Screening and Early Treatment of Migrants for Chronic Hepatitis B Virus Infection Is Cost-Effective

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BACKGROUND & AIMS: Persons with chronic hepatitis B virus (HBV) infection are at risk of developing cirrhosis and hepatocellular carcinoma. Early detection of chronic HBV infection through screening and treatment of eligible patients has the potential to prevent these sequelae. We assessed the cost-effectiveness in The Netherlands of systematically screening migrants from countries that have high and intermediate HBV infection levels. **METHODS:** Epidemiologic data of the expected numbers of patients with active chronic HBV infection in the target population and information about the costs of a screening program were used in a Markov model and used to determine costs and quality-adjusted life years (QALY) for patients who were and were not treated. **RESULTS:** Compared with the status quo, a 1-time screen for HBV infection can reduce mortality of liver-related diseases by 10%. Using base case estimates, the incremental cost-effectiveness ratio (ICER) of screening, compared with not screening, is euros (€) 8966 per QALY gained. The ICER ranged from €7936 to €11,705 based on univariate sensitivity analysis, varying parameter values of HBV prevalence, participation rate, success in referral, and treatment compliance. Using multivariate sensitivity analysis for treatment effectiveness, the ICER ranged from €7222 to €15,694; for disease progression, it ranged from €5568 to €60,418. **CONCLUSIONS: Early detection and treatment of people with HBV infection can have a large impact on liver-related health outcomes. Systematic screening for chronic HBV infection among migrants is likely to be cost-effective, even using low estimates for HBV prevalence, participation, referral, and treatment compliance.**

Infection with hepatitis B virus (HBV) is an important public health problem, with an estimated 350 million people chronically infected worldwide.[1] Persons with chronic HBV (CHB) are at risk of developing serious sequelae, such as cirrhosis and hepatocellular carcinoma. A mathematical modeling study estimated that 620,000 people died worldwide from HBV-related causes in the year 2000.[2] Primary prevention of HBV infection is available in the form of a highly effective vaccine, but, because universal HBV vaccination was introduced only about a decade ago in many countries,[3] the problem of existing cases of HBV infection remains. Screening for hepatitis B is a form of secondary prevention, aimed at early disease detection to allow antiviral treatment to prevent HBV-related liver disease. The possibilities for antiviral treatment have greatly improved over the past decade: Several registered drug therapies for CHB that have proven to be cost-effective are now available.[4–7] We recently estimated that treatment of CHB patients with active disease with a low resistance profile drug could reduce mortality related to liver disease in this group by 80%.[8]

However, whereas the potential impact of treatment is sizable, the current benefit is not optimal for several reasons. First, the proportion of patients actually receiving treatment among those who might benefit is low because of the largely asymptomatic nature of CHB infection, which makes case detection difficult. Patients often have progressive liver disease by the time infection is detected based on symptoms. Second, management in primary care of patients after detection is not optimal, and patients often do not see a specialist.[9] Last, not all patients who are eligible for treatment will start treatment. Early detection of CHB infection through screening, with follow-up and treatment of eligible patients, therefore, has the potential to contribute to secondary prevention of HBV.

In countries with low HBV endemicity, the prevalence of CHB infection varies widely among population subgroups. Migrants from countries with a relatively high HBV endemicity are the largest at-risk group, with a prevalence of chronic infection that is up to 25 times higher than that of the indigenous population.[10–13] Surveillance data show that 77% of CHB patients notified in The Netherlands were born abroad, almost all in intermediate- or high-endemic countries.[14] Migrants are

Abbreviations used in this paper: CHB, chronic hepatitis B; GP, general practitioner; ICER, incremental cost-effectiveness ratio; MPHS, Municipal Public Health Service; QALYs, quality-adjusted life-years.

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therefore an important target group for screening for CHB. Hutton et al[15] recommended screening of Asian and Pacific Islander adults in the United States, showing that such screening is likely to be cost-effective. In The Netherlands, recommendations for HBV screening of migrants do not exist. To support policy making, we carried out a cost-effectiveness analysis of systematic screening and treatment for CHB among migrants in The Netherlands from intermediate- and high-endemic countries.

Patients and Methods

We used a Markov chain model to assess the costs and health outcomes of a cohort of patients who either experienced the natural history of HBV infection or received antiviral treatment. Comparative outcomes of these models, in terms of mortality, quality of life, and health care costs, were entered into a separate cost-effectiveness model containing all relevant variables of the screening program. The status quo includes a baseline level of detection of CHB infections through the existing pregnancy screening program, testing resulting from medical complaints, contact tracing, or a checkup for sexually transmitted infections. Our analysis was performed from a health care perspective. The target population for screening consisted of migrants in The Netherlands born in intermediate- and high-prevalence countries, based on data from the World Health Organization.[16] This target population totaled approximately 1.3 million people or 8% of the Dutch population (Statistics Netherlands, January 1, 2006).

Assumptions Regarding Detection and Patient Management Under the Status Quo

To estimate the detection rate under the status quo, we divided the number of patients with CHB who were notified over a 5-year period (2002–2006) by the number of people expected to be hepatitis B surface antigen (HBsAg) positive in the target population. We assumed that there are currently 44,117 HBsAg-positive persons in the target population, based on the recently estimated HBsAg prevalence of 3.35%.[12] More than 5500 patients from the target group were notified over a 5-year period, corresponding to a detection rate of 12.6% under the status quo.

Subsequent to notification of a new HBV infection, either the Municipal Public Health Service (MPHS) or the general practitioner (GP) invites the patients for additional serologic investigation, source and contact tracing, and counseling. The patient is referred for further care according to a national referral guideline.[9,17] This guideline, based on a positive hepatitis B e antigen (HBeAg) test and/or elevated alanine aminotransferase (ALT) level, can successfully identify patients with a high viral load, who might qualify for antiviral treatment and should see a medical specialist.[18] Based on data from a recent study in Rotterdam, updated with 59 patients and now including 479 newly detected patients with CHB, we assumed that 48% of the patients who are detected in primary care meet the referral criteria and are referred for specialist care, including all HBeAg-positive patients, and 36% of HBeAg-negative patients.[18] Patients who do not meet the referral criteria, ie, those who are HBeAg negative and have normal ALT levels, are advised to see their GP for yearly ALT checks. A study following patients after referral for specialist care conducted in 1998–1999 showed that only 39% of the patients who met the referral criteria actually saw a specialist.[9] Based on this study, we assume that, under the status quo, referral is successful for 39% of patients meeting the referral criteria.

Current Dutch guidelines for treatment of CHB infection recommend that patients are eligible for antiviral treatment with HBV DNA $>10^5$ copies/mL (for patients who are HBeAg positive) or HBV DNA $>10^4$ copies/mL (for those who are HBeAg negative) and ALT levels at least 2 times the upper limit of normal.[19] Based on data from 479 patients seen at the MPHS Rotterdam, we calculated that 26% of HBeAg-positive patients and 19% of HBeAg-negative patients who meet the referral criteria are eligible for treatment according to these treatment guidelines and can be considered to have active CHB. Last, we assumed that 75% of the patients who see the specialist and are found eligible for treatment actually start treatment (R. de Man, personal communication). This assumption will be referred to as "treatment adherence."

Intervention and Assumptions Regarding Participation and Referral

The intervention we evaluate here consists of a one-off systematic screening effort and subsequent treatment of eligible patients. The target population for screening is identified in the municipal population registry, which contains information about the country of birth and the current postal address. People in the target population receive an invitation by mail with information and a laboratory form that they can take to a nearby laboratory to get tested. A reminder is sent after 6 weeks. Participants are tested according to the following algorithm: antibody to hepatitis B core antigen (anti-HBc); if positive, HBsAg and HBsAg confirmation, with HBeAg testing when HBsAg positive and ALT when HBeAg negative. Participants are asked to fill in the name of their GP on the laboratory form. Test results are sent to the participants and their GP. HBsAg-positive participants are advised to visit their GP (or the MPHS if the MPHS in their region has a program for direct referral of HBsAg-positive individuals) for further management and referral to secondary care if necessary. A study in Rotterdam found that this type of enhanced referral resulted in an increase from 39% to 58% in the proportion of referred patients who saw a specialist.[9] Because the referral guideline was recently included in the patient management guidelines for