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Title

An economic evaluation of contingency management for completion of hepatitis B vaccination in those on treatment for opiate dependence

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List of Abbreviations

Hepatitis B virus (HBV)

United Kingdom (UK)

People who inject drugs (PWID)

Confidence interval (CI)

Standard deviation – SD

Keywords

Viral hepatitis; methadone maintenance program; vaccination; incentives; economic; opiates, contingency management; injecting

Conflict of interest Statement

JS has contributed to UK guidelines which include consideration of the potential role of contingency management in the management of opiate addiction (NICE, 2007; chaired by JS), and JS also chaired the broader-scope pan-UK working group preparing the 2007 Orange Guidelines for the UK Departments of Health, providing guidance on management and treatment of drug dependence and misuse, including guidance on possible inclusion of contingency management and is also chairing the new Expert Group revising further and updating these Guidelines for the four UK Departments of Health. JS and JS's institution have received support and funding from the Department of Health (England) and National Treatment Agency (England), and JS and JS's institution have provided funded consultancy advice on possible novel addiction treatments, products and formulations to a range of pharmaceutical companies but these do not have any connection to the intervention being investigated nor the analyses in this paper. JS's employer (King's College London) has registered intellectual property on an innovative development in this area with which JS is involved, and JS has been named in a patent registration by a pharmaceutical company as inventor of a potential novel overdose resuscitation product, but these do not have any connection to the work being reported in this paper. A fuller account of JS's interests is on his personal web-page of the Addictions Department at http://www.kcl.ac.uk/ioppn/depts/addictions/people/hod.aspx .

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Author's contributions

RR and PJD undertook the modelling. RR drafted the paper. NM, JH, TW, and JS provided specific guidance on interpreting the trial and trial data. SB, HT, and RR undertook the costing. VDH and FN provided national sero-prevalence data and advised on its interpretation and on UK HBV epidemiology. All authors commented on the paper to produce a final version.

ABSTRACT (257 words)

Aims: To determine whether the provision of contingency management using financial incentives to improve hepatitis B vaccine completion in people who inject drugs entering community treatment represents a cost-effective use of healthcare resources.

Design: A probabilistic cost-effectiveness analysis was conducted, using a decision-tree to estimate the short-term clinical and healthcare cost impact of the vaccination strategies, followed by a Markov process to evaluate the long-term clinical consequences and costs associated with hepatitis B infection.

Settings and participants: Data on attendance to vaccination from a UK cluster randomised trial.

Intervention: Two contingency management options were examined in the trial: fixed vs. escalating schedule financial incentives.

Measurement: Lifetime healthcare costs and quality-adjusted life years discounted at 3.5% annually; incremental cost-effectiveness ratios.

Findings: The resulting estimate for the incremental lifetime healthcare cost of the contingency management strategy versus usual care was £22 (95% CI: -£12 to £40) per person offered the incentive. For 1,000 people offered the incentive, the incremental reduction in numbers of hepatitis B infections avoided over their lifetime was estimated at 19 (95% CI: 8 to 30). The probabilistic incremental cost per quality adjusted life year gained of the contingency management programme was estimated to be £6,738 (95% CI: £6,297 to £7,172), with an 89% probability of being considered cost-effective at a threshold of £20,000 per quality-adjusted life years gained (98% at £30,000).

Conclusions: Using financial incentives to increase hepatitis B vaccination completion in people who inject drugs could be a cost-effective use of healthcare resources in the UK as long as the incidence remains above 1.2%.

Many countries include universal Hepatitis B virus (HBV) vaccination in their national immunisation programmes(1). A few countries, including the United Kingdom (UK), have selective vaccination policies that target individuals at increased risk of HBV infection or complications from the disease including people who inject drugs or who live with injectors(2).

Despite these immunisation programmes, HBV infections remain an important public health problem among people who inject drugs (PWID) even in many countries with universal HBV vaccination(3). In England and Wales, the prevalence of current or past infection with HBV (measured by anti-HBc seropositivity) in current or past injectors has declined over the last 20 years from 30% in 2003 to 17% in 2012, due in part to the introduction of a national prison vaccination scheme in 2003(4;5). Monitoring data indicate that among current and past injectors in contact with specialist services, the self-reported hepatitis B vaccine uptake has increased from 50% in 2003 to 75% in 2012(4). Despite this improvement in the self-reported vaccine uptake, completion rates of HBV vaccination among current and past injectors, even those using specialist services, remains low, and vaccine uptake has plateaued in recent years(4). Public health benefits from HBV vaccination are not therefore fully realised in PWID and transmission continues (albeit at lower levels), with on-going potential for community outbreaks(6;7). Reasons for low completion of HBV vaccinations in community settings include the poor adherence to treatment among PWID and a high drop out from health care services(8).

Contingency management has been proposed as an approach to improve patient adherence and completion of public health interventions among hard-to-reach groups, including HBV vaccination in PWID using community-based services(9;10). It uses incentives to encourage attendance, reduce missed appointments, and improve successful intervention uptake(9). Studies conducted in Australia(11) and the US(12;13) showed significantly improved adherence and completion of HBV vaccination using contingency management in PWID. Similar findings were observed in the UK in a recent 3-arm cluster randomised controlled trial where PWID (including injectors, previous injectors and those at risk of injecting in the future) undergoing treatment for heroin dependence were randomised to either HBV vaccination with or without contingency management (14).

There have been no economic evaluations of the use of contingency management to enhance completion of HBV vaccination among PWID in routine drug treatment settings. This study evaluates whether the provision of financial incentives to improve HBV vaccination completion in PWID as undertaken in Weaver et al(14) represents a cost-effective use of healthcare resources.

METHODS

Model

A decision-analytic model was constructed in Microsoft Excel comprising a decision-tree to estimate the short-term (i.e. around vaccination attempts) clinical and cost impact of the vaccination strategies, followed by a Markov chain to evaluate the long-term clinical consequences and costs associated with HBV infection of a hypothetical cohort of PWID (including injectors, previous injectors and those at risk of injecting in the future as defined in the trial) undergoing treatment over the lifetime in England and Wales.

The decision-analytic model compares two strategies: HBV vaccination with and without contingency management. Two contingency management options were examined in the trial (fixed vs. escalating schedule financial incentives). Data from the two options evaluated in the trial were pooled in the economic model in the absence of differences(14). Further details on the trial and baseline characteristics of patients included in the trial are available in Weaver et al(14).

The structure of the decision tree model is presented in **Fig. 1.** with participants able to attend or not attend one, two or all three 'required' vaccination appointments. At the end of the HBV vaccination attempt, subjects within the model can be successfully vaccinated (as a result of one, two or three vaccine doses), or remain susceptible to HBV (as a result of failing to begin vaccination, failing to complete the vaccination course, or as a result of a lack of vaccine efficacy despite completing the course).

[INSERT FIGURE 1]

A Markov process (**Fig. 2.**), using a one year cycle length was used to simulate the long-term clinical and cost consequences of HBV-related infection. The model tracks progression through HBV disease states. Health states and transitions between health states were based on descriptions of the natural history of HBV infection in existing systematic reviews (15-18) and on published economic models including HBV(19-22). The economic model differentiates periods where individuals are at increased risk of HBV infection (are in the PWID population), and where individuals at lower risk of HBV infection (are ex-PWID). We assumed that individuals at increased risk of HBV infection have an ongoing rate of becoming immune to reflect the UK selective vaccination policy targeted to individuals at increased risk of HBV infection.

[INSERT FIGURE 2]

HBV incidence

The incidence of HBV infection among susceptible PWID in the UK was estimated at 2.16% per year using data from the national Unlinked Anonymous Monitoring Survey among current and past injectors and an approach similar to Sutton et al(23). Additional details are provided in supporting information.

Direct data informing the incidence of HBV among ex-PWID are lacking: it could range from zero to be the same level as in PWID. The base-case assumes HBV infection incidence in ex-PWID equals the general population incidence. General population HBV incidence was estimated at 4.08 per 100,000 using the annual incidence of reported acute hepatitis B in England(24) adjusted for under-reporting and asymptomatic cases (21).

Characteristics of the PWID population

The rate at which individuals cease injecting drugs(25) was used as a proxy for the probability of leaving the PWID population and ceasing to be at high HBV infection risk (Table 1). PWID can also become protected through existing targeted vaccination programs. We estimated this rate of vaccination using the prevalence of self-reported HBV vaccine uptake among current and past injectors in 2011 (76%(4)) and converting this into the annual probability of vaccination (28.8%) assuming a constant uptake prevalence and PWID population size. To account for partial protection in those reporting vaccination , we assumed 47.5% of self-reported vaccinations are successful (based on the distribution of vaccine dose given in prison(26) and evidence on the vaccine efficacy(27)).

The model accounts for elevated risk of all-cause mortality (Hazard Ratio 4.8; 95% confidence interval [CI]: 4.6–5.0) for persons in contact with drug-treatment services compared with the general population. The unadjusted mortality rate in the general population by age was from UK life tables for England and Wales(28).

Natural history of HBV

The transition probabilities characterising the natural history of HBV were derived from the published literature (Table 1) (15-18;29). Lacking data for PWID, transitions between HBV health states among the general population were used.

[INSERT TABLE 1]

Effectiveness of the vaccination strategies

The economic analysis uses data from Weaver et al.(14). The primary outcome in this trial was vaccination completion within 28 days. Attendance rates used in the economic model are presented in Table 2. To reflect clinical practice, we included delayed attendance (within a 3-month window from the start of the trial). The same probability of attending a subsequent appointment was used irrespective of whether the previous vaccination was received on time.

[INSERT TABLE 2]

Vaccine effectiveness

The effectiveness (sero-protection) associated with the receipt of one, two and three doses was obtained from the literature(27) as data were not routinely collected in the trial. In the economic model, we assumed that participants receiving one and three vaccine dose had a sero-protection of 15% and 76.4% respectively,(27) averaging these for individuals receiving two doses. We assumed that sero-protection was conferred after the last vaccine dose (one, two or three doses), that immunity is lifelong, and that the last dose was within 3 months from the first. Adverse reactions to the vaccine are rare and were neglected(27).

Costs

A UK National Health Service perspective is employed and therefore only direct medical costs are considered. Costs are discounted at 3.5% in the base-case as per the National Institute for Health and Care Excellence recommendation in the UK(30).

Staff, equipment and supervision costs were calculated from the trial, based on data collected in 10 clinics for 116 patients enrolled in the trial irrespective of vaccination arm. The costs estimated

include adjustment for staff time associated with non-attendance. Staff plus equipment costs were estimated to be £15.68±5.65 (standard deviation - SD) for individuals attending no vaccination appointment, £69.29±12.66 for individuals attending only one vaccination appointment, £98.91±16.21 for individuals attending only two vaccination appointments, and £112.35±16.30 for individuals attending all three vaccination appointments. The cost of training staff for contingency management was excluded from the base-case and the cost for Engerix (£12.99 per dose)(31) was assumed as benefits associated with prevention of hepatitis A were not included. People receiving contingency management were assumed to receive a £10 voucher per vaccination appointment attendance. Finally, for participants who attended at a later date an additional cost was included for every unscheduled vaccination, equivalent to the cost associated with non-attendance of the first vaccination appointment (£16).

In the economic model, PWID have a probability of vaccination through existing targeted programs. A cost per patient of £82 was applied to participants receiving these vaccinations based on the proportion of patients receiving one, two or three doses in prison,(26) assuming a cost of £29 for administration/preparation/administration per dose(32) (based on 30 minute nurse time) and the cost per vaccine dose (£12.99 per dose)(31).

Direct medical costs associated with the management of HBV infection are taken from the literature and assumptions when appropriate (supporting Table S1)(20;22;32-34).

Utilities

Health-related quality of life scores (utilities) are assigned to each of the modelled health states based on trial estimates or published literature. The baseline health utility for uninfected PWID and Ex-PWID was estimated as 0.57±0.34 (Range: -0.43 – 1.00) based on the mean (SD) Euroqol 5 dimensions score in trial subjects. The decrements in quality of life for patients with active chronic HBV, inactive chronic HBV, compensated cirrhosis, decompensated cirrhosis, hepatocellular carcinoma and post-liver transplant was taken from Ong et al(35) in non-PWID. Individuals with fulminant hepatitis were assumed to have the same decrement in quality of life as individuals with hepatocellular carcinoma. Similarly, the decrement in quality of life the first year following transplantation was taken as mean of the decrement in quality of life for patients with hepatocellular carcinoma and post-transplant patients (supporting Table 2). We assumed individuals with acute symptomatic hepatitis had a reduction in quality-adjusted life years of 0.0255 (accounting for the duration of illness)(36) and no reduction in quality of life for individual with asymptomatic hepatitis. Finally, no decrement in quality of life associated with vaccination was considered (27).

Analysis

Results are presented probabilistically to take account of the simultaneous effect of uncertainty relating to model parameter values. A total number of 1,000 simulations were performed in order to provide sufficient information on uncertainty. The results of the probabilistic analysis are also presented as cost-effectiveness planes and acceptability curves.

A number of one-way sensitivity analyses were conducted. Results are presented in the form of a Tornado diagram.

RESULTS

For 1,000 people offered the incentive, we estimated the number of HBV infections to be 44, compared with 62 in the absence of financial incentives (reduction in numbers of HBV infections of 19; 95% CI: 8 to 30) based on our mathematical model under our base-case assumptions.

The cost of delivering HBV vaccination (including staff costs, equipment, vaccine cost, and cost associated with contingency management) was estimated to be £156.73 (95% CI: £126.44 to £181.17) per participant receiving the intervention and £78.36 (95% CI: £52.50 to £101.62) per participant under treatment as usual. The model predicted that 48. 77% (95% CI: 43.08% to 52.86%) of participants receiving contingency management would be protected against HBV infection, compared with 26.54% (95% CI: 19.36% to 32.65%) for treatment as usual.

Providing contingency management in the manner of the trial would lead to a small gain in life years (0.0045; 95% CI: 0.0017 to 0.0075) and quality-adjusted life years (0.0032; 95% CI: 0.0013 to 0.0054) per patient, but at an increased cost (£21.86; 95% CI: -£12.20 to £39.86) despite the reduction in expected HBV management costs (-£53.34; 95% CI: -£96.24 to -£33.88) over a lifetime.

Under our base-case assumptions, the probabilistic incremental cost-effectiveness ratio associated with the provision of modest financial incentives to increase vaccination completion in PWID in contact with specialist services was estimated to be £6,738 (95% CI: £6,297 to £7,172) per quality-adjusted life years gained using a lifetime horizon.

The economic analysis was most sensitive to the time horizon, the chronicity rate following HBV exposure, the duration individuals remain at increased risk of HBV infection (i.e. remain PWID), the incidence rate for HBV, discount rates for both costs and benefits, the cost associated with training/supervision (**Fig. 3.**).

[INSERT FIGURE 3]

A major uncertainty in the model relates to the incidence of HBV infection in England and Wales among PWID and ex-PWID. In the base-case we assumed the incidence in PWID to be around 2.16% (95% CI: 1.76% to 2.67%) based on results estimated from the Unlinked Anonymous Monitoring Survey. However, there is uncertainty around this value. **Fig. 4.** shows that under our current base-case assumptions (assuming the incidence of HBV in ex-PWID to be the same as the general population), the incidence of HBV in PWID needs to be greater than 1.2% per year for the incremental cost per quality-adjusted life years gained to fall below a cost-effectiveness threshold of £20,000 per quality-adjusted life years gained. The incremental cost per quality-adjusted life years gained also improves as the incidence of HBV in ex-PWID becomes closer to the incidence in PWID and may lead to cost-savings (data not shown).

[INSERT FIGURE 4]

The cost-effectiveness acceptability curve and cost-effectiveness planes are presented in **Fig. 5(A).** and **Fig. 5(B).**. The use of contingency management have 88.51% and 97.60% probabilities of being considered cost-effective at a willingness to pay of £20,000 and £30,000 per quality-adjusted life years gained respectively under our base-case assumptions.

[INSERT FIGURE 5(A)]

[INSERT FIGURE 5(B)]

DISCUSSION

Contingency management using financial incentives to improve completion of hepatitis B vaccination in people injecting drugs entering community-based services is likely to be cost-effective under current willingness to pay(30). This is the first study to undertake an economic evaluation to calculate the cost-effectiveness of providing contingency management - financial incentives - to PWID to enhance hepatitis B vaccination completion.

Key strengths of this study include that it is based on a well-conducted cluster randomised controlled trial of contingency management versus treatment as usual in twelve specialist NHS services providing opiate substitution treatment in England(14). The trial included direct measurement of the costs of delivering contingency management including staff time, equipment and consumables.

The best available evidence was used. The structure of the model follows the representation of the natural course of HBV in previous systematic reviews describing the natural history of HBV infection(15-18) and previous economic evaluations(19-22). The incidence of HBV was estimated from cross-sectional survey data from the national Unlinked Anonymous Monitoring Survey, which provide robust estimates of prevalence trends of HBV infection and self-reported vaccination among current and past injectors in the UK.

The generalizability of our results requires careful consideration. The UK does not have a programme of universal HBV vaccination. However, intensive targeted efforts in the UK have resulted in improved coverage of HBV vaccination among PWID, and while the cohorts vaccinated at birth in countries that did implement universal programmes may now be approaching the age of first injection, coverage may be lowest among those most likely to inject. Similar trials conducted in Australia(11) and the US(12;13) showed that it is possible to significantly improve adherence to and completion of HBV vaccination programs using contingency management.

Another key factor in generalizability is the existing rate of HBV incidence. Studies conducted in other countries such as Australia, US and Netherlands report a HBV incidence in current and past injectors ranging between 1.8 to 30.7 per 100 person-years, (37) but these studies are dated. There is also likely to be large sub-national variation. However, our sensitivity analysis suggests that the ICER would fall below £20,000 per QALY gained when the incidence of HBV in PWID is over 1.20% per year.

As with any economic evaluation, there are some limitations. There are uncertainties on the future probability for a susceptible PWID to be reached by current targeted vaccination program in England and Wales, the duration individuals remain at increased risk of HBV infection, and the risk of HBV infection among ex-PWID. It is also difficult to predict sero-protection in this patient group as some PWIDs are protected after one vaccination and some are not even after three doses. There is also uncertainty around efficacy of incomplete vaccine course and the time to protection. Decrements in

utilities associated with hepatitis B were taken from non-UK data among non-PWID data. PWID may experience different decrements in quality of life due to high propensity for comorbidities. Transitions between HBV health states among PWID were also taken from studies conducted in cohorts that did not entirely comprise PWID. In order not to over-estimate the benefits of vaccination, we allowed for life-course reductions in risk of HBV infection by introducing an ex-PWID state. We conservatively assumed the risk of HBV infection among ex-PWID to be the same as the general population, in the absence of specific data for this group. In reality ex-PWID may have higher exposure to HBV than the general population, e.g. due to re-commencing injecting or sexual transmission.

In the trial, contingency management was shown to increase vaccination completion rapidity, therefore reducing the period at risk of infection. This is not captured in the economic model. Similarly, attendance at scheduled appointments was increased in patients receiving the intervention; which may therefore reduce the workload in clinic and increase efficiency and therefore may lead to a reduction in costs.

Further development of the modelling approach could consider secondary transmission (dynamic/transmission modelling) of HBV and the indirect effect of vaccination (herd immunity). The modelling presented here also does not consider outbreaks or co-infection associated with hepatitis A, hepatitis C and human immunodeficiency virus.

Our work suggests further research is needed to determine whether ex-PWID carry the same risk as PWID. Further research is also required to understand the dynamics of PWID and secondary transmission as well as the natural history in PWID and impact of hepatitis B on quality of life.

The central implication of our study for practice is that contingency management should be seriously considered as a worthwhile additional investment to improve health outcomes. The UK has seen a sustained programme to improve HBV vaccination coverage in high-risk groups, including offering HBV vaccination in syringe exchanges and prisons. Contingency managementis not a replacement for these efforts, but was able to additional benefits in a cost-effective manner. Provision of lower financial incentives may potentially be as effective, and determining the optimal incentive would be advantageous. In the trial, attendance at the first vaccination appointment was not different between the two strategies (75.4% vs 76.9%) despite different financial incentives (£5 vs £10)(14).

Wider use of contingency managementwill require guidance and monitoring. In clinical practice, people may not be so thoroughly screened for eligibility, resulting in more doses given to people with prior immunity. PWID may also not disclose their vaccination status to be eligible to receive the financial incentives. This has some cost implications, as more doses may be given, but it is unclear

whether the additional cost is outweighed by the benefits. In practice, it is advised to take blood when possible and give a vaccine dose if uncertain of someone's protective immunity.

This economic evaluation examined the provision of HBV vaccination only. Some sites in the trial offered a bivalent vaccine providing protection for both HBV and hepatitis A, at little extra cost. The demonstrated malleability of health-adherence behaviours in this population could potentially be leveraged to boost other interventions for little extra cost, e.g. hepatitis C virus testing. If provided in parallel to HBV vaccination, or even as standalone interventions with contingency management might lead to more PWID tested for hepatitis C virus coming back to get their results, and more of those testing positive then entering a Hepatitis C virus care pathway. Evaluation of such combined strategies will require additional research.

Finally, it is unclear whether results are transferable to other injectors, notably people who inject image and performance drugs.(38).

Conclusions

This is the first economic evaluation examining the cost-effectiveness of providing contingency management using financial incentives - to PWID in contact with specialist services in order to enhance hepatitis B vaccination completion. **We find that using** contingency management**to increase vaccination completion among this group is cost-effective under current willingness to pay thresholds.** However, there are considerable uncertainties that need fuller attention in future studies, notably the paucity of evidence on the incidence of HBV infection incidence and the likelihood of PWID being reached by existing targeted vaccination programmes such as prison vaccination in the future. The intervention is likely to be more cost-effective in settings with higher risk of HBV infection or if the occurrence of outbreaks is considered.

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Reference List

(1) WHO. Hepatitis B. Fact sheet N°204. 2014.
Ref Type: Generic

(2) Hepatitis B: the green book, chapter 18. 2013. Public Health England.
Ref Type: Generic

(3) Nick Walsh, Annette Verster, Andrew Doupe, Marco Vitoria, Ying-Ru Lo, Steven Wiersma. Chapter 3.1: The silent epidemic: Responding to viral hepatitis among people who inject drugs. In: The Global State of Harm Reduction 2010. Key issues for broadening the response. Edited by Catherine Cook. London: International Harm Reduction Association, 2010. ISBN 978-0-9557754-8-2
http://www.ihra.net/contents/1410; 2015.

(4) Health Protection Agency. Health Protection Services and Microbiology Services Unlinked anonymous monitoring survey of people who inject drugs in contact with specialist services: data tables. 2014. London: Health Protection Agency, 2012.
Ref Type: Generic

(5) Judd A, Hickman M, Hope VD, Sutton AJ, Stimson GV, Ramsay ME, et al. Twenty years of selective hepatitis B vaccination: is hepatitis B declining among injecting drug users in England and Wales? J Viral Hepat 2007 Aug;14(8):584-91.

(6) Lamagni TL, Hope VD, Davison KL, Parry JV, Gill ON. Failure to vaccinate current injecting drug users against hepatitis B in England and Wales. Commun Dis Public Health 2001 Mar;4(1):71-2.

(7) Andersson MI, Low N, Irish CJ, Verlander NQ, Carrington D, Horner P, et al. Investigation of a large community-based outbreak of hepatitis B infection in the United Kingdom. Epidemiol Infect 2012 Jan;140(1):47-57.

(8) Gossop M, Marsden J, Stewart D, Treacy S. Outcomes after methadone maintenance and methadone reduction treatments: two-year follow-up results from the National Treatment Outcome Research Study. Drug Alcohol Depend 2001 May 1;62(3):255-64.

(9) NICE. Drug misuse: psychosocial interventions (CG51). 2007. National Institute for Health and Care Excellence.
Ref Type: Generic

(10) Pilling S, Strang J, Gerada C. Psychosocial interventions and opioid detoxification for drug misuse: summary of NICE guidance. BMJ 2007 Jul 28;335(7612):203-5.

(11) Topp L, Day CA, Wand H, Deacon RM, van B, I, Haber PS, et al. A randomised controlled trial of financial incentives to increase hepatitis B vaccination completion among people who inject drugs in Australia. Prev Med 2013 Oct;57(4):297-303.

(12) Seal KH, Kral AH, Lorvick J, McNees A, Gee L, Edlin BR. A randomized controlled trial of monetary incentives vs. outreach to enhance adherence to the hepatitis B vaccine series among injection drug users. Drug Alcohol Depend 2003 Aug 20;71(2):127-31.

(13) Stitzer ML, Polk T, Bowles S, Kosten T. Drug users' adherence to a 6-month vaccination protocol: effects of motivational incentives. Drug Alcohol Depend 2010 Feb 1;107(1):76-9.

(14) Weaver T, Metrebian N, Hellier J, Pilling S, Charles V, Little N, et al. Use of contingency management incentives to improve completion of hepatitis B vaccination in people undergoing treatment for heroin dependence: a cluster randomised trial. Lancet 2014 Apr 8.

(15) McMahon BJ. The natural history of chronic hepatitis B virus infection. Hepatology 2009 May;49(5 Suppl):S45-S55.

(16) Fattovich G. Natural history of hepatitis B. J Hepatol 2003;39 Suppl 1:S50-S58.

(17) Fattovich G, Bortolotti F, Donato F. Natural history of chronic hepatitis B: special emphasis on disease progression and prognostic factors. J Hepatol 2008 Feb;48(2):335-52.

(18) Yim HJ, Lok AS. Natural history of chronic hepatitis B virus infection: what we knew in 1981 and what we know in 2005. Hepatology 2006 Feb;43(2 Suppl 1):S173-S181.

(19) Hu Y, Grau LE, Scott G, Seal KH, Marshall PA, Singer M, et al. Economic evaluation of delivering hepatitis B vaccine to injection drug users. Am J Prev Med 2008 Jul;35(1):25-32.

(20) Siddiqui MR, Gay N, Edmunds WJ, Ramsay M. Economic evaluation of infant and adolescent hepatitis B vaccination in the UK. Vaccine 2011 Jan 10;29(3):466-75.

(21) Tilson L, Thornton L, O'Flanagan D, Johnson H, Barry M. Cost effectiveness of hepatitis B vaccination strategies in Ireland: an economic evaluation. Eur J Public Health 2008 Jun;18(3):275-82.

(22) NICE. Hepatitis B (chronic) (CG165). 2013. National Institute for Health and Care Excellence.
Ref Type: Generic

(23) Sutton AJ, Gay NJ, Edmunds WJ, Hope VD, Gill ON, Hickman M. Modelling the force of infection for hepatitis B and hepatitis C in injecting drug users in England and Wales. BMC Infect Dis 2006;6:93.

(24) HPA. Acute hepatitis B (England): annual report for 2012. Volume 7 Numbers 35 Published on: 30 August 2013 . 2014.
Ref Type: Abstract

(25) Martin NK, Vickerman P, Grebely J, Hellard M, Hutchinson SJ, Lima VD, et al. Hepatitis C virus treatment for prevention among people who inject drugs: Modeling treatment scale-up in the age of direct-acting antivirals. Hepatology 2013 Nov;58(5):1598-609.

(26) Sutton AJ, Gay NJ, Edmunds WJ. Modelling the impact of prison vaccination on hepatitis B transmission within the injecting drug user population of England and Wales. Vaccine 2006 Mar 20;24(13):2377-86.

(27) ENGERIX®-B PRODUCT INFORMATION. 2014.
Ref Type: Internet Communication

(28) Beck CR, Cloke R, O'Moore E, Puleston R. Hepatitis B vaccination coverage and uptake in prisons across England and Wales 2003-2010: a retrospective ecological study. Vaccine 2012 Mar 2;30(11):1965-71.

(29) Tillmann HL, Zachou K, Dalekos GN. Management of severe acute to fulminant hepatitis B: to treat or not to treat or when to treat? Liver Int 2012 Apr;32(4):544-53.

(30) Guide to the methods of technology appraisal. London: NICE; 2013.

(31) BNF64. 2014. British National Formulary. 2014.
Ref Type: Generic

(32) Curtis L. Unit Costs of Health and Social Care. 2012.
Ref Type: Generic

(33) Brown RE, De CE, Colin X, Antonanzas F, Iloeje UH. Hepatitis B management costs in France, Italy, Spain, and the United Kingdom. J Clin Gastroenterol 2004 Nov;38(10 Suppl 3):S169-S174.

(34) NHS reference cost 2012-2013. 2013.
Ref Type: Generic

(35) Ong SC, Mak B, Aung MO, Li SC, Lim SG. Health-related quality of life in chronic hepatitis B patients. Hepatology 2008 Apr;47(4):1108-17.

(36) Luyten J, Marais C, Hens N, De SK, Beutels P. Imputing QALYs from single time point health state descriptions on the EQ-5D and the SF-6D: a comparison of methods for hepatitis a patients. Value Health 2011 Mar;14(2):282-90.

(37) Winter RJ, Dietze PM, Gouillou M, Hellard ME, Robinson P, Aitken CK. Hepatitis B virus exposure and vaccination in a cohort of people who inject drugs: what has been the impact of targeted free vaccination? J Gastroenterol Hepatol 2013 Feb;28(2):314-22.

(38) Hope VD, Mandal S, Cullen J K, Balogun K, Ncube F. Hepatitis B vaccination for people who inject drugs. Correspondence. The Lancet 385, No. 9963, 115-116. 2015.
Ref Type: Generic

Table 1: Model parameters used for Annual transitions (unless stated) in the natural history Markov model

	Base-case	Lower range reported in the literature	Upper range reported in the literature	Source
From 'Susceptible PWID'				
Probability of HBV infection	2.16%	1.76%	2.67%	Estimated from a catalytic model
Probability of future protection±	12.80%			Derived from (4;25-27)
Probability of leaving PWID population	9.09%	5.00%	16.67%	(25)
Remain susceptible - PWID	75.95%***			
From 'Susceptible – ex PWID'				
Probability of HBV infection	0.0041%	0%*	2.16%**	Assumption
Remain in 'Susceptible – ex PWID'	99.996***			
Proportion of HBV infection that are acute, fulminant and chronic				
Proportion of HBV infection that are acute (non-fulminant)‡	93.20%*			

	**			
Proportion of HBV infection that are fulminant‡	0.55%	0.30%	0.80%	(21)
Proportion of HBV infection that are chronic‡	6.25%	2.50%	10.00%	(29)
From 'Fulminant HBV'				
Proportion undergoing liver transplant‡	13.50%	10.00%	17.00%	(20)
Proportion of excess death‡	72.86%			Derived from (21)and(15)
Proportion of non-fatal fulminant HBV not undergoing liver transplant‡	13.64%**			
From 'Chronic HBV (HBeAg+ve)'				
Probability of seroconversion (CHB -ve or inactive)	11.50%	8.00%	15.00%	(15-17)
Proportion seroconvert to CHB – ve‡	15.00%	10.00%	20.00%	(15)
Probability of developing CC	4.00%	2.00%	6.00%	(16-18)
Probability of developing HCC	0.35%	0.10%	0.60%	(16;17)
Probability of excess death	0.55%	0.10%	1.00%	(16)
Remain in Chronic HBV (HBeAg+ve)	80.10%**			

From 'Chronic HBV (HBeAg-ve)'				
Probability of developing CC	9.00%	8.00%	10.00%	(18)
Probability of developing HCC	0.66%	0.01%	1.30%	(17;18)
Probability of excess death	0.55%	0.10%	1.00%	(16;17)
Remain in **Chronic HBV (HBeAg-ve)**	89.80%**			
Chronic HBV (Inactive) to:				
Probability of developing CC	2.00%	1.00%	3.00%	(17;18)
Probability of developing HCC	0.11%	0.02%	0.20%	(17;18)
Probability clear HbsAg	1.25%	0.50%	2.00%	(15)
Probability of excess death	0.03%	0.02%	0.04%	(17)
Remain in **Chronic HBV (HBeAg inactive)**	96.61%**			
From 'CC'				
Probability of developing DC	3.50%	2.00%	5.00%	(15-18)
Probability of developing HCC	2.85%	2.00%	3.70%	(15-18)
Probability of excess death	3.20%	2.90%	3.50%	(15-17)
Remain in CC	90.50%**			
From 'DC'				
Probability of developing HCC	7.50%	7.00%	8.00%	(18)

Probability of undergoing LT	4.40%	3.40%	5.40%	(20)
Probability of excess death	35.00%	20.00%	50.00%	(18)
Remain in DC	53.1%** *			
From 'HCC'				
Probability of undergoing LT	1.70%	1.50%	1.90%	(20)
Probability of excess death	35.00%	20.00%	50.00%	(18)
Remain in HCC	63.30%* **			
From 'LT'				
Probability of excess death – first year	21.00%	15.00%	27.00%	(22)
Probability of excess death – subsequent years	5.00%	3.00%	7.00%	(22)

* assumption; ** assumed to be the same as PWID, *** remaining probabilities (One minus probabilities above), ± calculated from self-reported vaccination, leaving rate, number of vaccine dose received in prison and vaccine effectiveness, ‡ proportion

PWID = People who inject drugs; HBV = hepatitis B virus; CHB = chronic hepatitis; LT = liver transplantation; CC = compensated cirrhosis; HCC = hepatocellular carcinoma; DC = decompensated cirrhosis; HBeAg = chronic hepatitis B e antigen.

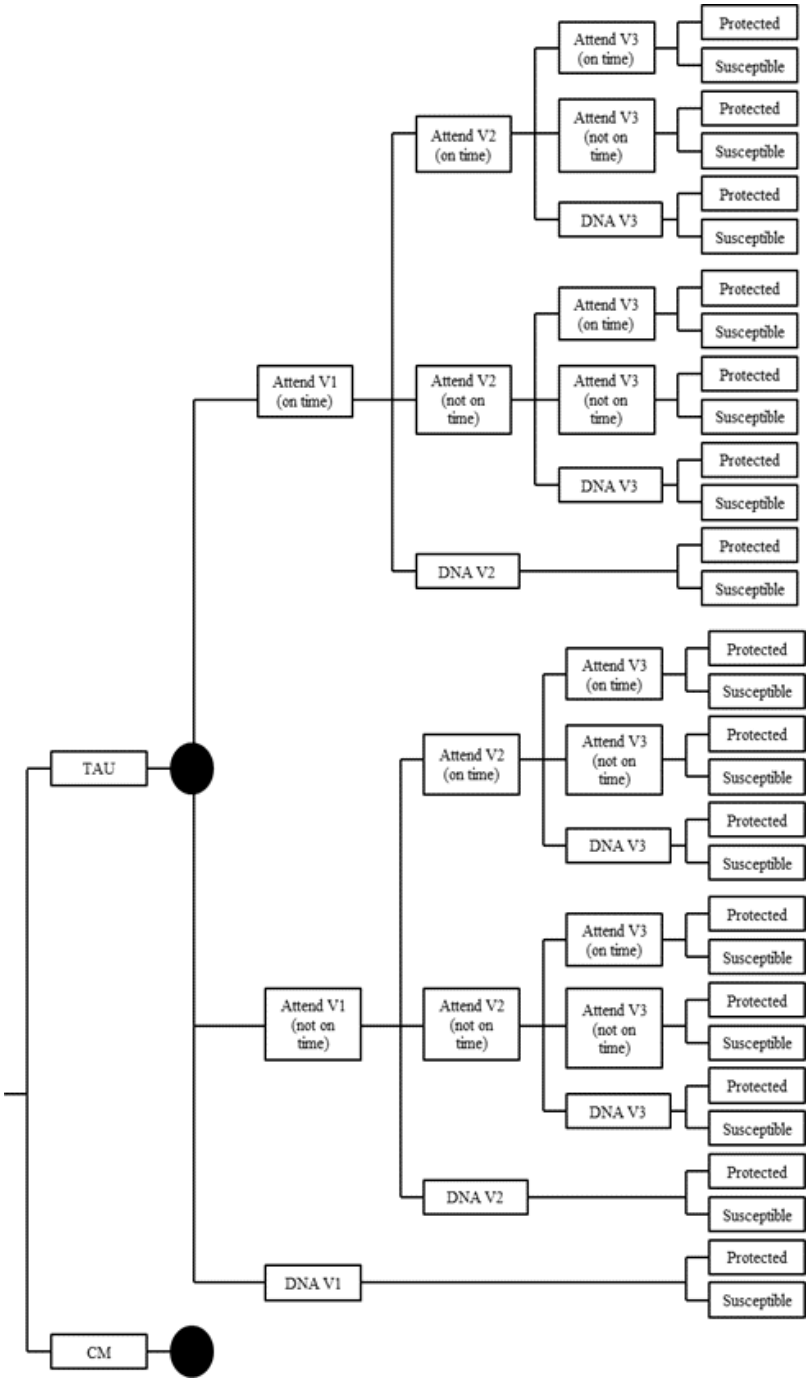
Table 2: Attendance at HBV vaccination appointments

	Treatment as usual		CM	
1st vaccination				
Expected to attend	67		143	
Did not attend	33	49%	34	24%
Attended on time	21	31%	97	68%
Delayed attendance	13	19%	12	8.%
2nd vaccination				
Expected to attend	31		105	
Did not attend	8	26%	13	12%
Attended on time	15	48%	84	80%
Delayed attendance	8	26%	8	8%
3rd vaccination				
Expected to attend	22		85	
Did not attend	8	36.%	15	18%
Attended on time	7	32%	64	75%
Delayed attendance	7	32%	6	7%

HBV = hepatitis B virus; CM = Contingency Management

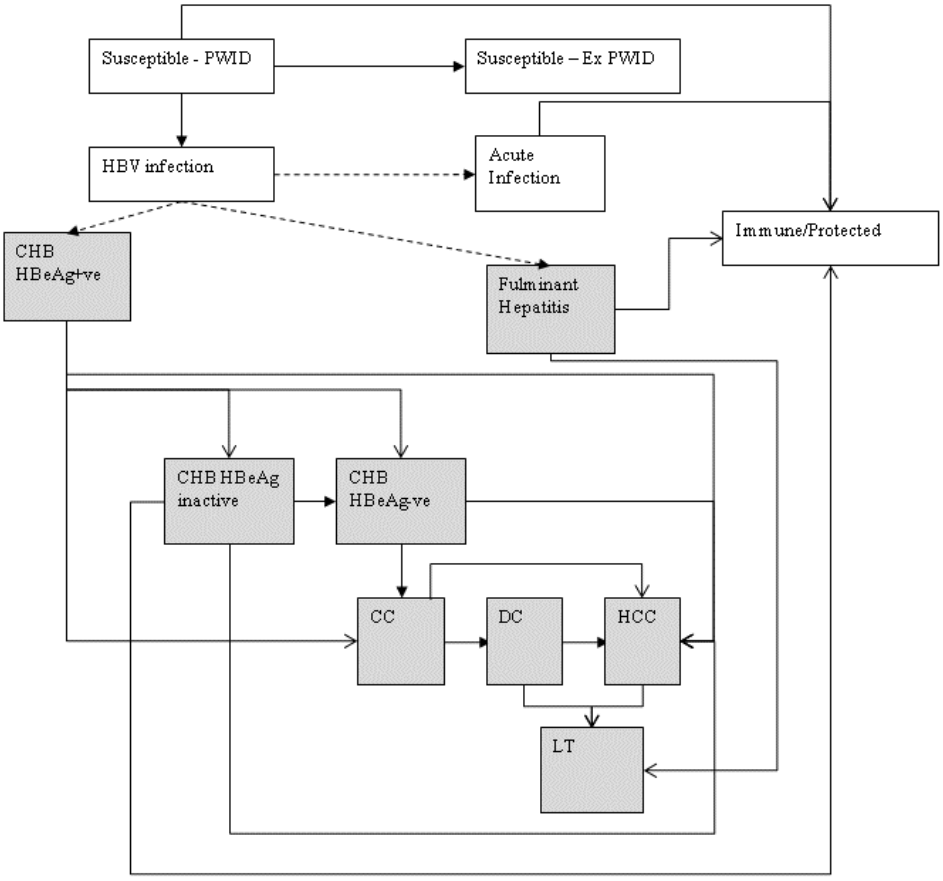
It should be noted that the number of individual expected to attend is different to the number of individuals who attended the previous round as some individuals were already immune and therefore did not need to return for another vaccine dose.

Fig. 1. <u>Decision tree model for hepatitis B vaccination strategies.</u> Back circle represent a decision node.



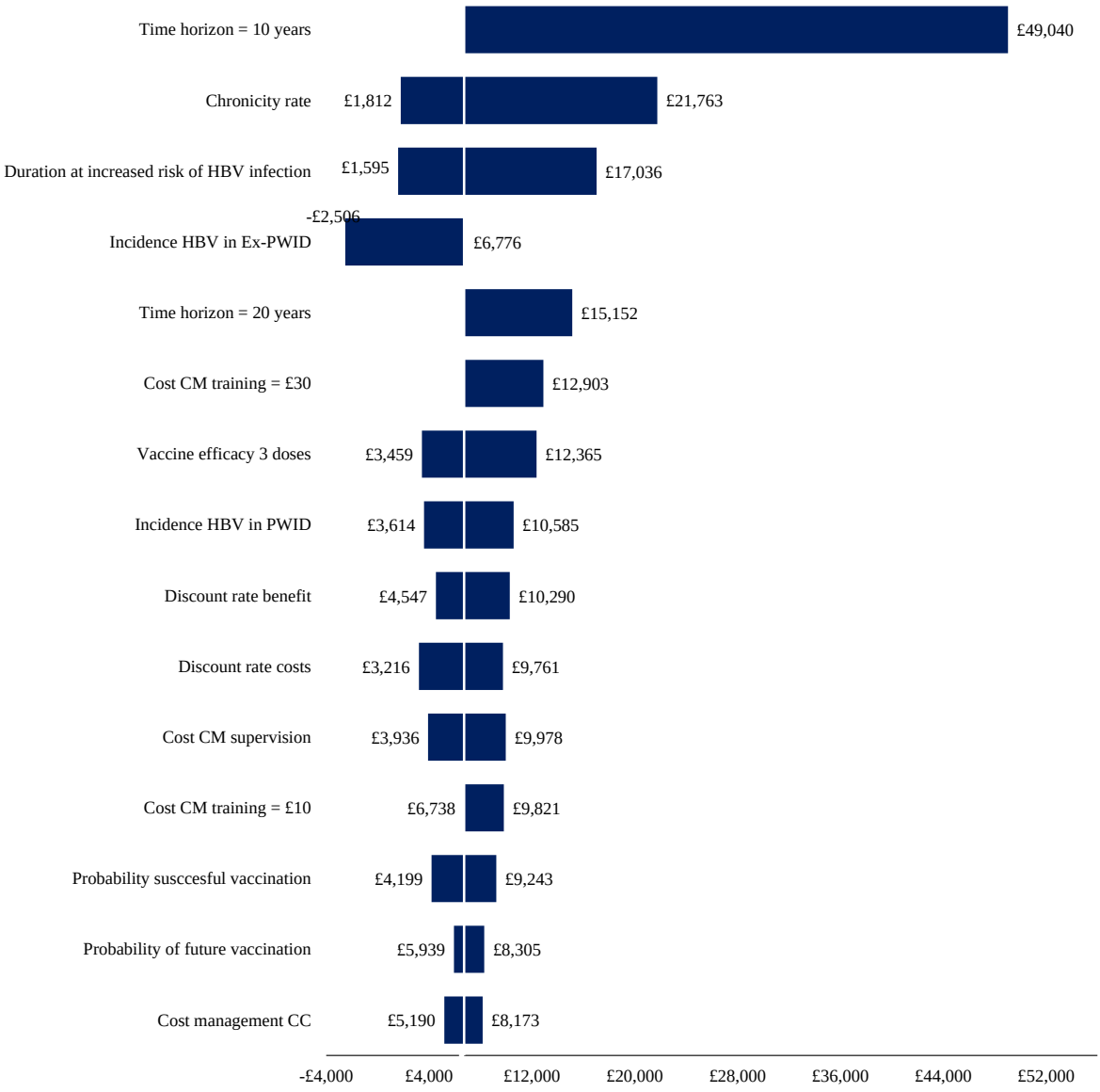
CM = Contingency Management; DNA = Do Not Attend; TAU = treatment as usual; V1 = 1st vaccination appointment; V2 = 2nd vaccination appointment; V3 = 3rd vaccination appointment

Fig. 2. Markov model of the long-term natural history of HBV infection. Transition between health states. People can die from general causes (age-specific) in any of the health states (not shown here). Boxed in Grey indicate excess mortality



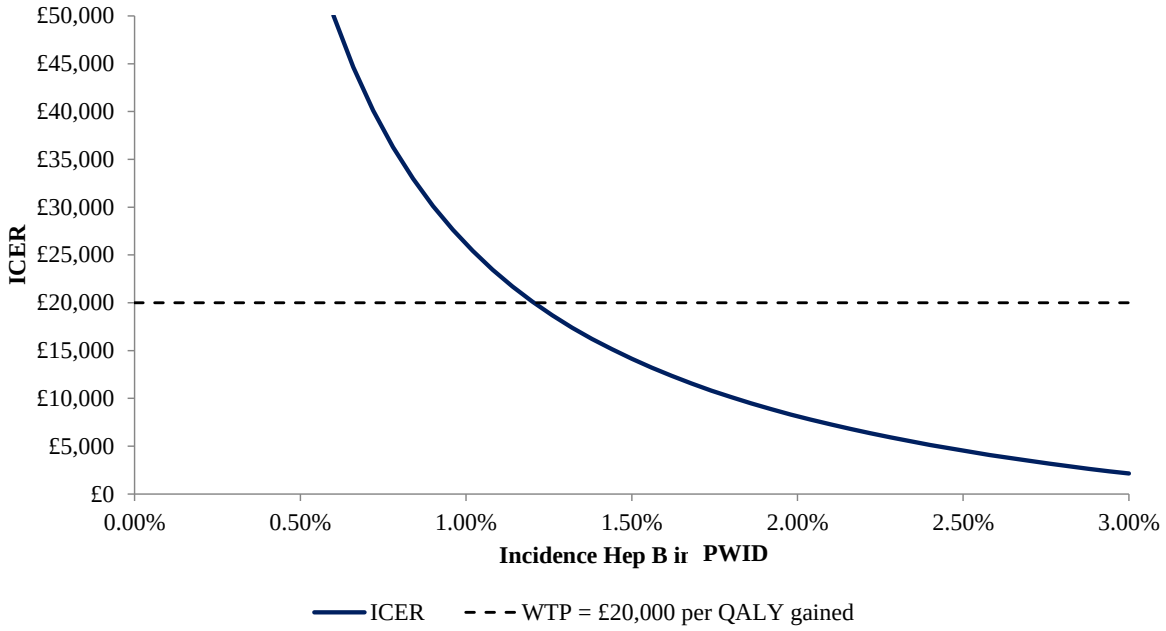
CC = compensated cirrhosis ; CHB = chronic hepatitis; DC = decompensated cirrhosis; HBeAg = chronic hepatitis B e antigen; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; LT = liver transplantation; PWID = People who inject drugs

Fig. 3. Univariate sensitivity analysis (most sensitive parameters). White line represent the base-case probabilistic ICER.



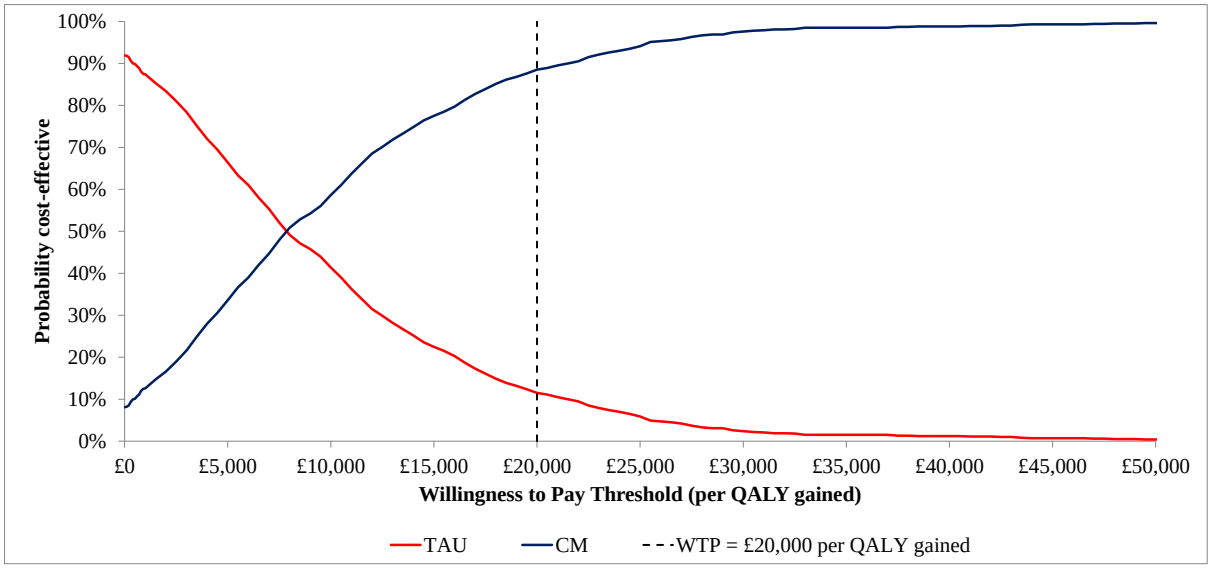
CC = compensated cirrhosis; CM = contingency management; HBV = hepatitis B virus; PWID = People who inject drugs

Fig. 4. Effect of varying the base-case incidence of HBV infection in PWID on the incremental cost per QALY gained of CM versus TAU. The blue solid line represents the ICER for CM compared with TAU assuming different incidence of Hepatitis B. The black dashed line represents the £20,000 per QALY gained WTP threshold.



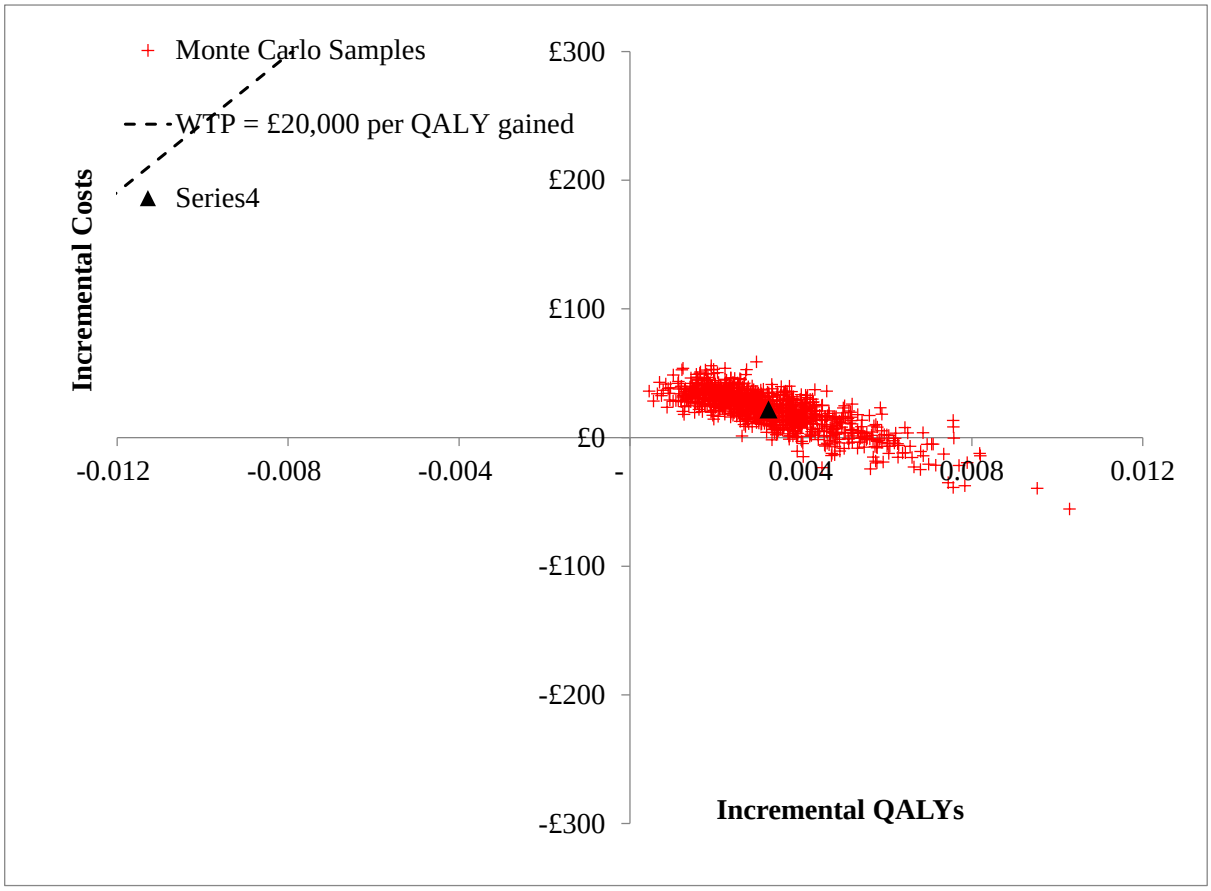
CM = contingency management; HBV = hepatitis B virus; ICER = incremental cost-effectiveness ratio; QALY = quality adjusted life years; TAU = treatment as usual; WTP = willingness to pay

Fig. 5(A). Cost effectiveness acceptability curves for the probability that CM is more cost effective than usual care. The blue solid line represents the probability for CM to be cost-effective at different WTP threshold. The red solid line represents the probability for TAU to be cost-effective at different WTP threshold. The black dashed line represents the £20,000 per QALY gained WTP threshold.



CM = contingency management; QALY = quality adjusted life years; TAU = treatment as usual; WTP = willingness to pay

Fig. 5(B). Cost effectiveness plane for CM vs. TAU. Solid points represent incremental cost and QALY results (intervention arm minus control arm) from the probabilistic analysis for each of the 1000 samples. The black dashed line represents the £20,000 per QALY gained WTP threshold.



CM = contingency management; QALY = quality adjusted life years; TAU = treatment as usual; WTP = willingness to pay