COST-EFFECTIVE INTERVENTIONS IN THE CONTROL OF CHRONIC HEPATITIS B (CHB) INFECTION

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ABSTRACT

The hepatitis B virus (HBV) causes infection in the liver that can lead to cirrhosis, liver cancer, and premature death. The disease is not widely recognised as a serious public health problem, and as a result, inadequate resources are being allocated to hepatitis B prevention and control. Vaccination against HBV has been a great success and has resulted in a reduction in the rate of chronic infection; however, the vaccine is of no help for those already infected. The big challenge is how to deliver effective and affordable care to those who are carriers and who are eligible for treatment, and affordable diagnostics to detect those who are not yet aware of their infection, to prevent the spread to susceptible individuals. This review intends to give the reader a brief overview of the types of control strategies that have been examined in recent cost-effectiveness studies on the control of chronic hepatitis B.

Keywords: Chronic hepatitis B, cost-effectiveness, vaccination, treatment, screening.

COST-EFFECTIVE INTERVENTIONS FOR CHB

Cost-effectiveness analysis (CEA) is a method used to evaluate the outcomes and costs of interventions designed to improve health.[1] The purpose of a CEA in healthcare is to help the decision-maker determine how to allocate resources across a defined number of competing needs in order to maximise health outcomes from a limited budget.[2] The quality-adjusted life year (QALY) is a measure of effectiveness - more time spent in good health. The incremental cost-effectiveness ratio (ICER) is the net increase in cost of the intervention compared to standard care/no treatment to gain 1 QALY. The ICER is the incremental costs of implementing an intervention over another intervention (or no intervention), divided by the incremental effectiveness (QALYs) from another intervention (or no intervention). The World Health Organization (WHO)[3] defines the threshold value for intervention cost-effectiveness as one-to-three times the gross domestic product per capita (GDP) of a country. An intervention is considered cost-saving if it is more effective and less costly than the comparator. Chronic hepatitis B (CHB) is a serious public health problem; an estimated 1 million people annually die of hepatitis B virus (HBV) related chronic active hepatitis, cirrhosis, and liver cancer. Therefore, the cost of this disease to public healthcare systems is considerable. For the control of this infectious and chronic disease, vaccination, screening, and treatment strategies have been studied in various settings and countries. Table 1 gives an overview of the recent cost-effectiveness studies.

VACCINATION

HBV vaccination created the first breakthrough in HBV prevention, which is the most effective measure to prevent new HBV infections and its consequences. Studies on cost-effectiveness from the UK and Ireland (low endemic countries) were carried out to estimate the impact of a universal infant vaccination programme;[4,5] both of these countries have a policy to selectively vaccinate individuals at high risk of HBV infection, but neither

have, as yet, introduced universal HBV vaccination policies. Siddiqui et al.[4] concluded that in order for universal infant vaccination to be considered cost-effective, the average cost of vaccinating should be reduced to £4.09, which is the average cost for vaccine and administration costs of all three doses. In Ireland, universal infant vaccination will be cost-effective with an ICER of €37,018, which the authors concluded compares favourably with other preventive programmes in Ireland. A study from Germany[6] concluded that the use of a vaccination strategy to reduce transfusion transmission of HBV would represent a potential cost reduction of €200 million over a 20-year period when compared with current mandatory testing in Germany, while also offering the near-elimination of transfusion infections with HBV.

Rein and Weinbaum[7] were interested in the cost-effectiveness of using hepatitis A/B combined vaccine versus HBV vaccine alone for high-risk heterosexuals in the US. They found the use of combination A/B vaccine to be substantially less cost-effective than other vaccination strategies against viral hepatitis. An ICER of administering combination vaccine to all high-risk heterosexuals aged 15-44 was $120,000/QALY gained, equal to almost three-times the GDP per capita. The authors concluded that the cost-effectiveness of this intervention appears to be at the outer reaches of acceptability by WHO standards.

Kuan et al.[8] compared the cost-effectiveness of HBV vaccination using heplisav - which uses fewer doses over a shorter time than currently licensed vaccines - in selected adult populations in the US compared to Engerix-B vaccine. The authors concluded that the results from this CEA demonstrate that Heplisav is cost-saving in patients with chronic kidney disease and end-stage renal disease, and is cost-effective ($25,000/QALY) in the diabetic population, healthcare workers, and for travellers. Hoerger et al.[9] examined the cost-effectiveness of a HBV vaccination programme for unvaccinated adults diagnosed with diabetes in the US. They concluded that HBV vaccination for diabetic adults aged 20-59 was modestly cost-effective ($75,094/QALY), while vaccination for adults 60 years and older was cost-ineffective ($2.7 million/QALY).

Kim et al.[10] assessed the cost-effectiveness of four strategies for vaccinating potentially high-risk adults attending two major types of publicly funded HIV counselling and testing sites: freestanding counselling and testing sites, and sexually transmitted disease clinics in the US. Results of this study implied that integrating routine HBV vaccination programs into existing HIV counselling and testing sites may be a cost-effective ($3,500-$4,400) public health intervention. Looking at various willingness-to-pay thresholds, Chen et al.[11] concluded that intramuscular hepatitis B immunoglobulin (HBIG) treatment for neonates of hepatitis B surface antigen (HBsAg) carrier mothers is likely to be cost-effective in addition to universal vaccination, particularly in settings with adequate healthcare infrastructure; however, in very resource-limited settings, universal vaccination alone is optimal. Two other studies from high endemic areas, China and Taiwan,[12,13] estimated that universal vaccination compared to no vaccination is cost-saving and even avoids loss of productivity. According to the study by Hutton et al.[14] catch-up vaccination among children and adolescents is a cost-saving strategy in China, where the endemicity is the highest in the world.

TREATMENT

Vaccination against hepatitis B has resulted in a reduction in the rate of chronic infection;[15] however, vaccine is of no help for those already infected. Antiviral therapy is the only option to control and prevent progression of disease in patients with active CHB.[16] The goal of therapy for 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, and death.[17] A review I recently compiled[18] gives an overview of cost-effectiveness studies on CHB treatment, where most of these studies primarily focused on entecavir and tenofovir monotherapy, followed by rescue therapy for patients who developed resistance.

SCREENING

Testing for CHB meets established public health screening criteria as formulated originally by Wilson and Junger.[1,19] It is a serious health disorder that can be diagnosed before symptoms develop,[2] and it can be detected by reliable, inexpensive, and minimally invasive screening tests.[4] Chronically infected patients have years of life to gain if medical evaluation, monitoring, or treatment is initiated early; also,[5] the costs of screening are reasonable in relation to the anticipated benefits.

Table 1: Summary of recently published cost-effectiveness studies.

Intervention	Country/Target Group	Summary of Study Strategy	Outcomes
Vaccination			
Siddiqui et al.[4]	UK/infants	Universal infant vaccination	Not cost-effective (£263,000/QALY) - if vaccine cost is reduced strategy becomes cost-effective
Tilson et al.[5]	Ireland/infants	Universal infant vaccination	Cost-effective (€37,018)
Fischinger et al.[6]	Germany/blood donors	Vaccination to reduce transfusion transmission	Cost-saving if tested for anti-HBs and receives a time-dependent booster vaccination
Rein and Weinbaum[7]	USA/high-risk heterosexuals	A/B combined vaccine versus B vaccine alone	$120,000/QALY
Kuan et al.[8]	USA/selected high-risk groups	Fewer doses over a shorter time versus currently licensed vaccines	Cost-effective ($25,000/QALY) in the diabetic population, healthcare workers, and travellers
Hoerger et al.[9]	USA/diabetic adults	Vaccination for diabetic adults	Cost-effective ages 20-59 ($75,094/QALY) not cost-effective age 60+ ($2.7 million/QALY)
Kim et al.[10]	USA/adults attending STD clinics	Vaccinating high-risk adults attending HIV counselling and testing sites	Cost-effective ($3,500-4,400)
Chen et al.[11]	Taiwan/neonates	Immunoglobulin for neonates in addition to universal vaccination	Cost-effective ($1,400-4,000)
Hung et al.[12]	Taiwan/infants	Universal infant vaccination versus no vaccination	Cost-saving
Lu et al.[13]	China/infants	Universal infant vaccination long-term outcomes	Cost-saving
Hutton et al.[14]	China/children and adolescents	Catch-up vaccination	Cost-saving
Treatment			
Toy[18]	Systematic review, Global	Overview of recent cost-effectiveness studies on treatment of CHB	CEA studies for CHB focused on entecavir and tenofovir monotherapy followed by rescue therapy for patients that develop resistance
Screening			
Hutton et al.[22]	USA/Asian and Pacific Islanders	Screening and vaccination	Cost-effective ($36,088-39,903)
Robotin et al.[23]	Australia/Asian-born adults	HCC surveillance versus HCC prevention (including CHB treatment)	HCC prevention strategy cost-effective (AUD $12,956/QALY)
Wong et al.[24]	Canada/foreign-born adults	Screen and treat versus no screening	Cost-effective (CAD $69,209/QALY)
Rossi et al.[25]	Canada/migrants and refugees	Screen and treat versus no screening	Cost-effective (CAD $40,880/QALY)
Veldhuijzen et al.[26]	Netherlands/migrants	Screen and treat versus no screening	Cost-effective (€8,966/QALY)

Intervention	Country/Target Group	Summary of Study Strategy	Outcomes
Screening (Continued)			
Eckman et al.[27]	USA/ asymptomatic outpatients	Screen and treat versus no screening	Cost-effective ($29,230/QALY)
Ruggeri et al.[28]	Italy/high-risk groups	Screen and treat versus no screening	Cost-effective (€17,179/QALY)
Davidson et al.[29]	Sweden/blood donors	Nucleic acid testing among blood donors	Not cost-effective ($2.7million/ QALY)
Zurawska et al.[30]	USA/patients with lymphoma	Screening for HBV before chemotherapy versus high-risk groups or no screening	Cost-effective ($32,589/QALY)
Adibi et al.[31]	Iran/adults prior to marriage	Screening versus no screening	Cost-effective ($197-202 per infection averted)
Other			
Guo et al.[32]	China/pregnant women	HBIG injection versus no HBIG	Cost-effective ($118)
Nayeri et al.[33]	USA/pregnant women	Lamivudine treatment at third trimester versus no treatment	Cost-saving
Unal et al.[34]	USA/pregnant women	Lamivudine or HBIG treatment at third trimester versus no treatment	Cost-saving
Toy et al.[35]	China/general population	Monitor (inactive) and treat (active) strategy CHB versus current practice (no monitoring)	Cost-effective ($2,996/QALY)

CHB: chronic hepatitis B; HBIG: hepatitis B immunoglobulin; HCC: hepatocellular carcinoma; STD: sexually transmitted disease.

One-time HBV screening may identify most individuals and will give the opportunity to vaccinate those who are susceptible, and to initiate effective antiviral therapy before the development of advanced liver disease.

In many high-risk areas, particularly those in Asia, HBV is transmitted from mother to newborn (vertical transmission); as many as 90% of infected babies develop chronic infection.[20] Hepatitis B screening during pregnancy, and postpartum immunoglobulin and HBV vaccination in neonates born to HBV-infected mothers is far from being universally implemented.[21] In low endemic countries, CEA studies are mainly focused on analysing whether various screening programmes that are specifically targeting migrants from endemic countries - those considered high-risk - are cost-effective. Hutton et al.[22] chose to target the Asian and Pacific Islander population in the US, since the incidence of liver cancer is more than three-times higher among this population, and around 60-80% of liver cancer cases are attributable to HBV infection. Hutton et al.[22] concluded that screening the Asian and Pacific Islander adult population is likely to be cost-effective ($36,088-$39,903/QALY gained). Robotin et al.[23] targeted the Asian-born adults in Australia as their study population for the different management strategies for the control of CHB. They concluded that the liver cancer prevention strategy coupled with antiviral treatment is cost-effective (AUD $12,956/QALY gained).

Wong et al.[24] were interested in the screening strategies for 20-65 year-old individuals who were

born abroad but are currently living in Canada. Their analysis suggested that the screening and treatment of all migrants is moderately cost-effective ($69,209/QALY gained). Another CEA study[25] from Canada concluded that HBV screening and treatment for newly arrived adult Canadian immigrants and refugees is reasonably cost-effective ($40,880 QALY gained); however, if they were to combine screening, treatment, and vaccination, this strategy would not be considered cost-effective ($437,335/QALY gained). According to Veldhuijzen et al.[26] systematic screening and early treatment of migrants in the Netherlands is a cost-effective strategy (€8,966/QALY gained).

Eckman et al.[27] examined screening, followed by treatment of those who were eligible, in asymptomatic outpatients living in a region in the US with an HBV infection prevalence of 2%, which was cost-effective ($29,230/QALY). Ruggeri et al.[28] examined a test strategy in Italy, where they define the high-risk group as: immigrants from high endemic countries, intravenous drug users, prisoners, individuals with other infections, patients undergoing dialysis, pregnant women, and subjects with high transaminase; it involved the administration of a screening test to patients at high risk, and the treatment of the infected, and it yielded an ICER of €17,179/QALY compared to no testing. The cost-effectiveness of introducing nucleic acid testing among blood donors in Sweden was studied by Davidson et al.,[29] where they concluded that the cost-effectiveness ratios for this intervention are far beyond what is considered cost-effective, with a cost of $12.7 million per avoided viral transmission, and $2.7 million/QALY gained. Zurawska et al.[30] were interested in whether HBV screening before chemotherapy for lymphoma was considered cost-effective, and concluded from their finding that, in patients receiving chemotherapy for lymphoma, screening all patients for HBV reduces the rate of HBV reactivation (10-fold) and is less costly ($32,589/QALY) than screening only high-risk patients or screening no patients.

A CEA approach on whether testing adults for HBV prior to marriage has an effect on the impact of transmission prevention and whether it is cost-effective in Iran or countries with similar cultural backgrounds was examined by Adibi et al.,[31] in which they concluded that it costs between $197-202 for each infection averted.

Three studies have examined the cost-effectiveness of maternal treatment to prevent perinatal HBV transmission.[32-34] Two of these studies, both from the US, aimed to estimate the cost-effectiveness of maternal lamivudine, or HBIG treatment, in addition to standard neonatal immunoprophylaxis; they concluded that both of these interventions, compared to doing nothing, were cost-saving across a wide range of assumptions. The third, also from the US, concluded that lamivudine administration in the third trimester of pregnancy is a cost-effective ($1,073/QALY) and, frequently, a cost-saving intervention. The group from China concluded that injecting immune globulin to infants after birth is more cost-effective ($118) compared to injecting immune globulin during pregnancy.

A study done by our group,[35] compared the current strategy - not monitoring inactive chronic HBV patients - to a monitor and treat (M&T) strategy in Shanghai, China. The M&T strategy would include twice-yearly assessment of HBV and alanine transaminase (ALT) levels in patients with chronic HBV. Our findings suggested that lifelong monitoring of inactive chronic HBV patients is cost-effective ($2,996/QALY), but relies on identifying more cases of HBV infection and also on increasing treatment, monitoring, and antiviral adherence to achieve health gains.

CONCLUSION

Governments around the world face budget constraints that compel them to make tough decisions about how to best invest funds for public health.[36] CEA is an essential evaluation tool that allows policymakers and health planners to compare the health gains that various interventions can achieve with a given level of input.[36] An example of a real-life impact of a CEA on health policy is the screening study where Hutton et al.[37] convinced the Centers for Disease Control (CDC) to update their recommendations; the CDC's most recent hepatitis B screening guidelines recommend screening all adult Asian and Pacific Islanders for hepatitis B as well as all adults born in areas of intermediate (2-7%) HBV prevalence. Also, Hutton et al.[37] were successful in influencing the China CDC with their analysis of the cost-effectiveness of the catch-up vaccination program: in April 2009, China decided to include free HBV catch-up vaccinations for all children under the age of 15. In most countries, estimating what it

would cost to expand the coverage of existing interventions or to add new interventions relies on assumptions. CEA will almost always include a series of assumptions as it is generally not possible to measure everything necessary for a comprehensive analysis.[38] CHB needs to be widely recognised as a serious public health problem, and as a result, resources need to be allocated to HBV prevention and control. The big challenge is how to deliver the cost-effective interventions to control the disease.

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