VIRAL HEPATITIS

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This edition of *Viral Hepatitis* is based on material presented at the Viral Hepatitis Prevention Board meeting on **Can the United Kingdom control viral hepatitis?** Edinburgh, United Kingdom, November 17-18, 2005.

Editorial

This issue of *Viral Hepatitis* reviews the topics covered at the Viral Hepatitis Prevention Board (VHPB) autumn meeting held on November 17-18, 2005 in Edinburgh, United Kingdom (UK). The aim of the meeting was to review the current UK practice relating to the control of viral hepatitis. Health policy, healthcare delivery, decision-making, research, and funding in England, Wales, Scotland, and Northern Ireland were examined, in particular with regards to their implementation at national level. An update on the epidemiological situation of hepatitis A, hepatitis B, and hepatitis C in the UK was provided. Specific aspects of viral hepatitis were discussed, including virological and clinical aspects, control measures, public health perspectives, and economic evaluations. Preventive national and regional strategies for the control of viral hepatitis in the UK were then presented and assessed, including testing, vaccination, and treatment options. The meeting was concluded with lessons learnt from the UK experience and future challenges to be met.

Control of viral hepatitis in the UK - achievements and challenges

With regards to the decision-making process ensuring prevention of viral hepatitis, the need was recognised for a continuous evaluation of the current risk-group vaccination policy, to be compared with results obtained with alternative strategies, such as universal vaccination programmes, in other comparable countries of the European Union. The need to carefully monitor such alternative strategies implemented at the regional level in the UK was recognised. The need to target specific groups, such as immigrant populations, in preventive programmes and treatment was also identified.

In terms of chronic disease management, discussions focussed on the need for national strategy and action plan in the case of hepatitis B while the establishment of Managed Clinical Networks (MCNs) should be ensured in the case of hepatitis C.

The control of viral hepatitis in the United Kingdom was also seen to be lacking a reliable surveillance system, based on standard laboratory reporting and case notifications. The need for enhanced epidemiological data was mentioned in order to avoid missed opportunities for prevention and treatment, and monitoring of successes or failures in implementing public health measures.

Finally, a careful weighing of parameters entering into economic evaluations of preventive strategies was strongly advocated, such as lowered vaccine costs, so as to ensure that recommendations leading to public health policy in the UK take potentially economically more attractive prevention scenarios into account.

Daniel Lavanchy and Steven Wiersma,
on behalf of the Viral Hepatitis Prevention Board

Can the United Kingdom control viral hepatitis?
- a VHPB Symposium Report -
Edinburgh, United Kingdom, November 17-18, 2005

Prevention of viral hepatitis in the United Kingdom: setting the scene

Public health structure and decision making in the United Kingdom

The United Kingdom (UK) National Health System (NHS) is structured around four departments of health, in England, Wales, Scotland, and Northern Ireland, respectively [1]. These four administrations share activities and their Chief Medical Officers advise the UK ministers of Health on the basis of recommendations made by the following common advisory bodies: the Advisory Group on Hepatitis (AGH); the Joint Committee on Vaccination and Immunisation (JCVI); the Expert Advisory Group on AIDS (EAGA); and the Advisory Committee on Dangerous Pathogens (ACDP).

Ultimate decisions regarding the control of viral hepatitis are made by Chief Executives at the NHS against the background of other health priorities.

The Health Protection Centre in each administrative entity is responsible for the collection of epidemiological data on the control of infectious diseases, as well as chemical and radiation hazards. This information is subsequently communicated to the common advisory bodies and is used for the development of prevention strategies.

With regards to prevention of viral hepatitis, the UK decision-making process can be summarised as a three-step procedure whereby:

The Health Protection Centre in each entity provides data on changing incidence of hepatitis A, hepatitis B, and hepatitis C.

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The AGH receives these data and provides advice on control of these infections to the Chief Medical Officer who advises UK ministers of health on related actions required.

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The JCVI delivers advice on childhood vaccination programmes.

In addition, specific provisions are made for healthcare delivery to chronic hepatitis B (CHB) and chronic hepatitis C (CHC) patients, according to the following principles:

1. The NHS National Institute for Health and Clinical Excellence (NICE) recommends cost-effective therapies, which must be made available within three months of recommendation. NICE is an independent organisation responsible for providing national guidance on the promotion of good health and the prevention and treatment of ill health [2].
2. Primary Care Trusts must commission care for their patients from general practitioners (GPs) or hospitals at standard tariff.
3. Care is delivered within Managed Clinical Networks (MCNs) in hepatology.
4. The Strategic Health Authority and Health Care Commission audit results and volume of care.

Several factors influence decisions relating to the implementation of prevention strategies, such as:

- the severity of infection under consideration;
- health-economic aspects: cost-effectiveness studies calculating the cost per life saved / cost per Quality Adjusted Life Year (QALY) gained;
- the impact on the effectiveness of existing vaccination programmes (perceived and actual side effects of a new vaccine to be added to a vaccination programme); and
- the implications for society outside health issues (e.g., taking the ethnicity component of targeted populations into account).

References

[1] UK Department of Health. http://www.dh.gov.uk/Home/fs/en [Accessed April 2006]
[2] National Institute for Health and Clinical Excellence (NICE). http://www.nice.org.uk/ [Accesssed April 2006]

Based on a presentation by Dr Howard Thomas, St Mary's Hospital, Liver Centre, School of Medicine, Imperial College, London, United Kingdom.

National strategies for prevention and control of hepatitis A, hepatitis B, and hepatitis C virus infection in the United Kingdom: an overview

Prevention and control of hepatitis A virus (HAV) infection in the United Kingdom (UK) is based on guidelines issued by the departments of health in England, Wales, Scotland, and Northern Ireland, and the Joint Committee on Vaccination and Immunisation (JCVI) [1], and the Public Health Leadership Society (PHLS) Guidelines [2]. The national strategy is articulated around public health measures involving improved hygiene, the use of human normal immunoglobulin (HNIg), and vaccination of high-risk groups.

Control of hepatitis B virus (HBV) infection is based on prevention measures and vaccination of high-risk groups, while treatment is offered to patients with chronic hepatitis B (CHB) as indicated by NICE guidelines published in 2005. However, no action plan is available for coordinated pathways of care to CHB patients.

Control of hepatitis C virus (HCV) infection is based on a series of preventative measures involving:

- Increased public and professional awareness
- Strengthened prevention services (e.g., needle-exchange programmes)
- Strengthened services for diagnosis and treatment

In the absence of a hepatitis C vaccine, the national action plan [3] for delivering interventions foresees increased testing for HCV infection and the establishment of Managed Clinical Networks (MCNs) for the delivery of co-ordinated pathways of care to anti-HCV-positive individuals.

Such networks should ensure delivery of healthcare as part of an integrated Hepatology Service, relying on expert clinicians and nurses. Also, access to accredited virology, liver pathology, and radiology laboratories should guarantee improved diagnosis and monitoring of chronic hepatitis C (CHC) patients. Appropriate management of viral hepatitis and complications, including a qualitative and quantitative assessment of therapy should be ensured as well.

Several measures are currently required in order for MCNs to achieve their objectives, including the conduct of an audit, assessing the adequacy of resources and service provision of existing centres. The identification of a lead Commissioner for MCNs within each Sector or Strategic Health Authority to advise Primary Care Trusts should also take place. Ring-fenced funds should be allocated for hepatology. Finally, the effects of the national strategy for prevention and control of HCV infection should be reviewed in five years time.

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[1] Department of Health, Welsh Office, Scottish Office Department of Health, DHSS (Northern Ireland). 1996. Immunisation Against Infectious Disease (*The Green Book*). Eds Salisbury DM, Begg NT. HMSO, London. http://www.dh.gov.uk/assetRoot/04/07/29/84/04072984.pdf [Accessed April 2006]

[2] Crowcroft NS, Walsh B, Davison KL, Gungabissoon U, on behalf of the PHLS Advisory Committee on Vaccination and Immunisation. Guidelines for the control of hepatitis A virus infection. *Commun Dis Public Health* 2001; 4:213-227.

[3] Department of Health. Hepatitis C: Action Plan for England 2004. http://www.dh.gov.uk/PublicationsAndStatistics/Publications/PublicationsPolicyAndGuidance/PublicationsPolicyAndGuidanceArticle/fs/en?CONTENT_ID=4084521&chk=QBPNen [Accessed April 2006]

Based on a presentation by Dr Howard Thomas, St Mary's Hospital, Liver Centre, School of Medicine, Imperial College, London, United Kingdom.

Prevention and control of hepatitis B in the United Kingdom

Hepatitis B virus biology

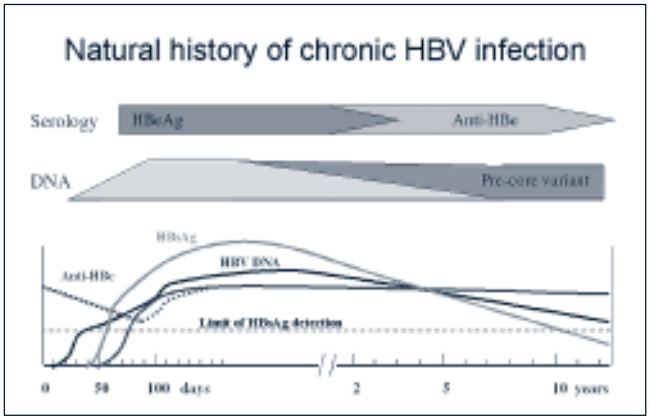
Eight genotypes (A-H) of hepatitis B virus (HBV) have been described to date based on nucleotide divergence, while ten subtypes or serotypes have been identified based on antigenic typing. Genotypes and subtypes can also be matched to specific ethnic groups and small geographical regions, and the prevalence of different HBV genotypes thereby reflects well-known patterns of human migration [1].

In particular, the analysis of the HBV genome has revealed specific findings, which play an important role in the choice of appropriate treatment, and the future development of therapeutic vaccines.

HBV genotypes are currently classified based on a nucleotide diversity of the whole genome of at least 8% [2] and correlate with ethnic origin, implying common immune selection. HBsAg mutations can result in a decreased or absent detectability by assays, based upon antibodies to the wild-type virus or in non-recognition by neutralising antibodies induced by vaccination [3].

HBV pre-core mutants are usually found in anti-HBe-positive patients with certain genotypes only and do not always correlate with disease progression; they may be associated with fulminant hepatitis. In terms of treatment, they do not directly predict response to interferon and they have no effect on nucleoside analogue therapy.

Since most HBsAg-positive persons are HBV DNA-positive, in case of available resources, consideration should be given to the wider use of HBV DNA detection as a primary diagnostic test for active liver disease, as illustrated by the natural history of chronic hepatitis B (CHB).



In this context, HBV DNA detection might play an important role for the diagnosis of occult HBV infection, although its clinical and diagnostic importance is still unclear at present.

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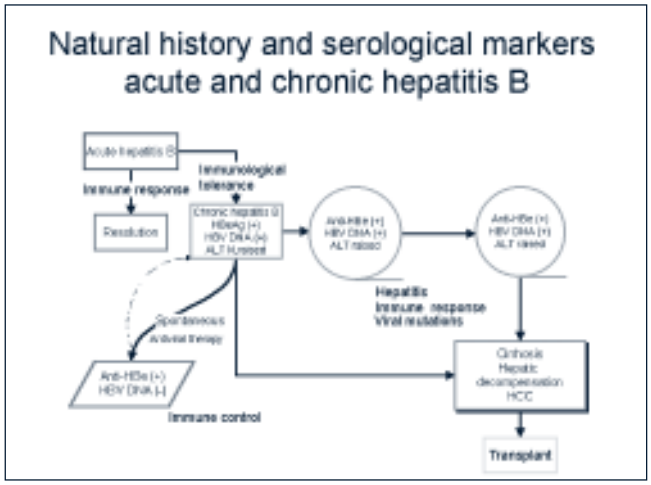
[1] Jazayeri MS, Basuni AA, Cooksley G, Locarnini S, Carman WF. Hepatitis B virus genotypes, core gene variability and ethnicity in the Pacific region. *J Hepatol* 2004; 41:139-146.
[2] Kramvis A, Kew MC. Relationship of genotypes of hepatitis B virus to mutations, disease progression and response to antiviral therapy. *J Viral Hepat* 2005; 12:456-464.
[3] François G, Kew M, Van Damme P, Mphahlele MJ, Meheus A. Mutant hepatitis B viruses: a matter of academic interest only or a problem with far-reaching implications? *Vaccine* 2001; 19:3799-3815.

Based on a presentation by Dr William Carman, Gartnavel General Hospital, West of Scotland Specialist Virology Centre, Glasgow, United Kingdom.

Clinical aspects of hepatitis B and treatment options

Hepatitis B virus (HBV) infection may cause liver damage ranging from mild chronic hepatitis to severe active hepatitis, cirrhosis, and hepatocellular carcinoma (HCC). Chronic hepatitis B (CHB) is defined as persistence of HBsAg in the blood circulation for at least six months; it is more frequent in males and more likely to follow infection acquired in childhood. CHB is a complex and multifaceted disease, which is heterogeneous in terms of its activity. The natural history and serological markers of acute and chronic hepatitis B are represented below [1].



HBV infection is usually diagnosed by the detection of HBsAg in serum. However, when resources are available, detection of HBV DNA is the optimal method of establishing hepatitis B viraemia, and is therefore particularly valuable for disease monitoring and the establishment of appropriate therapy.

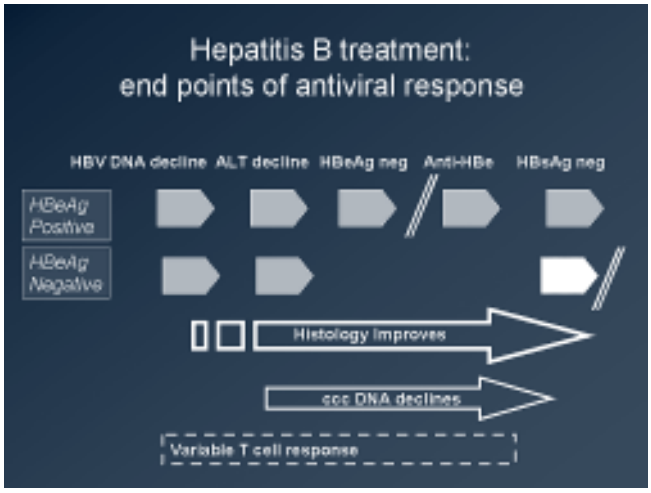
An appropriate assessment of CHB, leading to related therapy preventing disease progression should be made on the basis of a full clinical assessment, including assessment of symptoms and signs of hepatic decompensation, biochemical alterations (particularly ALT levels), serological detection of HBsAg, HBeAg, anti-HBe, HBV DNA, and HBV genotypes and mutants. A histological evaluation in the form of liver biopsy also provides helpful information on liver inflammation, necrosis, and fibrosis.

Chronic hepatitis B is characterised by a spectrum of markers related to either HBeAg-positive or -negative disease, with different implications in terms of disease management. HBeAg-positive disease mainly affects young individuals with HBV infection. Typically, high levels of HBV DNA (usually > 10^7 copies/ml) are detected. Serum ALT values may be normal or raised in the immunoactive phase of disease; higher seroconversion rates are observed in patients with raised ALT levels and genotype B (vs C) and genotype D (vs A).

The variability of markers that is typical of CHB and individual patient timing make disease management complex, time-consuming, and costly. Prognostic factors for disease progression to cirrhosis include older age, HBV DNA persistence, HBV genotype C, recurrent acute flares, histologic staging, alcohol consumption, and HCV/HDV/HIV co-infection. In particular, the presence of elevated HBV DNA levels has been shown to be directly correlated to a higher incidence of cirrhosis and HCC mortality rates, whereas liver biopsy provides a unique source of information and remains the standard for interpretation of disease stage and grade. However, the value of biopsy has been questioned as it entails a low finite risk but it is costly and constitutes a delay and barrier to treatment. Technological evolution may change the need for biopsy and its role in practice will be refined.

Baseline HBV DNA levels can predict disease as part of a spectrum of markers, provided that repeated assessments are made. Its presence can also predict prognosis in addition to assessments of activity and it is a marker of infection. In terms of indication for treatment, HBV DNA levels provide valuable information in conjunction with appropriate clinical and laboratory assessments.

In terms of disease monitoring, HBV DNA decline is a favourable paradigm in the case of HBeAg- and anti-HBe-positive disease, but it remains to be established whether absolute or relative measurements are required. On the other hand, the presence of HBV DNA and its slow decline are associated with viral resistance to treatment; however, other complex factors determine resistance.



Treatment concepts for CHB are aimed at prevention of disease progression to cirrhosis, end-stage liver disease, or HCC. If HBV replication can be suppressed, the accompanying reduction in histological chronic active hepatitis lessens the risk of cirrhosis and HCC. Patients with mild chronic hepatitis B should be monitored at appropriate intervals and therapy should be considered only if there is evidence of moderate to severe activity.

There are currently two main categories of drugs for treatment for CHB with different profiles: administration of pegylated interferon alpha and nucleoside / nucleotide analogues including lamivudine, adenovir dipivoxil (tenofovir), and entecavir. Clinical care is likely to evolve with the introduction of new nucleosides and nucleotides. Current decision making regarding treatment of hepatitis B in the United Kingdom is part of a broader control strategy where clinical and theoretical paradigms are not always reconciled with economic decisions such as those entailed in the National Institute for Health and Clinical Excellence (NICE) guidelines.

Hepatitis B is a complex disease and its clinical care is still evolving. It is influenced by the introduction of new drugs and the rapid evolution of data. Short-term studies have shown effectiveness of treatments while long-term studies have shown reduced disease morbidity.

Reference

[1] Dusheiko G. Candidates for therapy: HBV. *J Hepatol* 2006; 44(Suppl 1):S84-S89.

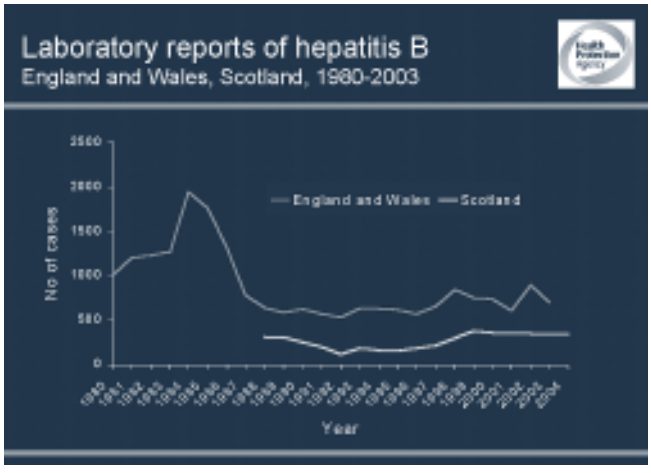
Based on a presentation by Dr Geoffrey Dusheiko, Royal Free und University College School of Medicine, Centre for Hepatology and Institute of Hepatology, London, United Kingdom.

Epidemiology and surveillance of hepatitis B in the United Kingdom

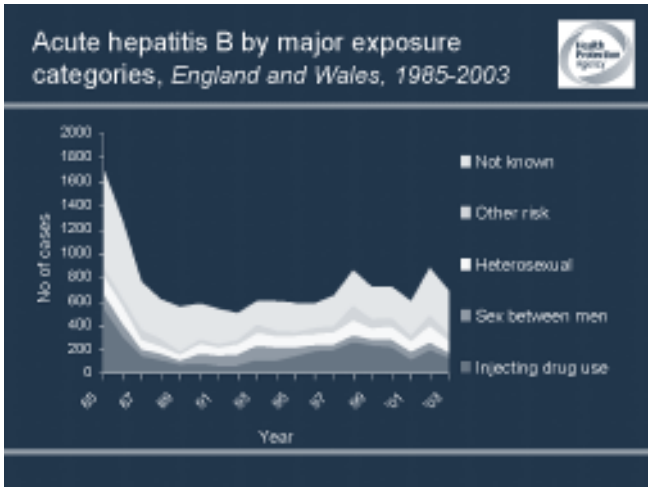
Chronic liver disease (CLD) is numerically the fifth most important cause of death in the United Kingdom (UK) and 4% of the UK population have abnormal liver function tests (LFTs). The main causes of CLD are alcohol- and obesity-related steatohepatitis, chronic hepatitis B (CHB) and chronic hepatitis C (CHC). The mortality rate from CLD is still increasing and directly correlated with increasing alcohol consumption and obesity rates. CHC prevalence is low in the UK (under 1%), with an estimated current pool of over 200,000 cases that is *probably* increasing, in particular due to a high and increasing prevalence among injecting drug users (IDUs) and a high prevalence in immigrant groups (e.g., from Eastern Europe). CHB prevalence is also low in the UK: less than 1% of the population is HBsAg-positive, with an estimated pool of 150,000-200,000 cases. However, it is also *probably* increasing, with a minority of chronic cases established as a result of infection acquired in the UK (around 200 per year) and an estimated 7,000 chronic cases imported every year as a result of immigration from high-prevalence areas.

Hepatitis B surveillance is conducted in England, Wales, Scotland, and Northern Ireland in order to determine incidence, prevalence, and burden of disease, as well as to identify outbreaks. Such data, based on statutory notifications, laboratory reports, and deaths, are used to establish and monitor control strategies.

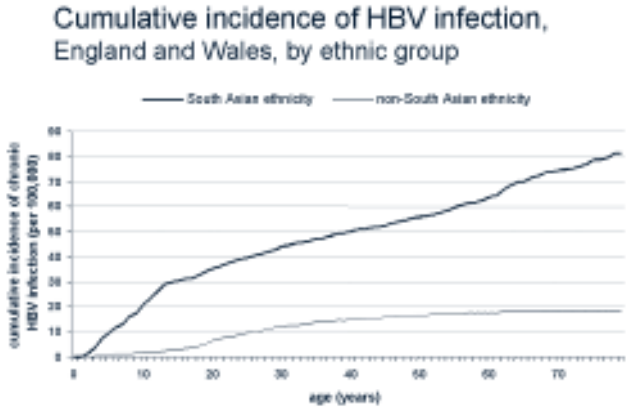
Laboratory reports of acute hepatitis B in England, Wales, and Scotland over the last two decades have shown that the incidence fell in the late 1980s and early 1990s, characterised by a fall among IDUs.



A minor increase among IDUs has been observed since the mid-1990s, influencing the overall epidemiological trend of hepatitis B in the UK. Reports from acute hepatitis B in England and Wales have shown that most cases occur in young adult males belonging to identified high-risk groups.

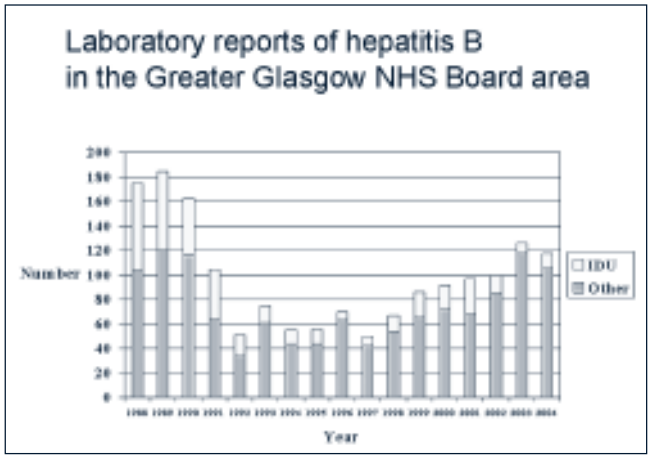


The estimated true incidence of acute and chronic hepatitis B, allowing for under-reporting and age-dependent probability of being symptomatic and of becoming a chronic carrier, amounts to an adjusted incidence rate of 5.5/100,000 per year, with no homogenous risk identified. An analysis of hepatitis B incidence among ethnic minority children has revealed a higher-than-background incidence among South Asian children, which is likely to be similar or higher for other ethnic minorities originating from high-prevalence countries.

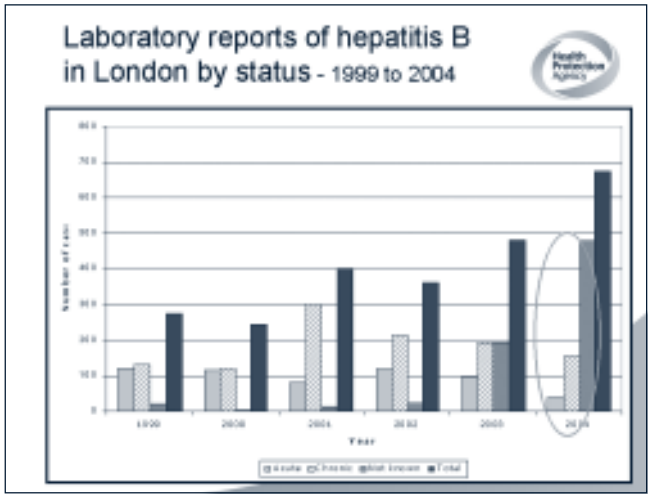


Laboratory reports on hepatitis B from the Greater Glasgow National Health Service Board (GGNHSB) have shown a decreasing trend from less than 180 reports in 1988 to ca. 50 reports in 1997.

Since then, yearly rates have increased again from less than 70 reports in 1998 to a provisional estimation of 118 reports for 2004, among which approximately one third occurred in the IDU



population and over one third among 25-34 year olds. These data confirm trends observed in England and Wales and are supported by specific data relating to sexual behaviour in the UK, showing an increase of risky behaviour among men who have sex with men (MSM), as well as among heterosexuals.



Laboratory reports on hepatitis B from the London area over the 1999-2004 period confirm the increasing trend seen in other UK entities, with an estimated 680 reports in 2004 against less than 300 reports in 1999.

Over this six-year period, a majority of acute cases of hepatitis B occurred in adult males aged 25-44 years while reports of chronic cases showed an excess among women of childbearing age probably due to an effect of selection / diagnosing bias.

However, less than 800 chronic cases among women of childbearing age were reported through the voluntary laboratory reporting scheme, added to ca. 100 reports of acute cases over the six-year period. These reveal significant underreporting since 1,200 women were diagnosed as hepatitis B carriers in pregnancy in London in 2004 alone.

Overall, approximately one third of cases occurred in the IDU population. Another risk group includes individuals from high-prevalence areas and their families who are at risk through perinatal and houshold transmission.

Half of the UK ethnic minorities live in London and represent at least one third of the London population overall, with an estimated pool of ca.122,000 hepatitis B carriers among the main ethnic minorities. A further risk group includes individuals who engage in behaviour leading to high-risk transmission.

Based on presentations by Dr Howard Thomas, St Mary's Hospital, Liver Centre, School of Medicine, Imperial College, London, United Kingdom; Dr Mary Ramsay, Health Protection Agency, Centre for Infections, Immunisation Division, London, United Kingdom; Dr Syed Ahmed, Communicable Diseases and Environmental Health, Department of Public Health, Greater Glasgow Health Board, Glasgow, United Kingdom; and Dr Helen Maguire, Health Protection Agency, London Regional Epidemiology Unit, London, United Kingdom.

Hepatitis B prevention: current practice in the United Kingdom

In accordance with the United Kingdom (UK) national prevention strategy against hepatitis B virus (HBV) transmission, selective hepatitis B vaccination of the following high-risk groups is recommended:

- Infants born to HBsAg carrier mothers - vaccination within 48 hours of birth
- Injecting drug users (IDUs)
- Individuals who change sexual partners frequently
- Men who have sex with men (MSM)
- Close family contacts of a case or carrier
- Families adopting children from countries with a high prevalence of hepatitis B
- Haemophiliacs
- Patients with chronic renal failure
- Healthcare workers (HCWs)
- Staff and residents of residential accommodation for those with severe learning disabilities
- Other occupational risk groups
- Inmates and staff of custodial institutions
- Travellers to high-prevalence areas
- Patients with chronic liver disease

Among those high-risk groups, IDUs, individuals who change sexual partners frequently (a not-well defined group), MSM, sex workers, travellers to areas of high hepatitis B prevalence, and close family contacts of a HBsAg carrier (in particular among immigrant families) have been identified as 'difficult-to-target' groups.

Specifically, hepatitis B vaccination practice of MSM in *England and Wales* is characterised by a major increase in coverage, in particular in genito-urinary medicine (GUM) clinics. Determining factors include the implementation of a sexual health strategy and the vaccine centrally provided to clinics. Similarly, after an initial failure to vaccinate in specialist services, vaccination coverage of IDUs has been improving slowly thanks to additional resources identified and a major drive to run hepatitis B vaccination programmes for prisoners. This is reflected by a 50% rise in the self-reported coverage rate of hepatitis B vaccine among IDUs attending services, from 25% in 1998 to over 50% in 2004, for a partial vaccination course at a 0, 1, 2-month schedule.

It is concluded from the implementation of preventive measures in England and Wales that the impact of hepatitis B vaccination is limited within the UK, in particular due to the high HBsAg carriage rates among ethnic minorities and the evidence that many carriers

acquired infection during childhood, prior to their immigration in the UK. The scope for improving current control is also recognised.

Several initiatives were also taken in *Glasgow* in terms of hepatitis B immunisation programmes for 'difficult-to-target' groups, which include:

- antenatal universal hepatitis B screening since 1993;
- special IDUs programmes in the community, including an 'Item of Service' (financial incentive measure) fee to general practitioners (GPs);
- a special hepatitis B vaccination programme in clinics for MSM;
- special clinics for female sex workers;
- several other initiatives relating to, e.g., HCWs, travel clinics, and contacts; and
- routine hepatitis B immunisation of the prison population since 1999, whose success is reflected by the self-reported hepatitis B vaccine coverage among IDUs, which was more than three times higher in 2004 (68%) than in 1993 (19%).

However, the success of these local initiatives is hampered by the numerous limitations of the selective UK hepatitis B vaccination programme, which is neither well-resourced nor well-co-ordinated, and entails remuneration issues for GPs. Also, hepatitis B vaccine coverage is not recorded systematically and the success of such recording often depends on enthusiasm and/or resources available. Target populations are not always well-defined and target groups are often not aware of the risks of HBV infection: a proportion of the population does not fall into any defined risk group and does not perceive itself as being at risk. A high proportion of young individuals are not registered with GPs; groups are often not 'captive'; and target groups are not identified before exposure to HBV infection. Also, selective vaccination programmes require a wider group of HCWs to be educated, compared to universal vaccination programmes. Finally, a selective hepatitis B vaccination programme targeted at ethnic groups who are at high risk of infection does not often work because of horizontal HBV transmission.

As an additional strategy, a two-stage adolescent hepatitis B vaccination programme was conducted in Glasgow between September 2001 and May 2002, which targeted 11,000 schoolchildren aged 11-12 years in 81 state, independent, and special schools where the vaccine was administered by nurses. This two-stage initiative included a focus group study revealing that: most pupils and parents knew little about HBV infection; risk factors for acquiring HBV infection were not irrelevant to parents/children; participants wanted more information about vaccine side effects; and most pupils and nearly all parents favour hepatitis B vaccination [1]. In a second step, a vaccination campaign took place during which 91.3% of participants received at least one dose of hepatitis B vaccine; 89.3% received at least two doses; and 80.2% received three doses, while the drop-off was greatest between the second and the third school visits [2].

As a follow-up on this universal hepatitis B vaccination programme initiative, the Joint Committee on Vaccination and Immunisation (JCVI) is currently examining the feasibility and cost-effectiveness of the various strategies including a status quo situation, a universal infant or adolescent vaccination programme, or both for a limited period of time.

Implementation of the recommended hepatitis B prevention strategy in the *London* area has shown, for example, an estimated 82% coverage of the third-dose vaccination of infants born to HBsAg-positive mothers over the period 2002-2005 (i.e., ca. 1,200 infants in this key risk group in 2004). On the other hand, hepatitis B vaccination coverage in London prisons in 2005 does not exceed 41% and is very poor in some London districts. Surveys have nonetheless shown an increase in self-reported hepatitis B vaccination coverage (53% received at least one dose of vaccine) and often attributed to having received it in prison, in particular in the case of IDUs. Coverage of at least one dose of hepatitis B vaccine amounts to 93% among MSM.

Several issues are identified in relation to hepatitis B surveillance and public health interventions in London, including:

- delays and non-reporting of HBV infections;
- 'difficult-to-reach' communities;
- lack of clarity of roles among partners in public health structures;
- not all patients are referred to specialist hepatology services because hepatitis B affects less advantaged and less articulated communities;
- contact tracing is complex and time-consuming in London due to multi-occupancy, extended families, and language and confidentiality barriers;
- new IDUs are still becoming infected and needle-exchange programmes are not sufficient.

A series of actions have been identified, which would contribute to improved prevention and control of HBV infection in London, such as improved completeness and participation in laboratory reports, and improved local surveillance. Clarification of roles and responsibilities within public health structures is required. Improved needle-exchange programmes should be implemented. Care pathways for infants born to HBsAg-positive mothers should be agreed and a full hepatitis B vaccination course should be ensured. Prisons and GUM clinics should be supported in delivery of hepatitis B vaccine. Measures should be taken so as to ensure that patients are referred to specialist hepatology services. Antenatal screening and hepatitis B vaccination of household contacts, especially children, should be improved; primary-care centres should be supported, encouraged, and assisted in this process.

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[1] Hinds A, Cameron JC. Acceptability of universal hepatitis B vaccination among school pupils and parents. *Commun Dis Public Health* 2004; 7:278-282.

[2] Bramley JC, Wallace LA, Ahmed S *et al.* Universal hepatitis B vaccination of UK adolescents: a feasibility and acceptability study. *Commun Dis Public Health* 2002; 5:318-320.

Based on presentations by Dr Howard Thomas, St Mary's Hospital, Liver Centre, School of Medicine, Imperial College, London, United Kingdom; Dr Mary Ramsay, Health Protection Agency, Centre for Infections, Immunisation Division, London, United Kingdom; Dr Syed Ahmed, Communicable Diseases and Environmental Health, Department of Public Health, Greater Glasgow Health Board, Glasgow, United Kingdom; and Dr Helen Maguire, Health Protection Agency, London Regional Epidemiology Unit, London, United Kingdom.

Hepatitis B prevention: economic aspects

There has been an ongoing debate regarding the cost-effectiveness of universal hepatitis B infant vaccination programmes in very low incidence countries – such as the United Kingdom (UK) – for some time [1]. An economic analysis of universal infant and adolescent vaccination was performed from the perspective of the healthcare provider.

A cohort model, adapted from that of Fenn *et al.* [2] was used. Individuals were assumed to be born 'susceptible', and if infected progress through different pathways and stages of hepatitis B infection. Health states modelled included 'acute infection', 'acute (fulminant) liver failure', 'chronic carrier', 'cirrhosis', 'decompensated cirrhosis', 'hepatocellular carcinoma (HCC)', 'immune',

'vaccinated', and 'death'. The costs and life expectancies of two cohorts were compared - those vaccinated and those not. The cohorts were followed from birth or 12 years of age, depending on whether an infant or adolescent hepatitis B vaccination strategy was being compared. The costs and benefits (calculated in life-years gained) were compared in two cohorts on the basis of universal infant three-dose versus adolescent two-dose hepatitis B vaccination programmes. Males and females were treated separately on the basis of different incidence and disease progression rates while hepatitis B virus (HBV) transmission was ignored, therefore underestimating benefits to some extent. In addition to universal programmes, geographically targeted programmes (aimed at areas with an ethnically diverse population) were also analysed.

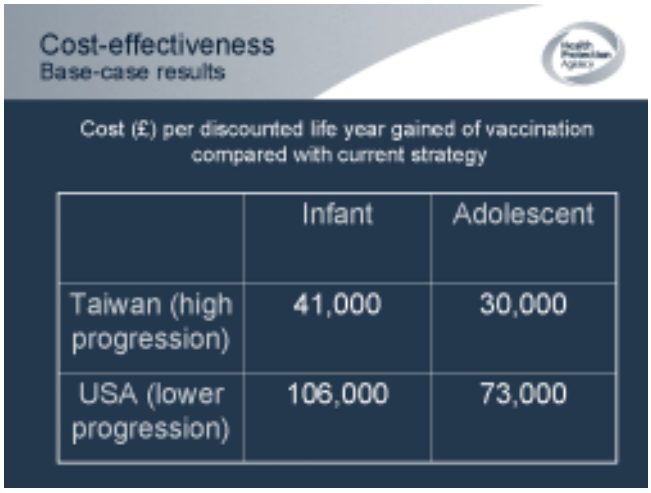
Incidence estimates from England and Wales were used for the general population and those of South Asian ethnic origin [3]. They were assumed to be stable through time. Transition probabilities between various hepatitis B stages were taken from the literature, and from fitting the model to data on the risk of developing liver cancer in carriers as observed in cohort studies from Taiwan and the United States of America (USA). Progression rates increased with age, and appeared to be significantly higher in the Taiwanese cohort. Hence, different progression rates were used in the analysis: high, based on Taiwanese rates; and low, based on USA rates. Women were assumed to have lower progression probabilities, based on comparing rates of chronic disease in Gambian men and women. Background mortality was taken from Office for National Statistics (ONS) data. Ninety percent hepatitis B vaccine coverage and 90% vaccine efficacy were assumed for both infant and adolescent programmes. Life-long immunity was assumed in the base case. Adolescent vaccination was given at 12 years. Future costs and health benefits were discounted at 3.5%, as recommended in UK Treasury guidance. Results were also presented in which benefits were undiscounted.

The base-case cost per hepatitis B vaccine course was assumed to be £15 including administration, for both the adolescent (two doses) and infant programme (three doses). Treatment costs (often based on hepatitis C disease) were taken from literature and standard sources. All costs were inflated to £2003.

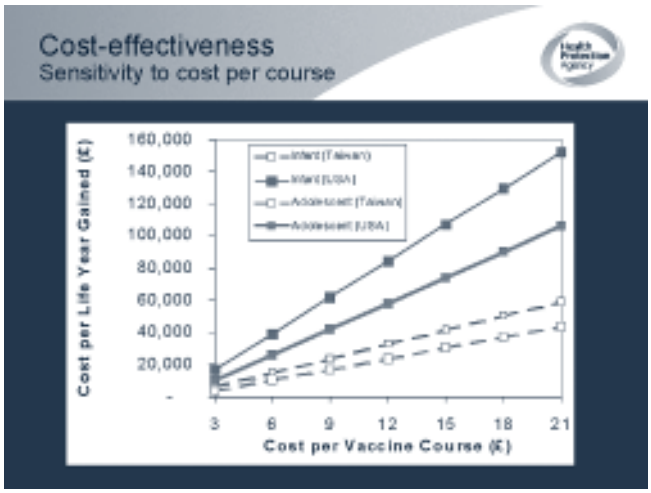
All epidemiological, demographic, and cost parameters were subject to sensitivity analyses.

The model estimated that between nine and 49 (depending on progression rates) deaths from chronic hepatitis B would be expected in an unvaccinated UK birth cohort over their lifetime. A further four deaths might be expected from acute disease. The annual burden of chronic hepatitis B disease is, however, much higher than this, as most carriers (> 95% [3]) immigrate to the UK, rather than acquire their infections in the UK. These would not be prevented by universal UK-based vaccination.

Base-case results suggest that adolescent hepatitis B vaccination is slightly less effective than infant vaccination but more cost-effective at £15 per course for both programmes (see below), as the vaccine is given closer to the age at which the risk of infection is highest. Taking the Taiwanese (high) progression rates, then adolescent hepatitis B vaccination reaches a commonly used threshold for interventions to be deemed cost-effective in the UK (£30,000 per Quality Adjusted Life Year – QALY – gained). Using the (possibly more appropriate) progression rates from the USA, it seems unlikely that either infant or adolescent universal hepatitis B vaccination would be deemed cost-effective. If health benefits are not discounted then both programmes would likely be deemed cost-effective – ca. £6,000 per Life-Year Gained (LYG) – and infant vaccination would be preferred.



The results were sensitive to the cost per vaccination course (below). This shows the potential impact of negotiating a lower vaccine price with vaccine manufacturers in order to increase the cost-effectiveness of hepatitis B vaccination programmes.



Since the incidence among South Asians and other ethnic groups is higher than among the overall UK population, it may be more cost-effective to target them. Under base-case assumptions if 40% of the population has an incidence similar to that estimated in those of South Asian ethnic origin [3], then the cost per LYG for infant vaccination would amount to £30,000 (with Taiwanese progression rates), thereby demonstrating that it might be cost-effective to target ethnically diverse geographical areas.

It is concluded from these modelling exercises that universal hepatitis B vaccination will have a limited impact on the burden of disease associated with chronic hepatitis B (CHB) and that universal infant / adolescent hepatitis B vaccination programmes are unlikely to be cost-effective in the UK, unless lower prices would be negotiable.

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Based on a presentation by Dr John Edmunds, Health Protection Agency, Modelling and Economics Unit, London, United Kingdom.

Prevention and control of hepatitis C in the United Kingdom

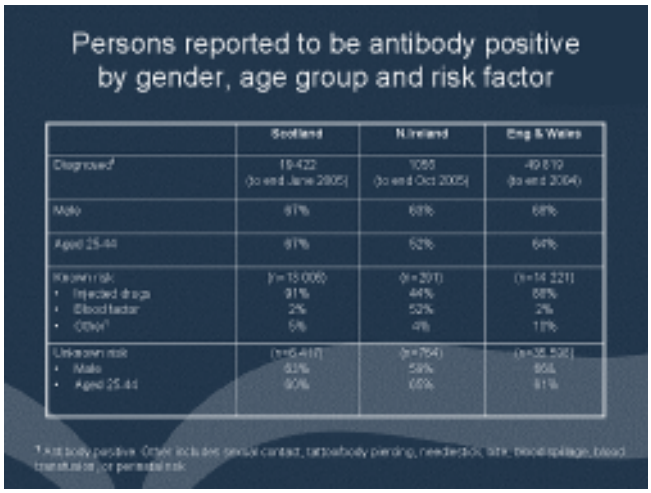
Hepatitis C virus infection: epidemiology, surveillance, and modelled burden of disease

Hepatitis C virus (HCV) infection is a major cause of acute hepatitis and chronic liver disease (CLD), including cirrhosis and liver cancer. These long-term complications pose the greatest burden. HCV is spread primarily by direct contact with human blood and the majority of cases of HCV infection are asymptomatic.

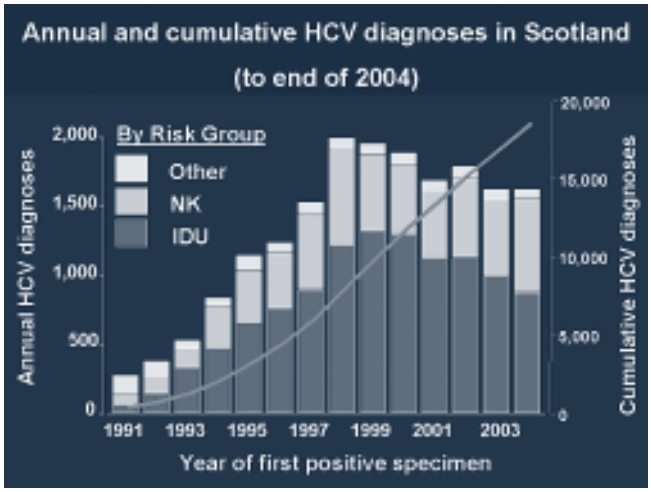
HCV infection prevalence data have been collected in different populations in the United Kingdom (UK):

- In healthcare workers (HCWs): 0.2-0.3% [1];
- In pregnant women: 0.2-0.4% among antenatal attenders [2,3] and 0.4% among childbearing women [4];
- In genito-urinary medicine (GUM) clinic attenders: 0.4-1.0% among heterosexual males, 0.3-0.7% among heterosexual females, and 0.6-1.0% among men who have sex with men (MSM) [5,6];
- In blood donors (2004): 0.03% in new donors and 0.001% in repeat donors [7];
- In prisoners: 58% in drug-injecting inmates vs 3.5% in non-injecting inmates [8];
- In injecting drug users (IDUs): 20-90% [9,10].

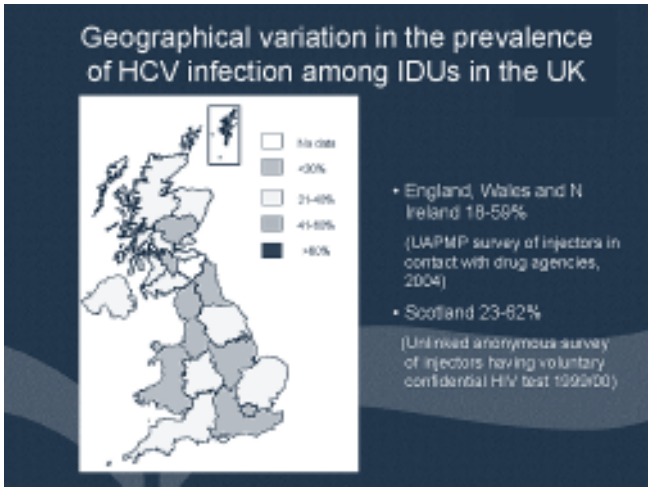
Estimates of the overall burden caused by HCV infection in the UK suggest that the prevalence is low, with an estimated 50,000 HCV-infected persons in Scotland (1% of the total population) [11] of whom only 35% are estimated to be diagnosed, versus 300,000 cases in England (0.5% of the total population) of whom only 17% are estimated to be diagnosed. Overall rates of reported HCV-positive individuals are 83/100,000 (2004 surveillance data) in England and Wales; 62/100,000 in Northern Ireland (2005), and 388/100,000 in Scotland (2005). Further epidemiological information by age group and risk factor is shown in the slide below.



Laboratory data on all persons diagnosed as anti-HCV-positive are collected as part of Scotland's nationwide surveillance system [12]. Data collected between 1991 and 2004, as given in the slide below, have shown a steady increase in the prevalence of known HCV infection in Scotland, where infection had been diagnosed in over 18,500 persons by the end of 2004, while the annual number of new diagnoses totals between 1,600 and 2,000 cases per year since 1998. A number of epidemiological characteristics are recorded in this database and the most cited risk factor for HCV infection was injecting drug use - in 90% of known-risk cases.



Trends of HCV infection among IDUs in the UK [10] indicate highest prevalence in Scotland. A common pattern is observed across all UK regions, characterised by a sharp decline in the proportion of IDUs who tested HCV-positive between 1990 (70-90%) and 1996 (20-60%), followed by a stabilised rate of 20-40% until 2002. Geographical variation in prevalence of HCV infection among IDUs in the UK is shown below.



Additional epidemiological data have been generated in Scotland on past and current severe HCV-related disease burden through the linkage of two unique data sets: i) a database, held at Health Protection Scotland, of all laboratory-confirmed anti-HCV-positive diagnoses made during 1991-2001 (involving 12,096 persons); and ii) a combined database, held at the Information Services Division, of all hospital discharge diagnoses, cancer registrations, and deaths in the country. Epidemiological characteristics of these 12,096 persons diagnosed with HCV infection in Scotland during 1991-2001 include: 12% had died by the end of 2001; 56% resided in an area of high deprivation; 17% had either been hospitalised with or died from an alcohol-related diagnosis; 5% were co-infected with HIV; and 88% were estimated to have ever injected drugs.

This record-linkage work also identified 514 persons diagnosed

with HCV who had presented to hospital with decompensated cirrhosis during 1991-2001. Interestingly, 69% of this group were aged less than 50 years at the time of hospitalisation with decompensated cirrhosis. One of the reasons for this young age distribution may relate to the observation that over 70% of HCV-diagnosed decompensated cirrhosis cases were recognised to have an alcohol problem from hospital and death records. The young age of decompensated patients presenting to hospital with both HCV infection and an alcohol problem (78% are less than 50 years old) suggests that the combined effect of these two factors accelerates liver disease progression more than only one (HCV: 48%; alcohol: 33%) or none of these factors (17%).

In Scotland, a forward projection model was developed to estimate the numbers of both current and former IDUs who acquired HCV and progressed to moderate and severe disease during 1960-2030 [13]. The model was designed to synthesise information on the incidence and cessation of injecting drug use, the incidence of HCV infection among IDUs, the rate of hepatitis C disease progression, and the annual number of IDUs developing decompensated cirrhosis. Model results indicate that, if transmission of HCV among IDUs continues at the same rate in the future as currently observed, the number of HCV-infected IDUs would increase from an estimated 45,000 in 2005 to 58,000 in 2020, of whom an estimated 34,000 and 40,000, respectively, will have chronic HCV. The estimated number of (current and former) IDUs with moderate HCV disease will increase from 9,000 in 2005 to over 18,000 in 2020.

The current and future burden of hepatitis C has also been modelled in England and Wales, although using a different, back-calculation approach. Data on HCV-related hepatocellular carcinoma (HCC) deaths are combined with estimated rates of disease progression to generate estimates of the incidence of infection over time, and then combined with knowledge on the progression of hepatitis C, incidence and prevalence of HCV-related severe disease is predicted [14]. Major results from this exercise have shown that the number of people living with hepatitis C-related cirrhosis has increased dramatically since 1990. The predicted number of HCV-infected people with cirrhosis or HCC in 2010 compared with 1990 will be six times higher. It is also predicted that there will be almost 6,000 cases of compensated cirrhosis due to HCV infection in 2010.

In conclusion, the epidemiology of HCV infection and related disease in the UK is characterised by an overall low but increasing prevalence rate, with a burden of infection highest among IDUs. HCV-related end-stage liver disease is not uncommon; it is also increasing and usually associated with alcohol consumption. Taking into account the uncertainty of models, critical findings resulting from modelled current and future HCV-related burden of disease in the UK have nonetheless highlighted the need to implement appropriate public health strategies in terms of hepatitis C prevention and treatment among an increasing number of IDUs in the UK population.

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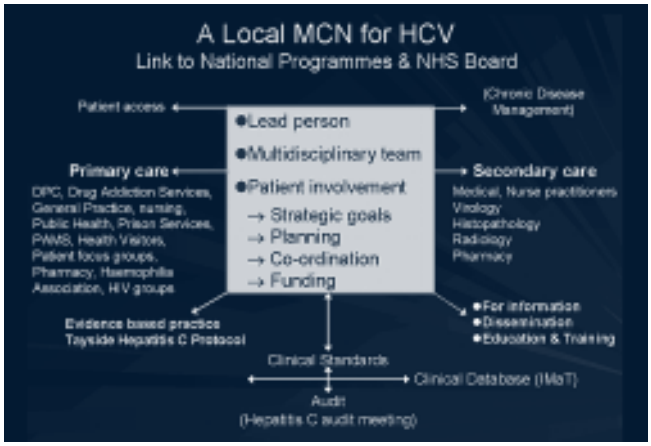
Based on presentations by Dr Sharon Hutchinson, Health Protection Scotland, BBV and STI Section, Glasgow, United Kingdom; and Dr Kirsty Roy, Health Protection Scotland, BBV and STI Section, Glasgow, United Kingdom.

Hepatitis C prevention and treatment: United Kingdom national strategy and current practice, including assessment of regional programmes

Prevention of hepatitis C virus (HCV) infection in the United Kingdom (UK) is articulated around national strategies, action plans, and guidelines. Concretely, these include a hepatitis C action plan and strategy for England and a hepatitis C *proposed* action plan for Scotland. Also, control measures are based on several guidelines including the British Society of Gastroenterology (BSG) guidelines; the Scottish Intercollegiate Guidelines Network (SIGN) hepatitis C guidelines; National Institute for Health and Clinical Excellence (NICE) guidelines, and Scottish Medicines Consortium (SMC) guidelines, as well as national and international clinical and laboratory guidelines.

A broad assessment of the UK guideline landscape reveals that England and Scotland have different public health policy agendas, while no guidelines are mentioned for Wales and Northern Ireland. Taking a closer look at the use of guidelines in order to ensure implementation of control measures, it might also be useful to question their utility and validity. In particular, when guidelines are evidence-based, their scope is limited by available evidence and when guidelines are not evidence-based, they lack the authority for forceful implementation. Such limitations are directly reflected in the noticeable gap in the delivery of therapy.

In accordance with the UK national plan for healthcare delivery to hepatitis C patients, Managed Clinical Networks (MCNs) should deliver interventions as part of an Integrated Hepatology Service.



As already outlined in the introductory section of this report, more effective functioning of MCNs would require a review of allocated resources and responsibilities, in particular since current practice in England and proposed practice in Scotland are not aligned. In particular, MCN audit and quality control should focus on the implementation of clinical standards, the measurement of relevant outcome and related resourcing, comparison of practice to standard, and adequacy to and implementation of the action plan. Such audits and quality controls should be repeated.

Recent surveillance and survey data suggest that HCV incidence and prevalence among injecting drug users (IDUs) is increasing [1-3]. Against this background an HCV transmission model among IDUs in London was developed, in order to explore the impact of harm-reduction interventions that may result in reductions in syringe sharing and other risk behaviours among this population. This model is based on epidemiological evidence of increasing incidence and prevalence of HCV infection among IDUs and estimated increasing injecting frequency and risk over the period 1968-2000, against an estimated reduction of 20%-50% in syringe coverage distribution [4-7].

Assuming that the structure of the current model is valid, it showed that small reductions in syringe sharing could reduce the HCV prevalence of new injectors while large reductions in syringe sharing are required to reduce prevalence of HCV infection among long-term IDUs. Furthermore, the model suggested that in order to have a substantial reduction of HCV prevalence to less than 10% it is critical that effective harm-reduction activities reach new IDUs (within six months of injecting) because HCV transmission is so very rapid; changes in risk behaviour must be sustained over a long period to achieve reductions in HCV prevalence; and syringe sharing has to be reduced to less than one-two occasions per month.

However, these findings are limited by data uncertainty relating to HCV biological and IDU behavioural parameters. In order to assess the contribution of such harm-reduction programmes to the control of HCV transmission in the UK, it is recommended that future modelling work be targeted at an IDU core group or higher-frequency syringe sharers, that the impact of increasing syringe distribution be explicitly assessed, and that injecting drug use prevalence / incidence be modelled over time.

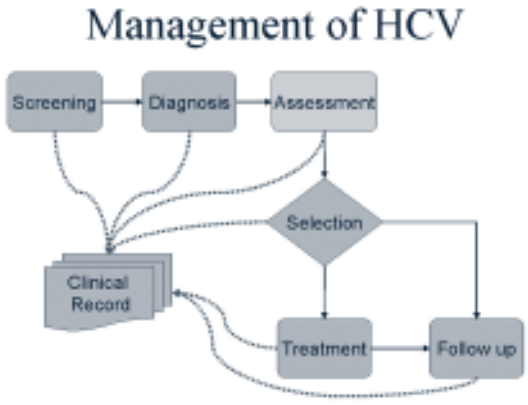
Numerous past IDUs have chronic hepatitis C (CHC) and remain undiagnosed in spite of screening being proposed among this group as part of the UK policy support to active case finding, in particular via the hepatitis C action plan for England (2004). Further support to this programme is provided by the All Party Parliamentary Group on Hepatitis, the Royal College of Physicians, and the European Association for the Study of the Liver (EASL).

Also, treatment options for hepatitis C have improved and, based on NICE guidance, pegylated interferon and ribavirin are standard and could be offered more effectively to diagnosed IDUs.

Assessment of case finding has been performed within the framework of the NHS Health Technology Assessment (HTA) programme in order to provide decision makers in the NHS with high-quality information on the costs, effectiveness, and broader impact of healthcare treatments and tests. The assessment focused on case finding in genito-urinary medicine (GUM) clinics and drug centres. It emphasised the importance of drug centres but revealed that case finding in GUM clinics is probably not cost-effective unless restricted to former IDUs. No evidence of behavioural change from knowledge of HCV infection was observed.

In order to estimate the clinical impact and cost-effectiveness of case finding for hepatitis C among former IDUs in different settings including drug and alcohol services, prisons, and general practice, a spreadsheet-based model of screening using enzyme-linked immuno-sorbent assay (ELISA) followed by polymerase chain reaction (PCR) tests and treatment using combination therapy with interferon alpha and ribavirin was developed [8]. Parameters included in the model were based on literature review, expert opinion, and current screening practice in England. A range of one-way sensitivity analyses were carried out to explore uncertainty in the results of cost-effectiveness. Several case-finding scenarios were modelled, showing that screening for HCV infection would probably be cost-effective, yielding benefits at around 28,000 pounds per Quality Adjusted Life Year (QALY) but less strikingly than cost-effectiveness of treatment. Uncertainty remains since this estimate was shown to be sensitive to the proportion of HCV-positive individuals who accept biopsy or treatment. Other areas of uncertainty include the effects of mortality from other causes in this population and the time at which symptoms would have led to presentation in the absence of a screening programme. Also, data are very limited in specific settings and for the injecting drug-using population in general. Further empirical studies are therefore required in order to confirm these findings.

The current management of diagnosed cases of HCV infection, which is illustrated in the graph below, requires careful patient assessment and selection for treatment.



Assessment protocols include viral genotyping (HCV genotype 1 has the most widely spread distribution and is unfortunately the most difficult to treat genotype); liver biopsy, which provides additional information on disease stage; compliance to treatment; psychiatric evaluation (depression is exacerbated by interferon therapy) and the presence of co-morbid conditions, such as ischemic

heart disease (IHD), chronic obstructive pulmonary disease (COPD), alcohol consumption, and a body mass index (BMI) problem.

Decisions regarding selection for treatment are made by the patient, a specialist nurse, a doctor, and a Drug & Alcohol (D&A) doctor as a panel, while selection criteria apply to the need for treatment according to the patient's views, severity of liver disease, absence of co-morbidity and the presence of non-liver symptoms; further selection criteria relate to compliance, likely response rates, and the ability to tolerate treatment.

The objectives of treatment include prevention of long-term sequelae, reversal of liver damage, elimination of virus, resolution of symptoms, and suppression of the source of infection. Combination therapy with pegylated interferon alpha and ribavirin is the current standard care for HCV patients and several clinical trials have studied the response to treatment in terms of the level of sustained viral response (SVR) achieved in this population, depending on viral genotype. Dose-reduction studies were also conducted in order to measure the possibility to reduce side effects of therapy. Studies with 'special cases' patients have shown that 95% of patients with acute hepatitis C (50% will progress to CHC) respond to treatment and that intervention within the first six months is therefore recommended, whereas 98% of liver transplant (LT) patients get re-infected, 10% have early graft loss, and these LT patients have a poor response to treatment.

Research into novel hepatitis C treatments includes evaluation of direct anti-viral therapy in the form of protease, polymerase, and helicase inhibitors, the replacement of ribavirin by viramidine, and therapeutic vaccination.

When measuring the outcomes of hepatitis C treatment in relation to its objectives, it appears that assessment and selection are essential, since only 30% of HCV-infected patients are treated, and that compliance with therapy is essential and requires the support of a full team, not only made of specialists and hepatologists. The outcomes of therapy remain nonetheless poor since only 50% of treated patients achieve SVR.

Follow-up of untreated patients with minimal fibrosis recommends a repeat biopsy every five years, while non-compliant patients should be managed at the level of lifestyle or psychological issues. Non-responders should also be monitored.

Current UK and European guidelines advocate no treatment for patients with histologically mild hepatitis C. In particular, the UK national policy is based on NICE guidelines, which concluded that for patients with *moderate* to *severe* chronic hepatitis C, either interferon or pegylated interferon combined with ribavirin is cost-effective and should be provided while the decision for patients with *mild* chronic hepatitis C is currently delayed due to lack of evidence. New guidance is expected by August 2006.

In this context, a NHS HTA study was conducted in order to evaluate the cost-effectiveness of antiviral therapy (either interferon or pegylated interferon combined with ribavirin) administered to hepatitis C patients at a mild stage compared to waiting and only treating those cases that progress to moderate disease [9]. A cost-effectiveness model was constructed to estimate long-term costs and outcomes for patients with mild chronic hepatitis C, using parameters including the effectiveness and cost data from the UK mild hepatitis C routine clinical trial (RCT), combined with estimates of disease progression and cost from observational studies. The model showed that for patients with genotype non-1, antiviral treatment at a mild rather than a moderate stage improved outcomes measured by QALYs gained. The mean cost per QALY gained for these patients was £4,535 with interferon alpha plus ribavirin and £7,821 with pegylated interferon alpha plus ribavirin, respectively, compared to treatment of these patients at a moderate stage. It is concluded from these modelled results that antiviral treatment with interferon / pegylated interferon combined with ribavirin is more cost-effective at a *mild* than at a *moderate* stage of hepatitis C disease. Treatment was not shown to be cost-effective for older patients (over 65) with HCV genotype 1. The validity of these findings should take into account the uncertainty of parameters, although they are considered as more conservative than previous estimates. Indeed, the disease was considered at an earlier stage, lower estimates of disease progression and lower SVRs based on pragmatic NHS RCT were considered, and empirical estimates of quality of life and cost were used.

In terms of control measures against HCV infection, this study highlights the need for further research into the establishment of priorities for patient subgroups to be eligible for treatment, not only taking efficiency but also equity into account. Also, more cost-effective administration of treatment should be investigated, such as shorter treatment regimens, nurse-led care, and fewer liver biopsies. Health-related quality of life and cost data are useful in order to assess the cost-effectiveness of prevention strategies, i.e., establishing a balanced investment in treatment versus prevention strategies. Finally, it is critical that investment and attention also be given to preventing the ongoing transmission of HCV among IDUs.

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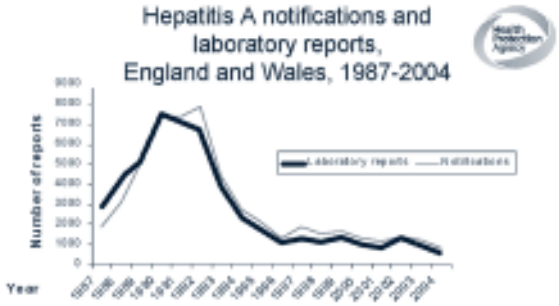
Based on presentations made by Dr John Dillon, University of Dundee, Ninewells Hospital and Medical School, Department of Digestive Diseases and Clinical Nutrition, Dundee, United Kingdom; Dr Richard Grieve, London School of Hygiene and Tropical Medicine (LSHTM), Department of Public Health & Policy, London, United Kingdom; Dr Matthew Hickman, University of Bristol, Department of Social Medicine, Glasgow, United Kingdom; Dr Ken Stein, Peninsula Medical School, Peninsula Technology Assessment Group (PenTAG), Devon, United Kingdom; and Dr Mark Thursz, Imperial College, Faculty of Medicine, London, United Kingdom.

Prevention and control of hepatitis A in the United Kingdom

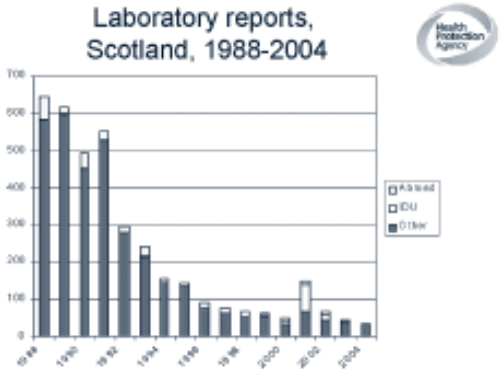
Hepatitis A: epidemiological and surveillance data

Epidemiological evidence and surveillance data used to determine incidence and prevalence of hepatitis A in the United Kingdom (UK) are based on statutory notifications, laboratory reports, mortality statistics, liver transplantation registries, reports to the Health Protection Agency (HPA) including incident database and bulletins, and modelling of surveillance data.

Viral hepatitis notifications in England and Wales fell from ca. 240,000 in 1969 to ca. 40,000 reports in 2001; initially notified as 'infectious hepatitis', we can now see that in the past 20 years, most of these cases were caused by hepatitis A virus (HAV). Hepatitis A reports and notifications from the past 20 years are generally correlated and are characterised by a steady decline, with less than 1,000 reports / notifications in 2004 after a peak observed in the early 1990s.



Laboratory reports fluctuate significantly across regions within England and Wales, with more than100 reports in Yorkshire & Humberside against less than 25 reports in Wales in 2004. Important differences between laboratory reports and notifications have been observed across regions in England and Wales between 2002 and 2004. On the other hand, laboratory reports from the past 15 years in Scotland have followed a declining pattern similar to that observed in England and Wales, with ca. 650 reports in 1988 against less than 50 reports in 2004.



Prevalence of HAV antibody has been shown to increase with age, with less than 10% reported in the one-to-nine years age group against more than 80% in the 70-plus years age group, as appears from an age-specific sero-epidemiological study conducted by Morris *et al.* in 1996 in England and Wales [1]. This reflects changing experience of infection in different cohorts (a cohort effect rather than an age effect); there is practically no community transmission of hepatitis A in the UK now. At least five liver transplantations had to be performed as a result of acute hepatitis A in the UK over the past 10 years and 63 hepatitis A-related deaths were reported during the past five years.

An evaluation of the hepatitis A surveillance system in England over 2004/2005 was performed, including a capture-recapture analysis of laboratory reported cases, cases identified through genotyping studies, and cases reported to two local Health Protection Units (HPUs), one in 2002 and the other in 2003, respectively. Sensitivity of laboratory reporting was found to vary greatly between the two units, from 28% to 78%. Further findings showed that the quality of laboratory surveillance is poor and deteriorating, mainly because less than 5% of the reports include information on travel history, injecting drug use, sexual or foodborne exposure, and ethnic group. Travel history information has fallen from 80% in 1990 to 3% in 2004. Also, information that is collected at local level is not integrated into national reporting. Poor reporting of hepatitis A outbreaks in the UK also came out of this 2004/2005 evaluation.

Several outbreaks were reported in men who have sex with men (MSM) in the mid to late 1990s, and in 2004 in London. The infection rate in this population in London in 1995 was estimated at 94/100,000. Several outbreaks in injecting drug users (IDUs) were reported in 2001-2002 in Scotland. A 2002 survey from the public health departments found that 20 outbreaks had occurred in England and Scotland since 1999 [2]. In 2004, three outbreaks were reported to the HPA incident database: one in a kebab shop, one in a primary school, and one among MSM.

In relation to the identification of groups at risk of HAV infection, laboratory reports from England and Wales have shown that the male:female ratio has ranged from over 1 to ca. 2.5 over the past 10 years, a trend confirmed by the distribution of laboratory reports by age and sex over the period 2001-2004. During that period, 15-44 year-old males were identified as a predominant at-risk group, with an average of more than 85 laboratory reports per year versus ca. 25 in individuals less than 15 years of age. This matches the age / sex distribution of IDUs, as well as being consistent with outbreaks in MSM. The mean HAV infection rate for children under 15 years in 2002 was 0.5/100,000, with a 0.1-1.5/100,000 range. The highest rates in children occur in the same areas reporting outbreaks and high rates in IDUs. Genotyping of HAV strains found in IDUs in the UK has also revealed interesting information regarding predominantly circulating strains in this population, with associated geographical patterns.

In terms of ethnic groups at risk, reports from the past 10 years have shown an average infection rate of 11.6/100,000 among South Asian populations, with peak rates of 28.5 and 23.5/100,000 among 5-9 and 10-14 year olds, respectively, while the average infection rate among other ethnic groups was 4.9/100,000. Also, 86% of HAV infections were acquired abroad among South Asians during that period, versus 28% of infections acquired abroad among other ethnic groups.

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Based on a presentation by Dr Natasha S. Crowcroft, Health Protection Agency, Centre for Infections Immunisation Department, London, United Kingdom.

Measures to prevent and control hepatitis A virus infection: from policy to reality - current practice in the United Kingdom

In the United Kingdom (UK), recommended measures to prevent hepatitis A virus (HAV) infection and to limit its spread rely on the reinforcement of concepts of good hygiene, the use of human normal immunoglobulin (HNIg), and risk-group vaccination. These recommendations form part of the UK public health policy, in accordance with guidelines issued by the departments of health in England, Wales, Scotland, and Northern Ireland, the Joint Committee on Vaccination and Immunisation [1], and Public Health Laboratory Service (PHLS) Guidelines [2].

The different settings defining the scope of these guidelines include contacts of cases: household and sexual contacts; outbreaks: institutional ('well-defined') and community-wide ('poorly defined'); and high-risk groups: occupational, injecting drug users (IDUs), homeless, men who have sex with men (MSM), clinical liver disease (CLD) patients, haemophiliacs, and travellers.

Hepatitis A vaccine is available since 1992 and is recommended in the UK for high-risk groups. It should be used in preference to HNIg for travellers, for outbreak control, and for protection of close contacts of cases provided that they can be vaccinated within one week of onset in the index case. HNIg is recommended for protection of close contacts of cases when the onset date in the index case is more than a week ago (and less than two weeks) and, as additional protection of vulnerable groups, together with the vaccine.

Additional guidance is provided for schools and nurseries regarding, for example, exclusion, which is only considered as justified for five days from onset of jaundice or stools going pale for less than five-year olds or where hygiene is poor. A guide for public health physicians and environmental health officers, *Preventing person to person spread following gastrointestinal infections*, recommends control of human source (statutorily notifiable as viral hepatitis), enteric precautions for cases, and supervised hygiene measures for contacts in schools and nurseries. This guidance recommends that all cases should be excluded for seven days after onset of jaundice and/or other symptoms, with no microbiological clearance required.

Several initiatives have also been taken towards hepatitis A vaccination of IDUs and several vaccination campaigns for prisoners have been successful, including the delivery of hepatitis A vaccine in combination with hepatitis B vaccination programmes.

Public health practice in the UK has also changed in regard to the use of hepatitis A vaccine versus HNIg for post-exposure prophylaxis. Post-exposure efficacy of 82% was reported for the vaccine but is only available from one study [3], while 47-95% efficacy rates were reported in various studies with HNIg. Pre-exposure vaccination efficacy was shown to be 95% in four studies [4-6].

Epidemiological data have shown that hepatitis A incidence is at historically low levels in the UK. However, surveillance data are incomplete and the utility of specific investigations, such as HAV genotyping, needs to be established. Identified highest-risk groups include IDUs, MSM, South Asians, and travellers. National UK prevention and control policies are based on hygiene, HNIg administration, and vaccination of risk groups, but local practice varies.

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Conclusions of the meeting

The Viral Hepatitis Prevention Board (VHPB) held its autumn meeting, November 17-18, 2005, in Edinburgh, United Kingdom (UK). The meeting comprised experts from the World Health Organization (WHO), the Centers for Disease Control and Prevention (CDC), as well as healthcare representatives, decision-makers, academics, and clinicians, with specialist expertise in the control of viral hepatitis.

The primary objective of the meeting was to review current practice relating to the control of viral hepatitis in the United Kingdom. In an introductory presentation, insight was provided on how England, Wales, Scotland, and Northern Ireland fit together in terms of health policy, healthcare, decision making, research, and funding. The meeting subsequently focussed on an update of the epidemiological situation of hepatitis A, hepatitis B, and hepatitis C in the United Kingdom, including information relating to virological and clinical aspects. An overview of national and regional prevention strategies was also presented while discussions focussed on testing, vaccination policies, disease management, as well as burden

of disease and health economics models. The meeting ended with lessons learnt from the UK experience.

Control of viral hepatitis in the UK: how England, Wales, Scotland, and Northern Ireland fit together

Prevention of viral hepatitis in the UK is articulated around a three-step decision-making process. The Health Protection Centres (HPC) in England, Wales, Scotland, and Northern Ireland collect epidemiological data that are used as a basis for the Advisory Group on Hepatitis (AGH) to provide advice to the ministers of health, while the Joint Committee on Vaccination and Immunisation (JCVI) eventually delivers advice on childhood vaccination programmes. In parallel to this process, delivery of care is based on guidelines from the National Health and Institute for Health and Clinical Excellence (NICE), recommending cost-effective therapies while treatment of patients with chronic hepatitis B (CHB) or chronic hepatitis C (CHC) should be managed within Managed Clinical Networks (MCNs).

In practice, hepatitis A and hepatitis B prevention in the UK is based on risk group vaccination, while many other European countries apply hepatitis B risk group vaccination in addition to universal hepatitis B vaccination programmes. In terms of prevention and treatment of chronic hepatitis, a national strategy and action plan are in place for CHC, including the establishment of MCNs, while such measures are not available but urgently needed for CHB. Improved prevention and delivery of treatment for CHC is also needed. Current epidemiological issues regarding rising mortality rates related to chronic liver disease (CLD) and missed prevention opportunities should be addressed, including alcohol consumption and obesity as complicating risk factors.

Hepatitis B: epidemiology and control

The UK is a low-incidence and low-prevalence country regarding hepatitis B. Acute hepatitis B cases predominantly occur in adults, mainly in identified but difficult-to-reach high-risk groups, while ethnic minority children may also be at risk. A substantial proportion of cases are also diagnosed in individuals with no known risk.

The role of universal hepatitis B vaccination appears to be limited in the UK because carriage rates are high in ethnic minorities, with a large proportion of carriers with infection acquired in childhood, prior to their immigration to the UK.

Current challenges for the improvement of hepatitis B control measures include the reinforcement of surveillance programmes, using reliable laboratory reporting and case notifications. Screening programmes also need to be enhanced and vaccination strategies implemented, favouring regional initiatives, such as those initiated in the Glasgow region. National immunisation programmes might also need to be reconsidered. In terms of secondary prevention, treatment strategies should be revised so as to reconcile theoretical paradigms with economic decisions.

Hepatitis C: epidemiology and control

The overall prevalence of hepatitis C virus (HCV) in the UK is low but the burden of infection is greatest among injecting drug users (IDUs), resulting in high incidence levels in this population comprising a large proportion of individuals who are unaware of their infection.

Current challenges for the control of HCV infection in the UK should mainly address the implementation of specific prevention measures among current IDUs, coupled with improved case-finding programmes among past IDUs.

Enhanced diagnosis of HCV-infected persons should contribute to the identification of individuals who most need therapy to prevent disease progression. Best treatment options should also be considered for mild- / moderate-stage patients as it might be more cost-effective to provide antiviral treatment at a mild rather than at a moderate stage.

Hepatitis A: epidemiology and control

Hepatitis A incidence is at historically low levels in the UK, with a majority of cases found in highest risk groups such as IDUs, men who have sex with men (MSM), South Asian immigrant populations, and travellers. Disease surveillance programmes are currently incomplete and need to be improved while the utility of hepatitis A virus (HAV) genotyping might need to be evaluated. National control policies are based on hygiene, administration of human normal immunoglobulin (HNIg), and hepatitis A vaccination, although local practice varies.

Concluding remarks and suggested areas for future research

The meeting was generally concluded with a statement agreed among all participants that the control of viral hepatitis in the UK might benefit from the lessons learnt in other countries of the European Union. There was also a general consensus that a more accurate appreciation of current UK needs and challenges in terms of prevention strategies should require a direct comparison with data obtained from other countries.

In terms of national health strategy against HCV infection, in addition to the need for improved control measures against hepatitis C, it was felt by the audience that more consideration should be given to the management of HCV-positive subjects who do not benefit from treatment after screening.

In terms of a national health strategy against hepatitis B virus (HBV) infection, it was recommended that, similarly to the current US recommendations [1], more emphasis should be put on preventive measures targeting specific groups, such as immigrant populations. It was also stated that specific groups should be targeted to benefit from hepatitis B treatment.

Results from modelled economic evaluations of selective and universal hepatitis B immunisation strategies should be interpreted with caution, taking balanced information into account. These should, for instance, include a price range for hepatitis B vaccine in sensitivity analyses as the procurement of vaccine through a call for tenders could considerably lower the cost of vaccination programmes and make these more economically attractive for implementation in the UK.

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***Viral Hepatitis* editorial procedure**

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