The Cost-Effectiveness of One-Time Birth Cohort Screening for Hepatitis C as Part of the National Health Service Health Check Programme in England

Jack Williams, MSc,[1,2,*] Alec Miners, PhD,[1,2] Ross Harris, PhD,[3] Sema Mandal, MSc, FFPH,[2,3] Ruth Simmons, PhD,[2,3]
Georgina Ireland, MPH,[2,3] Matthew Hickman, PhD,[4,5] Charles Gore, BA,[6] Peter Vickerman, DPhil[2,4,5]

[1]Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London, UK; [2]The National Institute for Health Research Health Protection Research Unit in Blood Borne and Sexually Transmitted Infections at University College London, UK; [3]National Infection Service, Public Health England, Colindale UK; [4]Population Health Sciences, Bristol Medical School, University of Bristol, UK; [5]The National Institute for Health Research Health Protection Research Unit in Evaluation of Interventions, UK; [6]The Hepatitis C Trust, London, UK.

A B S T R A C T

Background and Objectives: Birth cohort screening for the hepatitis C virus (HCV) has been implemented in the US, but there is little evidence of its cost-effectiveness in England. We aim to evaluate the cost-effectiveness of one-time HCV screening for individuals born between 1950 and 1979 as part of the National Health Service health check in England, a health check for adults aged 40 to 74 years in primary care.

Methods: A Markov model was developed to analyze add-on HCV testing to the National Health Service health check for individuals in birth cohorts between 1950 and 1979, versus current background HCV testing only, over a lifetime horizon. The model used data from a back-calculation model of the burden of HCV in England, sentinel surveillance of HCV testing, and published literature. Results are presented from a health service perspective in pounds in 2017, as incremental cost-effectiveness ratios per quality-adjusted life years gained.

Results: The base-case incremental cost-effectiveness ratios ranged from £7648 to £24 434, and £18 681 to £46 024, across birth cohorts when considering 2 sources of HCV transition probabilities. The intervention is most likely to be cost-effective for those born in the 1970s, and potentially cost-effective for those born from 1955 to 1969. The model results were most sensitive to the source of HCV transition probabilities, the probability of referral and receiving treatment, and the HCV prevalence among testers. The maximum value of future research across all birth cohorts was £11.3 million at £20 000 per quality-adjusted life years gained.

Conclusion: Birth cohort screening is likely to be cost-effective for younger birth cohorts, although considerable uncertainty exists for other birth cohorts. Further studies are warranted to reduce uncertainty in cost-effectiveness and consider the acceptability of the intervention.

Keywords: cost-benefit analysis, hepatitis C, mass screening, national health programs, health services.

VALUE HEALTH. 2019; ■(■):■–■

Introduction

Hepatitis C virus (HCV) is major global public health problem.[1] An estimated 143 000 people were living with HCV in England in 2015, and mortality related to HCV doubled between 2005 and 2014 as individuals acquiring their infections decades earlier progressed to advanced liver disease.[2,3] More recently, HCV-related deaths have fallen due to the rollout of new direct-acting antiviral (DAA) treatments.[3] DAAs can cure (achieve a sustained virological response [SVR]) more than 90% of

patients, are simpler to administer, and have fewer side effects than previously used interferon and/or ribavirin-based treatments.[4]

The World Health Organization's (WHO's) Global Health Strategy targets to eliminate viral hepatitis as a major public health threat include 90% diagnosis coverage and 80% treatment uptake.[5] Interventions to increase diagnoses and improve linkage to care are required if countries are to achieve WHO targets, and the efficiency, cost-effectiveness, and overall impact of these interventions needs to be evaluated.

Analysis of HCV antibody tests in England by birth cohorts shows a high proportion of positive tests among those born between the 1950s and mid-1980s, based on unpublished Public Health England (PHE) sentinel surveillance of bloodborne viruses (BBV) laboratory diagnoses from 2012-2016 (3.7%-6.5% for first recorded tests). Due to the asymptomatic nature of HCV, many infected individuals remain undiagnosed and do not associate their previous exposures to their current risk of infection.[6]

Cost-effectiveness analyses of birth cohort screening interventions have been performed in several countries, including the United States, Canada, Italy, Japan, and Korea.[7–12] Only the United States has implemented birth cohort screening, while Japan has recommended one-time testing for the general population.[5,13] Evidence on the cost-effectiveness of birth cohort screening in an English context is limited. A single abstract has reported that birth cohort screening in the United Kingdom was unlikely to be cost-effective.[14] Yet, the authors concluded that further studies should incorporate more accurate information on HCV prevalence by age and include cost implications associated with screening. One possible means of limiting the additional cost of screening could be to add HCV testing to the existing NHS health check programme. The NHS health check is a free health check delivered in primary care in England that is offered to adults aged 40 to 74 years, once every 5 years, to assess and reduce a person's risk of heart disease, diabetes, kidney disease, and stroke.[15] This possibility was highlighted in the National Institute for Health and Care Excellence (NICE) hepatitis testing guidelines, but it also states that more information is required before a recommendation can be made due to the uncertainty around its cost-effectiveness.[16]

In this study, we evaluate the cost-effectiveness of a one-time HCV screening intervention for individuals born between 1950 and 1979 included as part of the NHS health check, who have not previously been diagnosed with HCV.

Methods

Model Analysis

A state-transition Markov model was used to analyze the impact of a one-time HCV antibody test, given to those in each eligible birth cohort attending the NHS health check programme.[15] The model analyzed birth cohorts, in 5-year age bands, for those born between 1950 and 1979, and not previously diagnosed with HCV. Current practice includes those tested for hepatitis based either on their symptoms or risk status. No birth cohort screening, with current background testing only, was the only comparator in the model, with a background probability of HCV testing in England. Patients moved between discrete health states using a 6-month cycle length. The analysis was performed from the perspective of NHS England with results displayed in pounds in 2017, with the intervention modeled to begin in 2018. Outcomes were measured in quality-adjusted life years (QALYs). A lifetime time horizon was used, and all costs and outcomes were discounted at 3.5%, as per NICE guidelines.[17] The model calculated the incremental cost-effectiveness ratio (ICER), representing the incremental costs associated with the intervention divided by the incremental QALYs, to give a cost per QALY gained. The model was developed in TreeAge Pro 2017.

Model Population and HCV Prevalence

The prevalence and disease severity of undiagnosed HCV infection in England was estimated using an adapted version of a previously published back-calculation model.[2,18] Its details have

been published elsewhere, but essentially it uses UK hospital episode statistics and Office for National Statistics data on decompensated cirrhosis, hepatocellular carcinoma, and HCV-related mortality to estimate the burden of HCV.[6] The most recent model also incorporates the estimated people who inject drugs population size.[2]

The back-calculation model provides estimates for HCV birth cohort populations by diagnosis status, injecting drug user (IDU) status (current-, ex- and never-IDU), and disease severity, which informed the economic model parameters. It also provides statistical uncertainty in the form of credible intervals, which were used when estimating parameter uncertainty.

Our model assumed that birth cohort screening would not be used to identify current IDUs, providing a conservative estimate of the prevalence among health check attendees (since prevalence is higher amongst current IDUs), but assumed ex-IDUs were as likely to attend as non-IDUs. Details on the total estimated population in each birth cohort is provided in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006. A scenario was performed in which ex-IDUs were assumed to be 50% less likely to attend compared to non-IDUs (see Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006). A scenario performed in the back-calculation model analysis was also considered, in which the current IDU population size was estimated using longer hospital episode statistics data and not constrained by an informed prior, resulting in higher estimated prevalence, particularly in younger groups.[2]

Model Structure

The Markov model captured the natural history of HCV, and is similar to those used in previous economic evaluations, and also aligns with the data used to parameterize disease severity in the model.[19,20] It consists of 8 main health states (see Appendix Fig. 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006). Individuals enter the model as either uninfected or classified in a disease state according to the modified Histology Activity Index (Ishak) score in the following health states: mild HCV (F0-F2), moderate HCV (F3-F5), and compensated cirrhosis (CC) (F6), from which they experience further disease progression. From these states individuals progress to later disease states, decompensated cirrhosis, hepatocellular carcinoma, and liver transplant, in which the HCV status was assumed to be known due to the severity of the disease, an assumption that has been made in previous models.[2,19] Those testing positive but not receiving treatment were assumed to accrue health state costs after diagnosis.

The model does not capture disease transmission, and thus assumes that those uninfected will remain uninfected, and that those who achieve SVR cannot be reinfected. In addition to HCV-related mortality, age-adjusted background rates of mortality were applied to all health states in the model, to capture the risk of non-HCV related mortality.[21]

Background Probability of Testing and Linkage to Care

The background probability of testing of HCV for each birth cohort was estimated from PHE sentinel surveillance of BBV testing statistics and Office for National Statistics population statistics for England.[22] Testing from all reported care settings, excluding drug services and prison services, were included. All tests up to an individual's first positive test were included. The annual probability of testing ranged from 1.9% to 3.6% (Table 1), with the same rate across mild moderate and CC health states.

Table 1. Key economic model parameters.

Parameter	Mean value	Distribution	Source
Probabilities			
Intervention effect (uptake)	48.3%	Beta (α = 5 767 770, β = 6 176 881)	[28]
Proportion of reflex RNA tests	65%	Beta (α = 26 537, β = 14 319)	[23]
Proportion RNA positive	67.7%	Beta (α = 24 094, β = 11 475)	
Probability of referral and attendance	63.4%	Beta (α = 35.966, β = 20.7627)	[24,25]
Probability of treatment (postreferral)	50%	Uniform (0.35, 0.65)	Assumption
Costs			
HCV antibody test	£3.64	Uniform (£1.82, £5.46)	[38]
Nurse cost for test (10 min)	£38/hr	Uniform (£30.40, £45.60)	[39]
RNA test	£68.38	Uniform (£34.19, £102.57)	[38]
Cost additional consultation (RNA testing)	£32	Uniform (£25.60, £38.40)	[39]
Outpatient evaluation	£238	Uniform (£190.40, £285.60)	[49]
Further outpatient evaluation	£262	Uniform (£209.60, £314.40)	[49]
DAA treatment	£10 000	N/A	Assumption[40]
DAA treatment (re-treatment)	£15 000‡	N/A	Assumption[40]
DAA treatment monitoring	£1310	Uniform (£1048, 1572)	[49]
Prevalence of undiagnosed chronic HCV (RNA+ among health check attendees*			
1950-1954	0.10%	Beta (α = 38.1, β = 37 215)	[2]
1955-1959	0.16%	Beta (α = 53.4, β = 32 359)	
1960-1964	0.23%	Beta (α = 58.1, β = 25 614)	
1965-1969	0.27%	Beta (α = 68.1, β = 25 168)	
1970-1974	0.25%	Beta (α = 65.7, β = 26 137)	
1975-1979	0.19%	Beta (α = 68.2, β = 36 490)	
Annual probability of background testing†			
1950-1954	1.89%	Beta (α = 98.1, β = 5084)	[22]
1955-1959	2.09%	Beta (α = 97.9, β = 4580)	
1960-1964	2.19%	Beta (α = 97.8, β = 4358)	
1965-1969	2.26%	Beta (α = 97.7, β = 4218)	
1970-1974	2.67%	Beta (α = 97.3, β = 3550)	
1975-1979	3.57%	Beta (α = 96.4, β = 2601)	

DAA indicates direct-acting antivirals; HCV, hepatitis C virus.
*Prevalence excludes current-IDUs.
†Background rate of testing excluding drug services and prison settings.
‡Cost of retreatment assumed to be £5000 higher than first DAA treatment in scenario analyses.

While the prevalence of HCV is higher among those tested compared to the general population, by excluding current IDUs and those previously testing positive for HCV in this analysis, it is unknown whether the background rate of HCV testing would differ between those infected and uninfected; however, in the model we assumed it would be equal. We considered those infected having double the probability of testing in a sensitivity analysis. Because testing may be more likely with cirrhosis, a scenario with background testing 50% lower for mild and moderate HCV health states was performed.

All individuals without a previous HCV diagnosis and not current IDUs were included in the screening population. The PHE sentinel surveillance of BBVs suggests reflex RNA tests (performed on the same antibody positive sample to avoid repeat attendance) were performed on 65% of HCV antibody positive tests.[23] The remainder were assumed to be RNA tested at a subsequent appointment. Based on PHE statistics, 67.7% of antibody positive tests would be RNA positive. The proportion of patients successfully referred and attending their referral was based on the midpoint of the proportions referred from general practitioners in 2 retrospective studies of hepatitis care pathways in England (63.4%).[24,25] The uptake of DAA treatment for those attending their referral is unknown, but expected to be higher than published values for non-DAA treatments (21%).[23] We assumed 50% would receive treatment (35%-65% in sensitivity analyses).

Treatment outcomes for first-line DAA treatment were derived from real-world evidence with SVR rates of 92.8% and 90.8% for non-cirrhotics and cirrhotics, respectively.[26] Individuals not achieving SVR were assumed to be retreated once, with SVR rates for retreatment of 93.9% and 85.5% for people without and with cirrhosis, respectively.[27] Lower retreatment SVR rates (70%) were also considered. The analysis was pan-genotypic and did not stratify outcomes by HCV genotype.

Intervention Effect

We assumed that testing would take place alongside the NHS health check, of which 48.3% of those invited attended (as of January 2018), and we assumed all attendees were tested for HCV.[28] Lower uptake was considered in a sensitivity analysis. The intervention effect was assumed as additional to the background rate of HCV testing, which would continue in other settings. There is an opportunity for those not originally attending the health check to be tested at their next health check appointment 5 years later; however, this was not modeled.

Transition Probabilities

For mild, moderate, and CC health states, 2 sources of transition probabilities were identified and considered in the

model (see Appendix Tables 2 and 3 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006).

First, transition probabilities were derived from a health technology assessment in the United Kingdom by Shepherd et al,[29] based on clinical cohorts, which have been used in other HCV models,[19,20,30] and have informed NICE HCV testing guidelines,[16] with additional transition probabilities for progression of cirrhotic individuals achieving SVR.[31,32]

We also considered transition probabilities from mild, moderate, and cirrhotic health states generated by the back-calculation model by Harris et al, which used prior values from Sweeting et al, and estimated age-based transition probabilities in the model fitting process.[2,33]

While the probabilities from Shepherd et al[29] are comparable to other economic evaluations, those generated from the back-calculation model align with HCV prevalence and severity parameters derived from the same source, and are thus consistent with other model inputs.

A previously published analysis explored the differences between 2 models estimating costs and QALYs for HCV in the United Kingdom, based upon the 2 sources of transition probabilities described above.[34] The authors concluded that in addition to transition probabilities from Shepherd et al,[29] the age-dependent transition probabilities estimated by Harris et al should also be considered in future modeling work, due to considerable differences in estimated costs and QALYs. Because of the uncertainty around the most appropriate choice of transition probabilities, we present the base-case results using both sources.

For value of information analyses in which transition probabilities were available from both Shepherd et al[29] and the back-calculation model, a uniform distribution was created to capture the uncertainty in the estimates from the 2 sources. Addition details are provided in the Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006.

Utilities

Utility values were derived from a UK randomized controlled trial of mild HCV infection, and a UK study of patients with later-stage disease.[35,36] They were converted into a utility decrement and subtracted from UK general population utility estimates to provide age-adjusted values (see Appendix Table 4 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006).[37]

Costs

It was assumed that individuals would receive a HCV antibody test (£3.64).[38] The cost of administering this test was assumed to take 10 minutes by a practice nurse (band 5, £38/hour).[39] No other intervention costs were included. Costs associated with the NHS health check (eg, invitations) were not included as these are already established. Costs for RNA tests (£68.38) and subsequent appointments (£32, for those not receiving reflex testing) and outpatient visits prior to treatment were applied (Table 1).[23,38,39] The DAA acquisition costs for the NHS are confidential; however, an approximate £5000 price has been reported (reduced from list prices of >£30 000).[40] To remain conservative, we assumed DAA treatment costs of £10 000 for first treatment, and £15 000 for retreatment. We also considered DAA treatment costs of £5000, and show results across a range of DAA costs in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006. Treatment costs were conditional on achievement of SVR, as per NHS policy.[41]

Health state costs were derived from a previous health technology assessment, while costs associated with SVR were derived from Grishchenko et al (see Appendix Table 5 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006).[29,42] All costs were inflated to 2017 costs.[39] Individuals that were infected but undiagnosed were assumed not to accrue health state costs.

Sensitivity Analyses

One-way deterministic sensitivity analyses (DSAs) were performed for individual parameters and shown in a tornado plot to capture the impact upon the ICER. The key DSA results for 1 birth cohort are shown (full DSA results for 2 cohorts, by source of transition probabilities, are available in the Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006). Probabilistic sensitivity analysis was performed, with all probabilistic parameters sampled simultaneously over 10 000 model simulations.

Value of information analyses show the maximum amount that should be paid to eliminate the uncertainty in all model parameters (the expected value of perfect information [EVPI]). This considers the loss of health benefits and resources by making the wrong decision, due to uncertainty. The EVPI can also consider the maximum value of research for individual or groups of model parameters, known as the expected value of partial perfect information (EVPPI).[43]

The EVPI analysis was performed using 10 000 simulations, for each birth cohort. For each of the EVPPI analyses, we ran 1000 inner loops (relating to the probabilistic sensitivity analysis) and 1000 outer loops (relating to the parameter[s] of interest assessed as part of the EVPPI analysis). These inner and outer loop simulation numbers were chosen to provide a sufficient number of probabilistic simulations while considering the computational time required to perform all analyses. For probabilistic sensitivity analysis, EVPI and EVPPI analyses, we use a willingness-to-pay threshold of £20 000, representing the lower bound of NICE's threshold range.[17] The eligible population for EVPI and EVPPI calculations is provided in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006.

Results

The deterministic base-case results for each birth cohort are shown in Table 2. The ICERs for each birth cohort using the Shepherd et al[29] transition probabilities ranged from £18 681 to £46 024 with the most favorable ICERs for younger birth cohorts. When considering the back-calculation transition probabilities, the ICERs ranged from £7648 to £24 434, with ICERs below £20 000 for those born from 1955 to 1979.

Probabilistic Sensitivity Analysis

When using the transition probabilities from Shepherd et al[29] at the willingness-to-pay threshold of £20 000 per QALY gained, the intervention is unlikely to be cost-effective for those born between 1950 and 1964 (probability of 1%-27%), but is borderline cost-effective for those born between 1965 and 1979 (probability of 41%-53%, Fig. 1). Yet, when using transition probabilities from the back-calculation model, the intervention is likely to be cost-effective for those born from 1955 to 1959 (69% probability), and is highly likely to be cost-effective for those born from 1960 to 1979 (94%-99.5% probability).

Deterministic Sensitivity Analyses

One-way DSA was performed on the 1970-1974 birth cohort using Shepherd et al[29] transition probabilities (Fig. 2). The source

Table 2. Cost-effectiveness results per individual eligible to attend the NHS health check for each birth cohort, by source of transition probabilities.

Birth cohort	Testing option	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER
Shepherd et al[29]						
1950-1954	Background testing	15.21	10.1396			
	Birth cohort screening	23.68	10.1398	8.47	0.00018	£46 024
1955-1959	Background testing	27.33	11.7818			
	Birth cohort screening	38.47	11.7822	11.14	0.00036	£31 051
1960-1964	Background testing	38.28	13.2980			
	Birth cohort screening	52.04	13.2986	13.76	0.00056	£24 364
1965-1969	Background testing	40.92	14.8456			
	Birth cohort screening	55.99	14.8463	15.07	0.00071	£21 100
1970-1974	Background testing	36.97	16.2488			
	Birth cohort screening	49.87	16.2495	12.90	0.00067	£19 236
1975-1979	Background testing	29.96	17.6997			
	Birth cohort screening	38.84	17.7002	8.89	0.00048	£18 681
Back-calculation model						
1950-1954	Background testing	24.60	10.1387			
	Birth cohort screening	31.42	10.1390	6.82	0.00028	£24 434
1955-1959	Background testing	42.90	11.7801			
	Birth cohort screening	51.33	11.7806	8.43	0.00054	£15 535
1960-1964	Background testing	64.11	13.2948			
	Birth cohort screening	73.87	13.2957	9.76	0.00093	£10 542
1965-1969	Background testing	76.44	14.8404			
	Birth cohort screening	87.12	14.8418	10.68	0.00133	£8037
1970-1974	Background testing	68.63	16.2441			
	Birth cohort screening	78.17	16.2453	9.54	0.00125	£7648
1975-1979	Background testing	51.54	17.6963			
	Birth cohort screening	58.47	17.6972	6.93	0.00085	£8196

NHS indicates National Health Service; ICER, incremental cost-effectiveness ratios; QALY, quality-adjusted life year.

of transition probabilities had the largest impact upon the ICER, followed by the probability of attending referral and receiving treatment. The ICER was also sensitive to the assumed prevalence among testers (0.25% to 0.14%) and a higher antibody test cost (£10). Reducing the uptake of the intervention did not affect the ICER, since there was no fixed cost of the intervention; however, the overall health benefit would be reduced.

EVPI and EVPPI

Assuming the intervention remains viable for all individuals in each birth cohort to be invited to the NHS health check (5 years), the EVPI across all birth cohorts (representing the maximum value for future research) was £11 289 902 at £20 000/QALY, with the highest value in birth cohorts born between 1955 and 1969 (Table 3).

The aggregated EVPPI results across all birth cohorts showed the highest value in reducing uncertainty was in the linkage to care parameters (£3 587 609); the utility of those achieving SVR (£2 487 084); and the transition probabilities from mild, moderate, and compensated cirrhosis health states (£1 617 959, Table 3). Additional EVPI results and EVPPI results by birth cohort are available in the Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006.

Discussion

While previous studies show diagnosis and treatment should be prioritized among high-risk populations actively transmitting infection, we demonstrate that birth cohort screening as part of the NHS health check can also be cost-effective in England.[20,30,44]

Our findings indicate that the intervention is likely to be cost-effective for those born in the 1970s under the base-case modeling assumptions, but there is uncertainty as to whether the intervention would be cost-effective for those born between 1955 and 1969.

While the prevalence was slightly higher for younger birth cohorts, the lower ICERs also result from a longer duration of benefit associated with treatment at younger ages (due to higher utility associated with SVR). Our analysis also shows that further research for birth cohort screening as part of the NHS health check is justified to reduce the uncertainty and assess the acceptability of adding HCV testing to the NHS health check, with a high maximum value of future research of £11.3 million across birth cohorts. The EVPPI has shown future research is most valued in reducing the uncertainty in the linkage to care, the utility associated with SVR and HCV transition probabilities, as the uncertainty in these parameters caused the most uncertainty in the underlying decision upon cost-effectiveness. Deterministic analyses also demonstrated the impact of assumptions made surrounding the prevalence among testers. The sensitivity of the cost-effectiveness results to linkage to care also suggests case-finding interventions are more likely to be cost-effective following improvements in the proportion linked to care among those testing positive, and these improvements should precede or complement future investment in case finding interventions.

Our results also build upon previous work demonstrating the differences in model predictions using 2 sources of HCV transition probabilities.[34] In our analysis, the decision on cost-effectiveness for 3 of the 6 birth cohorts changed based only upon the source of transition probabilities. This supports previous conclusions that further research of progression rates is required to reduce the uncertainty for decision makers in the United Kingdom and elsewhere.[34]

Figure 1. Cost-effectiveness acceptability curves for each birth cohort, for 2 sources of transition probabilities, derived from (A) Shepherd et al[29] and (B) the back-calculation model.
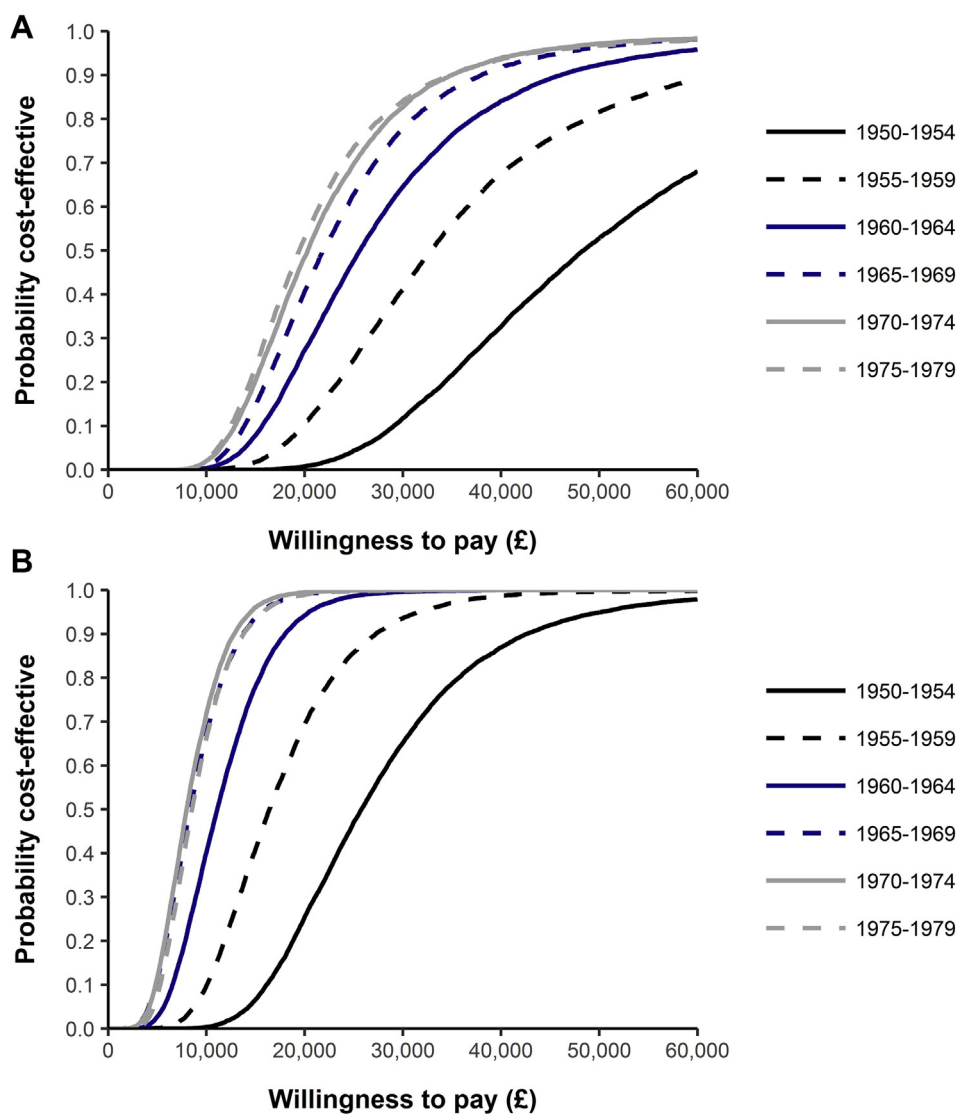

Comparison With Other Research

There is no other published evidence in the United Kingdom of the cost-effectiveness of birth cohort screening for HCV. Although our results differ considerably by transition probabilities, our results are similar to those derived from the US ($35 700-$37 720/QALY), Canada (Can$36 471/QALY), and France (cost-effective from €26 000-€60 000/QALY).[7–9,45,46] These analyses used higher DAA costs, but tended to use higher health state utilities and higher prevalence estimates. Further details on these comparisons are available (see Appendix in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.06.006.) Many European countries are developing national HCV elimination plans to meet WHO elimination targets.[47] Similar to the results from France, our results suggest that birth cohort screening can be cost-effective in areas of relatively low prevalence of HCV, if testing is added onto existing health services, such as the NHS's health check programme.

Limitations

In the absence of a study of the intervention itself, there is uncertainty about the extent to which current and ex-IDUs are likely to attend the health check, influencing the estimated prevalence among attendees. We assumed current IDUs and those previously testing positive could be tested through other targeted screening interventions; and ex-IDUs would attend at the same rate as never IDUs, an assumption that has a considerable impact upon cost-effectiveness. Furthermore, any inaccuracies in the estimated prevalence from the back-calculation model, which has its own methodological limitations, would significantly influence our results, and thus a study that estimates the seroprevalence among attendees would reduce the uncertainty of our results.[2] Moreover, while we have demonstrated the uncertainty in the estimated cost-effectiveness using 2 sources of transition probabilities, it is unclear which is most appropriate for economic evaluations in the United Kingdom. The use of transition

Figure 2. One-way deterministic sensitivity analysis for 1970 to 1974 birth cohort, using transition probabilities from Shepherd et al.[29]
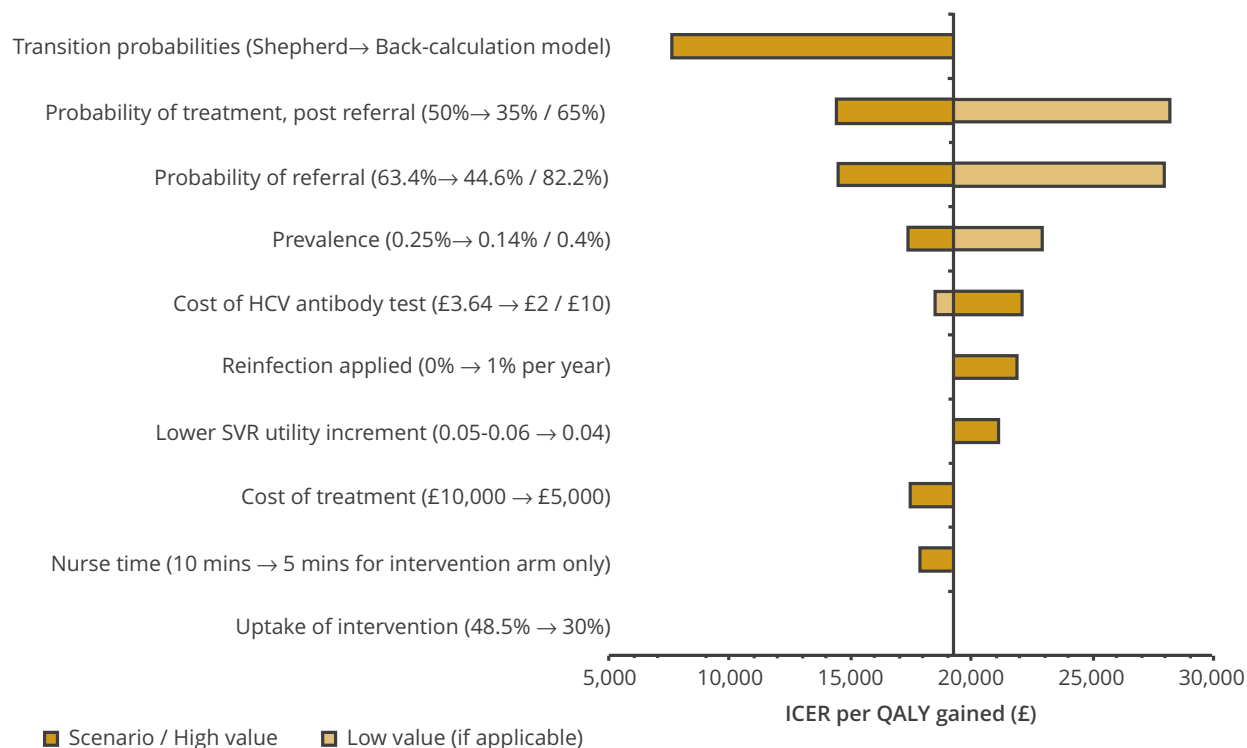
HCV indicates hepatitis C virus; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years; SVR, sustained virological response.

probabilities from Shepherd et al[29] creates an inconsistency between our economic analysis and other model inputs estimated by the back-calculation model (the distribution of prevalence and disease stage across age groups). Nevertheless, this can be

Table 3. EVPI and EVPPI for all birth cohorts.

Birth cohort/parameter	EVP(P)I at £20 000 WTP
EVPI	
1950-54	£175 023
1955-59	£2 264 784
1960-64	£3 577 217
1965-69	£2 270 456
1970-74	£1 644 936
1975-79	£1 357 486
Total	£11 289 902
EVPPI (Total for all birth cohorts)	
Linkage to care parameters*	£3 587 609
Utility of SVR health states	£2 487 084
Transition probabilities from mild, moderate and CC health states†	£1 617 959
Utility of non-SVR health states	£337 008
Health state costs	£98 650
Prevalence and initial values‡	£0
Background rate of testing	£0

CC indicates compensated cirrhosis; EVPI, expected value of perfect information; EVPPI, expected value of partial perfect information; SVR, sustained virological response; WTP, willingness to pay.
*Includes probability of referral and the probability of accepting treatment.
†Using uniform distributions estimated using values from both Shepherd et al[29] and back-calculation model.
‡Includes prevalence, probability of RNA+, and initial starting distribution (proportion mild/moderate/cirrhotic).

considered conservative, since a lower disease progression in the back-calculation model would have resulted in a higher estimated prevalence and therefore would have decreased the estimated ICERs.

There is also uncertainty surrounding the background HCV testing rate of infected and uninfected individuals. We assumed that infected individuals in this population would be tested at the overall population rate of testing, with no differences between those infected and uninfected. Methods to adequately capture the efficacy of expanding risk-based testing should be considered, as testing is likely to become less efficacious with upscaling, a trend observed in PHE sentinel surveillance data.[3,23] This will be important for future evaluations of case finding interventions in different population groups that may have differing rates of background testing. There could also be additional benefits to testing, such as testing among close contacts of those testing positive. Furthermore, we assume no disease transmission due to the assumptions around the population modeled.

Despite considerable uncertainty and the limitations of our analysis, value of information analyses have sought to address the impact of parameter uncertainty by evaluating where future research would be most valued to reduce uncertainty. Nevertheless, due to assumptions made in the model that were not parameterized, additional uncertainty exists that is not reflected in these results. This includes the absence of startup costs for the intervention, assumptions surrounding health check attendees (thus influencing the estimated prevalence), and assumed equal testing among those infected and uninfected in other testing settings. For this reason, the value of information estimates can be considered conservative. Furthermore, patients with existing pre-conditions, such as heart disease, kidney disease, diabetes, or previous stroke, may not receive a health

check invitation, thus uncertainty exists about how testing could be provided to these patients, or whether the prevalence of HCV in this group might differ.

Conclusions

Our analysis suggests any future research for birth cohort testing should prioritize younger birth cohorts, as these are the most likely to be cost-effective. We have also shown the importance of the care pathway on the cost-effectiveness of case-finding interventions, and the benefit of integrating HCV testing with existing health services. A feasibility study would allow a full costing analysis to be undertaken, and could capture the proportion of patients successfully linked to care and receiving treatment. Additional to the parameter uncertainty, this study could assess the acceptability of the intervention as part of the NHS health check to primary care providers, and to health check attendees to avoid unintended negative consequences, such as decreased attendance.

Finally, with many case-finding interventions in HCV currently being evaluated in the United Kingdom,[19,48] future modeling work should consider all potential testing interventions in combination to identify and prioritize the most cost-effective combination of interventions. For example, a more sophisticated risk-based testing algorithm may provide a more targeted approach to case-finding in primary care, although the sensitivity of these algorithms is unknown.[48] The use of more complex economic models comparing multiple case-finding interventions can help to inform the allocation of HCV resources in England to reduce disease burden and meet WHO targets.

Acknowledgments

Supplemental Material

Supplementary data associated with this article can be found in the online version at https: https://doi.org/10.1016/j.jval.2019.06.006.

REFERENCES

1. Degenhardt L, Peacock A, Colledge S, et al. Global prevalence of injecting drug use and sociodemographic characteristics and prevalence of HIV, HBV, and HCV in people who inject drugs: a multistage systematic review. *Lancet Glob Health*. 2017;5(12):e1192–e1207.

2. Harris RJ, Harris HE, Mandal S, et al. Monitoring the hepatitis C epidemic in England and evaluating intervention scale-up using routinely collected data. *J Viral Hepat*. 2019;26(5):541–551.

3. Costella A, Harris H, Mandal S, Ramsay M. Hepatitis C in England: 2018 report. Wellington House. London: Public Health England; 2018.

4. Stanaway JD, Flaxman AD, Naghavi M, et al. The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Lancet*. 2016;388(10049):1081–1088.

5. Easterbrook PJ, WHO Guidelines Development Group. Who to test and how to test for chronic hepatitis C infection - 2016 WHO testing guidance for low- and middle-income countries. *J Hepatol*. 2016;65(suppl 1):S46–S66.

6. Sweeting MJ, De Angelis D, Brant LJ, Harris HE, Mann A, Ramsay ME. The burden of hepatitis C in England. *J Viral Hepat*. 2007;14(8):570–576.

7. Rein DB, Smith BD, Wittenborn JS, et al. The cost-effectiveness of birth-cohort screening for hepatitis C antibody in U.S. primary care settings. *Ann Intern Med*. 2012;156(4):263–270.

8. McGarry LJ, Pawar VS, Panchmatia HR, et al. Economic model of a birth cohort screening program for hepatitis C virus. *Hepatology*. 2012;55(5):1344–1355.

9. Wong WW, Tu HA, Feld JJ, Wong T, Krahn M. Cost-effectiveness of screening for hepatitis C in Canada. *Can Med Assoc J*. 2015;187(3):E110–E121.

10. Ruggeri M, Coretti S, Gasbarrini A, Cicchetti A. Economic assessment of an anti-HCV screening program in Italy. *Value Health*. 2013;16(6):965–972.

11. Nakamura J, Terajima K, Aoyagi Y, Akazawa K. Cost-effectiveness of the national screening program for hepatitis C virus in the general population and the high-risk groups. *Tohoku J Exp Med*. 2008;215(1):33–42.

12. Kim DY, Han K-H, Jun B, et al. Estimating the cost-effectiveness of one-time screening and treatment for hepatitis C in Korea. *PLoS One*. 2017;12(1): e0167770.

13. Centers for Disease Control and Prevention (CDC). Recommendations for the identification of chronic hepatitis C virus infection among persons born during 1945–1965. *MMWR Recomm Rep*. 2012;61(4):1–32.

14. Selvapatt N, Ward T, Ananthavarathan A, et al. Cost-effectiveness of birth cohort screening and treatment for HCV in the UK: an exploratory analysis. *J Hepatol*. 2016;64:S465.

15. NHS Health Check. What is the NHS Health Check? National Health Service. https://www.nhs.uk/conditions/nhs-health-check/what-is-an-nhs-health-check-new/. Accessed October 2018.

16. Hepatitis B and C testing: people at risk of infection (PH43). National Institute for Health and Care Excellence. https://www.nice.org.uk/guidance/ph43. Accessed January 4, 2019.

17. Guide to the methods of technology appraisal 2013 (PMG9). National Institute for Health and Care Excellence. https://www.nice.org.uk/process/pmg9/chapter/foreword. Accessed August 14, 2018.

18. Harris RJ, Thomas B, Griffiths J, et al. Increased uptake and new therapies are needed to avert rising hepatitis C-related end stage liver disease in England: modelling the predicted impact of treatment under different scenarios. *J Hepatol*. 2014;61(3):530–537.

19. Miners AH, Martin NK, Ghosh A, Hickman M, Vickerman P. Assessing the cost-effectiveness of finding cases of hepatitis C infection in UK migrant populations and the value of further research. *J Viral Hepat*. 2014;21(9):616–623.

20. Martin NK, Vickerman P, Miners A, et al. Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. *Hepatology*. 2012;55(1):49–57.

21. National life tables, England: 2015-2017 dataset. Office for National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeaths andmarriages/lifeexpectancies/bulletins/nationallifetablesunitedkingdom/2 015to2017. Accessed November 14, 2018.

22. Estimates of the population for the UK, England and Wales, Scotland and Northern Ireland: mid 2016 dataset. Office for National Statistics. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/datasets/populationestimatesforukenglandandwales scotlandandnorthernireland. Accessed November 23, 2018

23. Simmons R, Ireland G, Irving W, et al. Establishing the cascade of care for hepatitis C in England—benchmarking to monitor impact of direct acting antivirals. *J Viral Hepat*. 2018;25(5):482–490.

24. Irving WL, Smith S, Cater R, et al. Clinical pathways for patients with newly diagnosed hepatitis C - what actually happens. *J Viral Hepat*. 2006;13(4):264–271.

25. Howes N, Lattimore S, Irving WL, Thomson BJ. Clinical care pathways for patients with hepatitis C: reducing critical barriers to effective treatment. *Open Forum Infect Dis*. 2016;3(1).

26. Irving WL, McLauchlan J, Foster G. Real world outcomes of DAA therapy for chronic hepatitis C virus infection in the HCV Research UK National cohort. *J Hepatol*. 2017;66(1):S504.

27. Bourlière M, Gordon C, Flamm S, et al. Sofosbuvir, velpatasvir, and vox-ilaprevir for previously treated HCV infection. *N Engl J Med*. 2017;376(22): 2134–2146.

28. Explore NHS health check data. National Health Service. https://www.healthcheck.nhs.uk/commissioners_and_providers/data/. Accessed January 10, 2018.

29. Shepherd J, Jones J, Hartwell D, Davidson P, Price A, Waugh N. Interferon alfa (pegylated and non-pegylated) and ribavirin for the treatment of mild chronic hepatitis C: a systematic review and economic evaluation. *Health Technol Assess*. 2007;11(11).

30. Martin NK, Vickerman P, Dore GJ, et al. Prioritization of HCV treatment in the direct-acting antiviral era: an economic evaluation. *J Hepatol*. 2016;65(1):17–25.

31. Van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. *JAMA*. 2012;308(24):2584–2593.

32. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. *Ann Intern Med*. 2013;158(5):329–337.

33. Sweeting MJ, De Angelis D, Neal KR, et al. Estimated progression rates in three United Kingdom hepatitis C cohorts differed according to method of recruitment. *J Clin Epidemiol*. 2006;59(2):144–152.

34. Gubay F, Staunton R, Metzig C, Abubakar I, White PJ. Assessing uncertainty in the burden of hepatitis C virus: comparison of estimated disease burden and treatment costs in the UK. *J Viral Hepat*. 2018;25(5):514–523.

35. Wright M, Grieve R, Roberts J, Main J, Thomas HC. UK Mild Hepatitis C Trial Investigators. Health benefits of antiviral therapy for mild chronic hepatitis C: randomised controlled trial and economic evaluation. *Health Technol Assess*. 2006;10(21):1–113.

36. Ratcliffe J, Longworth L, Young T, Bryan S, Burroughs A, Buxton M. Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. *Liver Transpl*. 2002;8(3):263–270.

37. Kind P, Hardman G, Macran S. *UK Population Norms for EQ-5D*. Centre for Health Economics, University of York; 1999.

38. Bradshaw D, Rae C, Rayment M, et al. HIV/HCV/HBV testing in the emergency department: a feasibility and seroprevalence study. *HIV Med*. 2018;19(suppl 1):52–57.

39. Curtis L, Burns A. Unit Costs of Health and Social Care 2017. Personal Social Services Research Unit, University of Kent. https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2017/. Accessed January 3, 2019.

40. Hurley R. Slashed cost of hepatitis C drugs spurs drive to eliminate the disease. *BMJ*. 2018;361:k1679.

41. Foster G, Huskinson P. 25,000 Hepatitis C patients receive new treatments. NHS England. https://www.england.nhs.uk/blog/25000-hepatitis-c-patients-receive-new-treatments/. Accessed January 8, 2018.

42. Grishchenko M, Grieve R, Sweeting M, et al. Cost-effectiveness of pegylated interferon and ribavirin for patients with chronic hepatitis C treated in routine clinical practice. *Int J Technol Assess Health Care*. 2009;25(2):171–180.

43. Briggs A, Sculpher M, Claxton K. *Decision Modelling for Health Economic Evaluation*. Oxford, England: Oxford University Press; 2006.

44. Martin NK, Vickerman P, Dore GJ, Hickman M. The hepatitis C virus epidemics in key populations (including people who inject drugs, prisoners and MSM): the use of direct-acting antivirals as treatment for prevention. *Curr Opin HIV AIDS*. 2015;10(5):374–380.

45. Canadian Task Force on Preventive Health Care. Recommendations on hepatitis C screening for adults. *Can Med Assoc J*. 2017;189(16):E594–E604.

46. Deuffic-Burban S, Huneau A, Verleene A, et al. Assessing the cost-effectiveness of hepatitis C screening strategies in France. *J Hepatol*. 2018;69(4):785–792.

47. Papatheodoridis GV, Hatzakis A, Cholongitas E, et al. Hepatitis C: the beginning of the end—key elements for successful European and national strategies to eliminate HCV in Europe. *J Viral Hepat*. 2018;25(S1):6–17.

48. Roberts K, Macleod J, Metcalfe C, et al. Hepatitis C – Assessment to Treatment Trial (HepCATT) in primary care: study protocol for a cluster randomised controlled trial. *Trials*. 2016;17:366.

49. Reference costs: National schedule of reference costs 2017-18. NHS Improvements. https://improvement.nhs.uk/resources/reference-costs/. Accessed March 7, 2019.