VIRAL HEPATITIS

PUBLISHED BY THE VIRAL HEPATITIS PREVENTION BOARD (VHPB)

December 2002

Volume 11 - Number 1

CONTENTS

This edition of *Viral Hepatitis* is based on material presented at the Viral Hepatitis Prevention Board meeting on **Public health challenges for controlling HCV infection,** Geneva, Switzerland, May 13-14, 2002

EDITORIAL

The Viral Hepatitis Prevention Board met May 13-14, 2002 in Geneva, Switzerland, to review epidemiological and public health aspects of hepatitis C virus (HCV) infection, and the various prevention and control strategies that are currently in place in Europe, Egypt, and the USA.

Approximately 3% of the global population is infected with HCV, representing approximately 170 million persons worldwide. Chronic hepatitis C infection leads to cirrhosis in at least twenty percent of patients within approximately twenty years after the onset of the infection. Cirrhosis and end-stage liver disease may also develop rapidly, particularly among patients who regularly consume alcohol.

HCV infection is still not yet fully understood. While alcohol intake and co-infections with other viruses (e.g., HIV or other hepatitis viruses) appear to influence the disease outcome, the interaction of these factors is not clear. There is also little consensus regarding precise alcohol levels that effect the disease outcome. Other factors, such as age, gender, genotype, and ethnic origin, may play a role in terms of recovery from HCV infection. The high genetic variability of the virus has hampered the development of an effective recombinant vaccine. Symptoms of HCV infection are often difficult to assess and quantify. Especially in the initial phases of the disease, if symptoms and early diagnosis go unrecognised, this may have consequences for possible recovery or for progression to chronic hepatitis.

Primary prevention includes routine screening of blood, rigorous implementation of infection control, and health education programmes for both health care workers and the general public. Unsafe injection practices, combined with an overindication of injections, account for an estimated 2.3 to 4.7 million HCV infections worldwide. These particularly occur in developing countries, which often lack the financial resources to support effective prevention and control programmes, and to make use of currently available therapeutic options. Secondary prevention strategies aim at reduction of further transmission of HCV from infected persons to others, by identifying carriers and acutely infected individuals, interrupting the chain of transmission, and reducing high-risk behaviour. It is evident that hepatitis C prevention activities should be integrated into existing prevention programmes targeted to both HBV and HCV infection, and HIV/AIDS and other sexually transmitted infections.

While some new antiviral combination therapies have shown promise in some patients, there is an urgent need for a vaccine against HCV. The VHPB, therefore, would welcome further clinical and epidemiological research that would help accelerate the development and marketing of such a vaccine to help reduce the global burden of HCV infection. The VHPB continues to encourage major public health efforts to prevent and control HCV infection.

Peter Grob and Guido François,
on behalf of the Viral Hepatitis Prevention Board

WHO informal consultation with VHPB
Public health challenges for controlling HCV infection
- a VHPB Symposium Report -
Geneva, Switzerland, May 13-14, 2002

The hepatitis C virus

Structure of the hepatitis C virus

The hepatitis C virus (HCV) was first identified in 1989, and was found to be the cause of 80% to 90% of cases of non-A, non-B hepatitis.[1-2] HCV is classified in the *Hepacivirus* genus within the Flaviviridae family of viruses, which also includes the classical flaviviruses, such as yellow fever and dengue viruses, and the animal pestiviruses.

The hepatitis C virus has an envelope with the glycosylated proteins E1 and E2, an inner protein structure / nucleocapsid composed of the core protein (C), and the viral RNA genome. The genome consists of a single-stranded RNA of positive polarity and approximately 9600 nucleotides. It encodes for a polyprotein that is processed by cellular and viral proteases, to yield not only the mentioned envelope glycoproteins and the core protein, but also non-structural proteins (NS2, NS3, NS4, NS5). Among them, the NS2-3 autoprotease and the NS3 serine protease are essential for processing the HCV polyprotein, NS4A being a cofactor for the NS3 serine protease. An RNA helicase encoded in the carboxy-terminal region of NS3, the NS4A polypeptide, and the NS5B RNA-dependent RNA polymerase are essential enzymes for viral replication. They have emerged as major targets for the design of specific inhibitors as antiviral agents.

HCV genotypes

During a long-term evolutionary process, six HCV genotypes have emerged, each with various subtypes,[3] and additional heterogeneous strains (quasispecies) co-existing in an infected individual. The worldwide distribution patterns of these genotypes and subtypes undergo changes due to high population migration. The current view is that these genotypes / subtypes are not associated with essentially different natural courses of infection,[4] although long-term follow-up data of large cohorts are lacking. However, it is evident that individuals infected with certain genotypes / subtypes show a different overall response to current antiviral therapy, with genotypes 2 and 3 responding better than genotype 1.

Worldwide distribution of HCV genotypes

Geographical area	Main genotypes
America	
- USA and Canada	1a, 1b, 2a, 2b, 3a
- South America	1a, 1b, 2, 3a
Europe	
- Northern Europe	1a, 1b, 2b, 3a
- Western Europe	1a, 1b, 2a, 2b, 3a
- Southern Europe	1b, 2c (Italy, Spain)
- Eastern Europe	1b
Asia	
- Turkey	1b
- Middle East	4
- China	1b, 2a, 2b
Africa	
- Parts of Northern Central Africa	4
- Egypt	4a
- South Africa	1, 2, 3, 5a
Pacific	
- Australia	1a, 1b, 2a, 2b, 3a
- Taiwan	1b, 2a, 2b
- Japan	1a, 2a, 2b
- Hong Kong	6a, 1b, 2a, 2b
- Thailand	1b, 2, 3, 6
- Malaysia	1b, 2, 3
- Vietnam	1b, 2, 6

Distribution of HCV genotypes in Switzerland
The table below shows HCV genotype distribution in Switzerland, a representative industrialised country in Western Europe, with a reletively high number of intravenous drug users (approximately 25,000-30,000 per 6.8 million inhabitants), often with genotypes 3 and 4, and a significant proportion of immigrants.

HCV genotypes	Zurich*	Geneva**
1	172 (51.9%) +	185 (52.9%)
2	35 (10.6%) ++	35 (10.0%)
3	100 (30.2%)	92 (26.3%)
4	22 (6.7%)	34 (9.7%)
5	1 (0;3%)	2 (0.6%)
6	1 (0.3%)	0
Mixed types	0	2 (0.6%)
Total	**331**	**350**

*Tested by Clinical Immunology, University Hospital, Zurich, between August 1999 and January 2000, using the Line-Probe Assay" (INNO-LiPA, Innogenetics, Ghent, Belgium)
**Tested by Gastroenterology and Hepatology, University of Geneva, between June 1998 and January 2000, using Restriction Fragment Length Polymorphism.
+ Subtypes 1a: 64; 1b:98; other subtypes 1:10
++ Subtypes 2a/2c:29; other subtypes 2:6

Co-infections with multiple HCV genotypes
Most patients with chronic hepatitis C are infected with one HCV genotype / subtype. However, infections with two or more genotypes / subtypes do occur, although these infections are rare and their clinical significance is not clear. In individuals infected with multiple HCV genotypes, one genotype often seems to prevail,[5] particularly genotype 1, and within this genotype, 1a prevails over 1b.

Viral life cycle
The life cycle of HCV takes place in hepatocytes, and the virus replicates in their cytoplasma. The daily viral production and clearance rate can reach 10^{12} copies. Some data suggest that HCV might also infect other cells, such as B lymphocytes, but whether the virus replicates in them is unclear. Little information is currently available regarding whether abortive and/or latent infections occur and if so, to what extent, and on the mechanisms of reactivation of latent infections. It is only when these points are clarified, that the viral reservoir can be defined.

HCV probably has little detrimental effect on the host cell (i.e., is non-cytopathogenic). The clearing-mechanisms of the virus are not fully known. Complex immune mechanisms are thought to play an important role, and also to be decisive for the pathogenic mechanisms leading to liver inflammation, hepatocyte destruction, fibrogenesis, carcinogenesis, extrahepatic vasculitis, etc.

Chronic HCV infection
More than 70-85% of HCV infections become chronic. The course of the disease is insidious, often with few symptoms or signs for the first ten to twenty years. Factors that may influence the course and outcome of the disease include age, sex, and possible ethnic / genetic and environmental influences. Risk factors such as alcohol intake and co-infections with other viruses (e.g., HAV, HBV, HIV, among others) also appear to influence the disease outcome. However, the interacting forces leading to or preventing complications of HCV infection are not fully understood.

Experimental systems used in HCV research
Chimpanzees are, besides humans, the only mammals known to be susceptible to HCV infection. Due to ethical and other regulatory considerations in using chimpanzees in large-scale trials,[6] two experimental approaches have now become available. The first approach involves HCV infection in immunodeficient mice reconstituted with human hepatoctyes.[7] The second approach involves an *in vitro* replicon system[8-9] that allows the defined steps (but not the full viral life cycle) of HCV RNA replication.

Future therapeutics and vaccines
New anti-viral agents are currently being developed, with the first candidates already in phase I and phase II clinical trials. These new agents are based on RNA helicase and the RNA-dependent RNA polymerase, both of which are specific inhibitors of the NS3 serine protease.

Development of an effective recombinant vaccine has been hampered by the high genetic variability of the hepatitis C virus. Strategies include development of peptide and protein vaccines, and dendritic cell-based vaccines. Also in development are vaccines using virus-like particles and DNA vaccines[10] with the aim of not only inducing protective antibodies but also of providing protection at the level of cellular immunity. Currently phase II clinical trials are in place with a first candidate therapeutic vaccine based on recombinant HCV E1.

References
[1]Lauer GM, Walker BD. Hepatitis C virus infection. *N Engl J Med* 2001;345: 41-52.

[2]NIH Consensus Program. National Institutes of Health consensus development conference panel statement: management of hepatitis C. *Hepatology* 1997; 26:2S-10S.

[3]Simmonds P, Alberti A, Alter HJ *et al*. A proposed system for the nomenclature of hepatitis C viral genotypes. *J Hepatol* 1997; 26:1-5.

[4]Mondelli MU, Silini E. Clinical significance of hepatitis C virus genotypes. *J Hepatol* 1999; 31(Suppl 1):65-70.

[5]Vargas HE, Laskus T, Wang LF *et al*. Outcome of liver transplantation in hepatitis C virus-infected patients who received hepatitis C virus-infected grafts. *Gastroenterology* 1999; 117:149-153.

[6]Prince AM, Brotman B. Biological and immunological aspects of hepatitis C virus infection in chimpanzees. *Curr Stud Hematol Blood Transfus* 1998; 62:250-265.

[7]Mercer DF, Schiller DE, Elliott JF *et al*. Hepatitis C virus replication in mice with chimeric human livers. *Nat Med* 2001; 7:927-933.

[8]Blight KJ, Kolykhalov AA, Rice CM. Efficient initiation of HCV RNA replication in cell culture. *Science* 2000; 290:1972-1974.

[9]Lohmann V, Korner F, Koch J *et al*. Replication of subgenomic hepatitis C virus RNAs in a hepatoma cell line. *Science* 1999; 285:110-113.

[10]Inchauspé G. DNA vaccine strategies for hepatitis C. *J Hepatol* 1999; 30:339-346.

Based on a presentation by Dr Peter Grob, University Hospital, Zurich, Switzerland.

Human immune response to hepatitis C virus

The hepatitis C virus is a positive-stranded RNA virus. The genome is about 9.6 kb in length and codes for a polyprotein from which 10 major proteins are produced by co- or posttranslational cleavage by proteases of host and viral origin. The structural proteins are the nucleoprotein (core), the envelope 1 protein (E1), and the envelope 2 protein (E2).

In studies of the immune response among humans and animals, the first lines of defence are natural killer (NK) cells, and NK T cells and antigen presenting cells (APC). Hepatocytes release intact HCV particles as well as HCV proteins which are taken up by APC. APC then process and present these antigens to CD4 T helper (Th) cells that produce a series of cytokines amongst which interferon gamma (IFN-g). CD8 cells may encounter HCV antigens on infected hepatocytes or on APC and become activated. Activated CD8 cells are able to kill HCV-infected cells via FasL-Fas interactions, via the perforine / granzyme mechanism, or via the release of TNF-a and/or IFN-g.

Study of the natural evolution of acute HCV infections has shown that approximately 30% of cases result in spontaneous clearance whereas 70 % evolve towards chronic infection:

Because the acute stages of HCV infection occur with very little and aspecific symptoms, they are very often clinically missed. Therefore most human studies have had to focus on patients with chronic HCV infection. These reports show that HCV-specific immune responses exert some control over virus replication but, in most cases, are unable to resolve or terminate persistent infection and chronic hepatitis. A vigorous NS3-specific CD4 response seems to have a beneficial effect on the course of the disease and is correlated with spontaneous clearance of acute infections and sustained antiviral response in chronic infections treated with interferon (alone or in combination with ribavirin).

At present, the only animal model for studying HCV infections is the chimpanzee. Studies are under way to examine the role of innate and adaptive immunity in animals inoculated with a defined strain of HCV. Although the chimpanzee is a valuable model, one should be careful in interpreting the data and extrapolating conclusions towards the human situation. Furthermore there are increasing ethical constraints in using chimpanzees in clinical studies, which stress the need for other animal models, preferentially a small animal model, to explore the role of the immune system in the clearance and immunopathogenesis of acute and chronic HCV infections.

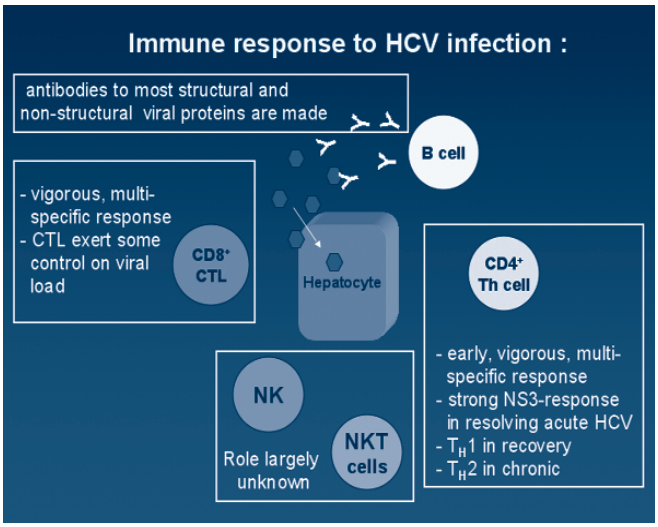
Kinetics of anti-HCV response

In an acute HCV infection that resolves, the antibody response is directed towards a limited set of HCV proteins and is also short-lived. In chronic HCV infections the antibody response targets more proteins and is usually higher-titred. This raises questions about the contribution of the humoral immune response to the clearance of the infection.

Several studies[1,2,3] examining the role of antibodies in clearing HCV infection have shown that HCV infection can be resolved in agammaglobulinaemic children without antibodies. Similarly, in a study with chimpanzees,[4] HCV clearance occurred in the absence of any antibody response to envelope proteins.

In another study,[5] patients were classified according to their clinical course and pattern of CD4+ T-cell responses. The results indicated that a virus-specific CD4+/Th1+ T-cell response that eliminates the virus during the acute phase of disease has to be maintained permanently to achieve long-term control of the virus.

Viral and immunological events that occur during the first few weeks after infection may determine the outcome. Early, vigorous and multi-specific response leads to clearance. The role of the innate immune system in the early phase of infection needs further exploration.



The potential mechanisms of viral persistence and viral evasion are shown below:

Inadequate HCV-specific immune response

- Inadequate innate immune response
  - NK cell function
  - Dendritic cell function
- Insufficient induction of adaptive immune response
  - Low level of viral antigen expression
  - Virus infection of antigen-presenting cells and dendritic cells
  - Inappropriate cytokine profile of Th
  - Lack or low frequency of neutralising antibodies
- Inability to maintain the adaptive immune response

Viral evasion mechanisms

- Replication in immune privileged sites
- Viral interference with antigen processing
- Viral suppression of host immune response
- Viral sequence variation
  - Escape from humoral immune response
  - Escape from cellular immune response
- Viral insusceptibility to cytokine-mediated inhibition of replication and gene expression

Development of HCV vaccines badly needed

Data are not always unanimous in terms of how HCV core proteins inhibit TL responses. Further studies will need to be carried out in order to understand better the mechanisms of immune protection

and clearance. Also crucial to HCV vaccine development will be a tissue culture system and a small animal model for HCV infection.

References

[1]Bjoro K, Froland SS, Yun Z *et al*. Hepatitis C infection in patients with primary hypogammaglobulinemia after treatment with contaminated immune globulin. *N Engl J Med* 1994;331:1607-1611.
[2]Adams G, Kuntz S, Rabalais G *et al*. Natural recovery from acute hepatitis C virus infection by agammaglobulinemic twin children. *Pediatr Infect Dis J* 1997; 16:533-534.
[3]Christie JM, Healey CJ, Watson J. Clinical outcome of hypogammaglobulinaemic patients following outbreak of acute hepatitis C: 2 year follow up. *Clin Exp Immunol* 1997; 110:4-8.
[4]Bassett SE, Thomas DL, Brasky KM *et al*. Viral persistence, antibody to E1 and E2, and hypervariable region 1 sequence stability in hepatitis C virus-inoculated chimpanzees. *J Virol* 1999; 73:1118-1126.
[5]Gerlach JT, Diepolder HM, Jung MC *et al*. Recurrence of hepatitis C virus after loss of virus-specific CD4(+) T-cell response in acute hepatitis C. *Gastroenterology* 1999; 117:933-941.

Based on a presentation by Dr Geert Leroux-Roels, University of Ghent, Belgium.

Laboratory and clinical diagnosis of HCV infection

A number of tests are currently available for diagnosis of HCV infection, and for assessing liver disease.

Non-specific liver tests include measurement of serum alanine aminotransferase (ALT) and AST levels, which are markers of response to antiviral therapy. However, they are of little value in prognosis of liver disease. Other markers include levels of serum bilirubin, alkaline phosphatase, and serum gamma-glutamyl transpeptidase.

Testing for serum ALT levels is non-invasive and is the least expensive means of determining disease activity. However, it is non-specific, providing only limited information about the severity of underlying liver disease.[1] In most studies, there is a weak association between ALT levels and severity of histopathological findings on liver biopsy. Although serial measurements over several months may provide a more accurate means of assessing liver injury, the accuracy of this approach has not been shown.[1]

While **liver biopsy** is important in defining baseline abnormalities of liver disease, it is not used as a diagnostic tool in identifying HCV infection. Its main purpose is to assess necro-inflammatory activity and fibrosis. Liver biopsy is, therefore, an important predictor of liver disease outcome, and is used to assess the indication for antiviral therapy. Liver biopsy is not routinely recommended for patients with normal ALT levels. Currently, serological markers of fibrosis and liver disease activity are being developed, but their performance is still not sufficient to replace liver biopsy in all its indications.

Screening for hepatocellular carcinoma (HCC) is indicated for patients with established or suspected cirrhosis. Alpha fetoprotein (AFP) and ultrasonic screening (every six months) were used in a single study of patients with cirrhosis secondary to HCV. However, identification of HCC was not increased in the screened population, and additional studies to identify new markers and screening protocols are needed.[1]

The following types of tests are used in HCC screening:

- Computerised tomography (CT);
- Spiral CT;
- Magnetic resonance imaging (MRI);
- Lipiodol CT;
- Hepatic angiography.

ELISA tests are used to detect anti-HCV antibodies. These tests are easy to use, inexpensive, and the best tests for screening at-risk groups, and for initial testing of patients for clinical liver disease. Third-generation ELISA tests have a specificity of 99%. They are very sensitive in immunocompetent persons; less sensitive in haemodialysis and immunodepressed patients.

Recombinant Immunoblot Assay tests are used as confirmatory assays in low-risk settings, for example in large-scale HCV screening of blood products. However, they have little utility in a diagnostic context.

Qualitative HCV RNA assays

Qualitative, non-quantitative HCV RNA assays are used if anti-HCV positivity is confirmed. Since HCV replicates at relatively low levels, and classical hybridisation-based techniques cannot detect HCV RNA in body fluids, amplification as an additional step is required. Based on *polymerase chain reaction (PCR),* double-stranded DNA copies of HCV cDNAs are synthesised. The commercially available PCR assay (Amplicor HCV v2.0, Roche) has a lower limit of detection of 50 IU/ml and a 97-99% specificity. Single-stranded RNA copies are generated in *transcription-mediated amplification (TMA).* The commercially available TMA assay (Versant HCV RNA Qualitative Assay, Bayer) has a lower detection limit of 10 IU/ml.

Quantitative HCV RNA assays

Testing for HCV RNA levels by quantitative assay provides accurate information on HCV viral titres. Assays may be based on:

- PCR
  - (Cobas) Amplicor HCV Monitor v2.0 (Roche)
  - Range of quantification: 600 to 500,000 IU/ml
- Branched DNA signal amplification
  - Versant HCV RNA 3.0 Quantitative Assay (Bayer)
  - Range of quantification: 615 to 7,700,000 IU/ml
- Other PCR-based tests: SuperQuant (NGI), LCx (Abbott), real-time PCR, etc.

Genotyping
HCV genotyping must be performed following a diagnosis of chronic hepatitis C, if antiviral therapy is indicated. Tests for genotyping include *direct sequencing*, available as:

- Home made: NS5B, E1 regions;
- 5' noncoding region (Trugene HCV 5' NC Genotyping Kit, Visible Genetics).

Reverse hybridization is another assay that is used worldwide, and available as INNO-LIPA, HCV II (Innogenetics).

Serotyping
Serological determination of HCV genotypes allows identification of the six types, but not the subtypes. The results can be inter preted in approximately ninety percent of patients with chronic hepatitis C, and has a ninety-five percent consistency with molecular tests.

Diagnosis of acute hepatitis C
The table below illustrates how the presence or absence of anti-HCV antibodies and HCV RNA markers may indicate acute hepatitis C. Where both markers are present, it is difficult to diagnose.

Anti-HCV antibodies	HCV RNA*	Diagnosis
-	-	Not acute hepatitis C
-	+	Acute hepatitis C
+	-	Probably not acute hepatitis C
+	+	Difficult to determine

*HCV RNA assay with lower limit of detection 50 IU/ml

Diagnosis of chronic hepatitis C
Chronic hepatitis C infection is diagnosed through (a) ELISA detection of anti-HCV antibodies; (b) confirmation by positive HCV RNA detection following positive ELISA result; (c) HCV RNA detection, if ELISA negative, in haemodialysis and immunodepressed patients.

References
[1]National Institutes of Health Consensus Development Conference Statement. Management of Hepatitis C: 2002. June 10-12, 2002. Preliminary Draft Statement. http://consensus.nih.gov

Based on a presentation by Dr Jean-Michel Pawlotsky, Hôpital Henri Mondor, Créteil, France.

Natural history of HCV infection

The clinical features of hepatitis C show an average incubation period of six to seven weeks, ranging from two to twenty-six weeks. Thirty to forty percent of patients develop clinical symptoms, and 20% to 30% develop jaundice. No protective antibody response has been identified.

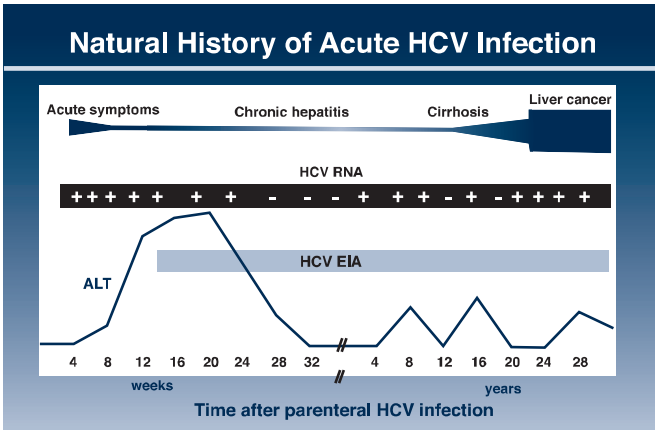
The outcome of acute hepatitis C infection depends on a number of different parameters:

- Peristent HCV viraemia without hepatitis;
- Persistent viraemia after resolved acute hepatitis (although this is not common);
- Persistent viraemia with chronic hepatitis (this is not unusual);
- Resolved acute viraemia with clearance of HCV (although this is not as clear as it is with HIV or HBV infections).

Hepatitis C
While symptoms of HCV infection occur frequently, they are difficult to assess and quantify. ALTs can be helpful as an indirect measure in the context of histological activity, but are not always reliable. Hepatitis C disease symptoms disappear after successful treatment. However, questions still remain as to whether only a minority of HCV-infected patients will go on to end-stage liver disease (ESLD), whether the disease, if untreated, will inevitably progress to end-stage, or will clear itself of infection.

Hepatitis C outcome
About twenty-five percent of acute infected cases become symptomatic with 90% having elevated ALTs, 50-70% being initially anti-HCV positive, and 95% RNA positive. The rate of chronicity reaches 50-85%; factors associated with spontaneous clearance of HCV infection appear to include younger age, female gender, and certain major histocompatibility complex genes. Each decade, 10-20% of cases evolve towards cirrhosis. However, the vast majority of those infected remain symptom-free for at least twenty years. It is not clear if healthy HCV carriers exist. A fulminant outcome is rare, but when it does occur is severe.

Chronic HCV is not a linear disease, and long-term evaluations have to be read with caution.



The various outcomes of hepatitis C infection are shown in the figure below. The long-term evolution of hepatitis C disease shows ESLD occurring only after many years of infection. This figure reflect the urgent need for a diagnostic tool in determining ESLD, particularly in countries with limited resources.

Hepatitis C outcome		
Survival (years)	5	10
Compensated liver	91%[1]	79%[1]
Decompensated liver	50%[2]	

HIV / HCV co-infection
HIV-related immunodeficiency, depending on CD4 counts, modifies the natural history of hepatitis C, roughly doubling the risk of developing cirrhosis.

Prognostic factors

It is known that symptoms of HCV infection deteriorate significantly with *alcohol consumption*. However, there is little consensus regarding the precise alcohol levels that may affect disease outcome. It is not known why, but some *younger persons* perform better, in terms of recovery from infection, than older persons. *Male gender*, an *immunosuppressed state*, an *older age* at time of infection increase this risk. There is little evidence that virologic factors, including viral load, viral genotype, and quasispecies diversity affect the risk of progression of liver disease. Concurrent *chronic hepatitis B* also appears to increase the risk of progressive liver disease. Other factors, such as *iron overload, nonalcoholic fatty liver disease, schistosomal coinfection*, potentially *hepatotoxic medications*, and *environmental contaminants*, may have some effects. *Ethnic origin* may play a role in disease prognosis. HCV *genotypes* 1 and 4 appear to be more difficult to treat than other genotypes.

Hepatitis C: outcome and treatment

All patients with chronic hepatitis C should be vaccinated against hepatitis A, and seronagative persons with risk factors for hepatitis B virus (HBV) should be vaccinated against hepatitis B.

All patients with chronic hepatitis C are potential candidates for antiviral therapy. Treatment is recommended for patients with an increased risk of developing cirrhosis. Most of these patients have persistently elevated ALT values, are characterised by detectable HCV RNA levels higher than 50 IU/ml, liver biopsy with portal or bridging fibrosis, and at least moderate inflammation and necrosis. In terms of identifying patients for treatment of hepatitis C infection, two approaches have been used:

- *The virological approach* seeks to identify (through viral load and genotype) patients with a high probability of response. Severity of liver disease, in this setting, is not a criterion for treatment. This patient treatment option is expensive, and requires specialised virological expertise; it is not the favoured approach in settings with limited resources.
- *The disease approach* focuses on treating acute disease or moderate to severe chronic hepatitis with a higher risk of progressing to cirrhosis over a relatively short period of time. This is the currently preferred approach in settings with limited resources.
- In general, early treatment produces better results, and patients should be treated before their disease reaches an irreversible stage (e.g., cirrhosis), especially if resources are limited.

Patient identification guidelines

- Patients with acute hepatitis (if recognised!) should be treated.
- Minimum requirements for treatment of chronic hepatitis C are detectable HCV RNA and abnormal ALTs for at least six months, with histological finding of moderate or severe hepatitis with fibrosis on liver biopsy.
- Liver biopsy is desirable unless clinically contra-indicated.
- Depending upon age and available resources, patients with *minimal hepatitis* are often not treated; they should be monitored periodically. This approach may be modified as more effective and cost-effective antiviral agents become available.
- Patients with *compensated cirrhosis* exhibit reduced responsiveness and significant side effects. Depending on age and available resources, these patients should receive the lowest priority for treatment in settings where careful monitoring is less likely to be applicable.
- For patients with *decompensated cirrhosis*, liver transplantation is the primary treatment option. Antiviral therapy is being studied but potentially life-threatening side effects have been observed.
- In carriers with persistently normal ALTs, treatment is currently not generally recommended. Most patients have histologically mild disease, some may progress to advanced fibrosis and cirrhosis. Expert opinion differs on whether to biopsy and treat these patients.

Hepatitis C treatment goals

The primary goals for treatment of hepatitis C are to reduce morbidity and mortality through: (1) Cure by complete elimination of HCV and normalisation of ALTs; (2) Stopping disease progression; (3) Improving quality of life; (4) Reducing the reservoir of chronic carriers, thereby diminishing transmission.

Conclusions

Available data show that short-term complications of hepatitis C infection are rare. Only after ten to thirty years of HCV infection can the full spectrum of symptoms be seen, which range from patients who exhibit no symptoms at all, to those patients who reach fatal end-stage liver disease. While the natural history is reasonably known for up to 20 years, we need assumptions to go beyond. Due to the uncertainty about the long-term prognosis of chronic hepatitis C, it is difficult to achieve a comprehensive estimate of the burden of disease and its public health consequences in order to make appropriate policy decisions.

References

[1]Fattovitch G, Giustina G, Degos F *et al.* Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997;112:463-472.

[2]Schalm SW, Brouwer JT, Bekkering FC *et al*. New treatment strategies in non-responder patients with chronic hepatitis C. *J Hepatol* 1999; 31(Suppl 1):184-188.

Based on a presentation by Dr Daniel Lavanchy, WHO, Geneva, Switzerland.

Global epidemiology of HCV infection

HCV infection is a global health problem affecting approximately 3% of the world's population. Based on currently available data (2002), approximately 170 million persons world-wide are chronic carriers of HCV, resulting in approximately half a million deaths per year.

In Southeast Asia, the anti-HCV prevalence rate is relatively low, under 2.5%. However, the sheer number of infections is significant with over 30 million cases of HCV infections. In the Western Pacific region, there are approximately 60 million cases of HCV infection. In the United States, with 3.9 million cases of HCV infection, 50,000 new cases occur annually, resulting in approximately 8,000 deaths per year, a figure that is expected to double within the next ten to twenty years. The table below shows global prevalence and mortality rates for hepatitis C, hepatitis B, and HIV/AIDS.

	Hepatitis C	Hepatitis B	HIV/AIDS
Global prevalence	3% / 170 million	35% / 1.2 billion	0.50% / 36.1 million
Chronic infection	2.3% / 129 million	6% / 350 million	0.50% / 36.1 million
Deaths per year	476,000[a]	0.5 million[b]	3.1 million
Annual death rate	0.40%	0.49%	7.80%
Lethality	7-10%		~ 100%

[a]Preliminary estimate currently under revision; [b]Expected to double within the next ten to twenty years.

In many countries the number of cases of HCV infection is under-reported. Well-designed prevalence studies of the general population still need to be carried out. Epidemiological studies also need to examine risk factors based on risk groups in a certain population. Such studies may be difficult to carry out in communities where religious, cultural, or political views discourage research among groups whose behaviour is not consistent with the norms of the prevailing population.

Schistosomiasis and HCV prevalence in Egypt

Schistosomiasis is a disease that occurs in areas with a large snail habitat such as irrigation canals, lakes, and ponds, and is transmitted via infected snails. The local population in such areas is at high risk for infection, chronic infection, and re-infection of schistosomiasis.

Beginning around 1900, the Nile River was dammed in order to increase agricultural production. Since completion of the Aswan High Dam in 1969 and the creation of Lake Nasser, there has been a total cessation of Nile flooding. Since then, the rural population's exposure to schistosomiasis has increased.

From the 1920s to the 1980s, parenteral anti-schistomosomal therapy (PAT) was carried out among the local population, consisting of a course of multiple injections. The PAT mass treatment scenario involved inadequate sterilisation procedures that consisted of twenty to thirty syringes in constant rotation with a maximum of one to two minutes for handling and sterilisation. The major risk factor for infection with HCV does not appear to be the population's exposure to schistosomiasis, but the parenteral therapy used in treatment of the disease.

The history of PAT is now recognised as a risk factor for HCV infection in Egypt, and has played a major role in the spread of HCV in rural areas. Although PAT was discontinued in the mid-1980s, there is continued transmission of HCV through other routes of exposure.[1] The HCV prevalence rate in Egypt is 18%. The most affected age cohorts are individuals:

- Born between 1950 and 1970 in Middle and upper Egypt;
- Born between 1950 to 1980 in Lower Egypt.

While schistosomiasis also occurs in other countries, no other country has used PAT as much as Egypt on a nation-wide basis. In contrast with the situation in Egypt, in other countries:

- Schistosomiasis is not as geographically widespread and prevalence not as high;
- Schistosomiasis treatment is not a political priority;
- Approaches other than intensive drug therapy have worked (e.g., molluscicides);
- Other health systems not as developed as Egypt's.

This is not simply an exercise in historical epidemiology, but is important in having identified a cohort of chronically infected persons who have begun to develop complications of HCV infection, such as liver cancer, and who are playing a role in current transmission of the virus.

The results of this research point to the need for further extensive, community-based epidemiological studies of the unique environment and history of a particular country in order to understand better the epidemiology of HCV infection.

References

[1]Frank C, Mohamed MK, Strickland GT *et al*. The role of parenteral antischistosomal therapy in the spread of hepatitis C virus in Egypt. *Lancet* 2000; 355:887-891.

Based on a presentation by Dr Daniel Lavanchy, WHO, Geneva, Switzerland.

How to collect and evaluate surveillance and epidemiological data for hepatitis C

In the United States, HCV is the most common chronic blood-borne infection and the leading cause of newly diagnosed liver disease. HCV also is the most common reason for liver transplantation.

Surveillance and epidemiological data are key components in HCV infection prevention programmes. Such data are needed to determine the level or burden of disease and enhance identification of persons at risk for infection in order to develop more effective guidelines and recommendations for prevention and treatment of HCV infection.

Establishing surveillance for HCV infection requires:

- Standardised case definitions for HCV infection;
- Guidelines for reliable and consistent laboratory reporting;
- An infrastructure for identifying cases that can identify biases that may affect the interpretation of data;
- Collection of information that will be useful for developing and monitoring programmes.

Epidemiological studies should be conducted to identify persons at high risk for infection, determine the amount of disease or infection attributable to specific risk factors, and provide guidance for surveillance and prevention programmes.

Types of epidemiological studies

Cohort or prospective studies directly measure risk by determining in a sample of the population the incidence of disease in persons with and without a specific exposure. Cohort studies usually require large sample sizes and long follow-up time, and are expensive. They also evaluate only a single exposure at a time.

Case-control or retrospective studies indirectly estimate risk. The study sample is based on the presence or absence of disease. The proportion of cases with a history of exposure before the onset of the disease is compared with a control group. The odds ratio will result in a good estimate of risk if certain assumptions are met, such as low frequency of HCV infection in the population (< 2% incidence/year). Another critical factor is that the cases must be representative of cases in the population and the controls representative of the population from which the cases were selected.

Compared with cohort studies, case-control studies involve reasonable sample sizes and logistics, and incur reasonable costs. However, both cohort and case-control studies will not detect rare events.

Cross-sectional or prevalence studies can demonstrate possible associations that require further study, but because the temporal relationship between exposure and infection is usually unknown,

they cannot establish an association or causal relationship. The presence of disease is determined in a sample of the population and either the proportion of cases with a history of exposure is compared with non-cases, or the prevalence of disease is compared for those with and without the exposure. The logistics required for prevalence studies are less complex and, therefore, less expensive. However, determining specific exposures that precede infection are problematic when the onset of infection is unknown or occurred many years ago.

There are also substantial differences in the methodology used in carrying out prevalence studies - some studies are population-based; others are based on highly selected groups, such as blood donors or clinic patients.

There are also inconsistent results among prevalence studies, such as under-estimating certain risk factors, and the difficulty in generalising the results to the rest of the population.

Risk factors associated with acquiring HCV infection
In the United States, the following risk factors are associated with acquiring HCV infection, based on a number of cohort and case control studies:

- Transfusion, transplant from infectious donors;
- Injecting drug use;
- Occupational blood exposure (needle sticks);
- Infected mother-to-infant transmission;
- Infected sex partner;
- Multiple sexual partners.

Exposures not associated with acquiring HCV
The results of case control studies of acute hepatitis C that were carried out in the United States between 1979 and 1985, suggest that the following types of exposures were not associated with acquiring the hepatitis C virus:

- Medical care procedures
- Dental work
- Health care work (no blood contact)
- Ear piercing
- Tattooing
- Acupuncture
- Incarceration
- Foreign travel
- Military service.

Sources of study populations affecting reliable interpretations
The type of study population selected can affect not only the reliability of the results but also the ability to generalise them to other populations. When highly selected rather than representative groups are used, biases may be introduced that cannot be measured. Studies using these groups may generate inconsistent results, and results not replicated consistently cannot be interpreted as associated with infection. Some examples of highly selected groups which may affect the reliabibilty of results include: (1) Cases: Asymptomatic (unknown onset) - Single source (referrals, e.g., gastro-intestinal clinics; clinics serving a disadvantaged population; highly specialised settings for specific conditions, e.g., orthopaedic back clinics) - Case reports; (2) Controls: Blood donors for any case population other than donors - Family members - Cases of other types of viral hepatitis - Single disease group.

Conclusions
Well-designed epidemiological studies and surveillance data based on standardised, consistent criteria are necessary to:

- Detect outbreaks of HCV infection;
- Assess the burden of disease and infection;
- Identify risk factors;
- Monitor disease trends;
- Identify and follow-up infected persons;
- Develop, implement, and evaluate disease prevention programmes;
- Provide guidance for allocation of resources.

Based on a presentation by Dr Miriam Alter, Centers for Disease Control and Prevention, National Center for Infectious Diseases, Division of Viral Hepatitis, Atlanta, Georgia, USA.

Controlling HCV infection: public health challenges

Until there is an effective vaccine against the hepatitis C virus, primary prevention strategies continue to focus on identifying carriers and acutely infected individuals for follow-up counselling and treatment, and interrupting the viral chain of transmission.[1-3]

Transfusion-transmitted HCV
In industrialised countries, the residual risk of transmitting HCV through transfusions is very low. However, the safety of blood supply remains a major source of public concern, and requires continual efforts to reach zero-risk probability. Nucleic acid testing (NAT) can shorten the window period and, consequently, further reduce the residual risk of HCV transmission. Measures to reduce the risk of transfusion-associated hepatitis C include:

- Solvent / detergent treatment of plasma and derivates (used successfully against enveloped viruses);
- Photochemical decontamination using psoralen and UV light (effective in inactivating a wide range of viruses).

Intravenous drug use
Intravenous drug use is the major source of HCV infection in many industrialised countries. In Europe, 60-70% of intravenous drug users (IVDUs) living in urban areas of major cities are anti-HCV positive. The rate of infection depends on the length of time of drug use, with 25% of infections occurring during the first year of addiction, 50% after five years, and up to 90% after more than five years of use.

Intravenous drug use prevention campaigns need to focus on extensive education programmes, especially for adolescents, in order to prevent first-time drug use, to enhance harm-reduction measures, and to increase awareness of the dangers of sharing syringes, needles, and other equipment.

For IVDUs who cannot or will not stop injecting drugs, there should be easy access to sterile syringes (e.g., Syringe Exchange Programmes or SEP), accompanied by counselling and health education. It should be noted, however, that in some countries there are legal restrictions on the sale and distribution of sterile syringes.

Nosocomial transmission
Nosocomial transmission may occur through unsafe injections and other medical procedures, or through unscreened blood - a major problem in developing countries. In industrialised countries, HCV is spread mainly by non-strict observance of universal precautionary measures, such as inadequate disinfection / sterilisation, sharing of medication vials and supplies, and contaminated equipment. Outpatient facilities (e.g., those providing endoscopic services) also represent high-risk settings.

In haemodialysis settings, precautions need to be even more stringent. Patients should have assigned specific dialysis stations, and clean and contaminated areas should be separated. However, isolating HCV-infected patients is not recommended.

The risk to health care workers in acquiring HCV in health care settings is very low. Follow-up studies of needlestick injuries from HCV-positive sources indicate a 1-10% seroconversion rate in recipients, or a mean risk of 1.8%. In an Italian study[4] carried out on 3,795 exposures to HCV, the rate of transmission was 0.4%, with 0.9% in cases of exposure to hollow needles, and 0.3% for conjunctival exposure. Standard barrier precautions and engineering controls should be implemented to prevent infection.

While HCV transmisison from health care workers to patients can occur, it is very rare. Health care workers must follow strict aseptic procedures and universal precautionary measures. There are no specific recommendations from the CDC or EASL, for example, for general screening of health care workers, or for restricting professional activities of infected health care workers. However, during a Consensus Conference[5] of the Istituto Superiore di Sanità (ISS) in Rome, it was recommended that HCV-infected (RNA-positive) health care workers should abstain from directly performing invasive or exposure-prone procedures, but with no other limitations placed on their other professional activities.

Sexual transmission of HCV
Although sexual transmission of HCV can occur, this route of transmission is rare. However, there is a large reservoir of sexually active HCV carriers that provide multiple opportunities for exposure to partners. There are no reliable markers for HCV that can predict transmission, either by genotype or by viral load.

Individuals in long-term monogamous relationships should be informed of the low risk of transmission, and encouraged to discuss the risk and use of barrier protections with sexual partners. The use of condoms is strongly recommended for individuals with multiple partners, with STIs and for IVDUs. There is no clear evidence that prophylaxis with immunoglobulin can prevent sexual transmission of HCV.

Household contacts and daily life
HCV can be transmitted percutaneously within families, and infected persons should be well informed of preventive measures, such as avoiding shared use of razors, toothbrushes, or any items that can pierce the skin. However, sharing meals or eating utensils is not a known risk factor. The so-called normal routine of daily life is not a risk factor, and there is no evidence to justify excluding anti-HCV positive individuals from social, educational, or employment activities.

HCV and pregnancy
Pregnancy is not contra-indicated in women infected with HCV, and they should not be counselled against becoming pregnant. Maternal infection does not appear to adversely affect pregnancy, nor does pregnancy have adverse effects on the course of liver disease.

The major issue raised by HCV infection during pregnancy is how to decrease the risk of viral transmission to the newborn. Available drugs cannot be used in pregnancy; ribavirin is teratogenic (it can cause malformations to the foetus) and interferon has adverse effects on foetal growth.

HCV transmission from mother to child
The risk of HCV transmission from a mother to her child is less than 5%, but higher among babies born to mothers who are HIV-co-infected. Transmission is restricted to babies whose mothers are viraemic (RNA-positive). The risk of infection increases with increasing viral load, but a specific cut-off value that predicts transmission cannot be defined. The probability of transmission is not related to specific genotypes.

There is no evidence that caesarean deliveries compared with vaginal deliveries reduce the risk of HCV transmission. The role of obstetric variables such as type of vaginal delivery (spontaneous, induced, operative), duration of rupture membranes, and timing of caesarean section (before or during labour) remains largely unexplored. The safety of obstetric procedures (use of monitoring devices and different instruments) during pregnancy in mothers who are HCV-positive is not well documented. Caution is recommended in using any invasive procedures (i.e., chorionic villous sampling, amniocentesis, cord blood sampling) that may expose the foetus or the neonate to maternal blood.

While HCV can be detectable in colostrum and milk, breastfeeding appears to be safe and is not contraindicated. Factors that might modify the risk of viral transmission by breastfeeding (i.e., duration of lactation, levels of HCV RNA in colostrum and milk, exposure to chapped nipples) require further studies.

Assisted reproductive techniques (ART)
There are insufficient data on the interaction between HCV infection and ART to make recommendations. If the woman is infected, the couple should be counselled on the potential risk of mother-to-child transmission. If the male is infected, there is a potential risk of transmission to the female if the semen contains HCV.

Over 1,400 intra-uterine insemination attempts with processed semen of HCV-positive males have been performed without a case of transmission to the uninfected partner.[6] There are no reports of HCV transmission through heterologous gametes by individuals infected with HCV. But it is recommended to select uninfected donors.

HCV screening
People who should be screened for HCV infection include:

- Individuals who have received transfusion or solid transplants prior to donor screening (Italy: 1991);
- Haemophiliacs;
- Health care workers after percutaneous or mucosal exposure to anti-HCV-positive blood;
- IVDUs;
- Haemodialysed patients;
- Donors of blood, organ, or tissue;
- Children born to HCV-infected mothers.

Screening is not recommended for the general population or for all pregnant women. However, it may be recommended for women who are undergoing prenatal invasive procedures, and for health

care workers who are involved in exposure-prone procedures. Counselling is also recommended prior to and after screening.

Future availability of effective drugs to treat HCV infections and a vaccine against HCV will undoubtedly lead to changes in current screening strategies.

References

[1]Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C (HCV) infection and HCV-related chronic disease. *MMWR* 1998; 47, RR19.
[2]EASL International Consensus Conference on Hepatitis C. Paris 26-28 February 1999. *J Hepatol* 1999; 30:956-961.
[3]Global Surveillance and Control of Hepatitis C. Report of a WHO Consultation organised in collaboration with the Viral Hepatitis Prevention Board, Antwerpen, Belgium. *J Viral Hep* 1999; 6:35-47.
[4]Ippolito G, Puro V, Petrosillo N, De Carli G, and the Studio Italiano Rischio Occupazionale da HIV (SIROH) group. Surveillance of occupational exposure to bloodborne pathogens in health care workers: the Italian national programme. *Eurosurveillance* 1999; 4:33-36.
[5]Mele A, Ippolito G, Craxi A *et al*. Risk management of HBsAg or anti-HCV positive healthcare workers in hospital. *Dig Liver Dis* 2001; 33:795-802.
[6]Sempirini AE. Personal communication.

Based on a presentation by Dr Alessandro Zanetti, University of Milan, Italy.

Development of HCV vaccines: state of the art

Why develop a therapeutic vaccine against HCV ?

Approximately 10,000 Americans die each year from HCV infection, and it is expected that this number will rise to 30,000 a year within a decade. And while the number of infected people is around 10,000,000 in industrialised countries, it is almost ten times higher in developing countries. Current antiviral therapies provide only about 50% success in infected individuals with genotype 1, which is still the dominant strain in the EU and the United States.

Only a limited number of people who are diagnosed positive for HCV actually completes the full course of therapy.[1] Current therapy is expensive and associated with side effects that for many are difficult or impossible to tolerate. Among those who are not receiving antiviral therapy, emotional distress has been reported in a significant number of patients.[2]

Developing a therapeutic HCV vaccine: constraints / progress

Although a number of distinct genotypes have been identified, currently there is insufficient knowledge about how meaningful these genotypes are in terms of vaccine development. For example, there is a lack of information on how an appropriate immune response to one genotype could react to other genotypes *in vivo*. There are also no viral replication systems in place, only surrogates such as a replicon system and micro arrays to study transcriptional changes. With no real virus neutralisation assays currently available, only surrogate tests are being used. Also, clearing an ongoing infection is much more complex than inducing an immune barrier to prevent infection.

Other constraints in vaccine development include the negative effect that chronic infection has on the immune capacity to external stimuli. The presence of lipids in viral particles in the circulation prevents the virus being recognised and neutralised effectively by vaccine-induced antibodies. In addition, there is insufficient knowledge of the relationship between type and antigen specificity of the immune response, and the clearance of acute infection in chimps and humans. Long follow-up periods following vaccination are also necessary.

Progress has been achieved, however, in chimpanzees, showing that immunity upon re-challenge can be induced and that this immunity is associated with IFN and cytolytic responses. However, using chimpanzees in large numbers for experimentation raises ethical issues and is subject to animal welfare regulations.

There are a number of various possible end points for therapeutic vaccines that include:

- Viral clearance;
- Transaminase level evolution;
- Liver pathology and evaluation of the histological activity index (HAI score);
- Liver pathology characterised by surrogate markers for fibrosis and inflammation;[3]
- Stabilisation of inflammation and fibrosis reduction of the viral PCR titres.

How to develop therapeutic HCV vaccines

A number of technologies are currently available to develop a therapeutic hepatitis C vaccine. Some of these technologies include:

- Use of recombinant antigens;
- Synthesising or expressing a string of relevant peptides in a polypeptide;
- DNA sequencing of HCV antigens as a primer and boosting with protein antigens;
- Anti-sense technology;
- Use of potent adjuvants or formulations to induce the appropriate immune response.

Ethical considerations

The current development of HCV vaccines is focused mainly on genotype 1 infections, which are prevalent mainly in developed countries, and the most difficult to treat with current antiviral therapy. Genotype 4, on the other hand, is low in the United States and EU, but high in developing countries, such as Egypt. Cost considerations in developing a vaccine specifically for genotype 4 would require collaboration between industry and WHO. Developing a vaccine for genotype 4 would also require experimentation with chimpanzees that are chronically infected with this HCV genotype.

Early success with Phase IIa trial of a therapeutic hepatitis C vaccine

Innogenetics, a Belgian biotechnology company, has recently issued the final results of a 48-week exploratory phase II study in patients chronically infected with the hepatitis C virus genotype 1. The primary objectives of the study were the exploration of the tolerability and the immune response of the candidate E1 vaccine.

The study involved 35 patients randomised at five centres in Belgium to receive either the candidate vaccine (26 patients) or a placebo (9 patients). As is normally the case in exploratory studies, the number of patients was limited and, therefore, precluded statistical comparisons between the two groups. The majority of the 35 patients had previously failed to respond adequately to current standard HCV treatment. The candidate vaccine was administered intramuscularly in a double-blind design, according to a primary vaccination schedule of 0, 4, 8, and 12 weeks, followed by a booster injection at 6 months.

The safety results showed no significant adverse events related to the intramuscular administration of the HCV E1 vaccine. Mild and transient reactions at the injection site were reported by five volunteers, and no changes in blood and urine tests, or ECG recording occurred.

Anti-HCV antibody titres were induced, with an increase in T-cell proliferation indices in the majority of patients vaccinated.

Based on these results, a new open-label study extension has been initiated, involving a course of six E1 injections at three-week intervals in 34 of the 35 patients who completed the previous study and re-enrolled. This new study is currently under way and the results are expected at the end of 2002.

References

[1]Falck-Ytter Y, Kale H, Mullen KD *et al*. Surprisingly small effect of antiviral treatment in patients with hepatitis C. *Ann Int Med* 2002; 136:288-292.

[2]Fontana RJ, Hussain KB, Schwartz SM *et al*. Emotional distress in chronic hepatitis C patients not receiving antiviral therapy. *J Hepatol* 2002; 36:401-407.

[3]Neuman MG, Benhamou JP, Malkiewicz IM *et al*. Kinetics of serum cytokines reflect changes in the severity of chronic hepatitis C presenting minimal fibrosis. *J Viral Hepat* 2002; 9:134-140.

Based on a presentation by Dr Erik D'Hondt, Innogenetics, Ghent, Belgium.

Prevention of hepatitis C virus infection: achievement through integration into established prevention programmes

Integrated prevention programmes

The burden of disease from chronic blood-borne viral infections is staggering. In the United States alone, more than four and a half million people are estimated to have chronic HBV, HCV, or HIV infection, resulting in an estimated 31,000 deaths per year.

A number of factors combine to justify integrating the prevention of HBV and HCV infection, and HIV/AIDS and other sexually transmitted infections (STI) into existing prevention programmes. These blood-borne infections all share similarities, with each of them characterised as major public health problems, having a substantial overlap of routes of transmission, with the potential of being brought under control through very effective prevention tools, such as immunisation, risk and harm reduction programmes, and treatment.

There is a high overlap of transmission routes among HBV, HCV, and HIV, with the main risk factors being injecting drug use, men having sex with men (MSM), and high-risk heterosexual activity.

In the United States, there are a number of well-established prevention programmes that have been designed to identify persons primarily at risk of HIV/AIDS and STI - one of the first steps towards preventing or reducing the risk of transmission of all blood-borne viral infections. These include:

- STI clinics;
- HIV/AIDS counselling and treatment programmes;
- Drug treatment and prevention centres; and
- Health programmes in correctional settings.

Prevention activities

The starting point of all hepatitis C prevention activities is to identify those at risk of infection in order to: (1) prevent acquisition of HCV (primary prevention); (2) prevent transmission of infection from HCV-infected persons (secondary transmission); and (3) prevent liver disease consequences among infected persons (tertiary prevention).

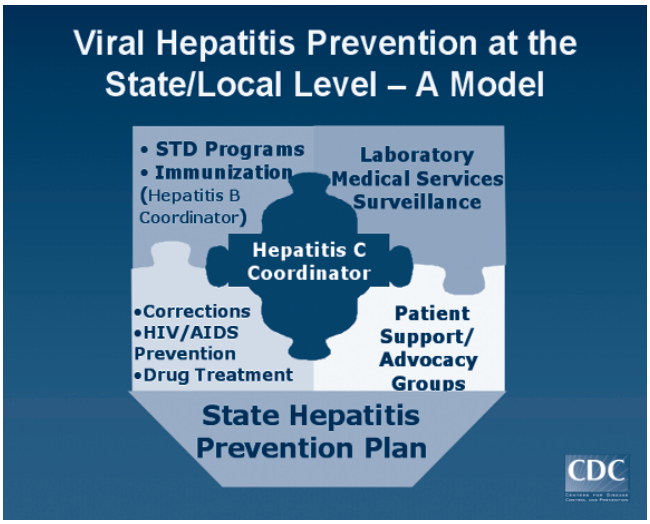
Persons who are at potential risk of infection are injecting drug users, persons who engage in high-risk sexual activities, persons exposed to nosocomial infection, and those who undergo blood transfusions and transplants. Other percutaneous exposures – occupational, tattooing, acupuncture – have not been shown to be risk factors for HCV infection among populations in which these exposures occur. However, persons exposed to a percutaneous injury with an HCV contaminated hollow-bore needle have been shown to have a 1% - 5% risk of infection.

Once a risk factor has been identified in an individual, that person should then be offered testing and counselling. The ultimate aim of counselling is to reduce their risk of infection or further HCV transmission, if already infected.

A third level of activity aims to reduce the risk of chronic liver disease, and involves testing, counselling, and medical management of infected persons. Medical management will usually involve evaluation of the patient for the degree of chronic liver disease and if antiviral treatment is indicated. In addition, treatment may be offered to individuals suffering from alcohol or drug abuse. Immunisation is also offered to protect against other viral infections - hepatitis A, hepatitis B, influenza, and pneumococcal pneumonia.

In addition to setting out and implementing a wide range of prevention activities, the United States' national hepatitis C prevention strategy also includes evaluation of the effectiveness of its activities, as well as ongoing surveillance, epidemiological studies to further define modes of HCV transmission and outcome of infection, as well as laboratory research to further characterise HCV, and develop new diagnostic tests and vaccines to prevent HCV infection.

Prevention activities take place at both State and local levels. A model of a typical State / local level hepatitis C prevention plan is shown below.



A well-developed hepatitis C prevention programme at State and local levels typically includes the following actions:

- Identifying stakeholders;
- Choosing a planning process (consensus meeting, consultants, internal);
- Adopting or modifying Centers for Disease Control and Prevention (CDC) recommendations;
- Identifying elements of the implementation framework;
- Writing a plan;
- Securing resources to implement the plan;
- Implementing the programme;
- Evaluating and modifying the programme.

Typical categories of stakeholders in hepatitis prevention programmes would include persons involved in:

- Communicable disease prevention programmes including surveillance;
- Immunisation programmes;
- HIV/AIDS prevention programmes;
- STI programmes;
- Substance abuse / mental health programmes;
- Corrections facilities;
- Programmes for high-risk youth;
- Public and private laboratories;
- Non-governmental organisations (NGOs);
- Advocacy groups;
- Clinical care and primary / speciality care.

Hepatitis prevention programmes: challenges and next steps

Funding remains one of the biggest challenges facing hepatitis prevention programmes. The aim of integrating prevention services can be complicated by the fact that funding of such services is often channelled through separate programmes for HIV/AIDS, STI, immunisation, and corrections. In addition, staff employed in other prevention programmes may not see the relevance of integrating hepatitis prevention in relation to their own job. Major efforts are still needed to ensure that viral hepatitis prevention messages become an integral part of any client-centred counselling services.

Several initiatives in moving towards fuller integration of prevention services include full evaluation of testing and counselling services, and assessment of the effectiveness of referrals for medical evaluation. Creation of new projects is also under way for minority populations. The ultimate goal of CDC's *National Hepatitis C Prevention Strategy* is for HCV testing and counselling, and hepatitis B vaccination to be offered in all HIV/AIDS, STI, drug treatment, and correction health programmes.

Based on a presentation by Dr Harold Margolis, Centers for Disease Control and Prevention, National Center for Infectious Diseases, Division of Viral Hepatitis, Atlanta, Georgia,USA.

HCV in injecting drug users: developing indicators of prevalence and responses

The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), located in Lisbon, Portugal, is engaged in collecting existing data on HIV, hepatitis B, and hepatitis C prevalence among injecting drug users (IDUs). An EU network has been established to provide additional data on seroprevalence in Europe through epidemiological studies and data from screening in routine settings, using comparable methodology and standardised reporting tables.

Existing data are compiled from a wide variety of sources, including drug treatment centres, hospitals, public health laboratories, STI clinics, prisons, as well as data relating to low threshold / low needle exchanges, overdose deaths, pregnant women, and from community studies and official notifications.

Some of the problems or limitations that have contributed to difficulties in interpreting existing data are that:

- Data from many *ad hoc* sources make comparability difficult;
- Non-injectors cannot always be excluded from the samples;
- Saliva-based or self-reported test results may be less reliable;
- Some sample sizes are too small to draw conclusions (e.g., in breakdowns on age or gender);
- Sampling / selection procedures are not always clear;
- While much drug treatment data are available, other sources are lacking;
- Few studies are repeated, so trends cannot be observed.

The EMCDDA have introduced a new standardised questionnaire / reporting table that helps eliminate ambiguity in interpreting existing data, which is already in use in many European countries. It requests overall prevalence and prevalence by age, gender, number of years injected, and use of opiates. In addition, the reporting table also covers:

- Methodological items such as type of data source, definition of injector (ever injected or current injector), serological markers;
- Total sample size of IDUs, number of valid tests, number of positive tests, percentage testing positive for each prevalence figure.

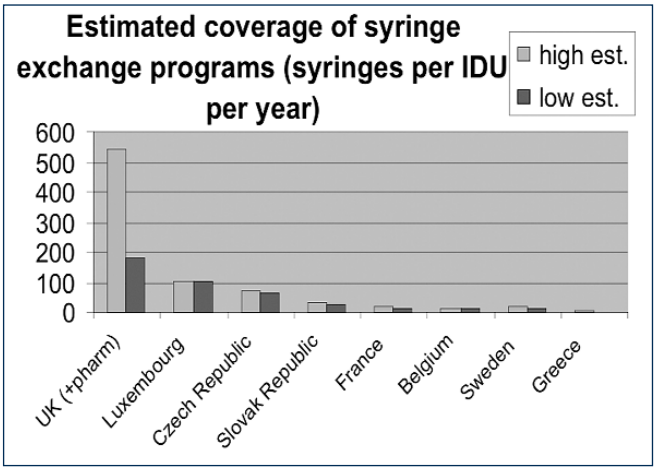
Work is going on to improve the comparability of data collecting and reporting. This includes validating saliva-based HCV tests and confirming self-reported results against the clinical records. Based on currently available data, potential indicators of HCV prevalence among IDUs include:

- IDUs in (first) drug treatment;
- IDUs in non-treatment settings (e.g., needle exchanges, low-threshold services, or 'street');
- IDUs under 25 years of age;
- New IDUs (injecting less than 2 years).

Prevalence among young or new IDUs is more sensitive to incidence than overall prevalence.

Prevention measures provided by syringe exchange programmes (SEP) should also include paraphernalia, such as swabs, spoons, and water as well as other harm reduction measures (e.g., HBV vaccination, counselling, and testing).

In the United Kingdom, the lower prevalence of HCV suggests that preventive measures, such as SEP, may be effective in some areas. In addition to SEPs, in several countries pharmacies are also important sources of clean needles for IDUs.



The EMCDDA continues to work with its European partners in developing IDU-specific surveillance of HCV, HBV, and HIV. Further information may be found on the EMCDDA website: http://www.emcdda.eu.int and in its annual report at http://annualreport.emcdda.org

Based on a presentation by Dr Lucas Wiessing, European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), Lisbon, Portugal.

Clinical manifestation of hepatitis C virus infection

Although hepatitis C is a systemic disease that can affect most organs, the liver is the primary target for the hepatitis C virus. The disease is insidious and subclinical. In the early stages of HCV infection, many patients show no symptoms or experience only mild fatigue. There may also be fluctuating ALT levels that are often detected during routine laboratory testing or screening of blood donations.

HCV infection: background - pathology

Viral hepatitis is defined as a diffuse necro-inflammatory liver disease caused by hepatotropic viruses. The basic morphologic patterns of acute or chronic hepatitis due to different hepatitis viruses are very similar irrespective of the virus causing the disease. Nevertheless, there are unique morphologic patterns that exist in HCV infection, which include:

- Lymphoid aggregates (57%);
- Bile duct injury (60%); and
- Steatosis (52%).

Liver biopsy in chronic hepatitis C?

There is a tendency to bypass liver biopsy, and the issue of whether it is still necessary remains open. There are still no good laboratory tools for assessment of liver disease. Establishing a diagnosis and degree of fibrosis is the primary aim for performing a biopsy. Other indications are to assess grade and stage of liver disease, exclude other or additional conditions (e.g., alcohol use), and to provide guidelines for management, and indications for follow-up therapy.

Clinical manifestations

The clinical manifestations of HCV infection, which are often inter-related, include fatigue, malaise, myalgia, depression, and cognitive dysfunction. These symptoms may be accompanied by:

- Nausea;
- Abdominal discomfort (may be present in acute as well as in chronic hepatitis);
- Dark urine and acholic stools;
- Vomiting;
- Jaundice;
- Pruritus;
- Arthralgia;
- Fever.

Acute HCV infection

Fulminant hepatitis is rare. Following acute infection, an HCV carrier state occurs in approximately 80% of HCV-infected patients, which may evolve into chronic hepatitis of variable severity. Cirrhosis may be clinically silent but occurs in 20-35% of cases of HCV infection, and may eventually lead to portal hypertension, ascites, esophageal and gastric varices which may bleed, or to hepatic encephalopathy. Hepatocellular carcinoma appears in 1-4% of cases, after two to three decades of infection. It is crucial that the disease be monitored in HCV-infected patients for a period of up to thirty years or longer.

Complications of acute HCV infection[1]

Average time between acute hepatitis C and	
Clinically significant liver disease	~ 10 years
Cirrhosis	~ 21.2 years
Hepatocellular carcinoma	~ 29 years

Hepatitis C virus infection also combines frequently with other infections, often viral, and can modify the natural course of other diseases and medical conditions, such as:

- Infection with other viruses (e.g., HBV, HIV, Herpes zoster);
- Infection of patients with schistosomiasis;
- Haemophilia, thalassaemia, sickle-cell anaemia, etc.;
- Haemodialysis and kidney transplantation;
- Iron overload;
- Alcoholic and non-alcoholic (N.A.S.H.) liver disease;
- Autoimmune hepatitis, primary biliary cirrhosis (PBC), primary sclerosing cholangitis (PSC);
- HCV re-infection following liver transplantation;
- Hepatocellular carcinoma.

Extrahepatic manifestations of hepatitis C virus infection
Numerous extrahepatic manifestations have been reported in HCV infection. Some of these are shown in the table below:

Extrahepatic manfestations of hepatitis C virus infection[2]

- Endocrine (e.g., thyroid abnormalities, diabetes mellitus)
- Salivary glands (sialadenitis)
- Ophthalmic (uveitis, ulcers)
- Haematological / lymphoid organs
- Skin
- Kidney, neuromuscular joints (e.g., glomerulonephritis, muscle weakness, arthritis / arthralgia, rheumatoid arthritis)
- Autoimmune diseases (e.g., pulmonary fibrosis, pulmonary vasculitis)
- Neurological and cognitive impairment
- Other

Conclusions
Because of the increasing number of extrahepatic manifestations of HCV infection, it is important that clinicians pay particular attention to the multi-systemic nature of the disease, including the effects it has on the general well-being and quality of life of the patient. The possibility that unrecognised HCV infection may be associated with a number of extrahepatic diseases or syndromes is an area that needs further investigation.

References
[1]Sharara AI, Hunt CM, Hamilton JD. Hepatitis C. *Ann Intern Med* 1996; 125:658-668.
[2]Hadziyannis SJ. The spectrum of extrahepatic manifestations in hepatitis C virus infection. *J Viral Hepat* 1997; 4:9-28.

Suggested reading
Alter HJ, Purcell RH, Shih JW *et al*. Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis. *N Engl J Med* 1989; 321:1494-1500.
Bruno S, Silini E, Crosignani A *et al*. Hepatitis C virus genotypes and risk of hepatocellular carcinoma in cirrhosis: a prospective study. *Hepatology* 1997; 25:754-758.
Fattovich G, Giustina G, Degos F *et al*. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. *Gastroenterology* 1997; 112:463-472.
Hamada H, Yatsuhashi H, Yano K *et al*. Impact of aging on the development of hepatocellular carcinoma in patients with posttransfusion chronic hepatitis C. *Cancer* 2002; 95:331-339.
Harris DR, Gonin R, Alter HJ *et al*. The relationship of acute transfusion-associated hepatitis to the development of cirrhosis in the presence of alcohol abuse. *Ann Intern Med* 2001; 134:120-124.
Ikeda K, Saitoh S, Koida I *et al*. A multivariate analysis of risk factors for hepatocellular carcinogenesis: a prospective observation of 795 patients with viral and alcoholic cirrhosis. *Hepatology* 1993; 18:47-53.
Poynard T, Ratziu V, Charlotte F *et al*. Rates and risk factors of liver fibrosis progression in patients with chronic hepatitis C. *J Hepatol* 2001; 34:730-739.
Sanchez-Quijano A, Andreu J, Gavilan F *et al*. Influence of human immunodeficiency virus type 1 infection on the natural course of chronic parenterally acquired hepatitis C. *Eur J Clin Microbiol Infect Dis* 1995; 14:949-953.
Serfaty L, Aumaitre H, Chazouilleres O *et al*. Determinants of outcome of compensated hepatitis C virus-related cirrhosis. *Hepatology* 1998; 27:1435-1440.
Wiley TE, McCarthy M, Breidi L *et al*. Impact of alcohol on the histological and clinical progression of hepatitis C infection. *Hepatology* 1998; 28:805-809.

Based on a presentation by Dr Daniel Shouval, Hadassah University Hospital, Jerusalem, Israel.

Hepatitis C: therapeutic options

Evolution of HCV therapies
Interferon (IFN) monotherapy was first used during the 1980s for treatment of hepatitis C infection. For many years it was the standard treatment for patients with chronic hepatitis C infection. However, only 10-15% of patients who underwent IFN monotherapy showed a sustained virological response.

Between 1992 and 1994, the standard IFN treatment [3 million units (MU) of IFN three times a week] was increased from six to twelve months, which resulted in a higher sustained virological response in approximately 20% of patients.

In 1998, combination therapy with IFN and ribavirin (3 x 3 MU IFN three times a week + 1000/1200 mg ribavirin daily) enhanced the virological response to 40%. It was also shown that among patients who relapsed following interferon monotherapy, approximately 50% achieved a sustained response when re-treated with IFN and ribavirin.[1] This combination therapy has now become standard therapy for both naïve and relapsed patients.

Treatment response, however, depends on the HCV genotype and baseline levels of HCV RNA.[2,3,4] Patients with genotype 1 and high viral load show the most unfavourable outcome, with nearly 75% not eliminating the virus through combination (IFN + ribavirin) therapy. Treatment with IFN + ribavirin is also not recommended for non-responder patients, as sustained virological response occurs in only 7.4%[5] of patients who had not responded previously to IFN monotherapy.

More recent treatment options
Polyethylene glycol (PEG) is a polymer that can be attached to proteins. Two *pegylated interferons* (alpha-2a and alpha-2b) are currently undergoing clinical trials. The two PEG-IFNs have different characteristics, with PEG-IFN alpha-2a metabolised primarily in the liver, and PEG-IFN alpha-2b eliminated renally.[6]

Clinical trials have shown a sustained virological response in over 50% of patients who have undergone combined treatment with *pegylated interferon and ribavirin*. Relatively higher sustained

responses are also seen in HCV-infected genotype 1 patients.

Another option to enhance virological response rates is *body-weight adjusted dosing*. However, response rates with this type of therapy increased only incrementally and further studies are needed.

Treatment duration has been shown to affect response rates. In a recent study[7] higher virological response was shown in patients with HCV genotype 1 following 48 weeks of therapy with optimal (high) ribavirin dosing, independent of viral load. Among patients with HCV genotypes 2 / 3, higher response is shown following 24 weeks of therapy, without the need for high ribavirin dosing.

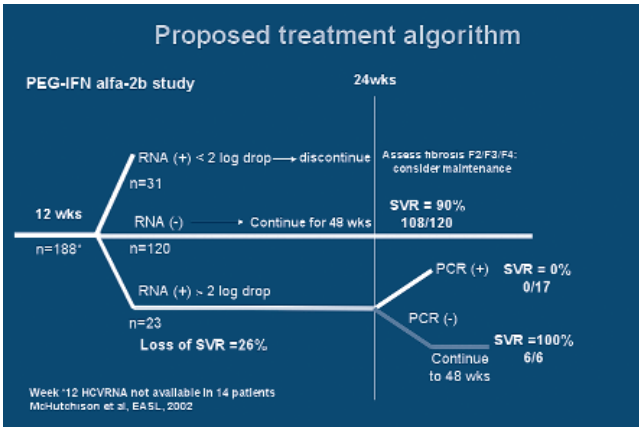
Several studies have shown that there is a significant and more rapid reduction of HCV RNA levels among patients treated by *daily dosing* schedules.[8-9] In another study[10] data suggest that daily dosing should be continued throughout the six to twelve months of treatment.

Other combination adjuncts

Recent clinical trials are focusing on supplemental drugs that may enhance the efficacy of interferon-alpha therapy. In addition to ribavirin, other possibilities are being evaluated: amantadine - rimantadine - non-steroidal anti-inflammatory agents - *N*-acetyl-cysteine - vitamin E - antibiotics - corticosteroid priming - ursodeoxycholic acid - pentoxifylline - thymosin alpha - extra-corporeal photophoresis - mycophenolate - maxamine. Although some of them may provide an additonal therapeutic effect, the results of many clinical trials have proven disappointing. However, several pilot studies[11,12,13] carried out in Italy show promising results using amantadine with IFN + ribavirin in non-responder patients.

Optimum duration to treatment response

According to a recent study[14] among negative HCV RNA patients, after twelve weeks of treatment with PEF-IGN alpha-2a, 97% of patients did not show a sustained virological response. The treatment algorithm used in the study is shown below:



Other patient groups

In a study[15] carried out among patients with *acute HCV infection*, ten to fifty percent recovered with PEG-IFN alpha + ribavirin treatment, showing promise for prevention of chronic HCV infection.

Among *non-responder* patients, the main therapeutic goals are to achieve viral clearance, histological response , and prevention of progression of the disease to chronicity. The Hannover study, which is currently under way and will be completed at the end of 2002, focuses on treatment of non-responders using consensus interferon (CIFN) and ribavirin.

Prevention of progression of fibrosis

IFN alfa has an anti-fibrotic effect through inhibition of collagen synthesis in cell culture and *in vivo*. Clinical experience has shown histological improvement with IFN-based therapy in responders and non-responders. Fibrosis regression has also been shown in subjects on maintenance IFN compared with subjects who have stopped IFN treatment. In all studies, there has been a decrease in development of chronic hepatitis C infection and/or a decrease in mortality rates.

Among patients who have undergone *liver transplantation*, combination therapy can lead to a number of problems:

- Ribavirin leads to anaemia and accumulation of iron;
- Significant side effects of IFN / ribavirin;
- Reported sustained response rates differ between different study centres;
- No data on long-term benefits of combination therapy are available yet.

The drop-out rate for combination therapy among patients with liver transplantation is 20-25%. Additional data from multicentre studies are needed for patients who have undergone liver transplantation, with the aim of deciding on the best immunosuppression regime to follow.

Summary

Naïve patients with elevated ALT and fibrosis	
- HCV genotype 1	PEG-IFN 48 weeks and high ribavirin (>10.6 mg ribavirin/kg)
- HCV genotype 2 / 3	PEG-IFN 24 weeks and 800 mg ribavirin
Acute hepatitis C	5 MU IFN qd 4 weeks, 5 MU IFN three times a week for 20 weeks or PEG-IFN once a week for 24 weeks (ongoing study)
Non-responders	
- No fibrosis	No treatment
- Fibrosis	Studies (PEG-IFN, CIFN, etc.)
- Advanced fibrosis / cirrhosis	Studies (long-term IFN)
Liver transplantation	Multicentre trials

References

[1]Davis GL, Esteban-Mur R, Rustgi V *et al*. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. International Hepatitis Interventional Therapy Group. *N Engl J Med* 1998; 339:1493-1499.

[2]Poynard T, Marcellin P, Lee SS *et al*. Randomised trial of interferon-alpha 2b plus ribavirin for 48 weeks or for 24 weeks versus interferon-alpha 2b for 48 weeks for treatment of chronic infection with hepatitis C virus. International Hepatitis Interventional Therapy Group (IHIT). *Lancet* 1998; 352:1426-1432.

[3]McHutchinson JG, Gordon SC, Schiff ER *et al*. Interferon alfa-2b alone or in combination with ribavirin as initial treatment of chronic hepatitis C. Hepatitis Interventional Therapy Group. *N Engl J Med* 1998;339:1485-1492.
[4]Lau JY, Qian K, Detmer J *et al*. Effect of interferon-alpha and ribavirin therapy on serium GB virus C/hepatitis G virus (GBV-C/HCV) RNA levels in patients chronically infected with hepatitis C virus and GBV-C/HGV. *J Infect Dis* 1997; 176:421-426.
[5]Wedemeyer H, Jackel E, Wedemeyer J *et a*l. Is combination therapy of chronic hepatitis C with interferon-alpha and ribavirin in primary interferon nonresponders indicated? An analysis of personal experiences and review of the literature. *Z Gastroenterol* 1998; 36:819-827.
[6]Manns MP, Cornberg M, Wedemeyer H. Current and future treatment of hepatitis C. *Ind J Gastroenterol* 2001; 20(Suppl 1):C49.
[7]Hadziyannis SJ, Cheinquer H, Morgan T *et al*. PEG-Interferon alfa-2a (40KD) (Pegasys) in combination with ribavirin (RBV): efficacy and safety results from a Phase III, randomized, double-blind, multicentre study examining effect of duration of treatment and RBV dose. *37th Annual EASL Meeting*, 18 April 2002, Madrid, Spain, Abstract 536.
[8]Buti M, Olive G, Stalgis C *et al*. Quantification of serum hepatitis C virus RNA with daily or standard interferon doses plus ribavirin in nonresponder patients with chronic hepatitis C. *Dig Dis Sci* 2000; 45:685-689.
[9]Neumann AU, Lam NP, Dahari H *et al*. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-alpha therapy. *Science* 1998; 282:103-107.
[10]Carithers RL, Zeuzem S, Manns MP *et al*. Multicenter, randomized, controlled trial comparing high dose daily induction interferon plus ribavirin versus standard interferon alfa-2b plus ribavirin (Abstract). *Hepatology* 2000; 32:631A.
[11]Brillanti S, Levantesi F, Masi L *et al*. Triple antiviral therapy as a new option for patients with interferon non-responsive hepatitis C. *Hepatology* 2000; 32:630-634.
[12]Brillanti S, Foli M, Di Tomaso M *et al*. Pilot study of triple antiviral therapy for chronic hepatitis C in interferon alpha non-responders. *Ital J Gastroenterol Hepatol* 1999; 31:130-134.
[13]Adinolfi LE *et al*. Interferon induction plus ribavirin and amantadine as a novel approach for treatment of interferon nonresponder chronic hepatitis C patients. *Hepatology* 2000; 32:Abstract.
[14]Fried MW *et al*. Ribavirin/PEG interferon alfa-2a combination may be more effective than standard of care for hepatitis C. Digestive Disease Week. Presentation of results of a multi-centre Phase II trial, University of North Carolina, USA, May 2001.
[15]Jaeckel E, Cornberg M, Wedemeyer H *et al*. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001; 345: 1452-1457.

Based on a presentation by Dr Michael Manns, Medizinische Hochschule Hannover, Germany.

Estimating the global burden of HCV infections associated with unsafe health care injections

In a study carried out in 1999 by Simonsen *et al*.,[1] it was estimated that every year, unsafe injections, together with overuse of injections, cause approximately 8 to 16 million HBV infections, 2.3 to 4.7 million HCV infections, and 80,000 to 160,000 HIV infections, worldwide. The study estimates that of the 8 to 12 billion injections that are given yearly, approximately 50% of them are unsafe in the developing world.

Injection drug use, transfusion of infected blood, and sexual exposures, the modes of HBV, HCV, and HIV transmission that are believed to predominate in industrialised countries are unlikely to account for most infections in developing countries. While HCV has traditionally been perceived as a pathogen associated with transfusion of contaminated blood, the high frequency of unsafe injections in most developing world regions probably accounts for a substantial proportion of new infections.

There are a number of reasons why unsafe injections are being given in developing countries. The main logistical reasons are the lack of sufficient quantities of needles and syringes and lack of sterilisation equipment or fuel to operate the equipment. In many regions, there is also a lack of basic understanding among health care administrators, health workers, and patients, of the risks of unsafe injections, and of what actually constitutes a safe injection. One common misconception is that reusing a syringe between patients is safe if the needle is changed. A high patient demand for injections - often overestimated by the describers - also contributes to the overuse of injections

A new study[2] has been carried out to estimate the number of new HCV infections and the future global burden of disease associated with HCV infection, attributable to unsafe health care injections in 2000. Overall, the results of the analysis suggest that in 2000, in developing and transitional countries, unsafe health care injections caused two million HCV infections (about 40% of the total). These results are validated by the results of epidemiological studies that examined the risk factors for HCV infection.

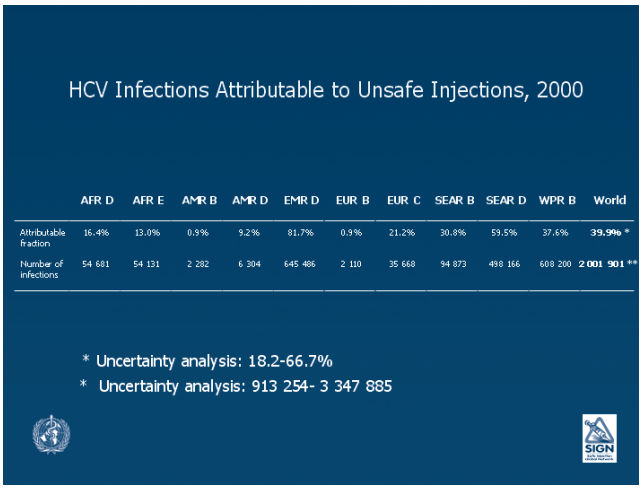
The methodology included two input parameters for injection practices (the annual number of injections per person and the proportion of injections given with reused equipment), and input parameters for HCV epidemiology. These were:

- WHO country prevalence estimates averaged by regions;
- Catalytic models used to estimate incidence on the basis of prevalence;
- Susceptibility estimated by age on the basis of prevalence and catalytic models;
- 1.8% transmission potential (on the basis of needlestick injury studies);
- Future deaths estimated on the basis of natural history and background mortality.

The limitations of the study included:

- Limited availability of injection practices studies;
- Limited number of epidemiological studies based on the incidence of HCV infection cases (more incident studies are needed);
- No inclusion of the dynamic effect of the model;
- Breaks in infection control practices only included reuse of injection equipment, and did not include:
  - Multi-dose vials
  - Work in contaminated environment
  - Breaks in universal precautions in other settings
- Poor documentation of the natural history of HCV infection, particularly in developing countries.

The graph below illustrates the significant differences between the numbers of HCV infections attributable to unsafe injection practices in developing regions, particularly in Asia and sub-Saharan Africa, compared with those in industrialised regions.



Some of the elements that support unsafe health care injections as the cause of a high proportion of new HCV infections in developing and transitional countries are the:

- High attributable fraction for health care injections in epide miological studies;
- Low prevalence of history of blood transfusions and injection drug use among HCV infection case patients in epidemiological studies;
- High frequency of injections worldwide;
- High prevalence in the population in some countries that can only be explained by a widespread exposure.

Safe Injection Global Network (SIGN)

The issue of unsafe injections is not complex, but safe injection initiatives must be approached from many different perspectives - at global, country, and local levels. The Safe Injection Global Network (SIGN) is an international coalition of stakeholders that is co-ordinated by the World Health Organization to support international efforts for the safe and appropriate use of injections worldwide. To assist with implementation of national plans, WHO published an aide-memoire on a national strategy for the safe and appropriate use of injections. The strategy addresses three key issues regarding injection safety targeted to:

- Behavioural change aimed at decreasing injection overuse and achieving safe injection practices among patients and health care workers;
- Increased availability of equipment and supplies, including use of auto-disposable syringes; and
- Management of sharps waste.

Further information on safe and appropriate use of injections can be found on the SIGN web site: http://www.injectionsafety.org and obtained via e-mail from the WHO SIGN Secretariat: sign@who.int

References

[1]Kane A, Lloyd J, Zaffran M *et al*. Transmission of hepatitis B, hepatitis C and human immunodeficiency viruses through unsafe injections in the developing world: model-based regional estimates. *Bull World Health Organ* 1999; 77:801-807.

[2]Unsafe health care practices. In: Quantifying selected major risks to health. World Health Report 2002: Reducing risks, promoting healthy life. Geneva: World Health Organization 2002: 78-79.

Based on a presentation by Dr Yvan Hutin, WHO, Geneva, Switzerland.

Country reports

NETHERLANDS

Health strategy on HCV infection in The Netherlands

Data on HCV prevalence in The Netherlands have been based on a small number of new blood donors and those figures extrapolated (five to ten times) to the general population, showing a prevalence between 0.3 and 0.4%, representing approximately 60,000 people. Overall HCV prevalence is comparable to other countries in Northern Europe (e.g., Belgium 0.8%, Germany 1.12%). HCV prevalence in specific risk groups in The Netherlands is shown below:

- Recipients of blood products 0.1%
- Intravenous drug users 0.08%
- Allochtonous 0.15%
- At risk behaviour < 0.1%

Dutch health authorities have acknowledged that patients have the right to relevant information regarding their disease, and that physicians should provide their patients with this information spontaneously, allowing patients to take responsibility for their own health. This is particularly important for HCV infected patients, as the general population lacks adequate knowledge about HCV, transmission routes, the disease, and possible treatment.

Some key recommendations from the Dutch Health Ministry include:

- Precise record keeping procedures in hospitals regarding the origin and use of blood products;
- Epidemiological research into HCV infection in various risk groups;
- Tracing and treating patients with increased risk of HCV infection
  - Haemophiliacs;
  - Haemodialysis patients;
  - Patients who undergo multiple transfusions;
  - Patients with organ transplants;
  - Patients with puncture wounds.

In 1998, the Dutch Health Ministry recommended that medical doctors of various disciplines receive further training in diagnosing HCV infection, and in counselling patients, especially regarding advice to HCV-infected patients to stop all use of alcohol. Information on basic hygiene procedures should also be provided to professionals who are at increased risk of HCV transmission through direct blood contact with infected clients.

Promotion campaigns targeted to the general public provide information on HCV - transmission, disease symptoms and complications, and possible available treatments. Specific

goal-oriented information is provided to risk groups to seek medical attention and, if necessary, to receive treatment. Immigrants should be informed of these medical options through intermediates who are trained specifically for that purpose.

A pilot study among former intravenous drug users is just beginning in The Netherlands. The study will be feasible through on-site drug user control programmes, where most drug addicts in The Netherlands are registered, and through additional training of present staff. The costs for interferon + ribavirin treatment, when indicated, would be reimbursed through mandatory Dutch health insurance.

Based on a presentation by Dr Jan van Hattum, UMC Utrecht - Liver Research, The Netherlands.

TURKEY

Viral hepatitis in Turkey

Hepatitis B virus infection is the primary cause of chronic hepatitis in Turkey, responsible for 46.5% of cases for the period 1994-1997. Hepatitis C virus infection is the second major cause of chronic hepatitis, and has increased by 12% between 1991 and 1997.

Viral agents remain the number one cause of liver cirrhosis in Turkey, increasing from 42.9% for the six-year period 1983-1989, to 59.5% for the period 1994-1997. The specific viral agents causing liver cirrhosis in Turkey are shown in the table below.

Viral agents in liver cirrhosis (%) in Turkey

	1990-1993	1994-1997
HBV	56.5	42.6
HCV	25.2	34.5
HDV	14.6	15.7
HBV+HCV	3.7	1.2
Alcohol + viral agent	-	6

Over 70% of HCV infections in Turkey are of genotype 1b. In terms of HCV seroprevalence, there are no apparent differences based on sex, educational status, or age. However, there is an enormous difference in seroprevalence rates between first-time and professional blood donors.

Characteristics of seropositive cases

• Age (in years)	18-28: 0.2%
	29-30: 0.3%
	40-50: 0.4%
	51-55: 0.6%
• First-time blood donors	0.2%
• Soldiers	2.4%
• Paid blood donors	20.0 %

Among the various risk groups, 41% of haemodialysis patients (2073 cases) in nine Turkish cities tested anti-HCV positive. For other risk groups, the highest percentage of anti-HCV seropositivity is among intravenous drug users (54.8%) and patients with cryptogenic cirrhosis (26.9%), thalassaemia (16.6-57.1%), renal transplantation (12.5-52.7%), and hepatocellular carcinoma (12.5-29%). Risk groups who tested considerably lower for anti-HCV seropositivity were diabetic patients (11.6%), sex workers (4.8%); prisoners (3.1%), and health personnel (0.9%).

Based on a presentation by Dr Selim Badur, University of Istanbul, Turkey.

CANADA

Integrating prevention, control, and therapy for viral hepatitis: the Canadian model

In Canada, there are thirteen health systems in place within the various regions and provinces of Canada, focusing on prevention, control, and treatment of viral hepatitis. The rationale for integrating prevention, control, and therapy for viral hepatitis is based on a conceptual model described as R = ßcD, where

- ß is the risk of transmission per contact;
- c is the number of contacts per unit time;
- D is the duration of infectiousness.

The two key messages implied in this model are that (1) acting on any one variable may not be sufficient to achieve an effective viral hepatitis prevention programme, and (2) ignoring those who are infected with viral hepatitis is not defensible.

Health promotion campaigns (e.g., safer sex; substance abuse), blood safety, regulation of food and water sources, occupational health practices, travel clinics, and macro-economic studies (with implications for funding), are all part of Canada's strategy in limiting the level of risk for contracting viral hepatitis. Immunisation, isolation methods (e.g., use of gloves / condoms; limiting parenteral exposure), and effective hygiene practices are used in reducing risk of transmission. Screening, diagnosis, and contact tracing, as well as non-curative treatments to eliminate infectiousness, are used in identifying those at risk of infection and in potential need of treatment.

In Winnipeg, Canada, a national laboratory is responsible for developing new diagnostic tests for hepatitis, quality assurance, and quality control, through evaluation of panels in hospital laboratories and blood donor system. The laboratory's mandate is surveillance, risk assessment, prevention, and control of viral hepatitis and emerging blood-borne pathogens. Its key activities include surveillance, targeted research, knowledge synthesis, analysis and policy development, and formulating recommendations on prevention and control.

A public health information system is in place at the Centre for Disease Control in British Columbia, operating electronically with real-time output of data from incoming reports. There are also plans for laboratory linkage involving testing, PCR and genotyping, as well as bar-coded labelling of specimens that provide a link between patient and outcome. A pilot treatment cohort tracking system is in place, as well as a number of ongoing specific studies on seroprevalence, enhanced surveillance, and IDU and MSM cohorts.

Non-governmental organisations, such as Health Canada, Canadian Liver Foundation, and the Canadian Viral Hepatitis Network, provide support to national programmes through public awareness programmes, and information exchange on infectious diseases through expert advisory groups, and technical and public health working groups.

Some of the major challenges Canada faces include IT funding (a major obstacle), multiple blood-borne infections in marginalised populations (e.g., substance use), historical problems and marginalisation for aboriginal groups, immigration, and more recent trends of reducing expenditure on social issues.

Based on a presentation by Dr David Patrick, Centre for Disease Control, University of British Columbia, Vancouver, British Columbia.

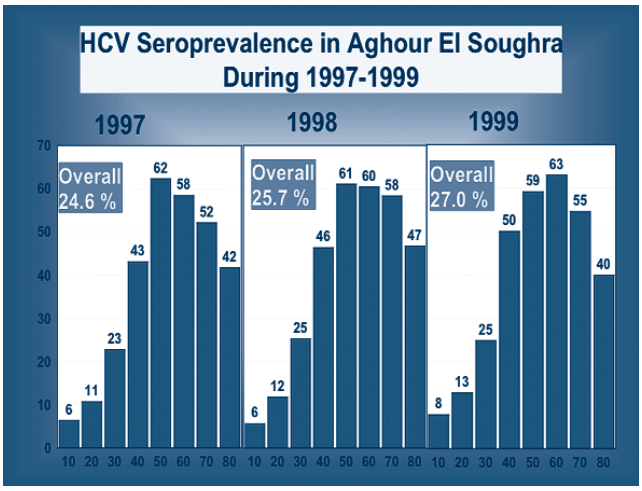
EGYPT

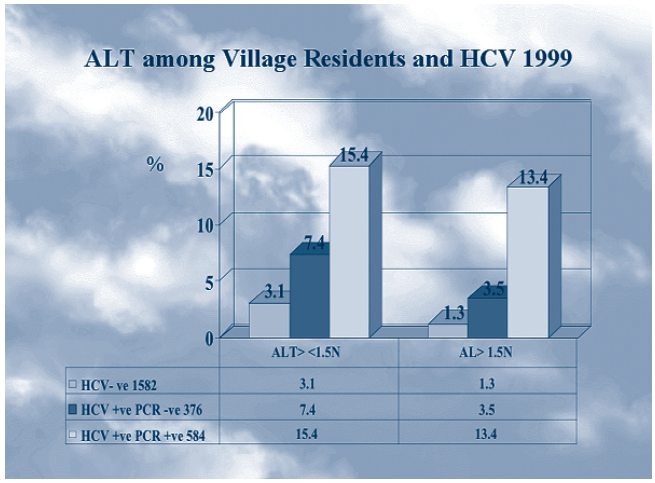
Epidemiology, and prevention and control programmes of hepatitis C in Egypt

Statistics: Egypt's population has increased from 62 million people in 1996 to 70 million in 2002. Sixty percent of the population lives in rural areas, and the life expectancy is sixty-six years.

Parenteral antischistosomal therapy (PAT) was widely used in treating schistosomiasis among the rural population in Egypt from the 1920s to the 1980s. It is now known that PAT is a risk factor for hepatitis C virus infection in Egypt. PAT consisted of a course of multiple injections, and was carried out using unsafe sterilisation procedures that resulted in very high chronic HCV rates in Egypt - a situation that clearly demonstrates the impact of unsafe injection procedures. Although PAT was discontinued in the mid-1980s, a large reservoir of chronic HCV carriers remains responsible for continued transmission of HCV through other routes of exposure.

The prevalence rates of HCV, HBV, and HBsAg in Egypt in 1996, were 14.5%, 22.5%, and 4.5%, respectively. A significant higher HCV prevalence rate was shown in the rural population where PAT was widely used compared to the urban population (18.9% vs 9.1%). Seroprevalence rates in Egypt show a steady rise with age.[1,2] However, increased serum ALT levels were detected in less than 20% of those with serum positive for HCV RNA. This is shown in the tables below.





The number of patients currently infected with HCV and needing treatment now is in the millions. In terms of costs of treatment and complications of HCV infection in Egypt, projected to 2008, there will be a loss of 2.6 billion Pounds in loss of production and, if this cohort remains untreated, will result in 38 billion Pounds in ten years' time.

Egypt's prevention programmes focus on:

- Blood banks for screening of blood / blood products, provision of laboratory equipment, training, supplies, and monitoring;
- Central and peripheral infection control committees;
- Development of guidelines for infection control.

Other prevention activities involve training of health care personnel, patients, and the general public in safe injection practices (disposal, sterilisation, barrier techniques, etc.).

Except for blood bank serology reporting, there are no laboratory or clinical networks in Egypt. Several liver disease societies collaborate on information exchange but no formal or common networks exist.

The Ministry of Public Health supports own research projects and projects conducted by Egyptian universities in collaboration with international agencies, such as the National Institutes of Health (USA), the Centers for Disease Control and Prevention (USA), the European Union, the French National Agency for HIV and HCV research (ANRS), and the World Health Organization. Physicians' syndicate authorities are active in organising meetings with national insurance authorities for developing guidelines for patient management. News and media organisations also play their part in raising public awareness of the benefits of preventing infectious diseases.

There is also a wide public appeal to the Egyptian authorities to develop guidelines for patient management, control of disease transmission, and public funding for treatment of infected individuals.

References

[1]Abdel-Aziz F, Habib M, Mohamed MK *et al*. Hepatitis C virus (HCV) infection in a community in the Nile Delta: population description and HCV prevalence. *Hepatology* 2000; 32:111-115.

[2]Habib M, Mohamed MK, Abdel-Aziz F *et al*. Hepatitis C virus infection in a community in the Nile Delta: risk factors for seropositivity. *Hepatology* 2001; 33:248-253.

Based on a presentation by Dr Mostafa Mohamed, Ain Shams University, Cairo, Egypt.

FRANCE

Surveillance of hepatitis C in France

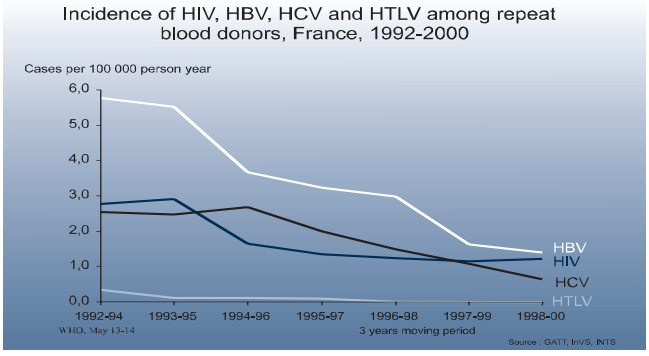
A national hepatitis C prevention and control plan, initiated by the French Ministry of Health, is centralised at national level, with decentralised activities at regional level. Primary prevention programmes include blood and organ donation safety, harm reduction policy among intravenous drug users, and control of iatrogenic transmission (i.e., induced by breaches in hygiene or other medical procedures in treating an illness). Secondary and tertiary prevention involves screening of risk groups, with the aim of achieving 70% coverage in 2002, and early follow-up, management, and treatment.

Gathering data is a key objective in hepatitis C surveillance in order to facilitate decision-making and to assess the burden of disease, epidemiological trends, and risk factors. Prevention and control programmes are evaluated for their effectiveness in terms of screening, blood safety and intravenous drug users harm reduction activities. Other surveillance objectives are targeted to outbreak detection, investigation, and control of HCV infection. These activities are linked with public health research efforts, and work in synergy.

Anti-HCV antibody screening activity is carried out through RENAHVC, a network set up in 2000, comprising 257 hospitals and public laboratories located throughout France. Quarterly data are compiled for each of France's twenty-two regions, based on screening activities, number of serologic tests done and number testing positive, test confirmation activity, and basic characteristics of positive tests.

Surveillance of chronic hepatitis C starts when chronic hepatitis C patients are newly admitted in one of the hepatitis C reference centres. These 30 centres co-ordinate a network of hepatology and medical wards, and specialists and general practitioners, for management, prevention, and information on hepatitis C. They also serve as referral centres. Since 2000, basic demographic, clinical, biological, and epidemiological information has been gathered on each new patient admitted to the reference centres as an outpatient or an in-patient. The objective is to monitor the trends over time of the modes of hepatitis C diagnosis, the severity of hepatitis C, the involved risk factors, etc., at first referral to the reference centres. This surveillance system aims to contribute to the ongoing evaluation of the national hepatitis C control and prevention programme.

Blood safety surveillance for HBV, HCV, and HIV markers is a collaborative effort carried out among blood centres and France's *Institut National de Veille Sanitaire* / National Institute for Viral Infections (InVS). The table below shows a significant decrease in incidence of HIV, HBV, HCV, and HTLV among repeat blood donors in France in the period 1992-2000.



Since France introduced nucleic acid testing in 2001, there has been a significant decrease in transmission of blood-borne viruses.

A national database (SIAMOIS), divided by district, provides monthly updates based on national and local monitoring of delivery indicators (quantity sold of syringes, steribox kits, subutex, methadone); the number of deaths by overdose; and arrests for drug offense. A sharp drop in 1 ml syringe sales in 2001 may indicate a decrease in safe injection practices, or possible increased use of synthetic drugs among younger people.

Notification of nosocomial infections became mandatory in France in 2001, and are based on criteria (not on positive or negative lists), and on HCV and HBV infection following medical care. Notification of such events must be made to local district health offices, inter-regional nosocomial co-ordination centres, and to the RAISIN-InVS at national level.

Seroprevalence and behavioural surveys of intravenous drug users are undertaken by the InVS, the *Institut National d'Etudes Démographiques* / National Institute for Demographic Studies (INED), and the *Agence Nationale de Recherches sur le SIDA* (ANRS). Specific studies that have been carried out include a national probability survey on HIV-HCV co-infection, a population survey aimed at evaluating HCV prevention, and a survey carried out in 1997 on mortality associated with hepatitis C.

Other public health research projects that are under way or are being planned under the auspices of the ANRS include:

- An ongoing case control study of HCV seroconversions;
- Cohort study of HCV-intravenous drug users;
- Sociological research: perception, barriers to screening, follow-up, treatment, quality of life, etc.
- Cost-efficacy studies.

Based on a presentation by Dr Jean-Claude Desenclos, Institut de Veille Sanitaire, Saint-Maurice Cedex, France.

SWITZERLAND

Tackling the HCV epidemic in Switzerland

Statistics: The Swiss population in 2001 · Resident population: 7,258,000 · Population density: 176 per km? · Foreign nationals: 20.1% (~ 1,460,000) · Excess of births over deaths: 13,000 per year · [Immigration] - [emigration] = + 41,500 per year

Notification of HCV infection has been mandatory in Switzerland since 1988. Based on the total number of compulsory declarations of HCV infection submitted to the *Office Fédéral de la Santé Publique* (OFSP) / *Bundesamt für Gesundheit* (BAG) / Swiss Federal Office of Public Health as of 2001, there are at least 24,068 HCV-infected patients (~ 2,500 per year) aware of their status, of which approximately 600 acute hepatitis C-patients (~ 60 per year).

Estimated prevalence (based on a survey among pregnant women in the general population) is 0.7-1%, representing 50,000 to 70,000 cases. However, official estimates may have under-estimated HCV prevalence in Switzerland. Although the study among pregnant women is representative in terms of ethnicity, women account for only 40% of the HCV-infected population, and only 2.4% of the pregnant women surveyed were over 40 years of age, compared with 39% of OFSP declarations.

In a recent study, a revised prevalence rate of 1.25-1.75% was calculated based on model predictions (assuming a median of 0.75% according to OFSP estimates) compared with the observed incidence of HCV-related deaths and orthotopic liver transplantation (OLT).[1] In the same study, future complications of a cohort of 77,595 HCV RNA-positive patients were evaluated, with the age distribution identical to that of the OFSP declarations. Based on this evaluation, it is predicted that within the next fifteen to twenty-five years:

- Annual incidence of hepatocellular carcinoma will increase by 70%;
- HCV-related mortality will increase by 90%;
- Incidence of HCV-related cirrhosis will decline.

Risk factors for acute hepatitis C in Switzerland include:

- Intravenous drug use (68.2%)
- Blood transfusion (6.8%)
- Health care workers 2.8%)
- Sexual contact (2.8%)
- Contact with anti-HCV-positive patients (1.9%)
- Unknown (15.7%)

Current antiviral therapy has a number of limitations. It reduces the annual HCV-related mortality by only 5%, since, according to Sagmeister *et al*. (2002),[1] only a minority of patients may have been diagnosed (~ 15%), and antiviral therapy may cure only 40% of HCV-infected patients. In addition, many patients are not eligible for antiviral therapy due to contraindications or to severe side effects of the treatment.

It is estimated that the annual direct costs for treating complications of HCV infection will double by 2020, amounting to 32.9 million US dollars, compared with 801 million US dollars of direct costs for chronic haemodialysis (CHD). Indirect costs, such as loss of productivity, would be 25.9 million US dollars annually.

HCV screening recommendations in Switzerland are indicated for:

- Present or former intravenous drug users;
- Individuals having received transfused blood before 1992 or blood derivatives before 1987;
- Patients undergoing dialysis;
- Children born to HCV-positive mothers;
- Health care workers after accidental exposure to blood;
- Patients with elevated transaminase levels.

However, these recommendations may help to identify only 50-60% of patients with chronic hepatitis C.

Current recommendations do not include general screening as it is deemed expensive, of limited usefulness, and out of proportion in relation to estimated results.[2] Additional screening options, however, could include anonymous testing and counselling, possibly linked with HIV or other prevention programmes, and other groups at risk:

- Individuals exposed to non-medical, invasive procedures;
- Individuals exposed in the past to potentially unsafe medical procedures / unsafe injections;
- Patients with extra-hepatic manifestations possibly linked to HCV infection.

However, systematic screening for chronic hepatitis C has not been evaluated in Switzerland - either clinically or in terms of cost-effectiveness. Further research would be needed to assess the possible benefits of implementing large-scale screening programmes.

References

[1]Sagmeister M, Renner EL, Mullhaupt B *et al*. Simulation of hepatitis C based on a mandatory reporting system. *Eur J Gastroenterol Hepatol* 2002; 14:25.

[2]Grob PJ, on behalf of the SEVHEP. Hepatitis C in der Schweiz - Für eine individuelle Information und Beratung. *Bull OFSP* 2001; 46:877-887.

Based on a presentation by Dr Francesco Negro, University Hospital, Geneva, Switzerland.

Conclusions of the meeting

1. In spite of the advances that have been made in our understanding of hepatitis C virus (HCV) biology, the epidemiology and natural history of HCV infection, and the progress in the primary and secondary prevention of HCV infection that has been made, major public health efforts to prevent and control this infection in the global population are still required.

2. Although the first clinical trials of a therapeutic type against HCV are under way, there is no short-term prospect for the introduction of any kind of vaccine against this virus. The conclusions and recommendations arising from this meeting are made in the context that hepatitis C would not be a vaccine-preventable disease in the foreseeable future.

3. Hepatitis C prevention should be viewed in the context of: (1) Primary prevention of newly infected persons; (2) Secondary prevention of transmission from known infected persons to others; (3) Tertiary prevention of the consequences of chronic HCV infection.

4. Primary prevention should focus on identifying persons at increased risk of HCV infection and providing HCV testing, counselling and health education concerning risk and harm reduction, and substance abuse treatment where appropriate.

5. There is a need for health education and awareness campaigns about HCV to be targeted both to the general public and to health care providers. Only a relatively small proportion of individuals infected with HCV are currently aware of their infection. Moreover, even in 2002, a large number of medical professionals are not sufficiently aware of HCV infection and its implications, and may fail to recognise the disease in their patients. In order to envision appropriate counselling, this lack

of awareness by health care professionals of risk factors for infection, diagnostic tests and recent advances in treatment options also needs to be rectified. In short, all health care providers need to be better informed about HCV infection and how to manage and counsel their patients with this infection. Collaboration with patient support groups should be sought and developed.

6. There is a need to identify those infected with HCV to achieve the goals of secondary and tertiary prevention, which includes counselling to reduce the risk of transmission through donating blood, serum, or organs; injecting drug use; and high risk sexual practices. These persons also need medical evaluation for possible treatment in order to prevent progression of their chronic liver disease. They need additional counselling with regard to: (1) Reduction of further liver injury from the consequences of alcohol consumption and co-infection with other hepatitis viruses and HIV; (2) Vaccination against hepatitis A and B, influenza, and possibly against *Streptococcus pneumoniae* infection.

7. Because of overlapping routes of transmission and populations that are at risk for viral hepatitis, HIV/AIDS, and other sexually transmitted infections, it is important that identification and prevention strategies should be integrated.

8. The problem of identifying all individuals infected with HCV and bringing them under medical attention is compounded by the fact that a large proportion of individuals with HCV infection live in developing and transitional economy countries where resources are scarce, screening of blood and blood products is not performed, the diagnosis of HCV infection is difficult, and treatment is not affordable.

9. There is still insufficient epidemiological data on the prevalence and incidence of HCV infection in many countries. Therefore, further studies, particularly evaluating the general population are warranted in most places. The complexity of reporting highlights the need for organisations such as WHO, CDC, and VHPB to develop guidelines on methods to obtain representative population-based HCV infection prevalence data and case definitions for reporting purposes.

10. Injecting drug use continues to be the source of HCV infections in most developed and some transitional economy countries. Because a high proportion of incarcerated persons have used injection drugs, there is a high prevalence (30-80%) of HCV infection in this population. This stresses the importance of the use of harm-reduction (harm-minimisation) procedures in prisons.

11. To minimise the spread of HCV among intravenous drug users, harm reduction involves more than just needle and syringe exchange. It must also involve swabs, filters, spoons, water, and any other equipment used. One of the major actions recommended is the necessity for needle exchange programmes to be introduced on a far larger scale, including the use of commercially available drug-paraphernalia (e.g., Stericup®). Collaboration with patient support groups should be sought to enhance the impact of prevention programmes.

12. Evidence-based information on nosocomial infections dramatically proves the impact of unsafe injection procedures, and the resulting high chronic HCV infection rates. In some countries unsafe injection techniques are now the predominant mode of acquisition of HCV infection. Particularly important in this regard are the following:

    - Using only sterilised medical equipment. Unsafe medical injections may be eliminated by: (1) Changing behaviour among patients and health care workers to decrease injection overuse and improve injection safety; (2) Providing access to necessary equipment and supplies.
    - Applying proper management of sharp waste.
    - Recent literature has stressed that in haemodialysis units, in particular, recommended procedures are not being carried out adequately, and hand-washing techniques remain faulty.

13. Multidose vials are also a cause of nosocomial transmission of HCV. Therefore:

    - Single-dose vials should be used wherever possible. If multidose vials must be used, the septum should always be pierced with a sterile needle, and a needle must not be left in place in the stopper.
    - Each injection should be prepared in a clean designated area where blood or body fluid contamination is unlikely.

14. Other routes of infection, such as through sexual activity or intra-familial transmission, play a much lesser role in spreading HCV.

15. Testing for HCV:

    - Of all patients with persistently raised serum ALT levels, 15% prove to be chronically infected with HCV. It is recommended that individuals with persistently raised serum ALT levels that are unexplained should be tested for HCV. Screening of the whole population is, however, not recommended.
    - Patients with defined extrahepatic manifestations of HCV should be tested for the virus.
    - It is self-evident that testing for HCV should be undertaken only if appropriate counselling can be given and appropriate treatment is available.

16. Disease progression - Controversy still exists over the proportion of patients acutely infected with HCV who progress to cirrhosis. Hospital-based data on patients with symptomatic chronic HCV infection give far higher rates of progression to cirrhosis than do analyses of all patients infected with the virus. When patients in the Irish outbreak of HCV infection caused by contaminated anti-D immunoglobulins were followed-up, only 2% developed cirrhosis, and in other large-scale studies in children with post-transfusion HCV infection and in intravenous drug users less than 5% progressed to cirrhosis.

17. In order to reduce the morbidity and mortality caused by HCV infection, the objective of treatment should be:

    • Cure by completely eliminating HCV and normalising serum ALT levels.
    If this is not possible, the objectives should be to:
    - Stop disease progression;
    - Improve quality of life;
    - Reduce transmission of the virus;
    - Reduce the pool of chronic carriers.

18. Despite a greater awareness of HCV infection, earlier diagnosis through improved laboratory techniques, and the recent introduction of more effective treatment, the overall outcome of HCV infection has not improved appreciably in recent years.

19. Treatment of chronic HCV infection with interferon does result in viral clearance in some patients, and in others it slows down progression to fibrosis. More recently, controlled trials have demonstrated that combined treatment with pegylated interferon and ribavirin has produced a greater number of sustained responses, depending on the genotype of the virus. Higher response rates are obtained with 6 months of treatment in patients with genotypes 2 and 3. Treatment of persons infected with genotype 1 produces less encouraging results and there is also the need to treat for 12 months.

20. Treatment of acute community-acquired HCV infections in younger patients appears to have a higher success rate with respect to viral clearance and progression to chronic infection. If confirmed, early treatment with interferon alone or in combination with other drugs should reduce the burden of HCV disease.

21. In spite of the advances in the treatment of HCV infection, given the fact that the majority of patients infected with this virus are not under medical care, the overall impact of therapy on the number of patients who are chronically infected with HCV is relatively small.

22. The VHPB aims to contribute to the prevention and control of hepatitis C by: (1) Raising awareness among health care providers and policymakers of the public health significance of hepatitis C; (2) Informing them about the risk of HCV transmission through blood or blood products, injecting drug use, and high-risk sexual practices; (3) Stressing the potential impact of preventive strategies, including the effect on the prevalence of other infectious diseases such as hepatitis B and HIV/AIDS; (4) Collecting and collating epidemiological data on hepatitis C, especially in Europe.

List of participants

Dr Miriam Alter, USA; Dr Selim Badur, Turkey; Dr Paolo Bonanni, Italy; Dr Norbert Declercq, Belgium; Dr Jean-Claude Desenclos, France; Dr Eric D'Hondt, Belgium; Dr Angela Domínguez, Spain; Ms Emmy Engelen, Belgium; Dr Guido François, Belgium; Dr Loic Frèrejouand, France; Dr Peter Grob, Switzerland; Dr Nicole Guérin, France; Dr Johannes Hallauer; Dr Yvan Hutin, Switzerland; Dr Wolfgang Jilg, Germany; Dr Michael Kew, South Africa; Dr Daniel Lavanchy, Switzerland; Dr Geert Leroux-Roels, Belgium; Dr Michael Manns, Germany; Dr Harold Margolis, USA; Dr Cathy Matheï, Belgium; Dr André Meheus, Belgium; Dr Mostafa Mohamed, Egypt; Dr Francesco Negro, Switzerland; Dr David Patrick, Canada; Dr Jean-Michel Pawlotsky, France; Dr Daniel Shouval, Israel; Ms Diana Steimle, Belgium; Dr Pierre Van Damme, Belgium; Dr Jan Van Hattum, The Netherlands; Mr Alex Vorsters, Belgium; Dr Deborah Wexler, USA; Dr Lucas Wiessing, Portugal; Dr Alessandro Zanetti, Italy.

The Viral Hepatitis Prevention Board (VHPB) is supported by grants from the pharmaceutical industry (GlaxoSmithKline Biologicals, Aventis Pasteur MSD, Merck Vaccine Division), several universities in Europe, and other institutions. VHPB has strict operational and scientific independence. The VHPB Executive Secretariat also benefits from being located at the Department of Epidemiology and Social Medicine of the University of Antwerp, Belgium, where it has the infrastructure and administrative services at its disposal.

Viral Hepatitis is produced and published by VHPB, and printed by WILDA, Antwerp, Belgium.
Photogravure made by Ability Design, Antwerp, Belgium.

For further information, please contact:
VHPB Executive Secretariat
Centre for the Evaluation of Vaccination
WHO Collaborating Centre for Prevention and Control of Viral Hepatitis
Department of Epidemiology and Social Medicine
University of Antwerp
Universiteitsplein 1
B-2610 Antwerp, Belgium

Tel 32 (0)3 820 25 23 Fax 32 (0)3 820 26 40
E-mail engelen@uia.ua.ac.be

http://www.vhpb.org