Screening for Hepatitis B and Hepatitis C among ethnic minorities born outside the UK

A report
for the National Screening Committee

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Contents

Introduction

1. This paper reviews screening for hepatitis B virus (HBV) and hepatitis C virus (HCV) amongst people who were born in countries with high or intermediate prevalence of HBV infection (as defined by the World Health Organisation (WHO)) against the UK National Screening Committee Criteria for appraising the viability, effectiveness and appropriateness of a screening programme (National Screening Committee 2003). This paper makes frequent references to a recent report from the Department of Health's Advisory Group on Hepatitis (AGH 2009) which recommended that:

   Primary Care Trusts (or equivalent bodies) should arrange case finding for chronic HBV and chronic HCV infected individuals from minority ethnic populations in their area who were born in countries with a high or intermediate prevalence of HBV infection (as defined by the World Health Organisation (WHO)) and ensure that there are care pathways in place for those who are found to be infected.

   Primary Care Trusts (or equivalent bodies) should arrange tracing and testing of all contacts of minority ethnic individuals testing positive for chronic hepatitis B or C infection. Such contact tracing should include family members (spouse, partners, grand-parents, parents, siblings, and children) and all individuals living in the same household. Contacts who are negative for evidence of HBV infection or immunity should be offered HBV vaccine.

2. The WHO classifies member states into high, intermediate, and low prevalence states with regard to chronic HBV infection (World Health Organization 2000):

   - high (≥ 8%) e.g. sub-Saharan Africa, and many countries in South America, Central and South eastern Asia, and the Pacific Islands
   - intermediate (2-7%) e.g. countries around the Amazon, southern parts of Eastern and Central Europe, the Middle East and the Indian sub-continent.
   - low (< 2%) e.g. most of Western Europe and North America.

3. According to 2001 UK Census data there were approximately 3 million UK residents who were born in countries with high or intermediate HBV prevalence (AGH 2009, sections 3.37 – 3.39) and who therefore represent the target group being considered for screening in this appraisal.

4. The AGH report proposes three possible options for 'active case-finding' of HBV and HCV infections in high-risk individuals (AGH 2009, sections 7.4 – 7.6):

   - 'Systematic case finding in high risk populations' (in which health services identify high risk individuals and invite them to be tested)
   - 'Opportunistic case-finding' (in which testing is offered to high risk individuals only when they happen to make contact with health services for some other reason)
   - 'Voluntary testing sessions' (in which, for example, testing sessions are offered at places of worship or other culturally relevant venues).

   This appraisal takes the view that only the first of these options is 'screening', though much of the material in this appraisal is relevant to all three.

5. It is UK NSC policy to offer screening for HBV, but not HCV, to all antenatal women (a group which, of course, includes some women who were born in high or intermediate HBV prevalence countries).

6. On 1st February 2010 the DH began an awareness campaign to improve detection, diagnosis and treatment of HCV (www.nhs.uk/hepc/southasian). For the first time, a group defined on the basis of place of origin (south Asia) was added to a 2008 list of groups for whom an HCV test should be offered those considered to be at risk of HCV (Chief Medical Officer and Chief Nursing Officer for England 2008).

7. This paper is based on a literature search conducted by the National Screening Committee, supplemented by material from the recent report from the Department of Health's Advisory Group on Hepatitis (AGH 2009) and personal communication with members of the AGH.

The Condition

The condition should be an important health problem

8. Chronic infection with either HBV or HCV can cause serious liver disease (cirrhosis and / or hepatocellular carcinoma (HCC)) decades after infection. Morbidity and mortality due to chronic hepatitis, cirrhosis and HCC are more common among ethnic minority than among white groups in the UK, as would be expected given the higher prevalence of infection with HBV and HCV among these groups (AGH 2009, sections 4.18 – 4.24).

9. HCV, but not HBV, also commonly reduces health-related quality of life (HRQoL) in the absence of advanced liver disease. Mild or moderate HCV disease is associated with reductions of 5–10% in various measures of health (Chong CA et al 2003). Fatigue, depression and neurocognitive deficits are among the most common complaints (Foster 2009). However, among individuals who are infected with HBV, but have not developed liver disease, HRQoL is comparable to that of normal controls (Ong et al 2008).

10. The scale of these problems is a function of the prevalence of the infections and the rate at which they progress to serious liver disease in the absence of treatment. These are discussed further below. Reasonable, but extremely approximate, estimates are that, among the target group of 3 million UK residents who were born in countries with high or intermediate prevalence of HBV infection, there may be:

    - 120,000 individuals with chronic HBV, of whom 20,000 may develop cirrhosis in the next 20 years if not treated.
    - 30,000 individuals with chronic HCV, of whom 5,000 may develop cirrhosis in the next 20 years if not treated.

    Screening could, in principle, be offered to this target group as a one-off catch-up exercise.

11. Each year an additional number of people who were born in countries with high or intermediate prevalence of HBV infection will migrate to the UK; the number will depend on UK immigration policy at the time. If this number were in the region of 300,000 individuals, approximately 10,000 (3.3%) might have chronic HBV infection (AGH 2009, para 3.26 and Table 2). Since there will be a continuing flow of new migrants, any hepatitis screening programme for this group would need to be offered on a continuing basis rather than as a one-off catch-up exercise.

12. Among approximately 650,000 antenatal women who are tested each year, the UK antenatal screening programme identifies chronic HBV infection in approximately 3,000 (personal communication from John Marshall at NSC). Most of these women are likely to have been born in countries with high or intermediate prevalence of HBV infection. They represent only a small proportion of the estimated 120,000 individuals with chronic HBV who were born in such countries and now live in the UK.

    <u>Prevalence of HBV among foreign-born black and minority ethnic (BME) groups already living in the UK</u>

13. The estimated prevalence of chronic HBV infection among the general population in the UK is 0.3%, equivalent to 180,000 people living with the infection (Department of Health 2002). Among the 3 million BME individuals currently being considered for

screening, the number with chronic HBV infection is not known with any degree of certainty. The AGH report suggests that it may be approximately 120,000, equivalent to a prevalence of 4% (AGH 2009, para 3.39). This figure is obtained by assuming a prevalence of 8% in all WHO high-prevalence countries (though most have prevalence > 8%) and a prevalence of 2% in all WHO intermediate-prevalence countries (though most have prevalence > 2%), then assuming that migrant communities living in the UK have the same prevalence as in their country of origin.

14. A recent large UK multi-centre study (Uddin et al 2010) illustrates the difficulties involved in trying to estimate HBV prevalence by this method. In this study the prevalence of HBsAg among south Asians born in India, Bangladesh and Pakistan was 0.1%, 1.5% and 1.8% respectively, but these figures show no consistent relationship with the WHO prevalence figures for India and Pakistan (4% and 3%, respectively). WHO gives no figure for Bangladesh, but Mahtab et al (2008) report prevalence of 5.5% in a Bangladeshi general population.

15. Appendix 1 presents data from all the studies identified in the course of this appraisal which reported the prevalence of HBsAg among various populations who have migrated to different European countries, and compares it to the WHO figure for prevalence in the country of origin. The reported prevalence among migrants is sometimes higher, but more often lower, than in their country of origin. Across these diverse studies the unweighted mean of HBsAg prevalence among migrants, relative to that in their country of origin, is 0.76. This ratio can be no more than a crude estimate, but there is no better alternative currently available.

16. Appendix 2 presents data on the number of UK residents born in each high and intermediate HBsAg prevalence country, and the WHO prevalence figure for each country. Multiplying these numbers for each country and summing the results yields a total of approximately 172,000 individuals. Multiplying this by 0.76 (to correct for the likelihood that prevalence is lower among migrants than among those who remain in their original country) yields a crude estimate that there may be approximately 130,000 individuals with chronic HBV infection among the ethnic minority groups being considered for screening. This is slightly higher than the AGH estimate of 120,000. Given the inevitable crude assumptions involved, the true figure could be substantially higher or lower than these estimates.

<u>Prevalence of HCV among foreign-born BME groups already living in the UK</u>

17. The prevalence of HCV among the general population of adults in England and Wales (before excluding the 25% of individuals who have antibodies to HCV but have spontaneously cleared the virus) is estimated to be 0.59%, equivalent to 191,000 people with antibodies to HCV (95% credibility interval 124,000 - 311,000 individuals) (De Angelis et al 2009). The prevalence of chronic HCV infection appears to be somewhat higher in Scotland (0.9%) (AGH 2009, para 3.29).

18. If data on HCV prevalence in countries of origin are used to estimate prevalence among the 3 million BME individuals being considered for screening in the UK, the estimated figure is approximately 1.5%, or 45,000 people (Appendix 3). However the WHO data for HCV infection are much less reliable than those for HBV. In many countries, the relevant data are simply not available, and WHO published data conflates general population studies with those in highly selected (and

unrepresentative) population sub-groups such as blood donors. Whilst some high prevalence countries can be unequivocally identified (e.g. Egypt, Pakistan), there are many countries where conclusions cannot be drawn with certainty (AGH 2009, para 6.6).

19. A different approach involves calculating the proportion of hospital episodes in England due to HCV-related end-stage liver disease or HCC that occurred among ethnic minority groups, then applying this proportion to the estimated total number adults in England and Wales with antibodies to HCV (191,000 individuals). Mann et al (2008) reported this proportion as 11.5%, which yields a estimate of approximately 22,000 ethnic minority individuals with antibodies to HCV (equivalent to 0.8% of the 2.7 million BME individuals being considered for screening in England and Wales). There are several difficulties with this method. It might be an underestimate, because ethnic group was unknown for more than a quarter of the hospital episodes due to HCV-related liver disease. It may also be an overestimate, for several reasons: some of the 11.5% would have been born within the UK, and hence not part of the target group currently proposed for screening; and ethnic minority individuals with antibodies to HCV might be over-represented among those admitted to hospital, as a result of longer duration of infection or higher prevalence of co-morbidities.

20. Based on the methods described above, reasonable prevalence estimates for the non-UK born ethnic minority populations being considered for screening are approximately 4% for HBV and 1% for HCV. There is a considerable margin of uncertainty around both these estimates.

Chronic HBV and HCV among new migrants to the UK

21. Based on data from the ONS International Passenger Survey and WHO country-specific HBsAg prevalence estimates, it was estimated that approximately 300,000 individuals (not all of them from countries with high / intermediate HBV prevalence) migrated to England and Wales each year during the period 1996-2000. Approximately 10,000 (3.3%) may have had chronic HBV infection (AGH 2009, para 3.26 and Table 2; Hahné et al 2004).

22. If systematic screening were to be implemented, it would presumably be offered to all individuals migrating to the UK from high or intermediate HBV prevalence countries. During the period 2004-2007, an annual average of 289,000 individuals who were born in a country outside the UK, the European Union or the Old Commonwealth migrated to the UK (Office for National Statistics 2009). This group of countries approximates to the list of countries with high / intermediate HBV prevalence.

23. Depending on migration policy at the time, the annual number of new immigrants who should be offered screening could be a significant percentage of the three million eligible individuals already living in the UK. From a global humanitarian perspective, it is irrelevant whether the health gains and cost-savings arising from screening and treating migrants occur in the UK or in other countries (if those migrants leave the UK within a few years of being screened). However, from an NHS health-economic perspective it does make a difference, since the NHS would need to meet the costs of screening and treatment, but might not realize the cost-savings from avoiding the long-term complications of chronic HBV or HCV. Different assumptions about migrants' length of residence of within the UK could have a substantial impact on the estimated cost-effectiveness of the screening programme.

The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately

understood and there should be a detectable risk factor, disease marker, latent period or early symptomatic stage

24. The epidemiology of HBV and HCV varies in different regions of the world. Among the general population born in the UK, HBV is mainly acquired in adulthood through injecting drug use and sexual transmission and HCV is acquired mainly through injecting drug use (AGH 2009, para 3.6).

25. In the developing world, chronic HBV is most often transmitted from infected mothers to their offspring, or by early childhood exposure to infected children. The main routes of transmission for HCV in the developing world are not clear but injection with unsterilized needles is probably a major cause (Uddin et al 2010, AGH 2009 para 3.3).

26. The rate at which infection progresses to liver cirrhosis among ethnic minorities appears to be broadly similar for HBV and HCV. Among those with chronic HCV, HCC occurs almost exclusively in patients who have progressed to cirrhosis, but HCC is sometimes found in with HBV patients without significant cirrhosis (But et al 2008).

Natural history of HBV

27. The risk of developing chronic HBV is inversely related to the age at which infection is acquired. Chronic infection occurs in 90% of those infected by mother-to-baby transmission, 20-50% of children infected between one and five years of age, and 6-10% of previously healthy people infected as adults (AGH 2009, para 3.9). Most individuals with chronic HBV infection are asymptomatic and unaware of their infection until the development of complications, such as cirrhosis or HCC (AGH 2009, para 2.7).

28. The natural history of chronic HBV infection is complex and the rates of progression to life threatening end-stage liver disease are highly variable (AGH 2009, sections 4.2-4.4). A widely quoted statistic is that, without therapy, between 20-30% of patients with chronic HBV infection will die of complications such as cirrhosis or HCC (AGH 2009, para 2.7). It is clear that HBV is responsible for a lot of cirrhosis and HCC. For example, Perz et al (2006) used odds ratios derived from case-control studies to estimate that, globally, 30% of cirrhosis and 53% of HCC can be attributed to infection with HBV. However, none of the sources reviewed in the course of this appraisal described an evidence-base for the statistic that 20-30% of patients with chronic HBV infection will die as a result of complications such as cirrhosis or HCC.

29. Fattovich et al (2008) performed a systematic review of cohort studies of patients with untreated HBV infection, to provide overall estimates of the incidence of serious liver disease over periods of 10-20 years. All the estimates relate to a period that begins with recruitment into a cohort study, rather than a period that begins with infection, so they should describe the natural history of infection from the point of detection by screening.

30. Studies were available from only two broad geographical areas, one including North America and West and South Europe, the other including several East Asian countries (Taiwan, China, Singapore, Korea and Japan). Among asymptomatic

carriers (which are the group that best represents those who would be diagnosed through screening) the incidence of various liver-related outcomes is about ten times greater in East Asian than in European or North American populations (Table 1). The longest mean period of follow-up for any cohort study of a non-European population is only 13.5 years (Xu et al 2003).

31. The greater risk of cirrhosis among East Asians may reflect earlier acquisition of the virus and hence longer duration of infection. Since the foreign-born UK ethnic minorities being considered in this appraisal are also likely to have been infected early in life, the rates for East Asians are more relevant than those for Europeans and North Americans. If one assumes that the rates of progression documented in East Asian cohorts up to nine years remain constant up to 20 years after diagnosis, 18% of those with chronic HBV infection would develop cirrhosis, 10% would develop HCC, and 16% would die from liver-related diseases within this period.

32. Systematic reviews have also found that the risk of HCC and death among people with HBV is associated with male sex, cirrhosis, family history of HCC, higher HBV viral level, certain viral characteristics, and heavy alcohol and tobacco use (Taylor et al 2009, McMahon 2009).

Table1: incidence of serious liver disease in chronic HBV

Outcome	Incidence (per 100 person years)	Mean duration of follow-up (years)
Cirrhosis		
Europe, North America	-	-
East Asia	0.9	9.1
Hepatocellular carcinoma		
Europe, North America	0.04	19
East Asia	0.5	9
Liver-related death		
Europe, North America	0.09	19.7
East Asia	0.8	8.7

Natural history of HCV

33. Acute HCV infection is asymptomatic in most patients. About a quarter of those infected clear the virus spontaneously, and rates of spontaneous clearance are higher among those who develop jaundice (Micallef et al 2006, Maheshwari et al 2008).

34. The rate of progression from HCV infection to serious liver disease among those who fail to clear the virus spontaneously has been studied among various groups infected up to 30 years previously. A relatively recent systematic review (Thein et al 2008) identified 111 studies from which the natural history of HCV infection could be inferred. Prospective cohort studies would offer the most reliable information, but none could be included in the review. The estimated incidence of cirrhosis following infection with HCV depended on the design of the study and the type of population studied. The incidence in retrospective-prospective studies (in which HCV-infected individuals were identified following an outbreak from a recognized source or through being screened as blood donors) was about half that in cross-sectional / retrospective studies (which comprise patients with liver disease presenting for clinical care, usually at tertiary care centres, where efforts were made to track the

liver disease responsible for the referral back to the presumed time of infection). The incidence in non-clinical populations (defined as individuals who were screened for HCV in a non-clinical setting, for example, a blood donation centre or regional centre) was about half that in clinical populations (defined as individuals who were identified and/or assessed for their HCV status and liver disease in a clinical/tertiary care setting).

35. Based on these definitions, retrospective-prospective studies of non-clinical populations would give the best indication of the natural history of HCV infection in apparently healthy individuals diagnosed through screening. Unfortunately, the review does not give a summary estimate of the incidence of cirrhosis in this subset of studies. However, in a group of 14 studies labelled as 'community' studies (defined as including 'HCV-infected individuals identified or participating in national health screening or studies conducted in nonclinical settings'), the summary estimate was that about 20% might develop cirrhosis after 20 years, rising to nearer 40% after 30 years. However, 9 of these 14 studies used a cross-sectional / retrospective design (which tends to produce estimates about double those found in retrospective-prospective studies). The incidence of cirrhosis is clearly presented in three of five studies that used a retrospective-prospective design, and is much lower: 5% after 15 years (Alter et al 1997); 2% after 17 years (Kenny-Walsh et al 1999); and 0.5% after 25 years (Wiese et al 2005). These figures may not be relevant to a mixed-gender population because the latter two studies involved all-female cohorts, and progression to cirrhosis may be slower in women.

36. Given these difficulties in interpreting the available evidence, an arguable position is to assume that the incidence of cirrhosis in a prospective community cohort might be about half that estimated by Thein et al (2008) for a community cohort using mainly cross-sectional / retrospective studies. That would imply that about 10% of a prospectively followed community cohort might develop cirrhosis within 20 years of infection, rising to about 20% after 30 years. This estimate is similar to the AGH estimate that 15-25% of individuals will develop cirrhosis after 30 years (AGH 2009, para 4.6).

37. All the estimates of progression to cirrhosis in the review by Thein et al (2008) are for a period that begins with infection with HCV, rather than recruitment into a research study. The opposite is true for the estimates provided by Fattovich et al (2008) for the incidence of cirrhosis in chronic HBV.

38. Amongst individuals with chronic CHV, the rate of progression to cirrhosis does not appear to be substantially greater among non-western than among western populations. However, since BME individuals are likely to have been infected in childhood it is important to know how disease progresses in the longer term.

39. The systematic review by Thein et al (2008) suggests that disease progression may accelerate between 20 and 30 years after infection. Information about progression beyond this time horizon is inevitably sparse. A large retrospective-prospective cohort study of Austrian plasma donors infected with HCV at plasma donation in the 1970s found that a third of patients had developed advanced fibrosis or HCC after 31 years (Ferenci et al 2007). However, this study is susceptible to substantial selection bias. The cohort was assembled in the year 2000 by running a media campaign to encourage infected donors to apply to a Foundation for support. Of an estimated

1,000 to 2,000 who may have been infected in the 1970s, only 485 were included in the cohort. It is therefore possible that individuals who had mild or virtually absent liver disease were not included, so that the frequency of progressive liver disease was overestimated. Conversely, some plasma donors may have died before the Foundation was established in 2000, in which case the number of deaths could be underestimated.

40. A small retrospective cohort study of men recruited into the US military between 1948 and 1954 provides the longest period of follow-up to date: during the 45-year follow-up, liver disease occurred in only 2 (12%) of the 17 HCV-positive persons (Seeff et al 2000). However, a retrospective study of HCV-infected patients who attended local hospitals in northeast London between 1992 and 2003 found a much higher prevalence of cirrhosis in Asian patients aged 61-80 years (78%) than among Caucasian patients of similar age (25%) (D' Souza et al 2005). In that study the prevalence of cirrhosis in Asian patients who had been infected for 20-40 years (15%) was in the range one would expect for an unselected population of individuals infected with HCV (based on the above discussion of the estimates produced by Thein et al 2008). This suggests that the high prevalence of cirrhosis in elderly Asian patients is more likely to reflect the long interval of six or seven decades since infection in childhood, rather than selective referral to hospital of patients with advanced disease. It raises the possibility that the majority of individuals infected early in life may eventually develop cirrhosis in old age. This possibility is supported by indirect evidence which shows that the ratio of HCC-related mortality to the prevalence of HCV is considerably higher in countries that appear, on the basis of diversity in the HCV genotype, to have older epidemics of HCV, and therefore a higher proportion of individuals who have been infected for many decades (Tanaka et al 2006).

41. Given the available evidence, an arguable estimate is that about 10% of an unselected cohort of people infected with HCV will develop cirrhosis within 20 years of infection, accelerating to 15-25% after 30 years. It is possible that the majority may develop cirrhosis after several decades, but the longer the time horizon involved, the greater the uncertainty of any possible estimates.

42. If one assumes that:

- after the first 20 years following infection with HCV, an additional 10% develop cirrhosis with each decade that passes and
- most HCV-positive BME individuals were infected at least 20 years prior to the implementation of a screening programme

Then, without therapy, 20% of screen-detected HCV-positive BME individuals would be expected to develop cirrhosis within 20 years of screening.

43. Once cirrhosis has developed, the annual risk of developing HCC is in the range of 1-4% (El-Serag 2002). A meta-analysis from Graham Foster's group shows a higher figure (personal communication from Graham Foster, reference awaited).

All the cost-effective primary prevention interventions should have been implemented as far as practicable

44. Among those individuals who are infected with HBV or HCV and who were born in countries with high or intermediate HBV prevalence, the vast majority will have acquired their infection while living outside the UK. An effective vaccine for HBV is available and many high and intermediate prevalence countries have introduced

universal childhood vaccination programmes since the World Health Assembly passed a resolution to recommend global vaccination against HBV in 1992. However, most of the target groups for the proposed screening programme were born before such programmes were established, and therefore missed the opportunity for primary prevention. There is no vaccine against HCV.

45. There is potential for primary prevention of the small number of infections that occur among sexual and household contacts of cases, through vaccination (against HBV) and education, but this depends on first identifying cases through case-finding or screening.

46. The number of cases of HBV that would be prevented as a result of contact-tracing and vaccination is very low (personal communication from Mary Ramsay). This may depend upon the group studied. In HBeAg positive teenagers, for example, the numbers may be very different (personal communication from Graham Foster and Will Irving).

If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

47. Not relevant to screening for HBV or HCV.

The Test

There should be a simple, safe, precise and validated screening test and

The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

48. A blood sample is tested initially for HBV surface antigen (HBsAg) and for antibodies to HCV (anti-HCV). Generic testing algorithms for HBV and HCV have been published by the AGH (AGH 2009, Appendix 3).

49. Testing for HBsAg is the gold standard diagnostic assay for HBV infection against which all other assays are compared. Positivity for HBsAg is the defining characteristic of HBV infection and a positive HBsAg result should not be issued unless the result has been confirmed, hence the test should be 100% specific. Assays using polyclonal antibody tests are recommended since they have slightly higher sensitivity than those using monoclonal antibodies (Will Irving, personal communication).

50. All anti-HCV positive results have to be confirmed by testing for HCV RNA before the result is issued to the clinician, hence the test should be 100% specific. Comparing anti-HCV detection with HCV RNA detection, one will find some patients who are RNA-positive but anti-HCV negative, so anti-HCV testing is not 100% sensitive. These are either patients who have recently acquired infection and have not yet had time to make antibody, or were immunosuppressed at the time of infection (Will Irving, personal communication).

The test should be acceptable to the population

51. There is no reason to think that a blood test would be unacceptable to the target population. However, uptake of HBV screening among ethnic minority groups was always less than 30% in the small number of screening initiatives identified in the course of this appraisal (see paras 79-81 below).

There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals

52. The British Viral Hepatitis Group has developed national testing and referral guidelines for people who are found to be HBsAg-positive (British Viral Hepatitis Group 2008). The AGH report includes a recommended care pathway (AGH 2009, Appendix 4).

53. A Department of Health guide for primary care advises that those who test positive for HCV antibodies should be tested for viraemia by a genome amplification assay such as the polymerase chain reaction (PCR) assay. Patients whose PCR test is negative should undergo repeat testing to exclude recent infection or a false negative result and then be reassured. All patients who are viraemic should be considered for treatment (Department of Health 2010).

If the test is for mutations the criteria used to select the subset of mutations to be covered by screening, if all possible mutations are not being tested, should be clearly set out.

54. Not relevant to screening for HBV or HCV.

The Treatment

There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment and

There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered

HBV

55. The main benefits that might follow detection of HBV are:

- antiviral therapy for prevention of cirrhosis and HCC
- protection of the liver, by avoiding excessive alcohol use
- identification of close contacts who require testing and subsequent vaccination (if identified as susceptible) or medical management (if identified as having chronic HBV infection)

Antiviral therapy for prevention of cirrhosis and HCC

56. The need for therapy for chronic HBV infection is determined by the phase of the disease, as reflected in HBeAg status (positive or negative), HBV DNA levels, liver function tests and the findings of liver biopsy or ultrasound. In inactive periods, when viral replication is not inducing liver damage, treatment is not indicated (AGH 2009, para 4.27).

57. Approximately 20% of people who are screen-positive for HBV will be candidates for antiviral therapy initially, and approximately another 30% are likely to become candidates for antiviral therapy over the next 20 years (Graham Foster, personal communication of East London HBV algorithm). Most HBV patients who are candidates for antiviral therapy will need to be treated for an indefinite period (Dienstag 2009).

58. Regarding the effectiveness of treatment, a recent systematic review found 16 RCTs of antiviral therapy for chronic HBV that reported clinical outcomes. None of them individually were of sufficient size or duration to draw any reliable conclusions about those outcomes. The data could not be pooled because the individual studies reported very few events, and compared different drugs and patients (Shamliyan et al 2009).

59. The likely effect of antiviral therapy on clinical outcomes therefore has to be inferred from its effect on biomarkers. Unlike HCV, clearance of HBV infection is rarely, if ever, achievable (Feld et al 2009), so there is no direct equivalent of the sustained viral response (SVR) that is used to assess the effectiveness of treatment for chronic HCV infection. However, HBV replication, as measured by serum HBV DNA levels, is strongly associated with clinical outcomes (Table 2) (Iloeje et al 2007).

Table 2: HBV DNA level and incidence of liver-related death

Baseline HBV DNA level (copies/mL)	Death from chronic liver disease or cirrhosis (per 1,000 patient years)	Death from HCC (per 1,000 patient years)
<300	0.09	0.73
300 - 9.9 x 10^3	0.48	0.48
1.0 x 10^4 - 9.9 x 10^4	0.75	1.74
1.0 x 10^5 - 9.9 x 10^5	1.43	6.92
> 1.0 x 10^6	2.67	8.16

60. Suppression of viral replication, as measured by serum HBV DNA levels, has become the major goal of therapy, particularly if maintained off therapy. The significance of viral levels depends on the stage of disease, degree of liver damage, and the type of therapy (Feld et al 2009).

61. Two different treatment strategies are currently applicable in both HBeAg-positive and HBeAg-negative CHB patients: treatment of finite duration with pegylated interferon alpha or nucleoside/ nucleotide analogues (NUCs), and treatment of indefinite duration with NUCs (European Association for the Study of the Liver (EASL) 2009). However, a recent BMJ review states that pegylated interferon is not often used in clinical practice because of its unpleasant side-effects (Cooke et al 2010).

62. A recent European guideline recommends that the most potent drugs with the optimal resistance profile (e.g. tenofovir or entecavir, both of which are NUCs) should be used as first-line mono-therapies (EASL 2009). Both these drugs have been approved by NICE (NICE 2008, NICE 2009); a decision whether to update these guidance documents is planned for March 2012, pending publication of the results of ongoing trials. Both tenofovir or entecavir are highly effective in suppressing HBV for one to three years after commencing therapy (Table 3) (Lai and Yuen 2008), but their long-term effects, safety and tolerability (i.e. after five to ten years) are still unknown (EASL 2009). At least 80% of patients treated with NUCs are likely to require treatment indefinitely (Dienstag 2009).

Table 3: Percentage of patients with undetectable HBV DNA by PCR after 1-3 years of continuous treatment (Lai and Yuen 2008)

	Entecavir	Tenofovir
HBeAg-positive patients		
1yr	67	76
2yrs	80	NA
3yrs	82	NA
HBeAg-negative patients		
1yr	90	93
2yrs	94	NA
3yrs	NA	NA

Antiviral therapy for HBV is much more effective prior to development of cirrhosis. Once cirrhosis has developed the risk of HCC is believed to remain (personal communication from Graham Foster).

Reduction in alcohol consumption

63. Heavy alcohol use is associated with faster progression of HBV-related liver disease (Taylor et al 2009). The literature search for this review did not look for studies that assessed whether knowledge of HBV or HCV status leads to a reduction in alcohol consumption among BME groups. If evidence on this issue turns out to be critical to the policy decision on screening, a separate search should be carried out.

Identification of close contacts who require testing and vaccination or medical management

64. In the UK, where the prevalence of HBV is very low and the incidence of acute hepatitis B is relatively low and stable, current policy is to immunise only those at high risk of infection – chiefly contacts of those who are infected, travellers to countries of high endemicity and those whose occupation (e.g. healthcare workers) or life style (men who sex with men or injecting drug users) is likely to increase their risk of infection (AGH 2009, para 4.25)

65. Following identification of an infected individual, the current UK recommendations are that sexual partners and close household contacts of an individual infected with HBV should be vaccinated. Sexual and other household contacts of those with chronic hepatitis B are at risk of infection and should be screened and offered vaccination (and Hepatitis B Immunoglobulin if appropriate) (AGH 2009, para 5.3–5.4).

66. Studies in the UK and other countries show that vaccination of contacts of those with chronic hepatitis B may be far from complete. A small-scale study in Wales found that only 27% of 91 household contacts of chronic HBV sufferers (most from ethnic minorities) had been vaccinated (Richardson et al 2001). Among babies born to mothers with HBV, only 75% of receive the recommended three doses of hepatitis B vaccine by 12 months of age (minutes from the 14 October 2009 meeting of the Joint Committee on Vaccination and Immunization (JCVI)). DH has initiated a project to investigate how information systems can be improved so that children that should be immunised against hepatitis B are vaccinated (action point from the 14 October 2009 meeting of the JCVI).

HCV

67. The benefits that might follow detection of HCV are:

- antiviral therapy, to improve quality of life and prevent cirrhosis and HCC
- protection of the liver, by avoiding excessive alcohol use
- education to reduce onward transmission of infection

68. Drug therapy for chronic HCV infection involves therapy with a combination of pegylated interferon and ribavirin for 48 weeks in patients with genotype 1 infection, and 24 weeks for patients with genotype 2 or 3. This treatment has been the subject of technology appraisals by NICE and is recommended for all chronically infected patients (AGH 2009, para 4.28). NICE Technology Appraisal Guidance 106 (NICE 2006) recommends that the decision on whether a person with mild chronic hepatitis C should be treated immediately or should wait until the disease has reached a moderate stage ('watchful waiting') should be made by the person after fully informed consultation with the responsible clinician. The likelihood that an individual patient will accept the offer of immediate treatment will depend on a number of factors such as genotype, viral load (which both impact on potential duration of therapy), state of liver disease, social circumstances etc. In addition, some patients with traditionally difficult-to-treat infection may prefer to wait for the imminent arrival of new specifically

targeted drugs rather than struggle with pegylated interferon and ribavirin alone (Will Irving, personal communication).

Antiviral therapy for improved HRQoL

69. Spiegel et al (2005) and Thein et al (2005) both provide systematic reviews of the impact of HCV in HRQoL. The review by Thein et al (2005) has the advantage that it translates the HRQoL data into utilities that can be applied directly in cost-effectiveness analyses. On a utility scale where 1.0 is represents perfect health and zero represents death, they estimated mean utilities of 0.82 for untreated chronic hepatitis, rising to 0.87 following a sustained virological response (SVR) to interferon-based treatment. Spiegel et al (2005) point out that most of the available studies included patients from tertiary care referral centres, and the resulting data may not be generalizable to community-based cohorts with HCV.

70. Some of these changes in HRQoL probably reflect the effects of receiving unfavourable or favourable test results, and not merely the effects of infection and treatment. Receiving a diagnosis of HCV, for example as a result of screening, reduces HRQoL by itself (Rodger et al 1999, Dalgard et al 2004, Zacks et al 2006). This could indicate either a negative impact from receiving the diagnosis, or a greater likelihood of being diagnosed among those with worse symptoms. The latter interpretation is possible in the Dalgard study, but was considered unlikely by Rodgers et al, because none of those who knew their HCV status had been tested because they were symptomatic.

71. Likewise, at least some of the improvement in HRQoL following a SVR may simply be the result of knowing the virus has been cleared, rather than a direct effect of treatment on the virus. One study (Bonkovsky and Woolley 1999) attempted to clarify this by asking patients to take the post-treatment HRQoL assessment before they learned whether they had achieved an SVR. Significant improvements in HRQoL were observed in SVR patients compared with non-responders. However, patients may have been aware of their liver test results, and these results were correlated with SVR status, so it is possible that the patients' reactions to their improved liver test results may have influenced the HRQoL results.

72. The importance of the above discussion is that conclusions regarding the cause of changes in HRQoL associated with diagnosis and treatment of HCV have a substantial impact on the benefit-harm ratio, and hence cost-effectiveness, of the proposed screening programme. If the changes in HRQoL are mainly the result of infection and treatment, the case for screening is strengthened: most people with undiagnosed chronic HCV would expect an improvement in HRQoL beginning shortly after screening and treatment and persisting for many years, thereby having a very substantial impact on the cost-effectiveness of screening for HCV (see, for example, Castelnuovo E et al 2006). Conversely, if the changes in HRQoL following diagnosis and treatment result mainly from receiving unfavourable or favourable test results, the case for screening is correspondingly weakened.

73. Two lines of evidence suggest that the changes in HRQoL associated with diagnosis and antiviral therapy reflect mainly the effects of infection and successful treatment, rather than the effects receiving unfavourable or favourable test results. First, replicating HCV virus has been found in central nervous tissues, and changes in

neurotransmitter levels in the frontal white matter of patients with chronic HCV are correlated with impaired attention and concentration. Second, although chronic HBV infection has a similar prognosis to chronic HCV infection, diagnosis and treatment of HBV are not associated with the changes in HRQoL that are observed with HCV (as would be expected if the changes were mainly the result of receiving unfavourable or favourable test results).

Antiviral therapy for prevention of cirrhosis and HCC

74. The literature search for this appraisal did not identify RCTs that provide long-term clinical outcome data for the currently recommended treatment combination of pegylated interferon and ribavirin. The long-term success of antiviral treatment is generally inferred from the more tangible goal of suppression of the virus (sustained viral response, or SVR). The logical sequence whereby the long-term impact of antiviral treatment is generally inferred from SVR rates is as follows:

- Non-randomized cohort studies (e.g. Yoshida et al 2002) have found that all-cause mortality is raised among HCV patients who are untreated, but not among those who are treated (even when the apparent impact of treatment is diluted by including patients who did not achieve an SVR).
- Several large, non-randomized cohort studies have demonstrated that, compared with HCV patients who are treated but do not achieve an SVR, patients who are treated and do achieve an SVR have a substantially reduced risk of serious liver disease or death (Table 4).

Table 4: Ratio of outcomes among HCV patients with an SVR to outcomes among HCV patients who were treated but did not achieve an SVR

	Yoshida et al (2002)	Kasahara et al (2004)	Veldt et al (2007)	Manesis et al (2009)
Number treated	2,430	2,668	479	993
% with SVR	33.6	27.7	29.6	44.8
Median duration of follow-up (yrs)	5.4	6.0	2.1	3.9
Liver-related deaths (SVR / non-SVR)	0.13	0.05	-	
Overall deaths (SVR / non-SVR)	0.31	0.24	-	
Death, liver failure or HCC (SVR / non-SVR)	-	-	0.2	
Liver failure or HCC (SVR / non-SVR)	-	-	-	0.26

- Once achieved, an SVR seems to be quite durable: 100% of 344 patients followed for up to18 years in the study by Maylin et al (2008), though only 80 out of 87 patients (92%) followed for up to seven years by Pradat et al (2007).
- Randomized controlled trials of new treatments can therefore use SVR rates as a reasonable indicator of likely long-term clinical impact.

75. The small, but ongoing risk of risk of developing HCC following an SVR is greatest among men, those with cirrhosis, and age older than 50 years at the time of treatment. Among 1,193 patients with SVR followed for up to 19 years (median 8.3 years) the crude rates of developing HCC at 5, 10, and 15 years were 1.5%, 2.4%

and 4.1% respectively (Hirakawa et al 2008). Among150 patients with SVR followed for 5 years, two patients with pre-treatment cirrhosis developed HCC, and one died (George et al 2009).

76. There are no trials of early vs. late treatment, but multivariate analyses of cohort data favour early treatment, in that older age at the start of treatment and more advanced liver disease are strong predictors of treatment failure (Thomson et al 2008). In the authors' model, the predicted probability of a patient with genotype 1 achieving an SVR fell from 72% for a 30 year old with mild hepatitis to only 6% for a 50 year old with cirrhosis; the corresponding figures for non-genotype 1 were 84% and 37% respectively.

Protection of the liver, by avoiding excessive alcohol use

77. Heavy alcohol use is associated with progression of HCV-related liver disease (Freeman et al 2001). The literature search for this review did not look for studies that assessed whether knowledge of HBV or HCV status leads to a reduction in alcohol consumption among BME groups. If evidence on this issue turns out to be critical to the policy decision on screening, a separate search should be carried out.

Education to reduce onward transmission of infection

78. The literature search for this review did not look for studies that assessed whether knowledge of HBV or HCV status leads to changes in behaviour that are likely to a reduce onward transmission of infection. If evidence on this issue turns out to be critical to the policy decision on screening, a separate search should be carried out.

Clinical management of the condition and patient outcomes should be optimised in all health care providers prior to participation in a screening programme

79. A 2007 audit of healthcare for HCV in England found that services across the country had improved since a previous audit in 2006, but that the improvements were patchy (All Party Parliamentary Hepatology Group 2008).

- 37 of the 63 (59%) responding NHS trusts reported that some of their patients had their treatment delayed for more than 3 months from their first hospital consultation.
- The waiting time from referral to a patient's first appointment with a consultant varied between 3 and 20 weeks. The waiting time between a recommendation of treatment and the first injection of interferon varied between 2 and 24 weeks.
- Less than two thirds (62%) of responding NHS Trusts are confident that they will have the infrastructure in place to ensure all hepatitis C patients can start treatment within 18 weeks by the December 2008 government deadline.

The Screening Programme

There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.

80. There have been no randomised controlled trials of screening for HBV or HCV that have assessed their impact on mortality or morbidity.

81. The likely impact of a screening programme on the burden of HBV- and HCV-related liver disease depends on the assumptions made when constructing a model. Two cost-effectiveness analyses of HBV screening of migrants estimated the proportion that is preventable through screening as 20% (Hutton et al 2007) and 10% (Veldhuijzen et al 2010).

There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public

82. In the USA, the Centres for Disease Control has recommended HBV testing for individuals born in countries with high or intermediate prevalence of HBV (Weinbaum et al 2008). CDC does not currently recommend testing this group for HCV. Based on the literature search for this appraisal, screening of migrants for HBV and / or HCV is not national policy in any European countries.

83. Large scale HBV case-finding initiatives have been conducted in New Zealand and Australia (Robinson et al 2005, Tipper and Penman 2009), and much smaller initiatives elsewhere.

84. Public acceptability of the proposed programme can be inferred from assessments of overall satisfaction with screening and, to a lesser extent, from uptake of screening.

Overall satisfaction

85. Among 269 individuals who screened positive for HCV in Miami, Florida, 44 (16%) completed a follow-up interview. Of these, 86% reported satisfaction with their decision to be tested; 51% reported at least one adverse effect related to knowing their positive anti-HCV status, most commonly difficulty obtaining health insurance (Trepka et al 2007).

Uptake of screening

86. The literature search for this appraisal did not identify any material from which the likely uptake of screening for hepatitis among UK ethnic minorities can be estimated directly, so it has to be inferred either from HBV screening initiatives outside the UK, or from ethnic minorities' uptake of other screening programmes within the UK.

87. In an HBV screening campaign conducted in New Zealand Between 1999 and 2002, high prevalence ethnic minority groups were targeted by radio and by opportunistic letters and phone calls from primary care. Estimated uptake in the target group was 27% (Robinson et al 2005).

88. A pilot of HBV screening among high-risk ethnic groups has been initiated in New South Wales, Australia (Tipper and Penman 2009), but no data on uptake of screening were available as of March 2010 (Tipper, personal communication).

89. In a study of HBV screening among 142 Chinese Americans in Seattle and Vancouver, 63% accepted an educational and motivational home visit from a lay health worker and a further 12% accepted a video and a pamphlet, but only 6% completed HBV screening (Taylor VM et al. 2009).

90. The UK Colorectal Cancer Screening Pilot found that uptake was much lower among south Asians (ranging from 32% among Muslims to 44% among Hindus) than among the non-Asian population community (64%) (UK CRC Screening Pilot Evaluation (Ethnicity) Team 2003).

The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment)

91. The main potential harms caused by screening for HBV and HCV are the psychological and social consequences of knowing that one is infected; complications of liver biopsy; and unpleasant side-effects from antiviral treatment.

Psychological and social consequences of knowing that one is infected

92. As discussed in para 63 above, receiving a diagnosis of HCV reduces HRQoL by itself (Rodger et al 1999, Dalgard et al 2004). Co´rdoba et al (2003) found that HRQoL was lower among HCV-positive blood donors after they had undergone a full medical assessment than when initially diagnosed, and interpreted this as the consequence of a process that includes frequent medical visits, blood tests, and possibly a liver biopsy. (Zacks et al 2006) found that a majority of HCV subjects alter common behaviors and report financial insecurity, internalized shame, and social rejection, regardless of the method of HCVacquisition. Screen-positive patients may also experience difficulty obtaining health insurance (Trepka et al 2007).

Liver biopsy

93. 30-40% of individuals with HBV infection will probably be advised to have a liver biopsy (Graham Foster, personal communication of East London HBV algorithm). Current NICE guidance for the management of HCV infection does not necessarily require a liver biopsy prior to starting treatment. However, a biopsy may recommended by the clinician, particularly if a strategy of watchful waiting, rather than immediate treatment, is chosen (National Institute of Health and Clinical Excellence 2006).

94. In a large French case series of liver biopsies, 20% of patients experienced moderate pain, 3% experienced severe pain requiring hospitalisation and 0.6% of patients experienced more serious complications such as bleeding, biliary leak, intestinal perforation, vasovagal hypotension and infection (Cadranel et al 2000). Non-invasive tests for detecting fibrosis/cirrhosis, which may potentially be used as an alternative to liver biopsy, are being developed (Cross et al 2008).

Side-effects of antiviral treatment

95. Patients tend to have more concerns about the side-effects of antiviral treatment than health professionals (Schackman et al 2008).

96. Associated side effects mean that pegylated interferon is not often used in clinical practice to treat HBV. The main side-effects of tenofovir are renal impairment and phosphate loss. Side-effects with entecavir are rare (Cooke et al 2010).

97. Common side-effects of antiviral treatment for HCV include depression, muscle pains, lethargy and flu-like symptoms, and these symptoms account for much of the dropout in clinical trials. In the UK mild hepatitis C trial only 79% completed 24 weeks and only 63% completed more than 36 weeks of treatment (Wright M et al 2006). Grieve et al (2006) estimated that HRQoL during anti-viral treatment was similar to that of patients with untreated moderate hepatitis (0.66).

The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (ie. value for money).

98. The literature search for this appraisal did not identify any analyses of the cost-effectiveness of a combined screening programme for HBV and HCV in migrants (though a scoping exercise for such an analysis is being drafted within the Department of Health). The literature search identified two analyses of the cost-effectiveness of screening migrants for HBV alone, and no studies of the cost-effectiveness of screening migrants for HCV alone.

HBV

99. Hutton et al (2007) modelled the cost-effectiveness in the United States of four potential screening, treatment and vaccination programs for HBV for all Asian and Pacific Islander adults, both US-born and foreign-born. The prevalence of chronic HBV infection in this population was estimated to be 10%. The programme that most closely matches the AGH proposal for the UK is described as the 'screen, treat and ring-vaccinate' strategy. Compared with the status quo (voluntary screening only and no incremental screening or vaccination), and using a lifetime time horizon, the incremental cost-effectiveness ratio of this strategy was approximately $38,000 per QALY gained. This estimate is probably conservative, because the model did not include the costs of identifying and inviting the target population, and assumed that all persons who are tested and found to be already infected will accept medical management. The result was most sensitive to the estimated effectiveness of anti-viral drugs in creating a durable response. Treatments incorporated in the model were mainly lamivudine and interferon, which are no longer the preferred drug therapies for many patients (Cooke et al 2010).

100. Veldhuijzen et al (2010) modelled the cost-effectiveness in the Netherlands of screening and treatment with entecavir (one of the currently recommended first-line drugs) for chronic HBV infection among migrants who had been born in intermediate- and high-prevalence countries (similar to the target population proposed by the AGH for a UK screening programme). HBV prevalence in this population was estimated to be 3.35%. Compared with the status quo (a baseline level of detection of chronic HBV infections through the existing pregnancy screening program, testing resulting from medical complaints, contact tracing, or a check-up for sexually transmitted

infections), and using a lifetime time horizon, the incremental cost-effectiveness ratio (ICER) of this strategy was €8,966 per QALY gained. The most influential variable in the sensitivity analysis was the estimated rate of disease progression in the natural history of infection. The ICER rose to €60,000 per QALY gained if all variables describing disease progression were assumed to take the most favourable values within the ranges derived from the literature. The model used cautious estimates for uptake of the screening test (35%), the proportion of those eligible for treatment who will see an appropriate specialist and be offered the appropriate treatment (58%), the proportion who will be eligible for antiviral treatment (10%), and the proportion who will accept the recommended treatment when offered it (75%). It also included the costs of identifying and inviting migrants. However, these costs would be higher in the UK because, whereas municipal population registries in the Netherlands contain both country of birth and current postal address, there is no equivalent population register in the UK.

101. When making its recommendation in favour of screening migrants for HBV the Centres for Disease Control decided against doing a cost-effectiveness analysis, apparently on grounds of feasibility: 'the cost-effectiveness of identifying persons with chronic HBV infection cannot be calculated because treatment options constantly are increasing the number of years of disease-free life, and the various treatments have diverse associated costs' (Weinbaum et al 2008).

HCV

102. A recent systematic review identified seven studies of the cost-effectiveness of screening for HCV, but none of these addressed screening in migrants (Sroczynski et al 2009) and all them have been overtaken by recent refinements in antiviral therapy. Among the studies that were based on currently recommended antiviral drugs (peginterferon plus ribavirin), the majority reported ICERs below €40 000 per QALY gained in populations with HCV prevalence above 10%, and higher ICERs (€77,000 - 1,150,000 per QALY gained) in low HCV prevalence populations, such as the foreign-born ethnic minorities being considered in this appraisal. The authors point out that these studies probably underestimate the benefits from screening in ethnic minority groups: they are likely to have acquired HCV in early childhood, so may have a higher risk of advanced liver disease and can expect more years of benefit following diagnosis; and they have a higher proportion of infections with HCV genotype 3, which is more responsive to antiviral therapy. Since all these analyses were performed there have also been refinements in antiviral therapy, such that overall SVR rates have improved, and the duration and cost of antiviral therapy for some patients has reduced.

103. A recent Japanese analysis of HCV screening (Nakamura et al 2008) gave estimated cost-effectiveness ratios that were all below $5,000 'per life expectancy', whether for screening the general population aged 40-70 years (prevalence 0.36%) or high risk groups aged over 40 (prevalence 0.81%). It is unclear whether the author's use of the term 'life expectancy' equates to the more common term 'life years gained'. If it does, the results are vastly more favourable than those of all previous studies of HCV screening in relatively low prevalence populations. If so, this might reflect the authors' exclusion of any costs of identifying and inviting participants, an assumption that all patients would complete antiviral therapy, or improvements in treatment strategy.

There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards

104. Consideration of this potential screening programme is at an early stage, so such a plan and standards do not yet exist. A major issue for the screening programme being considered is the lack of any UK population registers that contain country of birth and current address. Since 2007 it has been mandatory for GPs to record ethnicity for all new patient registrations, but it is likely to take some years before GP recording of ethnicity approaches completeness (Allaby et al 2009). A potential solution would be to use name recognition software to identify individuals who are more likely to have been born in a country of high- or intermediate HBV prevalence, then write to all those identified with an invitation to attend for screening if they were indeed born in such a country. Appendix 4 provides an assessment by the designer of the Experian 'Origins' tool of its potential for identifying individuals who are more likely to have been born in a country of high- or intermediate HBV prevalence. Based on their assessment, the tool appears promising for this purpose.

Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

105. It is unlikely there would be any problem at the laboratory end in dealing with an increased throughput of samples for HBsAg or anti-HCV assays. The increase in load for each laboratory is not going to be enormous. Both of these assays are run on automated platforms, so the hands-on labour element is minimal. In January 2010 the DH appointed Dr Martin Lombard as National Clinical Director for Liver Disease, with responsibility for leading the development of a National Strategy for Liver Disease. This is likely to include ensuring that the national provision of liver services can cope with the national burden of liver disease (Will Irving, personal communication).

All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost effective intervention could be introduced or current interventions increased within the resources available.

106. This cannot be assessed until better information is available regarding the cost-effectiveness of the proposed screening programme.

Evidence-based information, explaining the consequences of testing, investigation and treatment, should be made available to potential participants to assist them in making an informed choice.

Evidence-based information is available to potential participants via the NHS Choices website at http://www.nhs.uk/conditions/Hepatitis-B and http://www.nhs.uk/conditions/Hepatitis-C

Public pressure for widening the eligibility criteria, for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

107. The Executive Summary of the AGH Report recommends 'case-finding for chronic HBV and chronic HCV infected individuals from minority ethnic populations in their area who were born in countries with a high or intermediate prevalence of HBV infection'. However, Section 6 of the AGH Report (Recommendations for Action) has a more inclusive recommendation: 'Case-finding for both HBV and HCV infection should be targeted to those minority ethnic communities originating from the countries with a high or intermediate prevalence of HBV infection' (Recommendation 2). This more inclusive definition of the target group for case-finding is qualified by Recommendation 3: 'If prioritisation of case-finding is necessary, this should be targeted at first generation immigrants', because infection rates for both HBV and HCV are higher in first generation immigrants than in later generations born in the UK (AGH 2009, para 6.10).

108. It seems likely there may be pressure to offer screening to minority ethnic communities who originate from countries with high or intermediate prevalence of HBV infection, but who were not born there. In 2008/2009 the DH began an advertising campaign to raise awareness of HCV in South Asians in England, "Hepatitis C. The more you know, the better" (www.nhs.uk/hepc/southasian). South Asians were added to a 2008 list of groups for whom an HCV test should be offered those considered to be at risk of HCV (Chief Medical Officer and Chief Nursing Officer for England 2008). The DH campaign advocates case-finding among 'people who originate from south Asia', not 'people who were born in south Asia'.

Key research questions on systematic screening of ethnic minorities for HBV and HCV

1. What is the sensitivity, specificity and acceptability of the following 2-step process for identifying which GP-registered individuals were born in a country where HBV prevalence ≥ 2%:
   - Use the best available software package (currently the Experian 'Origins' package seems the best bet) to identify individuals with names which indicate they may have been born in a country where HBV prevalence ≥ 2%.
   - Write to all those who are flagged up by step 1, asking them to state their country of birth.

   It may be challenging to answer this research question, because we don't have gold-standard data against which to evaluate the process. The best answer available may be one from the (self-selected) population of people who are willing to respond to a letter asking where they were born.

2. How does systematic screening (following the approach outlined above) compare with opportunistic screening in primary care, in terms of acceptability and number of new diagnoses of HBV and HCV?

3. In a systematic screening programme, what proportion of UK residents who were born in a country where HBV prevalence ≥ 2% will accept an offer of testing for HBV and HCV?

4. What is incremental cost-effectiveness of systematic over opportunistic screening for HBV and HCV in individuals who were born in a country where HBV prevalence ≥ 2%?

   In addition to all the variables that are typically included in existing C-E studies, this needs to incorporate the following:

   - effectiveness and costs of identifying and inviting the target population
   - proportion of HBV-positives who receive anti-virals (Graham Foster estimates 20% initially, with a further 30% over the next 20 years)
   - effect of antiviral therapy on HRQoL in HCV
   - emigration of immigrants after screening & treatment (liver disease avoided in these individuals will not represent cost-savings to the NHS)
   - impact of broadening criteria to include 4 million people who originate from, but were not born in, countries with > 2% HBV prevalence.

Other questions that are not yet adequately answered, but are less critical to the policy decision

5. How many cases of HBV will be avoided by vaccination of household and sexual contacts of cases detected by screening foreign-born ethnic minorities for HBV?

Appendices

1. Prevalence of HBsAg among migrants to different European countries, compared to the WHO figure for prevalence in the country of origin.

Country of origin	Country of arrival	HBsAg prevalence in country of origin (from AGH 2009 Appendix 1)	HBsAg prevalence among migrants in country of arrival	Ratio	Comments	Source
China (including Hong Kong)	UK	12	12.8	1.07		Kawsar et al 2002
Ghana	Italy	12	16.1	1.34		Chiaramonte et al 1998
Somalia	UK	10	5.7	0.57		Aweis et al 2001
	Italy		3.3	0.33	Refugees from Sudan, Liberia, Eritrea and Ethiopia	Faustini et al 1994
Sudan	Italy	10	8.3	0.83		Palumbo et al 2008
Vietnam	UK	12	15.0	1.25	All refugees	Chadwick et al 1982
Bangladesh	UK	*5.5*	1.1	0.20		Uddin et al 2010
India	UK	4	0.2	0.05		Uddin et al 2010
Iraq	Italy	5	2.2	0.44		Chironna et al 2003
Pakistan	UK	3	1.5	0.50		Uddin et al 2010
Russian Federation	Israel	4	3.0	0.75		Almog et al 1999
Turkey	Italy	4	6.8	1.70		Chironna et al 2003
Sub-Saharan Africa (mean for Ghana, Kenya, Malawi, Mauritius, Nigeria, Sierra Leone, Somalia, South Africa, Sudan, Tanzania, Uganda, Zambia and Zimbabwe)	France	10.57	7.5	0.71	All antenatal	Roudot-Thoraval et al 1989
	France		6.5	0.62	All antenatal	Denis et al 2004
	France		4.6	0.44	All antenatal	Denis et al 1994
	Spain		10.9	1.03		Lopez-Velez et al 1997
	Spain		7.8	0.73		Toro et al 2006
	Spain		7.7	0.73		Manzardo et al 2008
	Spain		18.2	1.72		Valerio et al 2008
	Spain		6.6	0.62	All children	Huerga and Lopez-velez 2002
	Spain?		2.5	0.24		Ramos et al 2003
	Italy		9.3	0.88	All illegal immigrants	Majori et al 2008
Unweighted mean across all studies				**0.76**		

2. Estimated numbers living in the UK with HBV who were born in countries with high or intermediate HBV prevalence (Source: AGH 2009, Table 4 and Appendix 1)

Country	HBV prevalence	No. in UK	No. in UK with HBV	Country	HBV prevalence	No. in UK	No. in UK with HBV
China (including Hong Kong)	12	149,010	17,881	Egypt	4	24,705	988
Ghana	12	56,113	6,734	Federal Republic of Yugoslavia	4	31,233	1,249
Kenya	12	129,635	15,556	Greece	3	35,174	1,055
Korea, Republic of	12	12,307	1,477	Guyana	2	20,875	418
Malawi	12	12,344	1,481	India	4	467,634	18,705
Malta and Gozo	12	30,179	3,621	Iran	5	42,495	2,125
Mauritius	8	27,077	2,166	Iraq	5	32,231	1,612
Nigeria	12	88,378	10,605	Israel	2	11,899	238
Philippines	10	40,123	4,012	Italy	3	107,242	3,217
Sierra Leone	12	17,051	2,046	Jamaica	2	146,409	2,928
Singapore	12	40,473	4,857	Japan	2	37,539	751
Somalia	10	43,532	4,353	Lebanon	4	10,454	418
South Africa	8	141,404	11,312	Malaysia	5	49,883	2,494
Sudan	10	10,673	1,067	Morocco	4	12,351	494
Tanzania	9	32,635	2,937	Pakistan	3	321,164	9,635
Thailand	8	16,256	1,300	Poland	2	60,708	1,214
Uganda	12	55,207	6,625	Portugal	2	36,556	731
Vietnam	12	23,340	2,801	Russian Federation	4	15,644	626
Zambia	12	21,533		Spain	2	54,482	1,090
Zimbabwe	10	49,529	4,953	Trinidad and Tobago	2	21,287	426
Afghanistan	4	14,876	595	Turkey	4	54,088	2,164
Algeria	5	10,672	534	Ukraine	2	11,908	238
Bangladesh	*5.5*	154,354	8,489	Yemen	4	12,500	500
Brazil	2	15,215	304	**Totals**	**6.0**	**2,810,377**	**169,024**

Note: These figures to not include approximately 237,000 individuals who were born in countries with high or intermediate HBV prevalence but from which there are fewer than 10,000 individuals living in the UK (AGH 2009, para 3.39). This is unlikely to alter the overall estimate of prevalence.

3. Estimated numbers living in the UK with HCV who were born in countries with high or intermediate HBV prevalence (Source: AGH 2009, Table 4 and Appendix 1)

Country	HCV prevalence	No. in UK	No. in UK with HCV	Country	HCV prevalence	No. in UK	No. in UK with HCV
China (including Hong Kong)	3	149,010	4,470	Egypt	18.1	24,705	4,472
Ghana	2.8	56,113	1,571	Federal Republic of Yugoslavia	NA		
Kenya	0.9	129,635	1,167	Greece	1.5	35,174	528
Korea, Republic of	1.7	12,307	209	Guyana	NA		
Malawi	NA			India	1.8	467,634	8,417
Malta and Gozo	NA			Iran	NA		
Mauritius	2.1	27,077	569	Iraq	0.5	32,231	161
Nigeria	1.4	88,378	1,237	Israel	0.4	11,899	48
Philippines	3.6	40,123	1,444	Italy	0.5	107,242	536
Sierra Leone	2	17,051	341	Jamaica	0.3	146,409	439
Singapore	0.5	40,473	202	Japan	2.3	37,539	863
Somalia	0.9	43,532	392	Lebanon	NA		
South Africa	1.7	141,404	2,404	Malaysia	3	49,883	1,496
Sudan	3.2	10,673	342	Morocco	1.1	12,351	136
Tanzania	0.7	32,635	228	Pakistan	2.4	321,164	7,708
Thailand	5.6	16,256	910	Poland	1.4	60,708	850
Uganda	1.2	55,207	662	Portugal	0.5	36,556	183
Vietnam	6.1	23,340	1,424	Russian Federation	2	15,644	313
Zambia	NA	21,533		Spain	0.7	54,482	381
Zimbabwe	7.7	49,529	3,814	Trinidad and Tobago	4.9	21,287	1,043
Afghanistan	NA			Turkey	1.5	54,088	811
Algeria	0.2	10,672	21	Ukraine	1.2	11,908	143
Bangladesh	2.4	154,354	3,704	Yemen	2.6	12,500	325
Brazil	2.6	15,215	396	**Totals**	**2.1**	**2,647,921**	**54,362**

Note: These figures to not include approximately 237,000 individuals who were born in countries with high or intermediate HBV prevalence but from which there are fewer than 10,000 individuals living in the UK (AGH 2009, para 3.39). This is unlikely to alter the overall estimate of prevalence.

4. Personal communications (April 2010) from Prof Richard Webber and Dave Nisbet re the extent to which the Experian 'Origins' tool can distinguish people who are likely to have been born in countries with high or intermediate prevalence of HBV infection from those who were not.

The level of accuracy varies according to the level of resolution. Thus Origins is very efficient indeed in identifying that a name is Thai or Lao but is much less accurate in identifying which ones are Thai and which ones Lao. For some people identifying people right down to “Thai” or “Lao” is important but for others being able to identify a name as “Thai or Lao” is sufficient.

The Origins software attributes ethnicity with comparatively high confidence to Eastern and Central Europe, the Middle East and the Indian sub-continent.

In general Origins is very good at distinguishing people from the Muslim world and from sub Saharan Africa but these are regions where names do not map so well onto individual countries, even if for instance we can nevertheless differentiate Turks; North Africans; Arabs; Iranians and Pakistanis; all with a reasonably high degree of accuracy.

Pacific Islanders are very easy to identify as are Hawaiians.

Generally the system is good at identifying Vietnamese, but less good (though better than it was) at identifying Indonesians. Chinese, Koreans and Japanese are generally able to be distinguished from each other well.

The system is good at identifying people of South and Central American origin but at the moment is not good differentiating within this region, except between Portuguese and Spanish speaking countries.

We have quite a good capability of differentiating within India by religion and between the north and south of the country. Southern Indians are distinguishable from non Tamil Sri Lankans but the two Tamil communities fall mostly into a single group.

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