follows. This has not been adopted by WHO.

- Clinical case definition: persons with chronic HBV infection may be asymptomatic. They may have no evidence of liver disease or may have a spectrum of disease ranging from chronic hepatitis to cirrhosis or liver cancer. Stigmata of end stage liver disease (ESLD) include spider angiomata, splenomegaly, caput medusa, ascites, jaundice, asterixis and encephalopathy.
- Laboratory case definition: anti-HBc+ and HBsAg+; plus:

  HBV DNA+ or ALT elevation (either >30 in males or >19 in females).
- Classification: a confirmed case is one that meets the laboratory criteria or has stigmata of ESLD.

Hepatitis Atlas

The World Hepatitis Alliance, in collaboration with WHO, are developing a Hepatitis Atlas, which was launched at the EASL meeting in April 2010. The atlas consists of a review of Member State policies and was developed following a web survey.

Overall, the importance of focusing on feasible objectives for which resources are available was underlined, rather than targeting numerous desirable objectives.

Reference

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Based on a presentation by S. Wiersma, Immunization, Vaccines & Biologicals EPI, Geneva, Switzerland.

Management and treatment of identified persons with chronic viral hepatitis

In contrast to the case of HBV, for which treatment can only suppress the virus and control the disease progression, treatment for HCV can be curative.

Treatment of HBV

Currently, seven antiviral agents are licensed for HBV treatment which, when used in combination, can provide the best possible treatment outcomes. The primary goal of HBV treatment should be to improve quality of life by preventing progression of the disease, which can be achieved if HBV replication can be suppressed in a sustained manner.

Indications

Risk factors for chronic HBV-related cirrhosis are the presence of HBeAg and HBV DNA, advanced age, increased ALT levels, co-infections with HDV, and diabetes mellitus. The risk of progression to cirrhosis increases significantly with increasing HBV DNA levels, independently of the presence of HBeAg and the status of ALT [1, 2]. The decision to treat should not be based on the status of HBV replication only, but other biomarkers are needed to indicate which patients are likely to have disease progression.

EASL guidelines base the indication for HBV treatment on a composite picture of the disease, independent of the HBeAg status, including the level of HBV DNA replication (>2,000 IU/ml), accompanied by raised serum aminotransferases (> upper limit of normal, or ULN), and histological stage and activity [3]. These indications for treatment must also take into account age, health status, and availability of antiviral agents in the individual countries.

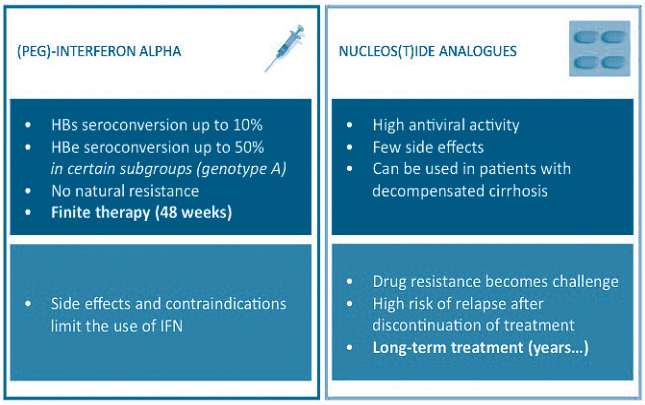
In clinical practice, putting together this composite picture of the disease can be difficult and decisions often need to be based on longitudinal follow up results. Patients that require longitudinal monitoring include HBeAg+ immunotolerant individuals who are mostly under the age of 30, have very high levels of HBV DNA, normal ALT and no family history of liver cancer or cirrhosis. These patients do not require immediate treatment. For patients with mild disease (ALT level not very elevated and mild inflammation or fibrosis of the liver), treatment should be deferred. In both cases, longitudinal monitoring is necessary because the disease is very dynamic.

Treatment strategies

Historically, HBV has been treated with IFN, the first drug licensed to treat HBV. More recently, nucleos(t)ide analogues have been introduced. Treatment with nucleos(t)ides is simpler and safer, but not curative. Currently, 5 nucleos(t)ide analogues are licensed: Lamivudine, Adefovir, Entecavir, Telbivudine and Tenofovir. Most patients respond to treatment and have an improvement in their quality of life, but most patients still need continued treatment and suboptimal treatment may influence the outcome.

The advantages and disadvantages of the two treatment strategies for HBV (PegIFNα or Nucleos(t)ide analogues) are summarized in the Figure below.

HBV treatment: different concepts



IFN responses depend on the type of infection and the different phases of the disease. Treatments cannot be used in all the different settings. It is possible to induce HBs antigen seroconversion, but this does not mean a cure, and reactivation after immune suppression can occur when treatment is interrupted. Studies by the European Concerted Action on Viral Hepatitis (EUROHEP) have shown that IFN can reduce the incidence of cirrhosis, and reduce mortality [4]. In general, if a response to IFN is seen after a short treatment period (16 weeks), the patient will have a survival advantage. IFN also has the benefit of not inducing resistance. However, it can only be used for a finite period, is costly, relapse after treatment termination is high, and its side effects and contraindications can limit its use.

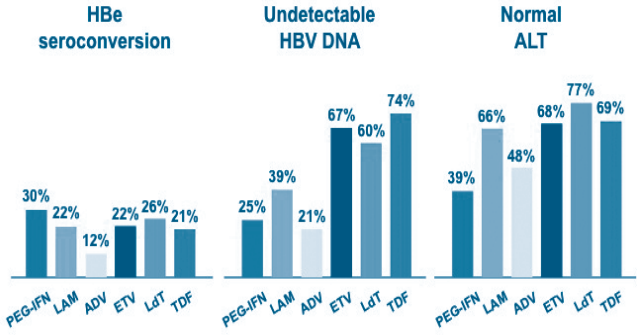
IFNα should be used in patients with HBV genotype A, who have high ALT and a low HBV DNA levels. Patients with genotype A respond better to treatment than those that are infected with genotype D. Follow up data have shown that there is more likely to be seroconversion in the long term in those patients with genotype A [5]. Although genotype alone should not determine the treatment algorithm, the inclusion of genotype testing as a parameter should be recommended. Unfortunately, in many countries genotype testing is not reimbursed or not performed at all.

Polymerase inhibitors should be used to treat HBV, when the use of IFN is contraindicated. The nucleos(t)ide analogues are highly active with few side effects and can be used for a long period. If the patient has no cirrhosis, any approved nucleos(t)ide analogue can be used taking into account viral load and resistance profile. Data from the last two years support the view that treatment with nucleos(t)ides analogues improves the outcome and therapeutic endpoints in the longer term.

Nevertheless, resistance development is a problem when mono-nucleoside analogues are used for long-term treatment. In particular, Lamivudine monotherapy produces high rates of resistance. However, due to the relative low cost of Lamivudine, monotherapy is started in some countries, despite the guidelines.

Continued treatment with nucleos(t)ides analogues is required for the majority of HBeAg+ patients, as well as HBeAg- patients; therefore resistance could become a drawback in the future. Only about 25-30% of HBeAg+ patients treated for one year will seroconvert, irrespective of whether they are taking IFN or nucleos(t)ides analogues. The majority of patients do not seroconvert, and must carry on nucleos(t)ide analogue treatment. After one year of treatment the majority of HBeAg+ patients show suppression of viral replication (see Figure below).

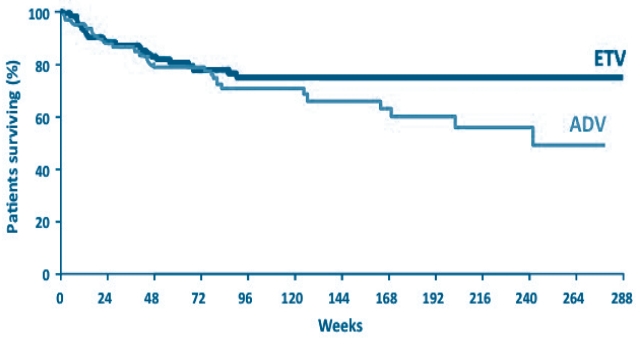
Response to treatment after one year in HBeAg positive patients



For HBeAg- patients, the treatment goal is probably loss of surface antigen (HBsAg); therefore the majority of those patients will require continued treatment. Use of such life-long treatments raises resistance and toxicity issues, and careful consideration should be given before starting treatment.

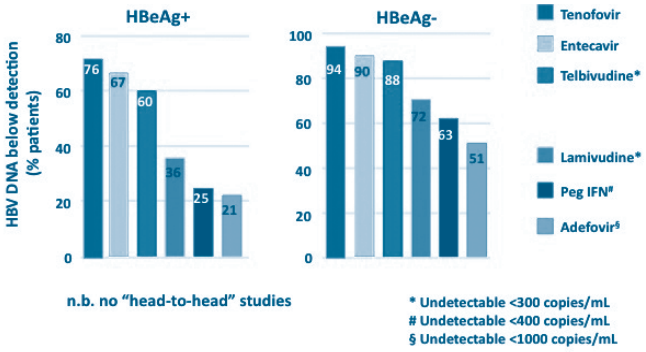
Patients with cirrhosis and detectable HBV DNA should be treated with highly potent nucleos(t)ide analogues with a high resistance barrier or a combination therapy, irrespective of the level of replication at this stage, which may be low. Patients presenting with decompensated cirrhosis who have ascites and encephalopathy require urgent antiviral treatment and should also be considered for liver transplantation. Recent studies suggest that patients with cirrhosis can benefit from treatment. Following drug treatment, liver fibrosis can regress and early cirrhosis is reversible. Several trials in patients with decompensated cirrhosis have shown that treatment can improve survival rates [6, 7] (see Figure below), and the rate of HCC progression [7].

Overall survival following treatment with Entecavir (ETV) versus Adefovir (ADV) in decompensated HBV-infected patients [6]



Guidelines recommend that a high genetic barrier drug, with low risk of initiating resistance, but with strong antiviral efficacy should be used. Treatment of HBeAg- patients in clinical trials (48-52 weeks) resulted in up to 9 out of 10 patients becoming HBV DNA negative, as shown in the Figure below [8-13].

Antiviral efficacy of available drugs for HBV treatment in clinical trials.



In clinical trials, there is no reported resistance for Tenofovir and for Entecavir, resistance is rare. However, it is possible that resistance could become a problem outside the clinical trial setting where compliance is lower. If resistance is induced, polymerase variations may have consequences at the HBsAg coding level and these may have an impact on vaccine effectiveness, but more data are needed to determine whether this will have a clinical impact.

To prevent resistance to nucleoside analogues there should be:

- A clear indication for starting therapy;
- Promotion of patient compliance;
- Maximised antiviral activity;
- HBV DNA suppression to lowest possible level;
- Maximised genetic barriers;
- Avoidance of sequential treatment; and
- Avoidance of treatment interruptions.

Besides the treatment of HBV, nucleos(t)ide analogues play an integral role in liver transplantation. They can also be used effectively for treating fulminant HBV and in the prophylaxis of patients receiving chemotherapy. Other opportunities for the use of nucleos(t)ides include management of extra-hepatic disease, HIV co-infected patients, pregnancy and post sur-

gery treatment of HCC. IFN and Lamivudine have also been approved for the treatment of children infected with HBV.

Unfortunately few, if any, new drug or new treatment approaches for chronic HBV are in the pipeline; which limits the possibilities of treatment if resistance occurs or when contra indications get the upper hand.

Treatment of HDV

It is estimated that 15-20 million HBV infected people are affected by HDV worldwide [14] and the related disease is considered to be the most severe form of viral hepatitis in humans. In Germany, more patients die from HDV than from HIV. Of those that are infected, 80% are not German-born [14]. A long-term outcome study conducted in Italy found that 60% of HDV patients had liver cirrhosis, and liver failure was the main cause of death [15]. In a trial in Turkey and Greece, it was shown that PegIFN leads to sustained suppression of HBV-RNA in about 25% of HDV-infected patients [16]. More research is needed to understand the natural history of HDV and to develop novel treatment tailored to this severe form of hepatitis.

Treatment of HCV

Indications

Recent research shows that the response rate for treatment of acute HCV is higher than in chronic patients, especially when treatment is started early after exposure to the virus. The ideal timing and treatment regimen for acute disease still need further research. However, since acute HCV is clinically mild, and consequently infrequently diagnosed, treatment is unlikely to have a major impact on the prevalence of the disease.

Chronic HCV is generally slowly progressive and is not necessarily benign. Cirrhosis develops within 20 years in about 10-20% of individuals, but this proportion is much lower in children. The variability in rates of progression of the disease makes the prediction of ultimate outcomes very difficult. Factors shown to accelerate the progression to cirrhosis in HCV patients include: acquiring HCV at an older age; being male; high alcohol consumption; and co-infection with either HBV or HIV. There is no evidence of a DNA intermediate, or integration of viral nucleic acid, and yet these patients seem to be at risk of HCC through cirrhosis and regeneration of liver cells.

A decision to initiate treatment should be based on:

- Quantification of viral load (HCV RNA);
- Evaluation of liver disease;
- The HCV genotype; and
- Exclusion of co-infection.

Most clinicians prefer to have an indication of the histological stage of the disease, but increasingly non-invasive biomarkers are being used, assuming these are reliable.

General management involves careful clinical monitoring and providing advice to patients in the hope that this will have an impact on outcome. Information should be provided about:

- The aggravating effects of alcohol;
- Co-morbidities, such as HBV, HIV, obesity, hepatic steatosis, diabetes and insulin resistance;
- Disease transmission; and
- Vaccination.

All HCV patients, irrespective of the degree of fibrosis, are potential candidates for treatment; even within the current costs of treatment, the accessibility of treatment, and response rates. Some patients with mild disease do not require immediate treatment. Psychiatric co-morbidities may worsen with IFN treatment, and these patients should be stabilized if treated. Most HCV patients with raised serum ALT are positive for HCV RNA, however 25-50% with ongoing HCV replication may have persistently normal serum ALT. For this reason, ALT cannot be used as a single criterion to initiate treatment, as sometimes low grade fibrosis can be present in patients with normal ALT levels.

Factors that adversely determine response to treatment.

- Genetic polymorphism: TT IL28b polymorphism;
- High baseline viral load;
- Age greater than 50 years;
- High body mass index;
- Poor adherence to therapy;
- Excess alcohol
- Genotype 1 versus genotype 2 or 3;
- Genotype 4, and probably 5 and 6;
- Advanced fibrosis, cirrhosis or advanced liver disease;
- Hepatic steatosis;
- Low platelet count;
- High homeostasis model assessment index (HOMA);
- Failure to achieve Rapid Viral Response (RVR);
- African American ethnicity; and
- HIV and HCV co-infection.

The IL28B gene variant is strongly associated with IFN response [17] and has shown to be predictive of response in clinical trials. The presence of this gene variant may explain the poor response of African Americans to IFN. Detection of this variant could be proposed as a useful tool in clinical practice.

Virological response to re-treatment was shown to be dependent on the stage of disease [18]. Fibrosis can be treated, or even retreated, and patients achieving sustained virological response have improved prognosis, they are less likely to decompensate and less likely to develop HCC. Other groups that are challenging to treat include: active IDU; patients with decompensated cirrhosis; patients that experience recurrence after liver transplant; non-responders; and HIV co-infected patients.

Treatment strategies

In trials, PegIFN and Ribavirin can cure at least 50% of patients, however in real life the results are much lower (10-20%). Side effects of treatment are common. The AASLD

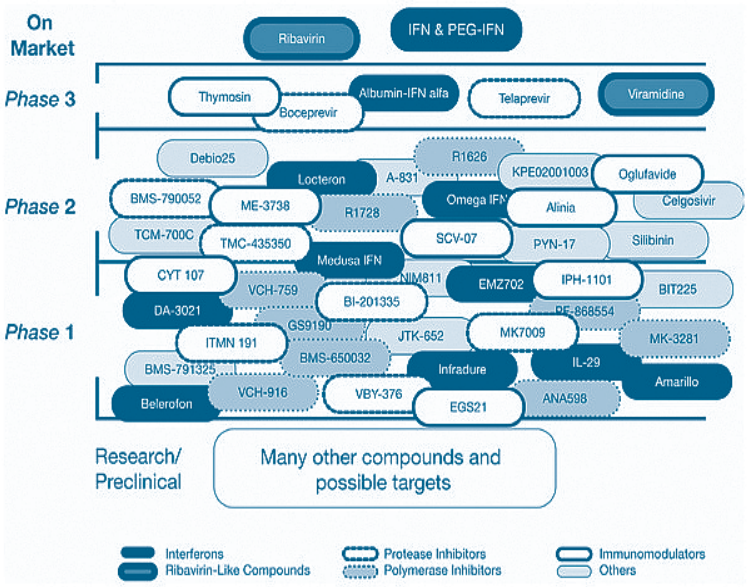
recommendation published in 2009 [19], and the New German guidelines, recommend that HCV treatment should be individualized based on response kinetics. Patients with a fast response may benefit from a shorter treatment, whereas patients with a slow response may need longer treatment, e.g., up to 72 weeks [20]. Therefore, it was recommended that HCV RNA should be tested with a highly sensitive assay shortly before the start of the treatment and at week 12 and 24. Depending on the results, the treatment regimen can be adapted. EASL will be issuing clinical guidelines for HCV treatment soon.

Due to contraindications, only 50% of HCV patients are eligible for HCV treatment and benefit from curative treatment. Although treatment is effective, in real life only a very small percentage of patients complete treatment due to side effects.

Future treatment of HCV

Numerous new drugs for HCV therapy are in development; results seem to be very promising and might provide the opportunity to avoid IFN use in future, see Figure below [21].

Clinical development of new anti-HCV drugs



Thompson et al, 2009 [21]

Two compounds, Telaprevir and Boceprevir, will hopefully be licensed by 2011. By using combination therapy with protease inhibitors and polymerase inhibitors, an increase in efficacy of 20-30% could be achieved and this could allow the shortening of treatment duration to 24 weeks or even 12 weeks, which may improve the compliance and the success rate of HCV treatment markedly.

With the various treatment options currently in development, treatment in the 2020s could involve cocktails of antivirals, ideally in one tablet. However, there is strong concern that resistance to these agents, not previously encountered, may become a clinical problem.

There are a number of anticipated advantages of new treatments that are in development. These, and the potential disadvantages, are detailed below.

New agents for HCV: anticipated advantages and potential disadvantages

Anticipated advantages	Potential disadvantages
• Improved response rates - naive and non-responders	• New concerns raised
• Rapid reduction in HCV RNA	• Unequal effect genotypes and subtypes
• Shorter duration therapy	• Triple or even quadruple combinations
• Better tolerated therapy?	• Antiviral resistance
• Treatments equally efficacious across all genotypes and subtypes?	• New drug interactions
• Ribavirin-sparing effect?	• Dosing frequency
• Eventual IFN-sparing effect?	• Additive or new side effects
• Cost effective and cost benefits?	• Reduced cost effectiveness

In the case of HCV, one of the Wilson and Jungner criteria is met, however treatment options are limited and treatments are associated with side effects and contraindications. The availability of new anti-viral drugs should be taken into account, and continuous evaluation of the other screening criteria is advisable.

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Based on presentations by H. Wedemeyer, European Association for the Study of the Liver, Geneva, Switzerland; G. Dusheiko, Centre for Hepatology, Royal Free Hospital, London; S. Schalm, Liver Doc, Rotterdam, The Netherlands.

Need for long term evaluation of therapy in chronic HBV

Knowing the long term outcome of the available AVT in terms of reduction in morbidity and mortality, and especially the impact of antiviral resistance and side effects, would be beneficial for public health decision making.

A systematic review conducted in 2009 for The National Institutes of Health Consensus Development Conference to evaluate the long term effectiveness of AVT for adults with chronic HBV concluded that, "Evidence was insufficient to assess treatment effect on clinical outcomes or determine whether improvements in selected intermediate measures are reliable surrogates" [1]. The paper also concluded that, "future research is needed to provide evidence-based recommendations about optimal AVT in adults with chronic hepatitis B infection". However, all studies performed outside the USA and those including fewer than 1,000 patients were excluded, rendering the review incomplete. Therefore these conclusions should be interpreted with caution.

Long term efficacy of treatment still needs to be proven. There is evidence that treatment of both HBV and HCV will decrease mortality of patients with ESLD and cirrhosis, but there is currently no evidence to show that, in the long term, mild or moderate disease benefits from treatment in terms of decreasing overall morbidity and mortality. The drawback of treatment for HBV is that people who are inappropriately treated may develop resistance; and the drawbacks for HCV treatment are the toxicity and side effects of the drugs.

Long term treatment with Lamivudine

In a placebo-controlled study of 600 chronic HBV patients that had advanced, non-decompensated cirrhosis, it was shown that Lamivudine had an effect on clinical outcome by reducing liver failure [2]. There was also an indication that there was a reduction in HCC, although this effect was barely significant. When considering non-responders (i.e., patients that become resistant to Lamivudine), the natural progression of the disease was unchanged. Among the subgroup of responders to Lamivudine (about 50%), progression to liver failure and mortality rate was low, demonstrating that responding to a nucleos(t)ide analogue can be of clinical benefit and reduce mortality significantly.

In another long term study on HBeAg- cirrhotic patients treated with Lamivudine [3], 50% had a response and 50% developed resistance. Also in this study, response to Lamivudine prevented decompensation, and reduced the incidence of HCC. However, the effect of Lamivudine monotherapy on survival could not be studied because Adefovir was added to the treatment for those that developed resistance.

Studies evaluating long term antiviral drug use are often hampered by ethical considerations or regulatory requirements. Therefore, modelling the burden of disease for a country cohort of patients with chronic viral hepatitis without and with treatment is considered a valuable alternative. A Markov mathematical model was used to assess the potential impact

of AVT and antiviral resistance on chronic HBV burden of disease, within a median follow up of 20 years, of a patient cohort in the Netherlands [4]. Input for this model included annual probabilities of progression from chronic hepatitis to cirrhosis, decompensated cirrhosis, HCC and finally death obtained from systematic reviews published in the literature. The model predicted that, in a 20-year period of treatment of non-cirrhotic patients, when a drug with a high resistance profile (i.e., a drug likely to cause resistance, such as Lamivudine) was used, liver-related mortality would be reduced by 52%. However, if a low resistance profile drug (i.e., a drug unlikely to cause resistance such as Entecavir) or salvage therapy was used, the reduction in mortality would be about 90%. In the cirrhotic population, Lamivudine would achieve a 40% reduction in predicted mortality following treatment, compared with a 62% reduction using low resistance profile drugs or salvage therapy.

The beneficial effect of AVT is due to both the reduction in complications of cirrhosis, and preventing the development of cirrhosis. The model findings indicate that clinical benefits of AVT may be strongly reduced when high resistance profile drugs are used, or antiviral resistances remain unaddressed. The cohort-based model provides a realistic tool to estimate country-specific HBV-related mortality and morbidity and the potential impact of AVT. Long term AVT with low resistance profile drugs will have a major preventive effect on liver related mortality and morbidity of chronic HBV. Antiviral resistance, when unaddressed, may reduce the clinical benefits of AVT by almost 50%.

In conclusion, small-sized European studies indicate that AVT is of clinical benefit for chronic HBV patients when persistent viral suppression is achieved. The model findings predict an impressive reduction of mortality at national level if long term AVT with minimal antiviral resistance is initiated in all active chronic hepatitis carriers. The high prices of drugs that are more effective than Lamivudine are still preventing their use as a first line treatment. Field studies are urgently needed to confirm the findings of the model, in view of the paralysing effect of treatment uncertainty upon public health action. Such studies could include a cohort with therapy, which would allow outcome comparison with the model; and a case control study that compares compliant versus non-compliant groups.

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Based on presentations by
S. Schalm, Liver Doc, Rotterdam, The Netherlands;
B. McMahon, Alaska Native Medical Center, Liver Disease and Hepatitis, Anchorage, Alaska.

Economics of chronic HBV and HCV

The economic aspects of antiviral treatment have become an increasing focus of discussion for physicians, policymakers, and those responsible for healthcare budgets.

Public health burden of HCV projected for 2010-2019

The predicted 1.5-2 fold increase in HCV mortality for several countries (including US, France, Spain, Switzerland, England, Australia and Canada) will lead to substantial increases in medical care costs for liver disease (e.g., for the USA the total cost, excluding the cost of antiviral treatment, will be $11 billion). The average annual per-patient cost of drugs to treat HBV, at current US wholesale prices, varies from $4,524 for Lamivudine to $28,277 for PegIFNα (www.redbook.com). Management of treatment following an appropriate algorithm and accounting for discontinuations observed in a randomized trial decreased costs by 43% [1].

Cost-effectiveness analysis considers not only the costs of drugs, but also of drug monitoring, side effects, and the effects of disease. Models rely on an understanding of the natural history of the disease and the effects of therapy, accounting for disease-related death and morbidity. Randomized lifetime clinical trials are impractical, therefore the computer simulation models, such as the Markov model, are used.

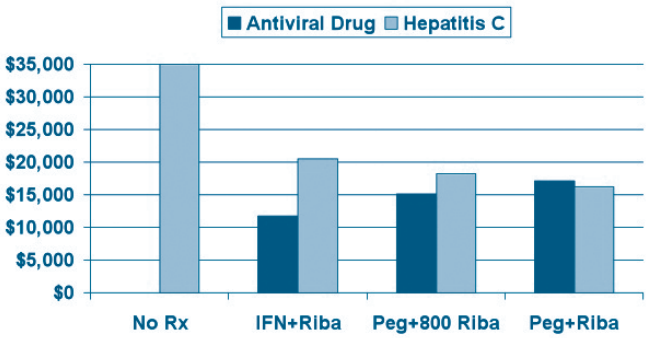
The HBV model takes into account different serologies; chronic hepatitis versus cirrhosis; decompensated states; development of HCC; and death from causes as occur in the general population or from liver disease [2]. For example, the projected life expectancy of an individual who is HBeAg+ and not treated with AVT is 24 years with a lifetime HBV-related healthcare cost of $63,000 (in 1995 costs). Converting an HBeAg+ patient to HBeAg- status would extend that patient's life expectancy by 10 years and reduce lifetime disease cost by $20,000.

Besides efficacy and safety, questions have arisen as to efficiency or the value provided by medical therapies, particularly expensive ones. Incremental cost-effectiveness analysis (the additional cost divided by the additional benefit of a new therapy versus standard care) is the most commonly accepted measure of societal value provided by new medical technologies and is used to help inform reimbursement and policy making.

In the case of HCV: without AVT, disease costs would be about $35,000 per HCV patient (see Figure below, [2]). Treatment with standard IFN plus Ribavirin would decrease

disease costs because some patients would be converted into sustained viral responders; however, money would need to be spent on drugs in order to save that future cost. As sustained viral response increases with more powerful drugs, disease costs decline further, but the antiviral drug treatment costs increase.

Costs of treating HCV, in dollars per patient



Cost-effectiveness analyses depend on the comparative effectiveness of the therapies examined, and the patient population being studied. Based on reviews of published studies on AVT, incremental cost-effectiveness ratios range from being cost-saving up to $33,900 per quality adjusted life year (QALY) gained for HBV treatment and up to $120,000 per QALY gained for HCV treatment. According to the WHO (WHO-CHOICE, www.who.int/choice), determining whether an intervention is cost-effective depends on a particular country's willingness to pay and this should be related to their Gross Domestic Product (GDP). Therefore, WHO divides Europe into three regions and, based on 2005 GDP, the thresholds for being cost-effective range from $24,000 per QALY for Eastern, $28,000 for Central and $91,000 per QALY for Western European countries.

Finally, when calculating cost-effectiveness of improved health on an individual and a population level, heterogeneity in populations needs to be considered, as there may be high variability in risk factors, levels of seeking health care, access to health care, and screening and treatment decisions taken by health care providers and public health systems.

In conclusion, HBV and HCV are associated with substantial morbidity, mortality, and costs. Studies suggest that treatments for HBV and HCV will be cost-saving or cost-effective, but with new drug development there is a continuing need to perform health economic analyses in order to assure patients, physicians and policymakers that their cost and effectiveness versus established therapies provide sufficient societal and individual patient value to justify their use and approval.

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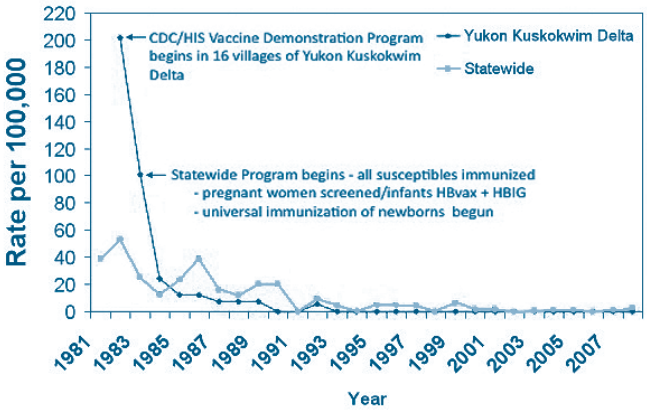
Based on a presentation by J. Wong, Division of Clinical Decision Making, Tufts University School of Medicine, Tufts Medical Center, Boston, USA.

Programmes for chronic HBV and HCV in Alaska Natives

HBV among Alsaka Natives

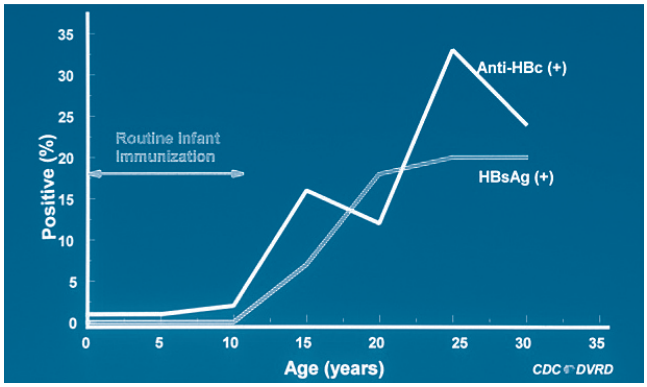
In 1978, a registry of HBsAg+ individuals was established. In the early 1980s when the HBV vaccine became available, the Alaska Native Hepatitis B programme was initiated and ran from 1983 until 1987 [1]. Two thirds of the total population were screened (53,000), including 90% of people in the endemic areas of Western Alaska. In addition to universal newborn vaccination, 40,000 susceptible individuals (of the 53,000 screened) were vaccinated. Universal vaccination of newborns and a catch up programme of persons susceptible to HBV were started in 1984. Vaccination has had a dramatic effect on the incidence of acute symptomatic HBV (see Figure below). In the most endemic area, no HBV case has been reported since 1993.

The incidence of symptomatic HBV in Alaska Natives 1981-2008



In the rest of Alaska, the incidence has dropped to less than 1 per 100,000. One serosurvey showed that 10 years after the introduction of the universal vaccination given at birth, none of the tested children younger than 10 years of age, were HBsAg+. In contrast, in the group that was born before the start of the immunization programme (aged 25-35 years), 20% were HBsAg+ [2] (see figure below).

Age-specific prevalence of HBV infection in Bristol Bay Eskimos, 1994



The incidence of HCC in children (<20 years), which had previously been fairly high (approaching 3 per 100,000), has fallen.

A cohort of 1,560 HBsAg+ chronically infected persons with median age at entry of 20 years old was followed for a median of 21 years. All clinical and laboratory data from this Chronic HBV Alaska cohort (including over 20,000 sera samples) were processed in the Alaska Native Tribal Health Consortium (ANTHC) programme to follow up HBV carriers. All results are managed in a computerized registry, which is also used to disseminate information to patients, including invitations for check ups and information on new treatments.

Alaska Native Medical Center (ANMC) tests for ALT, AST, HBeAg/anti-HBe and α fetoprotein (AFP, a liver tumor marker), every 6 months in all HBV carriers. If ALT or AST were above normal levels, then the HBV DNA level was investigated in order to determine the stage of the disease. Additional tests performed included: liver panel and complete blood count (CBC); HCV; and HDV. Since only one HDV+ case was found, HDV testing was stopped. Due to the high number of females with autoimmune hepatitis in Alaska, autoimmune markers were checked if HBV DNA was lower than 2,000 IU/ml.

Although the AFP test is not very specific or sensitive, it can indicate active liver disease, or whether individuals are susceptible to developing liver cancer in the future. HBV carriers with an AFP level greater than10 ng/ml are referred for an ultrasound. Patients with elevated ALT and HBV DNA greater than 2,000 IU/ml are recommended for a liver biopsy at ANMC, to assess whether treatment is required. Patients are treated if they have moderate or severe inflammation or fibrosis.

Genotype may have an effect on the transmission route and may indicate how the disease will progress. Perinatal transmission often takes place when mothers are infected with genotype C, given that HBeAg seroconversion occurs decades later with genotype C compared to other genotypes. Five HBV genotypes and 6 sub-types were found in Alaska.

- Genotypes A2 (12.3% of cohort) and D (56.4% of cohort) are associated with HCC in older persons with a mean age >60 years.
- Genotype C2 (6.7%) is associated with HCC in middle aged people (~age 50). These people are prone to more flares of ALT (greater than twice the normal levels) and more liver disease.
- Genotype F1 (20.4%) is associated with HCC in children and young adults (mean age 22 years).
- Genotype B6 (4.2%) is similar to B1 (predominantly found in Japan) and is common in elderly people (over 70 years). This genotype has not yet been shown to be associated with HCC or liver decompensation. However, the mean age of the populations in Alaska is in the mid 40s while the B1 genotype in Japan is associated with HCC in very elderly individuals. B6 is a new genotype found in Greenland and North Canada that is unique to Alaska Natives.

Over a 21 year period [3], 50% of initially HBeAg+ Alaska Natives infected with HBV genotypes A, B, D and F cleared HBeAg antigen, meaning that by the time they reach childbearing age most will have low viral load. For genotype C2, the median age of clearance was higher than for other types, approximately 50 years of age. Thus the majority of those women infected with genotype C2 will have high viral loads throughout pregnancy leading to a very high risk of perinatal transmission unless HBV vaccine and Hepatitis B Immune Globulin vaccine (HBIG) are administered at birth.

Elevated ALT levels are very common in HBV carriers, and over a follow up of 8 years, half of the patients had elevated ALT. However, only a quarter of patients develop ALT and HBV DNA above 2,000 IU/ml, indicative of chronic HBV. In 28% excessive alcohol consumption caused the elevated ALT, and 25% had non alcoholic fatty liver disease.

HCV among Alaska Natives and American Indians

There is no HCV screening strategy covering the total population in Alaska. A small proportion (10%) of individuals get tested privately outside Alaska, but the majority of screening of Alaska Natives is carried out in two laboratories who report the positive cases to the ANMC office. The epidemiology and burden of HCV in the US was studied in the US CDC's National Health and Nutrition Examination Survey (NHANES). However, Alaska Natives and American Indians were under represented in the NHANES survey. In Alaska Natives the prevalence of HCV, risk factors, genotype distribution, and the proportion of people who recovered were the same as in the overall NHANES estimates for the US, except that in Alaska there was a slightly increased proportion of HCV genotype 3.

Currently from the 1994 HCV positive cases, 1,201 were enrolled in treatment studies. During a period of 7 years, 10% of the 1,201 HCV patients had developed complications, as shown below.

HCV complications

End stage liver disease (ESLD) total: 122/1,201

- ESLD without HCC: 105
- ESLD with HCC: 17
- liver transplant: 5

Hepatocellular carcinoma (HCC) total: 29/1,201

- HCC with ESLD 18 (3 living)
- HCC without ESLD 11 (5 living)

A retrospective and prospective population-based study, in a cohort of 960 Alaska Native chronically infected HCV patients investigated risk factors associated with adverse outcome from HCV infection between 1994 and 2005 [4].

A history of high alcohol consumption was associated with the highest incidence of ESLD and liver-related death (LRD), regardless of whether patients were chronically infected or recovered from HCV infection. If patients consumed more than 50g alcohol/day, ESLD and LRD incidence was significantly higher regardless of whether patients were chronically infected or had recovered from HCV infection. Multivariate analysis showed that older age, heavy alcohol use, and HCV genotype 3 were associated with ESLD.

Even with universal health care and addition of newer medications, over 50% of HCV patients will be difficult to treat, partly because many patients are difficult to reach and many have medical or psychiatric contraindications. As a result, very few patients actually complete treatment. Access to care and ability to afford treatment can be an additional barrier to HCV treatment (e.g., in US). Between 25% and 50% of HCV+ individuals are eligible for treatment, but only 5%-15% are eligible and want treatment. Of those who begin treatment, only 25%-70% complete the course, and only about 50% of those that are treated get cured.

Unlike many places in Europe, medical care for Alaska Natives is free, therefore this is not a barrier to individuals being tested and treated. The Treatment Eligibility Study examined treatment barriers for Alaska Natives with chronic HCV in 2003 over a period of one year (see Table below).

Patients were sent appointment reminders every 6 months and the study was repeated in 2007. The results show that the proportion of patients that did not receive treatment dropped by 50%.

Reason not treated (%)	2003 N=90	2007 N=132
Did not keep appointments	35.6	18.2
Alcohol or drug abuse within 6 months	17.0	22.0
Patient decision to defer treatment	17.0	27.3
Liver biopsy without fibrosis or normal ALT	8.5	3.0
Psychiatric condition	7.4	6.8
Concurrent medical condition	6.4	9.1
Decompensated cirrhosis	3.3	5.3
Age >65 years	2.2	1.5
Considering treatment/treatment planned	0	5.3
Other	0	1.5

In general, the drop-out rate for the general population in real life is much higher than in controlled studies. Among a national cohort of HCV-infected veterans in care (n = 134,000) from 1998 to 2003, 11.9% were prescribed treatment and among those with at least one year follow up, 22.5% completed a 48 week treatment course [5]. Only 1.7% of the total HCV-infected cohort completed their treatment.

In 2010, the Alaska HCV programme aims to treat people with HCV genotypes 2 and 3, and genotype 1-infected persons with advanced fibrosis. From 2010-2013, the programme aims to treat people with genotype 1 with grade 3-4 fibrosis with PegIFN, Ribavirin plus protease inhibitor. From 2014-2015 and beyond, the programme aims to treat all eligible patients with an oral IFN-free regimen if this regimen becomes licensed.

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Based on a presentation by
B. McMahon, Programme Alaska Native Medical Center and Arctic Investigations Program, Anchorage, Alaska.

Country sessions

Belgium

Burden of disease

HBV

Passive surveillance of acute, chronic and asymptomatic cases through mandatory notification.
HBsAg prevalence=0.66% in 2003 (N=1,836) and 0.70% in 1993 [1].

Belgian Association for the Study of the Liver registry (BASL) (2008-2009, N=1421):
Risk factors among HBsAg+: 14% blood transfusion; 9% IDU, 6% surgery; 38% risky sexual behaviour; and 33% familial transmission. 12% co-infected (HDV, HCV and/or HIV) [2].
Stage (N=641 with liver biopsy):
40% F0-F1; 24% F2; 19% F3; and 17% F4.
Phase: 0.7% immune tolerant; 17% HBeAg+; 29% HBeAg–; 44% inactive carrier; 9% not classified.

Belgian Health Care Knowledge Centre registry (Jan-Jun 2009), N=544 HBsAg+ at consultation (51% European; 9% Turkish; 22% African and 18% Asian).
2% hepatocellular carcinoma; 11% transplants; 14% cirrhosis.
4% immune tolerant; 34% inactive carriers; 20% HBeAg+; 40% HBeAg-; and 2% HBsAg- [3]

HCV

Passive surveillance through mandatory notification, since 2009 no longer in all regions. Flanders decided to stop notification of HCV cases.
In 2003 (N=1836) tested: 0.12% anti-HCV+ (0.87% in 1993) [1].
From these 318 anti HCV+: 87% PCR+; 66% abnormal ALT.
Risk factors: 27% IDU (under-represented); 23% blood transfusion;

11% invasive medical procedures, 23% unknown [4].
Stage: 43% F0-F1; 35% F2; and 22% F3-F4.
Genotypes: 1 (59%); 3 (19%); and 4 (14%) [5].

In 2002 among IDU (N=147): 70% anti-HCV+ [6] and most are genotype 3 (49%). In 2001-2003 among HIV+ (N=37):10-15% anti-HCV+ with 56% ≥F3 [7].

Screening strategy

Target population

HBV

- Pregnant women;
- Donors and recipients of blood, blood products and tissue.

HCV

(opportunistic screening by GP and gastroenterology centre)

- History of IDU;
- People with conditions associated with a high HCV prevalence, including HIV+, haemophiliacs who received blood products prior to 1987; haemodialysis patients; those with unexplained abnormal aminotransferases;
- Recipients of blood transfusions or organ transplants prior to July 1992;
- Children born to HCV+ mothers;
- Health care, emergency medical and public safety workers after needle stick injury or mucosal exposure to HCV+ blood;
- Current sexual partners of HCV+.

Goals/Implementation

- Screening of blood/blood products/tissue since 1972 (HBV) and since 1990 (HCV);
- Universal precautions in health care setting;
- Screening of pregnant women: HBV routinely; HCV only if risk-behaviour;
- Opportunistic screening by GPs and gastroenterologists;
- National screening days for HCV (2001, 2004) sponsored by a medical company;
- No coordinated screening at national level.

Follow up (treatment) strategies

HBV

Lamivudine (1st line), but resistance monitoring is advised. Adefovir (2nd line), Entecavir and Tenofovir (1st and 2nd line).
Follow up every 3-6 months + ultrasound every 6 months for F3-F4.

HCV

Genotype 1, 4, 5, 6: liver biopsy required;
48 weeks PegIFNα 2a or 2b and Ribavirin.
Genotype 2, 3: 24 weeks PegIFNα 2a or 2b and Ribavirin. Follow up as for genotypes 1, 4, 5, 6.

Cost evaluation

Follow up/ treatment

HBV

Treatment reimbursed by National Institute for Health and Disability Insurance since January 2010 if liver biopsy and viral load criteria fulfilled (inflammation and/or fibrosis, elevated ALT at 2 time points, and HBV DNA >2000 IU/ml).

HCV

Liver biopsy required for treatment reimbursement for genotype 1, 4, 5, 6: not for genotype 2, 3: Treatment costs: ~ €10,200/24 weeks or ~ €18,700/48 weeks of PegIFNα 2a or 2b and Ribavirin. 98% paid by National Institute for Health and Disability Insurance. Patient pays ~ €35/24 weeks or 48 weeks.
Treatment of mild HCV (F1) with genotype 1, 4, 5, 6. costs €23,000/QALY; with genotype 2, 3 costs €4,600/QALY (treatment cost effective if <€50,000/QALY).
Among liver transplants: 29% due to HCV. Immediate treatment of mild HCV (F1) (more expensive, but fewer complications, higher % cured)

Evaluation of screening strategy

Strengths/ challenges and lessons learnt

- No coordinated screening or prevention strategy at country, regional or community level;
- STI clinics and IDU centres should be screening for HIV, HBV, HCV;
- IDU centres do not systematically vaccinate against HAV/HBV;
- Prevention plan installed;
- Universal HBV vaccination advised for all babies and children (11-12 years) since 1999;
- HBV vaccine reimbursed for some risk groups since 1980s.

Future plans

Specialists should encourage GPs to screen ‘at-risk population’.

France

Burden of disease

HBV

Passive surveillance through mandatory notification of acute HBV since 2004. Surveillance network of hepatology reference centres since 2008.

National Serosurvey (2004)
Incidence: 2,580 new infections/year; 4.1 persons/100,000.
Prevalence: Anti-HBc: 7.3%.
HBsAg: 0.65%, 5 times higher in men than women. Prevalence

strongly related to continent of birth (e.g., Sub-Saharan Africa: 5.25%). 78% of newly referred patients from endemic countries.
1,330 HBV deaths in 2001.

HCV

2 national population-based serosurveys (1994 and 2004) (age group 20-59 years):
1994: 1.05% anti-HCV+; 81% RNA+;
2004: 0,71% anti-HCV+; 57% RNA+.

Reduction is probably the result of effective treatment programmes. Results vary with age and country of birth.
Chronically infected: 232,000 (est.). Annual incidence 2,700-4,400 (est.). Deaths attributable to HCV=2,646 in 2001.
Around 60% of patients presenting at hepatology centres have active chronic hepatitis and 10-12% have cirrhosis with or without HCC at referral [8].
Modelling predicts mortality peak in 2010 followed by decline due to AVT [9].

Screening strategy

Target population

HBV

•Blood donors;
•Pregnant women (mandatory);
•At-risk population before (proposal of) vaccination.

HCV

- Blood donors.

Recommendations of the French Agency of Evaluation 2001:

- Transfusion before 1992;
- Previous heavy surgery, hospitalization in intensive care unit, digestive bleeding, difficult delivery; tissue, cells or organ transplant before 1992;
- Invasive acts (endoscopy) before 1997;
- Haemodialysis;
- IDU and nasal drug use;
- Sexual partner and household contacts of HCV+ individual;
- Newborn to HCV+ mother;
- Prisoners;
- Persons having received care in high endemic countries (Asia, Middle East, Africa, South America);
- Unexplained and prolonged asthenia.

Goals/Implementation

Goals: target at-risk populations to:

- Avoid transmission to household members, sexual contacts, occupational contacts;
- Prevent the development of cirrhosis and cancer through early treatment;
- Achieve public health policy (law of 9/8/2004) aim: reduce HCV/HBV-related morbidity/mortality by 30%;
- Plan 2009-2011: achieve 65-75% of patients aware of status with access to treatment.

Implementation:

- GPs, first line;
- Social security medical centres (according to new screening policy);
- All physicians (for patients with risk factors);
- Self request (e.g., in free anonymous screening centres);
- Screening by GPs and specialists widely encouraged since 1996;
- Campaigns for general public and health care professionals; booklets for doctors and patients; training for health care workers.

Follow up (treatment) strategies

HBV

- All antiviral drugs currently approved by European Medicines Agency (EMA) are available;
- First prescription by specialists only;
- Patients must be eligible for full Social Health Insurance (SHI).

HCV

- Reference therapy (PegIFN + Ribavirin) offered to all patients, following recommendations of French Conference of Consensus (2002);
- Indications extended to include patients with normal ALT, non responders or relapsers to a first treatment;
- Contraindications to treatment have been limited by use of adjuvant treatments;
- First prescription by specialists only;
- Patients must be eligible for full SHI.

Impact on public health

HBV

46% of HBsAg+ patients are aware of their status (2004).

HCV

Prevalence: slight reduction over 10 years, esp. in progression of RNA+ patients.
56% of HCV patients are aware of their status (2004), up from 24% (1994).

Highest proportion of treated patients (16%) among European countries in 2005 [10]. By 2009, est. 30% of patients (more than half of those diagnosed) have been treated at least once.
Due to increased screening rates in IDU, > 90% of IDU are aware of their HCV status [11].
Recipients of transfusions pre-1991 notified in regular campaigns. Individuals contracting HCV via other routes harder to notify.

Cost evaluation

Screening programme

HBV

65% of the cost of screening markers (HBsAg, anti-HBs, HBc Ab) reimbursed by SHI. New guidelines and screening algorithm being developed for 100% coverage by SHI.

HCV

Screening test 100% reimbursed by SHI.

Follow up/ treatment

Patients with chronic active liver disease or cirrhosis eligible for 100% treatment and follow up costs reimbursed by SHI.

Evaluation of screening strategy

Strengths/ challenges and lessons learnt

Strengths

High % diagnosed, high % treated for HCV; low dropout rates during treatment; impact on morbid-mortality already visible (modelling data).

Efficient surveillance system.

Challenges

- Improve network between hospitals, GPs and physicians caring for at-risk groups;
- Improve level of HBV diagnosis;
- Reach at-risk populations (migrants and IDU) to screen;
- Tackle delay between exposure, diagnosis of HCV and access to care;
- Achieve appropriate management of difficult-to-reach patients;
- Actual follow up of hepatitis treatment is mainly done by hospital specialists, but to lighten the burden for the hospital the involvement of the GPs should be encouraged.
- Screening strategy has slight impact on HCV prevalence.

Future plans

Ongoing National Plan for HBV and HCV (2009-2011):

- Reinforce HBV and HCV screening (esp. migrants, prisoners, at-risk populations);
- Plan actions by new regional health agencies;
- Establish a committee in charge of follow up;
- Evaluate by end of plan period.

Quantitative goal of plan: 65% of HBV and 75% of HCV patients to be aware of their infection status.

Italy

Burden of disease

~2.5 million individuals affected by HBV or HCV [12]; 21,000 deaths/year from cirrhosis or HCC. Costs of managing chronic liver disease increasing.

In last 30 years: mortality from cirrhosis deaths decreased slightly [13]; HCC mortality increased to 6000 deaths/year (probable underestimate) [13]. In the last decade, HBV as pathogenic factor in chronic hepatitis has decreased while HCV increased.

HBV

Current low incidence of acute HBV (mostly sexually transmitted) and low endemicity (HBsAg <2%).

HBV incidence significantly declined in Italy in past decades (result of prevention e.g., vaccination of children and at-risk groups). Long term protection achieved in immunocompetent individuals vaccinated as infants and teenagers (now aged <30 years).

It was predicted that more non-D genotypes will be imported from abroad; and higher circulation of antiviral-resistant mutation.

HCV

Prevalence of HCV RNA in general population varies: by region (highest in the South Islands) and by age (highest in women over 55, probably result of using non-disposable medical equipment in 1950s and 1960s).

Screening strategy

Target population

HBV

- People with elevated liver enzymes and/or clinical sign of hepatitis;
- Patients with liver cirrhosis or fibrosis;
- Patients with HCC;
- History of IDU who share or have ever shared needles;
- Long term prisoners;
- Haemodialysis patients;
- MSM or heterosexuals with multiple partners;
- People with HIV or HCV infection;
- Families and household members or sexual partners of persons infected with HBV;
- Patients and staff in psychiatric institutions;
- Pregnant women, newborns of infected mothers;
- Recipients of transplants and blood products;
- Blood and organ donors;
- Patients before or during immunosuppressive treatment or chemotherapy;
- Migrants from high prevalence HBV countries;
- Unvaccinated healthcare workers carrying out exposure-prone procedures.

HCV

- Persons with elevated liver enzymes/hepatitis symptoms;
- Liver cirrhosis or fibrosis patients;
- IDU who share or have ever shared needles;
- Long-term prisoners;
- Recipients of haemodialysis/repeated percutaneous injections;
- Recipients of blood transfusions/other blood-derived products/organs and tissue transplants outside EU (or pre-1992 in EU);
- People having invasive procedures (medical, paramedical, dental) in countries with high HCV prevalence/poor hygiene;
- Blood and organ donors;
- Haemophiliacs receiving concentrated coagulation factors pre-1987;
- People with HIV infection;
- People with body piercings;
- Children of HCV-infected mothers;
- Migrants from high HCV prevalence countries.

Goals/Implementation

Goals:

- Consensus was reached that testing for HBV and HCV in risk groups with high prevalence probably more cost effective than mass screening (public and pharmaceutical companies have pressed for mass screening in the past);
- Well managed screening for signs and symptoms of liver disease and risk factors is key to prevention.

Implementation:
- Mandatory HBsAg screening of pregnant women;
- Use of highly sensitive HBV and HCV tests (e.g., nucleic acid testing) for blood donations;
- Screening for risk factors of viral hepatitis and subsequent testing of those who are found to be HBsAg+ or anti-HCV+;
- Case finding by GPs, primary care physicians.

Follow up (treatment) strategies

HBV

Guidelines are under review [14] for treatment of:
- HBeAg+ and HBeAg- patients with chronic HBV;
- Compensated and decompensated cirrhosis;
- Immunosuppressed patients;
- Co-infection with HCV; HDV; HDV + HCV; HIV

HCV

Practice guidelines for specific situations [15]:
- Acute HCV patients;
- Individualised therapy;
- Non-responders and relapsers;
- Antiviral treatment in HCV cirrhosis;
- HCV reinfection after liver transplantation;
- HIV/HCV co-infection;
- HBV ± HDV co-infection;
- Elderly patients;
- Patients with normal ALT levels.

Cost evaluation

Follow up/ treatment

National Health System covers the entire population. Liver-related costs are increasing due to:
- More individuals with long-lasting HBV and HCV infections;
- Introduction of new costly therapies;
- Increase in metabolic and behavioural causes (overweight, alcohol use, physical inactivity).

Evaluation of screening strategy

Strengths/ challenges and lessons learnt

Case-finding not well managed in Italy:
- Recommendations not followed for people with increased ALT levels, or 'vulnerable' subjects (immigrants from endemic areas, prisoners and IDU);
  GP study: 70% of patients underwent at least one ALT determination; 10% had substantial ALT increase; 37% of the patients with ALT increase had anti-HCV testing; 54% of anti-HCV+ underwent HCV RNA testing [16].
  46% of individuals at IDU primary care centres tested for HCV, 42% tested for HBV [17];
- No comprehensive strategy to identify infected prisoners, yet study of 973 prisoners found 30% IDU; 7.5% HIV; 38% HCV; 52.7% anti-HBc+; 6.7% HBsAg+ [18];
- No comprehensive strategy to identify infected amongst Italy's 3-4 million immigrants. Study of 182 illegal immigrants from Sub-Saharian regions: 67.6% antiHBc+; 9.3% HBsAg+; 4.4% anti-HBs+ (vaccinated); 2.7% anti-HCV+ [19];
- Need to translate recommendations and guidelines into practice;
- Need to coordinate screening efforts.

Future plans

- Reinforce dissemination of case-finding guidelines, including screening programmes for high risk groups;
- Implement best practice in targeted screening strategies;
- Translate recommendations and guidelines into clinical practices;
- Campaigns to increase awareness, screening uptake;
- Reduce health inequalities: focus on most vulnerable, least likely to actively manage their health (prisoners, IDU, immigrants);
- Promote and fund research on prevention and cure of HBV and HCV;
- Promote healthy lifestyles and behaviours.

Italian Foundation for Research in Hepatology (FIRE) aims to:
- Increase awareness of liver disease;
- Translate recommendations and guidelines into good clinical practice.

Scotland

Burden of disease

HBV

No specific screening strategy

HCV

Prevalence of chronic HCV: 38,000 by end 2006; of which 90% (active/past) IDU. <50% diagnosed (undiagnosed are mainly IDU). 20% had ever received specialist care; 5% had ever received treatment. Since 1996, number of HCV patients in hospital setting with HCC or ESLD has increased.

Screening strategy

Target population

HBV
- Routine screening for blood donors, pregnant women.

HCV

(Scottish Intercollegiate Guidelines Network)

Required testing
- Blood/tissue donors;
- Haemodialysis patients;
- Health care workers undertaking exposure-prone procedures.

Recommended testing
- Otherwise unexplained persistently high ALT;
- History of IDU;

- Child with anti-HCV+ mother;
- HIV+ people;
- Recipients of blood clotting factor concentrates pre-1987;
- Recipients of blood and blood components pre-September 1991, organ/tissue transplants in UK pre-1992;
- Healthcare workers following percutaneous or mucous membrane exposure to suspected HCV-infected blood.
- Recipients of medical/dental treatment in HCV-prevalent country with poor infection control.
- Had tattoo or body piecing with suboptimal infection control.
- Had a sexual partner/household contact who is HCV infected.

Goals/Implementation

Goals

HCV Action Plan aims to:

- Prevent spread of HCV esp. in IDU;
- Diagnose HCV-infected people, esp. those that would most benefit from treatment;
- Optimal treatment and support for infected people.

Implementation

- Awareness campaigns organised to promote testing;
- Develop new approaches to improve testing and referral by GPs and community workers in non-primary care setting, e.g., drug treatment centres, mosques, pharmacy;
- HCV test database established.

Follow up (treatment) strategies

All HCV+ patients (UK residents) are entitled to treatment under UK National Health Service (NHS).

Goal of Phase II Action Plan: at least 1500 treated/year (2010-2011).

- Establish managed "care networks" for all health boards;
- Develop clinical standards;
- Introduce workforce training initiatives;
- Develop services to increase numbers treated in community and prison (25% inmates HCV-infected);
- Develop a national clinical database and patient management system;
- Treat up to 48 weeks with PegIFN and Ribavirin

Impact on public health

HCV

Screening identified 26,786 HCV cases by Sept 2009.

Number starting HCV AVT treatment: 450 (2007/2008); 561 (in 2008/2009); 900 in 2009/2010.

Number receiving AVT has doubled in 2 years. Too early to assess impact on health care system

Cost evaluation

Screening programme

HCV

No GP funding allocated for HCV testing.

Government invested £43.2 million over 4 years (2008-2011) in Action Plan for:

- Testing, treatment, care and support(£30.1 million);
- Prevention programmes (£8.2 million);
- Information-generating initiatives (£3.3 million);
- Co-ordinating the plan (£1.6 million).

Evaluation of screening strategy

Strengths/challenges and lessons learnt

- Need high quality data (e.g., test database);
- Need to understand barriers/facilitators to testing (e.g., for IDU);
- Need imaginative testing approaches (e.g., drug treatment and harm reduction centres, mosques, pharmacies);
- Careful timing of awareness campaigns (e.g., ensure treatment initiatives are in place);
- Need integrated multi-disciplinary approach;
- Involve patient self-help/representative groups.

Future plans

HCV

Complete phase II of HCV Action Plan in 2011.

Phase III to run from 2011-2014, subject to receiving funding from government, potential cost increase due to introduction of protease inhibitors, and increased patient numbers.

HBV

Testing and treating HBV may be included in Phase III.

UK

Burden of disease

HBV

Low overall prevalence: 0.3% (180,000 cases). 6,000-7,000 new cases/year.

At least 2 million migrants from high/intermediate HBV prevalence (WHO definition) countries; at least 120,000 with chronic HBV.

95% of HBV cases are immigrants with chronic HBV.

Highest prevalence among black minority and ethnic (BME) community.

HCV

Prevalence relatively low (200,000-250,000 cases) and driven by

IDU (highest prevalence amongst non-IDU=migrants).

Evidence that HBV and HCV are more severe in BME populations (possibly because infected with more pathogenic HBV types, presenting later for diagnosis, higher co-morbidity rates?)
Mathematical model predicted a doubling of compensated cirrhosis in 10 years (2005-2015).

Screening strategy

Target population

- Minority ethnic communities originating from countries with high or intermediate prevalence of HBV; priority target: first generation migrants.
- Extend contact tracing and contact testing for individuals with HBV and/or HCV. Those negative for HBV to be offered HBV immunisation.

Goals/Implementation

Goals: Department of Health Advisory Group on Hepatitis report on HBV/HCV testing recommends:

- Systematic screening in high risk populations (most expensive);
- Opportunistic screening of individuals from at-risk populations who present to the health care system;
- Voluntary testing (active screening) encouraged by community workers; using community buildings as screening clinics.
- Tailor the methods to fit to the situation

Follow up (treatment) strategies

Care pathways

- HBV/HCV-infected individuals to be referred to specialist;
- Treat with IFN/nucleos(t)ide analogues for HBV and PegIFN/Ribavirin for HCV.
- HBV vaccination should be offered to households and contacts of HBV+.

Cost evaluation

Screening programme

Screening general population not cost effective, but pilot cost effectiveness analysis favoured the 3 other screening methodologies.

Follow up/ treatment

National Institute for Health and Clinical Excellence (NICE) evaluates cost-effectiveness of treatments in use. Both IFN/nucleos(t)ide analogues for HBV and PegIFNα/Ribavirin for HCV are considered cost effective by NICE.
NICE guidance on protease inhibitors is awaited

Evaluation of screening strategy

Strengths/ challenges and lessons learnt

- Health inequality to be minimised;
- Full cost effectiveness analysis of screening missing in AGH Working Group Report (analysis may take up to 3 yrs).

Future plans

A Department of Health policy for testing HBV and HCV.

USA

Burden of disease

HBV

Infections are notifiable.
Prevalence: 0.3% of general population (~0.8-1.4 million chronic HBV cases); 2,000-4,000 deaths/year.
Chronic HBV infection found in: 4-17% of HIV-infected; 3-6% IDU; 1-3% MSM; 3.5-9% sexual contacts of HBsAg+; 3-20% household contacts of HBsAg+ individuals; 1 in 12 Asian/Pacific Islanders (for whom leading cause of cancer death); 40,000 new entrants to the USA per year [20, 21, 22].
Acute HBV: 4,519 reported but real figure est. 13,000 (2007). 5% of population infected at some time. Mortality 3,000/year [23, 24].

HCV

Chronic HCV: 3.2 million (1.6% of general population). Mortality 8,000-10,000/year. Highest prevalence: 40-49 year age group; blacks (2 x rate for whites) (NHANES study, 1999-2002).
25% of HIV-infected are co-infected with chronic HCV (mainly IDU).
In 2007, 849 cases were reported, but only 1 in 20 cases are actually reported. Est. acute clinical cases was 2,800 and est. number of new infections was 17 000. Up to 1.9% of population may have been infected with HCV.
Mortality: liver disease deaths due to HCV=12,000/year; deaths from chronic HCV in blacks/Hispanics/native Americans=2 x rate for whites [25, 26].

Screening strategy

Target population

HBV

(CDC recommendations for Identification and Management of Persons with Chronic HBV Infection, 2008) [27].

Existing recommendations:

- Pregnant women;

- Infants born to HBsAg+ mothers;
- Household contacts, partners of HBV+ people;
- Persons whose exposure to blood or body fluid warrants post-exposure prophylaxis;
- HIV persons infected.

New recommendations:

- People born in regions with HBsAg prevalence of ≥2%;
- US-born unvaccinated individuals with parents born in regions with HBsAg ≥8%;
- IDU;
- MSM;
- People with elevated ALT/AST of unknown aetiology;
- People with selected medical conditions requiring immunosuppressive therapy.

HCV

(CDC Recommendations for Prevention and Control of Hepatitis C Virus (HCV) Infection and HCV-Related Chronic Disease, 1998) [28]

- History of IDU;
- Recipients of clotting factors pre-1987/ of blood or organs pre-July 1992;
- Chronic haemodialysis;
- Evidence of liver disease.

Goals/Implementation

HBV

Goals:

- Primary prevention: reduce transmission by managing exposures to HBV-infected;
- Secondary prevention for those infected: Reduce risks of chronic liver disease by medical management and AVT; address issue of undetected infection (e.g., 2/3 of chronically infected Asian Americans were unaware of their status).

HCV (National HCV Prevention strategy, 2001)

Goals:

- Prevent HCV infection;
- Detect and control chronic liver disease;
- Evaluate effectiveness of activities;
- Conduct surveillance and research to advance HCV prevention and control;
- Primary prevention: reduce transmission via high risk activities such as IDU, risky sexual practices;
- Secondary prevention: reduce risk of chronic liver disease by identifying those at risk;
- 51% of the people with chronic HCV are not aware of their HCV infection status.

Follow up (treatment) strategies

AASLD recommendations [29, 30].

Evaluation of screening strategy

Strengths/ challenges and lessons learnt

HBV

- Testing programmes inadequate. Asian/American community organizations working on acceptability and access;
- Improve contact management, and long term follow up of pregnant HBV+ women and family contacts;
- Educate patients in own languages, educate providers;
- Improve link from positive test to care;
- Develop surveillance registries for chronic HBV cases;
- Increase funds for testing/screening.

HCV

- Risk-based testing strategies ineffective: only 40% of chronic cases reached.

Future plans

HCV

- Improve screening strategies;
- New recommendations for testing in 2012;
- Evaluate new rapid HCV tests for use in IDU settings;
- Integrate HCV and HIV testing;
- Study alternatives to risk-based HCV screening: age-based, birth cohort; 'opt out' testing (people in managed care settings being tested unless they object);
- Gather data on care access and outcome;
- Build model prevention and referral programmes;
- Collect data on natural history and access to HCV/HBV services;
- CDC working with other agencies e.g., in health services research and Health Resource Service Administration.

Russia

Burden of disease

HBV

Acute HBV: sharp decline last 9 years (probably result of vaccination programmes and funding boost in 2000). 39.6/100,000 (2000) – 2.7/100,000 (2009).

Chronic HBV incidence: ~15 cases/100,000 over last decade, not declined significantly over time. Highest prevalence: far east, north west.

HBV carrier incidence: from 96/100,000 (2000) to 31/100,000 (2009)

HBsAg prevalence in Moscow (2004-2009) was ~2%.

Estimates in Russia in absolute nr: 2.8 million HBsAg+ and 645,000 chronic HBV cases.

(Carriage state and chronic HBV distinguished by levels of ALT and signs of liver disease. Viral load rarely used) [31].

HDV

Not a notifiable disease. In some regions, among HBsAg+ individuals, a study found up to 50% anti-HDV+ [32, 33].

HCV

Chronic HCV ~40/100,000 in 2008 (est. 3.6 million chronic HCV cases; 5.9 million anti-HCV+ cases) [31]. In last 11 years incidence of chronic HCV increased, acute HCV declined (20.9/100,000 (2000) – 2/100,000 (2008).

Incidence of HCV carriers: 87.5/100,000 in 2008. HCV carriers no longer reported since 2009.

Rate of HCV in general population is ~ 4%.

Screening strategy

Target population

HBV and HCV

- Blood donors at each donation;
- Pregnant women during 1st and 3rd trimester;
- Newborns of women with chronic HBV or HCV at 0, 3, and 6 months and 1, 2 and 3 years;
- Health care workers, on hiring then annually;
- In-patients on admission;
- Out patients (drug and alcohol abuse clinics and STI clinics) at first appointment then annually;
- Patients on haemodialysis at first appointment then regularly;
- Orphans on entry to orphanage then annually;
- Households and contacts at index case identification then annually;
- Military personnel on hiring then annually.

Goals/Implementation

Goals: reduced incidence of acute HBV and HCV; reduce chronic HBV and HCV burden by early disease detection and interrupting transmission.

Implementation

Patients testing HBsAg+ or anti-HCV+ reported within 24hrs to local infectious disease surveillance, then to local out-patient clinic. Patient, household and other contacts evaluated.

Confirmed diagnosis patient referred to specialist hepatology centre, and diagnosis reported back to Local Administration for monthly report at federal level.

Follow up (treatment) strategies

4 treatment programmes:

- National Public Health Project for HIV co-infected individuals;
- Federal Target 5-year programme (2007-2011) to improve diagnostic techniques and antiviral drug (programme restricted due to economic situation);
- Additional Drug Supply Programme for special benefit groups (e.g., disabled);
- High-Tech Medical Care State Programme for liver transplantation.

Only 6 transplantation centres, low funds, few patients benefit.

Chronic HBV

- Nucleos(t)ide analogues (Lamivudine, Telbivudine and Entecavir);
- IFNs (standard, pegylated);

Chronic HCV

- IFNs (standard, pegylated).
- Ribavirin.

Impact on public health

HBsAg detection (2007):
newborns of HBsAg+ mothers: 1.7%;
pregnant women: 0.9%;
blood donors: 0.5%.

Anti-HCV (2007):
health care workers: 1.7%;
pregnant women: 1.6%;
blood donors: 1.1% [34].

Moscow inpatients (2010):
HBsAg: 1.3%; anti-HCV: 2.8%.

Decrease in hospital-acquired infection: 59.6% (1990) to 2.4% (2000).

Decrease among patients receiving blood transfusion: 10.2% (1990) to 0.9% (2000) [35].

Cost evaluation

Screening programme

Cost-effectiveness of screening not evaluated.

Cost for screening pregnant women for HBsAg: $2.52 million (2007); for anti-HCV: $2.52 million.
Detection cost: $156 per HBsAg-infected woman; $87 per HCV-infected woman.

HBsAg, anti-HCV screening and confirmatory tests covered by mandatory health insurance.

Follow up/ treatment

Covered by mandatory health insurance:

- Blood chemistry (3-6 monthly);
- Abdominal ultrasound (6-12 monthly);
- Liver biopsy (in some regions).

Patient pays for:

- Viral load testing (HBV and HCV);
- Viral genotype testing (HCV and HBV);
- Drug resistance testing;
- Liver biopsy;
- Non-invasive fibrosis, disease activity assessment.

Most patients must pay for treatment. Assuming affordability means that costs are less than one-third of income: Lamivudine is affordable to 61.4% of patients; Entecavir to 4.1%; PegIFN to <1.5% of patients.

Evaluation of screening strategy

Strengths/ challenges and lessons learnt

- 10 obligatory screening programmes cover major risk groups for HBV, HCV. Paid by mandatory insurance;
- Only half of regions have electronic surveillance;
- No federal viral hepatitis patients' register; some regional registers; many not electronic;

- Some problems after referral to out-patient clinics; confirmed diagnoses not always reported to local administration; not all regions have hepatology centres;
- Limited access to treatment programmes for chronic HBV.

Future plans

- Screening cost effectiveness analysis needed (was cost effective when incidence high, needs to be reassessed now incidence rates lower);
- Implement nationally-integrated electronic surveillance systems for regions without such system;
- Develop chronic viral hepatitis patients' register (regional and federal);
- Urgent: develop affordable treatment strategy for chronic HBV/HCV.

The Netherlands

Burden of disease

HBV and HCV notifiable in Public health law

HBV

~250 acute cases and ~1500 chronic cases per year.
Prevalence: est. 0.2%-0.4% of general population; 3.5% in migrants (8% of Dutch population are migrants). 80% of chronic cases are people born in endemic countries.

HCV

52 recorded acute HCV cases (2009). The increase in acute HCV cases in the last years is probably due to use of high quality tests and the increased testing.

Screening strategy

Target population

HBV

- Pregnant women
- Blood donors

Prior to vaccination

- MSM/sex workers;
- IDU;
- Heterosexuals with multiple partners;
- Contacts of affected people;

In different projects

- Chinese groups;
- Turkish groups.

HCV

- IDU;
- General public: pilot projects 2007/2008
- General public HCV campaign (Sept 2009-Feb 2010): pre-1992 blood transfusion recipients; past hard drugs users; anyone born in HCV-endemic country.

Goals/Implementation

HBV

Goals

- Pregnancy screening; primary prevention by vaccinating newborns;
- Risk group screening: IDU, MSM, sex workers, (screening heterosexuals with multiple partners stopped in 2007); screened pre-vaccination to exclude those already immune and identify chronic infections;
- Contact screening to prevent secondary transmission;
- Screening Chinese and Turkish groups: secondary prevention.

HCV

Goals

- Secondary prevention by identifying affected people;

Implementation:

National

- IDU identified at drug user services;
- Contacts of cases identified through Public Health Service;
- Information campaigns to general public;

Regional

- Campaigns target migrant populations.

Follow up (treatment) strategies

HBV (similar to EASL guildeline)
Referral guidelines from primary to secondary care: Patients HBeAg+ and/or elevated ALT referred to specialist. If ALT normal, followed up by family doctor. Treatment may be with PegIFN or low-resistance nucleos(t)ide analogues.

HCV

All HCV patients referred to specialist, treated with PegIFN and Ribavirin.

Impact on public health

Patient numbers low so impact on health system limited, difficult to assess due to limited follow up.
950 HBsAg+ women identified in antenatal care. Newborns vaccinated, little known about treatment of mothers, many not treated whilst pregnant.
From 2002-2007 [36].
18,510 MSM vaccinated, 148 (0.8%) HBsAg+;
9,391 sex workers vaccinated, 94 (1%) HBsAg+;
13,482 IDU vaccinated, 94 (0.7%) HBsAg+;
39,297 heterosexuals with multiple partners vaccinated, 236 (0.6%) HBsAg+.
Regional project, Rotterdam: 293 IDU screened for HCV in 2 years, 81 HCV RNA+. Of these, 64 referred for treatment, 35 started treatment.

Pilot project, Rotterdam Chinese population (2009): 1,100 tested, 94 (8.5%) HBsAg+; 32 HBeAg+ or elevated ALT (34% of HBsAg+). 18 eligible for antiviral treatment.

Pilot project, Arnhem Turkish population: 709 tested, 18 (2.8%) HBsAg+; 2 (0.3%) HCV+.

Cost evaluation

Screening programme

National programmes government-funded.
Regional pilots funded by municipal public health service, hospitals, pharmaceutical companies, health insurance.

Follow up/ treatment

Counselling and source and contact tracing paid for by Public Health Service (government).
Follow-up and treatment costs covered by private health insurance. Health insurance is obligatory.

Evaluation of screening strategy

Strengths/ challenges and lessons learnt

- Coverage for pregnancy screening good;
- Poor follow up for women screened positive in pregnancy;
- Risk group screening (incl. migrants) high prevalence confirms correctly targeted;
- Low coverage in risk groups (only 16% of MSM are tested);
- Migrants only screened in local initiatives;
- Contact-tracing results for HBV not reported, follow up unknown;
- Referral from primary to secondary care needs improving;
- Pregnant women testing positive should see specialist before third trimester;
- Need systematic approach, outreach campaigns, to reaching migrants;
- Migrants could be reached by outreach campaigns, possibility of systematic approach on national level should be studied.

Future plans

- Combine HBV and HCV screening;
- Screen nationwide targeting migrants.

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Based on presentations by
I. Colle, Hepatology and Gastroenterology, University Hospital, Ghent, Belgium;
F. Roudot-Thoraval, Departement de Santé Publique, Hôpital Henri Mondor, Creteil, France;
D. Prati, Department of Transfusion Medicine and Hematology, Ospedale Alessandro Manzoni, Lecco, Italy;
D. Goldberg, Immunisation and Respiratory Team, Health protection Scotland; Glasgow, Scotland;
W. Irving, Department of Microbiology, Queens Medical Centre, Nottingham, UK;
G. Beckett, NCHHSTP/DVH Prevention Branch, Centers for Disease Control and Prevention, Atlanta, USA;
V. Chulanov, Central Research Institute of Epidemiology Reference Center for Viral Hepatitis, Moscow, Russia;
I. Veldhuijzen; Division of Infectious Disease Control, Municipal Public Health Service Rotterdam-Rijnmond, Rotterdam, The Netherlands.

Conclusions

Screening guidelines, programmes and effectiveness

- Defining criteria for screening is a dynamic, iterative process. The Wilson and Jungner criteria for screening, first published in 1968, are still held as the gold standard but have been revisited and refined over the last 40 years. Screening criteria need to respond to changes in medical practice, new trends and emerging technological developments, all of which raise new considerations. Most of the new proposals are variations on the original set of criteria. In several countries guidelines for screening of viral hepatitis exist, but some are inconsistent.
- The design and management of screening programmes raises ethical and equity issues. Decision-making should be patient-centred, evidence-based (systematic reviews, scientific publications), and system-driven to ensure practicality and enable the use of routine screening. Decision guidelines for population screening should be developed to provide greater transparency and potential for revision. Methods need to be refined to determine who to screen and how, taking into account that different risk groups require tailored and targeted approaches (for instance, in the cases of migrants and ex-prisoners, the threshold for access to health services may be high and compliance with treatment tends to be low).
- Recurring issues of screening programmes in general include the consideration of added benefits, whether benefits outweigh harms and what are the opportunity costs. It should be well evaluated where a programme fits in the 'screening continuum' between mass screening and clinical testing, the one not excluding the other. Programmes should meet the needs and reflect the perspectives of individuals, and need to target populations at risk and society in general. There should be transparency about choices.
- Screening is much more than a test. Programmes must at least cover laboratory testing, clinical services, counselling and management. Lessons have been learnt about screening programmes in general, and some are being re-evaluated as a result. When evaluating potential screening programmes experiences with existing screening programmes (e.g., on pregnant women) should be taken into account in cost-effectiveness analyses. Innovative approaches, e.g., use of dry blood spot testing, should be considered.
- Primary health-care providers in the USA met under auspices of the Hepatitis B Foundation to design a simple, clear algorithm (based on existing guidelines) for screening, initial evaluation and management of HBV-infected patients.
- There is a growing use of health economics and modelling to support decisions. More analyses are required on the results of early screening plus treatment, to prove patient benefit and cost effectiveness even in the long term. Review of effectiveness of screening programmes in Europe showed cost-effectiveness for HCV in IDUs and migrants, and for HBV in pregnant women. A literature review of HCV screening and early diagnosis followed by treatment showed the potential for increasing life-expectancy.

Burden of disease

- There have been changing patterns in epidemiology, knowledge of natural history, migration, treatment, and clinical developments.
- Viral hepatitis can be a 'silent' disease causing slow, burdensome and costly illness. Worldwide there are more than 350 million people chronically infected with HBV (most in the Asia-Pacific region), resulting in 600,000 deaths per year. There are 130-170 million chronically infected with HCV, and this causes more than 350,000 deaths per year. Together HBV and HCV cause more

deaths in USA than HIV. Prevalence of viral hepatitis is highly variable within and between countries. Even in 'low-prevalence' countries, high prevalence rates are found in high-risk groups, in particular in migrants.
- Available baseline data are weak. There are 10 million migrants officially in the EU, but the effective figure could be nearer 20 million. Hepatitis prevalence is particularly high in migrant groups and has an important impact on the host country's burden of disease: data from the UK suggest that immigration could lead to a doubling of the number of HBV cases over the next five years. There are gaps in knowledge about the prevalences of: HBsAg in the general population; HBV in low-prevalence countries (possibly underestimated); and HBV and HCV in blood donors, pregnant women, and high-risk groups.
- High proportions of individuals do not know that they are infected (65%-75% of HBV and HCV-infected individuals in USA are unaware of their status).
- The natural history of HCV disease is becoming clearer, although disease progression and the long-term outcome of asymptomatic HCV virus infection is currently still unpredictable.
- HIV coinfection is a problem, both in terms of disease progression, and also affecting the outcome of treatment.
- The burden of disease due to HDV should not be overlooked. There are 15-20 million people infected worldwide, and chronic infection leads to severe liver disease.

Surveillance

- The collection of data on viral hepatitis cases at national and regional levels responds to different needs and requests, for example, national; European (ECDC); regional (WHO Euro); and global (WHO). ECDC conducted a survey of surveillance and prevention programmes, and the results underline a wide variation in reported data and surveillance methodology with a lack of coordination. All efforts to achieve enhanced surveillance with harmonized case definitions were encouraged.
- There is a lack of information about national policies for prevention and control of viral hepatitis; in particular surveillance data are not available to evaluate the effectiveness of those policies. A WHO review of national policies is under way.
- Data from surveillance and screening are used at three levels:
  - political - to decide on public health policies and strategies;
  - clinical - for treatment and management; and
  - individual - to identify patients who need treatment, or who are at risk of infection, and to provide preventive interventions for the individual and their contacts.
- There are insufficient epidemiological data to base policy decisions on. Better quality of data are required to be used in models, as well as to support and evaluate current practice. Surveillance data are not validated because of the use of inconsistent case definitions, ICD for coding and (in some cases) coding for the purpose of reimbursement of costs.

Awareness raising and information initiatives about chronic viral hepatitis

Stakeholders such as governments, intergovernmental organizations and non-governmental organizations (e.g., the International Centre for Migration Health and Development), need to define their roles and levels of cooperation in initiatives to raise awareness of chronic viral hepatitis. Medical and educational institutions (e.g., NICE, CDC, university partners), and the pharmaceutical industry are important stakeholders. Associations such as EASL (European) and ELPA (European) are valuable forums, advocates and educators. It is important that the initiatives focus on patients at individual level, but their families and contacts also need to be involved.

- There are still gaps in knowledge of viral hepatitis among general public, healthcare workers (in particular physicians), and policy-makers. Nevertheless, there is a wealth of information amongst some stakeholders (European Parliament's written declaration, patients' associations; information and educational web sites, etc.).
- There is a hope that 2010 will be remembered as 'the year of hepatitis' and there are expectations that it will be followed by global policy decisions:
  - at the May 2010 World Health Assembly, WHO member states adopted a resolution, including the designation of a World Hepatitis Day, that calls for WHO to develop a comprehensive approach to the prevention and control of viral hepatitis;
  - the role and work of the ECDC on hepatitis is expected to be consolidated; and
  - several awareness initiatives were initiated and major conferences were/will be held such as the Hepatitis B and C summit conference, organised in October 2010 in Brussels to encourage the formulation of a European-wide strategy on the communication, prevention and management of Viral Hepatitis as a healthcare priority.

Treatment

- New developments in treatment are imminent, but analysis of data from clinical trials is needed in order to determine efficacy. It appears to be difficult to conduct clinical trials once efficacious drugs are already licensed. There are many new drugs for HCV therapy in the pipeline that seem to be very promising. Costs of treatments that follow screening have increased the pressure for prevention of viral hepatitis.
- HBV is different from HCV; HBV can be prevented but not cured, whereas HCV can be cured. HBV screening is important, because the vaccine can be used to limit further transmission and prevent infection after exposure. Early treatment can also delay the progression and transmission of the disease. For HCV, the risk for HCC is linked to liver fibrosis, while normal liver function can still be observed and late intervention can still be effective. Because there is a curative treatment solution for HCV, it is justifiable to further evaluate routine HCV screening in well defined risk groups.
- Barriers to treatment are related to issues of: access, counselling, affordability, eligibility, desire to be treated, and the likelihood of treatment being completed.

HBV
- Excellent drugs are now available for the treatment of HBV; treatment forms part of the control of HBV. There is a continued reliance on PegIFN and nucleos(t)ide analogues. Most patients respond to treatment with these drugs, resulting in improvement in quality of life and reduction in disease progression, but they are not cured. IFN has the benefit of inducing no resistance but can only be used for finite periods (< 48 weeks), it is costly, has side-effects, and contraindications limit the use.
- Few, if any, new drugs or new approaches for HBV are in development. Resistance is an issue with most compounds and, after discontinuation of treatment, the relapse rate is very high. Resistance develops most rapidly with the cheapest drug, Lamivudine. There is a suggestion for a policy to eliminate Lamivudine as a first-line drug.
- Optimum duration of treatment remains to be determined, as this has important policy and cost implications. Small scale studies show the clinical benefit of long term treatment but these need confirmation.

HCV
- In contrast to HBV, numerous new compounds (~30) are in` development for the treatment of HCV; with the prospect of two

being licensed by end 2011.
- All patients with chronic HCV, irrespective of the degree of fibrosis, are potential candidates for treatment. However several factors influence the response to treatment: high viral load, raised ALT, genetic polymorphisms, age, and excessive alcohol consumption.
- Of patients with HCV, 50% are eligible for treatment and will benefit from treatment, which is curative. However in real life only a very small percentage of patients complete treatment due to side effects.
- The long-term outcome of successful treatment of HCV is unknown beyond 5-10 years.

Countries' common themes

The issues arising from studies in different countries are similar:
- Denominators for people at risk are often not known.
- Recommendations are often not followed and vary from country to country. Existing screening programmes should be reinforced and revisited. There is a need for translation into good clinical practice. There is a need for better disease management by GPs, specialists and other relevant care providers.
- Interventions and recommendations should be evaluated but it remains to be defined how their effectiveness should be assessed. In some countries interventions are not restricted to treatment, they also include measures to change behaviour in order to limit transmission, control alcohol consumption and promote vaccination.
- Difficult access to screening and therapy is a barrier in many countries. Compliance with treatment and follow-up remains an important issue.
- In countries where cost-effectiveness analysis has been done, screening for HBV in risk groups is cost-effective.

Challenges, needs and future steps

- The quality of surveillance data needs to be substantially improved. There is an urgent need for standardization of data and use of a common electronic medium for collection. Strong coordination of surveillance, collection and collation of data, and analysis are required. There is a need for leadership.
- For nearly two decades the list of risk groups has not drastically changed. Target groups and populations must be clearly defined, based on better risk analysis. Specific policies must be designed for special populations, in particular prisoners (including community programmes for continuity of treatment) and migrants.
- The current allocation of resources and health spending is questionable. For instance, there are comparatively very small budget allocations for HBV and HCV in comparison with other diseases. Although the cost for most screening programmes is covered by health insurance, patients sometimes face high out-of-pocket costs for treatment or follow-up; more resources are needed.
- The concept of cost-effectiveness should be extended to a series of screening strategies that includes identification of patients who are good candidates for treatment.
- The process of defining criteria for screening is dynamic and iterative, reflecting changing epidemiological and demographic circumstances, clinical practices and new technical developments. Robust standardized screening methods, with ethical screening and treatment follow up must be established.
- Screening and testing programmes should be integrated into primary health care and other programmes. A comprehensive approach including primary and secondary prevention, screening, counselling, management and treatment if indicated would be most successful.
- The purpose of screening must be clearly defined. The aims of screening are:
  - to prevent development of disease by screening for chronically infected individuals who can then enter treatment and management programmes and whose families may benefit from counselling and relevant prevention services (e.g., vaccination and healthy behaviour);
  - to prevent transmission of the disease by identification of subjects who are not infected, but are at risk, and who can be offered preventive interventions (e.g., vaccination).
- In addition, greater effort should be put into secondary prevention of HBV and HCV, and this could yield considerable health gains. Apart from the multiple benefits, potential harms of screening should also be considered.
- Recommendations must be translated into a managed programme with an action plan that guarantees assignment of responsibility, setting of priorities, adequate funding, necessary medical resources, monitoring and evaluation. Screening programmes should not be implemented until preparations for the steps to follow are in place: patient management, treatment, access, feasibility. There is no 'one-size-fits-all' action plan; any plan should be adapted to local epidemiology, infrastructure and financial realities. European countries should have an action plan. The value of setting goals in legislation should be assessed.
- There are currently not enough data and evidence that justifies the introduction of general screening for HBV or HCV; but for some defined groups, such as pregnant women, routine HBV screening is clearly recommended. Further research is needed in several areas, including:
  - identification of optimal target groups and settings for cost-effective screening;
  - burden of disease and mortality due to liver disease, including HCC (especially through registries);
  - effectiveness of screening and treatment programmes;
  - long-term health economic impact of hepatitis screening;
  - improvement of diagnostic testing including laboratory quality control panels for HBV DNA testing and the development of quick tests; and
  - development of technologies to replace liver biopsy.
- There is a need for a greater understanding of decision-making processes at political levels (World Health Assembly, WHO regional offices, ECDC, EU entities, national, etc.). It is necessary to reduce the number of top-down decisions and mechanisms, in favour of patient- and community-based programmes.
- Preparation should be in place to build on the adoption of the World Health Assembly resolution on viral hepatitis (May 2010) and the steps it urges, including advocacy, awareness raising, promoting screening, strengthening national surveillance systems and enhancing access to treatment.
- As in HIV/AIDS, the high cost of existing drugs excludes millions of people from treatment; the VHPB urges lower prices for appropriate medicines and increased financial support for programme implementation in proportion with the burden of the diseases.
- The meeting concluded with a general call for better education and treatment, and for more field work and practicable interventions. In addition to the work achieved during this meeting, a call for another meeting was made:
  - to summarize what has been done and discussed in the last 20 years including approaches that were successful and those that were not;
  - to put more emphasis on the role of patient organizations and community-based interventions;
  - to develop innovative and creative approaches for enhanced surveillance; and
  - to share data on burden of disease, screening programmes and treatment strategies in individual countries not present at this meeting.

Adapted from a presentation by D. FitzSimmons, WHO.

List of Participants

Andermann Anne	USA	McMahon Brian J	USA
Badur Selim	Turkey	Mercer David	Denmark
Beckett Geoff A	USA	Muehlberger Nikolai	Austria
Blystad Hans	Norway	Norder Helene	Sweden
Bonanni Paulo	Italy	Papaevangelou Vana	Greece
Chulanov Vladimir	Russia	Piorkowsky Nadine	Germany
Cody Rowan	Switzerland	Prati Daniele	Italy
Colle Isabelle	Belgium	Roudot-Thoraval Françoise	France
Coulie Patrick	Belgium	Salminen Mika	Sweden
de Jong Paul E	The Netherlands	Schalm Solko	The Netherlands
Delpire Veronique	Belgium	Semaille Caroline	France
Dominguez Angela	Spain	Shouval Daniel	Israel
Dusheiko Geoffrey	UK	Stroczynski Gaby	Austria
Engelen Emmy	Belgium	Suditsu Lucian	Sweden
Eramova Irina	Denmark	Van Damme Pierre	Belgium
FitzSimons David	Switzerland	van de Laar Marita	Sweden
Goldberg David	Scotland, UK	Vanderpooten Anita	Belgium
Hallauer Johannes	Germany	Van Herck Koen	Belgium
Hendrickx Greet	Belgium	Veldhuijzen Irene	The Netherlands
Irving Will	UK	Vorsters Alex	Belgium
Jilg Wolfgang	Germany	Ward John	USA
Kane Mark	USA	Wedemeyer Heiner	Switzerland
Lavanchy Daniel	Switzerland	Wiersma Steven	Switzerland
Macura-Biegun Anna	Belgium	Wong John	USA
Marinho Rui Tato	Portugal	Zanetti Alessandro	Italy

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For further information, please contact:
VHPB Executive Secretariat
Centre for the Evaluation of Vaccination
Vaccine and Infectious Disease Institute
Faculty of Medicine
University of Antwerpen (Campus 'Drie Eiken')
Universiteitsplein 1, B-2610 Antwerpen, Belgium
Tel +32 (0)3 265 25 23, Fax +32 (0)3 265 26 40
E-mail: info@vhpb.org