# The Public Health Impact of Antiviral Therapy for Chronic Hepatitis B

**Mehlika Toy**

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# The Public Health Impact of Antiviral Therapy for Chronic Hepatitis B

**Het publieke gezondheidseffect van antivirale therapie voor chronische hepatitis B**

Proefschrift

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| | Prof.dr. A.I.M. Hoepelman |

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Chapter 1

# General Introduction

Of the approximately 2 billion people who have been infected worldwide with the hepatitis B virus (HBV), more than 350 million are chronic carriers.[1] HBV infection accounts for 600,000-1,200,000 deaths each year.[2,3] Chronic viral hepatitis B is a major global public health problem, an important cause of morbidity and mortality from sequelae, which include chronic hepatitis, cirrhosis, and primary liver cancer. Because the course of the disease can go without clinical symptoms for a long time it is a 'silent' disease, and the contribution of chronic hepatitis B to global morbidity and mortality is generally underestimated.

## Epidemiology

On the basis of sero-epidemiological surveys, the World Health Organization (WHO) has classified countries into three levels of endemicity according to the prevalence of chronic HBsAg carriage: high (>8%), intermediate (2−8%) and low (<2%).[4]

Man is the only reservoir of HBV. However, the extremely high ability of HBV to replicate leads to production of high amounts of infective viral particles that are present in blood and body fluids from infected subjects, thus making hepatitis B a highly transmissible infection. Spread to susceptible persons may occur through several mechanisms.

Most people become chronically infected at childbirth when the mother is a hepatitis B carrier (vertical transmission), while others become infected by close personal contact (infancy, unprotected sex) or by injections (medical and dental instruments or intravenous drug use) (horizontal transmission). The risk of developing chronic HBV infection after horizontal transmission is between 30% and 50% for children infected between birth and 5 years of age, but only 7−10% thereafter. It has been unclear why vertical transmission is common in some areas of the world such as Asia and horizontal transmission in children is the dominant mode in other parts of the world such as the Mediterranean region, Eastern Europe, Alaska, and sub-Saharan Africa. The age at which seroconversion from HBeAg to anti-HBe occurs in infected persons appears to be a key determinant in whether HBV is transmitted at or after birth.[5]

Eight genotypes of HBV ranging from A to H have been identified worldwide.[6] Epidemiological studies indicate that these genotypes are common in different parts of the world: genotype A in Western Europe, North America and Africa; genotype B in North and Southeast Asia; genotype C in Asia and the Pacific; genotype D in Southern Europe (Mediterranean countries, Middle East); genotype E in West Africa; and genotype F in Central and South America and Alaska, genotype G in some European countries and North America; and genotype H has been recently reported from Central America. Most genotypes can be further divided into subgenotypes. The most relevant distinct distribution is made in subgenotype A. Subgenotype A1 is the dominant subgenotype in Africa and India, and

A2 in Europe.[6] Evidence suggests that HBV genotype and subgenotype are strong factors in predicting outcome of chronic HBV infection.[5] Several cross-sectional studies have been conducted examining the association of genotypes C and B with hepatocellular carcinoma (HCC) and in most studies, genotype C has been associated with an increased risk of HCC.[7,8]

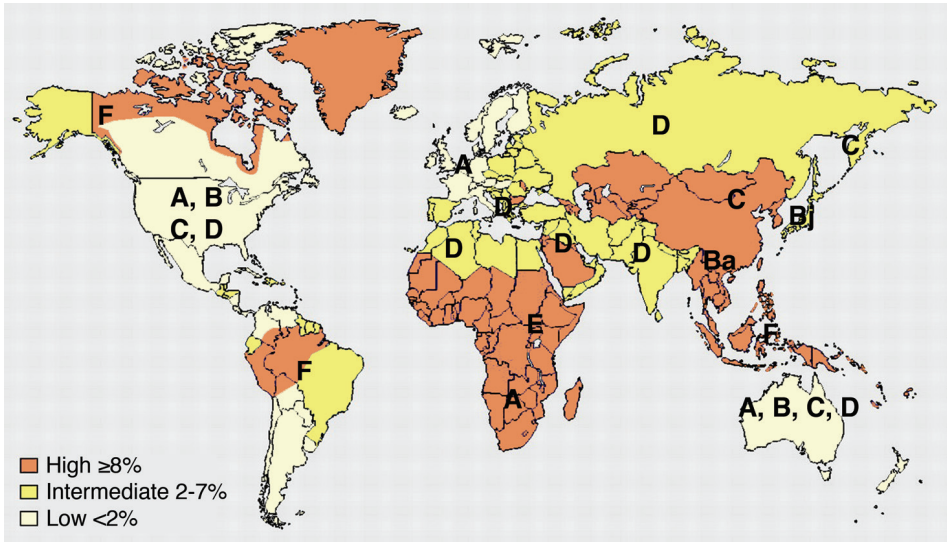


**Figure 1** | Geographical map displaying the levels of HBV endemicity in the world and the areas of predominance of the various HBV genotypes.

## Natural History

The Hepatitis B virus genome has a circular, partially double stranded DNA. It belongs to the hepadnaviridae family of viruses and replicates within infected liver cells.The natural course of HBV infection is characterized by distinctive phases that differ in the replicative activity of the virus and the intensity of the host immune response[9,10] (Figure 1). The course can be divided into four phases: Immune tolerance, immune clearence, low or non-replication, and reactivation. The initial immune tolerant phase is characterized by the presence of hepatitis B e antigen (HBeAg), high serum levels of hepatitis B virus DNA (HBV-DNA), but normal or minimally elevated ALT and normal liver or only minimal histological activity and scant fibrosis. Most carriers with perinatally acquired HBV infection present in the immunotolerant phase with HBeAg positive chronic hepatitis with normal ALT. The immune tolerant phase

can persist for 10–30 years in perinatally infected subjects, whereas it is generally short-lived or absent in childhood or adult-acquired HBV infection. After a variable period of HBeAg positivity, depending on the age at acquisition of HBV infection, immune tolerance to the virus is lost and the immune system mounts an attack on infected hepatocytes. This second immunoactive phase is characterized by fluctuating, but progressively decreasing HBV-DNA levels, elevated ALT and hepatic necroinflammation. Patients with late childhood, adolescence or adult-acquired chronic HBV infection usually present in the immunoactive phase with HBeAg positive chronic hepatitis with elevated serum ALT and moderate or severe necroinflammation with variable amounts of fibrosis on liver biopsy. Serum HBV-DNA levels generally exceed $10^5$ copies/ml among patients with HBeAg positive chronic hepatitis. An important outcome of the immunoactive phase is seroconversion from HBeAg to anti-HBe, marking the transition to the third low or non-replication phase (inactive HBsAg carrier state) which is characterized by HBeAg negativity and anti-HBe positivity, undetectable or low levels of HBV-DNA, persistently normal ALT levels and inactive liver histology with a usually minimal amount of fibrosis.

The fourth reactivation phase is characterized by HBeAg negativity with anti-HBe positivity, detectable serum HBV-DNA levels $10^4$–$10^8$ copies/ml, ALT elevation and moderate or severe necroinflammation with variable amounts of fibrosis on liver biopsy (HBeAg negative chronic hepatitis). About 15−30% of patients experience disease reactivation.[11-13]

In patients with HBeAg positive chronic hepatitis, the 5-year cumulative incidences of cirrhosis in East Asian countries and European countries are 8% and 17%, respectively.[14]

In patients with HBeAg negative chronic hepatitis, the 5-year cumulative incidences of cirrhosis in East Asian and European countries are 13% and 38%, respectively.[14] In studies in East Asian countries, the 5-year HCC cumulative incidences were 1%, 3% and 17% among inactive carriers, in patients with chronic hepatitis B but without cirrhosis and in subjects with compensated cirrhosis, respectively. In studies in Europe and the United States, the 5-year HCC cumulative incidences were 0.1%, 1% and 10% in inactive carriers, in patients with chronic hepatitis B without cirrhosis, in patients with compensated cirrhosis, respectively.[14]

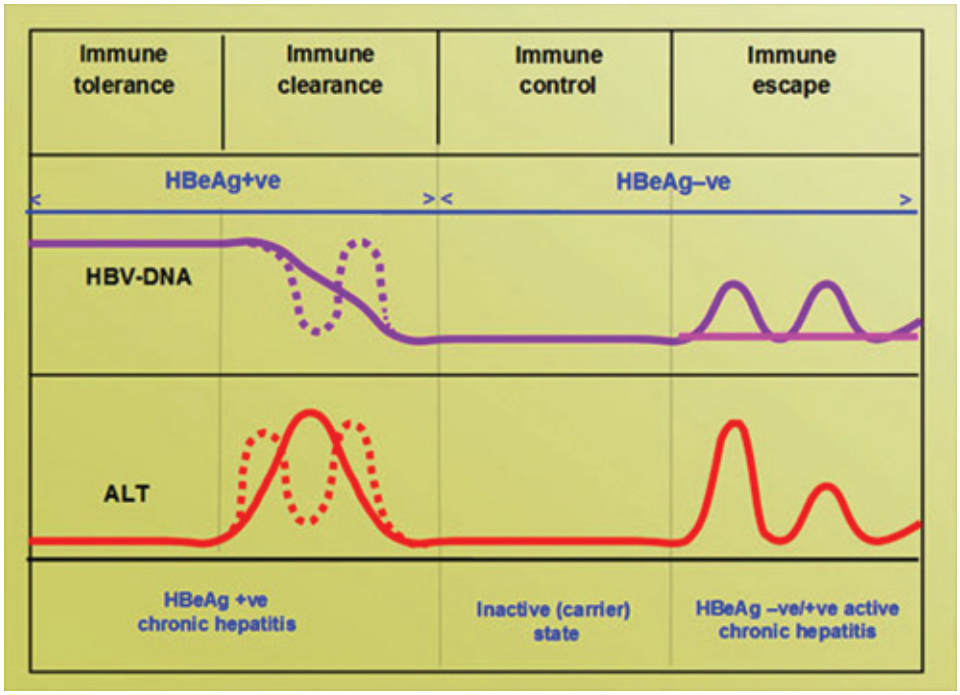


**Figure 2** | Phases of HBV infection

## Diagnosis

The diagnosis of acute hepatitis can be made on the basis of history, serum alanine aminotransferase (ALT) values, and the hepatitis B surface antigen. The HBsAg is the first to appear after infection and around 8 weeks later antibodies to hepatitis B core antigen (anti-HBc) can be detected. When an acute infection is cleared successfully, HBsAg disappears within 6 months after infection. After the acute illness, patients may experience complete resolution of their physical symptoms, and quire protective levels of anti-HBs, and gain lifelong immunity.

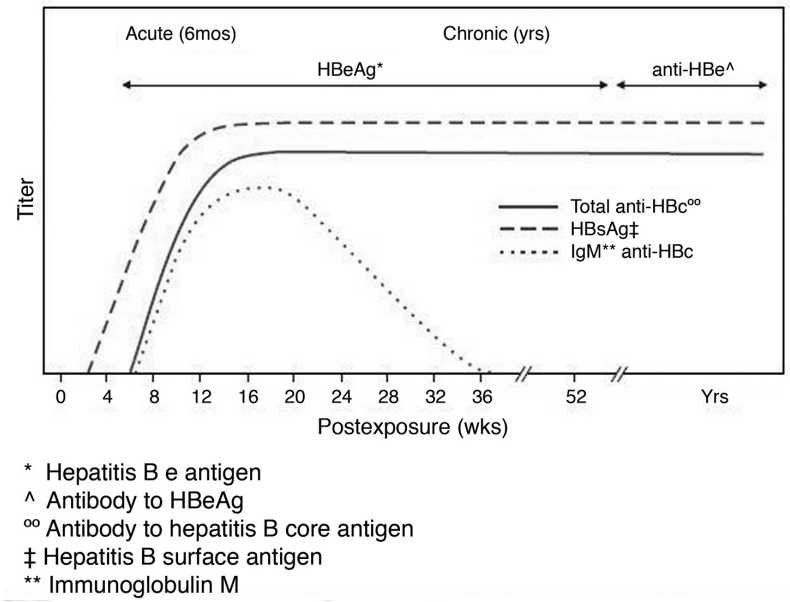


**Figure 3** | HBV serology

## Treatment for chronic hepatitis B

Hepatitis B virus vaccines created the first breakthrough in HBV prevention. The next breakthrough came with therapy for CHB, which has the potential to prevent progression to cirrhosis and hepatocellular carcinoma (HCC).[15] The aim of therapy for hepatitis B is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, HCC and death. Therapy must reduce HBV DNA to as low level as possible, to ensure a degree of virological suppression that will then lead to biochemical remission, histological improvement and prevention of complications.

Seven drugs are now available for the treatment of CHB, including conventional interferon alpha, pegylated interferon alpha, and Nucleos(t)ide analogues. Nucleos(t)ides for CHB therapy belong to three classes: L-nucleosides (lamivudine and telbivudine), deoxyguanisine analogues (entecavir) and acyclic nucleoside phosphonates (adefovir and tenofovir). Interferon and nucleos(t)ide analogues have different mechanisms of action. Interferon, either conventional or pegylated, has a predominantly immunomodulatory effect and weak antiviral activity. These dual actions result in suppression of viral replication and clearance of infected hepatocytes. Nucleos(t)ide analogues have a potent antiviral effect by inhibiting the reverse transcriptase and DNA polymerase activity of HBV.[16] Because of these

intrinsic differences between the two drug classes, interferon can be given for a finite duration, yet has a more durable off-treatment response. In contrast, nucleos(t)ide analogues are usually given for a prolonged duration and are associated with a less durable off-treatment response, even after HBeAg seroconversion or adequate HBV DNA suppression.[17] Therefore, different time points are usually used to assess the treatment outcome for these two different therapies

The indications for treatment are generally the same for both HBeAg-positive and HBeAg-negative CHB. This is based mainly on the combination of three criteria: Serum HBV DNA levels, serum ALT levels, and histological grade and stage.[18]

One peculiar feature of the use of nucleos(t)ide analogues is the possibility of drug resistance. The development of drug resistance may lead to virological breakthrough, biochemical flare-up, histological deterioration, hepatic decompensation and increased risk of hepatic complications.[19-21] Although salvage therapies, which are rescue therapies once resistance occurs, are available, it is not always possible to achieve good viral suppression.

## Chronic Hepatitis B model

Evaluating the effectiveness of a public health prevention program is complex, particularly when the course from infection, health behaviour, exposure, or genetic predisposition to disease spans multiple decades, when new activities are building upon existing interventions, and when resource constraints limit the range of reasonable choices. Specifically, it is often impossible to observe the complete course of chronic diseases, and even the best available data are generally based on surrogate markers and intermediate endpoints. It is often not feasible to conduct randomized controlled trials of every potential treatment approach. The public health impact of antiviral therapy may extend beyond individual patients and may not be measured easily from observational data. The information required to develop policies requires the synthesis of data from many sources. Mathematical models can be useful tools in overcoming these challenges because they provide a framework for synthesizing data from multiple sources in an internally consistent and epidemiologically plausible way. By identifying the most influential variables, mathematical models can be used to identify a range of feasible options for policy makers, support the development of clinical guidelines, highlight key information gaps for researchers, and help prioritize data from new studies**.** Decision analytic methods may be applied to a wide range of clinical, public health, and policy issues, including decisions facing individual patients and their providers, public health decisions that will affect a population, and health decisions such as infectious diseases that will affect future generations. The CHB population model (Figure 4) allows us to forecast health and economic consequences in various countries from low to high endemicity, and helps to address a wide

range of policy questions concerning the burden of disease, in terms of morbidity, mortality and costs in different parts of the world.

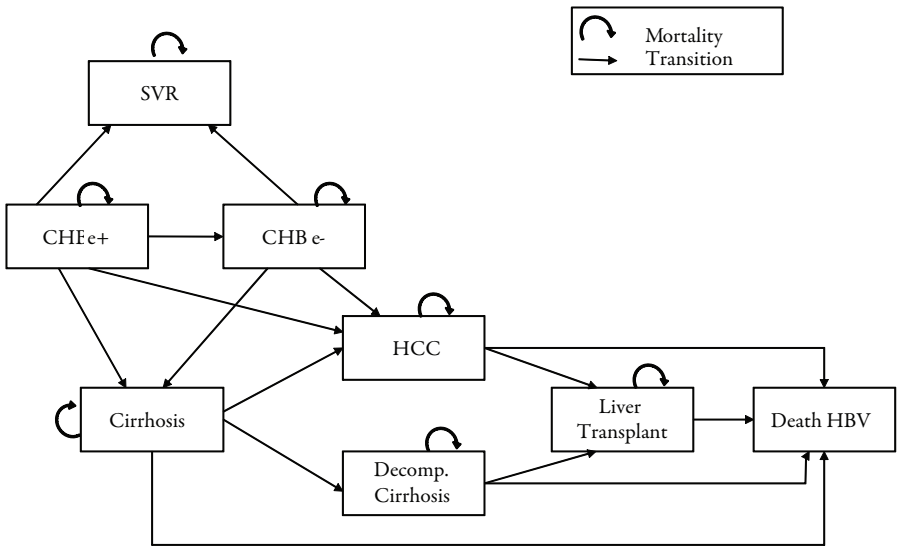


**Figure 4** | In the CHB population model, patients enter the model either in the chronic hepatitis B (CHB) state, or the cirrhosis state, and transition between states according to annual transition estimates. Abbreviations: CHB e+, chronic hepatitis B e antigen positive; CHB e-, chronic hepatitis B e antigen negative; Decomp, decompensated; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; SVR, sustained virological response.

## Cost-effectiveness analysis

Advances in medical care have introduced a wide array of treatment options with varying efficacy and cost. Cost-effectiveness analysis compares the costs and health effects of an intervention to assess the extent to which it can be regarded as providing value for money. This informs decision-makers who have to determine where to allocate limited healthcare resources

The quality-adjusted life year (QALY) is a measure of disease burden, including both the quality and the quantity of life lived. The QALY is based on the number of years of life that would be added by the intervention. An incremental cost effectiveness ratio (ICER) is calculated to determine the additional cost to obtain one unit of effectiveness.

## Research questions and outline of the thesis

This thesis deals with the public health impact of antiviral therapy for chronic hepatitis B. We focused our studies on two countries: the Netherlands, which is a low endemic country, and Turkey, which is an intermediate endemic country for hepatitis B infection.

I will address the following research questions in this thesis:

1. What is the epidemiology of chronic hepatitis B in the Netherlands and in Turkey?
2. What is the potential public health impact of long-term nucleot(s)ide analogue therapy of chronic hepatitis B and possible antiviral resistance?
3. What is the cost-effectiveness of antiviral treatment regimens in CHB patients with and without cirrhosis?
4. Is screening on and treatment of CHB in migrants in low endemic countries cost-effective?

The studies that address these questions are presented in the following six chapters. The first research question is addressed in chapter 2 and 3. Chapter 2 describes the genotypes and transmission routes of chronic hepatitis B patients in the Netherlands. In chapter 3, the age and region specific prevalence of CHB in Turkey is described. The outcomes from chapter 2 and 3 were used to incorporate into the population model for both countries. The second research questions is presented in chapter 4 and 5, which are based on mathematical modeling studies in a low and intermediate endemic area. The third research question is presented in chapter 5 and 6. In these chapters, cost-effectiveness analyses of all major treatments including combination therapies in the Netherlands and in Turkey are presented. The fourth research question is presented in chapter 7, where we have performed a cost-effectiveness analysis on screening and treatment of migrants in a low endemic country. The discussion is chapter 8, where the research questions are answered and discussed.

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Chapter 2

# Transmission routes of hepatitis B virus infection in chronic hepatitis B patients in The Netherlands

M. Toy[1]
I.K. Veldhuijzen[2,3]
M.C. Mostert[2]
R.A de Man[3]
J.H. Richardus[1,2]

[1]Department of Public Health, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, the Netherlands
[2]Division of Infectious Disease Control, Municipal Public Health Service Rotterdam-Rijnmond, Rotterdam, the Netherlands
[3]Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Centre Rotterdam, Rotterdam, the Netherlands

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## ABSTRACT

The Netherlands is a low endemic country for hepatitis B virus (HBV). Rotterdam, a city in The Netherlands harbours a large group of chronic hepatitis B (CHB) patients of which most are born abroad. The study included 464 consecutive CHB patients who were reported to the Municipal Public Health Service in Rotterdam from January 1, 2002 to September 15, 2005. The HBV genotypes, possible transmission routes of infection and travel history of CHB patients born in The Netherlands, were compared with those CHB patients living in The Netherlands but who were foreign-born, taking into account the ethnicity of the mother.

Of the 464 patients with CHB infection, 14% were Dutch-born and 86% were foreign-born**.** The CHB patients in the Dutch-born group had genotypes A (35%), B (15%), C (11%), D (37%) and G (2%). In the foreign-born group, the distribution of genotypes was A (20%), B (15%), C (11%), D (40%) and E (15%). In the Dutch-born group, sexual transmission accounted for a larger proportion of infections ($P<0.0001$) compared to the foreign-born group, whereas perinatal transmission is reported to be higher in the foreign-born group and in the Dutch-born group with a foreign mother. The genotypes of the chronic HBV strains determined corresponded well with the HBV genotypes expected from the countries of origin of the patients or their mothers. Genotype A and D are predominant in CHB patients in the Netherlands.


**Key words**: Hepatitis B virus, chronic hepatitis B, genotypes, transmission, risk

## INTRODUCTION

Two billion people worldwide have evidence of Hepatitis B virus exposure, and an estimated 400 million are chronically infected. Worldwide the prevalence of hepatitis B virus varies greatly. In highly endemic areas, such as China, Southeast Asia, Western Pacific, and sub-Saharan Africa, the chronic HBV infection rate exceeds 8% and transmission occurs mainly from mother to child at the time of birth, as well as by horizontal transmission among children less than five years of age, and to a lesser extent between sexually active adults. In North America and Western Europe, less than 1% of the population is chronically infected, the cause of infection being drug use, sexual transmission or emigration from endemic areas.[1] In The Netherlands, population prevalence of HBsAg-positivity is around 0.2% and 2.1% have serum markers of a past but cured infection according to the study by Veldhuijzen *et al.*,.[2] However, migrants and other risk-groups are thought to be underrepresented in this serosurveillance study, and therefore the estimate of 0.2% for HBsAg-positivity prevalence is thought to be an underestimate. The prevalence of chronic hepatitis B (CHB) in Rotterdam, a city in The Netherlands, is likely to be higher as it has a large migrant population.

Between 2002 and 2005, 7,352 cases of hepatitis B were diagnosed and reported to the Health Inspectorate of The Netherlands.[3] Eighty percent of these HBV infections were chronic, 16% had an acute HBV infection and in 4% the stage of infection was unknown. The most often reported route of transmission for chronic HBV infection was mother-child transmission (40%). In nine percent of patients with chronic HBV infection, sexual contact was the most likely route of transmission and in 36% the route of transmission was unknown. Seventy percent of the cases are reported to be infected abroad, mostly in intermediate or highly endemic regions. Three-quarters of the chronic HBV patients were born abroad, nearly all in intermediate or highly endemic regions.[4]

Since it is difficult to determine the transmission route of chronic infections, molecular analyses of the DNA of the virus may be helpful. Eight genotypes of HBV ranging from A to H have been identified.[5] Epidemiological studies indicate that these genotypes are common in different parts of the world: genotype A in Western Europe, North America and Africa; genotype B in North and Southeast Asia; genotype C in Asia and the Pacific; genotype D in Southern Europe (Mediterranean countries, Middle East); genotype E in West Africa; and genotype F in Central and South America and Alaska, genotype G in some European countries and North America; and genotype H has been recently reported from Central America.[5-7] Most genotypes can be further divided into subgenotypes. The most relevant

distinct distribution is made in subgenotype A. Subgenotype A1 is the dominant subgenotype in Africa and India, and A2 in Europe.[5]

Rotterdam harbours a large group of chronic HBV patients, including both immigrants and Dutch-born patients. With the help of molecular analyses, it becomes feasible to study the origin and transmission routes of HBV among both groups. The present prospective, population-based study was undertaken to identify possible transmission routes of HBV among Dutch-born patients and compare these with foreign-born patients.

## PARTICIPANTS AND METHODS

The Municipal Public Health Service in Rotterdam (MPHS) covers a population of approximately 800,000. All newly diagnosed HBV cases are obligatorily reported to the MPHS and are invited to the MPHS for source and contact tracing and counselling. In the period between January 1, 2002 until September 1, 2005, approximately 1,050 patients were reported to the MPHS. Approximately 850 (81%) were chronic infections, and of those 850 patients, 464 (55%) participated in the study.

Patients were diagnosed as chronic HBV infection based on serology, interviews and background. If no complaints were reported and there were no reason for exposure of an acute infection, the person was assumed to have a chronic infection.

After verbal permission from the patient, a peripheral blood sample obtained for routine serological analysis was also used for molecular analysis, and the public health nurse completed a structured questionnaire during the interview with the patient. Information obtained included: country of birth of the patient as well as the parents; level of education; risk factors (intravenous drug use (IVD); prostitution; tattoos: piercing; medical treatment and dentistry); number of years lived in The Netherlands; travel history; sexual behavior; reason for examination; results of diagnostic tests; and possible transmission mode of infection. On the basis of this information provided by the patient, and from additional source and contact tracing, the public health nurse made an assessment of the most likely mode of transmission. The transmission route was stated as perinatal when mother-to-child transmission was assumed. Horizontal transmission was assumed if the transmission was most likely due to small wounds, wound exudates, saliva, bites and health care related blood exposure incidents (e.g. needle stick injuries). If the transmission was assumed to be most likely due to sexual contact, the transmission route was stated as sexual. IVD transmission was registered if the patient is or was an intravenous drug user. As it is difficult to distinguish between perinatal

and horizontal transmission as the time of infection was often a long time ago, perinatal and horizontal transmission were grouped together in the analyses.

All patients included were classified according to their country of birth as either Dutch or foreign-born. The Dutch-born group was categorized further into two groups: Dutch-born, born from a Dutch mother, and Dutch-born, born in The Netherlands from a foreign mother.

Permission for this study was received from the Medical Ethical Review Board of the University Medical Centre Rotterdam (Erasmus MC).

## HBV DNA genotyping

Serum samples from each patient were tested for the presence of HBV DNA by a validated PCR test. HBV DNA was isolated from serum using the Magnapure LC isolation station (Roche Applied Science, Almere, The Netherlands) with a modified HBV-02 protocol [Pas and Niesters, 2002]. This allowed us to sequence samples with a viral load above 1,000 copies per ml. A product of 878 bp of the preS and part of the S gene was amplified with 20 pmol/rx of the primers HT26/5 (sense, 5'-CAGGCCATGCAGTGGAA-3') and YMDD2 triple primer mix (anti-sense, 5'-ACCCCATCTTTTTGTTTTGTTAGG-3', 5'-ACCCCATCTTTTTGTTTT-3' and 5'-ACCCCAACGTTTGGTTTTATTAGG-3') to enable sequencing of the different genotypes. If needed, a semi-nested PCR was used with HT26/2 as a sense primer (5'-CCTGCTGGTGGCTCCAGTTC-3'), producing an amplicon of 805 bp. The amplicon was sequenced with 5 pmol/rx of HT26 (sense, 5'-cctgctggtggctccagttc-3'), HT26/2, HT26/3 (anti-sense, 5'-ataaaacgccgcagacacatccagcga-3', S1 (sense 5'-gtatgttgcccgtttgtcctc-3') and YMDD2 triple using the Big Dye terminator V3.1 cycle sequencing kit (Applied Biosystems, Nieuwerkerk a/d IJssel, The Netherlands). The products were separated on an ABI 3100 sequencer (Applied Biosystems) and the sequence data were analyzed using Sequence Navigator software sequencer (Applied Biosystems) and Lasergene Seqman 7.1.0 (DNASTAR, Madison, WI, USA). Genotype reference sequences from Genbank and a 752 basepair fragment of the patient sequences were aligned using ClustalW. The phylogenetic relations were calculated with bootstrap test (n=1000) using the Kimura two-parameter neighbour-joining method[8] in BioEdit 7.0.1. (Tom Hall, Ibis Therapeutics, Carlsbad, CA, U.S.A.).

In 2002, samples that could not be sequenced because the HBV DNA level was too low, were tested with INNO-LiPA HBV Genotyping assay (LiPA HBV GT; Innogenetics N.V., Gent, Belgium). As a result, there were four samples with genotype A for which the subgenotype was not available.

### Statistical analysis

Data were analysed in SPSS 13.0. The mean age of patients in both groups was compared by the t-test. Categorical data were compared by means of the chi-squared test.

## RESULTS

The majority of the 464 participants were foreign-born (392, 86%), 64 (14%) were Dutch-born, and the birthplace was missing for eight cases. Dutch-born patients were more often male (41, 64%), compared to foreign patients (194, 49%) ($p$=0.019). The mean age was 34 years for both Dutch- and foreign-born patients ($p$<0.0001).

There were various reasons why the patients were screened for HBV infection in both groups. In the Dutch-born group, common reasons for screening were pregnancy screening (16%), general health complaints (16%), contact tracing (14%) i.e. after partner was diagnosed with HBV, as part of testing for sexually transmitted infections (11%) and pre-vaccination screening as a part of the HBV project (vaccination intervention for risk groups) (8%). In the foreign-born group, mostly the same reasons for screening applied, among which the most common reasons were pregnancy screening (27%) and general health complaints (24%).

The HBV genotypes could be determined from 46 of 64 (72%) Dutch-born patients, and from 260 of 392 (66%) foreign-born patients by standard phylogenetic analyses of amplified sequences. In the remaining cases, genotyping was not possible, due to absent or very low viremia at the time of enrolment. The subgenotype was determined for genotype A in 62 (94%) out of 66 genotype A cases. Table 1 shows Dutch-born HBV cases according to genotype and country of birth of the mother. Of the 46 Dutch-born patients of whom the genotypes were identified, the country of birth of the mother was The Netherlands in 22 (48%) cases. The most common genotype in this group was A (72%). The 23 (50%) cases of mothers born outside The Netherlands all had genotypes reflecting the region where the mother was born.

The 392 foreign-born patients in this study came from 55 different countries, including 89 patients from Turkey (23%), 55 from China (14%), 44 from Surinam (11%), 26 from the Cape Verde Islands (7%), and 22 from Morocco (6%). Of the 260 foreign-born patients of whom the genotypes were identified, the most reported birth region was the Mediterranean, with genotype D reported most often in 74 (94%) cases (Table 2).

**Table 1** | Dutch-born cases according to HBV genotype and birth country of the mother

| **Mothers Birth Country** | **Genotypes** | | | | | | |
|---|---|---|---|---|---|---|---|
| | **A1** | **A2** | **B** | **C** | **D** | **G** | **All** |
| The Netherlands | | 15 | 1 | | 5 | 1 | 22(48) |
| Turkey | | | | | 9 | | 9(20) |
| China | | | 3 | 3 | | | 6(13) |
| Indonesia | | | 1 | | 2 | | 3(7) |
| Hong Kong | | | | 1 | | | 1(2) |
| Cape Verde Islands | | | | 1 | | | 1(2) |
| Surinam | | | 2 | | | | 2(4) |
| Pakistan | | | | | 1 | | 1(2) |
| Unknown | | 1 | | | | | 1(2) |
| **Total no. (%)** | | **16(35)** | **7(15)** | **5(11)** | **17(37)** | **1(2)** | **46(100)** |

**Table 2** | Foreign-born cases according to HBV genotype and region of birth

| **Birth Region** | **Genotypes** | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | **A[a]** | **$A_1$** | **$A_2$** | **B** | **C** | **D** | **E** | **All** |
| Mediterranean[b] | 1 | 1 | 3 | | | 74 | | 79(30) |
| Asia | | | | 30 | 28 | 7 | | 65(25) |
| Sub-Saharan Africa | 2 | 17 | 4 | | | 3 | 39 | 65(25) |
| Central/South America and Caribbean | | 16 | 3 | 8 | | 9 | | 36(14) |
| Eastern Europe and Russia | 1 | | 1 | | | 10 | | 12(4) |
| Western Europe[c] | | | 1 | 1 | | | 2 (1) | |
| North America | | | | | | 1 | | 1(1) |
| Total no. (%) | 4(2) | 34(13) | 12(5) | 39(15) | 28(11) | 104(40) | 39(15) | 260(100) |

[a]Subgenotype not available for four samples that could not be sequenced but were genotyped with the INNO-LiPA test.
[b]Mediterranean includes Turkey and Morocco.
[c]The Netherlands is not included.

When comparing genotype according to reported transmission route in the Dutch-born group, genotype A was found most often in cases reported as sexual transmission (52% of the

cases that could be genotyped). In cases reported as perinatal and horizontal transmission, genotype D was most prevalent (41% of the cases that could be genotyped).

After dividing the Dutch-born group into Dutch-born with a Dutch mother, and Dutch-born with a foreign mother, shown in Table 3, the native Dutch group ("mother Dutch") has the highest reported cases 16 (60%) of sexual transmission. In the Dutch-born group, sexual transmission is significantly higher ($P<0.0001$) compared to the foreign-born group, whereas perinatal and horizontal transmission is reported to be higher in the foreign-born group and the Dutch-born to a foreign mother group.

**Table 3** | Comparing transmission routes of Dutch-born and foreign-born HBV patients[a]

| Transmission Route | Dutch-born mother Dutch no. (%) | Dutch-born foreign mother no. (%) | Foreign-born no. (%) |
|---|---|---|---|
| Perinatal and Horizontal | — | 27 (75) | 184 (47) |
| Sexual | 16 (60) | 3 (8) | 22 (5) |
| IVD | 1 (3) | — | 1 (1) |
| Unknown[b] | 10 (37) | 6 (17) | 185 (47) |
| **Total** | **27** | **36** | **392** |

*$p<0.05$

[a]This table includes the cases whose genotypes could not be identified.

[b]More than one transmission route could be identified.

From the survey, the travel history of the Dutch-born group was analysed. The most visited countries were Italy (10, 16%), Turkey (9, 14%), East Asia (8, 12%), Greece (8, 12%), and Surinam (5, 8%). Among those who travelled to Turkey, perinatal and horizontal transmission (56%) was the most frequently reported route of transmission. For those who had travelled to highly endemic countries such as China, perinatal and horizontal transmission (62%) was the most frequent reported route of transmission as well.

From the survey, we also analysed whether any of the Dutch-born patients had lived outside of The Netherlands. There were nine patients who had lived abroad in Greece, Germany, United States, Italy, Spain, Curacao, Japan, Surinam, Libya and Belgium. In this group, the possible transmission routes, genotypes, number of lifetime sex partners, gender, mother's country of birth and country lived in was compared. Sexual transmission was the

most frequent route of transmission in the nine patients who lived abroad and all had more than 10 lifetime sex partners.

Focusing specifically only on the 22 Dutch-born patients with a Dutch mother of whose genotypes were known, it was found that the majority had genotype A (15, 68%). All of these patients were homosexual males, with genotype A and all with more than 10 lifetime sex partners. Two out of these 15 homosexual male patients had a co-infection with HIV. From this group, it appears that the transmission route was sexual in nearly all, and travel abroad was reported in only two cases. Another five (23%) Dutch-born HBV patients with Dutch mothers had genotype D. Details of this group are shown in Table 4. One of the patients with genotype D had a history of travel to Italy, Spain, Morocco and Surinam.

**Table 4** | Dutch-born Hepatitis B patients with Dutch Mothers

| Patient nr. | Genotype | Gender | Sexual preference | Transmission Route | No. of sex partners in life time | Country travelled |
|---|---|---|---|---|---|---|
| 1 | D | M | heterosexual | Sexual | >10 | — |
| 2 | D | F | heterosexual | Unknown | 1 | — |
| 3 | D | M | heterosexual | Sexual | >10 | — |
| 4 | D | M | heterosexual | Sexual | >10 | — |
| 5 | D | M | heterosexual | Sexual | >10 | Italy, Spain, Morocco, Surinam |
| 6 | B | M | heterosexual | IVD | >10 | Spain, Germany |
| 7 | G | M | homosexual | Unknown | — | — |
| 8-22 | A | M | homosexual | Sexual | >10 | — |

In November 1989, routine 16-week screening for hepatitis B surface antigen (HBsAg) in all pregnant women was introduced in The Netherlands. There were two cases born in The Netherlands after November 1989, one was a 13-year old girl with genotype D, whose mother's birth country was Turkey. The other was an 8-year old boy with genotype C, whose mother's birth country was China.

## DISCUSSION

In this study, we compared possible transmission routes, genotypes and travel behavior of 64 chronic HBV patients born in The Netherlands with 392 foreign-born chronic HBV patients living in the Netherlands. The genotypes of the chronic HBV strains infecting the patients generally corresponded well with the HBV genotypes expected from the countries of origin of the patients. The genotype that is typically expected in The Netherlands, genotype A, was found in less than half of the Dutch-born patients that were genotyped. The remaining Dutch-born patients had mostly genotype D HBV strains. Genotype A was closely associated with sexual transmission, whereas genotype D was more closely associated with perinatal and horizontal transmission.

Of the 17 patients with genotype D in the Dutch-born group, the mother's country of birth was Turkey in nine (53%) cases. As observed in other European cities, children residing in households of first generation immigrants from countries where HBV infection is endemic are particularly affected.[9] A genotype study[10] indicates that the predominant genotype with HBV patients in Turkey, like in other Mediterranean countries, is genotype D. The first generation of immigrants living in The Netherlands originate mainly from the Mediterranean area, which explains the predominance of genotype D in the Netherlands. The two cases that were born in The Netherlands after the introduction of the screening program of pregnant women in 1989 could indicate that the coverage was not optimal or could be explained by a breakthrough in spite of vaccination.

In the Dutch-born patients, there are mainly two modes of transmission that affect this group. Perinatal transmission is more common among the cases where the mother has a different ethnic background than Dutch. The group in which the mother's ethnicity is Dutch, the mode of transmission is mostly sexual and mainly concerns homosexual male patients who have a high number of life-time sex partners.

Travel history in the Dutch-born group with chronic HBV was mainly to Mediterranean countries and Asia. A study by Hahne *et al.*[11] suggests that travel to the country of ethnic origin carries a higher risk of acquiring HBV than other travel. This observation may be due to the nature or the duration of travel by this group and sexual transmission could play a role as a co-factor. Travel as a risk factor in CHB patients born in the Netherlands from Dutch mothers does not seem to play an important role in our study. Of the 22 native Dutch patients, one patient had a travel history suggesting an infection acquired abroad.

The strength of our study is that it is a prospective study including not only clinical cases, but chronic HBV cases from the general population in Rotterdam. Interviews were

taken by experienced nurses and laboratory tests supported the findings. Most studies report transmission routes of acute HBV cases only.[12-14] A limitation of our study is that not all the cases could be genotyped due to low viral load. The proportion of successful genotyped cases, however, was approximately the same for the Dutch and non-Dutch-born groups. Most information on sexual behavior was derived from self-reporting by the patient during the interview. This might suggest under reporting or information bias on sexual behavior. The nurses, however, were well trained for this type of survey. Kretzschmar *et al.*[15] acknowledges the problem of self-reported data on sexual behavior, and refers to a large survey conducted in The Netherlands on sexual behavior that includes 1,001 respondents.[16] These studies suggest that surveys taken by experienced nurses are optimal ways of obtaining data on sexual behavior.

Within the native population of The Netherlands, HBV circulates primarily in high risk groups of limited size such as men having sex with men and very sexually active heterosexuals. In a large part of the general population, the virus cannot maintain itself without the import of new cases from the outside.[15] Import is observed, primarily through contacts (e.g. intermarriage) with the migrant population. Travel related infections do not appear to contribute significantly to the reservoir of chronic HBV infections in individuals born in The Netherlands.

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Chapter 3

# Age and region specific hepatitis B prevalence in Turkey estimated using generalized linear mixed models

Mehlika Toy[1,2]
Fatih Oguz Önder[3]
Tanja Wörmann[4]
A.Mithat Bozdayi[5]
Solko W Schalm[2,6]
Gerard J Borsboom[1]
Joost van Rosmalen[1]
Jan Hendrik Richardus[1]
Cihan Yurdaydin[5,7]

[1]Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands
[2]LiverDoc, Rotterdam, the Netherlands
[3]Department of Gastroenterology, Yuksek Ihtisas Hospital, Ankara, Turkey
[4]Department of Public Health Medicine, School of Public Health, University of Bielefeld, Germany
[5]Institute of Hepatology, Ankara University, Ankara, Turkey.
[6]Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands
[7]Department of Gastroenterology, School of Medicine, Ankara University, Ankara, Turkey

## ABSTRACT

Chronic hepatitis B infection (CHB) is a serious global health problem because of its worldwide distribution and adverse sequelae, including cirrhosis, liver failure, and hepatocellular carcinoma. Turkey is an endemic country with many migrants living in the European Union. Numerous studies in Turkey are available on the HBsAg-prevalence (marker for chronic hepatitis B infection) in specific groups such as blood donors, military, pregnant women, and high-risk groups, and in defined communities through random sampling. To provide a clear picture of the current hepatitis B situation, we set out to estimate the age and region-specific prevalence of CHB in Turkey. A total of 339 studies with original data on the prevalence of HBsAg in Turkey and published between 1990 and 2009 were identified through a search of electronic databases, by reviewing citations, and by writing to authors. After a critical selection we included 133 studies, divided into 'age-specific', 'region-specific', and 'specific population group' studies. To account for the differences among the studies, a generalized linear mixed model was used to estimate the overall prevalence over all age groups and regions. For specific population groups we calculated the weighted mean prevalence. The estimated overall population prevalence was 4.6% (95% CI 3.6–5.8%) and the total number of CHB cases about 3.3 million. The age-group specific outcomes varied from 2.8% for the 0-14 year olds to 6.4% in 25–34 year olds. The prevalence among military conscripts and pregnant women was 3.6% and 2.8%, respectively. The prevalence among health care workers between the years 1990 and 1999 was 3.3%, while this decreased to 2.3% between the years 2000 and 2009. Hepatitis B remains a significant public health problem in Turkey. The HBsAg estimates of this study can inform hepatitis B prevention policies in both Turkey and countries with large Turkish migrant populations.

## INTRODUCTION

Globally, hepatitis B is one of the most common infectious diseases. Estimates indicate that at least 2 billion people have been infected with the hepatitis B virus (HBV), with over 378 million people being chronic carriers (6% of the world population). Of all chronic hepatitis B (CHB) cases, approximately 40% will develop cirrhosis, liver failure or hepatocellular carcinoma (HCC).[1,2] According to the World Health Organization (WHO) classification, Turkey belongs to the countries with intermediate (2–8%) endemicity for hepatitis B. This information has been derived mainly from studies in blood donors. Based on these data, the overall prevalence of the hepatitis B surface antigen (HBsAg), which is a marker for chronic hepatitis B infection, has been reported to be between 4% and 5%,[3] which has decreased to 2% in recent years.[4] However, this HBsAg prevalence appears to differ considerably in various parts of the country. For example, a study on the seroprevalence of HBV in children in Eastern Anatolia reveals an HBsAg-prevalence of 9.8%.[5] There is no clear picture of the current HBV situation in Turkey.

For the planning and implementation of adequate health promotion and intervention measures it is important for both healthcare providers and policy makers to know the real burden of CHB in region and population specific groups. In addition, migration from Turkey to the European Union (EU) has important public health implications. Prevalence of hepatitis B in migrant populations in low endemic EU countries is likely to reflect the prevalence of their region of origin. Therefore it is of equal importance for EU countries with Turkish migrants to know the region specific prevalence of hepatitis B in order to make health policy decisions for migrants in their country.[6] This is particularly important for the timely identification and treatment of chronic HBV carriers. To make a best estimate for the age specific, region specific and finally country specific prevalence of HBsAg, we performed a systematic review of the literature on HBsAg prevalence in Turkey, focussing on age and region specific prevalence rates.

For optimal insight into the HBsAg prevalence in Turkey we included several study types: (i) studies employing random cluster sampling in the population; (ii) large scale studies among blood donors and military conscripts; (iii) studies in various groups that have health related concerns such as pregnant women and medical personnel; and finally (iv) studies in high risk groups.

## MATERIAL AND METHODS

### Main search strategy

This systematic review conforms to the guidelines outlined by the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) recommendations.[7] For English and/or Turkish language studies, the databases MEDLINE, PUBMED, EMBASE and UlakBim (Turkish Medical Index) were searched by using the following terms: 'Hepatitis B [and] Turkey', 'HBsAg prevalence [and] Turkey'. All articles were reviewed and their corresponding reference lists inspected to identify additional material, including unpublished (grey) literature, which initially had not been detected. These were later either retrieved by a new electronic search or searched manually. The period for the meta-analysis for the age and region specific studies ranges from 1999−2009, so the data is coupled with results obtained after the advent of the universal immunization program in Turkey in 1999. HBsAg prevalence was estimated within 7 broad age groups (0-14, 15-24, 25-34, 35-44, 45-54, 55-64, and 65 years and older). The age groups were selected to best fit the available data extracted from the literature. The period for the other studied groups was set from January 1990 up to June 2009. For the studies on healthcare workers, a comparison was made between the studies from 1990−1999 and 2000−2009, in order to retrieve the risk group vaccination effect.

### Eligibility criteria

First-round review criteria for selection of studies included were the availability of explicit data on the country region, setting (e.g. hospital), study period, risk group studied, number of subjects studied and number of subjects positive to HBsAg, or stated crude prevalence. Information related to age-specific outcome was also extracted. We took measures to detect and extract overlapping reports on the same study population. These measures included comparing the study period, sample size, centers where studies were performed and author names.

The provinces of Turkey comprise 7 census-defined regions (bölge). For the purpose of this study, we pooled some regions together based on several factors such as geography, population size, and socioeconomic status. The following division of regions was done; Region A: Marmara and Aegean region, B: Black Sea, Central Anatolia and Mediterranean region, C: Eastern and Southeastern region (Figure 1).

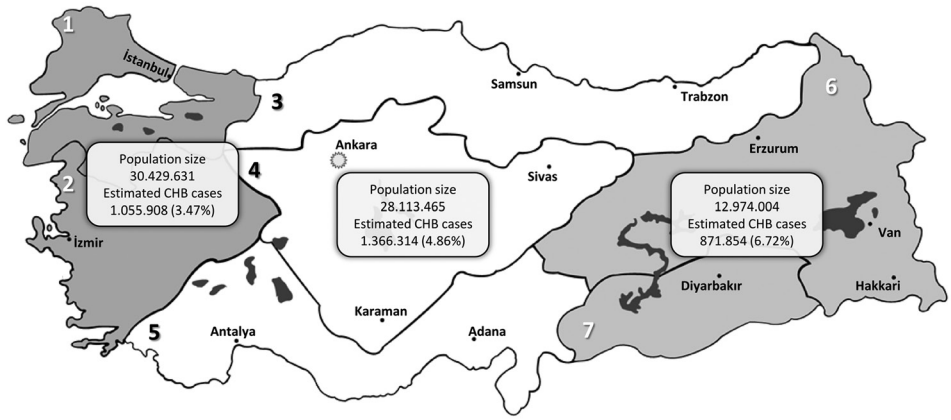


**Figure 1 |** Map of Turkey according to regions, population size per region and the number of estimated CHB cases. Map of Turkey according to regions; 1: Marmara region, 2: Aegean region, 3: Black Sea region, 4: Inner Anatolia region, 5: Mediterranean region, 6: Eastern Anatolia region, 7: South-eastern Anatolia region. Regions with similar socioeconomic status and HBsAg seroprevalence are grouped as A (1 and 2), B (3, 4 and 5) and C (6 and 7).

## Data extraction and data analysis

Once a study was included, the following data were extracted and entered into tables: age group, study region, population type in terms of risk, total number of persons studied, number of persons positive for HBsAg, and year of publication. Two of the authors (MT and FOÖ) checked all data used in the analysis. When disagreement arose, these were resolved by consensus. The unpublished studies (grey literature) were included in the analysis if they met the inclusion criteria. The unpublished material consists of abstracts presented at conferences and of personal communications with clinicians that have constructed the sero-epidemiology studies. The author names, affiliations and setting of the unpublished studies are listed in the appendix and referred to separately from the published literature.

The meta-analysis and data synthesis were done separately for the studies that included both region and age-specific prevalence data, since these were mainly randomized community sampling studies. To account for the differences among the included studies, a generalized linear mixed model was used to estimate the overall prevalence over all age groups and the three regions. The overall prevalence was estimated as the predicted value from a model that contained only a fixed intercept and a random intercept for the different studies. The model

parameters were estimated using data from all studies and separately using only data from published studies, The same method was used with region as a predictor to obtain region specific estimates. These models were fitted with proc glimmix in SAS version 9.2 using adaptive Gaussian quadrature to approximate the log-likelihood function.

From the data of primary studies we calculated the exact binomial 95% confidence interval (CI) for the crude prevalence of each study. We calculated the weighted mean prevalence (WMP) to limit the bias caused by the heterogeneous nature of the reports. WMP was calculated as follows: $WMP=\sum(\omega_i prev_i)/\sum\omega_i$, where $\omega_i=1/[prev_i(1-prev_i)/N_i]$, $prev_i$ is the fraction of (HbsAg positive patients) in study i, and $N_i$ is the number of patients in study i. WMP is regarded as the most accurate method to estimate HBsAg prevalence when considering several reports. This method has proven to be reliable when combining a number of studies with inherent heterogeneity in sample and effects size.[8] The WMP was calculated for all data (published and unpublished), and also for the published data separate, Two-sided Mann-Whitney tests were used to compare the prevalence distribution of published and unpublished studies.

## RESULTS

### General scope

The results of the search strategy and final distribution of the studies are shown in Figure 2. The electronic search identified 254 papers, while manual reference checking identified an additional 84 references, and we received 1 unpublished dataset on military recruits. Out of the 197 studies that were reviewed, 136 studies were in Turkish, of which 19 were finally excluded. The list of references arranged by various criteria can be found in Tables 1-5. The systematic review identified 136 studies that provided prevalence estimates that were split into different sub-groups.

### Age and region specific studies

Thirty studies, of which 22 published[9-30] and 8 unpublished (appendix; a-h), reported the age and region-specific prevalence of hepatitis B. The study-specific prevalence, age and region-specific pooled prevalences and the overall population prevalence are shown in Table 1. The overall age group prevalence for regions A, B and C yields prevalences of 3.5%, 4.9% and 6.7%, respectively. Figure 3 shows the age group and region-specific curves of the pooled prevalence data. The estimated overall population prevalence was 4.6% (95% CI 3.6-5.8%).

The generalized linear mixed model was also estimated using only the published data, which yielded a population prevalence of 5.1% (95% CI 4.2%-6.3%). When this prevalence is extrapolated to the total population living in Turkey (71.5 million), the total number of CHB cases will be about 3.3 million (Figure 1).

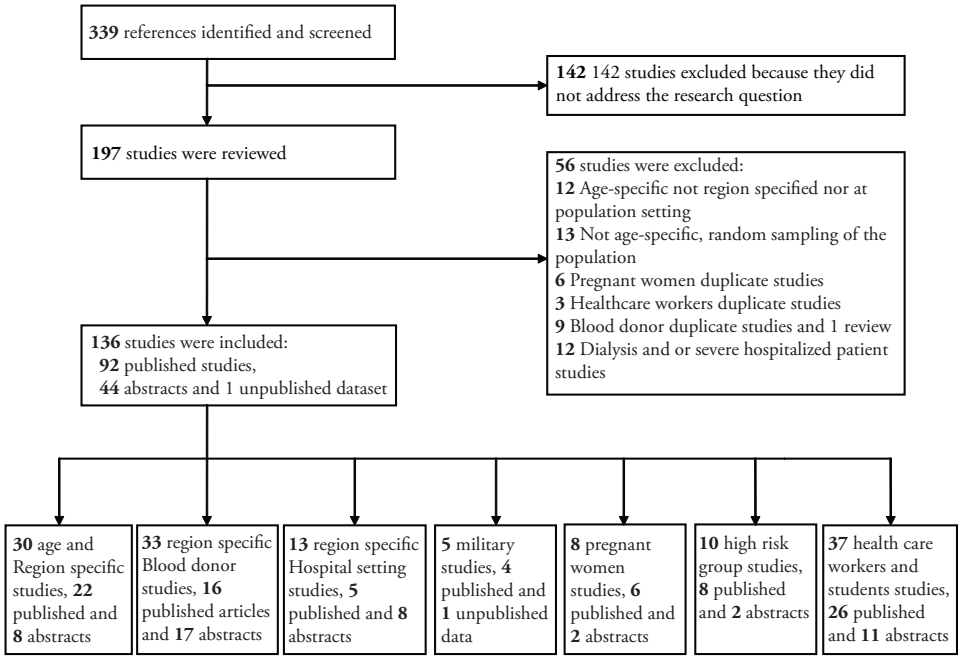


**Figure 2** | Flow diagram (Selection Strategy) of included studies

## Blood donors and hospital setting (non-donor population) by region

A total of 33 blood donor studies, of which 16 published[31-46] and 17 unpublished (appendix; i-y). In total 13 hospital setting studies were identified of which 5 were published[47-51] and 8 unpublished (appendix; z-gg), separated into region-specific outcomes. The weighted mean prevalence (WMP) of HBsAg increases from region A to C, from 2.5% to 4.7%, respectively. The same trend is seen in the hospital setting weighted mean prevalences. For both study groups there were fewer studies in region C than in the other 2 regions (Table 2).

## Table 1| Age and region specific HBsAg prevalence

| Age and region specific HBsAg prevalence | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | | | | B | | | | C | | | |
| | **Ref** | **N** | **n** | **%HBsAg (95% CI)** | **Ref** | **N** | **n** | **%HBsAg (95% CI)** | **Ref** | **N** | **n** | **%HBsAg (95% CI)** |
| 0–14 | a | 420 | 14 | 3.33 (1.83–5.52) | [9] | 460 | 7 | 1.52 (0.61–3.11) | [10] | 402 | 13 | 3.23 (1.73–5.47) |
| | b | 249 | 11 | 4.41 (2.22–7.76) | [11] | 875 | 26 | 2.97 (1.95–4.32) | c | 158 | 9 | 5.70 (2.64–10.54) |
| | d | 230 | 6 | 2.60 (0.96–5.59) | [12] | 1131 | 80 | 7.07 (5.64–8.73) | [13] | 853 | 84 | 9.84 (7.93–12.04) |
| | e | 1952 | 67 | 3.43 (2.66–4.34) | f | 1278 | 22 | 1.72 (1.08–2.59) | [14] | 700 | 29 | 4.14 (2.79–5.90) |
| | [15] | 176 | 3 | 1.70 (0.35–4.90) | [16] | 420 | 13 | 3.10 (1.66–5.23) | [17] | 74 | 6 | 8.10 (3.03–16.81) |
| | [18] | 6788 | 84 | 1.24 (0.99–1.53) | g | 100 | 2 | 2.00 (0.24–7.03) | [19] | 802 | 22 | 2.71 (2.45–2.97) |
| | [20] | 423 | 8 | 1.89 (0.82–3.69) | [28] | 454 | 4 | 0.88 (0.24–2.24) | | | | |
| Total | | 10238 | 193 | 1.88 (1.63–2.16) | | 4718 | 154 | 3.26 (2.77–3.81) | | 2989 | 163 | 5.45 (4.66–6.32) |
| **Total overall‡** | | 17945 | 510 | 2.84 (2.60–3.10) | | | | | | | | |
| 15–24 | [21] | 129 | 6 | 4.65 (1.72–9.85) | [9] | 1058 | 43 | 4.06 (2.96–5.44) | [10] | 183 | 7 | 3.82 (1.55–7.72) |
| | [15] | 440 | 46 | 10.45 (7.75–13.70) | [22] | 238 | 12 | 5.04 (2.63–8.64) | [30] | 213 | 46 | 21.60 (16.27–27–73) |
| | [18] | 2822 | 178 | 6.31 (5.44–7.27) | f | 2431 | 114 | 4.69 (3.88–5.60) | [17] | 187 | 29 | 15.50 (10.63–21.50) |
| | [23] | 7237 | 98 | 1.35 (1.10–1.65) | [24] | 350 | 11 | 3.14 (1.58–5.55) | h | 96 | 3 | 3.21 (0.65–8.86) |
| | | | | | [25] | 155 | 20 | 13.00 (8.06–19.22) | | | | |
| | | | | | [28] | 193 | 7 | 3.62 (1.47–7.32) | | | | |
| | | | | | [29] | 340 | 22 | 6.47 (4.09–9.63) | | | | |
| Total | | 10628 | 328 | 3.08 (2.76–3.43) | | 4765 | 229 | 4.81 (4.21–5.45) | | 679 | 85 | 12.51 (10.12–15.24) |
| **Total overall‡** | | 15636 | 617 | 3.94 (3.65–4.26) | | | | | | | | |

| Age and region specific HBsAg prevalence | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | | | | B | | | | C | | | |
| | Ref | N | n | %HBsAg (95% CI) | Ref | N | n | %HBsAg (95% CI) | Ref | N | n | %HBsAg (95% CI) |
| 25–34 | [15] | 226 | 18 | 7.97 (4.79–12.29) | [9] | 833 | 53 | 6.36 (4.80–8.24) | [10] | 219 | 19 | 8.67 (5.30–13.21) |
| | [18] | 3674 | 235 | 6.40 (5.62–7.24) | f | 2431 | 114 | 4.69 (3.88–5.60) | [30] | 324 | 60 | 18.50 (14.43–23.18) |
| | | | | | [28] | 193 | 7 | 3.62 (1.47–7.33) | h | 435 | 26 | 5.98 (3.94–8.63) |
| | | | | | [29] | 238 | 12 | 5.04 (2.63–8.64) | | | | |
| Total | | 3900 | 253 | 6.49 (5.73–7.30) | | 3695 | 186 | 5.03 (4.35–5.78) | | 978 | 105 | 10.73 (8.86–12.85) |
| **Total overall‡** | | 7950 | 506 | 6.36 (5.83–6.90) | | | | | | | | |
| 35–44 | [15] | 142 | 7 | 4.93 (2.00–9.89) | [26] | 85 | 10 | 11.76 (5.79–20.57) | [10] | 17 | 2 | 11.77 (1.46–36.44) |
| | [18] | 4323 | 249 | 5.76 (5.08–6.49) | [9] | 741 | 71 | 9.58 (7.55–11.93) | [30] | 271 | 41 | 15.13 (11.08–19.96) |
| | | | | | f | 3208 | 170 | 5.30 (4.55–6.13) | h | 555 | 38 | 6.84 (4.90–9.28) |
| | | | | | [28] | 193 | 7 | 3.63 (1.47–7.33) | | | | |
| | | | | | [29] | 173 | 7 | 4.05 (1.64–8.16) | | | | |
| Total | | 4465 | 256 | 5.73 (5.07–6.45) | | 4400 | 265 | 6.02 (5.33–6.76) | | 843 | 81 | 9.60 (7.70–11.80) |
| **Total overall‡** | | 8980 | 557 | 6.20 (5.70–6.70) | | | | | | | | |
| 45–54 | [15] | 85 | 7 | 8.23 (3.37–16.23) | [26] | 55 | 5 | 9.09 (3.02–19.95) | [10] | 17 | 2 | 11.76 (1.46–36.44) |
| | [18] | 2170 | 100 | 4.60 (3.76–5.58) | f | 3208 | 170 | 5.30 (4.55–6.13) | [30] | 244 | 29 | 11.88 (8.10–16.62) |
| | | | | | [9] | 288 | 27 | 9.37 (6.27–13.35) | h | 469 | 34 | 7.24 (5.07–9.98) |
| | | | | | [28] | 346 | 12 | 3.47 (1.80–5.98) | | | | |
| | | | | | [29] | 143 | 5 | 3.50 (1.14–7.97) | | | | |
| Total | | 2255 | 107 | 4.75 (3.90–5.70) | | 4040 | 219 | 5.42 (4.74–6.16) | | 730 | 65 | 8.90 (6.94–11.20) |
| **Total overall‡** | | 6468 | 357 | 5.52 (4.96–6.08) | | | | | | | | |

| Age and region specific HBsAg prevalence | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | | | | B | | | | C | | | |
| | **Ref** | **N** | **n** | **%HBsAg (95% CI)** | **Ref** | **N** | **n** | **%HBsAg (95% CI)** | **Ref** | **N** | **n** | **%HBsAg (95% CI)** |
| 55–64 | [15] | 32 | 0 | 0 | f | 4031 | 129 | 3.20 (2.68–3.79) | [10] | 17 | 2 | 11.76 (1.46–36.44) |
| | [18] | 631 | 32 | 5.07 (3.49–7.08) | [9] | 56 | 1 | 1.78 (0.05–9.55) | [30] | 125 | 15 | 12.00 (6.87–19.01) |
| | | | | | [28] | 346 | 12 | 3.47 (1.80–5.98) | h | 463 | 30 | 6.48 (4.41–9.12) |
| | | | | | [29] | 118 | 11 | 9.32 (4.75–16.06) | | | | |
| Total | | 663 | 32 | 4.83 (3.32–6.74) | | 4551 | 153 | 3.36 (2.85–3.93) | | 605 | 47 | 7.77 (5.76–10.19) |
| **Total overall‡** | | **5238** | **191** | **3.65 (3.14–4.15)** | | | | | | | | |
| 65+ | [27] | 165 | 15 | 9.09 (5.17–14.55) | f | 204 | 5 | 2.45 (0.80–5.63) | [10] | 17 | 2 | 11.76 (1.46–36.44) |
| | [15] | 89 | 2 | 2.24 (0.27–7.88) | [28] | 714 | 29 | 4.06 (2.74–5.78) | [30] | 127 | 10 | 7.87 (3.84–14.00) |
| | [18] | 1115 | 35 | 3.14 (2.20–4.34) | [29] | 83 | 3 | 3.61 (0.75–10.20) | h | 1140 | 28 | 2.45 (1.64–3.53) |
| Total | | 1369 | 52 | 3.80 (2.84–4.95) | | 1001 | 37 | 3.70 (2.61–5.06) | | 1284 | 40 | 3.11 (2.23–4.21) |
| **Total overall‡** | | **2431** | 98 | 4.03 (3.25–4.81) | | | | | | | | |
| **Overall Prevalence**** | | | | 4.57 (3.58–5.76) | | | | | | | | |

Abbreviations: Ref, reference; N, number of subjects; n, number of cases

† Region A: Marmara and Aegean, B: Black Sea, Central Anatolia and Mediterranean, C: Eastern and South-eastern

‡ Total number of persons, cases and the pooled prevalence for each age-group

** The overall prevalence over all age-groups and the three regions

**Table 2** | Weighted mean region-specific HBsAg prevalence in blood donors and hospital settings

| Study group | | | | | %HBsAg prevalence (range) | | | |
|---|---|---|---|---|---|---|---|---|
| **Category** | **no. studies** | **N** | **n** | **Region*** | **Weighted mean all data** | **Weighted mean published data** | ***P* value** | **References** |
| Blood donors | 13 | 658662 | 16788 | A | 2.53 (1.10–8.70) | 2.33 (1.70–2.75) | 0.51 | (31–37) (i–n) |
| | 16 | 223949 | 6389 | B | 2.68 (1.70–4.22) | 3.44 (2.60–4.20) | 0.14 | (38–43) (o–x) |
| | 4 | 149918 | 6675 | C | 4.25 (1.70–4.90) | 4.45 (2.92–4.90) | 0.50 | (44–46) (y) (47) (z–cc) |
| Hospital† | 5 | 37497 | 2977 | A | 3.40 (1.30–13.80) | 1.30 (0.90–1.63) | 0.40 | |
| | 6 | 100343 | 7781 | B | 7.15 (2.9–13.60) | 5.73 (2.90–13.60) | 1.00 | (48–49) (dd–gg) |
| | 2 | 28392 | 6037 | C | – | 10.88 (9.60–21.30) | – | (50–51) |

Abbreviations: N, number of subjects; n, number of cases

†Studies based in hospital settings on non-liver related conditions

* Region A: Marmara and Aegean, B: Black Sea, Central Anatolia and Mediterranean, C: Eastern and South-eastern P value calculated by the Two-sided Mann-Whitney test (difference in prevalence of all data and only published data)

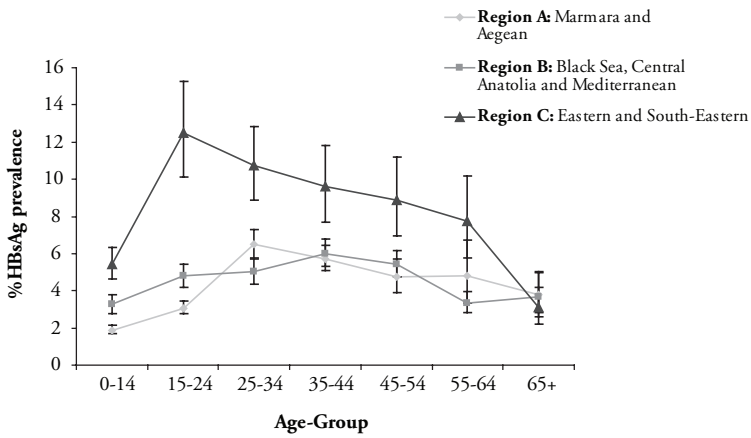


**Figure 3 |** Age and region specific HBsAg prevalence

## Pregnant women and military conscripts (age-range 17-41 years)

The results for pregnant women[52-57] and military recruits[58-61] are presented in Table 3. Military service is compulsory in Turkey for men between the ages 17–39 years. The age ranges in the studies of pregnant women varied from 17–41 years, which is in the same range as the military recruits, and this is why we put these two study population in the same table. From the results of the WMP we observe a gender difference, which is 3.3% for military recruits and 2.8% for pregnant women.

## Healthcare workers and students

As there have been vaccination policies for healthcare workers in Turkey since 1999, we separated the results into two sections in this group. We compared the prevalence rates of studies between 1990–1999, and 2000–2009 for both healthcare workers (HCW)[62-83] and healthcare students (HCS).[84-87] Table 4 shows the decrease in prevalence within the 10-year periods before and after vaccination for HCW and HCS; the WMP has decreased from 3.3% to 2.3%, and from 3.3% to 2.1%, respectively.

## High-risk groups

To show the prevalence among those with a high risk for hepatitis B, we present the results for the following groups; high risk occupations, prison inmates and female sex workers. The high risk occupation group consisted of studies among hairdressers, butchers, garbage men

and coffee house workers. There were 5 studies[88-91] of which 4 published and 1 unpublished (appendix; vv), that were eligible and used to calculate the WMP, which was 8.1%. There were 3 prison inmate studies in total, which were all unpublished (ww-yy) and yielded a WMP of 6.7%. Two studies, of which 1 was published[92] and the other unpublished (appendix; zz), were analyzed for the female sex worker (FSW) group, which yielded a WMP of 7.0%.

**Table 3** | Weighted mean HBsAg prevalence in the Military and in pregnant women

| **Study group** | | | | **%HBsAg prevalence (range)** | | | |
|---|---|---|---|---|---|---|---|
| **Category** | **no. studies** | **N** | **n** | **Weighted mean all data** | **Weighted mean published data** | ***P* value** | **Reference** |
| Pregnant Women | 8 | 17165 | 612 | 2.79 (1.30–9.30) | 2.71 (1.31–4.40) | 0.07 | (52–57) (hh–ii) |
| Military | 5 | 90914 | 3539 | 3.60 (2.16–9.80) | 3.83 (2.16–9.80) | 0.80 | (58–61) (jj) |

*P* value calculated by the Two-sided Mann-Whitney test (difference in prevalence of all data and only published data)

**Table 4** | Weighted mean HBsAg prevalence rates of health care workers and students prior to and after vaccination

| **Risk-group** | | | | | **%HBsAg prevalence (range)** | | | |
|---|---|---|---|---|---|---|---|---|
| **Category** | **year** | **Nr of studies** | **N** | **n** | **Weighted mean all data** | **Weighted mean published data** | ***P* value** | **Reference** |
| HCW | 1989-1999 | 15 | 4147 | 191 | 3.34 (1.60–8.60) | 3.86 (1.90–8.00) | 0.97 | (62-74) (kk-ll) |
| HCW | 2000-2009 | 15 | 5146 | 137 | 2.29 (1.40–5.90) | 2.35 (1.40–5.90) | 0.60 | (74-83) (mm-rr) |
| HCS | 1989-1999 | 4 | 1022 | 39 | 3.31 (2.40–8.60) | 3.42 (2.60–8.60) | 0.50 | (84-86) (ss) |
| HCS | 2000-2009 | 3 | 438 | 8 | 2.08 (1.00–2.40) | 2.00 (0.20–3.70) | 1.00 | (87) (tt-uu) |

Abbreviations: N, number of subjects; n, number of cases; HCW, health care worker; HCS, health care student
*P* value calculated by the Two-sided Mann-Whitney test (difference in prevalence of all data and only published data)

## DISCUSSION

### Age and region-specific prevalence estimates

The age and region-specific analysis was based primarily on community based studies from various regions. The results yielded a marked difference in the overall estimated prevalence, which ranges from 3.5% to 6.7%. The age-specific prevalence also varied remarkably between the lowest prevalence in age group 0−14 years (2.8%) and the highest in age-group 25−34 years (6.4%). The overall country specific prevalence was 4.6%, retrieved from the meta-analysis, over all the regions and age groups.

### Region specific HBsAg prevalence estimates for different sample populations

Population sample groups such as blood donors have been used as convenient samples to estimate the country specific prevalence of HBV.[4] Since blood donation in Turkey is voluntary and the pre-donation eligibility assessment is quite strict, there will be a healthy donor effect in this sample population, which eventually will lead to an underestimation of the true HBV prevalence. Blood donors in this case cannot be representative of an entire population. Our results showed a difference in the region specific estimates, where the weighted mean prevalence (WMP) ranges from 2.5% to 4.2%. When compared with the age and region specific outcomes, these results are in the low range with this sample population, while the hospital setting studies are in the high range. This implies that results based on blood donors and hospital settings should be interpreted with caution.

Another convenient sample of population-based studies is the military conscripts. Military service prevalence studies provide good estimates for the comparable general population of men between the ages of 17 to 41, while pregnant women studies represent the female population of the same age range. Both these sample groups are more representative and are thus more appropriate. Although routine screening for HBV in pregnant women is not yet applied in Turkey, pregnant women are likely to be tested in some way or another during their pregnancies, either for research or for health purposes. Our WMP results comparing these two groups suggest that HBV is more prevalent among males.

### Strengths and limitations

The main strength of this systematic review is that it includes all available Turkish studies, including published and non-published abstracts (grey literature), to overcome publication bias, in particular language bias. Due to the paucity of English language studies from Turkey on hepatitis B, this review provides a wealth of information that otherwise cannot be reached

and interpreted by scientists and policy makers from other countries in the world. We used an innovative approach to fit generalized linear mixed models in estimating the prevalence from various studies. A limitation is its dependence on the quality of the original reports. The strength of the study simultaneously represents a weakness in that conventional wisdom points towards an inverse correlation between quantity and quality. Despite this limitation, we believe that the study provides useful data on the epidemiology of hepatitis B in Turkey for health planning strategies, both in Turkey as well as with Turkish migrant population. We suggest that researchers that are preparing observational research, such as sero-survey studies, pay attention to their reporting by implementing the STROBE guidelines[93] to ensure clear presentation of what was planned, done, and found in an observational study.

### Pre-post vaccination

Since the implementation of universal vaccination in 1998 of all children and risk groups, a decline in prevalence has been observed.[4] Although this study does not address this issue directly, the presence of age-specific prevalence rates in the post-vaccination era enables us to make meaningful comparisons in children from studies in the pre-vaccination era. In this context, Kanra et al.[94] studied the prevalence in all regions of Turkey among children before the vaccination policy was implemented. Their overall country prevalence finding among the 0−15 year olds of 5.9% compares favourably to the current overall country prevalence rate of 2.8% reported in this study for the same age group. The vaccination impact was also assessed on healthcare workers and healthcare students. The WMP estimates in the post vaccination studies clearly show a decline, which could be explained by the impact of the vaccination campaign or, as a secondary explanation, that HBV has the tendency to decrease over the years. A study from the United States shows similar patterns in the success of vaccination application to healthcare workers.[95]

### Implications for health policy

Nearly every country with a large or diverse geographic area is expected to have regional differences in HBV prevalence, and the extent of the geographic variation can be very important. The large regional prevalence differences in Turkey are mainly due to differences in socio-economic status, life-styles, infrastructure and access to health services. In the south-eastern and eastern regions of Turkey all reasons mentioned above apply in a negative way, though the latest years have witnessed much improvement in the socio-economic, hygienic and sanitary conditions in this region and in Turkey in general. This region also lags behind in coverage of HBV vaccination. Although it consists of 18% of the total population, the

estimated number of CHB cases is almost equal to the other regions, which have higher population numbers (see Figure 1). Much migration has taken place from the southeast and east to the west of the country, mainly for economic reasons. The scarcity of reports from southeast and east Turkey, despite the magnitude of the problem, may be an indirect reflection of the health infrastructure of this region.

Turkey has a large proportion of young people (more than 66% of the total population). It is a dynamic society with a growing number of educated people, where the proportion of the population living in cities has increased drastically in recent decades and now accounts for approximately 70% of the population. With an average prevalence of 3.5% in young people aged 0-24 years, hepatitis B remains a significant public health problem in Turkey.

Another important facet of the data in this study is linked to disease awareness. This is certainly not confined to Turkey if one considers that chronic hepatitis B patients are mostly asymptomatic. With an overall HBV prevalence of 4.6%, the estimated number of HBV carriers in Turkey is 3.3 million. If one takes the very conservative assessment that 10% of them would need treatment, there are 330,000 chronic HBV cases eligible for treatment in Turkey alone. 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%.[96] It needs to be stressed that in Turkey viral hepatitis treatment is fully reimbursed through the national insurance system. According to net sold medication counts per year, it was calculated that no more than 10% of them receive active treatment,[97] indicating a massive shortcoming in treating eligible patients with life prolonged and even life saving treatments.

The importance of our study is certainly not confined to the borders of Turkey. Recent evidence suggests that the overall decline in HBV prevalence in the last decade in industrialized countries of Europe appears to have reached a plateau. The most likely reason why the progressive decline in HBV prevalence has come to a halt is migration from endemic areas. There are currently more than 3 million immigrants, descendants of immigrants, and naturalized citizens and political refugees from Turkey in Western Europe, representing the largest immigrant group in the European Union. The public health implications of the current study thus go far beyond the border of Turkey.

## CONCLUSION

Despite the availability of a safe and effective vaccine for more than 20 years, CHB remains a serious health problem, also due to its asymptomatic nature. On the basis of this study, age and region-specific prevalence estimates provide insight into the burden of already existing CHB cases in Turkey. Knowing the diversity in prevalence of CHB in Turkey, public health organizations should turn their attention, means and actions increasingly to the areas and groups that are lagging behind.

## CONFLICTS OF INTEREST AND SOURCE OF FUNDING

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Chapter 4

# Potential impact of long-term nucleoside therapy on the mortality and morbidity of active chronic hepatitis B

Mehlika Toy[1,2]
Irene K. Veldhuijzen[3,4]
Robert A. de Man[4]
Jan Hendrik Richardus[1,3]
Solko W. Schalm[2,4]

[1]Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands
[2]LiverDoc, Rotterdam, the Netherlands
[3]Division of Infectious Disease Control, Municipal Public Health Service Rotterdam-Rijnmond, Rotterdam, the Netherlands
[4]Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands

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## ABSTRACT

The potential impact of long-term antiviral therapy on the burden of chronic hepatitis B has hardly been documented. The aim of this study was to estimate the effects of prolonged antiviral therapy and antiviral resistance on the mortality and morbidity of active chronic hepatitis B patients. A population cohort of chronic hepatitis B patients in the Netherlands was constructed and stratified according to 10-year age groups, prevalence of hepatitis B surface antigen, hepatitis B virus DNA level, alanine aminotransferase level, hepatitis B e antigen status, and presence of cirrhosis. A Markov model was created to mathematically simulate the cohort's progression through a finite series of health states. The analysis was performed on the basis of four scenarios: natural history, long-term therapy with a high-resistance profile drug without or with salvage, and therapy with a low-resistance profile drug. It has been estimated that there were 64,000 people (0.4%) suffering from chronic hepatitis B infection in the Netherlands in 2005, with 6521 (10%) of them having high viremia and elevated alanine aminotransferase levels. Within a 20-year period, 1725 (26%) of the 6521 patients in the active chronic hepatitis B cohort will die because of liver-related causes. Of the 5685 without cirrhosis at entry, 1671 (29%) will develop cirrhosis. Of those 836 with cirrhosis at entry, 619 (74%) will die within a 20-year period. If this active chronic hepatitis B cohort is fully detected and treated, mortality related to liver disease can be reduced by 80% if a low-resistance profile drug is chosen from the start. The effect is due to both the reduction in complications of cirrhosis and the prevention of the development of cirrhosis.

**Conclusion:** Long-term antiviral therapy with a strategy that minimizes or controls resistance will have a major preventive effect on liver-related mortality and morbidity.

## INTRODUCTION

Worldwide, about 360 million people have a chronic hepatitis B (CHB) infection and each year, 500,000 to 700,000 deaths are estimated to arise from hepatitis B virus (HBV)-related cirrhosis and hepatocellular carcinoma (HCC); therefore, CHB ranks as the 10th leading cause of death worldwide.[1] Most HBV-related deaths occur in developing countries. However, in many developed countries, mortality from hepatitis B-related cirrhosis and HCC is also substantial and exceeds that of other infectious causes, including human immunodeficiency virus.[2,3]

Vaccination is often seen as the key intervention to address the problem of HBV-related mortality over time. Although HBV vaccination programs clearly contribute to the reduction of new cases of HBV infection,[4] vaccination does not have any impact on preexisting CHB. Antiviral therapy is the only option to control and prevent progression of disease in patients with active CHB. Evidence has accrued for the efficacy of continuous nucleot(s)ide analogue therapy, which provides highly effective HBV suppression.[5-7] However, antiviral therapy has its limitations; with long-term use, it can be associated with the development of viral resistance that eventually can create serious clinical problems.[5,8]

Public health planners would benefit from knowing the possible future outcome of antiviral therapy in active CHB infection in terms of reductions in morbidity and mortality and the impact of antiviral resistance in a low endemic country with migration from highly endemic countries. The impact of antiviral therapy can be assessed in a mathematical model, with cohort studies providing progression rate estimates for the natural history, and information on the outcome of treatment with different antiviral drugs from clinical trials is now available. The aim of this study was to quantify with a mathematical model the morbidity and mortality of active CHB infection and to evaluate the potential impact of long-term nucleot(s)ide analogue therapy and antiviral resistance in a population of active CHB patients for a median follow-up period of 20 years.

## PATIENTS AND METHODS

### Cohort definition

A population cohort of CHB patients was constructed with the recently updated age-stratified prevalence of hepatitis B surface antigen (HBsAg) in the Dutch population.[9] We projected the

age-stratified HBsAg prevalence to the total Dutch population, which was 16 million in 2005 (Statistics Netherlands).[10]

The HBsAg-positive cohort was first divided into two groups, active CHB and inactive CHB, based on hepatitis B e antigen (HBeAg) status, HBV DNA level, and serum alanine aminotransferase (ALT) level. The age-specific distribution of these factors was derived from a large database with 479 newly diagnosed CHB patients who were seen at the Municipal Public Health Service (Rotterdam-Rijnmond), the Netherlands.[11] The differentiation between active CHB and inactive CHB is essential because progression of the disease is different in these two groups. Patients with high HBV DNA levels (HBV DNA $\geq 10^4$ copies/mL for HBeAg-negatives and $\geq 10^5$ for HBeAg-positives) and elevated ALT (>2 times the upper limit of normal) are classified as having active CHB, have potentially progressive liver disease, and are candidates for HBV antiviral therapy,[12,13] whereas those with low or undetectable HBV DNA and normal ALT levels usually are inactive HBsAg carriers with a low risk of disease progression. Lastly, we classified the active CHB patients into two categories, with cirrhosis and without cirrhosis, using age group-specific proportions from large HBeAg-positive and HBeAg-negative clinical trials, respectively.[14,15]

## Markov model

A Markov mathematical simulation was used to model the outcome of the Dutch cohort of treatment-naïve active CHB patients with high viremia for each age group over a time period of 20 years, which is sufficient time to allow for all possible HBV-related outcomes (development of cirrhosis, liver failure, HCC and death) to occur. The model describes disease progression and determines the long-term morbidity and mortality of the cohort during follow-up. The model uses annual probabilities of transition from CHB to virologic response and of progression to cirrhosis, decompensated liver disease or HCC, and finally death; these were obtained mostly from systematic reviews published in the literature (Table 1 and 2).[16-26] These include both cohort studies describing the natural history of CHB and clinical trials reporting the effect of treatment. As the probability estimates for progression from chronic CHB are clearly different in younger patients and adults, the cohort was split by age, with age groups of 0 to 24 years and 25 to 65+ years. When progression rates were reported, these were transformed into annual probabilities using a standard formula: $P=1-e^{-r't}$, where $P$ is the probability, $e$ is the base of the natural logarithm, $r$ is the event rate, and $t$ is the time interval.[27] The term *morbidity* was defined as events related to decompensated cirrhosis, HCC, and liver transplantation, whereas *hepatic death* was death related to liver failure or other liver-related complications. Other causes of death not related to liver disease are included in the model

as age-specific mortality rates derived from Statistics Netherlands.[10] Mortality is the model's major outcome, but the expected number of cirrhosis, decompensated cirrhosis, HCC and liver transplant cases is also quantified. The model was built with TreeAge Pro 2006 (TreeAge Software, Inc., Williamstown, MA).

### Scenario analyses

Four different scenarios were analyzed in the study. In the first scenario, the natural history of active CHB was simulated: patients received all medical care except antiviral medication to suppress the viral infection. In the second scenario, patients received antiviral treatment with a high-restance profile drug.[5] In the third scenario, patients received the high-restance profile drug and salvage therapy[17] upon the development of resistance. In a fourth scenario, patients received antiviral medication with a low-resistance profile.[20] In all four scenarios we followed the cohort over a period of 20 years through a series of Markov cycles governing patients' transitions between relevant health states.

### Scenario 1: Natural History

In this scenario, active CHB patients progressed according to the natural history; annual rates of progression derived from systematic reviews were followed (Table 1).[16,17] *Spontaneous virologic response* was defined as seroconversion to antibody against hepatitis B e antigen (anti-HBe) for HBeAg-positive patients and as persistent HBV DNA suppression and ALT normalization for HBeAg-negative patients. Deviations in the transmission estimates from Kanwal et al.[16,17] were introduced when new information on the progression rates of specific diseases states or the impact of antiviral drugs became available. Such deviations are mentioned in the text and in Table 2.

The probabilities of receiving a liver transplant for decompensated cirrhosis and liver cancer were calculated on the basis of data from the European Liver Transplant Registry and the Dutch Transplantation Organization.[28,29] Yearly, four liver transplants are estimated to take place because of liver cancer, 80% of which is HCC. This corresponds to an annual probability of receiving a liver transplant for liver cancer of 1.2% as 264 cases of HCC were reported in 2005. The annual probability of receiving a liver transplant for decompensated cirrhosis was calculated to be 3.3%; this was based on an estimated number of 300 cases of decompensated cirrhosis and 10 liver transplantations for this condition.

### Scenario 2: High-resistance profile drug

In this scenario, patients received long-term therapy with the first licensed antiviral HBV drug, which is associated with a high incidence of resistance;[5] such monotherapy is still being practiced in many countries with limited resources.[30] In HBeAg-positive patients, *virological response* was defined as HBe antigen loss and development of anti-HBe. In HBeAg-negative patients, *virological response* was defined as HBV DNA levels undetectable by polymerase chain reaction. We assigned different rates of virologic response under long-term therapy between resistant and nonresistant patients (Table 2). Following current practice guidelines, we assigned patients who did not respond to initial therapy or who experienced relapse after initial response to long-term therapy.

According to the assumptions in the systematic reviews,[16,17] the disease stops progressing in patients who develop virologic response, whereas in cases of nonresponse and viral resistance, the disease progresses as in the natural history. However, the rate of progression from compensated cirrhosis to decompensated cirrhosis is higher in patients presenting with resistance versus those following the natural history.[17]

### Scenario 3: High-resistance profile drug followed by salvage therapy

In this scenario, the same high-resistance profile drug used in scenario 2 was given. Once resistance occurred, patients were salvaged by the addition of a second antiviral drug with potency against the resistant strain (salvage therapy).[17] Patients without resistance continued to receive the initial drug.

### Scenario 4: Low-resistance profile drug

The same patient management strategy used in scenario 2 was applied. The annual probability of resistance developing in those receiving a low-resistance profile drug was much lower than in scenario 2 and was set at 1% per year on the basis of a recent study that reported data after 4 years of follow-up.[20] The treatment-related probability estimates are shown in Table 2.

### Sensitivity analysis

To study the robustness of our results, we performed a sensitivity analysis on the low and high ranges of the transition estimates in the natural history scenario (Table 1). First, a so-called best case scenario was assessed by the application of the high ranges of progression to spontaneous virological response and by the application of the low ranges of the estimates of disease progression. Second, a worst case scenario was assessed by the application of the low progression rates to spontaneous virological response and by the application of the high ranges of the disease progression estimates.

**Table 1 |** Annual transition estimates of the natural history of chronic hepatitis B by initial state and age group

| | | Age group: 0–24 years | | Age group: 25–65+ years | |
|---|---|---|---|---|---|
| **Initial state** | **Outcome** | **Estimate (%)*** | **Reference** | **Estimate (%)*** | **Reference** |
| Chronic hepatitis B e+ | Spontaneous virologic response | 9.4 (8.3–23) | 22,23 | 6.9 (2.0–23) | 16,17 |
| | Cirrhosis | 0.1 (0.0–0.1) | 22,23 | 2.7 (1.6–3.8) | 21 |
| | Hepatocellular carcinoma | 0.1 (0.0–0.1) | 22,23 | 0.4 (0.3–0.6) | 21 |
| | Chronic hepatitis B e- | 0.4 (0.2–0.6) | 22,23 | 1.9 (1.0–3.8) | 21 |
| Chronic hepatitis B e- | Spontaneous virologic response | 9.4 (8.3–11) | 22,23 | 1.6 (0.0–11) | 16,17 |
| | Cirrhosis | 0.1 (0.0–0.1) | 22,23 | 6.2 (2.8–9.7) | 21 |
| | Hepatocellular carcinoma | 0.1 (0.0–0.1) | 22,23 | 0.4 (0.3–0.6) | 21 |
| Cirrhosis e+ | Decompensated cirrhosis | 3.9 (2.0–7.9) | 24–26 | 3.9 (2.0–7.9) | 24-26 |
| | Hepatocellular cancer | 1.8 (0.9–3.8) | 24–26 | 1.8 (0.9–3.8) | 24-26 |
| | HBV-related death | 3.1 (3.1–3.8) | 21,24–26 | 3.1 (3.1–3.8) | 21,24-26 |
| Cirrhosis e- | Decompensated cirrhosis | 2.7 (1.4–5.4) | 24–26 | 2.7 (1.4–5.4) | 24-26 |
| | Hepatocellular cancer | 2.9 (1.0–5.6) | 24–26 | 2.9 (1.0–5.6) | 24-26 |
| | HBV-related death | 3.1 (3.1–3.8) | 21,24–26 | 3.1 (3.1–3.8) | 21,24-26 |
| Decompensated Cirrhosis | Liver transplantation | 3.3 (1.0–8.4) | 28,29 | 3.3 (1.0–8.4) | 28,29 |
| | HBV related death | 26 (15–62) | 21 | 26 (15–62) | 21 |
| Hepatocellular carcinoma | Liver transplantation | 1.2 (0.2–5.0) | 28,29 | 1.2 (0.2–5.0) | 28,29 |
| | HBV-related Death | 35 (20–60) | 16,17 | 35 (20–60) | 16,17 |
| Liver transplant | HBV-related death | 6.6 (2.0–12) | 16,17 | 6.6 (2.0–12) | 16,17 |

Abbreviation: HBV, hepatitis B virus, * Ranges are shown in parentheses

**Table 2 |** Treatment-related annual transition estimates[†]

| Initial state | To | Estimate (%) | | | | | |
|---|---|---|---|---|---|---|---|
| | | High-resistance profile drug | | Low-resistance profile drug | | Salvage therapy | |
| | | HBeAg+ | HBeAg- | HBeAg+ | HBeAg- | HBeAg+ | HBeAg- |
| CHB Initial therapy¶ | Sustained virological response | 20 | 10 | 22‡ | 11‡ | 12 | 10 |
| | Cirrhosis* | 0.5 | 1.2 | 0.2 | 0.6 | 0.5 | 1.2 |
| | Hepatocellular carcinoma** | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| CHB long-term therapy | Sustained virological response | 24 | 10 | 27‡ | 11‡ | 12 | 10 |
| | Cirrhosis* | 0.5 | 1.2 | 0.2 | 0.6 | 0.5 | 1.2 |
| | Resistance | 23 | 23 | 1 | 1 | 1.3 | 1.3 |
| | Hepatocellular carcinoma** | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| Resistant CHB long-term therapy | Sustained virological response | 4.5 | 0 | 5‡ | 0.5‡ | 4.5 | 0 |
| | Cirrhosis* | 2.7 | 6.2 | 2.7 | 6.2 | 2.7 | 6.2 |
| | Hepatocellular carcinoma** | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |
| Cirrhosis Initial therapy | Sustained virological response | 20 | 10 | 22‡ | 11‡ | 12 | 10 |
| | Hepatocellular carcinoma** | 0.9 | 1.5 | 0.9 | 1.5 | 0.9 | 1.5 |
| Cirrhosis long-term therapy | Sustained virological response | 24 | 1 | 27‡ | 11‡ | 12 | 1 |
| | Resistance | 2 | 2 | 1 | 1 | 5 | 5 |
| | Decompensated Cirrhosis | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 |
| | Hepatocellular carcinoma | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 |
| | HBV-related death | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 |

| Initial state | To | Estimate (%) | | | | | |
|---|---|---|---|---|---|---|---|
| | | High-resistance profile drug | | Low-resistance profile drug | | Salvage therapy | |
| | | HBeAg+ | HBeAg- | HBeAg+ | HBeAg- | HBeAg+ | HBeAg- |
| Resistant Cirrhosis long-term therapy | Sustained virological response | 4.5 | 0 | 5‡ | 0.5‡ | 4.5 | 0 |
| | Decompensated Cirrhosis | 7.9 | 7.9 | 7.9 | 7.9 | 7.9 | 7.9 |
| | Hepatocellular carcinoma | 1.8 | 2.9 | 1.8 | 2.9 | 1.8 | 2.9 |
| | HBV-related death | 3.1 | 3.1 | 3.1 | 3.1 | 3.1 | 3.1 |
| Decompensated Cirrhosis | Liver Transplantation§ | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 |
| | HBV-related death | 26 | 26 | 26 | 26 | 26 | 26 |
| Hepatocellular carcinoma | Liver Transplantation§ | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 |
| | HBV-related death | 35 | 35 | 35 | 35 | 35 | 35 |
| Liver Transplantation | HBV-related death | 6.6 | 6.6 | 6.6 | 6.6 | 6.6 | 6.6 |

Abbreviations: CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBV, hepatitis B virus.

† Estimates were taken from Kanwal et al.[16,17] ‡ Estimates were taken from recent clinical trials by Chang et al.,[18] Lai et al.,[19] and Colonno et al.[20]

* Estimates were calculated under the assumption that the natural progression rates of chronic hepatitis B taken from Kanwal et al.[16,17] are reduced by antiviral therapy. Similar to Kanwal's assumption of no progression of disease in HBeAg seroconversion, we assumed no progression of disease when HBV DNA was undetectable by polymerase chain reaction. In the studies from Chang et al.[18] and Lai et al.,[19] full suppression of HBV DNA was observed in 80% with a high-resistance profile drug and in 90% with a low-resistance profile drug. We took these percentages for our calculations.

** Estimates were based on the reduction of progression rates by nucleoside analogue therapy of 50%.[5]

§ Liver Transplantation estimates for the Netherlands.

¶ Initial therapy was the first 12 months (48 weeks) of therapy.

Our assumption that disease progression to decompensated cirrhosis is higher in patients with cirrhosis who develop resistance versus patients who progress according to the natural history might underestimate the efficacy of the high-resistance profile drug. To judge the impact of this possible underestimation, we calculated liver-related mortality under the assumption that progression from cirrhosis to decompensated cirrhosis in case of resistance equals the progression in natural history.

## RESULTS

### Cohorts and natural history

Table 3 shows the total population of the Netherlands in 2005 with the age-specific prevalence of HBsAg. Around 64,000 individuals (0.4% of the total population) are estimated to be HBsAg carriers, with 10,802 (17%) of them having HBeAg-positive CHB and 53,046 (83%) having HBeAg-negative CHB. The total number of patients with active CHB was 6521 or 10% of the total HBsAg-positive cohort, 26% of HBeAg positives, and 7% the HBeAg-negatives. The proportion of cirrhosis increased by age: from 2% to 34% among HBeAg-positive CHB patients and from 5% to 56% among HBeAg-negative CHB patients.

### Natural History of the active CHB cohort

The estimated burden of active CHB infection in 20 years of follow-up is shown in Fig. 1 for the natural history scenario. If the active cohort of 6521 individuals remains untreated, 1725 (26%) will die because of liver-related complications. Within 20 years, there will be 1283 (20%) morbidity events, with 575 decompensation events (9%) and 670 HCC events (10%), and 38 cases will undergo liver transplantation (0.6%). At entry into the cohort in the year 2005, 836 cases (13%) are already in the cirrhotic stage (Table 3). By the year 2025, another 1671 (29%) of 5685 cases will have developed cirrhosis, and this will have led to a cumulative number of 2507 cirrhotics (38%) in the eligible cohort.

### Subgroups: noncirrhosis vs cirrhosis

At entry 5685 (87%) of 6521 cases had no signs of cirrhosis, with 47% being HBeAg-positive and 53% being HBeAg-negative. If these noncirrhotic cases are left untreated, 1106 (19%) of the 5685 cases will die because of liver-related complications within 20 years. This proportion differs by HBeAg status and is 9% for HBeAg-positives and 28% for HBeAg-negatives. About 1671 (29%) of the noncirrhotic cases will develop cirrhosis (12% and 44% for HBeAg-

**Table 3** | Age group-specific distribution of chronic hepatitis B in the Netherlands by HBeAg and stage of liver disease

| Age group | | | | | | Active CHB | | Cirrhosis | | | | Chronic hepatitis (no cirrhosis) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| (years) | Population | HBsAg+ (%) | | HBeAg+ | HBeAg- | HBeAg+ | HBeAg- | HBeAg+ (%) | | HBeAg- (%) | | HBeAg+ | HBeAg- |
| <15 | 3,009,000 | 2,708 | (0.09%) | 812 | 1,896 | 211 | 133 | 4 | (2%) | 7 | (5%) | 207 | 126 |
| 15–24 | 1,948,000 | 14,415 | (0.74%) | 4,325 | 10,091 | 1,124 | 706 | 22 | (2%) | 35 | (5%) | 1,102 | 671 |
| 25–34 | 2,185,000 | 10,051 | (0.46%) | 2,010 | 8,041 | 523 | 563 | 31 | (6%) | 39 | (7%) | 491 | 524 |
| 35–44 | 2,622,000 | 16,519 | (0.63%) | 2,643 | 13,876 | 687 | 971 | 48 | (7%) | 146 | (15%) | 639 | 825 |
| 45–54 | 2,315,000 | 16,437 | (0.71%) | 822 | 15,615 | 214 | 1,093 | 53 | (25%) | 306 | (28%) | 160 | 787 |
| 55–64 | 1,938,000 | 2,713 | (0.14%) | 190 | 2,523 | 49 | 177 | 16 | (33%) | 90 | (51%) | 33 | 87 |
| 65+ | 2,288,000 | 1,005 | (0.08%) | 0 | 1,005 | 0 | 70 | 0 | (0%) | 39 | (56%) | 0 | 31 |
| Total | 16,305,000 | 63,848 | (0.39%) | 10,802 | 53,046 | 2,808 | 3,713 | 176 | (6%) | 663 | (18%) | 2,633 | 3,051 |

Abbreviations: CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

positives and HBeAg-negatives, respectively), 360 (6%) will develop decompensated cirrhosis (4% and 9% for HBeAg-positives and HBeAg-negatives, respectively), 481 (8%) will develop HCC (4% and 13% for HBeAg-positives and HBeAg-negatives, respectively), and 30 (0.5%) will undergo liver transplantation (0.3% and 0.7% for HBeAg-positives and HBeAg-negatives, respectively).

Thirteen percent of the cohort had cirrhosis at entry (836/6521), with 21% being HBeAg-positive and 79% being HBeAg-negative. If left untreated, 619 (74%) of the 836 members of the cirrhotic cohort will die because of liver-related complications. This proportion does not differ by HBeAg status. The morbidity in this cohort will be 412 (50%) of 836 (again the same for HBeAg-positives and HBeAg-negatives); 215 (26%) cases will develop decompensated cirrhosis (32% and 24% for HBeAg-positives and HBeAg-negatives, respectively), 189 (23%) will develop HCC (10% and 26% for HBeAg-positives and HBeAg-negatives, respectively), and 8 (1%) will undergo liver transplantation (1% and 1% for HBeAg-positives and HBeAg-negatives, respectively). Table 4 and Figure 1 show the different outcomes in all scenarios for the noncirrhotic and cirrhotic subgroups.

If the active CHB cohort is not treated, 138 individuals (3%) of the 0 to 24 age group (n=2174) and 1661 (38%) of the 25 to 65+ age group (n=4345) will die because of liver related complications within a 20-year period. The morbidity will be 34 cases (2%) in the 0 to 24 age group and 1249 (29%) in the 25 to 65+ age group.

## Impact of treatment

A reduction of hepatitis B-related mortality and morbidity was observed in model projections when treatment was applied. Treating the cohort with a high-resistance profile antiviral drug will decrease the mortality to 971 cases (15%; Figure 1) and the number of morbidity events to fewer than 822 (13%). Treating the same patients with a low-resistance profile drug will further decrease the mortality to 339 liver related deaths (5%) and the morbidity events to around 229 (3%). Eight hundered sixty-one (15%) new cases of cirrhosis are to be expected if the active CHB cohort is treated with a high-resistance profile drug, whereas treatment with a low-resistance profile drug will yield only 112 (2%) new cases of cirrhosis after 20 years of follow-up. When salvage therapy is applied without delay to the cases that become resistant, mortality and morbidity will be 333 (5%) and 386 (6%), respectively.

Comparing the four scenarios, we find that a low-resistance profile drug will prevent 1386 cases (80%) of liver-related death, whereas an antiviral with a high incidence of resistance will prevent only 754 cases (44%) of CHB-related deaths. Applying salvage therapy without delay to the cases who become resistant will prevent 1339 cases (77%) of CHB-related death. The

burden of antiviral resistance in this model is 632 deaths (36% of the total number of liver-related deaths).

**Table 4 |** Morbidity and mortality of active chronic hepatitis B by HBeAg status in the natural history scenario

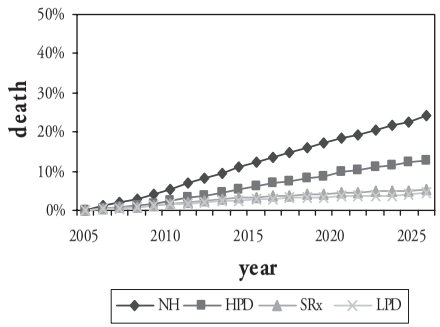
| **CHB stage at entry** | **Outcome** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | **Cirrhosis (%)** | | **De-compensated cirrhosis (%)** | | **HCC (%)** | | **Liver transplant (%)** | | **Death (%)** | |
| *No cirrhosis* | | | | | | | | | | | |
| HBeAg+ | 2634 | 317 | (12%) | 94 | (4%) | 93 | (4%) | 8 | (0.3%) | 248 | (9%) |
| HBeAg- | 3051 | 1354 | (44%) | 266 | (9%) | 388 | (13%) | 22 | (0.7%) | 858 | (28%) |
| all no cirrhosis | 5685 | 1671 | (29%) | 360 | (6%) | 481 | (8%) | 30 | (0.5%) | 1106 | (19%) |
| *Cirrhosis* | | | | | | | | | | | |
| HBeAg+ | 174 | 174 | (100%) | 55 | (32%) | 17 | (10%) | 2 | (1.1%) | 127 | (73%) |
| HBeAg- | 662 | 662 | (100%) | 160 | (24%) | 172 | (26%) | 6 | (0.9%) | 492 | (74%) |
| all cirrhosis | 836 | 836 | (100%) | 215 | (26%) | 189 | (23%) | 8 | (1.0%) | 619 | (74%) |
| Total | 6521 | 2507 | (38%) | 575 | (9%) | 670 | (10%) | 38 | (0.6%) | 1725 | (26%) |

Abbreviations: CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HCC, hepatocellular carcinoma.

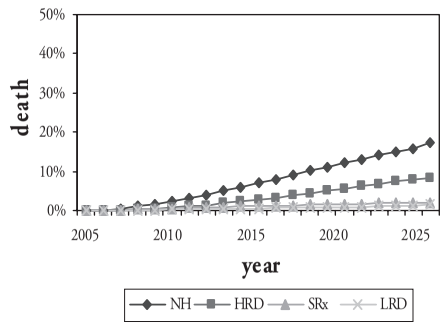
Comparing the scenarios in terms of morbidity, we find that a low-resistance profile drug would prevent 1054 cases (82%) from proceeding to complications, whereas an antiviral drug with high-resistance will prevent 461 cases (36%) from proceeding to CHB-related complications. The burden of antiviral resistance in terms of morbidity is 593 cases (46%). If salvage therapy is applied, this scenario will prevent 950 cases (74%) from proceeding to liver-related complications.

## Sensitivity analysis

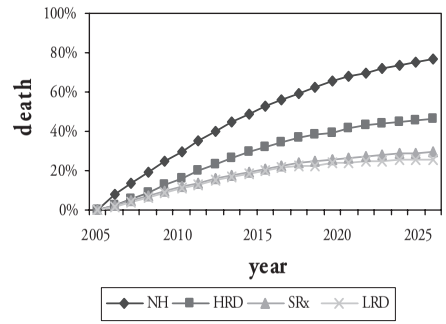
The sensitivity analysis for the natural history scenario show that, in comparison with the base case, in which the mortality of the active CHB cohort is 26%, the mortality ranges from 13% in the best case scenario to 39% in the worst case scenario. When assessed by subgroups, in the best and worst case scenarios, mortality ranges from 3% to 26% for HBeAg-positive chronic hepatitis, from 8% to 36% for HBeAg-negative chronic hepatitis, and from 60% to 91% for cirrhosis independent of HBeAg status.



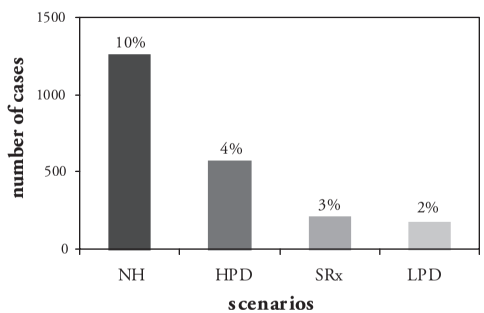

a. Mortality of the active CHB cohort (n = 6521)



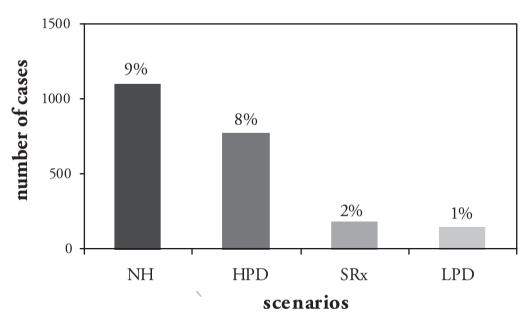

b. Mortality of the noncirrhotic group (n = 5685)



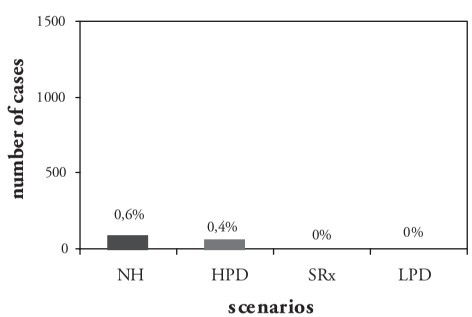

c. Mortality of the cirrhotic subgroup (n = 836)




d. Cumulative Hepatocellular Carcinomas
in the active CHB cohort (n = 6521)




e. Cumulative Decompensated Cirrhosis
in the cohort with high viremia (n = 6521)




f. Cumulative Liver transplants
in the cohort with high viremia (n = 652)

**Figure 1** | Liver related mortality and morbidity of the hypothetical Dutch cohort with active CHB (2005-2025) by four different scenarios. (NH=Natural History, HRD=High-resistance profile drug, SRx=Salvage therapy, LRD=low-resistance profile drug)

Combining these ranges with the treatment-related outcomes indicates that a low-resistance profile drug can prevent 59% of liver-related deaths in the best case scenario for natural history and 87% in the worst case scenario with its high disease progression rate.

The sensitivity analysis regarding progression from cirrhosis to decompensated cirrhosis in the case of resistance shows that mortality in the high-resistance profile drug scenario decreased from 15% to 13% when the rate of progression in resistance is changed from higher than that in natural history to equal to that in natural history.

## DISCUSSION

If all patients with high viremia and elevated ALT from the total cohort of CHB patients are fully treated with a low-resistance profile drug, liver-related mortality can be reduced by 80% (sensitivity analysis range, 59%–87%). Because liver-related mortality is approximately 26% (sensitivity analysis range, 13%–39%), a high relative reduction in mortality will also translate into a high absolute number of cases in which mortality can be prevented.

Treating the cohort with a high-resistance profile drug will reduce the liver-related mortality and morbidity by only 47%. The burden of antiviral resistance if no salvage therapy is applied is considerable: about 42% of the potential benefit of antiviral therapy is lost by resistance. In the Netherlands, in which reimbursement of salvage therapy is without restraint, adding a second antiviral agent in case of resistance appears as good as starting with a low-resistance profile drug. In the model, the efficacy of salvage therapy might be overestimated because the start of salvage therapy is programmed at the time of occurrence of resistance. In practice, the start of salvage therapy will often be delayed. In addition, current evidence shows that salvage therapy can become ineffective in the long run.[31]

The beneficial effect of antiviral therapy is due to both the reduction in complications of cirrhosis and the prevention of the development of cirrhosis. Liaw et al.[5] documented the beneficial effect of long-term nucleoside analogue therapy on clinical outcome in patients with cirrhosis. Our study underlines the potential efficacy of long-term antiviral therapy in patients with potentially progressive disease who are still in the noncirrhosis stage.

The aforementioned findings are related only to the subgroup of CHB patients with potentially progressive disease, that is, those with high viremia and elevated ALT. In a low endemic country such as the Netherlands, 10% of newly diagnosed CHB cases fall into this category, with about equal numbers of HBeAg-positives and HBeAg-negatives.

The active CHB cohort was constructed in a way that captured relevant aspects related to disease progression and response to treatment, that is, age, HBe antigen status, HBV DNA and ALT levels, and presence of cirrhosis. In assessing the cohort's progression through the various health states, we used transition estimates that were based on extensive systematic reviews[16,17] and updated with recently available robust findings.[5,18-26] We performed the analyses by simulating the cohort separately for each age-specific group, HBe antigen status, and stage of liver disease, as these factors affect prognosis, thereby approaching the real-life situation as much as possible. For the treatment scenarios, the model simulated long-term treatment as it is now emerging in guidelines.[13] We developed the model in such a way that with small adaptations it can be used to estimate the hepatitis B burden and impact of antiviral therapy in various countries or regions according to their profiles, such as prevalence by age-specific group, and treatment characteristics, such as the drug type chosen for initial therapy and percentage application of salvage therapy.

We chose to apply the simulation to the specific cohort of high-viremia patients with elevated ALT because our main goal was to define the impact of antiviral drugs on clinical outcome and these patients would qualify for treatment according to recent guidelines.[12,13] Patients with high viremia and ALT levels within the normal range were not included in the cohort as these patients are often in the immune-tolerant phase of their infection and treatment is currently not recommended for this group. However, the context of how antiviral therapy should be used remains a difficult question, particularly with respect to which patients with CHB should be treated and what ALT level (abnormal, twice normal, or greater than 5 times normal) should be used for the criteria.[32] The transition estimates for disease progression in our natural history model were taken from various international studies. Although the patients included in these studies were mainly patients with active CHB (i.e., with elevated ALT levels), some studies were based on a mixed population of CHB patients and also included patients with normal ALT levels. For this reason, the progression rates used in the natural history model might underestimate the morbidity and mortality of a strict cohort of active CHB patients with a high viral load and elevated ALT levels in natural history, and this implies an even higher impact of treatment.

In a further study, the outcome of patients with low viremia and those with high viremia but normal ALT will be assessed as well as the effect of antiviral therapy in specific subgroups such as noncirrhotic and cirrhotic patients, with transition estimates specifically applicable to these patients that are in different disease phases.

A limitation of our study is that we used simplified assumptions (e.g., we did not consider coinfection with other viruses or toxins such as alcohol that will accelerate progression), and

we assumed the cohort to be static, so there were no new cases added to the cohort. Assuming that the development of resistance with a low-resistance profile drug for the coming 20 years will stay at 1% per year likely underestimates what will happen as longer term data are collected.

The proportion of patients without cirrhosis in our cohort at baseline is comparable to that found in a recent Italian longitudinal cohort study of untreated adult Caucasian patients with CHB, 87% of whom presented without cirrhosis at diagnosis.[33] In the Italian study, 27% of the CHB patients developed cirrhosis during the follow-up period, and this is similar to our study, in which 29% of CHB cases develop cirrhosis over a period of 20 years. At the end of 20 years of follow-up, 26% of patients in the active CHB cohort will die of CHB-related causes, whereas this was 16% in the Italian cohort. However, the Italian cohort consisted of only 70 patients and the 16% mortality rate fell within the sensitivity range of our mortality estimate. A possible explanation for the difference in mortality between our study and the Italian cohort study is that our cohort consists of patients with high viremia and ALT >2 the upper limit of normal, whereas the Italian study used HBeAg status as an indicator of high viremia. HBeAg-negative patients were not included in the Italian study, and these patients have a higher progression rate to cirrhosis.

Even the most precise mathematical modeling is only an estimate of the real-life situation.[34] However, in the case of CHB, modeling might reflect real life better than official mortality data because epidemiological data based on death certificates have been shown to be extremely unreliable in estimating mortality from CHB.[35,36]

This study, like a preliminary one in Spain,[37] focused on quantifying the impact of therapy and antiviral resistance at the population level. Other studies of hepatitis B have used mathematical modeling to compare cost effectiveness among various antiviral drugs,[16,17] and to predict the impact of vaccination programs in preventing HBV-related death.[38] These studies mainly give an economic message, whereas we focused our study on the health aspect of the burden of disease. Apparently, CHB is not only a problem of the less developed countries with high HBV endemicity but also a problem of countries with a low endemicity because there is a high absolute number of preventable liver-related deaths in a 20-year period.

The important clinical benefits described in this study can be obtained only if the full subgroup of active CHB patients is detected and treated for many years with high compliance. Currently, most of the eligible individuals are not treated because of limited screening activities to identify eligible cases. There are also major shortcomings in referral to specialist care,[39] where treatment can be started and monitored.

On the basis of this study, public health organizations should turn their attention, means, and actions increasingly to CHB and take the responsibility for identifying CHB and selecting those patients with potentially progressive disease for referral to treatment centres.

## ACKNOWLEDGEMENTS

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Chapter 5

# Mortality and morbidity of chronic hepatitis B and the cost-effectiveness of treating eligible patients in a median endemic country

Mehlika Toy[1,2]
Fatih Oguz Onder[3]
Ramazan Idilman[4]
Gokhan Kabacam[4]
Jan Hendrik Richardus[1]
Mithat Bozdayi[6]
Meral Akdogan[3]
Zarife Kuloglu[6]
Aydan Kansu[6]
Solko Schalm[2,7]
Cihan Yurdaydin[4]

[1]Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands
[2]LiverDoc, Rotterdam, the Netherlands
[3]Department of Gastroenterology, Yuksek Ihtisas Hospital, Ankara, Turkey
[4]Department of Gastroenterology, School of medicine, Ankara University, Ankara, Turkey
[5]Hepatology Institute, School of Medicine, Ankara, Turkey
[6]Department of Pediatric Gastroenterology and Hepatology, School of Medicine, Ankara, Turkey
[7]Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands

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## ABSTRACT

**Background/Aims:** Chronic hepatitis B (CHB) infection is a serious public health problem due to its potential liver disease sequelae and highly expensive medical costs such as the need for liver transplantation. The aim of this study was to quantify the burden of active CHB in terms of mortality and morbidity in a median endemic country, the eligibility of antiviral treatment and to assess various treatment scenarios and possible salvage combinations for cost-effectiveness.

**Methods:** A population cohort from a large data base of chronic hepatitis B patients was constructed and stratified according to 10-year age groups, the prevalence of HBsAg, HBV DNA level, ALT level, HBeAg status and the presence of cirrhosis. An age-specific Markov model for disease progression and cost-effectiveness analysis was constructed and calibrated for the specific population setting for a period of 20 years.

**Results:** Around 3.2 million people (4.57% of the total population in Turkey) are estimated to be HBsAg carriers, of which 25 % are eligible for treatment. If the active cohort remains untreated, 31% will die due to liver related complications. Within a 20-year period, 11% will have developed decompensated cirrhosis, 12% liver cancer and 6% will need liver transplantation. Treating the cohort with tenofovir monotherapy, yielded the most quality adjusted life years (QALYs), and was the most cost-effective option for both HBeAg-positive and negative, cirrhotic and non-cirrhotic patients when compared with the "no treatment", lamivudine, adefovir salvage, pegylated interferon, roadmap concept, and entecavir scenarios.

**Conclusion:** In a country with considerable amount of active chronic hepatitis B patients such as Turkey, monotherapy with a highly potent 3$^{rd}$ generation drug has the most health-gain, and is cost-effective in both HBeAg-positive and negative in all stages of liver disease.

## INTRODUCTION

Chronic hepatitis B (CHB) is a major global public health problem and an important cause of morbidity and mortality from sequelae related to CHB which include, cirrhosis development, decompensation and hepatocellular carcinoma. Despite the availability of highly effective vaccine against hepatitis B virus (HBV), there are still more than 350 million chronic carriers. Worldwide, HBV infection accounts for 0.6–1.2 million deaths each year.[1]

Antiviral therapy is the only option to control and prevent progression of disease in chronic patients. The goal of therapy for chronic hepatitis B (CHB) is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated cirrhosis, end-stage liver disease, hepatocellular carcinoma (HCC) and death. The indications are generally the same for HBeAg-positive and negative patients. These are based mainly on the combination of three criteria: serum HBV DNA and ALT levels, and the stage of liver disease.[2]

Evaluating the public health impact of control/prevention programs is complex, particularly in the case of CHB. The course from infection exposure to the development of complications related to CHB infection may span multiple decades. Once diagnosed, treatment may modify the natural course for the better. The American and European guidelines on treatment of chronic hepatitis B recommend treatment with pegylated interferon or the nucleos(t)ide analogs (NA) entecavir or tenofovir.[2-3] The latter two NAs are preferred over other NAs because of their antiviral potency and a high genetic barrier to resistance. However, at least in areas outside the industrialized world, treatment options may need to be balanced with resource constraints. It should be of global concern that resource limitations are especially evident where hepatitis B is endemic or hyperendemic such as in the Far East or in Sub-Saharan Africa.[4-5] The consequences and costs of treatment strategies may help in contributing to the build up of health strategies. Currently, licenced drugs for treating CHB include lamivudine, adefovir, tenofovir, entecavir, telbivudine, pegylated interferon alpha 2a and the conventional interferons (IFN). The main aim of this study was to assess the long-term impact of antiviral therapy in preventing adverse outcomes of CHB infection. Assessment of cost-effectiveness of various treatment strategies and possible salvage treatment approaches were another aim of the study. For these goals, Turkey was used and investigated as a representative median endemic country. We first estimated the number of CHB cases in this country. Next, the burden of CHB in terms of morbidity and mortality was quantified. Finally, we assessed various treatment scenarios and possible salvage combinations for cost-effectiveness.

## PATIENTS AND METHODS

### Cohort definition

A population cohort of CHB patients was constructed from a recent meta-analysis of age- and region specific hepatitis B surface antigen (HBsAg) prevalence in Turkey.[6] We projected the age-stratified HBsAg prevalence to the total Turkish population which was 71.5 million in 2009.[7]

The HBsAg positive cohort was first divided into two groups, active and inactive CHB, based on hepatitis B e-antigen status, HBVDNA level, and serum alanine aminotransferase (ALT) level. The age-specific distributions of these factors were derived from a newly constructed patient database of the gastroenterology departments of the University of Ankara, and a state hospital in Ankara (Turkiye Yuksek Ihtisas Hastanesi) with 1453 newly diagnosed CHB patients. Both of these hospital departments receive patients from around the country. The differentiation of active and inactive CHB is essential since progression of the disease is different in these two groups. Patients with high HBV DNA levels HBV DNA $\geq 10^4$ copies/mL and elevated ALT (>2x ULN) have potentially progressive liver disease and are candidates for HBV antiviral therapy,[2] while those with low or undetectable HBV DNA and normal ALT levels usually are inactive HBsAg carriers with a low risk of disease progression. Lastly, we classified the active CHB patients into four categories, namely HBeAg (+) and HBeAg (-) CHB with or without cirrhosis, respectively, using age group-specific proportions from large HBeAg-positive and HBeAg-negative clinical trials.[8-9]

### Model and clinical probability estimates

We evaluated the cohort of treatment-naïve active CHB patients for mortality, morbidity, impact of treatment and cost-effectiveness of various treatment strategies for a follow-up time of 20 years, with the TreeAge Pro 2009 software (TreeAge Software, Inc., MA,USA). The model uses annual probabilities of transition from CHB to virologic response, and of progression to cirrhosis, decompensated liver disease or hepatocellular carcinoma, liver transplantation, and finally death. The natural history and treatment related annual probabilities are obtained mostly from systematic reviews published in the literature for the European context (Table 1-3).[10-35] These include both cohort studies describing the natural history of CHB, and clinical trials reporting the effect of treatment. When progression rates were reported, these were transformed into annual probabilities using a standard formula ($P=1-e^{-r't}$), where $P$ is the probability, $e$ is the base of the natural logarithm, $r$ is the event rate, and $t$ is the time interval.[36] Other causes of death not related to liver disease are included in the model, as age specific

mortality rates derived from the Turkish statistics institute.[7] The probabilities of receiving a liver transplant were calculated based on personal communications with 6 major liver transplantation centres distributed throughout Turkey. There are annually around 500 liver transplantations performed in Turkey, of which about 150 are for HBV alone (no co-infections included), and of these 150, about 120 have decompensated cirrhosis (120/500=24%) and around 30 have HCC (30/500=6%) as indication for liver transplantation.

**Table 1** | Annual Transition Estimates of the Natural History of Chronic Hepatitis B by Initial State

| Initial state | Outcome | Estimate (%)* | Reference |
|---|---|---|---|
| Chronic hepatitis B e+ | Resolution | 6.9 (2.0–23) | 10 |
| | Cirrhosis | 3.8 (1.6–5.9) | 11 |
| | Hepatocellular carcinoma | 0.3 (0.3–0.6) | 11 |
| | Chronic hepatitis B e- | 1.9 (1.0–3.8) | 11 |
| Chronic hepatitis B e- | Resolution | 1,6 (0.0–11) | 10 |
| | Cirrhosis | 9.7 (2.9–16.3) | 11 |
| | Hepatocellular carcinoma | 0.3 (0.3–0.6) | 11 |
| Cirrhosis e+ | Decompensated cirrhosis | 3.9 (2.0–7.9) | 12,13,14 |
| | Hepatocellular cancer | 1.8 (0.9–3.8) | 12,13,14 |
| | HBV related Death | 3.1 (3.1–3.8) | 12,13,14 |
| Cirrhosis e- | Decompensated cirrhosis | 2.7 (1.4–5.4) | 12,13,14 |
| | Hepatocellular cancer | 2.9 (1.0–5.6) | 12,13,14 |
| | HBV related Death | 3.1 (3.1–3.8) | 12,13,14 |
| Decompensated Cirrhosis | Liver transplantation | 23 (15–25) | personal communication[a] |
| | HBV related Death | 26 (15–62) | 12,13,14 |
| Hepatocellular carcinoma | Liver transplantation | 6 (3.0–7.0) | personal communication[a] |
| | HBV related Death | 35 (20–60) | 10 |
| Liver transplant | HBV related death | 6.6 (2.0–12) | 10 |

Abbreviation: HBV, hepatitis B virus.

* Ranges are shown in parentheses a The probabilities of receiving a liver transplantation for decompensated cirrhosis and hepatocellular carcinoma were calculated on the basis of data from six major transplant centres in Turkey

**Table 2** | Treatment-related annual transition estimates†

| | | Estimate (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Initial state** | **Outcome** | **Lamivudine** | | **Entecavir** | | **Adefovir Salvage** | | **Tenofovir** | | **Tenofovir Salvage** | |
| **HBeAg status** | | + | - | + | - | + | - | + | - | + | - |
| CHB Initial therapy¶ | Sustained virological response | 20 | 10 | 22c | 11c | 12 | 10 | 23 | 11 | 19 | 11 |
| | Cirrhosis* | 0.5 | 1.2 | 0.2 | 0.6 | 0.5 | 1.2 | 0,2 | 0,6 | 0.5 | 1.2 |
| | Hepatocellular carcinoma** | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0,2 | 0,2 | 0.2 | 0.2 |
| CHB long-term therapy | Sustained virological response | 24 | 10 | 27† | 11^ | 12 | 10 | 27 | 11 | 19 | 11 |
| | Cirrhosisd | 0.5 | 1.2 | 0.2 | 0.6 | 0.5 | 1.2 | 0.2 | 0.6 | 0.5 | 1.2 |
| | Resistance: year 1 | 23^ | 23^ | 0.1 | 0.1 | 6" | 6" | 0 | 0 | 0 | 0 |
| | year 2 | 42^ | 42^ | 0.3 | 0.3 | 21" | 21" | 0 | 0 | 1 | 1 |
| | year 3 | 53^ | 53^ | 0.4 | 0.4 | 21" | 21" | 0.4 | 0.4 | 1 | 1 |
| | year 4 | 70^ | 70^ | 0.8 | 0.8 | 21" | 21" | 0.8 | 0.8 | 1 | 1 |
| | year 5 | 74^ | 74^ | 1 | 1 | 21" | 21" | 1 | 1 | 1 | 1 |
| | Hepatocellular carcinomag | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| resistant CHB long-term therapy | Sustained virological response | 4.5 | 0 | 5^ | 0.5^ | 4.5 | 0 | 5 | 0,5 | 5 | 0,5 |
| | Cirrhosis* | 2.7 | 6.2 | 2.7 | 6.2 | 2.7 | 6.2 | 2.7 | 6.2 | 2.7 | 6.2 |
| | Hepatocellular carcinomag | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |
| Cirrhosis Initial therapy | Sustained virological response | 20 | 10 | 22^ | 11^ | 12 | 10 | 23 | 12 | 19 | 11 |
| | Hepatocellular carcinomag | 0.9 | 1.5 | 0.9 | 1.5 | 0.9 | 1.5 | 0.9 | 1.5 | 0.9 | 1.5 |
| Cirrhosis long-term therapy | Sustained virological response | 24 | 10 | 27^ | 11^ | 12 | 10 | 27 | 11 | 19 | 11 |
| | Resistance: year 1 | 23^ | 23^ | 0.1 | 0.1 | 6” | 6” | 0 | 0 | 0 | 0 |
| | year 2 | 42^ | 42^ | 0.3 | 0.3 | 21" | 21" | 0 | 0 | 1 | 1 |

| | | Estimate (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Initial state** | **Outcome** | **Lamivudine** | | **Entecavir** | | **Adefovir Salvage** | | **Tenofovir** | | **Tenofovir Salvage** | |
| **HBeAg status** | | + | - | + | - | + | - | + | - | + | - |
| | year 3 | 53^ | 53^ | 0.4 | 0.4 | 21" | 21" | 0.4 | 0.4 | 1 | 1 |
| | year 4 | 70^ | 70^ | 0.8 | 0.8 | 21" | 21" | 0.8 | 0.8 | 1 | 1 |
| | year 5 | 74^ | 74^ | 1 | 1 | 21" | 21" | 1 | 1 | 1 | 1 |
| | Decompensated Cirrhosis | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 |
| | Hepatocellular carcinoma | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 |
| | Death HBV | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 |
| resistant Cirrhosis long-term therapy | Sustained virological response | 4.5 | 0 | 5^ | 0.5^ | 4.5 | 0 | 5 | 0,5 | 5 | 0,5 |
| | Decompensated Cirrhosis | 7.9 | 7.9 | 7.9 | 7.9 | 7.9 | 7.9 | 7.9 | 7.9 | 7.9 | 7.9 |
| | Hepatocellular carcinoma | 1.8 | 2.9 | 1.8 | 2.9 | 1.8 | 2.9 | 1.8 | 2.9 | 1.8 | 2.9 |
| | Death HBV | 3.1 | 3.1 | 3.1 | 3.1 | 3.1 | 3.1 | 3.1 | 3.1 | 3.1 | 3.1 |
| Decompensated Cirrhosis | Liver Transplantation§ | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 |
| | Death HBV | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 |
| Hepatocellular carcinoma | Liver Transplantation§ | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 |
| | Death HBV | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 |
| Liver Transplantation | Death HBV | 6.6 | 6.6 | 6.6 | 6.6 | 6.6 | 6.6 | 6.6 | 6.6 | 6.6 | 6.6 |

† Estimates from Kanwal 2005 and 2006 et al. Ref. 10,15. ‡ Initial therapy is 12 months (48 weeks) of therapy. * Estimates from recent clinical trials: Chang et al. 2006, Lai et al. 2006 and Colonno 2007, Ref. 16-18. d Estimates calculated by the author, based on the assumption that the natural progression rates of chronic hepatitis B are reduced by antiviral therapy. Estimates derived from natural history estimate similar to Kanwal's assumption of no progression of disease in HBeAg seroconversion, we assume no progression of disease in case HBV DNA is undetectable by PCR. In the papers from Chang and Lai full suppression of HBV DNA was observed in 80% with a high resistance profile drug, and 90% with a low resistance profile drug. We took these percentages for our calculations. Ref. 16,17. ** Estimates for Lamivudine resistance from Lai et al. And Moskovitz et al. Ref. 19,20. § Adefovir salvage resistance estimates from Lee et al., Chen et al. And Yeon et al. Ref. 21-23. ¶ Estimates based on reduction of progression rates by nucleoside analogue therapy of 50 % Ref. 24. ^ The probabilities of receiving a liver transplantation for decompensated cirrhosis and hepatocellular carcinoma were calculated on the basis of data from six major transplant centres in Turkey. ^^ Estimates for entecavir resistance from Colonno et al. 2006, Colonno et al. 2007 and Tenny et al. 2009 Ref. 18,25,26. " Tenofovir monotherapy estimates Ref. 27. "" Tenofovir salvage scenario estimates from van Bommel et al. 2004, Sarin et al., van Bommel et al. 2009 and Reijnders et al. Ref. 28-31.

**Table 3** | Annual costs and health state utilities for chronic hepatitis B

| Parameter | Base-case estimate TL (€) | (range) | Reference |
|---|---|---|---|
| *Drug costs (year 2009 values)* | | | |
| Lamivudine treatment (100mg) | 1.176 (585) | n.a | 45 |
| Adefovir salvage treatment (10mg) | 12.012 (5.976) | n.a | 45 |
| Entecavir treatment (0,5mg) | 11.292 (5.618) | n.a | 45 |
| Tenofovir (245mg) | 8.028 (3.994) | n.a | 45 |
| Peg-INF alfa 2a (INJVL 180MCG/ML) | 19.344 (9.624) | n.a | 45 |
| *Medical management costs* | | | personal communication[a] |
| Monitoring of CHB | 720 (358) | n.a | |
| Compensated Cirrhosis | 1.204 (602) | n.a | |
| Decompensated Cirrhosis | 5.364 (2.668) | n.a | |
| Hepatocellular carcinoma | 14.300 (7.114) | n.a | |
| Liver transplantation | 174.050 (86.592) | n.a | |
| *Health state utilities** | | | |
| Durable response to treatment | 1.00 | (0.95–1.00) | 46 |
| Chronic HBV | 0.68 | (0.66–0.70) | 46 |
| Compensated cirrhosis | 0.69 | (0.66–0.71) | 46 |
| Decompensated cirrhosis | 0.35 | (0.32–0.37) | 46 |
| Hepatocellulr carcinoma | 0.38 | (0.36–0.41) | 46 |
| Liver transplantation | 0.67 | (0.64–0.69) | 46 |

[a] Obtained from a retrospective analysis of medical records of a sample of 3000 hospital admissions unpublished work
* See Levy et al. (Ref. 46 ) for the age-specific utilities

**Scenarios**

The following scenarios were analyzed in this study:

"*Natural History (no antiviral treatment)*" scenario: In this scenario, active CHB patients progress according to the natural history, following annual rates of progression derived from systematic reviews (Table 1). We assumed that patients were followed clinically but did not receive antiviral therapy for CHB. Patients followed the natural history according to their HBeAg and disease status (with or without cirrhosis). Resolution was defined as seroconversion to anti-HBe in HBeAg positive patients, and as persistent HBV DNA suppression and ALT normalization in HBeAg negative patients. We assumed that all patients

received regular ongoing care and that patients developing cirrhosis, decompensated cirrhosis and hepatocellular carcinoma were managed for these complications. We assumed that a proportion of patients with decompensated cirrhosis and HCC became eligible for liver transplantation.

"*Lamivudine monotherapy*" scenario: In this scenario, patients received 100mg orally once daily with the first licensed antiviral HBV drug that is associated with a high incidence of resistance.[24] Such monotherapy is still being practiced in many countries with limited resources.[5,37] We defined sustained virological response (SVR) in HBeAg positive patients as HBe-antigen loss and development of antibodies against HBeAg (anti-HBe). In HBeAg negative patients, therapy response was defined as HBV DNA levels < 300-400 copies/mL. We assigned different rates of disease progression under long-term therapy between resistant and non- resistant patients (Table 2).

"*Entecavir monotherapy*" scenario: Patients in this strategy received 0.5mg entacavir once daily.[38-39] The treatment related probability estimates are shown in Table 2.

"*Tenofovir monotherapy*" scenario: In this scenario patients received 245mg of tenofovir for a continuum of 20 years. The annual probability of resistance in this scenario was 0% for the first and second years of treatment.

"*Adefovir salvage*" scenario: In this scenario, patients initially receive lamivudine. Once resistance occurs, patients are salvaged add-on by add-on adefovir. Patients without resistance continued to receive lamivudine.

"*Tenofovir salvage*" scenario: In this more up-to-date scenario, patients who have developed resistance during lamivudine therapy are switched to treatment with tenofovir.[31] "*Pegylated Interferon, followed by Tenofovir*" scenario: In this scenario patients receive 180 mcg/ml of pegylated interferon once a week subcutaneously, for 48 weeks. If the patients do not respond or relapse , they start tenofovir in the following year. The annual transition rates for SVR after 72 weeks of Peg-IFN was 30% for HBeAg-postive and 20% for HBeAg-negative patients.[32-34,40] The withdrawal rate was 2% and 5% for HBeAg-positive and negative patients, respectively.[35]

*"Roadmap concept"* scenario: A new modification issued in 2009 by the department within Turkish Health Authorities responsible for reimbursement decisions states that lamivudine should be the first line therapy in all non-cirrhotic patients with viral load lower than $10^7$copies/mL. In this scenario we applied the 'roadmap concept'[41] to the sub-group of CHB non-cirrhotic HBeAg-negative cases treated with lamivudine since lamivudine because of its low price continues to be widely used in HBV endemic areas. In this scenario, HBeAg (-) CHB patients with HBV DNA levels <$10^7$copies/mL start therapy with lamivudine; after 24 weeks virologic response on treatment is assessed. If HBV DNA is undetectable (50 UI/mL, 300

compies/mL), patients continue their treatment with lamivudine until resistance or virologic breakthrough occurs, after which patients are switched to tenofovir. However, if HBV DNA is above 300 copies/mL at 24 weeks, lamivudine is switched to tenefovir monotherapy already at week 24. 71 % of patients are expected to become HBV DNA negative at week 24 of treatment.[42] Annual resistance rate in these patients on lamivudine treatment is 2%.[43-44] Annual rate of HBV DNA relapse is 8.2% (28% at 4 years).[44]

### Assumptions

An assumption was that HBeAg-positive non-cirrhotic patients stop treatment after receiving one year consolidation treatment after HBeAg seroconversion and achieving undetectable HBV DNA levels,[2] while HBeAg-negative patients continue treatment[38] for the follow-up period of 20 years. Also our model assumes that the resistance for entecavir and tenofovir scenarios stays low as recent studies report. After the third year of treatment tenofovir resistance is assumed to be the same as entecavir. We took different time points to assess the outcomes for Pegylated interferon and nucleos(t)ide analogues. For the Peg-IFN scenario we assumed that the non-responders continued with long-term tenofovir treatment both in HBeAg-positive and negative patients. For the road map concept the annual resistance of 2% estimate was derived from the GLOBE telbivudine vs. lamivudine trial.[43]

### Costs and utility estimates

We conducted our analysis from the perspective of a third-party payer and used the indirect health care costs for many therapies, physician visits, diagnostic tests, and the complications in liver diseases. Medical costs are obtained from a retrospective analysis of the medical records of a sample of 542 patients (3000 hospital admissions), where a random sample of patients was selected from inactive carriers, CHB active, cirrhosis, HCC and liver transplantation cases. An average annual medical treatment cost (excluding antiviral treatment) per patient in each health state was calculated (unpublished work). The costs of antiviral drugs are obtained from the Turkish Ministry of Health.[45] A wide range of age-specific health state utilities are obtained from a multinational study on chronic hepatitis B.[46] Table 3 contains the specific cost and utility estimates. All costs and utilities were discounted at a rate of 3% per year.

### Sensitivity analysis

To study the effect of uncertainty of the robustness of our results we performed a sensitivity analysis on the low and high ranges of the transition estimates in the natural history scenario (Table 1). First, a so called best case scenario was assessed by applying the high

range of achieving spontaneous virological response, and the low ranges for the estimates of disease progression. Second, a worst case scenario was assessed by applying the low rates for spontaneous virological response, and the high ranges for the disease progression estimates. In addition, we performed a Monte Carlo simulation assuming that all variables followed a triangular distribution, with base case, low and high range of values. We simulated 10.000 trials and plotted the results on cost-effectiveness acceptability curve stratified by willingness to pay threshold to determine which treatment to use under different budgetary restraints.

### Outcomes

By applying the Markov cohort analysis, the cumulative mortality, and the cumulative probability of developing cirrhosis, decompensated cirrhosis , HCC, and getting a liver transplant were quantified for a 20-year time period. We measured costs (2009 Euro and Turkish Lira), quality adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER), to determine the additional cost to obtain one QALY. In the cost-effectiveness analysis approach, a scenario was cost-saving if costs were lower and effects higher compared to the natural history (no antiviral treatment) scenario.

## RESULTS

### Cohort

Table 4 shows the total population of Turkey in 2009 with the age-specific prevalence of HBsAg. Around 3.2 million people (4.6% of the total population) were estimated to be HBsAg carriers, with 22.6% of them having HBeAg-positive CHB and 77.4% having HBeAg-negative CHB. The total number of patients with active CHB was about 828.000 or 25% of the total HBsAg-positive cohort, of which 57% had HBeAg-positive and the rest HBeAg-negative CHB. The proportion that had cirrhosis in the active CHB cohort was 13%.

### Mortality and morbidity in the active CHB cohort

The estimated age-specific CHB burden in a 20-year follow up is shown in Table 5 for the natural history scenario. If the cohort of 828.347 individuals remains untreated, it is estimated that 256.788 (31%) will die due to liver related complications. Within a 20-year period, 11% will have developed decompensated cirrhosis, 12% HCC and 6% will need liver transplantation. At the entry into the cohort in the year 2009, 108.928 (13%) cases were estimated to be already in the cirrhotic stage. By the year 2029, another 247.261 (30%) cases

will have developed cirrhosis if left untreated, and this will have led to a cumulative number of 356.189 (43%) patients with cirrhosis in the eligible cohort.

### Impact of antiviral treatment on burden of disease

Treating the cohort with lamivudine monotherapy will decrease the mortality from 256.787 (31%) to 124.253 (15%) of cases and when salvage therapy without delay is applied once cases become resistant to lamivudine, mortality will further decrease to 49.700 (6%) cases. With the Peg-IFN (followed by tenofovir) strategy mortality will be reduced to 82.834 (10%) cases. Treating the same patients with entecavir or tenefovir monotherapy will decrease the mortality to 41.417 liver related deaths (5%).

### Cost-effectiveness

A plot of the outcomes of the various strategies on the cost-effectiveness plane according to HBeAg and disease status is shown in Figure 1. The total costs, QALYs gained, incremental QALYs, incremental costs and ICERs for each scenario are presented in table 6.

#### *CHB (non-cirrhosis)*

The increasing health gain achieved over a period of 20-years for both HBeAg-positive and negative patients have been assessed for lamivudine, the roadmap concept (for HBeAg-negative only), adefovir salvage, tenofovir salvage, pegylated interferon (followed by tenofovir), entecavir and tenofovir therapy strategies.

The natural history (no-treatment) strategy resulted in 14 and 9.3 QALYs and total discounted 20-year CHB related healthcare costs of 25.781 TL (€12.826) and 48.198 TL (€23.979) for the HBeAg-positive and negative cohort, respectively.

Both tenofovir and entecavir had equal incremental QALYs, however, entecavir compared to tenofovir, in a 20 year follow up period was 11.252 TL (€5.598) and 52.159 TL (€25.949) more expensive in HBeAg-positive and negative patients, respectively. The incremental cost-effectiveness ratio (ICER) of tenofovir versus no treatment was 638 TL (€318) and 15.573 TL (€ 7.747) for HBeAg-positive and negative patients, respectively. The next lowest ICER for HBeAg-negative CHB was for the roadmap concept scenario (ICER= 15.829 TL, € 7.875).

**Table 4** | Age Group Specific Distribution of Chronic Hepatitis B in Turkey by HBeAg and Stage of Liver Disease

| Age Group | | | | | Active CHB | | Cirrhosis | | Chronic hepatitis (No Cirrhosis) | |
|---|---|---|---|---|---|---|---|---|---|---|
| (years) | Population | HBsAg+(%) | HBeAg+ | HBeAg- | HBeAg+ | HBeAg- | HBeAg+(%) | HBeAg-(%) | HBeAg+ | HBeAg- |
| 0-14 | 18.788.587 | 533.596(2.84) | 283.828 | 249.768 | 90.621 | 47.586 | 1.818(2) | 2.379(5) | 88.808 | 45.207 |
| 15-24 | 12.441.662 | 490.201(3.94) | 176.473 | 313.729 | 91.504 | 45.804 | 1.830(2) | 2.290(5) | 89.674 | 43.514 |
| 25-34 | 12.328.944 | 784.121(6.36) | 159.961 | 624.160 | 113.892 | 132.322 | 6.834(6) | 9.263(7) | 107.058 | 123.059 |
| 35-44 | 10.070.734 | 624.386(6.20) | 62.439 | 561.947 | 35.222 | 96.610 | 2.466(7) | 14.491(15) | 32.756 | 82.118 |
| 45-54 | 7.927.348 | 437.590(5.52) | 22.655 | 414.935 | 11.923 | 74.353 | 2.981(25) | 20.819(28) | 8.943 | 53.534 |
| 55-64 | 5.066.402 | 184.924(3.65) | 12.753 | 172.170 | 5.070 | 41.595 | 1.673(33) | 21.214(51) | 3.397 | 20.382 |
| 65+ | 4.893.423 | 197.205(4.03) | 18.260 | 178.945 | 4.565 | 37.280 | 0 | 20.877(56) | 4.565 | 16.403 |
| Total | 71.517.100 | 3.252.022(4.57) | 736.367 | 2.515.655 | 352.797 | 475.550 | 17.595(9) | 91.333(19) | 335.202 | 384.217 |

Abbreviations: CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

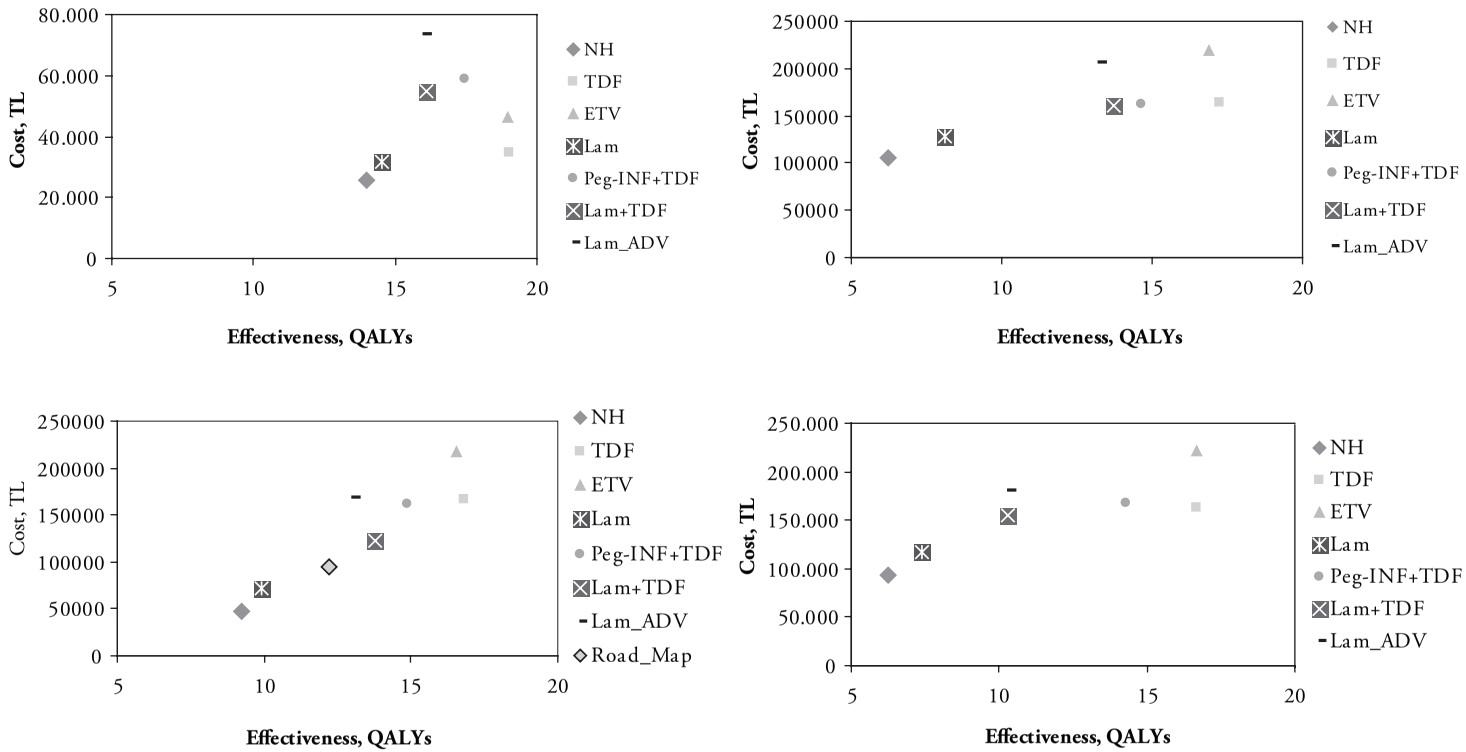


**Figure 1** | Results of cost-effectiveness analysis stratified by hepatitis B e antigen (HBeAg) and stage of liver disease: (**A**) HBeAg-positive (non-cirrhosis) (**B**) HBeAg-negative (non-cirrhosis) (**C**) HBeAg-positive (cirrhosis) (**D**) HBeAg-negative (cirrhosis). Results plotted on a cost-effectiveness plane. The x-axis represents the gain in QALYs with each strategy, and the y-axis the total healthcare costs (year 2009 values).

***CHB (cirrhosis)***

The no-treatment strategy resulted in 6.2 QALYs and total healthcare costs of 104.859 TL (€52.168) and 93.954 TL (€46.743) for the cirrhotic HBeAg-positive and negative cohort, respectively. The lowest ICER was achieved with the tenofovir scenario versus no treatment which was 5.328 TL (€2.650) and 6.609 TL (€ 3.288) in the HBeAg-positive and negative cohort, respectively.

## Sensitivity analysis

The sensitivity analysis for the natural history scenario shows that, in comparison with the base case, in which the mortality of the active CHB cohort is 31%, the mortality ranges from 17% in the best case scenario to 42% in the worst case scenario. When assessed by subgroups, in the worst case scenario, mortality ranges from 4% to 28% for HBeAg-positive chronic hepatitis, from 8% to 35% for HBeAg-negative chronic hepatitis, and from 62% to 91% for cirrhosis independent of HBeAg status.

The height of the threshold value is of great influence on decisions in the reimbursement process and intervention policy. The World Health Organization defines the threshold value for intervention cost-effectiveness as three times the gross domestic product (GDP) of a country. The threshold value for Turkey is 36.212 TL (€ 18.016).47 The probabilistic sensitivity analysis indicated that the no-treatment strategy was preferred at cost-effectiveness thresholds less than approximately 30.000 TL (€ 14.925) per QALY, and tenofovir had the highest probability of being optimal above this threshold (Figure 2) for the HBeAg-positive (non-cirrhosis) patients. For the HBeAg-negative (non-cirrhosis) patients, tenofovir had the highest probability of being optimal above 30.000 TL (€ 14.925) per QALY.

For the HBeAg-positive cirrhotic patients, at a 15.000 TL (€ 7.462) per QALY threshold, tenofovir had the greatest net health benefit in 34% of the simulations, and pegylated Interferon (followed by tenofovir) in10 % of the simulations. In HBeAg-negative cirrhotic patients, tenofovir had a net health benefit of 46% and pegylated interferon (followed by tenofovir) 14% at a 15.000 TL (€ 7.462) per QALY threshold.

## Program costs for treating the eligible patients

In addition to the cost and QALY gained per patient, we calculated the total program costs if the active CHB patients are identified and treated with the most cost-effective strategy. Tenofovir monotherapy had the lowest ICER for all sub-groups (HBeAg-positive; 638 TL (€ 318), HBeAg-negative; 15.573 TL (€ 7.747), HBeAg-positive cirrhosis; 5.328 TL, (€ 2.650), HBeAg-negative cirrhosis; 6.609 TL, (€ 3.288)), with ICERs far below the 36.212

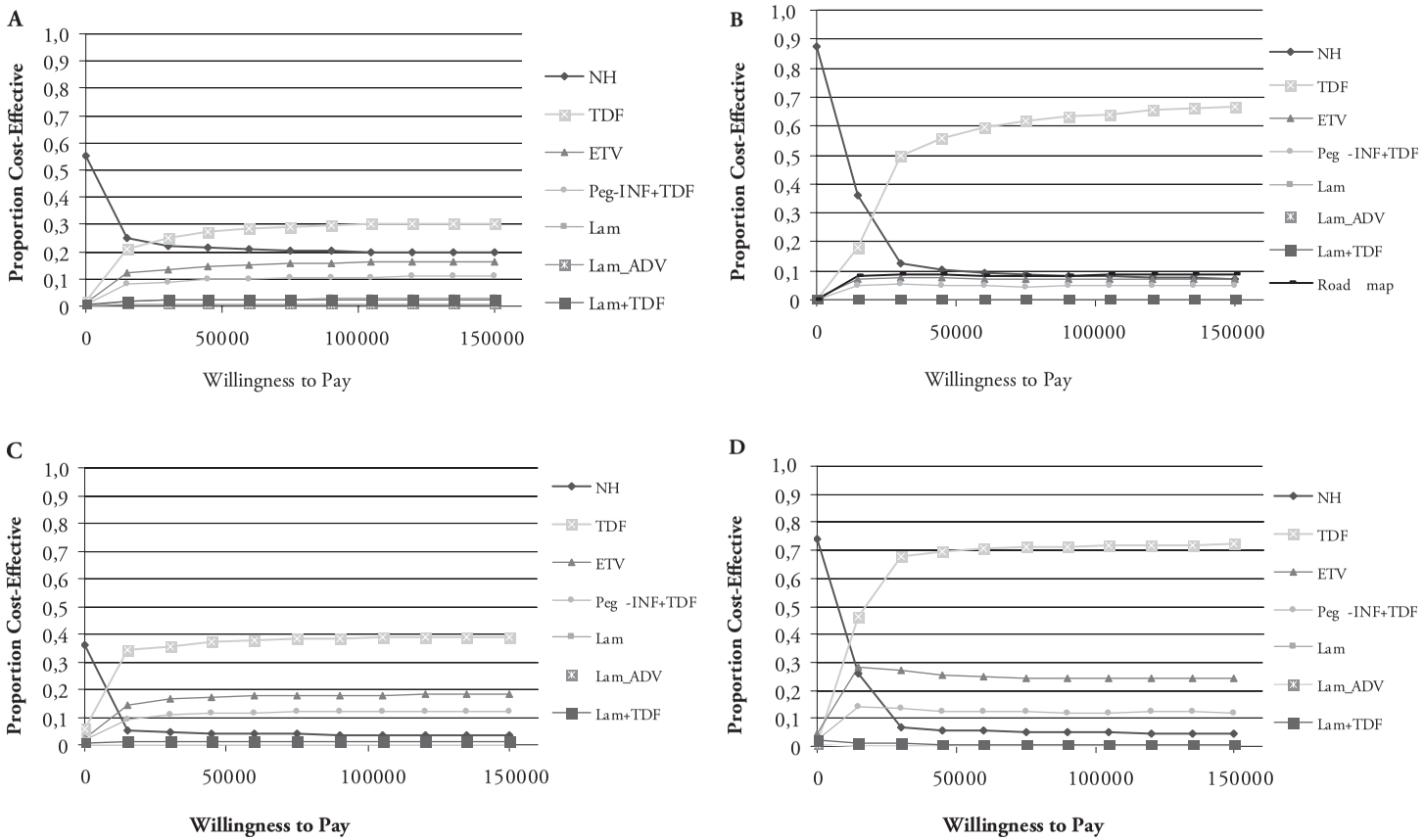


**Figure 2 |** Cost-effectiveness acceptability curves showing the probabilities of net benefits achieved by each strategy for different willingness to pay thresholds (the maximum amount a person is willing to pay for a good) in HBeAg-positive (non-cirrhosis) (**A**), HBeAg-negative (non-cirrhosis) (**B**), HBeAg-positive (cirrhosis) (**C**), and HBeAg-negative (cirrhosis) (**D**). The vertical axes represent the probability of cost-effectiveness. The horizontal axes represent willingness-to-pay threshold to gain one additional quality adjusted life year (QALY).

**Table 5** | Age-specific clincal outcome of Active Chronic Hepatitis B by HBeAg status in the Natural History Scenario

| HBeAg status | | Outcome | | | | |
|---|---|---|---|---|---|---|
| **Age-Group** | **n** | **Cirrhosis (%)** | **Decompensated Cirrhosis (%)** | **HCC (%)** | **Liver Transplant (%)** | **Death (%)** |
| *HBeAg+* | | | | | | |
| <15 | 90.621 | 819 (1) | 863 (1) | 1.234 (1) | 503 (0.5) | 2.574 (3) |
| 15-24 | 91.504 | 833 (1) | 877 (1) | 1.257 (1) | 512 (0.5) | 2.617 (3) |
| 25-34 | 113.892 | 35.401 (31) | 12.082 (11) | 8.461 (7) | 5.776 (5) | 27.276 (24) |
| 35-44 | 35.222 | 10.966 (31) | 3.694 (11) | 2.561 (7) | 1.769 (5) | 8.316 (24) |
| 45-54 | 11.923 | 3.783 (32) | 1.741 (15) | 1.050 (9) | 825 (7) | 3.842 (32) |
| 55-64 | 5.070 | 1.630 (32) | 779 (16) | 452 (9) | 359 (7) | 1.689 (33) |
| 65+ | 4.565 | 1.574 (34) | 241 (5) | 206 (5) | 109 (2) | 526 (12) |
| All HBeAg+ | 352.797 | 55.006 (16) | 20.277 (6) | 15.221 (4) | 9.853 (3) | 46.840 (13) |
| *HBeAg-* | | | | | | |
| <15 | 47.586 | 424 (1) | 680 (1) | 1.153 (2) | 412 (1) | 2.465 (5) |
| 15-24 | 45.804 | 406 (1) | 657 (1) | 1.110 (2) | 400 (1) | 2.389 (5) |
| 25-34 | 132.322 | 99.242 (75) | 22.392 (17) | 26.464 (20) | 11.770 (9) | 67.484 (51) |
| 35-44 | 96.610 | 73.924 (76) | 16.424 (17) | 19.322 (20) | 8.695 (9) | 50.237 (52) |
| 45-54 | 74.353 | 54.278 (73) | 12.640 (17) | 15.614 (21) | 6.692 (9) | 39.407 (53) |
| 55-64 | 41.595 | 28.285 (68) | 7.071 (17) | 8.319 (20) | 3.744 (9) | 22.045 (53) |
| 65+ | 37.280 | 25.723 (69) | 4.846 (13) | 5.592 (15) | 2.237 (6) | 13.794 (37) |
| All HBeAg- | 475.550 | 323.374 (68) | 76.088 (16) | 90.355 (19) | 38.044 (8) | 223.509 (47) |
| Total | 828.347 | 356.189 (43) | 91.118 (11) | 99.402 (12) | 49.701 (6) | 256.788 (31) |

TL (€ 18.016) threshold value. If the total 828.347 active CHB patients (table 5) are treated, it will cost about 4.6 billion TL (€2.3 billion) annually, if not treated the total costs are tripled due to progression to liver failure and the high costs of medical treatment (hospitalization) and the need for liver transplantation.

## DISCUSSION

In a country where the estimated number of HBsAg-positive cases is more than 3.2 million, the total amount of treatment eligible patients, which is quantified through population data and the large patient database constructed for this study, is 828 thousand, and of these, around 108 thousand are patients with liver cirrhosis. If these eligible patients are not identified and treated, about 12.800 deaths are expected to occur each year due to liver related complications, leading to a cumulative number of 256.788 (31%) in 20 years. The number of liver transplant patients in Turkey is 400−500 per year and this treatment is covered by the health insurance.[48] If we would modestly assume that 50% of liver transplantations are due to HBV, there will be a total of about 4.000 liver transplantations that will take place in 20 years, while the demand will be around 49 thousand, according to our estimates. On top of all the life years lost and more severe treatment options as liver transplantation are needed, the 20 year cumulative medical management cost of an untreated active HBeAg-positive and HBeAg-negative CHB (no-cirrhosis) patient will be 25.781 TL (€12.800), and 48.198 TL (€23.900), respectively. The medical management cost (no antiviral therapy) of a cirrhotic HBeAg-positive and negative patient will be 104.858 TL (€52.200) and 93.959 TL (€46.700), respectively.

If the estimated active CHB cohort is identified and treated with the most cost-effective drug, liver related mortality and morbidity can be reduced by almost 80%. Comparing treatment scenarios to the do nothing scenario in all the sub-cohorts, the tenofovir strategy was the most cost-effective. The ICER for HBeAg-positive and negative CHB (non-cirrhosis), and HBeAg-positive and negative cirrhosis was 638 TL (€306), 15.573 TL (€7.800), 5.300 TL (€2.600), and 6.609 TL (€3.300), respectively. Both entecavir and tenofovir, compared to the do nothing scenario, had the same amount of health gain. A recent systematic review and Bayesian meta-analysis concludes that in the first year of treatment for CHB, tenofovir and entecavir are the most potent oral antiviral agents for HBeAg-positive patients, while for HBeAg-negative patients tenofovir is most effective.[49] According to net sold medication counts per year in Turkey, it was calculated that no more than 10% of active CHB patients

receive antiviral treatment, indicating a massive shortcoming in reducing eligible patients with life prolonged and even life saving treatments.

The future public health burden of chronic hepatitis B could potentially be reduced by antiviral treatment.[50] The recommendations by the Turkish Association for the Study of the Liver (TASL)[51] to treat eligible patients are in line with the European Association for the Study of the Liver[2] criteria, except that liver biopsy evidence is always required to start treatment in patients with no established cirrhosis. Almost all patients are reimbursed for treatment of viral hepatitis through the national insurance system in Turkey. A new modification issued in 2009 by the department within Turkish Health Authorities responsible for reimbursement decisions, states that lamivudine should be the first line therapy in all patients with viral load lower than $10^7$copies/ml. This is partially due to the low costs of lamivudine and to the recent data on on-treatment monitoring approach, using serum HBV DNA level as a predictor for efficacy and drug resistance. In our scenario analysis we have analyzed this concept on HBeAg-negative non-cirrhotic patients alone, because for this sub-group sufficient data was available. Both tenofovir monotherapy and the roadmap concept scenarios were almost equally cost-effective, with an ICER of 15.573 TL (€7.747), 15.829 (€7.875), respectively. Although the ICERs of both scenarios were almost the same, the healthy life gain compared to the do nothing strategy differed considerably among scenarios. Almost 8 healthy life years were gained by tenofovir monotherapy while this was only 3 health life years gained for the roadmap concept scenario.

According to our outcomes the roadmap concept could be an alternative strategy to consider for a country with a large HBeAg-negative disease, where the active infection represents an advanced stage of disease.[52] And this scenario could be also suggested in recourse scarce settings, with high HBV endemicity. HBV genotype D, which is predominant in Turkey, is associated with a higher prevalence of HBeAg-negative infection and is more common in Southern-Europe. Patients with HBeAg-negative active infection are usually older than patients with HBeAg-positive infection and are more likely to have cirrhosis at the time of their first presentation.[52-53] This kind of pattern was seen in the age group specific cohort we have constructed (Table 4). The clinical trials used to estimate the probability of SVR in Peg-INF scenario under represents genotype D outcomes. We therefore assume that our outcomes for the Peg-INF scenario are an overestimation for the setting of a country that is genotype D dominant as patients with genotype D appear to respond Peg-IFN less compared to other genotypes.[54]

A limitation of our study is that we used simplified assumptions (e.g., we did not consider coinfection with other viruses or toxins such as alcohol that will accelerate progression),

and we assumed the cohort to be static, so there were no new cases added to the cohort. Also the assumption that the development of resistance both with entecavir and tenofovir for the coming 20-years will stay at 0−1% per year may underestimate what will happen as longer term data are collected. We took a rather conservative approach by only including high HBV DNA and ALT>2xULN. If like in the guidelines, we had taken elevated ALT levels but starting at 1xULN, the number of eligible patients would have increased. Another factor that surely plays an important role in the estimation of eligible patients is the inclusion of data from tertiary centres. In Turkey, data on viral hepatitis is collected at the provincial health directorate, but only for acute (incident) cases. The data thus on CHB patients is derived from clinical settings, although not all patients coming to the hospital have active disease. Some patients are detected during the diagnostic process for other diseases and referred to the hepatology department. We conclude that the cohort data from Turkey is therefore likely to be biased towards more active CHB cases, which could mean that the number of eligible patients might be an overestimation. Any attempt to predict the future is likely to be biased. Therefore, our projections and estimates regarding future treatment rates and liver-related deaths are only intended to provide a crude overview of the public health impact of antiviral therapy.

Identification of chronic hepatitis B infected individuals is essential to ensure that infected persons receive necessary care to prevent or delay onset of significant liver disease and services to prevent transmission to others. Testing for CHB meets established public health screening criteria.[55] Chronic hepatitis B can be detected by reliable, inexpensive, and minimally invasive screening tests. The cost of HBsAg testing in populations with 2% or greater prevalence is substantially lower than the costs per case identified for many fetal and new born hearing disorders [56]. In a future study, the outcome of screening programs to identify and treat CHB cases will be assessed, to make resource allocation decisions.

Given the substantial mortality and morbidity attributable to HBV related chronic liver diseases, the control of progression to cirrhosis, decompensated cirrhosis and liver cancer will continue to be an important public health priority. CHB patients have years of life to gain in medical evaluation, monitoring, or if therapy is initiated early, before symptoms develop.

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Chapter 6

# Modelling age-specific health gain and costs of antiviral therapy for active chronic hepatitis B

Mehlika Toy[1,2]
W. Ken Redekop[3]
Irene K. Veldhuijzen[4]
Jan Hendrik Richardus[1,4]
Solko W. Schalm[2,5]

[1]Department of Public Health, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands
[2]LiverDoc, Rotterdam, the Netherlands
[3]Institute for Medical Technology Assessment, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands
[4]Division of Infectious Diseases Control, Municipal Public Health Service Rotterdam-Rijnmond, Rotterdam, the Netherlands
[5]Department of Gastroenterology and Hepatology, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands

## ABSTRACT

**Objectives:** The aim of this study was to estimate the cost-effectiveness of long-term antiviral therapy of various nucleos(t)ide analogues, salvage therapy in case of resistance, and a sequential strategy with pegylated interferon followed by nucleoside analog in case of absence of response, compared to a do-nothing strategy (no antivirals) in chronic hepatitis B (CHB) patients.

**Methods:** A Markov model was used to estimate the 20-year cost and quality adjusted life years (QALYs) of HBeAg-postive and HBeAg-negative patients, with or without cirrhosis. Six interventions (lamivudine mono, entecavir mono, tenofovir mono, adefovir salvage, tenofovir salvage and pegylated interferon followed by tenofovir) compared to the natural history (no antivirals) scenario were chosen for analysis.

**Results:** The tenofovir and entecavir mono therapies yielded the most QALYs for both HBeAg-positive and negative patients, with or without cirrhosis, when compared to the natural history (no antivirals) scenario. The incremental cost-effectiveness ratio (ICER) of tenofovir for the CHB non-cirrhotic HBeAg-positive and negative patients were € 18.100 and € 10.300, respectively. For the cirrhotic group, again tenofovir monotherapy was the most cost-effective option with an ICER for HBeAg-positive and negative of € 5.200 and € 5.300, respectively.

**Conclusion:** All treatment scenarios compared to the do nothing (no antiviral) scenario were cost-effective. The cost of treating patients at a younger age and an earlier stage is significantly less then the cost of treating older patients in advanced stage of disease.

## INTRODUCTION

Chronic hepatitis B (CHB) infection is a long-time serious public health problem due to its potential morbidity and mortality from liver disease. It is estimated that about 360 million people are chronically infected worldwide and that 500,000 – 700,000 people die of the disease annually.[1] The availability of vaccination against hepatitis B has resulted in a reduction in the rate of chronic infection,[2] and thereby to a general attitude that vaccination will solve the problem of chronic hepatitis B. However, since vaccine is of no help for those already infected, the enormous reservoir of patients with chronic hepatitis B remains a major public health problem. Antiviral therapy is the only option to control and prevent progression of disease in patients with active CHB.[3] Therapy with antiviral agents suppresses hepatitis B virus (HBV) replication. Maintaining suppression of HBV replication by antivirals may reduce the incidence rate of decompensation of cirrhosis to less than 1% year; the progression rate to hepatocellular carcinoma (HCC) in patients with advanced fibrosis or cirrhosis falls with 50%.[4]

Despite the considerable potential benefits of antiviral drugs, only a minority of chronic hepatitis B patients are receiving this treatment.[5] An important problem of prolonged therapy with nucleos(t)ide analogues is the emergence of drug resistance, which may negate the therapeutic benefit. This problem can now be overcome by using 3rd generation drugs with minimal resistance in treatment-naïve patients.[6] A second problem is the high costs of treatment. This problem is particularly relevant in case of salvage therapy, use of pegylated interferon and 3rd generation drugs.

In a previous study,[7] we estimated the effects of prolonged (up to 20 years) antiviral therapy and antiviral resistance on the mortality and morbidity of active CHB. Knowing that a strategy of long-term antiviral therapy will minimize or control liver-related mortality and morbidity, we now studied the cost-effectiveness of long-term antiviral therapy of various nucleos(t)ide analogues, salvage therapy in case of resistance, and a sequential strategy with pegylated interferon followed by nucleoside analog in case of absence of response, compared to a do-nothing strategy (no antivirals).

# METHODS

## Cohort definition

In a previous study we have constructed a population cohort of CHB patients.[7] The HBsAg positive cohort was first divided into two groups, active and inactive CHB, based on hepatitis B e-antigen status, HBVDNA level, and serum alanine aminotransferase (ALT) level. The age-specific distribution of these factors were derived from a data base with 479 newly diagnosed CHB patients who were seen at the Municipal Public Health Service in Rotterdam-Rijnmond (MPHS), the Netherlands. Patients with high HBV DNA levels (HBV DNA $\geq 10^4$ copies/mL for HBeAg negative and $\geq 10^5$ for HBeAg positive) and elevated ALT (>2 ULN) have potentially progressive liver disease and are candidates for HBV antiviral therapy.[8-10] We have classified the CHB patients for our analysis into two categories, with or without cirrhosis, using age group-specific proportions from large HBeAg-positive and HBeAg-negative clinical trials, respectively.[11-12]

## Cost-effectiveness Model and clinical probability estimates

We evaluated the Dutch cohort of treatment-naïve active CHB patients aged > 25 years for a cost-effectiveness analysis with a follow-up time of 20 years, with TreeAge Pro 2009 (TreeAge Software, Inc., MA,USA). A follow-up time of 20-years was chosen to project the current clinical practice as realistic as possible for a defined period of time. The model describes disease progression and determines the long-term morbidity and mortality of the cohort during follow up. The model uses annual probabilities of transition from CHB to virologic response, and of progression to cirrhosis, decompensated liver disease or hepatocellular carcinoma, and finally death. The natural history and treatment related annual probabilities are obtained from our previous modelling study, and recent available studies. (Table 1 and 2).[13-38] When progression rates were reported, these were transformed into annual probabilities using a standard formula ($P=1-e^{-r\times t}$), where $P$ is the probability, $e$ is the base of the natural logarithm, $r$ is the event rate, and $t$ is the time interval.[39] Other causes of death not related to liver disease are included in the model, as age specific mortality rates derived from Statistics Netherlands.[40] The age-group specific analysis was done separately for HBeAg-positive and negative subgroups, with and without cirrhosis. Also a weighted average was taken for each age-group specific outcome. We defined virologic response in HBeAg positive patients as HBe-antigen loss and development of antibodies against HBeAg (anti-HBe). In HBeAg negative patients, virologic response during antiviral therapy was defined as HBV DNA levels undetectable (< 300 copies/mL) by polymerase chain reaction.

**Table 1** | Annual Transition Estimates of the Natural History of Chronic Hepatitis B by Initial State

| Initial state | Outcome | Estimate (%) * | Reference |
|---|---|---|---|
| Chronic hepatitis B e+ | Resolution | 6.9 (2.0–23) | 14,15 |
| | Cirrhosis | 2.7 (1.6–3.8) | 16 |
| | Hepatocellular carcinoma | 0.4 (0.3–0.6) | 16 |
| | Chronic hepatitis B e- | 1.9 (1.0–3.8) | 16 |
| Chronic hepatitis B e- | Resolution | 1,6 (0.0–11) | 14,15 |
| | Cirrhosis | 6.2 (2.8–9.7) | 16 |
| | Hepatocellular carcinoma | 0.4 (0.3–0.6) | 16 |
| Cirrhosis e+ | Decompensated cirrhosis | 3.9 (2.0–7.9) | 17-19 |
| | Hepatocellular cancer | 1.8 (0.9–3.8) | 17-20 |
| | HBV related Death | 3.1 (3.1–3.8) | 16-19 |
| Cirrhosis e- | Decompensated cirrhosis | 2.7 (1.4–5.4) | 17-19 |
| | Hepatocellular cancer | 2.9 (1.0–5.6) | 17-20 |
| | HBV related Death | 3.1 (3.1–3.8) | 16-19 |
| Decompensated cirrhosis | Liver transplantation | 3.3 (1.0–8.4) | 20,21 |
| | HBV related Death | 26 (15–62) | 16 |
| Hepatocellular carcinoma | Liver transplantation | 1.2 (0.2–5.0) | 20,21 |
| | HBV related Death | 35 (20–60) | 14,15 |
| Liver transplant | HBV related death | 6.6 (2.0–12) | 14,15 |

Abbreviation: HBV, hepatitis B virus. * Ranges are shown in parentheses

## Scenario Analysis

Seven different scenarios were analyzed in this study.

"*Natural History (no antiviral treatment)*" scenario: In this scenario, active CHB patients progress according to the natural history, following annual rates of progression derived from systematic reviews (Table 1). We assumed that patients were followed clinically but did not receive antiviral therapy for CHB. Patients followed the natural history according to their HBeAg and disease status (with or without cirrhosis). Spontaneous virologic response was defined as seroconversion to anti-HBe in HBeAg positive patients, and as persisitent HBV DNA suppression and ALT normalization in HBeAg negative patients. We assumed that all patients received regular ongoing care, and that patients developing cirrhosis, decompensated cirrhosis and hepatocellular carcinoma were managed for complications. We assumed that

a proportion of patients with decompensated cirrhosis and HCC became eligible for liver transplantation. The probabilities of receiving a liver transplant were calculated based on figures from the European liver transplant registry and the Dutch transplantation organization.[19-20]

"*Lamivudine monotherapy*" scenario: In this scenario, patients received 100mg orally once daily of the first licensed antiviral HBV drug. This drug is known to be associated with a high incidence of resistance.[4] Such monotherapy is still being practiced in many countries with limited resources.[41] We assigned different rates of virologic response under long-term therapy between resistant and non- resistant patients (Table 2). Following current practice guidelines we assigned patients who did not respond to initial therapy or who experienced relapse after initial response, to long-term therapy until they developed a subsequent virologic response.

"*Adefovir salvage*" scenario: In this scenario, the patients initially receive lamivudine. Once resistance occurs, patients were salvaged by adefovir, which is a relevant therapeutic alternative. Patients without resistance continued to receive the initial drug lamivudine.

"*Entecavir monotherapy*" scenario: Patients in this strategy received 0.5mg entacavir once daily, for a 20 year follow-up time.[42-43] The treatment related probability estimates are shown in Table 2.

"*Tenofovir monotherapy*" scenario: In this scenario patients received 245mg of tenofovir for a continuum of 20 years. The annual probability of resistance in this scenario was 0%, but with a sensitivity analysis we also had higher ranges.

"*Tenofovir salvage*" scenario: This alternative is a new approach in the combination therapy.[34] The patients initially receive lamivudine, and once resistance occurs, patients are salvaged by tenofovir.

"*Pegylated Interferon, followed by Tenofovir*" scenario: In this scenario patients receive 180 mcg/ml of injectable pegylated interferon once a week, for 48 weeks. If the patient does not respond or relapses in the second year of off-treatment, they start tenofovir.

## Model assumptions

Treatment guidelines often recommend a finite period of therapy with oral nucleoside analogs for patients with HBeAg-positive CHB who undergo HBeAg seroconversion with patients with evolving HBeAg-negative CHB and active HBV DNA replication (> $\log^4$ IU/ml) and patients with cirrhosis prolonged therapy is to be considered.[9,44-46] More recent publications[42] suggest continuation of long-term nucleos(t)ide analogue treatment, irrespective of the occurrence of HBeAg seroconversion in HBeAg-positive patients. Following these recent findings, our model assumes continued antiviral therapy for HBeAg-positive patients even if seroconversion occurs. Also our model assumes that the resistance rate for entecavir and tenofovir remain as

low as recent studies report. The model built for Peg-IFN assumed that non-responders and relapsers continue with long-term tenofovir treatment both in HBeAg-positive and negative patients.

### Utilities

We incorporated a wide range of relevant age-specific health state utilities in our model, obtained from a multinational study on chronic hepatitis B.[47] In that study, utilities were elicited using an interview administered survey from populations in six countries, with a total of 534 HBV-infected patients and 600 uninfected respondents. Table 4 contains the specific utility estimates. We discounted all utilities at 3% per year.

### Cost estimates

We conducted our analysis from the perspective of a third-party payer and used the indirect health care costs for physician visits, diagnostic tests, and the management of complications in liver diseases (Table 4). Medical costs are expressed as Diagnosis Treatment Combinations (DBCs) which are used in the Netherlands for the registration and reimbursement of hospital and medical specialist care since 2005.[48] DBCs are defined as the whole set of activities and interventions of the hospital and medical specialist resulting from the first consultation and diagnosis of the medical specialist in the hospital. The costs for the antiviral drugs are obtained from the Dutch Health Care Insurance Board (CVZ).[49] We discounted all costs at 3% per year.

### Outcomes

Quality-adjusted life-years (QALYs) is the standard parameter that allows cost-effectiveness to be assessed.[50-51] Our analysis also reports the ICER (incremental cost effectiveness ratio), to determine per scenario the additional cost to obtain one extra QALY. The outcome is age-specific as well as a weighted average outcome for the whole cohort (sub-groups).

### Sensitivity analysis

A Monte Carlo simulation was conducted, assuming that all variables followed a triangular distribution, with base case, low and high range of values. We simulated 10.000 trials and plotted the results on cost-effectiveness acceptability curve stratified by willingness to pay threshold. The standard deviations of low and high ranges from the sensitivity analysis were applied to the health gain outcomes.

**Table 2** | Treatment-related annual transition estimates†

| **Turkish** | | **Estimate (%)** | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Initial state** | **Outcome** | **Lamivudine** | | **Entecavir^^** | | **Adefovir Salvage** | | **Tenofovir** | | **Tenofovir Salvage”"** | |
| HBeAg status | | + | - | + | - | + | - | + | - | + | - |
| CHB Initial therapy¶ | Sustained virological response | 20 | 10 | 22‡ | 11‡ | 12 | 10 | 23 | 11 | 19 | 11 |
| | Cirrhosis* | 0.5 | 1.2 | 0.2 | 0.6 | 0.5 | 1.2 | 0.2 | 0.6 | 0.5 | 1.2 |
| | Hepatocellular carcinoma** | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| CHB long-term therapy | Sustained virological response | 24 | 10 | 27‡ | 11‡ | 12 | 10 | 27 | 11 | 19 | 11 |
| | Cirrhosis* | 0.5 | 1.2 | 0.2 | 0.6 | 0.5 | 1.2 | 0.2 | 0.6 | 0.5 | 1.2 |
| | Resistance: year 1 | 23^ | 23^ | 0.1 | 0.1 | 6” | 6” | 0 | 0 | 0 | 0 |
| | year 2 | 42^ | 42^ | 0.3 | 0.3 | 21” | 21” | 0 | 0 | 1 | 1 |
| | year 3 | 53^ | 53^ | 0.4 | 0.4 | 21” | 21” | 0.4 | 0.4 | 1 | 1 |
| | year 4 | 70^ | 70^ | 0.8 | 0.8 | 21” | 21” | 0.8 | 0.8 | 1 | 1 |
| | year 5 | 74^ | 74^ | 1 | 1 | 21” | 21” | 1 | 1 | 1 | 1 |
| | Hepatocellular carcinoma** | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 | 0.2 |
| resistant CHB long-term therapy | Sustained virological response | 4.5 | 0 | 5‡ | 0.5‡ | 4.5 | 0 | 5 | 0.5 | 5 | 0.5 |
| | Cirrhosis* | 2.7 | 6.2 | 2.7 | 6.2 | 2.7 | 6.2 | 2.7 | 6.2 | 2.7 | 6.2 |
| | Hepatocellular carcinoma** | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 | 0.4 |
| Cirrhosis Initial therapy | Sustained virological response | 20 | 10 | 22‡ | 11‡ | 12 | 10 | 23 | 12 | 19 | 11 |
| | Hepatocellular carcinoma** | 0.9 | 1.5 | 0.9 | 1.5 | 0.9 | 1.5 | 0.9 | 1.5 | 0.9 | 1.5 |
| Cirrhosis long-term therapy | Sustained virological response | 24 | 10 | 27‡ | 11‡ | 12 | 10 | 27 | 11 | 19 | 11 |
| | Resistance: year 1 | 23^ | 23^ | 0.1 | 0.1 | 6” | 6” | 0 | 0 | 0 | 0 |
| | year 2 | 42^ | 42^ | 0.3 | 0.3 | 21” | 21” | 0 | 0 | 1 | 1 |
| | year 3 | 53^ | 53^ | 0.4 | 0.4 | 21” | 21” | 0.4 | 0.4 | 1 | 1 |
| | year 4 | 70^ | 70^ | 0.8 | 0.8 | 21” | 21” | 0.8 | 0.8 | 1 | 1 |

| Turkish | | Estimate (%) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Initial state | Outcome | Lamivudine | | Entecavir^^ | | Adefovir Salvage | | Tenofovir | | Tenofovir Salvage”” | |
| HBeAg status | | + | - | + | - | + | - | + | - | + | - |
| Cirrhosis long-term therapy *(Cont.)* | year 5 | 74^ | 74^ | 1 | 1 | 21” | 21” | 1 | 1 | 1 | 1 |
| | Decompensated Cirrhosis | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 | 1.9 |
| | Hepatocellular carcinoma | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 | 1.6 |
| | Death HBV | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 | 2.4 |
| resistant Cirrhosis long-term therapy | Sustained virological response | 4.5 | 0 | 5‡ | 0.5‡ | 4.5 | 0 | 5 | 0.5 | 5 | 0.5 |
| | Decompensated Cirrhosis | 7.9 | 7.9 | 7.9 | 7.9 | 7.9 | 7.9 | 7.9 | 7.9 | 7.9 | 7.9 |
| | Hepatocellular carcinoma | 1.8 | 2.9 | 1.8 | 2.9 | 1.8 | 2.9 | 1.8 | 2.9 | 1.8 | 2.9 |
| | Death HBV | 3.1 | 3.1 | 3.1 | 3.1 | 3.1 | 3.1 | 3.1 | 3.1 | 3.1 | 3.1 |
| Decompensated Cirrhosis | Liver Transplantation§ | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 | 3.3 |
| | Death HBV | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 |
| Hepatocellular carcinoma | Liver Transplantation§ | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 | 1.2 |
| | Death HBV | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 |
| Liver Transplantation | Death HBV | 6.6 | 6.6 | 6.6 | 6.6 | 6.6 | 6.6 | 6.6 | 6.6 | 6.6 | 6.6 |

† Estimates from Kanwal 2005 and 2006 et al. Ref. 13,14. ‡ Estimates from recent clinical trials: Chang et al. 2006, Lai et al. 2006 and Colonno 2007, Ref. 15-17. * Estimates calculated by the author, based on the assumption that the natural progression rates of chronic hepatitis B are reduced by antiviral therapy. Estimates derived from natural history estimate similar to Kanwal's assumption of no progression of disease in HBeAg seroconversion, we assume no progression of disease in case HBV DNA is undetectable by PCR. In the papers from Chang and Lai full suppression of HBV DNA was observed in 80% with a high resistance profile drug, and 90% with a low resistance profile drug. We took these percentages for our calculations. Ref. 15,16. ** Estimates based on reduction of progression rates by nucleoside analogue therapy of 50 % (ref. 4). § Liver Transplantation estimates for the Netherlands. ¶ Initial therapy is 12 months (48 weeks) of therapy. ^ Estimates for Lamivudine resistance from Lai et al. And Moskovitz et al. Ref. 16,19. ^^ Estimates for Entecavir resistance from Colonno et al. 2006, Colonno et al. 2007 and Tenny et al. 2009. Ref. 17,20,21. “ Adefovir salvage resistance estimates from Lee et al., Chen et al. And Yeon et al. Ref. 22-24. “” Tenofovir salvage scenario estimates from van Bommel et al. 2004, Sarin et al., van Bommel et al. 2009 and Reijnders et al. Ref. 25-28

**Table 3** | Annual Transition estimates for Pegylated Interferon

| Initial State | Outcome | HBeAg+ | HBeAg- | Reference |
|---|---|---|---|---|
| CHB | Sustained virological response* | 27 | 15 | 37,38 |
| | 72 weeks post-treatment* | 7 | 2 | 37,39 |
| | Withdrawal* | 2 | 5 | 37,40 |
| | Cirrhosis^ | 2.7 | 6.2 | 16 |
| | HCC^ | 0.4 | 0.4 | 16 |
| Cirrhosis | Sustained virological response* | 27 | 15 | 37,38 |
| | 72 weeks post-treatment* | 7 | 2 | 37,39 |
| | Withdrawal* | 2 | 5 | 37,40 |
| | Decompensated cirrhosis^ | 3.9 | 2.7 | 17-19 |
| | HCC^ | 1.8 | 2.9 | 17-19 |
| | HBV-related death^ | 3.1 | 3.1 | 16-19 |
| Sustained Virological Response | Relapse** | 17 | 17 | 39 |

* Reference Lau et al., Marcellin et al. And Cooksley et al. Ref. 37,38 ** Estimate from Piratvisuth et al. Ref. 39
^ Estimates from the Natural History model

## RESULTS

Table 5 shows the total population of the Netherlands in 2009 with the age-specific HBsAg, HBeAg and disease status. The total number of patients with active CHB was 4857 or 8% of the total HBsAg-positive cohort, 27% of the HBeAg-positives and 4% of the HBeAg-negatives. The total number of non cirrhotic CHB patients was 4300 and of the cirrhotics 557.

The outcomes of the treatment scenarios evaluated are presented in Table 6. The weighted averages of the results were taken for the final outcomes for each scenario and subgroup. A plot of the outcomes of the various scenarios on the cost-effectiveness plane according to HBeAg and disease status is shown in Figure 1. In Figure 3, the age-specific health gain of the different strategies compared to the natural history is shown.

## CHB (non-cirrhosis)

The results of cost-effectiveness in CHB (non-cirrhosis) subgroups are shown in Figure 1a and b, where the total costs ranges from € 14.000- € 123.000**.** All treatment scenarios were more effective compared to the no treatment scenario. The number of QALYs over a period of 20-years for both HBeAg-positive and negative patients increased from lamivudine, adefovir salvage, pegylated interferon (followed by tenofovir), tenofovir salvage, to entecavir and tenofovir.

**Table 4** | Annual costs and health state utilities for chronic hepatitis B

| Parameter | Base-case estimate | (range) | Reference |
|---|---|---|---|
| **Medical management costs** | | | |
| Monitoring of CHB | € 693 | n.a | 49 |
| Compensated Cirrhosis | € 2,035 | n.a | 49 |
| Decompensated Cirrhosis | € 7,068 | n.a | 49 |
| Hepatocellular carcinoma | € 15,600 | n.a | 49 |
| Liver transplantation | € 125,000 | n.a | 49 |
| **Drug costs (year 2009 values)** | | | |
| Lamivudine treatment (100mg) | € 1,059 | n.a | 50 |
| Adefovir salvage treatment (10mg) | € 5,842 | n.a | 50 |
| Entecavir treatment (0,5mg) | € 5,987 | n.a | 50 |
| Tenofovir (245mg) | € 4,697 | n.a | 50 |
| Peg-INF alfa 2a (INJVL 180MCG/ML) | € 9,375 | n.a | 50 |
| **Health state utilities*** | | | |
| Durable response to treatment | 1.00 | (0.95–1.00) | 51 |
| Chronic HBV | 0.85 | (0.66–0.90) | 51 |
| Compensated cirrhosis | 0.69 | (0.66–0.71) | 51 |
| Decompensated cirrhosis | 0.35 | (0.32–0.37) | 51 |
| Hepatocellulr carcinoma | 0.38 | (0.36–0.41) | 51 |
| Liver transplantation | 0.67 | (0.64–0.69) | 51 |

* See Levy et al. (ref. 51) for the age-specific utilities

**Table 5** | Age-Group specific distribution of chronic hepatitis B in the Netherlands by HBeAg and stage of liver disease.

| | | | | | Active CHB | | Cirrhosis | | Chronic Hepatitis (no cirrhosis) | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Age Group (Years)** | **Population** | **HBsAg+ (%)** | **HBeAg+** | **HBeAg-** | **HBeAg+** | **HBeAg-** | **HBeAg+** | **HBeAg-** | **HBeAg+** | **HBeAg-** |
| 25–34 | 2.000.393 | 9.202 (0.46) | 1.470 | 7.732 | 397 | 309 | 24 | 22 | 373 | 288 |
| 35–44 | 2.532.178 | 15.953 (0.63) | 1.914 | 14.038 | 517 | 562 | 36 | 84 | 481 | 477 |
| 45–54 | 2.429.228 | 17.248 (0.71) | 1.035 | 16.213 | 279 | 649 | 70 | 182 | 210 | 467 |
| 55–64 | 2.121.729 | 2.970 (0.14) | 178 | 2.792 | 48 | 112 | 16 | 57 | 32 | 55 |
| 65+ | 2.471.815 | 1.977 (0.08) | 0 | 1.977 | 0 | 79 | 0 | 44 | 0 | 35 |
| Total | 11.555.343 | 47.350 | 4.597 | 42.753 | 1.241 | 1.710 | 146 | 389 | 1.096 | 1.321 |

Abbreviations: CHB, chronic hepatitis B; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen

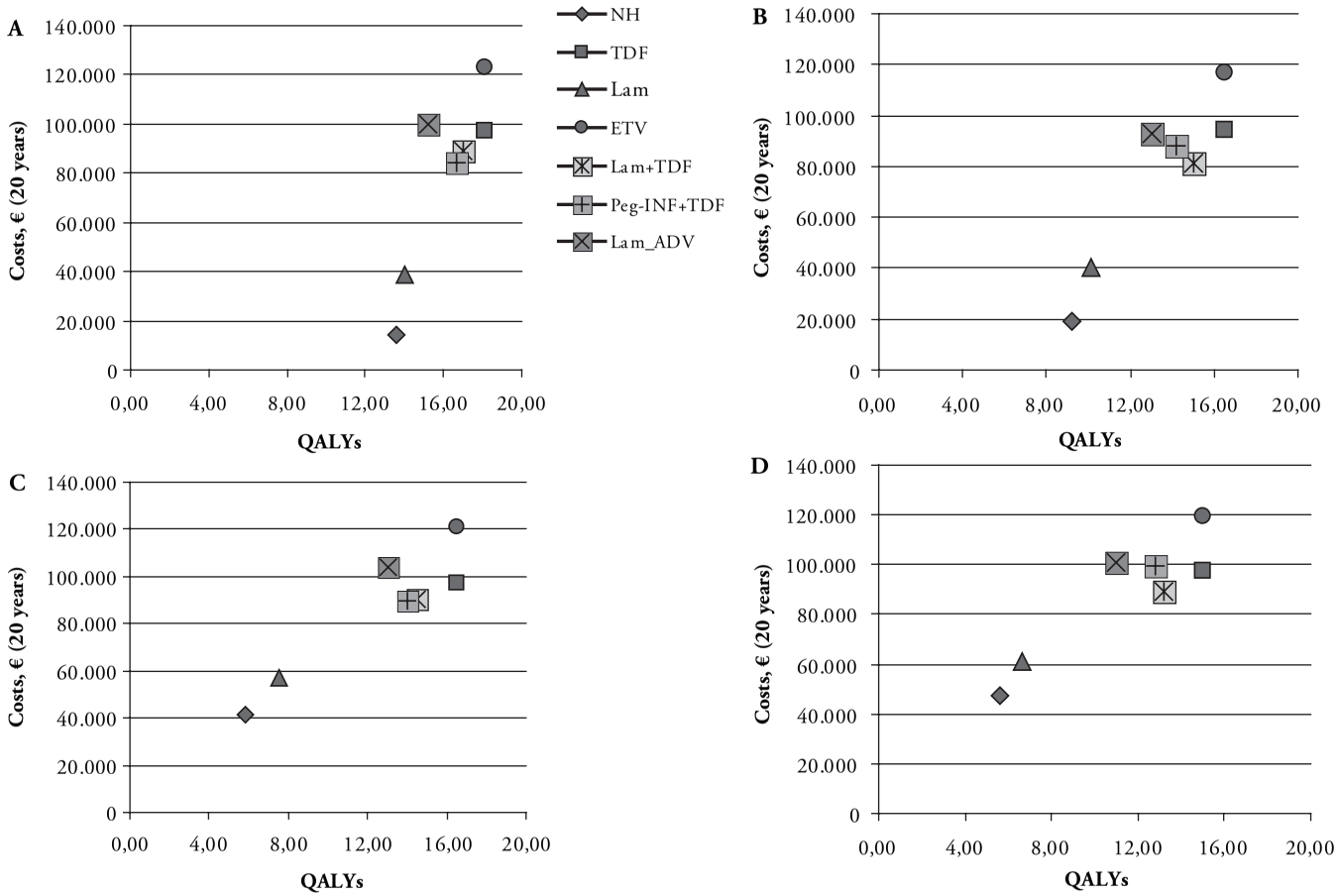


**Figure 1** | Results of cost-effectiveness analysis stratified by hepatitis B e antigen (HBeAg) and stage of liver disease: (**A**) HBeAg-positive (non-cirrhosis) (**B**) HBeAg-negative (non-cirrhosis) (**C**) HBeAg-positive (cirrhosis) (**D**) HBeAg-negative (cirrhosis). Results plotted on a cost-effectiveness plane. The x-axis represents the gain in QALYs with each strategy, and the y-axis the total healthcare costs (year 2010 values).

**Table 6** | Base-case results of alternative strategies (for the hypothetical Dutch cohort of age >25 active CHB patients by HBeAg and disease status): costs, quality-adjusted life years (QALYs) gained, incremental QALYs, incremental costs and incremental cost-effectiveness ratios (ICERs).

| **Treatment** | **NH*** | | **Lam** | | **Lam+ADV** | | **ETV** | | **TDF** | | **Lam+TDF** | | **Peg_IFN+TDF** | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **HBeAg status** | + | - | + | - | + | - | + | - | + | - | + | - | + | - |
| *CHB (no cirrhosis)* | | | | | | | | | | | | | | |
| Cumulative costs (x1000 €) | 14.2 | 19.0 | 38.5 | 40.1 | 100.0 | 93.0 | 123.2 | 116.5 | 97.3 | 94.1 | 88.9 | 81.1 | 84.3 | 88.1 |
| Cumulative QALYs | 13.6 | 9.2 | 14.0 | 10.0 | 15.2 | 13.0 | 18.1 | 16.5 | 18.1 | 16.5 | 17.0 | 15.0 | 16.6 | 14.1 |
| Incremental costs (x1000 €) | - | - | 24.3 | 21.1 | 85.8 | 74.1 | 108.9 | 97.5 | 83.0 | 75.1 | 74.6 | 10.8 | 70.0 | 69.1 |
| Incremental QALYs | - | - | 0.4 | 0.9 | 1.7 | 3.8 | 4.6 | 7.3 | 4.6 | 7.3 | 3.4 | 5.8 | 3.1 | 5.0 |
| ICER (x1000 €/QALY) | - | - | 56.9 | 23.0 | 51.0 | 19.6 | 23.8 | 13.4 | 18.1 | 10.3 | 21.8 | 10.7 | 22.7 | 13.9 |
| *Cirrhosis* | | | | | | | | | | | | | | |
| Cumulative costs (x1000 €) | 41.4 | 47.3 | 57.4 | 60.7 | 103.9 | 100.6 | 120.7 | 119.5 | 97.4 | 97.2 | 90.2 | 89.5 | 89.9 | 99.8 |
| Cumulative QALYs | 5.8 | 5.6 | 7.6 | 6.7 | 13.0 | 11.0 | 16.5 | 15.0 | 16.5 | 15.0 | 14.5 | 13.2 | 14.0 | 12.8 |
| Incremental costs (x1000 €) | - | - | 16.0 | 13.4 | 62.6 | 53.3 | 79.3 | 72.2 | 56.1 | 49.9 | 48.9 | 42.2 | 48.5 | 52.5 |
| Incremental QALYs | - | - | 1.7 | 1.0 | 7.1 | 5.3 | 10.7 | 9.4 | 10.7 | 9.4 | 8.6 | 7.6 | 8.1 | 7.2 |
| ICER (x1000 €/QALY) | - | - | 9.4 | 12.9 | 8.8 | 9.9 | 7.4 | 7.6 | 5.2 | 5.3 | 5.6 | 5.5 | 6.0 | 7.3 |

"NH (no treatment)" was the baseline scenario compared with other treatment scenarios

Abbreviations: NH, natural history; Lam, lamivudine; Lam+ADV, adefovir salvage therapy; Peg_IFN+TDF, pegylated interferon followed by tenofovir; ETV, entecavir; TDF, tenofovir.

Both tenofovir and entecavir were equally effective compared to the other scenarios. Compared to the least effective drug, these drugs resulted in an increase of about 4 healthy life years in HBeAg-positive patients, and 6 years in HBeAg-negative patients. Entecavir is more expensive than tenofovir (€ 1290/per year). The cost per QALY gained (incremental cost-effectiveness ratio (ICER)) of tenofovir versus no treatment was € 18.143 and € 10.294 for HBeAg-positive and negative patients, respectively. There is a visible age-specific healthy life years to gain among age groups. Once treatment is applied to younger age groups the difference is about 2 healthy life years in HBeAg-positive and about 3 healthy life year gain in HBeAg-negative patients with the most effective drug. The results are valid for each age-specific group, however, the health gain tends to diminish in older populations.

### CHB (cirrhosis)

The results of cost-effectiveness in cirrhotic subgroups are shown in Figure 1c and d. Over a 20-year period the no-treatment strategy resulted in 5.8 and 5.6 QALYs and total healthcare costs of € 41.349 and € 47.340 for the cirrhotic HBeAg-positive and negative cohort, respectively. The number of QALYs gained by antiviral therapy scenario designed to control or prevent resistance was impressive and range from 9.4 to 10.7 QALYs, and the associated ICERs range from € 5.200 to € 7.600. The QALYs gained in the HBeAg-negative group is higher and costs lower compared to the HBeAg-positive group. Also in the cirrhotics, these outcomes were valid for each specific age-group. The age-specific incremental QALYs gained in the cirrhotic group is higher compared to the non-cirrhotic group (Figure 3c and d). In cirrhotics, the more potent drug (tenofovir and entecavir scenarios) result in 10 more QALYs gained than compared to the least effective drug (lamivudine monotherapy scenario).

### Sensitivity analysis

The results of the probabilistic sensitivity analysis indicated that the no-treatment strategy was preferred at cost-effectiveness thresholds less than approximately € 18.000 per QALY, and tenofovir had the highest probability of being the most cost-effective strategy above this threshold (Figure 2) for the HBeAg-positive (non-cirrhosis) patients. For the HBeAg-negative (non-cirrhosis) patients, tenofovir had the highest probability of being most cost-effective if the willingness to pay (WTP) threshold was above € 10.000 per QALY.

For the HBeAg-positive cirrhotic patients, at a € 50.000 per QALY threshold, tenofovir had 35% chance of being the most cost-effective strategy, and pegylated interferon (followed by tenofovir) had a chance of 15%. In HBeAg-negative cirrhotic patients, tenofovir scenario had 60% chance of being the most cost-effective, and pegylated interferon (followed by tenofovir) 12% at a € 50.000 per QALY threshold.

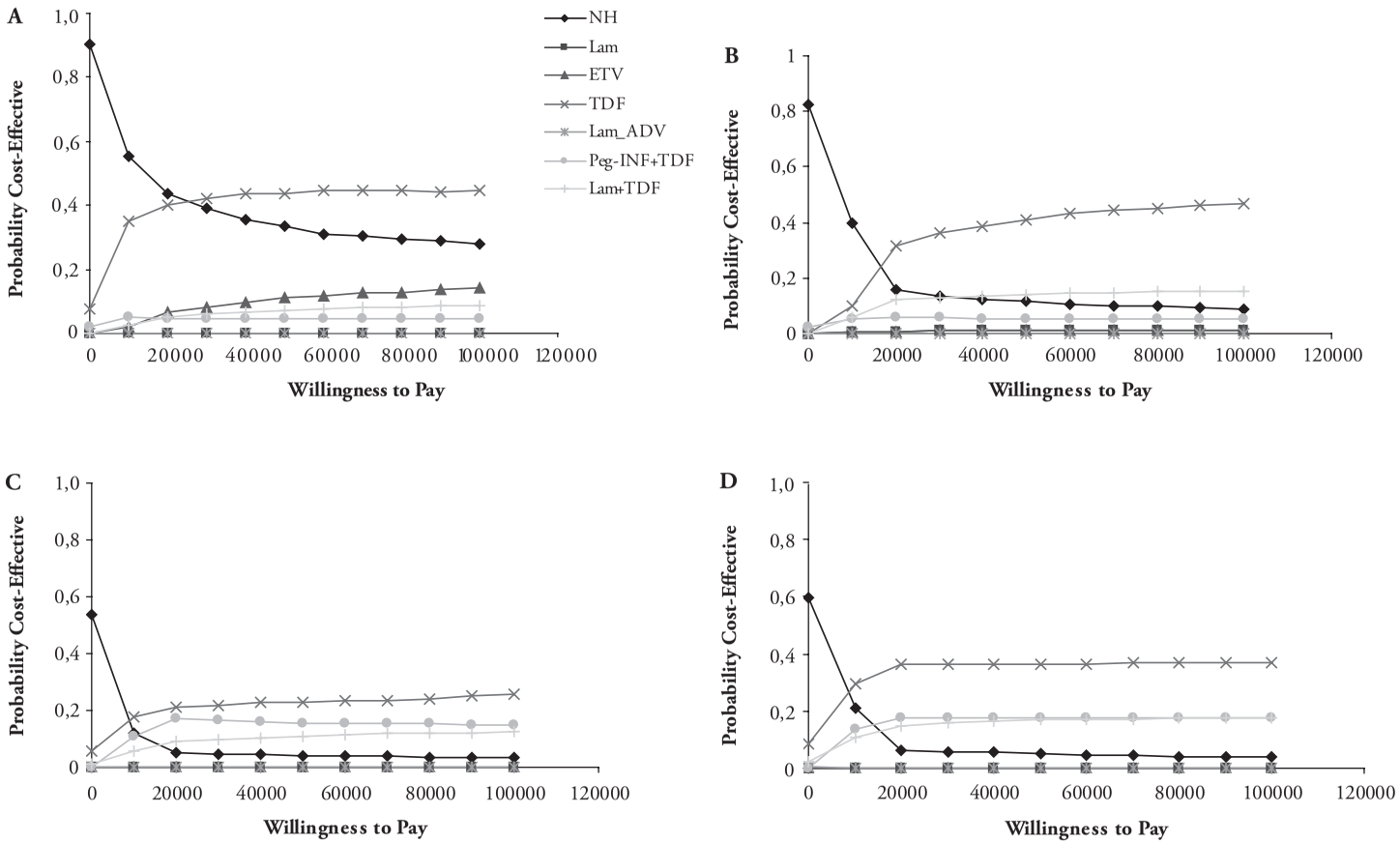


**Figure 2 |** Cost-effectiveness acceptability curves showing the probabilities of net benefits achieved by each strategy for different willingness to pay thresholds (the maximum amount a person is willing to pay for a good) in HBeAg-positive (non-cirrhosis) (**A**), HBeAg-negative (non-cirrhosis) (**B**), HBeAg-positive (cirrhosis) (**C**), and HBeAg-negative (cirrhosis) (D). The vertical axes represent the probability of cost-effectiveness. The horizontal axes represent willingness-to-pay threshold to gain one additional quality adjusted life year (QALY).

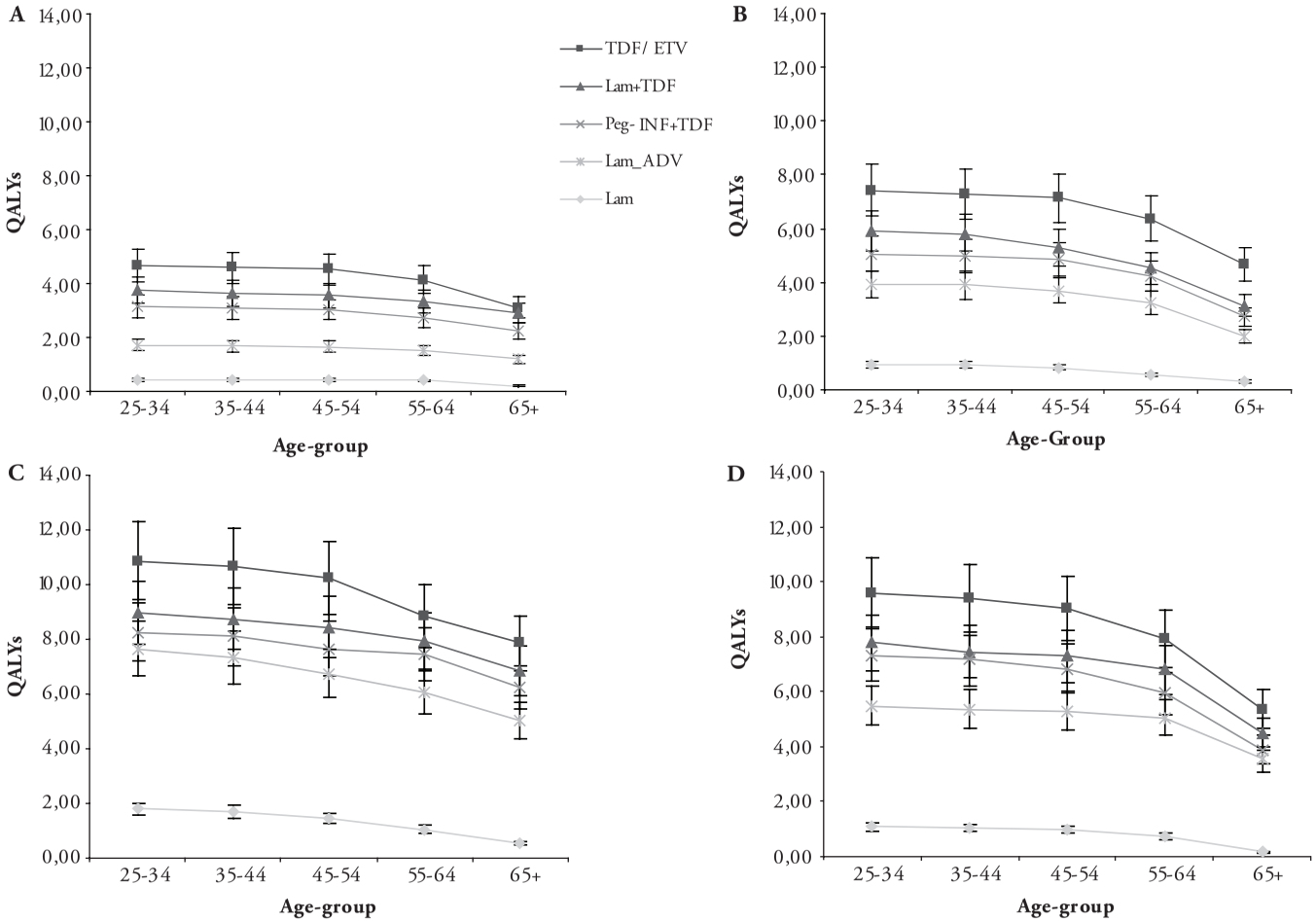


**Figure 3 |** Age-specific incremental QALYs by age-group compared to the do nothing scenario, for subgroups; HBeAg-positive (non-cirrhosis) (**A**), HBeAg-negative (non-cirrhosis) (**B**), HBeAg-positive (cirrhosis) (**C**), and HBeAg-negative (cirrhosis) (D).

## DISCUSSION

In this study, we conducted an age-specific cost-effectiveness analysis of various new treatment scenarios for chronic hepatitis B in HBeAg-positive and negative and cirrhotic and non-cirrhotic patients. If we treat patients with active CHB with a 3rd generation drug with a low resistance profile such as entecavir and tenofovir we gain 7 years and 3 months of life in HBeAg-negative and 4 years and 6 months in HBeAg-positive patients (non-cirrhosis). For this impressive health gain, we end up paying € 18.100- € 23.800 per QALY for HBeAg-positive and € 10.300- € 13.400 per QALY for HBeAg-negative CHB. In the cirrhotic group the health gain is even greater. For € 5.200- € 7.400 and € 5.300- € 7.600 we gain a life year in HBeAg-positive and negative patients, respectively.

The probabilistic sensitivity analysis indicated that in HBeAg-positive patients the threshold of being the optimal strategy was above the threshold of € 20.000, while this was € 10.000 in HBeAg-negative patients. According to this outcome the optimal gain and less costs is far more in the HBeAg-negative patients. This outcome is similar in the cirrhotic group. The HBeAg-negative patients have a net health benefit of 50% with tenofovir while this benefit is 35% in the HBeAg-positive patients at a € 50.000 threshold.

The Dutch National guidelines for the treatment of CHB, suggests that Peg-IFN should always be considered as first-line therapy in eligible patients because of the higher chance of achieving sustained off-treatment response compared with nucleos(t)ide analogues. The guideline also suggests that NA therapy should be considered in patients not responding to or not eligible for Peg-INF therapy. Initial treatment with Peg-IFN (followed by tenofovir), compared to doing nothing, costs € 22.700 and € 13.900 for HBeAg-positive and negative patients (non-cirrhsosis) per QALY gained, respectively. In the cirrhotic patient group this costs is € 6.000 and € 7.300 for HBeAg-positive and negative patients, respectively. In both cirrhotic and non-cirrhotic patient groups, the ICERs for Peg-IFN are well below the reference threshold of € 23.000- € 69.000 per QALY gained, which is defined as the threshold value for intervention cost-effectiveness as 1-3x the gross domestic product (GDP) of a country by the World Health Organization (WHO).[52]

We presented our analysis according to age-groups to help inform decisions and to quantify the impact of health-gain for each scenario compared to no antiviral treatment.[53] The age-specific results show that the potential health gain of antiviral treatment is higher for the age groups 25-54 years compared to the age groups above 55 years. This supports the need for early identification of patients in order to provide timely medical care. The age-specific information that is incorporated into the model varies from the life expectancy, utility,

to cirrhosis prevalence data. We assumed that intervention costs such as; hospitalization, physician visits, liver transplantation, and antiviral therapy would be the same at all ages. A bias in such an assumption would be that the co morbidities and functional losses of elderly persons would suggest that their costs would be higher. In the model, the age-specific utilities compensate for that, except the higher costs is not included in the analysis for the older age-groups. QALYs are calculated by multiplying the time a person spends in a health state by a number between 0 and 1, called QALY weight, which reflects the desirability of that health state. In general, the elderly will be in poorer health than younger people, and thus their time, for either the intervention or the natural history state (no antiviral therapy), will be multiplied by lower weights. Our model assumes continued antiviral therapy for HBeAg-positive patients (non-cirrhosis) even if seroconversion occurs. This assumption certainly has an impact on the costs for this group. If the costs for treatment for 20-year follow up were less, because patients stopped using medication once they developed seroconversion (especially in the low resistance profile drug scenarios), the cost-effectiveness of antiviral therapy would be more favourable. Also the assumption that the development of resistance both with entecavir and tenofovir for the coming 20-years will stay at 0-1% per year likely underestimates what will happen as longer term data are collected. Because long-term treatment efficacy data are lacking, extrapolations and assumptions for rates of disease progression and duration of treatment efficacy had to be done. Strength of this study is that we used the latest therapeutic disease management data from guidelines and most recent studies, especially regarding treatment duration for HBeAg-positive and negative patients.

Various studies have examined the cost-effectiveness of antiviral therapy for CHB and have concluded that treatment is cost-effective versus no treatment.[13-14,54-56] Most CEA studies have been sponsored by industry and should be interpreted with caution. In addition, most studies do not make the distinction between CHB with out and with cirrhosis. However, Kanwal et al.[13-14] analyzed non-cirrhosis and cirrhosis patients separately. Kanwal et al.[13] found that lamivudine monotherapy strategy was more expensive and less effective than treatment with interferon or salvaged by adefovir. According to our analysis (outcomes), lamivudine monotherapy was less effective as well, but it was not more expensive compared to other treatment strategies. This can be explained by the fact that there is more than 5 years elapsed between both studies during which the price of lamivudine decreased. Buti et al.[57] concludes that first-line treatment with tenofovir is cost-effective for both HBeAg-positive and negative patients, in comparison with other antivirals. They also concluded that tenofovir was more effective than entecavir, which in contrast to our results which the efficacy equality was equal for both drugs, and in all patient groups. There is large variety among cost-effectiveness studies,

which is one of the main reasons is that costs data and results are not easily extrapolable across countries. There seems also to be differences in the clinical assumptions made by the authors, which is crucial for the validity of the model. Rajendra and Wong[58] summarized published cost-effectiveness analysis for the treatment of hepatitis B and mention the variation between these analyses which differ in the rate of histological progression to cirrhosis, mortality rates associated with compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and many other included rates. Further critical review of previous cost-effectiveness studies is beyond the scope of this article. Evidence is growing that the involvement of industry in cost effectiveness analysis can affect the findings.[59-60] A study recently published in the *International Journal of Technology Assessment in Health Care* concludes that results of industry sponsored pharmacoeconomic analyses should be interpreted with caution.[61]

In a previous study we concluded that long-term antiviral therapy with a strategy that minimizes or controls resistance will have a major preventive effect on liver-related mortality and morbidity in active CHB patients.[7] By knowing this, and knowing the currently approved agents for CHB, costs and effects should be taken into account when formulating recommendations. National and international guidelines for the treatment of chronic hepatitis B do not provide specific recommendations as to whether PEG-IFN or NA's to choose for first-line therapy. Many factors such as the HBV DNA, ALT, HBeAg, HBV genotype and stage of liver disease play an important role. We tried to construct the active CHB cohort in a way that captured relevant aspects related to disease progression and response to treatment, that is, HBeAg stutus, HBV DNA and ALT levels, and presence of cirrhosis. In the past few years, there is growing evidence suggesting that HBV genotypes influence clinical outcomes, HBeAg seroconversion rates and response to antiviral treatment.[62-63] We wanted to implement genotype data into the natural history model, but after an elaborative search and personal communication with experts, we found that there is a major shortage of prospective population based studies for genotype specific disease progression. We chose to apply the simulation to the specific cohort of high-viremia patients with elevated ALT because our main goal was to assess the cost-effectiveness of antiviral therapy compared to no treatment, as these patients would be eligible for treatment according to the recent guidelines.[8,10] In conclusion, it is now accepted that treatment of CHB is cost-effective versus no treatment. In the Netherlands, reimbursement for optimal treatment is available. The big question is which antiviral to use specifically in first-line treatment. Besides understanding the risks, benefits and economics of treatment, recommendations should take country-specific burden, costs and effects into consideration when policy decisions are being made. Also clinicians are being asked to consider economic consequences of their treatment choices.

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Chapter 7

# Screening and early treatment of migrants for chronic hepatitis B virus infection is cost-effective

Irene K. Veldhuijzen[1,2*]
Mehlika Toy[3,4*]
Susan J.M. Hahné[5]
G. Ardine de Wit[5,6]
Solko W. Schalm[2,4]
Robert A. de Man[2]
Jan Hendrik Richardus[1,3]

[1]Division of Infectious Disease Control, Municipal Public Health Service Rotterdam-Rijnmond, Rotterdam, the Netherlands
[2]Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Center Rotterdam, Rotterdam, The Netherlands
[3]Department of Public Health, Erasmus MC, University Medical Center Rotterdam, Rotterdam, the Netherlands
[4]LiverDoc, Rotterdam, the Netherlands
[5]National Institute of Public Health and the Environment (RIVM), Bilthoven, the Netherlands
[6]Julius Center for Health Sciences and Primary Care, University Medical Center, Utrecht, t he Netherlands
* both authors contributed equally to the manuscript

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## ABSTRACT

**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 have the potential to prevent these sequellae. 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 that were and were not treated.

**Results:** Compared to the status quo, a one-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 to not screening, is € 8,966 per QALY gained. The ICER ranged from € 7,936 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 €7,222 to €15,694; for disease progression it ranged from €5,568 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.

## INTRODUCTION

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, while 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 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.

## 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 check-up 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 about 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 5,500 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 GP invites the patients for additional serological 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, i.e., 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 GPs[17] and the screening program would be expected to raise awareness of HBV, we assume that in the context of a systematic HBV screening program, 58% of patients meeting the referral criteria are successfully referred. We took the 39% from the study by Mostert et al.[9] as the lower boundary for this estimate, and 75% (the similar difference) for the upper boundary.

To estimate the participation in screening, we took the age-specific response rates among migrants from a population-based seroprevalence study conducted in 2006, the Pienter study (L. Mollema, RIVM, personal communication). Adjusted for the age distribution of the target population, the response was 21%. Because the Pienter study also required taking a blood sample but was proposed as a research study and participants did not receive their test results, we assume that the response in the Pienter study can be taken as the lower boundary estimate for the expected response to screening. For the upper boundary, we took the participation in cervical cancer screening among migrant women, which was 48%.[20] We took 35% as the base-case estimate for participation, which is the midpoint between the lower and upper boundaries.

## Cohort

We calculated the number of CHB patients in the target population based on recently published estimates for the Netherlands.[12] The HBsAg prevalence was estimated at 3.35%, corresponding to a total number of 44,117 HBsAg-positive persons in the target group (Table 1). Ten percent of these people are expected to have active CHB (based on HBV DNA and ALT level), corresponding to almost 4,500 persons eligible for treatment. The number of patients actually receiving treatment is based on base-case assumptions regarding participation in the screening program and management of patients with CHB, i.e., referral, eligibility for treatment, and adherence, as specified above. The costs and health outcomes for the patients who are actually treated and for those who remain untreated are calculated in the Markov models for treatment and natural history, respectively.

## Markov model and clinical probability estimates

To compare the incremental clinical and economic outcomes of screening and subsequent treatment of eligible HBV carriers under the status quo (no screening), we used a Markov model that describes disease progression and assesses the long-term morbidity and mortality of a cohort of patients during follow-up. The estimates for the progression probabilities were obtained from the literature. The structure of the model and the estimates used have been described in detail elsewhere[8] and are included in Tables 2 and 3.[4,21-33] We assume that eligible patients receive treatment with entecavir, an antiviral drug with a low resistance profile.[34] For HBeAg-positive patients, we consider sustained HBeAg seroconversion the endpoint after which treatment can be stopped.[35,36] For HBeAg-negative patients, we assume that long-term or indefinite treatment is necessary to sustain virologic response.[37]

**Table 1** | Estimated HBsAg prevalence in migrants from intermediate and high endemic countries (derived from Marschall et al, 2008, ref. 12) by disease status and estimated number of patients starting treatment in the status quo and following screening.

| | | | | | | Patients starting treatment | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Age group (years)** | **Population** | **HBsAg+** | **(%)** | **Active CHB*** | **(%)** | **Status quo** | **(%)** | **Base-case** | **(%)** |
| <15 | 66,267 | 1,829 | 2.76% | 232 | 13% | 6 | 3% | 49 | 21% |
| 15–24 | 164,167 | 6,551 | 3.99% | 832 | 13% | 51 | 6% | 94 | 11% |
| 25–34 | 291,540 | 9,665 | 3.31% | 1,044 | 11% | 59 | 6% | 123 | 12% |
| 35–44 | 318,519 | 13,486 | 4.23% | 1,354 | 10% | 36 | 3% | 215 | 16% |
| 45–54 | 220,816 | 9,467 | 4.29% | 753 | 8% | 13 | 2% | 123 | 16% |
| 55–64 | 139,834 | 2,475 | 1.77% | 206 | 8% | 6 | 3% | 42 | 20% |
| 65+ | 114,807 | 645 | 0.56% | 45 | 7% | 2 | 4% | 7 | 15% |
| Total | 1,315,950 | 44,117 | 3.35% | 4,466 | 10% | 173 | 4% | 652 | 15% |

* Active CHB is HBV DNA >10e5 AND ALT >2 ULN for HBeAg+ and HBV DNA >10e4 AND ALT >2 ULN for HBeAg-

## Costs

We included direct health care costs of the screening program, consultations, diagnostic tests, medical management, and entecavir therapy. Patients who do not participate in the screening and are not detected by other means follow the natural history. Because we assume that these patients do not have symptoms in the first stages of disease, we did not include costs for management in the CHB and compensated cirrhosis health states. For participants with CHB, the costs for a consultation for referral and source and contact tracing are included, as well as the costs of follow-up by the GP for patients not referred to specialist care. For patients who are found ineligible for treatment after specialist evaluation, the costs for specialist evaluation and subsequent follow-up by the GP are taken into account. Because the initial screening consists of an anti-HBc test and further testing is carried out only for those who are anti-HBc positive, the prevalence of anti-HBc was calculated assuming that 6.5% of the patients who are anti-HBc positive are HBsAg positive.[38,39]

Table 4 gives the cost estimates. The costs of laboratory tests and of medical care were based on data from the Dutch Healthcare Authority.[40] Medical costs are expressed as Diagnosis Treatment Combinations (DBCs), which have been used in the Netherlands for registration and reimbursement of hospital and medical specialist care since 2005.[41] DBCs are defined

as the whole set of activities and interventions of the hospital and medical specialist resulting from the first consultation and diagnosis of the medical specialist in the hospital. The entecavir costs were obtained from the Dutch Health Care Insurance Board,[42] and we discounted all costs at 3% per year.

**Table 2** | Annual progression estimates in natural history of active CHB

| Initial state | To | Estimate (range) in % | | Reference |
|---|---|---|---|---|
| Chronic hepatitis B e+ | Spontaneous virologic response* | 6.9 | (2.0–23) | 4, 21 |
| (adults >24 years) | Cirrhosis | 2.7 | (1.6–3.8) | 22 |
| | Hepatocellular carcinoma | 0.4 | (0.3–0.6) | 22 |
| | Chronic hepatitis B e- | 1.9 | (1.0–3.8) | 22 |
| Chronic hepatitis B e+ | Spontaneous virologic response* | 9.4 | (8.3–23) | 23, 24 |
| (children (0–24 years) | Cirrhosis | 0.1 | (0.0–0.1) | 23, 24 |
| | Hepatocellular carcinoma | 0.1 | (0.0–0.1) | 23, 24 |
| | Chronic hepatitis B e- | 0.4 | (0.2–0.6) | 23, 24 |
| Chronic hepatitis B e- | Spontaneous virologic response* | 1.6 | (0.0–11) | 4, 21 |
| (adults >24 years) | Cirrhosis | 6.2 | (2.8–9.7) | 22 |
| | Hepatocellular carcinoma | 0.4 | (0.3–0.6) | 22 |
| Chronic hepatitis B e- | Spontaneous virologic response* | 9.4 | (8.3–11) | 23, 24 |
| (children (0–24 years) | Cirrhosis | 0.1 | (0.0–0.1) | 23, 24 |
| | Hepatocellular carcinoma | 0.1 | (0.0–0.1) | 23, 24 |
| Cirrhosis e+ | Decompensated cirrhosis | 3.9 | (2.0–7.9) | 25-27 |
| | Hepatocellular cancer | 1.8 | (0.9–3.8) | 25-27 |
| | HBV related Death | 3.1 | (3.1–3.8) | 22, 25-27 |
| Cirrhosis e- | Decompensated cirrhosis | 2.7 | (1.4–5.4) | 25-27 |
| | Hepatocellular cancer | 2.9 | (1.0–5.6) | 25-27 |
| | HBV related Death | 3.1 | (3.1–3.8) | 22, 25-27 |
| Decompensated Cirrhosis | Liver transplantation | 3.3 | (1.0–8.4) | 28, 29 |
| | HBV related Death | 26 | (15–62) | 22 |
| Hepatocellular carcinoma | Liver transplantation | 1.2 | (0.2–5.0) | 28, 29 |
| | HBV related Death | 35 | (20–60) | 4, 21 |
| Liver transplant | HBV related death | 6.6 | (2–12) | 4, 21 |

* Spontaneous virologic response was defined as seroconversion to antibody against hepatitis B e antigen (anti-HBe) for HBeAg-positive patients and as persistent HBV DNA suppression and ALT normalization for HBeAg-negative patients

**Table 3** | Treatment-related annual transition estimates*

| Initial state | To | Estimate in % (range) | | | |
|---|---|---|---|---|---|
| | | HBeAge+ | | HBeAg- | |
| CHB Initial therapy† | Sustained virological response‡ | 22 | (17–27) | 11 | (5.5–22) |
| | Cirrhosis§ | 0.2 | (0.1–0.5) | 0.6 | (0.3–1.2) |
| | Hepatocellular carcinoma‖ | 0.2 | (0.1–0.5) | 0.2 | (0.1–0.5) |
| CHB long-term therapy | Sustained virological response‡ | 27 | (17–27) | 11 | (5.5–22) |
| | Cirrhosis§ | 0.2 | (0.1–0.5) | 0.6 | (0.3–1.2) |
| | Resistance‡ | 1 | (0.0–2.0) | 1 | (0.0–2.0) |
| | Hepatocellular carcinoma‖ | 0.2 | (0.1–0.5) | 0.2 | (0.1–0.5) |
| resistant CHB long-term therapy | Sustained virological response‡ | 5 | (2–7) | 0.5 | (0.2–1.0) |
| | Cirrhosis | 2.7 | (1.6–3.8) | 6.2 | (2.8–9.7) |
| | Hepatocellular carcinoma | 0.4 | (0.3–0.6) | 0.4 | (0.3–0.6) |
| Cirrhosis Initial therapy | Sustained virological response‡ | 22 | (17–27) | 11 | (5.5–22) |
| | Hepatocellular carcinoma‖ | 0.9 | (0.3–1.4) | 1.5 | (0.7–3.0) |
| Cirrhosis long-term therapy | Sustained virological response‡ | 27 | (17–27) | 11 | (5.5–22) |
| | Resistance | 1 | (0.0–10) | 1 | (0.0–10) |
| | Decompensated Cirrhosis | 1.9 | (0.9–3.8) | 1.9 | (0.9–3.8) |
| | Hepatocellular carcinoma | 1.6 | (0.8–3.2) | 1.6 | (0.8–3.2) |
| | Death HBV | 2.4 | (1.2–4.8) | 2.4 | (1.2–4.8) |
| resistant Cirrhosis long-term therapy | Sustained virological response‡ | 5 | (2–7) | 0.5 | (2–7) |
| | Decompensated Cirrhosis | 7.9 | (4–15) | 7.9 | (4–15) |
| | Hepatocellular carcinoma | 1.8 | (0.9–3.8) | 2.9 | (1.0–5.6) |
| | Death HBV | 3.1 | (3.1–3.8) | 3.1 | (3.1–3.8) |
| Decompensated Cirrhosis | Liver Transplantation¶ | 3.3 | (1.0–8.4) | 3.3 | (1.0–8.4) |
| | Death HBV | 26 | (15–62) | 26 | (15–62) |
| Hepatocellular carcinoma | Liver Transplantation¶ | 1.2 | (0.2–5.0) | 1.2 | (0.2–5.0) |
| | Death HBV | 35 | (20–60) | 35 | (20–60) |
| Liver Transplantation | Death HBV | 6.6 | (2–12) | 6.6 | (2–12) |

* Estimates from Kanwal et al. 2005 and 2006, and Fattovich et al. 2008 Ref. 4, 21, 22. † Initial therapy is 12 months (48 weeks) of therapy. ‡ Estimates from recent clinical trials: Chang et al. 2006, Lai et al. 2006 and Colonno et al. 2007, Ref. 30-32. § Estimates calculated by the author, based on the assumption that the natural progression rates of chronic hepatitis B are reduced by antiviral therapy. Estimates derived from natural history estimate. Similar to Kanwal's assumption of no progression of disease in HBeAg seroconversion, we assume no progression of disease in case HBV DNA is undetectable by PCR. In the papers from Chang and Lai full suppression of HBV DNA was observed in 90% with a low resistance profile drug. We took these percentages for our calculations. Ref. 31, 32. || Estimates based on reduction of progression rates by nucleoside analogue therapy of 50 % (Liaw et al. 2004, Ref. 33). ¶ Liver Transplantation estimates for the Netherlands, Ref. 28.

**Table 4** | Costs estimates*

| **Overall program costs†** | |
|---|---|
| Campaign, personnel | € 500,000 |
| range for sensitivity analyses | ± € 250,000 |
| Invitation and reminder | € 1.80 |
| *Test and follow up costs‡* | |
| Blood test administration costs | € 12.60 |
| Anti-HBc test | € 13.80 |
| HBsAg test (including confirmation test) | € 40.35 |
| HBeAg test | € 13.45 |
| ALT test | € 2.55 |
| Source and contact tracing† | € 63.13 |
| Follow up (patients not meeting referral criteria)§ | € 72.45 |
| Consultation referral (patients meeting referral criteria) | € 9.00 |
| Consultation specialist but not eligible for treatment§ | € 765.45 |
| *Annual CHB medical management costs‡* | |
| Monitoring of CHB | € 693 |
| Compensated cirrhosis | € 2,035 |
| Decompensated cirrhosis | € 7,068 |
| Hepatocellular carcinoma | € 15,600 |
| Liver transplantation | € 125,000 |
| Treatment with low resistance profile drug‖ | € 5,875 |

* For test and medical costs ranges were not applicable. † estimated by the authors

‡ data from the Dutch Healthcare Authority (NZa). § costs of 3 annual ALT checks through the GP are included. ‖ data for entecavir from the Dutch Health Care Insurance Board (CVZ)

## Health outcomes and utilities

Health outcomes were estimated in the Markov model as discounted quality-adjusted life-years (QALYs). Age-specific utility estimates (Table 5) were obtained from a recent multi-national study on CHB.[43] We discounted all utilities at 3% per year.

## Sensitivity analysis

By performing univariate sensitivity analyses taking the low and high ranges of each estimate, we explored the effect of the following assumptions on the cost-effectiveness estimates: the prevalence of CHB in the target population, the overall program costs, participation in the screening program, and the percentage of successful referrals and treatment adherence (Table 5).

The effect of assumptions on the effectiveness of treatment and on disease progression in natural history was assessed separately. Because disease progression is not a single variable, we performed multivariate sensitivity analyses for all variables included in the Markov model describing disease progression and utilities both in natural history and under treatment. Tables 2, 3, and 5 give the ranges for each variable used in the sensitivity analysis. We also assessed the effect of applying discounting according to the Dutch guidelines, with costs at 4% and effects at 1.5%.

**Table 5 |** Assumption and range for sensitivity analysis regarding prevalence, the screening program, subsequent patient management and utilities

| Variable | Base-case estimate | (range) | Reference |
|---|---|---|---|
| **Epidemiological, screening, and patient management** | | | |
| HBsAg prevalence | 3.35 | (2.23–4.47) | 12 |
| Participation | 35 | (21–48) | 20, personal communication L. Mollema |
| Successful referral | 58 | (39–75) | 9 |
| Treatment adherence | 75 | (50–100) | personal communication R. de Man |
| **Utilities*** | | | |
| Durable response to treatment | 1.00 | (0.95–1.00) | 43 |
| Chronic HBV | 0.68 | (0.66–0.70) | 43 |
| Compensated cirrhosis | 0.69 | (0.66–0.71) | 43 |
| Decompensated cirrhosis | 0.35 | (0.32–0.37) | 43 |
| Hepatocellular carcinoma | 0.38 | (0.36–0.41) | 43 |
| Liver transplantation | 0.67 | (0.64–0.69) | 43 |

* See Levy et al. (ref 43) for the age-specific utilitiesD

## RESULTS

The target population of 1.3 million migrants includes an estimated 44,000 HBsAg carriers of whom 4,466 are estimated to have active CHB. In the status quo, only 4% of patients with active CHB (173/4466) are expected to start treatment; the remainder are expected to follow the natural history of disease progression (Table 1). Lifetime follow-up of the cohort of active CHB patients suggests that 1,073 (24%) of the 4,466 patients will die of HBV-related diseases.

With a one-off screening program, under base-case assumptions, the proportion of patients with active CHB who start treatment increases to 15% (652 patients) (Table 1). During lifetime follow-up of the total cohort of active CHB patients after a one-time screening, 965 patients will have died. Screening can thus prevent 108 HBV-related deaths, corresponding to a 10% reduction in mortality (Table 6).

With base-case assumptions, the costs of the screening program (including costs of testing, referral, follow-up, and source and contact tracing) amount to €23.4 million and the health costs related to disease progression and treatment to €145 million. The average lifetime costs of treatment amount to almost €100,000 per patient. The lifetime incremental cost difference between the status quo and a scenario following screening and subsequent treatment of eligible patients amounts to €59.3 million (Table 6). In the base-case estimate, the incremental difference in health gains between the two scenarios is 6,614 QALYs, resulting in an Incremental Cost-Effectiveness Ratio (ICER) of €8,966 per QALY gained. Applying discounting according to the Dutch guidelines, with costs at 4% and effects at 1.5%, resulted in a slightly lower ICER of €8,823 per QALY gained.

### Sensitivity analyses

Univariate analysis showed that the ICER for screening varied between €7,936 and €11,705 per QALY gained (Figure 1). The assumptions regarding the proportion of successful referral of patients to specialist care and the proportion of eligible patients who actually start treatment had the largest effect on the ICER. When the lower boundary estimate was assumed for the prevalence of HBsAg, the ICER would increase to €10,998 per QALY gained. For the low and high boundaries of the participation, referral and treatment adherence estimates, the proportion of patients with active CHB starting treatment varied between 9% and 20%. When the upper boundary was assumed for all three factors, the proportion of patients that starts treatment increased to 35%.

The multivariate sensitivity analyses for treatment effectiveness and disease progression in natural history showed ICER estimates ranging between €5,568 and €60,418 per QALY gained (Figure 2). The higher range estimate was obtained when assuming relatively slow disease progression in natural history.

**Table 6** | Costs and Health Outcomes of Screening and Treatment

| **Costs, €1000** | **Status Quo** | **Screening** |
|---|---|---|
| Program costs | | 3,580 |
| Test costs | 458 | 15,954 |
| Referral and follow up costs | 838 | 3,074 |
| Source and contact tracing | 296 | 806 |
| Healthcare costs of patients receiving treatment | 17,177 | 64,753 |
| Healthcare costs of patients in natural history | 90,409 | 80,312 |
| *Total costs* | *109,178* | *168,480* |
| **Health Outcomes** | | |
| HBsAg positive patients identified in target population | 5,565 | 15,159 |
| Active CHB patients in target population | 4,466 | 4,466 |
| Active CHB patients receiving treatment | 173 | 652 |
| Active CHB patients following natural history | 4,293 | 3,813 |
| HBV related deaths | 1,073 | 965 |
| QALYs experienced | 113,411 | 120,025 |

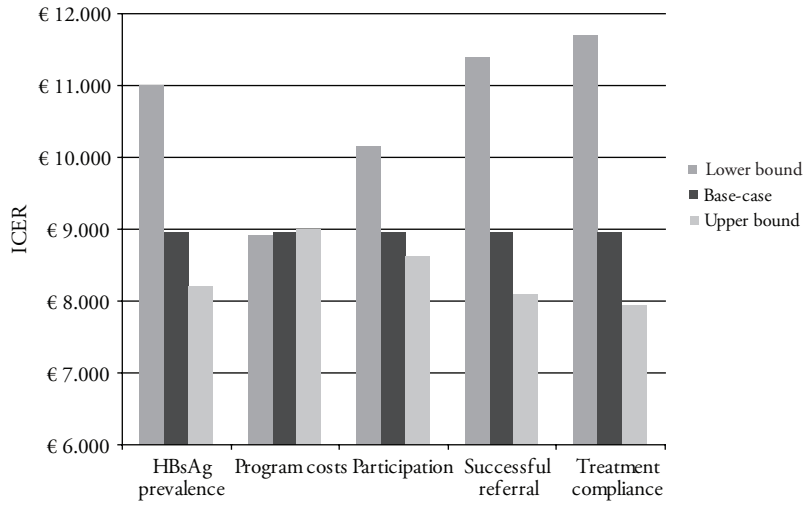


**Figure 1** | Incremental Cost-Effectiveness Ratio (ICER) for screening in univariate sensitivity analyses for the lower and upper boundaries of the estimates related to prevalence, the screening program, and patient management.

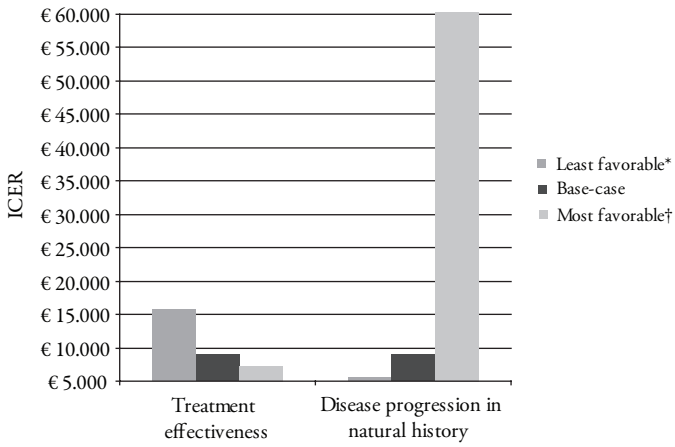


**Figure 2** | Incremental Cost-Effectiveness Ratio (ICER) for screening in multivariate sensitivity analyses for most favorable (slower progression) and least favorable (faster progression) scenarios of the estimates related to treatment effectiveness and disease progression in natural history.

* The least favorable scenario, with faster disease progression, was assessed by applying the low progression rates for spontaneous or sustained virologic response with the high ranges of disease progression and emergence of resistance, and the low ranges for the utility estimates. † The most favorable scenario, with slower disease progression, was assessed by applying the high range of progression to spontaneous or sustained virologic response, the low ranges for estimates of disease progression and emergence of antiviral resistance, and the high ranges for the utility estimates.

## DISCUSSION

We found that screening migrants for CHB infection with the goal of improving CHB outcome by early detection and treatment is cost effective compared to the status quo. We estimate that the ICER of screening is around €9,000 per QALY gained, well below the threshold of €20,000 per QALY gained that is commonly accepted in the Netherlands.[44] Under the status quo, we estimated that only 4% of the population eligible for treatment is actually treated. By improving case detection through the screening program and improving referral of eligible patients to specialist care, approximately 15% of the cohort with active CHB would receive treatment, resulting in fewer deaths and complications arising from CHB. The univariate and multivariate sensitivity analyses suggested that screening and treatment are likely to be cost effective even when varying main assumptions.

This study is the first to explore the possible public health effects and cost-effectiveness of interventions aimed at identifying and treating eligible patients with CHB. Previous cost-effectiveness studies on interventions have either assessed the outcome of treating all patients in the cohort or assumed relatively high compliance with the screening intervention and 100% acceptance of medical management of persons found to be chronically infected.[4, 15, 45] These assumptions might be too optimistic considering the complexity of the medical management of chronically infected patients.[35,36] From previous research into the referral from primary to specialist care, we know that a relatively small proportion of identified patients actually consult a specialist after referral.[9] We used this information to make more realistic assumptions. It may be that the proportion of patients referred to a specialist and who actually receive a consultation might be higher for patients identified through a screening program in which they voluntarily participated, compared to patients who are identified in other ways. In that case, our base-case assumption of the proportion of patients who see a specialist might be an underestimation. On the other hand, we assumed that all patients who see the specialist and qualify for treatment based on HBV DNA and ALT level are offered treatment, even though practice guidelines include additional diagnostic tests, e.g., a liver biopsy, to assess patient eligibility for treatment.[19, 36] Patients with high HBV DNA levels but ALT levels between normal and twice normal are not included in our cohort of patients eligible for treatment. However, the ALT cutoff above which treatment is recommended remains a difficult issue and is subject to change.[46,47]

Previous studies of the cost-effectiveness of treatment or screening and treatment took the costs of medical care into account for patients following a natural history, except for the costs for antiviral treatment.[4,15,48] However, because the patients in the natural history model

are assumed not to be identified as CHB patients, this assumption implies an overestimation of the costs of these active CHB patients. To avoid this overestimation, we did not include costs for medical management of CHB and compensated cirrhosis in the natural history assumptions.

Because many countries have started universal HBV vaccination in the past decade, we might have overestimated the prevalence of HBsAg among young migrants. However, this possibility will probably not have a large influence on the cost-effectiveness of screening in this group because sensitivity analysis showed that the influence of HBsAg prevalence on the ICER was relatively small.

A limitation of our study is the lack of data to support the assumptions regarding participation in the screening program. As long as screening programs have not been implemented, we can only speculate about adherence to systematic screening for HBV. Experience from New Zealand, where a community-based hepatitis B screening program tested 27% of the target population, illustrates that achieving a high participation rate is a major challenge.[49] Furthermore, no data are available on the proportion of patients who actually start treatment among those who qualify for treatment. Sensitivity analysis for treatment adherence indicated that this factor, together with the proportion of patients successfully referred, had a relatively large effect on the ICER. Although a screening program probably would not influence treatment adherence, this finding emphasizes the importance of effective referral for the success of a screening program. The ICER for screening went up to €60,000 per QALY gained when hepatitis B sequelae in the natural history were assumed to occur at a lower rate, resulting in a lower disease burden. However, this outcome is the result of an extreme scenario, in which we assumed all factors describing disease progression to take the most favorable range.

Cost-effectiveness is an import aspect of policy making. However, in decisions about the appropriateness of a screening program, other criteria, as described by Wilson and Junger,[50] should also be taken into account. For hepatitis B screening, most of their criteria are met because CHB is an important public health problem for which an acceptable early detection test is available. The natural history of the disease is well known, but in spite of the demonstrable effectiveness of treatment on intermediate outcomes, evidence of effects on clinical outcomes remains insufficient.[51] Also, exploration is required of the ethics involved in identifying patients with a CHB infection when only a subset of these patients will be eligible for treatment.

We show the predicted effect and cost-effectiveness of a screening program at the population level. Screening can achieve considerable health gains, but compared to the size

of the problem, even with the upper boundary estimates for the participation, referral and treatment rate, approximately 65% of the total population with active CHB would still not be identified and thus would not benefit from treatment. Therefore, other methods of improving access to treatment, e.g., adding opportunistic screening to systematic screening, need to be explored.

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Chapter 8

# General discussion

In the present **chapter,** I discuss the main findings of the studies in this thesis, in the context of current literature, and answer the research questions posed in the introduction. I will emphasize the public health and clinical implications of our findings, and provide suggestions on direction of future research.

## Research question 1:

**What is the epidemiology of chronic hepatitis B patients in the Netherlands and in Turkey?**

***Answer:***

*The Netherlands is a low endemic country for hepatitis B virus (prevalence 0.4%), with a large group of chronic hepatitis B patients that are born abroad. Turkey is a country with intermediate endemicity for hepatitis B, with a prevalence that differs considerably in various parts of the country (3.5%–6.7%).*

***Discussion:***

Rotterdam harbors a large group of chronic HBV patients, including both immigrants and native (Dutch-born) individuals. We conducted a prospective, population based study to identify transmission routes and genotypes among foreign-born and Dutch-born patients, which is described in **chapter 2**. The genotypes of the chronic HBV strains infecting the patients generally corresponded well with the HBV genotypes expected from the countries of origin of the patients. The genotype that is typically expected in the Netherlands, genotype A, was found in less than half of the Dutch-born patients that were genotyped. The remaining Dutch-born patients had mostly genotype D HBV strains. Genotype A was closely associated with sexual transmission, whereas genotype D was more closely associated with perinatal and horizontal transmission. The first generation of immigrants in the Netherlands originates mainly from the Mediterranean area, which explains the predominance of genotype D in the Netherlands. Within the native population of the Netherlands, HBV circulates primarily in high risk groups of limited size, such as men having sex with men and promiscuous heterosexuals. In a large part of the general population the virus cannot maintain itself without import of new cases from outside. Import is observed, primarily through contacts (e.g. intermarriage) with the migrant population. With a prevalence of 0.4%, the estimated number of HBV carriers in the Netherlands is around 64.000.

In **chapter 3** we describe the prevalence of HBV in Turkey. According to our findings Turkey has a prevalence that varies between 3.5% and 6.7%, from West to South-East. After a systematic review of community based studies from various regions and age groups, we calculated an overall country specific prevalence of 4.6%. The age-specific prevalence varied remarkably, with the lowest prevalence in age group 0–14 years (2.8%), and the highest prevalence in age-group 25–34 years (6.4%). The predominant genotype in HBV patients in Turkey is genotype D.1 The most common route of transmission is horizontal. Nearly every country with a large or diverse geographic area is expected to have regional differences in HBV prevalence, and the extent of the geographic variation can be very important. The large regional prevalence differences in Turkey are mainly due to differences in social-economic status, life-styles, infrastructure and access to health services. In the South-Eastern and Eastern regions of Turkey are poor, but much improvement has occurred in the socio-economic, hygienic and sanitary conditions in general in recent years. This region also lags behind in coverage of HBV vaccination. Although it consists of 18% of the total population, the estimated number of CHB cases is almost equal to the other regions taken together. Another important facet of the data in this study is linked to disease awareness. This is certainly not confined to Turkey if one considers that chronic hepatitis B patients are mostly asymptomatic. With an overall HBV prevalence of 4.6%, the estimated number of HBV carriers in Turkey is 3.3 million. If one takes the very conservative assessment that 10% of them would need treatment, there are 330.000 chronic HBV cases eligible for treatment in Turkey alone.

Recent evidence suggests that the overall decline in HBV prevalence in the last decade in industrialized countries of Europe appears to have reached a plateau. The most likely reason why the progressive decline in HBV prevalence has come to a halt is migration from endemic areas. There are currently more than 3 million immigrants, descendants of immigrants, and naturalized citizens and political refugees from Turkey in Western Europe, representing the largest immigrant group in the European Union. Prevalence of hepatitis B in migrant populations in low endemic EU countries is likely to reflect the prevalence of their region of origin. Therefore it is of equal importance for EU countries with Turkish immigrants to know the region-specific prevalence of hepatitis B in order to take health policy decisions for migrants in their country. This is particularly important for the timely identification and treatment of chronic HBV carriers.

Although vaccination against hepatitis B is available, it is not universally applied and is not of value to patients who have already been infected. Knowing the age-specific prevalence, genotypes and possible transmission routes of HBV cases gives us insight into the burden of

the disease and to the geographic areas and population groups that are lagging behind. This knowledge will help support a national policy for the prevention of HBV.

### Research question 2:

**What is the potential public health impact of long-term nucleot(s)ide analogue therapy of chronic hepatitis B and possible antiviral resistance?**

***Answer:***

*If all patients with high HBV DNA levels and elevated ALT from a total cohort of active CHB are fully treated with a low-resistant profile drug, liver-related mortality can be reduced by 80% over a period of 20 years, reducing the number of deaths from 1725 to 339 in the Netherlands and from 256.000 to 41.417 in Turkey.*

***Discussion:***

We developed a Markov model to estimate the effects of prolonged antiviral therapy and antiviral resistance on the mortality and morbidity of active chronic hepatitis B patients over a period of 20 years. The population based natural history and treatment models were developed in such a way that with small adaptations they can be used to estimate the hepatitis B burden and impact of antiviral therapy in various countries or regions, based on their profiles such as prevalence by age-specific group, and treatment characteristics such as drug type chosen for initial therapy and percentage application of salvage therapy.

Population cohorts of chronic hepatitis B patients in the Netherlands (**chapter 4**) and Turkey (**chapter 5**) were constructed and stratified according to 10-year age groups, prevalence of hepatitis B surface antigen, hepatitis B virus DNA level, aminotransferase level, hepatitis B e antigen status, and presence of cirrhosis. The age-specific distribution of these factors were derived from large databases of newly diagnosed CHB patients who were seen at the Rotterdam Municipal Public Health Service in the Netherlands, at Ankara Medical Faculty, department of Gastroenterology in Turkey, and at Jia Tong University, Rui Jin hospital in Shanghai, China (not included in this thesis). The analysis was performed on the basis of four scenarios: natural history, long-term therapy with high resistant profile drug without or with salvage therapy, and therapy with a low-resistance profile drug. The estimated number of people with chronic HBV infection in the Netherlands, Turkey and Shanghai was 64.000, 828.000 and 673.000, respectively. The eligible proportion for treatment was 10%, 25% and 44%, respectively. The treatment eligibility criteria for these patient cohorts were derived from

treatment guidelines.[2-4] These three patient cohorts differ mainly by the endemicity, HBeAg antigen status prevalence, genotypes and transmission routes. The variability between these three countries is also due to differences in national guidelines. For instance, a liver biopsy in Turkey is routinely performed before antiviral therapy is considered, if the patient has no cirrhosis. In the Netherlands, a liver biopsy is considered in the case of a persistent and slight elevated ALT level. However, liver biopsies are not performed routinely in CHB in Asian countries for treatment decisions, mainly because of the high risks of this procedure.

In the Netherlands, all newly diagnosed CHB patients are identified at the Municipal Public Health Service. This includes patients found through population based screening programs (e.g. pregnancy screening), and at primary, secondary and tertiary care levels. The Dutch cohort of CHB cases is therefore less likely to be biased due to the heterogeneity of the patients. In Turkey, data on viral hepatitis is collected at the provincial health directorate, but only for acute (incident) cases. In China, the data is also derived from clinical settings, although not all patients coming to the hospital have active disease. Some patients are detected during the diagnostic process for other diseases and referred to the hepatology department. We conclude that the cohort data from Turkey and China are therefore likely to be biased towards more active CHB cases, compared to the Netherlands.

In the Mediterranean region, >50% of CHB cases are related to HBeAg-negative disease. HBeAg-negative active infection represents an advanced stage of disease, where mutations in HBV genome are likely to be present.[5] HBV genotype D, which is predominant in Turkey, is associated with a higher prevalence of HBeAg-negative infection. Patients with HBeAg-negative active infection are usually older than patients with HBeAg-positive infection and are more likely to have cirrhosis at the time of their first presentation. This trend was seen in our Turkish CHB cohort. In the Dutch patient data base this was also the case due to the mixed population of chronic hepatitis B patients in the Netherlands, caused partially by immigration from endemic regions. In China however, HBeAg-positivity in the active cases was dominant. It is important to know this relation, because the progression of disease and the treatment outcomes for HBeAg-negative and positive patients are different. In the past few years, there is growing evidence suggesting that HBV genotypes influence clinical outcomes, HBeAg seroconversion rates and response to antiviral therapy.[6,7] We wanted to implement genotype data in to the natural history model, but after an elaborate search and personal communication with experts, we found that there is a major shortage of prospective population based studies for genotype specific disease progression. This type of information will be very useful in a country like the Netherlands, which has a large variety in CHB genotype distribution.[8]

The burden of antiviral resistance if no salvage therapy is applied is considerable; about 42% of the potential benefit of antiviral therapy is lost by resistance. HBV DNA levels should be monitored in all patients receiving nucleoside analogs to document an initial virological response and to monitor for treatment failure during therapy in those who achieved an initial virological response. A reasonable monitoring schedule would be at baseline and every 3 months until HBV DNA becomes undetectable, and then every 3–6 months while on treatment.

It has been demonstrated in several separate large-scale prospective cohort studies,[9-11] that the risk of HCC is proportional to the elevation of HBV DNA measured years before the onset of HCC. Although the relationship between treatment and HCC risk reduction has not yet been studied, there is evidence that treatment of CHB will reduce the overall risk of progression of disease, both in patients with and without cirrhosis.[12,13] According to our analysis, 481 (8%) cases in the non-cirrhotic group will develop HCC within a 20 year period if not treated; in the cirrhotic group this is 189 (23%) cases. If active patients are treated with a low resistance profile drug, the patients that will develop cirrhosis is reduced to 130 (2%).

Given the substantial mortality and morbidity attributable to HBV related chronic liver diseases, the control of progression to cirrhosis, decompensated cirrhosis and liver cancer will continue to be an important public health priority. By monitoring and controlling for antiviral resistance and reducing the liver related complications, the impact of treatment will become visible in the coming years.

## Research question 3:

**What is the cost-effectiveness of antiviral treatment regimens in CHB patients with and without cirrhosis?**

***Answer:***

*Antiviral treatment with a low resistance profile drug is cost-effective in all active CHB patients with or without cirrhosis, but the health gain and costs differ by age, HBeAg status and the presence of cirrhosis.*

***Discussion:***

When applying a population based model for various settings, the difference among countries in terms of medical costs such as liver transplantation, antigen tests, monitoring, hospitalization, and the costs of drugs is very considerable. Also, the height of the threshold

value is of great influence on decisions in the reimbursement process and intervention policy. The World Health Organization defines the threshold value for intervention cost-effectiveness as 1-3x the gross domestic product (GDP) of a country.[14] The threshold values for the Netherlands (low endemic), Turkey (median endemic) and China (high endemic), for one healthy life year is between € 23.000-€ 69.000, € 6.005-€ 18.016, and € 5.250-€ 15.750, respectively. According to our study described in **chapter 6**, the most cost-effective strategy was tenofovir monotherapy, regardless of HBeAg status and the presence of cirrhosis. The gain achieved in healthy life years from this strategy differs according to age; with most health gain seen in younger age-groups (35−55 years). Most practice guidelines do not discuss age as a consideration in deciding on treatment, whereas in our cost-effective analysis for the Dutch population, health gain and costs were analyzed by various age-groups, starting therapy from age 25. Differences in terms of health gain and costs in HBeAg-positive and negative, with and without cirrhosis are considerable. This difference is due to the faster progression of disease in HBeAg-negative patients, where the health gain is considerably larger than in the HBeAg-positive group, and to whether cirrhosis is present. If we have identified and decided to treat (with the most cost-effective drug) the estimated active CHB patients in the Netherlands, being 2951 cases of age 25 and above, the average total cost for a 20-year period will be €58.000 per case for each subgroup. Comparing to the no treatment strategy, once patients are treated, we will gain an average of six healthy life-years for the non-cirrhotics and an average of 9 healthy life-years for the cirrhotic group.

Antiviral therapy for CHB in Turkey is almost fully reimbursed by the state. The recommendations by the Turkish Association for the Study of the Liver (TASL)[15] to treat eligible patients are in line with the European Association for the Study of the Liver[2] criteria, except that liver biopsy evidence is always required to start treatment in patients with no established cirrhosis. A new modification issued in 2009 by the department within Turkish Health Authorities responsible for reimbursement decisions, following the suggestions of some hepatologists, states that lamivudine should be the first line therapy in all patients with viral load lower than $10^7$copies/mL. The recommendation to use lamivudine as first line therapy is currently under discussion among Turkish hepatologsists. In **chapter 5**, we took this recommendation into consideration in our cost-effectiveness analysis of various treatment strategies. We developed a scenario for the roadmap concept that outlines a plan for the management of patients with an inadequate virological response after 24 weeks of oral antiviral therapy, to the HBeAg-negative non-cirrhotic subgroup. This strategy was the second most cost-effective strategy for the HBeAg-negative patients. In countries with limited resources, different strategies could be tested by means of mathematical modelling, from most

recent data available on treatment outcomes. Besides understanding the risks, benefits and economics of treatment, recommendations should take country-specific burden, costs and effects into consideration when policy decisions are being made. Also clinicians are being asked to consider economic consequences of their treatment choices.

In many countries still, publicly funded access to effective hepatitis B antiviral therapy is restricted. The excuse for this restriction is often that no survival benefit has been shown yet and that there is a lack of cost-efficacy data. Hopefully, our studies in **chapter 5** and **6** showing a potential health gain in the non-cirrhotic and cirrhotic patients will positively influence acceptance of the use of potent antiviral therapy for CHB.

At individual level the association of disease progression with increased cost of disease management suggests that measures to prevent or delay progression of CHB related liver diseases will be economically beneficial. At population level however, the impact of therapy on the overall number of people with chronic infection will remain limited as long as the majority of infected patients will not receive treatment due to lack of resources for optimal treatment.

## Research question 4:

**Is screening on and treatment of CHB in migrants cost-effective in low endemic countries?**

***Answer:***

*Yes, systematic screening for and antiviral treatment of CHB patients from migrant populations in a low endemic country is cost-effective.*

***Discussion:***

Improving the identification and public health management of persons with chronic HBV infection is essential to ensuring that those infected receive necessary care to prevent or delay onset of liver disease and are empowered to prevent transmission to others. Also, the availability of safe and effective antiviral treatment against CHB provides a greater imperative to identify persons who might benefit from treatment. A strategy to improve detection of cases is active screening of risk groups. A study by Robotin et al.[16] on cost-effectiveness of antiviral therapy and HCC screening, concludes that the burden of CHB and HCC in developed nations is likely to increase significantly in the future, due to the large population at risk, changing patterns of immigration and the long latency for progression from CHB to HCC.

In the Netherlands, almost three quarter of chronic hepatitis B infections is found in migrants from countries with a relatively high HBV endemicity.[8] To inform policy makers,

we investigated the cost-effectiveness of a systematic screening program targeted at first generation migrants in the Netherlands. This study, combining epidemiological and a Markov model for treatment estimates, is described in **chapter 7**. A study targeting Asian and Pacific Islanders in the United States, found that identifying persons with chronic HBV infection through screening was cost-effective at low prevalence levels,[17] although cost-effectiveness is difficult to establish because treatment options are increasing years of disease-free life, and the various treatments have diverse associated costs. Our attempt was more realistic in terms of assumptions regarding participation, referral and treatment compliance based on previous research into the referral from primary to specialist care.[18] Using mathematical modeling we compared the costs and health effects of a systematic screening program for migrants to the status quo, which included a certain detection rate of patients through the pregnancy screening program and because of screening for other reasons. We found that the screening program is cost-effective, with an incremental cost-effectiveness ratio (ICER) compared to the status quo of around €9.000 per QALY gained. In sensitivity analysis varying parameter values of CHB prevalence in the target group, participation in screening, successful referral and treatment compliance, the ICER varied between approximately € 8.000 and €12.000 per QALY gained.

Chronic hepatitis B infection is consistent with the main generally accepted public health screening criteria as formulated originally by Wilson and Junger:[19] (1) It is a serious health disorder that can be diagnosed before symptoms develop; (2) it can be detected by reliable, inexpensive, and minimally invasive screening tests; (3) chronically infected patients have years of life to gain if medical evaluation, monitoring, or treatment is initiated early; and 4) the costs of screening are reasonable in relation to the anticipated benefits. Our findings are in accordance to these criteria for low endemic areas. If we would apply screening to intermediate or high endemic areas such as Turkey or China, we need to find out whether it will be cost-effective in these settings as well. The identified cases will need lifelong medical management and care, and it is not known whether it would be feasible to apply this to resource limited settings.

All individuals with CHB infection will need ongoing medical management and those eligible will need ongoing treatment. This demand for care will increase as screening programs expand, and additional health care providers are necessary for CHB monitoring and treatment.

# CONCLUSIONS AND RECOMMENDATIONS

Chronic hepatitis B represents a major public health burden that is preventable. The studies presented in this thesis quantify the burden of disease in a low and intermediate endemic country for HBV, by prevalence, mortality, morbidity and impact of antiviral therapy. On the basis of our studies we formulate the following conclusions and recommendations.

## Conclusions

- Age-specific prevalence, genotypes and transmission routes of HBV cases provides added insight into the burden of the disease and to the geographic areas and population groups that are in need of care.
- The future public health burden of chronic hepatitis B can be reduced substantially by low resistant antiviral treatment regimens for eligible patients.
- The impact of treatment of chronic hepatitis B will become apparent through a reduction of liver-related complications.
- Chronic hepatitis B patients can achieve a significant increase in healthy life-years through regular medical evaluation, monitoring of disease progression and with treatment before symptoms develop.
- Systematic screening and antiviral treatment of chronic hepatitis B patients from migrant populations in low endemic countries for HBV is cost-effective.
- Mathematical modeling shows that treatment compared to no treatment, both in cirrhotic and non-cirrhotic chronic hepatitis B patients, provides significant health gain.
- The demand for care of patients with chronic hepatitis B will increase as screening programs expand.

## Recommendations

***Policy***

- New information systems and registries should be implemented to facilitate the notification, counseling, and medical management of persons with chronic HBV infection in countries with intermediate and high endemicity.
- National guidelines for the management of chronic hepatitis B patients should take into account the latest country-specific cost-effectiveness studies.

- As screening programs expand, and the demand for ongoing medical management and treatment increases, additional health care providers will be needed in the field of chronic hepatitis B monitoring and treatment.

***Future research***

- There is a need for prospective population based studies for the disease progression of chronic hepatitis B according to genotype.
- There is a need for research on the impact of antiviral therapy on the transmission of HBV in the population.
- There is a need for utility studies on treatment outcomes for chronic hepatitis B that can be used for mathematical modeling of disease progression and treatment outcome.
- Randomized controlled trials on antiviral therapy for chronic hepatitis B should define treatment response by specific clinical outcomes taking into account the severity of liver disease.

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Chapter 9

# Summary
# Samenvatting
# Özet

# Summary

The aim of this thesis was to assess the public health impact of antiviral therapy for chronic hepatitis B patients in terms of mortality, morbidity and cost-effectiveness in various endemic settings.

In **chapter 1** we give a general introduction to the epidemiology, natural history, diagnosis, treatment and the chronic hepatitis B model. Persons with chronic hepatitis B infection can remain asymptomatic for years, unaware of their infections and of their risks for transmitting the virus to others, and for having serious liver disease later in life. Improving the public health management of those with chronic hepatitis B infection can help prevent serious sequelae of chronic liver disease. Hepatitis B virus vaccines created the first breakthrough in HBV prevention. The next breakthrough comes with therapy for active chronic hepatitis B, which has the potential to prevent progression to cirrhosis and hepatocellular carcinoma.

For the purpose of this thesis, a mathematical population based CHB model was constructed. to forecast health and economic consequences in various countries from low to high endemicity, and to address a wide range of policy questions concerning the burden of disease, in terms of morbidity, mortality and costs in the Netherlands, which is a low endemic country, and Turkey, which is a intermediate endemic country for HBV infection.

In this thesis, we address the following research questions:

1. What is the epidemiology of chronic hepatitis B in the Netherlands and in Turkey?
2. What is the potential public health impact of long-term nucleot(s)ide analogue therapy of chronic hepatitis B and possible antiviral resistance?
3. What is the cost-effectiveness of antiviral treatment regimens in CHB patients with and without cirrhosis?
4. Is screening on and treatment of CHB in migrants in low endemic countries cost-effective?

In **chapter 2**, we describe the transmission routes and genotypes of 464 chronic hepatitis B patients in the Netherlands. The HBV genotypes, possible transmission routes of infection and travel history of CHB patients born in The Netherlands, were compared with those CHB patients living in The Netherlands but who were foreign-born, taking into account the ethnicity of the mother. Of the 464 patients with CHB infection, 14% were Dutch-born and 86% were foreign-born**.** The CHB patients in the Dutch-born group had genotypes A (35%),

B (15%), C (11%), D (37%) and G (2%). In the foreign-born group, the distribution of genotypes was A (20%), B (15%), C (11%), D (40%) and E (15%). In the Dutch-born group, sexual transmission accounted for a larger proportion of infections ($P$<0.0001) compared to the foreign-born group, whereas perinatal transmission was reported to be higher in the foreign-born group and in the Dutch-born group with a foreign mother. In conclusion, the genotypes of the chronic HBV strains determined corresponded well with the HBV genotypes expected from the countries of origin of the patients or their mothers. Genotype A and D are predominant in CHB patients in the Netherlands.

In **chapter 3**, we set out to estimate the age and region-specific prevalence of chronic hepatitis B in Turkey to provide a clear picture of the current burden. A generalized linear mixed model was used to estimate the overall prevalence over all age-groups and regions, from randomized community sampling studies. The estimated overall population prevalence was 4.6% (95% CI 3.6−5.8%) and the total number of CHB cases about 3.3 million. The age-group specific outcomes varied from 2.8% for the 0−14 year olds to 6.4% in 25−34 year olds. The prevalence for military conscripts and pregnant women was 3.6% and 2.8%, respectively. The prevalence among health care workers between the years 1990 and 1999 was 3.3%, while this decreased to 2.3% between the years 2000 and 2009. Hepatitis B remains a significant public health problem in Turkey. The HBsAg estimates of this study can inform hepatitis B prevention policies in both Turkey and EU countries with large Turkish migrant populations.

The potential impact of long-term antiviral therapy on the burden of chronic hepatitis B had hardly been documented. In **chapter 4,** we estimated the effects of prolonged antiviral therapy and antiviral resistance on the mortality and morbidity of active chronic hepatitis B patients. A population cohort of chronic hepatitis B patients in the Netherlands was constructed and stratified according to 10-year age groups, prevalence of hepatitis B surface antigen, hepatitis B virus DNA level, alanine aminotransferase level, hepatitis B e antigen status, and presence of cirrhosis. A Markov model was created to mathematically simulate the cohort's progression through a finite series of health states. The analysis was performed on the basis of four scenarios: natural history, long-term therapy with a high-resistance profile drug without or with salvage, and therapy with a low-resistance profile drug. It has been estimated that there were 64,000 people (0.4%) suffering from chronic hepatitis B infection in the Netherlands in 2005, with 6521 (10%) of them having high viremia and elevated alanine aminotransferase levels. Within a 20-year period, 1725 (26%) of the 6521 patients in the active chronic hepatitis B cohort will die because of liver-related causes. Of the 5685 without cirrhosis at entry, 1671 (29%) will develop cirrhosis. Of those 836 with cirrhosis at entry, 619 (74%) will die within a 20-year period. If this active chronic hepatitis B cohort

is fully detected and treated, mortality related to liver disease can be reduced by 80% if a low-resistance profile drug is chosen from the start. The effect is due to both the reduction in complications of cirrhosis and the prevention of the development of cirrhosis. From this study we conclude that long-term antiviral therapy with a strategy that minimizes or controls resistance will have a major preventive effect on liver-related mortality and morbidity.

After the construction of the age-specific natural history and treatment model for CHB, which was used to estimate mortality, morbidity and impact of treatment in the Dutch population, we calibrated it for the Turkish population in **chapter 5**. The first aim of this study was to estimate the number of CHB cases in the Turkey. Secondly, we aimed to quantify the burden of CHB in terms of mortality, morbidity of active CHB patients that are eligible for antiviral treatment, and to assess the impact of antiviral therapy. Finally, we assessed various treatment scenarios and possible salvage combinations for cost-effectiveness. The HBsAg positive cohort was first divided into two groups, active and inactive CHB, based on hepatitis B e-antigen status, HBVDNA level, and serum alanine aminotransferase (ALT) level. The age-specific distributions of these factors were derived from a newly constructed patient database of the gastroenterology departments of the University of Ankara, and a state hospital in Ankara (Turkiye Yuksek Ihtisas Hastanesi) with 1453 newly diagnosed CHB patients. Both of these hospitals departments receive patients from around the country. The following scenarios were analyzed: Natural history (no treatment), lamivudine monotherapy, entecavir monotherapy, tenofovir monotherapy, adefovir salvage, tenofovir salvage, pegylated-interferon (followed by tenofovir), and a roadmap concept (lamivudine, following add-on, and switch to alternatives). We measured costs (2009 Euro and Turkish Lira), quality adjusted life years (QALYs), and the incremental cost-effectiveness ratio (ICER), to determine the additional cost to obtain one QALY. If the cohort of 828.347 individuals remains untreated, 256.788 (31%) will die due to liver related complications. Within a 20-year period, 11% will have developed decompensated cirrhosis, 12% HCC and 6% will need liver transplantation. Treating the cohort with tenofovir monotherapy, yielded the most quality adjusted life years (QALYs), and was the most cost-effective option for both HBeAg-positive and negative, cirrhotic and non-cirrhotic patients when compared with the “no treatment”, lamivudine, adefovir salvage, pegylated interferon, roadmap concept, and entecavir scenarios. The risks and mortality also decreased to 5%. We conclude that in a country with considerable amount of active chronic hepatitis B patients such as Turkey, tenofovir monotherapy seems to have the most health-gain, and is cost-effective and cost-saving in both HBeAg-positive and negative in all stages of liver disease.

After estimating the effects of prolonged (up to 20 years) antiviral therapy and antiviral resistance on the mortality and morbidity of CHB, in **chapter 6** we studied the cost-effectiveness of long-term antiviral therapy of various nucleos(t)ide analogues, salvage therapy in case of resistance, and initial combinationtherapy with pegylated interferon, compared to a do-nothing strategy (no antivirals). The analysis was done separately for HBeAg-positive and negative subgroups, with and without cirrhosis. We conducted our analysis from the perspective of a third-party payer and used the indirect health care costs for physician visits, diagnostic tests, and the management of complications in liver diseases. Medical costs are expressed as Diagnosis Treatment Combinations (DBCs) which are used in the Netherlands for the registration and reimbursement of hospital and medical specialist care since 2005. The analysis was done separately for each age-group >25 and the weighted averages were taken for the final outcomes for each strategy and subgroup. Treating with pegylated interferon (followed by tenofovir) provided 16.6 QALYs for € 53.625 and 14.1 QALYs for € 57.286 in positive and negative patients, respectively. However, pegylated interferon strategy was dominated by tenofovir strategy, which provided 18.1 QALYs for € 58.178 in HBeAg-positive and provided 16.5 QALYs for € 55.428 in HBeAg negative patients. The QALYs gained and total costs are lower in the cirrhotic HBeAg-positive group compared to the cirrhotic HBeAg-negative group. It is now accepted that treatment of CHB is cost-effective versus no treatment. In the Netherlands, reimbursement for optimal treatment is available.

In **chapter 7**, we assessed the cost-effectiveness of systematic screening for chronic hepatitis B of first generation migrants from intermediate and high endemic countries in the Netherlands. For this analysis we used 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 that were and were not treated. Compared to the status quo, a one-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 to not screening, is € 8,966 per QALY gained. The ICER ranged from € 7,936 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 €7,222 to €15,694; for disease progression it ranged from €5,568 to €60,418. We conclude that 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.

In **chapter 8** we provide answers to the research questions and discuss these. The chapter leads to the following conclusions and recommendations:

## CONCLUSIONS

- Age-specific prevalence, genotypes and transmission routes of HBV cases provides added insight into the burden of the disease and to the geographic areas and population groups that are in need of care.
- The future public health burden of chronic hepatitis B can be reduced substantially by low resistant antiviral treatment regimens for eligible patients.
- The impact of treatment of chronic hepatitis B will become apparent through a reduction of liver-related complications.
- Chronic hepatitis B patients can achieve a significant increase in healthy life-years through regular medical evaluation, monitoring of disease progression and with treatment before symptoms develop.
- Systematic screening and antiviral treatment of chronic hepatitis B patients from migrant populations in low endemic countries for HBV is cost-effective.
- Mathematical modeling shows that treatment compared to no treatment, both in cirrhotic and non-cirrhotic chronic hepatitis B patients, provides significant health gain.
- The demand for care of patients with chronic hepatitis B will increase as screening programs expand.

## RECOMMENDATIONS

### Policy

- New information systems and registries should be implemented to facilitate the notification, counseling, and medical management of persons with chronic HBV infection in countries with intermediate and high endemicity.
- National guidelines for the management of chronic hepatitis B patients should take into account the latest country-specific cost-effectiveness studies.

- As screening programs expand, and the demand for ongoing medical management and treatment increases, additional health care providers will be needed in the field of chronic hepatitis B monitoring and treatment.

**Future research**

- There is a need for prospective population based studies for the disease progression of chronic hepatitis B according to genotype.
- There is a need for research on the impact of antiviral therapy on the transmission of HBV in the population.
- There is a need for utility studies on treatment outcomes for chronic hepatitis B that can be used for mathematical modeling of disease progression and treatment outcome.
- Randomized controlled trials on antiviral therapy for chronic hepatitis B should define treatment response by specific clinical outcomes taking into account the severity of liver disease.

# Samenvatting

Het doel van dit proefschrift was vast te stellen welke impact antivirale behandeling van patiënten met chronische hepatitis B heeft op de volksgezondheid in termen van mortaliteit, morbiditeit en kosteneffectiviteit, in verschillende endemische settings.

In **hoofdstuk 1** geven we een algemene inleiding in de epidemiologie, het natuurlijke beloop, de diagnostiek en de behandeling van chronische hepatitis B (CHB), en bespreken we het CHB-model. Mensen met een chronische hepatitis B-infectie kunnen jarenlang symptoomvrij blijven, waardoor ze zich er niet van bewust zijn dat ze de infectie hebben, het virus kunnen overdragen op anderen en kans lopen om later in hun leven ernstige leverziekte te ontwikkelen. Een beter beheer van de gezondheidszorg voor mensen met een chronische hepatitis B-infectie kan helpen voorkomen dat de infectie uitmondt in ernstige chronische leverziekte. Hepatitis B-virus (HBV)-vaccins hebben voor de eerste doorbraak in hepatitis B-preventie gezorgd. Een volgende belangrijke stap werd gezet met de komst van een behandeling voor actieve chronische hepatitis B, die de potentie heeft om progressie tot cirrose en hepatocellulair carcinoom te voorkomen.

Voor dit proefschrift werd een mathematisch populatiegebaseerd CHB-model ontwikkeld om gezondheidsgerelateerde en economische gevolgen van behandeling van CHB in verschillende landen, met lage tot hoge endemiciteit, te voorspellen, en om licht te werpen op tal van beleidskwesties inzake de ziektelast, in termen van morbiditeit, mortaliteit en kosten. De modellering werd uitgevoerd voor Nederland, een laag-endemisch land voor HBV-infectie, en Turkije, een middel-endemisch land.

In dit proefschrift hebben we de volgende onderzoeksvragen gesteld:

1. Wat is de epidemiologische toestand van chronische hepatitis B in Nederland en Turkije?
2. Wat zijn de potentiële volksgezondheidsgevolgen van langdurige behandeling van chronische hepatitis B met nucleot(s)ide-analogen en van de daarbij mogelijk optredende antivirale resistentie?
3. Wat is de kosteneffectiviteit van antivirale behandelregimes bij CHB-patiënten met en zonder cirrose?
4. Is screening op en behandeling van CHB bij migranten in laag-endemische landen kosten-effectief?

In **hoofdstuk 2** beschrijven we de transmissieroutes en genotypen van HBV bij 464 patiënten met chronische hepatitis B in Nederland. De HBV-genotypen, mogelijke transmissieroutes van infectie en de reisgeschiedenis van de dragers werden vergeleken tussen in Nederland geboren patiënten en in Nederland wonende maar in het buitenland geboren patiënten, waarbij de etniciteit van de moeder in aanmerking werd genomen. Van de 464 patiënten met CHB-infectie was 14% in Nederland geboren en 86% in het buitenland. In de groep van in Nederland geboren CHB-patiënten werden de genotypen A (35%), B (15%), C (11%), D (37%) en G (2%) aangetroffen. Bij de in het buitenland geboren patiënten was de verdeling van genotypen: A (20%), B (15%), C (11%), D (40%) en E (15%). In de groep van in Nederland geboren patiënten was seksuele overdracht in een relatief groter aantal gevallen ($P$<0,0001) verantwoordelijk voor infectie dan in de groep van in het buitenland geboren patiënten, terwijl perinatale overdracht juist vaker voorkwam onder in het buitenland geboren patiënten en onder in Nederland geboren patiënten met een buitenlandse moeder. Er kan geconcludeerd worden dat de genotypen van de gedetermineerde HBV-stammen goed overeenkwamen met de genotypen die men zou verwachten op basis van het land van herkomst van de patiënten of hun moeders. Bij CHB-patiënten in Nederland komen hoofdzakelijk genotypen A en D voor.

In **hoofdstuk 3** hebben we ons tot doel gesteld de leeftijds- en gebiedsspecifieke prevalentie van chronische hepatitis B in Turkije te schatten, om een helder beeld te krijgen van de huidige ziektelast. Er is een gegeneraliseerd lineair gemengd model gebruikt om op basis van aselecte steekproefonderzoeken onder de bevolking de totale prevalentie over alle leeftijdsgroepen en gebieden te bepalen. De geschatte prevalentie in de totale bevolking was 4,6% (95%−BI: 3,6−5,8%) en het totale aantal CHB-gevallen was ongeveer 3,3 miljoen. Voor specifieke leeftijdsgroepen varieerden de prevalentiecijfers van 2,8% voor de groep van 0- tot 14-jarigen tot 6,4% voor de leeftijdsgroep van 25 tot 34 jaar. Onder dienstplichtige militairen en zwangere vrouwen was de prevalentie respectievelijk 3,2% en 1,6%. De prevalentie onder gezondheidswerkers tussen 1990 en 1999 was 3,3%, en nam af tot 2,3% in de jaren tussen 2000 en 2009. Hepatitis B vormt in Turkije nog altijd een groot probleem voor de volksgezondheid. De bepalingen van hepatitis B-oppervlakteantigeen (HBsAg) in dit onderzoek kunnen als informatie dienen voor het hepatitis B-preventiebeleid in zowel Turkije als EU-landen met grote Turkse migrantenpopulaties.

De potentiële invloed van langdurige antivirale behandeling op de ziektelast van chronische hepatitis B was nog amper gedocumenteerd. In **hoofdstuk 4** hebben we de effecten onderzocht van langdurige antivirale behandeling en van antivirale resistentie op de mortaliteit en morbiditeit van patiënten met actieve chronische hepatitis B. Er is een populatiecohort van patiënten met chronische hepatitis B opgezet, dat is gestratificeerd naar 10-jaars leeftijdsgroepen,

prevalentie van HBsAg, hepatitis B-virus-DNA-concentratie, alanine-aminotransferase (ALT)-spiegel, hepatitis B-e-antigeen (HBeAg)-status, en aanwezigheid van cirrose. Vervolgens is een Markov-model gecreëerd om de progressie van het cohort door een eindig aantal ziektestadia wiskundig te simuleren. Deze analyse werd uitgevoerd voor vier scenario's: natuurlijk beloop, langdurige behandeling met een geneesmiddel met een hoge kans op resistentieontwikkeling, al dan niet gevolgd door salvagetherapie, en behandeling met een geneesmiddel met een lage kans op resistentieontwikkeling. Naar schatting waren er in 2005 in Nederland 64.000 mensen (0,4%) met een chronische hepatitis B-infectie, waarvan er bij 6521 (10%) sprake was van hoge viremie en verhoogde alanine-aminotransferasespiegels. Van het cohort van 6521 patiënten met actieve chronische hepatitis B zullen er volgens onze analyse in een periode van 20 jaar 1725 (26%) overlijden door levergerelateerde oorzaken. Van de 5685 patiënten die bij opname in het cohort nog geen cirrose hadden, zal zich bij 1671 (29%) cirrose ontwikkelen. Van de 836 patiënten die al wel cirrose hadden, zullen er 619 (74%) binnen 20 jaar overlijden. Indien de actieve chronische hepatitis B bij alle patiënten in dit cohort wordt ontdekt en behandeld, kan de sterfte aan leverziekte met 80% worden teruggebracht als vanaf het begin een geneesmiddel met een lage kans op resistentieontwikkeling wordt gekozen. Deze reductie wordt veroorzaakt doordat complicaties van cirrose worden verminderd en de ontwikkeling van cirrose wordt voorkomen. We concluderen uit dit onderzoek dat langdurige antivirale behandeling volgens een strategie waarbij resistentieontwikkeling wordt geminimaliseerd of onder controle gehouden, een belangrijk preventief effect heeft op levergerelateerde mortaliteit en morbiditeit.

Nadat we dit model voor simulatie van het natuurlijke beloop van CHB en het beloop bij behandeling hadden gebruikt om de leeftijdsspecifieke mortaliteit, morbiditeit en impact van behandeling in de Nederlandse bevolking te schatten, kalibreerden we het model in **hoofdstuk 5** voor de Turkse bevolking. Het eerste doel van dit onderzoek was schatting van het aantal CHB-gevallen in Turkije. Het tweede doel was kwantificering van de ziektelast van CHB, in termen van mortaliteit en morbiditeit van patiënten met actieve CHB die in aanmerking komen voor antivirale behandeling, en schatting van de impact van antivirale therapie hierop. Ten slotte beoordeelden we de kosteneffectiviteit van diverse behandelscenario's en mogelijke salvagecombinaties. Het HBsAg-positieve cohort werd eerst in twee groepen verdeeld: een groep met actieve CHB en een groep met inactieve CHB. We baseerden ons hierbij op de HBeAg-status, HBV-DNA-concentratie en serum-ALT-spiegel. De leeftijdsspecifieke verdeling van deze parameters werd verkregen uit een nieuw opgezette patiëntendatabase van de gastro-enterologieafdelingen van de University of Ankara en een publiek ziekenhuis in Ankara (Türkiye Yüksek İhtisas Hastanesi) die de gegevens bevat van

1453 nieuw gediagnosticeerde CHB-patiënten. Beide ziekenhuisafdelingen nemen patiënten op uit het hele land. De volgende scenario's werden geanalyseerd: natuurlijk beloop (geen behandeling), monotherapie met lamivudine, monotherapie met entecavir, monotherapie met tenofovir, salvagetherapie met adefovir, salvagetherapie met tenofovir, peginterferon (gevolgd door tenofovir), en een zogenaamd 'roadmap'-concept (lamivudine, gevolgd door 'add-on'-behandeling dan wel overschakeling op alternatieven). We berekenden de kosten (euro en Turkse lira, 2009), aantallen QALY's ('quality adjusted life years', voor kwaliteit van leven gecorrigeerde levensjaren), en de incrementele kosteneffectiviteitsratio (ICER), om de extra kosten voor het winnen van één QALY vast te stellen. De analyse wees uit dat als het cohort van 828.347 personen onbehandeld blijft, er 256.788 (31%) personen zullen overlijden aan levercomplicaties. Bij 11% zal binnen een periode van 20 jaar gedecompenseerde levercirrose ontstaan, bij 12% hepatocellulair carcinoom en 6% zal een levertransplantatie nodig hebben. Behandeling van het cohort met tenofovir-monotherapie leverde de meeste QALY's op en was de meest kosteneffectieve optie voor zowel HBeAg-positieve als HBeAg-negatieve, cirrotische en niet-cirrotische patiënten, in vergelijking met geen behandeling, lamivudinebehandeling, salvagetherapie met adefovir, behandeling met peginterferon, behandeling volgens het roadmap-concept, en entecavirbehandeling. De risico's en mortaliteit daalden ook tot 5%. We concluderen dat in een land als Turkije, waar een aanzienlijk aantal mensen actieve chronische hepatitis B heeft, tenofovir-monotherapie de grootste gezondheidswinst lijkt op te leveren. De behandeling is bovendien kosteneffectief en kostenbesparend voor zowel HBeAg-positieve als -negatieve patiënten in alle stadia van leverziekte.

Nadat we aldus de effecten van langdurige (tot 20 jaar) antivirale therapie en antivirale resistentie op de mortaliteit en morbiditeit van CHB hadden geschat, onderzochten we in **hoofdstuk 6** de kosteneffectiviteit van verschillende langdurige antivirale behandelingen versus geen behandeling (geen antivirale middelen). De onderzochte antivirale behandelingen waren: behandeling met verschillende nucleos(t)ide-analogen, salvagetherapie in geval van resistentie, en initiële combinatietherapie met peginterferon. Subgroepen van HBeAg-positieve en HBeAg-negatieve patiënten, met en zonder cirrose, werden apart geanalyseerd. We voerden de analyse uit vanuit het perspectief van een derde betaler en gebruikten de indirecte gezondheidszorgkosten voor doktersbezoeken, diagnostische tests, en management van complicaties bij leverziekten. Medische kosten zijn uitgedrukt in diagnosebehandelcombinaties (DBC's), die in Nederland sinds 2005 worden gebruikt voor de registratie en vergoeding van kosten voor ziekenhuiszorg en medisch-specialistische zorg. De analyse werd

voor elke leeftijdsgroep >25 apart uitgevoerd en voor de einduitkomsten werden voor elke strategie en subgroep de gewogen gemiddelden genomen. Behandeling met peginterferon (gevolgd door tenofovir) leverde voor HBeAg-positieve en -negatieve patiënten een winst op van respectievelijk 16,6 QALY's tegen € 53.625 en 14,1 QALY's tegen € 57.286. De behandeling met peginterferon werd echter overtroffen door de behandeling met tenofovir, waarmee HBeAg-positieve patiënten 18,1 QALY's wonnen tegen € 58.178, en HBeAg-negatieve patiënten 16,5 QALY's tegen € 55.428. Het aantal gewonnen QALY's en de totale kosten zijn lager in de cirrotische HBeAg-positieve groep dan in de cirrotische HBeAg-negatieve groep. Er bestaat geen twijfel meer over dat behandeling van CHB kosteneffectief is in vergelijking met geen behandeling. In Nederland kunnen patiënten een optimale behandeling vergoed krijgen.

In **hoofdstuk 7** hebben we de kosteneffectiviteit bepaald van systematische screening op chronische hepatitis B van eerstegeneratiemigranten in Nederland, afkomstig uit middel- en hoog-endemische landen. Voor deze analyse hebben we epidemiologische gegevens over de verwachte aantallen patiënten met actieve chronische HBV-infectie in de doelpopulatie en gegevens over de kosten van een screeningsprogramma gecombineerd in een Markov-model, met het doel inzicht te krijgen in de kosten en te winnen QALY's voor patiënten die wel en niet behandeld worden. Ten opzichte van de status quo, kan een eenmalige screening op HBV-infectie de sterfte aan leverziekten met 10% verlagen. Uitgaande van 'base case'-schattingen is de incrementele kosteneffectiviteitsratio (ICER) van screenen ten opzichte van niet screenen € 8.966 per gewonnen QALY. Bij univariate sensitiviteitsanalyse, waarin de parameterwaarden voor HBV-prevalentie, het percentage patiënten dat deelneemt aan screening, het percentage dat wordt doorverwezen, en het percentage dat feitelijk start met behandeling werden gevarieerd, varieerde de ICER van € 7.936 tot € 11.705 per gewonnen QALY. Bij multivariate sensitiviteitsanalyse voor effectiviteit van behandeling varieerde de ICER van € 7.222 tot € 15.694, en voor ziekteprogressie van € 5.568 tot € 60.418. We concluderen dat vroege opsporing en behandeling van personen met HBV-infectie een groot effect kan hebben op levergerelateerde gezondheidsuitkomsten. Systematische screening van migranten op chronische HBV-infectie is waarschijnlijk kosteneffectief, zelfs bij lage schattingen van HBV-prevalentie, deelname, verwijzing en behandeling.

In **hoofdstuk 8** geven we antwoorden op de onderzoeksvragen en bespreken we deze. We komen tot de volgende conclusies en aanbevelingen:

## CONCLUSIES

- Schatting van de leeftijdsspecifieke prevalentie van CHB en vaststelling van de genotypen en transmissieroutes van HBV bij patiënten vergroten het inzicht in de ziektelast en maken duidelijk welke geografische gebieden en bevolkingsgroepen aandacht behoeven.
- De last die chronische hepatitis B op de volksgezondheid legt kan in de toekomst aanzienlijk worden verminderd door patiënten die daarvoor in aanmerking komen een antivirale behandeling te geven met een lage kans op resistentieontwikkeling.
- De impact van behandeling van chronische hepatitis B zal blijken uit een vermindering van levergerelateerde complicaties.
- Door regelmatige medische controle, monitoring van ziekteprogressie en behandeling voordat symptomen ontstaan, kunnen patiënten met chronische hepatitis B gezonde levensjaren winnen.
- In laag-endemische landen voor HBV is systematische screening en antivirale behandeling van chronische hepatitis B-patiënten in migrantenpopulaties kosteneffectief.
- Wiskundige modellering laat zien dat het behandelen van chronische hepatitis B belangrijke gezondheidswinst oplevert ten opzichte van niet behandelen, zowel voor cirrotische als niet-cirrotische patiënten.
- Met de uitbreiding van screeningsprogramma's zal de vraag naar zorg voor patiënten met chronische hepatitis B toenemen.

## AANBEVELINGEN

### Beleid

- In middel- en hoog-endemische landen zouden nieuwe informatiesystemen en registers geïmplementeerd moeten worden om de melding, counseling, en medische behandeling van mensen met een chronische HBV-infectie te vergemakkelijken.
- In de nationale richtlijnen voor de behandeling van mensen met chronische hepatitis B dient rekening te worden gehouden met de meest recente onderzoeken naar de landspecifieke kosteneffectiviteit.
- Naarmate de screeningsprogramma's worden uitgebreid, en de vraag naar voortdurend medisch beheer en medische behandeling toeneemt, zullen er op het gebied van hepatitis B-monitoring en -behandeling meer zorgverleners nodig zijn.

## Toekomstig onderzoek

- Er moeten prospectieve populatiegebaseerde studies worden verricht naar de ziekteprogressie van chronische hepatitis B voor de verschillende genotypen.
- Er is behoefte aan onderzoek naar de invloed van antivirale behandeling op de transmissie van HBV in de bevolking.
- Er zouden 'health utility'-studies van de behandelingsresultaten voor chronische hepatitis B moeten worden uitgevoerd, die als uitgangspunt kunnen dienen voor wiskundige modellering van ziekteprogressie en behandelingsresultaat.
- Gerandomiseerde gecontroleerde onderzoeken naar antivirale therapie voor chronische hepatitis B moeten de respons op behandeling definiëren in termen van specifieke klinische uitkomsten, waarbij de ernst van de leverziekte in aanmerking wordt genomen.

# ÖZET

Bu tezin amacı kronik hepatit B (KHB) hastalarında kullanılan antiviral tedavinin halk sağlığı üzerine olan etkilerinin mortalite, morbidite ve maliyet-etkinlik açısından araştırılmasıdır.

Bölüm 1'de hepatit B'nin epidemiyolojisi, doğal seyri, tanısı, tedavisi ve kullanılan hepatit B modeli hakkında bilgiler verilmiştir. Hepatit B'li kişiler yıllarca asemptomatik, enfeksiyonlarından ve hastalığı bulaştırma risklerinden habersiz kalabilir ve yaşamlarının ilerleyen dönemlerinde ciddi karaciğer hastalıkları ile geliştirebilirler. Kronik hepatit B'si olanların tedavi ve takiplerinde iyileşme sağlanması ile kronik karaciğer hastalığının olumsuz sonuçları engellenebilir. Hepatit B aşısı hastalığın önlenmesinde çığır açan ilk yöntemdir. Bundan sonraki önemli gelişme, siroza ve hepatosellüler kansere ilerlemeyi engelleme potansiyeli olan kronik aktif hepatit B'nin terapisi ile sağlanmıştır.

Bu tezin amacına uygun olarak, hastalığın toplum sağlığına ve ekonomiye olan etkilerini; Hollanda gibi düşük endemisiteli ve Türkiye gibi orta endemisiteli endemisiteli ülke örneklerinde incelemek için, sağlık politikaları oluşturulurken ortaya çıkan morbidite, mortalite ve maliyet bazında hastalığın sonuçları gibi çok çeşitli soruları yanıtlamak için, KHB'de toplum tabanlı bir matematik modeli oluşturulmuştur.

Bu tezde aşağıdaki araştırma soruları incelenmiştir:

- Hollanda'da ve Türkiye'de kronik hepatit B'nin epidemiyolojisi nedir?
- Kronik hepatit B'de nükleot(z)id analogları ile tedavinin ve ilaç direncinin uzun dönemde halk sağlığına olan etkileri nelerdir?
- Sirozu olan ve olmayan KHB hastalarında anti-viral tedavi rejimlerinin maliyet-etkinliği nedir?
- Düşük endemisiteli ülkelerde göçmenlerin taranması ve tedavi edilmesi maliyet-etkin midir?

Bölüm 2'de Hollanda'daki 464 kronik hepatit B'li hastanın bulaş yolları ve genotipleri tanımlanmıştır. Hollanda'da doğmuş olan bireylerin HBV genotipleri, enfeksiyonun olası bulaş yolları ve seyahat hikayeleri Hollanda'da yaşayan başka ülke doğumlu olanlarınkiler ile annenin etnik kökeni de dikkate alınarak karşılaştırıldı. Bu 464 hastanın, %14'ü Hollanda doğumlu ve %86'sı Hollanda dışı doğumlu idi. Hollanda doğumlu KHB hastalarında genotip A (%35), B(%15), C (%11), D (%37) ve G (%2) sıklıkta tespit edildi. Yabancı doğumlu

grupta genotiplerin dağılımı A(%20), B(%15), C(%11), D(%40) ve E(%15) olarak bulundu. Hollandalı hastaların grubunda cinsel yol ile bulaş diğer gruba göre anlamlı olarak yüksek tespit edilirken (p<0,0001) Hollanda dışı doğumlu grupta ve annesi yabancı uyruklu olan grupta perinatal bulaş sıklığı daha yüksek bulundu. Sonuç olarak, tespit edilen kronik hepatit B genotiplerinin hastaların annelerinin köken aldıkları toplumlarınkiler ile uyumlu oldukları tespit edildi. Hollanda'lı hastalarda en sık tespit edilen genotipler A ve D olarak bulundu.

Bölüm 3'de kronik hepatit B'nin neden olduğu sorunları daha net ortaya koyabilmek için gerekli olan Türkiye'de yaşa bağlı KHB prevalansını tespit etmeye çalıştık. Randomize toplum tabanlı örneklem çalışmalardan yararlanılarak ve generalize lineer miks model kullanılarak tüm yaş gruplarında, bölgelerde genel prevalans tahmin edilmeye çalışıldı. Hesaplanan tüm toplumdaki prevalans %4,6 (%95 G.A. : %3,6−5,8) ve toplam KHB hastası sayısı 3,3 milyon olarak bulundu. Yaşa göre hastalık prevalansı 0-14 yaş grubunda %2,8 ile 25−34 yaş grubunda %6,4 arasında değişmekteydi. Askerliğe alınan erkeklerde %3,2 ve gebelerde %1,6 olarak bulundu. Sağlık çalışanlarından 1990-1999 yılları arasında %3,4 ve 2000−2009 yılları arasında %1,9 olarak tespit edildi. Hepatit B Türkiye'de sağlık sorunları arasında önemini korumaktadır. Bu çalışmadaki HBsAg pozitifliği sıklığı hakkındaki veriler Türkiye'deki ve Türkiye'den çok sayıda göçmeni barındıran AB ülkelerinde sağlık politikalarının tespitinde katkılar sağlayacaktır.

Kronik hepatit B tedavisinde anti-viral kullanımının uzun dönemde hastalığın toplum sağlığına getirdiği yüke olan potansiyel etkileri net olarak ortaya konulmamıştır. Bölüm 4'de kronik aktif hepatit B hastalarında uzun süreli anti-viral tedavinin ve tedavi direncinin morbiditeye ve mortaliteye olan etkileri incelenmiştir. HBsAg prevalansı, HBV DNA düzeyleri, serum alanine aminotransferase düzeyleri, HBeAg durumu ve siroz varlığı sıklığının onar yıllık yaş gruplarına göre dağılımı dikkate alınarak oluşturulan KHB hasta kohortu kullanıldı. Hasta kohortunun hastalığın sonlanım noktalarına ilerlemesini simule etmek amacı ile bir Markov model oluşturuldu. Analiz 4 senaryo temelinde gerçekleştirildi: doğal seyir, kurtarma tedavisi ile beraber veya olmadan yüksek direnç profiline sahip ilaç ile uzun süreli tedavi ve düşük direnç profiline sahip ilaç ile tedavi. 2005 yılında Hollanda'da 64.000 (%0,4) KHB hastası olduğu ve bunların 6521'inin (%10) yüksek viremi ve alanine aminotransferase düzeyleri sonucunda aktif hastalık bulundurduğu tahmin edildi. Yirmi yıllık süre zarfında 6521 hastanın 1725'inin (%26) karaciğere bağlı nedenler ile öleceği hesaplandı. Bazalde sirozu olmayan 5685 hastanın 1671'inde (%29) siroz gelişeceği hesaplandı. Bazalde sirozu olan 836 hastadan 619'unun (%74) 20 yıl zarfında kaybedileceği öngörüldü. Eğer bu aktif KHB kohortu tümüyle tespit edilebilir ve başından itibaren düşük direnç profilli bir ilaç ile tedavi edilir ise karaciğer bağlı mortalitede %80 azalma kaydedilebileceği öngörüldü.

Bu sonuç hem siroza bağlı komplikasyonların hem de sirozun engellenmesine bağlıdır. Bu çalışmada, direnç gelişmesini en aza indirmeyi hedefleyen uzun süreli anti-viral terapi ile KHB hastalarında karaciğere bağlı mortalite ve morbiditede en etkin azalmayı sağlanabileceği sonucuna varılmıştır.

KHB için, yaşa bağlı doğal seyir ve tedavi modeli inşa edildikten ve mortalite ve morbiditeye olan etkisi Hollanda toplumunda incelendikten sonra bu model Türkiye toplumu için bölüm 5'de kalibre edilmiştir. Çalışmanın ilk amacı Türkiye'deki KHB hastalarının sayısının tahmin edilmesidir. İkinci olarak, KHB'nin aktif hastalarda neden olacağı mortalite, morbiditeyi ve tedaviye uygun hastalarda tedavinin etkilerini öngörmeyi amaçladık. Son olarak, çeşitli tedavi senaryolarını ve olası kurtarma tedavisi kombinasyonlarını maliyet-etkinlik açısından karşılaştırdık. HBsAg pozitif hasta kohortu öncelikle serum HBV DNA düzeyleri, HBeAg durumu ve serum alanin amino transferase (ALT) düzeyleri dikkate alınarak aktif ve inaktif olmak üzere iki gruba ayrıldı. Bu faktörlerin yaşa bağlı dağılımı, Ankara Üniversitesi'nin ve Türkiye Yüksek İhtisas Hastanesinin Gastroenteroloji bölümlerinde takip edilen 1453 hastanın verilerinden yararlanılarak oluşturulan yeni veri tabanından elde edildi. Her iki hastane de tüm ülke genelinden hasta kabul etmekteydi. Çalışmada şu senaryolar analiz edildi: Doğal seyir (tedavisiz takip), lamivudine monoterapisi, entecavir monoterapisi, tenefovir monoterapisi, adefovir kurtarma tedavisi, tenofovir kurtarma tedavisi, pegile interferon (ertesinde tenofovir) ve yol-haritası konsepti (lamivudine, gerekirse add-on veya alternatiflere değişim). Maliyetler (2009 EURO ve Türk Lirası), kalitesi sağlanmış yaşam yılı (KSYY) ve 1 yıllık KSYY kazanılması için harcanması gereken maliyet yani; tedrici maliyet-etkinlik oranı (TMEO) olarak hesaplandı. Eğer 828.347 hastalık kohort tedavisiz olarak takip edilir ise, 256,788'inin (%31) karaciğere bağlı nedenler ile kaybedileceği öngörüldü. Yirmi yıl zarfında, %11 hasta dekompanze siroz geliştirecek, %12'si hepatosellüler kanser geliştirecek ve %6'sı karaciğer nakline ihtiyaç duyacaktır. Kohortun tenofovir monoterapisi ile tedavi edilmesinin en fazla KSYY'i sağladığı; sirotik veya sirotik olmayan, HBeAg pozitif veya negatif tüm hastalar açısından tedavi seçeneği olarak tedavisiz takip, lamivudine, adefovir kurtama, pegile interferon, yol haritası konsepti ve entekavir seçeneklerine göre en maliyet-etkin tedavi olarak öne çıktığı tespit edilmiştir. Ayrıca mortalite riski %5'e düşmektedir. Türkiye gibi ciddi sayıda KHB hastası bulunan Türkiye gibi ülkelerde, karaciğer hastalığının tüm evrelerinde HBeAg pozitif ve negatif hastalarda tenofovir monoterapisi sağlıkta en fazla kazanım sağlayan, en maliyet etkin ve maliyeti en çok azaltan tedavi seçeneğidir.

Uzun dönemde (20 yıla kadar) anti-viral terapinin ve anti-viral direncinin KHB'de mortalite ve morbidite üzerine olan etkilerini hesapladıktan sonra, bölüm 6'da çeşitli nükleos(t)id analoglarının ,direnç halinde kullanılacak kurtarma tedavilerinin ve pegile-

interferon tedavisi ve kombinasyonlarının maliyet etkinliğini hesapladık. Analiz sirotik veya sirotik olmayan, HBeAg pozitif ve negatif gruplar için ayrı ayrı yapıldı. Analizimizi, bağımsız bir geri ödeme kuruluşunun perspektifinden, doktor vizite ücretleri, tanısal testler, komplikasyonların tedavisi gibi dolaylı sağlık harcamalarını da dikkate alarak gerçekleştirdik. Sağlık harcamaları, Hollanda'da 2005 yılından beri hastanede ve uzman hekim kontrolünde yapılacak olan harcamaları kapsayan Tanı-Tedavi Kombinasyonları (TTK) paketi olarak tanımlandı. Analiz 25 yaş üzeri yaş grupları için ayrı ayrı gerçekleştirildi ve her strateji ve alt grup için ağırlıklı ortalamalar alındı. Tedavide Pegile interferon (gerekirse ertesinde tenofovir) kullanılması HBeAg pozitif ve negatif hastalarda sırası ile 16,6 KSYY'yi 53,625 € ve 14,4 KSSY'yi 57,286 € maliyete sağlamaktaydı. Ancak, tenofovir monoterapisinin; HBeAg pozitif ve negatif hastalarda sırasıyla 18,1 KSYY'yi 58,178€ ve 16,5 KSYY'yi 55,428€ maliyete sağlayarak pegile-interferon stratejsine üstün geldiğini tespit ettik. HBeAg pozitif sirotik grupta, sirotik HBeAg negatif grupla karşılaştırıldığında kazanılan KSYY ve maliyet daha düşük bulundu. Günümüzde KHB'nin tedavi edilmesinin, tedavisiz takibe göre maliyet-etkin olduğu kabul edilmektedir. Hollanda'da optimal tedavi için yapılan harcamanın geri dönüşü mümkün olmaktadır.

Bölüm 7'de, orta ve yüksek endemik ülkelerden Hollanda'ya gelen ilk nesil göçmenlerin hepatit B pozitifliği için yapılacak olan sistematik taramalarının maliyet-etkin olup olmadığını araştırdık. Bu analiz için hedeflenen popülasyonda aktif KHB enfeksiyonlu bireylerin epidemiyolojik verisi, tarama için kullanılacak olan programın maliyeti bir Markov model içerisinde kullanılarak hastaların tedavi edilmesi ve edilmemesi halinde kazanılacak KSYY'leri hesaplandı. Mevcut statükonun aksine, HBV enfeksiyonu açısından 1 kez tarama yapılması karaciğere bağlı mortalitede %10 azalma sağlayabilir. Tarama yapılmasının TMEO'su tarama yapmamak ile karşılaştırıldığında kazanılan her KSYY için 8966€ bulunmuştur. Çeşitli HBV prevalansı değerleri, taramaya katılım oranları, hastaneye başvuru düzenleri ve tedavi uyumları dikkate alındığında; tek değişkenli sensitivite analizine göre TMEO değerlerinin 7936€-11,705€ arasında değiştiği bulunmuştur. Tedavi etkinliği açısından çok değişkenli sensitivite analizi yapıldığında, TMEO'nun 7,222€-15,694€ arasında değiştiği; hastalık progresyonu dikkate alındığında 5,568€−60,418€ arasında değiştiği tespit edilmiştir. HBV enfeksiyonu olan hastaların erken tespit edilip tedavi edilmelerinin karaciğere bağlı sağlık sorunlarının önlenmesinde önemli sonuçları olacağı sonucuna vardık. HBV prevalansı, katılım, yönlendirme ve tedavi uyumu açısından alt sınırdaki değerler dikkate alınsa dahi, göçmenlerin HBV enfeksiyonu açısından sistematik olarak taranmasının maliyet-etkin olabileceği sonucuna vardık.

Bölüm 8'de araştırmada ortaya konan sorulara yanıtlar ve bu yanıtların tartışması sunulmuştur. Bu bölüm aşağıdaki sonuçlara ve önerilere varmaktatır:

## ÇIKARIMLAR

- Yaşa göre prevalans, genotip ve bulaş yollarının dikkate alınması; ilgilenilmesi gereken toplumlardaki ve bölgelerdeki HBV'ye bağlı doğacak sağlık sorunlarına daha derin bir bakış açısı getirmektedir.
- Düşük direnç profilli ilaçların uygun hastalarda tercih edilmesi ile ileride HBV'ye bağlı olarak ortaya çıkacak olan sağlık sorunları önemli ölçüde azaltılabilir.
- Kronik hepatit B'nin tedavisinin etkinliği karaciğer ile ilişkili komplikasyonların önlenmesi ile daha belirgin hale gelecektir.
- Kronik hepatit B hastaları, düzenli sağlık kontrollerinden geçirilmeleri, hastalık progresyonunun takip edilmesi ve semptomlar gelişmeden tedavilerin başlatılması ile sürdürecekleri sağlıklı yaşam yıllarında anlamlı kazançlar elde edebilirler.
- Düşük HBV prevelansına sahip ülkelere gelen göçmenlerin HBV açısından sistematik olarak taranması ve tedavi edilmesi maliyet-etkindir.
- Matematik model ortaya koymuştur ki; sirotik olsun olmasın hastalarda tedavi uygulanması, tedavisiz takibe göre sağlık kazanımlarında anlamlı iyileşmeler sağlamaktadır.
- Tarama programları genişletildikçe kronik hepatit B hastalarının bakımı için olan talep de artacaktır.

## ÖNERILER

### Sağlık Politikaları

- Orta ve yüksek endemisiteli ülkelerde kronik hepatit B hastalarının tespit, takip ve tedavisinin düzenlenmesi için yeni enformasyon ve kayıt sistemlerine ihtiyaç vardır.
- Ulusal tedavi klavuzları, kronik hepatit B hastalarının takip ve tedavisinin planlanmasında güncel ülkeye özgü maliyet-etkinlik analizlerini dikkate almalıdır.
- Tarama programları genişletildikçe, sürdürülmesi gereken tıbbi takip ve tedaviye olan ihtiyaç artacaktır. Kronik hepatit B'nin tespit ve tedavi edilmesi için ek sağlık çalışanına ihtiyaç duyulacaktır.

## İleriye Yönelik Araştırma Önerileri

- Hepatit B'nin genotiplerine göre progresyon oranlarının tespit edilmesi için toplum tabanlı araştırmalara ihtiyaç vardır.
- Anti-viral terapinin toplumda HBV'nin bulaşmasına olan etkileri hakkında araştırmalara ihtiyaç vardır.
- Matematik modellemelerde kullanılmak üzere, tedavi altında hastalığın progresyon hızlarını ve sonuçlarını araştıran çalışmalara ihtiyaç vardır.
- Anti-viral terapiler üzerine yapılan randomize kontrollü çalışmalar, tedavi yanıtını ve klinik sonuçlarını karaciğer hastalığının ciddiyetini de dikkate alarak sunmalıdırlar.

# Abbreviations

| | |
|---|---|
| AASLD | American Association for the Study of Liver Disease |
| ADV | Adefovir |
| ALT | Alanine aminotransferase |
| Anti-HBc | Antibodies to the hepatitis B virus core antigen |
| Anti-HBe | Antibodies to the hepatitis B virus e antigen |
| Anti-HBs | Antibodies to the hepatitis B virus surface antigen |
| CEA | Cost-effectiveness analysis |
| CHB | Chronic hepatitis B |
| CI | Confidence interval |
| CVZ | College voor zorgverzekeringen (Dutch Health care insurance board) |
| DBC | Diagnose behandeling combinatie (diagnosis treatment combination) |
| EASL | European Association for the Study of the Liver |
| ETV | Entecavir |
| EU | European Union |
| GDP | Gross Domestic Product |
| GP | General Practitioner |
| HBeAg | Hepatitis B Virus e Antigen |
| HBeAg- | Hepatitis B Virus e Antigen negative |
| HBeAg+ | Hepatitis B Virus e Antigen positive |
| HBsAg | Hepatitis B virus surface Antigen |
| HBV | Hepatitis B virus |
| HBV DNA | Hepatitis B virus deoxyribonucleic acid |
| HCC | Hepatocellular carcinoma |
| HCS | Health care student |
| HCW | Health care worker |
| HPD | High resistance profile drug |
| ICER | Incremental cost-effectiveness ratio |
| IFN-alpha | Interferon-alpha |
| IVD | Intravenous drug use |
| IU | International unit |
| IU/mL | International unit per millilitre |
| LAM | Lamivudine |

| | |
|---|---|
| LPD | Low resistance profile drug |
| LT | Liver transplant |
| MPHS | Municipal Public Health Service |
| NA | Nucleos(t)ide analogue |
| NH | atural History |
| NZa | Nederlandse Zorg Autoriteit (Dutch health care authority) |
| PCR | Polymerase chain reaction |
| Peg | Polyethylene glycol |
| Peg-IFN | Pegylated interferon |
| QALY | Quality-adjusted life year gained |
| RCT | Randomized controlled trial |
| SG | Standard gamble |
| SRx | Salvage therapy |
| SVR | Sustained virological response |
| TASL | Turkish Association for the study of the Liver |
| TDF | Tenofovir |
| ULN | Upper limit of normal |
| WHO | World Health Organization |
| WMP | Weighted Mean Prevalence |

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# Curriculum vitae

In 2005 Mehlika Toy started her Master of Science in Clinical Epidemiology at the Netherlands Institute of Health Sciences (NIHES), Erasmus MC, Rotterdam. During her masters she did a public health internship in South Africa, and started working on hepatitis B. After obtaining her masters she started the Doctor of Science program at NIHES, where she continued working on hepatitis B and the development of a natural history and treatment model for the Dutch population. At the time she was employed by the department of Gastroenterology and Hepatology of Erasmus MC, and LiverDoc, and collaborated with GGD Rotterdam-Rijnmond and the department of Public Health of Erasmus MC. After the modelling of the Dutch population cohort of chronic hepatitis B patients, she started working at the department of Public Health of Erasmus MC where her PhD study officially started. In 2008 she received a fellowship from the European Association of the Liver Studies (EASL) to do chronic hepatitis B research in the Turkish population, at the department of Gastroenterology, Ankara School of Medicine, Ankara University. During this fellowship she collected patient data and prepared the calibration of the model for the Turkish setting of the disease. During her PhD she had the opportunity to do a fellowship at Rui Jin hospital in Shanghai, China. She collaborated with experts in the field of Hepatology, liver transplantation and public health, where she constructed a patient data base of over 2000 chronic hepatitis B patients. The collaborations with Turkey and China are continuing.

Erasmus MC
Universitair Medisch Centrum Rotterdam

# PhD Portfolio Summary

| | |
|---|---|
| Name PhD student: **Mehlika Toy** | PhD period: **2008–2010** |
| Erasmus MC department: **Public Health** | Promotor: **prof.dr.J.H.Richardus** |

| PhD training | Year | Workload (hours) |
|---|---|---|
| **Presentations** | | |
| Antalya, Turkey, National Gastroenterology meeting: "Prevention of mortality and morbidity due to hepatitis B and the monitoring and treating of eligible patients in Turkey: a cost-effectiveness analysis" | 2010 | 20 |
| Mainz, Germany, International congress on health, culture and the human body: "Hepatitis B prevalence in Turkey and the relevance for two major host countries" | 2010 | 12 |
| Izmir, Turkey, National Hepatoloy conference: "Hepatitis B prevalence in Turkey: A systematic review" and "The burden of chronic hepatitis B in Turkey: a mathematical approach" | 2010 | 36 |
| Lyon, France, VIRGIL Symposium on Antiviral Drug Resistance: "The potential impact of long-term nucleoside therapy on the mortality and morbidity of high viremic chronic hepatitis B" | 2008 | 18 |
| Zagreb, Croatia, Zagreb International Medical Summit (ZIMS): "Transmission routes of hepatitis B virus infection in chronic hepatitis B patients in the Netherlands" | 2006 | |

| PhD training | Year | Workload (hours) |
|---|---|---|
| **Poster presentations** | | |
| Boston, U.S.A, The annual liver meeting of the American Association for the study of Liver diseases (AASLD): "The cost-effectiveness of treating eligible chronic hepatitis B and cirrhotic patients in a median endemic country" | 2010 | 26 |
| Boston, U.S.A, The annual liver meeting of the American Association for the study of Liver diseases (AASLD): "The Burden of chronic hepatitis B and the cost-effectiveness of treating eligible patients in Shanghai, China" | 2010 | 26 |
| Istanbul, Turkey, EASL Monothematic Conference on Delta Hepatitis: "An aggregated analysis of delta hepatitis in Turkey and the quantification of burden of disease" | 2010 | 14 |
| Boston, U.S.A, The annual liver meeting of the American Association for the study of Liver diseases (AASLD): "The burden of chronic hepatitis B in a median endemic country: a mathematical approach" | 2009 | 26 |
| Boston, U.S.A, The annual liver meeting of the American Association for the study of Liver diseases (AASLD): "The burden of delta hepatitis projected using a mathematical model in a delta endemic country" | 2009 | 24 |
| San Francisco, U.S.A, The annual liver meeting of the American Association for the study of Liver diseases (AASLD): "Impact of nucleoside analogue therapy in the Netherlands" | 2008 | 24 |
| Paris, France, International Conference of Hepatitis B and C Virus Resistance to Antiviral Therapies: "Potential impact of antiviral therapy and drug resistance" | 2008 | 12 |
| Lyon, France, VIRGIL Symposium on Antiviral Drug Resistance: "Mathematical modelling of chronic hepatitis B disease burden" | 2007 | 12 |

| PhD training | Year | Workload (hours) |
|---|---|---|
| **Attended conferences and seminars** | | |
| The Liver Meeting 2010, 61st Annual Meeting of the American Association for the study of Liver Diseases (AASLD), October, Boston, MA, United States of America. | 2010 | 24 |
| International Congress on Health, Culture and the Human Body, September, Mainz, Germany. | 2010 | 20 |
| European Association for the Study of the Liver (EASL) Monothematic Conference on Delta Hepatitis, September, Istanbul, Turkey. | 2010 | 16 |
| Asian Pacific Association for the Study of the Liver (APASL) meeting, March, Beijing, China. | 2010 | 20 |
| The Liver Meeting 2009, 60th Annual Meeting of the American Association for the study of Liver Diseases (AASLD), October, Boston, MA, United States of America. | 2009 | 24 |
| National Hepatology Conference, Turkish Association of the Study of the Liver, June, Izmir, Turkey. | 2009 | 26 |
| The Liver Meeting 2008, 60th Annual Meeting of the American Association for the study of Liver Diseases (AASLD), October, San Francisco, CA, United States of America. | 2008 | 28 |
| Viral Hepatitis Prevention Board (VHPB) meeting on Prevention and Control of Viral Hepatitis in the Netherlands, November, Rotterdam, the Netherlands. | 2008 | 12 |
| European Vigilance Network for the Management of Antiviral Drug Resistance (VIRGIL) Symposium on Antiviral Drug Resistance, May, Lyon, France. | 2008 | 14 |
| International Conference of Hepatitis B and C Virus Resistance to Antiviral Therapies, February, Paris, France. | 2008 | 16 |
| European Vigilance Network for the Management of Antiviral Drug Resistance (VIRGIL) Symposium on Antiviral Drug Resistance, May, Lyon, France. | 2007 | 12 |
| Zagreb International Medical Summit (ZIMS), November, Zagreb, Croatia. | 2006 | 14 |

| PhD training | Year | Workload (hours) |
|---|---|---|
| **Attended lectures abroad** | | |
| Health Economics, Economic Evaluation and Evidence-based Decision making, Charite Institute of Tropical Medicine Berlin, Germany | 2009 | 90 |
| Global Health course, Cambridge University, UK | 2007 | 55 |
| **Other academic activities** | | |
| Member of knowledge team, LiverDoc, Rotterdam, the Netherlands, DocTop, Risk scores. | 2007-current | |
| Advisor hepatitis B burden, Burden of Disease study Bielefeld, Germany. | 2010-current | |
| European Vigilance Network for the Management of Antiviral drug Resistance (VIRGIL) platform member | 2007–2008 | |
| **Lecturing** | | |
| Ankara School of Medicine, PhD students and medical staff. Topic: 'Mathematical modelling in Epidemiology' | 2008 | 14 |
| Izmir, Dokuz Eylul Medical Faculty, medical students. Topic: 'Hepatitis B and modelling of infectious diseases' | 2008 | 14 |
| **Review of scientific papers** | | |
| Liver International | | 16 |
| BMJ | | 6 |
| Alimentary Pharmacology & Therapeutics | | 6 |
| Gut | | 6 |
| Journal of Viral Hepatitis | | 10 |
| Journal of Hepatology | | 6 |

| PhD training | Year | Workload (hours) |
|---|---|---|
| **Periods of research abroad** | | |
| Shanghai, China: **Rui Jin hospital, Jia Tong University**, Department of Hepatology<br>Grant: Internal Fellowship of Department of Public Health, Erasmus MC | 2010 | 350 |
| Ankara, Turkey: **School of Medicine, Ankara University**, Department of Gastroenterology Grant: European Association of Liver Studies (EASL) Sheila Sherlock short-term fellowship | 2009 | 310 |
| Cape Town, South Africa: **Maitland Cottage Home**, Paediatric Orthopaedic hospital Public Health internship through the International Federation of Medical Students' Association the Netherlands (IFMSA) | 2006 | 300 |