

Feasibility of reaching world health organization targets for hepatitis C and the cost-effectiveness of alternative strategies

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Summary

New drugs for treating hepatitis C have considerably increased the probability of being cured. Treatment uptake, however, is still low. The objectives of this study were to analyse the impact of initiatives that may increase the proportion of infected people on treatment and interventions aimed at reducing the incidence of new infection among people who inject drugs. A compartmental model for Norway was used to simulate hepatitis C and related complications. We analysed 2 different screening initiatives aimed to increase the proportion of infected people on treatment. Interventions aiming at reducing the hepatitis C incidence analysed were opioid substitution therapy (OST), a clean needle and syringe programme and a combination of both. The most cost-effective strategy for increasing hepatitis C treatment uptake was screening by general practitioners while simultaneously allowing for all infected people to be treated. We estimated that this intervention reduces the incidence of hepatitis C by 2030 by 63% compared with the current incidence. The 2 harm reduction strategies both reduced the incidence of hepatitis C by about 70%. Combining an increase in the current clean needles and syringe programme with OST was clearly the most cost-effective option. This strategy would reduce the incidence of hepatitis C by 80% compared with the current incidence by 2030. Thus, interventions to reduce the burden and spread of hepatitis C are cost-effective. Reaching the WHO target of a 90% reduction in hepatitis C incidence by 2030 may be difficult without combining different initiatives.

KEYWORDS

costs and cost analysis, harm reduction, hepatitis, mass screening, resource allocation

1 | BACKGROUND

The disease burden of hepatitis C is considerable worldwide.¹⁻³ With the introduction of direct-acting antivirals (DAAs), treatment of hepatitis C

patients has been revolutionized with more than 90% being cured with considerably less side effects than the previous interferon-based treatment. Despite their high prices,^{2,4} these new drugs have been shown to be cost-effective for some or all genotypes in jurisdictions such as the UK,⁵ Canada,⁶ France,⁷ United States,⁸ Australia⁹ and Norway.¹⁰

Historically, <10% of hepatitis C patients have received treatment in most European countries.¹¹ In recent years, there has been

Abbreviations: DAAs, direct-acting antivirals; HCV, hepatitis C virus; NOK, Norwegian kroner; NSP, needle and syringe programmes; OST, opioid substitution therapy; PWID, people who inject drugs; QALY, quality-adjusted life year.

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a slight increase, including Norway, although recent estimates indicate that only about 10% of Norwegian patients with hepatitis C had been cured before the introduction of sofosbuvir in 2014.¹² The proportion of infected people on treatment stands in sharp contrast to the WHO goals of reducing the incidence of hepatitis C by 90% and mortality by 65% by 2030 (<http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf?ua=1>). To reach this goal, the uptake to hepatitis C virus (HCV) treatment must increase substantially; the question is, how? In Norway, most hepatitis C patients have been infected through injecting drugs.^{13,14} Therefore, to increase the number of individuals treated, screening initiatives would likely be best aimed at these populations.

There are several possible strategies available aimed at reducing the burden of hepatitis C. High-quality evidence of efficacy of these strategies, such as systematic reviews of randomized controlled trials are, however, limited in number. Interventions such as opioid substitution therapy (OST) and needle and syringe programmes (NSP) have several important health outcomes including reduced incidence of hepatitis, although the evidence is limited. Given the high prices of the new medications, it is important to assess whether interventions that increase uptake of these medications are as cost-effective as other strategies, such as harm reduction initiatives. Thus, there is an urgent need to combine the best available evidence on potential initiatives and assess which of these are the most cost-effective.

Birth cohort screening has been analysed in several jurisdictions previously,¹⁵⁻¹⁷ but is not a relevant policy for a Norwegian setting as the prevalence of hepatitis C is similar in all adult cohorts born after 1950. More broad screening alternatives have been analysed from both a United States and Canadian setting.^{18,19} Both these analyses found screening likely to be cost-effective.

Previous health economic evaluations of interventions to reduce the hepatitis C burden have mainly focused on hypothetical scenarios, without taking into account the cost of programmes to increase the number of people tested and treated.^{3,20,21} There is a need to assess which realistic alternatives can be performed and what kind of health

impact these may have among people who either inject or have previously injected drugs. These analyses should, as far as possible, be based on evidence of the efficacy of new drugs, but also of the efficacy of the interventions applied to increase treatment among patients.

The primary objective of this study was therefore to evaluate the cost-utility of different interventions that may reduce the burden of hepatitis C in the Norwegian population, focusing on screening to increase HCV treatment uptake and harm reduction initiatives. Secondary objectives included assessing to what extent the interventions applied could facilitate elimination defined as a 90% reduction of hepatitis C incidence in Norway.

2 | METHODS

We based our analyses on a compartmental Markov model which has been used in modelling the burden of hepatitis C in Norway and the cost-effectiveness of drugs for patients with hepatitis C.^{1,10} Transition probabilities and uncertainty surrounding these have been thoroughly described in previous publications.^{1,10} All analyses have been performed in the open software R (<https://www.r-project.org/>).

Each health state in the model is assigned a utility weight reported in Table 1. In order for quality-adjusted life years (QALYs) to be comparable to most other economic evaluations, we chose to base utility weights on EQ-5D, as this is the most used instrument.²² For most health states, utility values were based on a systematic review and meta-regression of utility estimates by McLernon et al²³

The cost of drugs was based on pharmaceutical prices as announced by the Norwegian Medicines Agency, NoMA (www.legemiddelverket.no). The cost of treatment in different health states is based on principles suggested by NoMA related to reimbursement applications for hepatitis C drugs in Norway as developed by Tollefsen et al²⁴ Costs inputs were based on Norwegian 2016 averages of in-hospital and outpatient treatment²⁵ and official tariffs for primary care treatment.²⁶ More details on cost estimation in Appendix Table A1.

Interventions	Reductions by 2030 in %		Life year gain compared to current
	Incidence	Mortality	
Current	55	6	
Identify PWID in addiction treatment institutions	55	6	57
Identify PWID in addiction treatment institutions and treat all diagnosed cases of HCV	57	8	527
Screen at GP offices	55	1	1080
Screen at GP offices and treat all diagnosed cases of HCV	63	6	7577
Clean needles and syringes (NSP)	74	7	30 942
Opioid substitution therapy (OST)	69	7	20 334
OST and NSP	80	6	56 797

TABLE 1 Reductions in incidence and mortality by 2030

GP, general practitioner; HCV, hepatitis C virus; NSP, needles and syringes programme; OST, opioid substitution therapy; PWID, people who inject drugs.

In the analyses, we assumed that all patients on hepatitis C treatment would use the drugs that were shown to be the most cost-effective for Norway at the end of 2016.¹⁰ The assumption underlying the current analyses therefore suggests that all patients with genotype 1 used the combination treatment comprising paritaprevir, ritonavir, ombitasvir and dasabuvir, with subgroups of patients with cirrhosis or genotype 1A receiving ribavirin in addition. We also assumed that genotype 2 patients receive sofosbuvir and ribavirin and genotype 3 patients sofosbuvir, peginterferon alpha 2a and ribavirin.

In this analysis, we analysed 2 different screening strategies; screening for people who inject drugs (PWID) at harm reduction facilities and drug treatment clinics or screening former and present PWID at GP clinics. These screening initiatives were analysed assuming only those with advanced liver fibrosis receive treatment and with all hepatitis C positive receiving treatment. In addition to screening strategies, we analysed 3 different harm reduction strategies; an increase in the established needles and syringes programme (NSP), OST or a combination of both (NSP & OST). The different strategies were compared to the policy as of 2016, when treatment with DAAs was restricted in Norway to those with moderate or advanced liver fibrosis. As the analysis has a focus on hepatitis C, specifically, other potential effects of the interventions were not modelled directly, such as HIV and potential overdoses.

Data on the effect and cost of each treatment option were based on a wide range of different sources (see Appendix Table A2). Where randomized controlled trial data were available, these were used for informing the effect of interventions in the model. Where randomized controlled trials were not available, evidence was based on systematic reviews of observational studies.

In 2016, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) issued a report on hepatitis C among drug users in Europe.²⁷ In the report, evidence on current status and the efficacy of interventions have been summarized. In the report, the effect of OST was indicated to be OR = 0.41 (0.21-0.82) based on a meta-analysis by Turner et al²⁸ In the model, this estimate was first recalculated into a relative risk and thereafter applied based on the assumption that 50% of the injecting drug users may be included in an OST programme.

The effect of a NSP was also available from the EMCDDA report.²⁷ Data were presented comparing more than a 100% coverage vs less than a 100% coverage with an adjusted odds ratio of 0.48 (0.24-0.93). In Norway, we have estimated coverage of around 75% (see Appendix), indicating that we would expect to see about half as many infections if a scale-up was introduced. Results similar to those found in the EMCDDA report have also been found by others, for instance, Bluthenthal et al²⁹ Current volume of clean needles and syringes handed out is used as a proxy for all clean user equipment as a definition of the current situation. If other user equipment is handed out to a less extent than needles and syringes, we may underestimate the effect of expanding the programme. Similarly, there is uncertainty, both about the extent of the NSP programme in Norway today, the realism of

an increase beyond the current coverage, and the effect of such an increase on the incidence of hepatitis C. We therefore conducted sensitivity analyses looking at which interventions would be most cost-effective if we assume only half of the effect shown in the EMCDDA report.

The efficacy of screening interventions was largely based on results reported in a meta-analysis by Aspinall et al³⁰ In Aspinall's review, 2 RCT's by Hickman et al and Sahajan et al had screened for HCV at institutions with large numbers of drug users.^{31,32} Because the proportion tested in the control group was closer to a Norwegian setting in Hickman's study, indicating similar populations, we based the efficacy of that in our model.³¹

The only RCT we found concerning screening at GP offices is by Roudot-Thoraval et al³³ The increase in number screened in the Roudot-Thoraval trial resulted in an increase in number of positive hepatitis C test (RR = 1.37) which was close to that reported in a much larger, but nonrandomized study by Litwin et al reporting an RR of 1.26.³⁴ We based our analyses on the RCT, to be consistent with our goal of including RCTs whenever possible. For the screening at GP strategy, we assumed all GPs in Norway were sent a letter informing them about which questions to ask to test those with a previous injection history for hepatitis C. For screening at facilities, we assumed an increase in the number of nurses available to recruit attendees for screening at a rate of one nurse per 20 treated.

We assumed that the interventions modelled were started at the beginning of 2016. Within-cycle correction was applied using Simpson's 1/3rd rule, which has proven to be superior to, for example, half-cycle correction.³⁵ As described in previous publications, the model was based on data from 1975 and onwards.^{1,10} Model of transmission was performed until 2030,¹ while health effects for all who acquire disease by 2030 will be modelled until these individuals die or are 100 years old.¹⁰

The model was made probabilistic by representing all uncertain variables in the model by probability distributions. The specification of distributions is given as part of the specification of each parameter (Appendix Tables A1 and A2). All uncertain input parameters were simulated with 1000 iterations, and the model was subsequently run 1000 times using these different input parameters.

The cost-effectiveness of interventions provided in Norway is traditionally evaluated against thresholds of cost-effectiveness that are relatively close to the Norwegian gross domestic product per person. For 2015, this was reported to be around NOK 600 000. In a recent review of decisions made based on cost-utility in Norway, NOK 700 000 per QALY gained was the reported average threshold. We therefore used this in our analyses.³⁶ Other thresholds suggested for Norway have varied between NOK 275 000 and NOK 1.2 million. For calculations of net health benefit, we assumed NOK 700 000 per QALY as the cost-effectiveness threshold. Based on this threshold, the most cost-effective strategy was defined to be the strategy that maximized net health benefit.

TABLE 2 Incremental costs and effects of screening sorted by increasing effectiveness

Strategies	QALYs compared to current	Costs (mill. NOK) compared to current	ICER	INHB compared to current
Identify PWID in addiction treatment institutions	25	7012	280 480 000	-9992
Screen at GP offices	433	581	1 342 307	433
Identify PWID in addiction treatment institutions and treat all diagnosed cases of HCV	611	6832	17 510 050	-9558
Screen at GP offices and treat all diagnosed cases of HCV	4794	-29	-62 274	4794

GP, general practitioner; HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio compared to current practice; INHB, Incremental net health benefit (at threshold of NOK 700 000 per QALY); NOK, Norwegian kroner; PWID, people who inject drugs; QALY, quality-adjusted life year.

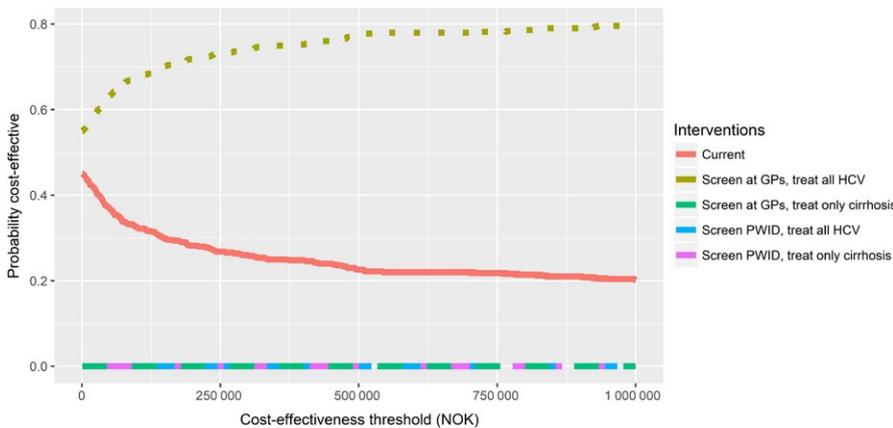


FIGURE 1 Cost-effectiveness acceptability curve for screening alternatives compared to current situation. GP, general practitioner; HCV, hepatitis C virus; NOK, Norwegian kroner; PWID, people who inject drugs

3 | RESULTS

The different interventions are expected to result in incidence reductions of between 55% and 74% in the years up to 2030, while combinations of interventions may decrease incidence by up to 80% (Table 1 and Appendix Figures A1 and A2). Over a lifetime perspective for all current, future and previous PWID in the period up to 2030 increases in life expectancy ranges between 57 and 57 000 (Table 2). The largest reduction in incidence (74% by 2030) and largest gain in quality-adjusted life expectancy due to a single initiative would be expected if the NSP was increased to more than 100% coverage.

The health gains of some initiatives are substantial, but so are the costs, too. In some instances, however, the interventions may reduce so much of the future disease burden that future cost implications are negative, implying that the intervention costs are less than what will be saved in future treatment costs (Table 2). When comparing health benefits and costs to proposed Norwegian cost-effectiveness thresholds, the most effective and cost-effective among the screening strategies are clearly screening at GPs combined with treating all individuals identified with hepatitis C. This combination would result in a reduction in hepatitis C incidence of 63%, leading to an almost 5000-QALYs increase in addition to a NOK 300 million reduction in costs. If only patients suffering from cirrhosis are treated, neither intervention will be cost-effective

nor the QALYs gained will be modest. The cost-effectiveness acceptability curve shows that regardless of the cost-effectiveness threshold, the stated combination has the highest probability of being cost-effective among the screening options (Figure 1). Given a Norwegian cost-effectiveness threshold of NOK 700 000 per QALY, we are 79% certain that screening at GPs and treating all hepatitis C patients is the most cost-effective.

The most cost-effective single harm reduction initiative is increasing the clean needle and syringes programme to a coverage above 100%. Compared to current practice, increasing the clean needle and syringes programme is expected to gain more than 12 000 QALYs among the population and decrease health spending by NOK 1.3 billion. If the Norwegian cost-effectiveness threshold represents the opportunity cost, the 1.3 billion NOK saved could gain about 1700 QALYs elsewhere in the healthcare system, resulting in approximately 14 000 QALYs gained in total by this intervention. When combining interventions, the combination of OST and increasing the clean needles and syringes programme was the most cost-effective combination (Table 3). The expected incidence reduction by 2030 with this combination is 80%, coming relatively close to the goal of 90%. In simulations, 97% of iterations resulted in the combination of clean needles and OST being the most cost-effective, implying that, given our assumptions, we are 97% certain that clean needles and syringes combined with OST are the most cost-effective strategy (Figure 2).

TABLE 3 Incremental costs and effects of harm reduction sorted by increasing effectiveness

Strategies	QALYs compared to current	Costs (mill. NOK) compared to current	ICER	INHB compared to current
Opioid substitution therapy	8728	1965	Dominated	5921
Clean needle and syringe programme	12 251	-1165	Dominated	13 915
OST and NSP	20 662	-6109	Dominant	29 389

ICER, incremental cost-effectiveness ratio; INHB, Incremental net health benefit (at threshold of NOK 700 000 per QALY); dominated strategies are less efficacious and more costly than the most cost-effective strategy, dominant signifies a strategy with higher expected QALYs and lower expected costs than all other options; NOK, Norwegian kroner; NSP, needles and syringes programme; OST, opioid substitution therapy; QALY, quality-adjusted life year.

FIGURE 2 Cost-effectiveness acceptability curve of combinations and single harm reduction initiatives. NOK, Norwegian kroner; NSP, needles and syringes programme; OST, opioid substitution therapy

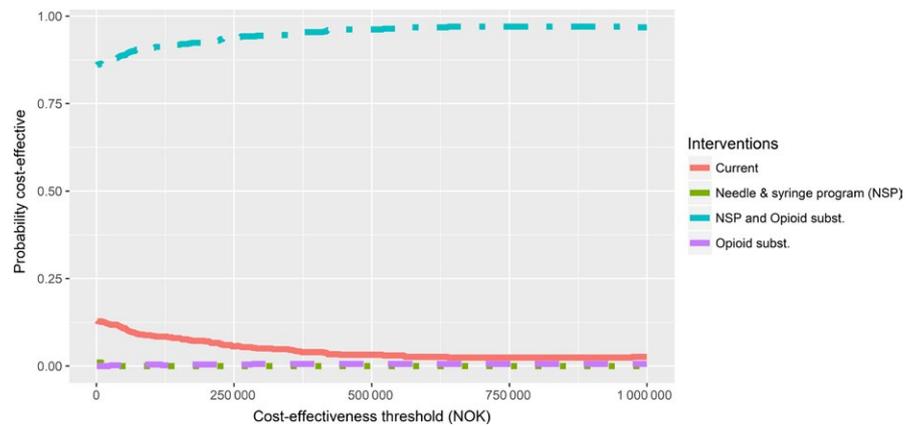
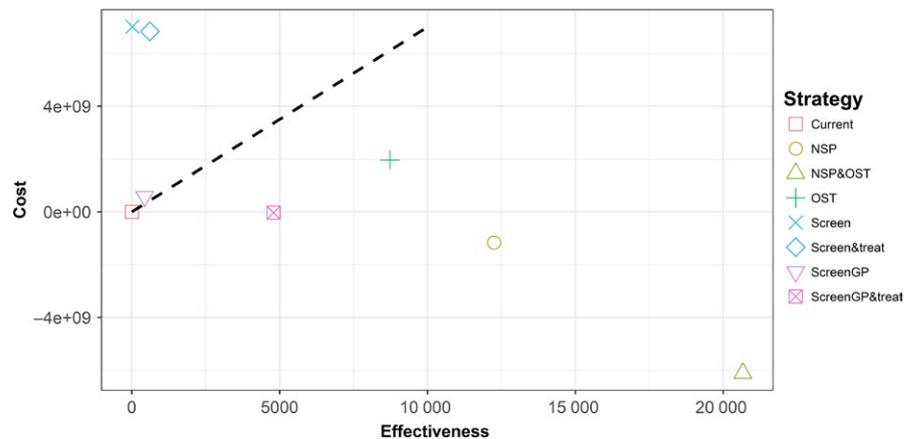


FIGURE 3 All interventions in one cost-effectiveness plane (produced with functions provided by the DARTH group.^{49,50} NSP, needles and syringes programme; OST, opioid substitution therapy; screen, screen at; screenGP, screen at GP offices; treat, treat all infected



If we look at the different harm reduction and screening initiatives compared to each other, we find the combination of NSP and OST will be the most cost-effective. In Figure 3, we clearly see that among the interventions below the WTP line, the combination of OST and NSP has the longest distance to the line, which also implies having the highest incremental net benefit. Combining the uncertainties around all these interventions also shows that the probability of the combination of OST and NSP being the most cost-effective is 97% at a threshold of NOK 700 000 per QALY.

Regarding scale-up of an NSP programme, there are several uncertainties. For instance, the current level of NSP coverage in

Norway and the transferability of effect from other jurisdictions. We have therefore performed the harm reduction analyses with only half of the NSP effect. These analyses show that if the effect of NSP is halved, the combination of OST and NSP is still the most cost-effective, but we are now only 62% certain, while OST alone has a 32% probability of being the most cost-effective (Figure 4).

4 | DISCUSSION

Our results show that both harm reduction and screening initiatives combined with treatment are cost-effective in a Norwegian

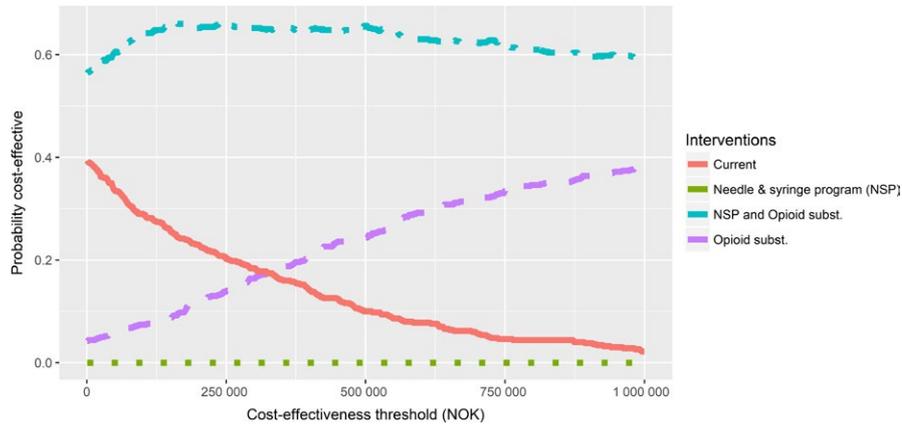


FIGURE 4 Cost-effectiveness acceptability curve of harm reduction initiatives assuming half effect of NSP. NOK, Norwegian kroner; NSP, needles and syringes programme; OST, opioid substitution therapy

setting. Treating all identified as having hepatitis C at screening is clearly improving the cost-effectiveness. Although all interventions are assumed to have a cost to implement, some of the interventions and combinations are assumed to decrease the subsequent cost of treatment and complications for this patient group to an extent that decreases the overall cost of the interventions, despite taking implementation costs into account. The biggest overall cost reductions are seen for the clean needles and syringes programme, which could save more than one billion NOK on the healthcare budget.

Our model analyses have incorporated the effect on both current people infected by hepatitis C and those who could potentially be infected in the coming years. This aspect has been left out of many health economic evaluations within hepatitis C, although it is recommended that it is included.²

Other researchers have previously performed economic evaluations of screening and other interventions aimed at reducing the burden of hepatitis C for other jurisdictions earlier. In a review from 2012, John-Baptiste et al summarized interventions aimed at reducing hepatitis C in the pre-DAA era.³⁷ Ten of 21 economic evaluations included were concerned with screening, 8 with treatment and 3 addressed prevention. Given the introduction of DAAs, the results from these economic evaluations are of minimal interest in comparison with our present analysis.

Martin et al³⁸ analysed different strategies for scaling up treatment. Their results showed that immediate maximum intensity, given the budget, would give the lowest total healthcare costs over time. In Scott et al⁹ analysis of potential scale-up strategies, they found that reaching WHO targets is feasible and cost-effective in an Australian setting.

Vickerman et al³⁹ conducted a study exploring the impact of NSP and OST in a UK setting. The analysis was based on the same meta-analysis as that used in our present analyses.²⁸ In their analyses, they found that scaling up NSP and OST could reduce HCV prevalence considerably, although this required high coverage.

The present analysis has several limitations. The most impactful is the lack of randomized evidence of the efficacy of interventions to reduce the hepatitis C burden. Among interventions analysed, most have been proven effective in a randomized controlled trial, but few

have been tested for reproducible efficacy in different RCTs. Given that nonrandomized evidence has some inherent bias related to design, the results have to be interpreted with this limitation in mind. In addition, in cases where only one RCT has been published, such as for screening at GP offices, we cannot be certain of the transferability of the effect to other jurisdictions.

Some of the interventions we analysed were specifically aimed at hepatitis C, while others had a broader scope, and thereby also have effects on other outcomes. For instance would it be reasonable to assume that an OST would also reduce the number of overdoses, which, in turn, considerably impact both health and resource use. The exclusion of these effects is a clear limitation of the analyses from an overall perspective. Note, however, that the underlying mortality is assumed to be higher among injecting drug users than among previous drug users, which would make this limitation less impactful. In addition, some of the interventions may not be carried out exactly as we assumed in our analysis. For instance, although screening at GP offices would mainly be aimed at previous injecting drug users in Norway, it would probably also be aimed at some other high-risk groups as well. Since current and previous injecting drug users constitute the vast majority of hepatitis C cases in Norway, this latter omission is not likely to have a considerable impact on the results.

The different interventions analysed are aimed at different populations. The screening initiative among GPs has a broad focus, while screening at harm reduction facilities and drug treatment clinics is a more focused intervention. The focused interventions are likely to have a bigger impact among those identified, but have reached a somewhat limited number of people. The broader initiatives, on the other hand, are likely to identify more people, but may have a more limited impact on interventions for those identified. With our model, we have evaluated the combined effects of these issues to obtain a prioritized list of initiatives that can be used in decision-making. The results, however, depend heavily on the assumptions made. Thus, conducting new research to be able to be more certain about these decisions will be important. One could, for instance, combine the most promising screening and harm reduction initiatives in one analysis, if this combination is a likely strategy in a given jurisdiction.

Some of the cost inputs are based on weak evidence, either with regard to point estimate, uncertainty or both. The cost of needles and syringes is based on information provided by Oslo Municipality. Although this estimate may be rough, we have identified other sources, such as an online firm selling clean equipment (www.brugerutstyr.no), which reports prices somewhat lower for only the cost of the equipment only, without including other costs. Hence, the estimate used in our analyses is probably not too far off from reality.

In general, one can never be certain as to whether studies performed in one jurisdiction are valid in another. All studies of the effect of the different interventions used in this cost-utility analysis are all from different countries and none of these are from the area we studied (Norway). Hence, all results rest on the assumption of the transferability of results to a Norwegian setting.

In conclusion, harm reduction initiatives and screening for hepatitis C are cost-effective strategies to reduce burden of hepatitis C in a Norwegian setting, but reaching WHO targets is not likely without combining several interventions.

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CONFLICTS OF INTEREST

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AUTHORS' CONTRIBUTIONS

All authors contributed in the design of the study. RW and HM constructed the compartmental model. TW constructed the code to perform health economic analyses. All authors contributed to writing of the manuscript and approved the final version.

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REFERENCES

- Meijerink H, White RA, Lovlie A, et al. Modelling the burden of hepatitis C infection among people who inject drugs in Norway, 1973-2030. *BMC Infect Dis.* 2017;17:541.
- Chhatwal J, He T, Lopez-Olivo MA. Systematic review of modelling approaches for the cost effectiveness of hepatitis C treatment with direct-acting antivirals. *Pharmacoeconomics.* 2016;34:551-567.
- 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;61:530-537.
- Chidi AP, Rogal S, Bryce CL, et al. Cost-effectiveness of new antiviral regimens for treatment-naïve U.S. veterans with hepatitis C. *Hepatology.* 2016;63:428-436.
- Martin NK, Vickerman P, Dore GJ, et al. Prioritization of HCV treatment in the direct-acting antiviral era: an economic evaluation. *J Hepatol.* 2016;65:17-25.
- Wong W, Krahn M, Lee K, Singh S. *Drugs for Chronic Hepatitis C Infection: Cost-Effectiveness Analysis.* Ottawa, ON: Canadian Agency for Drugs and Technologies in Health; 2016.
- Deuffic-Burban S, Obach D, Canva V, et al. Cost-effectiveness and budget impact of interferon-free direct-acting antiviral-based regimens for hepatitis C treatment: the French case. *J Viral Hepat.* 2016;23:767-779.
- Najafzadeh M, Andersson K, Shrank WH, et al. Cost-effectiveness of novel regimens for the treatment of hepatitis C virus. *Ann Intern Med.* 2015;162:407-419.
- Scott N, Iser DM, Thompson AJ, Doyle JS, Hellard ME. Cost-effectiveness of treating chronic hepatitis C virus with direct-acting antivirals in people who inject drugs in Australia. *J Gastroenterol Hepatol.* 2016;31:872-882.
- Wisløff T, White R, Dalgard O, et al. Economic evaluation of direct acting antivirals for hepatitis C in Norway. *Pharmacoeconomics.* 2018;36(5):591-601.
- Lettmeier B, Muhlberger N, Schwarzer R, et al. Market uptake of new antiviral drugs for the treatment of hepatitis C. *J Hepatol.* 2008;49:528-536.
- Midgard H, Bramness JG, Skurtveit S, Haukeland JW, Dalgard O. Hepatitis C treatment uptake among patients who have received opioid substitution treatment: a population-based study. *PLoS One.* 2016;11:e0166451.
- Kielland KB. *Mortality, Morbidity and Treatment Uptake Related to Hepatitis C Among People who Have Injected Drugs in Norway.* Oslo: University of Oslo; 2015.
- Nilsen Ø, Blystad H, Kløvstad H, Barlind R. [Blood- and Sexually Transmitted Infections in Norway 2016]. Oslo: Norwegian Institute of Public Health; 2017. ISBN: 978-82-8082-856-9. In Norwegian.
- Liu S, Cipriano LE, Holodniy M, Goldhaber-Fiebert JD. Cost-effectiveness analysis of risk-factor guided and birth-cohort screening for chronic hepatitis C infection in the United States. *PLoS One.* 2013;8:e58975.
- McGarry LJ, Pawar VS, Panchmatia HR, et al. Economic model of a birth cohort screening program for hepatitis C virus. *Hepatology.* 2012;55:1344-1355.
- 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;156:263-270.
- Coffin PO, Scott JD, Golden MR, Sullivan SD. Cost-effectiveness and population outcomes of general population screening for hepatitis C. *Clin Infect Dis.* 2012;54:1259-1271.
- Wong WW, Tu HA, Feld JJ, Wong T, Krahn M. Cost-effectiveness of screening for hepatitis C in Canada. *CMAJ.* 2015;187:E110-E121.
- Martin NK, Vickerman P, Grebely J, 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;58:1598-1609.
- Leidner AJ, Chesson HW, Xu F, Ward JW, Spradling PR, Holmberg SD. Cost-effectiveness of hepatitis C treatment for patients in early stages of liver disease. *Hepatology.* 2015;61:1860-1869.
- Wisløff T, Hagen G, Hamidi V, Movik E, Klemp M, Olsen JA. Estimating QALY gains in applied studies: a review of cost-utility analyses published in 2010. *Pharmacoeconomics.* 2014;32:367-375.
- McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. *Med Decis Making.* 2008;28:582-592.

24. Tollefsen KB, Kristiansen IS, Asphjell MK, Falch NS, Sæther EM. [Hepatitis C - New Drugs Give Better Treatment Options]. Oslo: Oslo Economics; 2014. In Norwegian
25. [Performance-Based Financing 2016]. Oslo: Norwegian Directorate of Health; 2015. ISBN: 978-82-8081-417-3. In Norwegian
26. *Normal Tariff for Contract Specialists 2015-2016*. Oslo: The Norwegian Medical Association.
27. *Addiction EEMCfDaD. Hepatitis C Among Drug Users in Europe: Epidemiology, Treatment And Prevention*. Luxembourg: Publications Office of the European Union; 2016.
28. Turner KM, Hutchinson S, Vickerman P, et al. The impact of needle and syringe provision and opiate substitution therapy on the incidence of hepatitis C virus in injecting drug users: pooling of UK evidence. *Addiction*. 2011;106:1978-1988.
29. Bluthenthal RN, Anderson R, Flynn NM, Kral AH. Higher syringe coverage is associated with lower odds of HIV risk and does not increase unsafe syringe disposal among syringe exchange program clients. *Drug Alcohol Depend*. 2007;89:214-222.
30. Aspinall EJ, Doyle JS, Corson S, et al. Targeted hepatitis C antibody testing interventions: a systematic review and meta-analysis. *Eur J Epidemiol*. 2015;30:115-129.
31. Hickman M, McDonald T, Judd A, et al. Increasing the uptake of hepatitis C virus testing among injecting drug users in specialist drug treatment and prison settings by using dried blood spots for diagnostic testing: a cluster randomized controlled trial. *J Viral Hepatitis*. 2008;15:250-254.
32. Sahajian F, Bailly F, Vanhems P, et al. A randomized trial of viral hepatitis prevention among underprivileged people in the Lyon area of France. *J Public Health (Oxf)*. 2011;33:182-192.
33. Roudot-Thoraval F, Monnet E, Mercet P, Bastie A, Dhumeaux D, Miguet JP. Strategies of hepatitis C screening in general practice. Results of a two-center randomized trial. *Gastroenterol Clin Biol*. 2000;24:1037-1041.
34. Litwin AH, Smith BD, Drainoni ML, et al. Primary care-based interventions are associated with increases in hepatitis C virus testing for patients at risk. *Dig Liver Dis*. 2012;44:497-503.
35. Elbasha EH, Chhatwal J. Theoretical foundations and practical applications of within-cycle correction methods. *Med Decis Making*. 2016;36:115-131.
36. Foss P. [The pharmaceutical industry view on health economics]. 2016. In Norwegian
37. John-Baptiste A, Yeung MW, Leung V, van der Velde G, Krahn M. Cost effectiveness of hepatitis C-related interventions targeting substance users and other high-risk groups: a systematic review. *Pharmacoeconomics*. 2012;30:1015-1034.
38. Martin NK, Pitcher AB, Vickerman P, Vassall A, Hickman M. Optimal control of hepatitis C antiviral treatment programme delivery for prevention amongst a population of injecting drug users. *PLoS One*. 2011;6:e22309.
39. Vickerman P, Martin N, Turner K, Hickman M. Can needle and syringe programmes and opiate substitution therapy achieve substantial reductions in hepatitis C virus prevalence? Model projections for different epidemic settings. *Addiction*. 2012;107:1984-1995.
40. Seeff LB. The history of the "natural history" of hepatitis C (1968-2009). *Liver Int*. 2009;29(Suppl 1):89-99.
41. Dalgard O, Mauss S. No strategy to meet the HCV epidemic. *BMC Infect Dis*. 2014;14(Suppl 6):S2.
42. Martin NK, Vickerman P, Miners A, et al. Cost-effectiveness of hepatitis C virus antiviral treatment for injection drug user populations. *Hepatology*. 2012;55:49-57.
43. Sangiovanni A, Prati GM, Fasani P, et al. The natural history of compensated cirrhosis due to hepatitis C virus: a 17-year cohort study of 214 patients. *Hepatology*. 2006;43:1303-1310.
44. Hutchinson SJ, Bird SM, Goldberg DJ. Modeling the current and future disease burden of hepatitis C among injection drug users in Scotland. *Hepatology*. 2005;42:711-723.
45. Gjersing L, Bretteville-Jensen AL. Gender differences in mortality and risk factors in a 13-year cohort study of street-recruited injecting drug users. *BMC Public Health*. 2014;14:440.
46. McDonald SA, Hutchinson SJ, Palmateer NE, et al. Decrease in health-related quality of life associated with awareness of hepatitis C virus infection among people who inject drugs in Scotland. *J Hepatol*. 2013;58:460-466.
47. Townsend R, McEwan P, Kim R, Yuan Y. Structural frameworks and key model parameters in cost-effectiveness analyses for current and future treatments of chronic hepatitis C. *Value Health*. 2011;14:1068-1077.
48. Melberg HO, Lauritzen G, Ravndal E. *What Benefit, for Whom and at What Cost?*. Oslo: Norwegian Institute for Alcohol and Drug Research (SIRUS); 2003.
49. Jalal H, Pechlivanoglou P, Krijnkamp E, Alarid-Escudero F, Enns E, Hunink MGM. An overview of R in health decision sciences. *Med Decis Making*. 2017;37:735-746.
50. Krijnkamp EM, Alarid-Escudero F, Enns EA, Jalal HJ, Hunink MGM, Pechlivanoglou P. Microsimulation modeling for health decision sciences using R: a tutorial. *Med Decis Making*. 2018;38:400-422.

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APPENDIX

Table A1 Probabilities of transitions in the model (all incorporated as beta distributions with alphas and betas as specified)

Probability	Source	Value	Low ^a	High ^a	Alpha	Beta
Probability of acute HCV infection when in susceptible	Expert opinion	0.083	0.081	0.085	6401	70 598
Probability of chronic HCV infection when in acute HCV infection	Seeff (2009) ⁴⁰	0.733	0.721	0.766	1087	395
Proportion with chronic HCV infection who will get drug treatment	Dalgard & Mauss (2014) ⁴¹	0.046	0.041	0.050	330	6915
Probability of cirrhosis when in chronic HCV infection	Martin et al (2012) ⁴²	0.014	0.014	0.015	1299	90 378
Proportion of cirrhosis patients who will get drug treatment	Expert opinion	0.306	0.297	0.338	596	1350
Probability of HCC when in cirrhosis	Martin et al (2012) ⁴² /Sangiovanni et al (2006) ⁴³ /Hutchinson et al (2005) ⁴⁴	0.021	0.019	0.021	1491	69 831
Probability of being transplanted when in cirrhosis	Expert opinion	0.001	0.001	0.006	0.98	791
Probability of mortality when in cirrhosis	Hutchinson (2005) ⁴⁴ /Sangiovanni (2006) ⁴³	0.034	0.032	0.035	2226	62 824
Probability of being transplanted when in HCC	Martin et al (2012) ⁴²	0.056	0.031	0.056	73	1243
Probability of mortality when in HCC	Hutchinson et al (2005) ⁴⁴	0.555	0.547	0.628	321	258
Probability of chronic HCV infection when transplanted	Expert opinion	0.326	0.116	0.485	7.8	16
Probability of mortality when transplanted	Hutchinson et al (2005) ⁴⁴	0.165	0.126	0.177	137	694
Excess PWID mortality	Gjersing et al (2014) ⁴⁵	0.022	0.017	0.031	45	127
Yearly probability of ex-PWID relapse	Meijerink et al (2017) ¹	0.116	0.037 ^b	0.230 ^b	4.6	35.3
Yearly probability of PWID temporary cessation	Meijerink et al (2017) ¹	0.114	0.036 ^b	0.229 ^b	4.5	35.0
Yearly probability of PWID permanent cessation	Meijerink et al (2017) ¹	0.025	0.002 ^b	0.077 ^b	1.5	58.4

HCC, hepatocellular carcinoma; HCV, hepatitis C virus; PWID, people who inject drugs.^a Low and high are assumed 95% confidence intervals. These are used to calculate alphas and betas for the beta distributions.^b Estimates of uncertainty made wide due to lack information on uncertainty.

Table A2 Health state costs per year

Health states in the model	Yearly cost (€)
HCV acute infection	797
HCV chronic	511
Cirrhosis	6580
Hepatocellular carcinoma	92 746
Transplanted	15 272
Transplanted first year	254 475

HCV, hepatitis C virus.

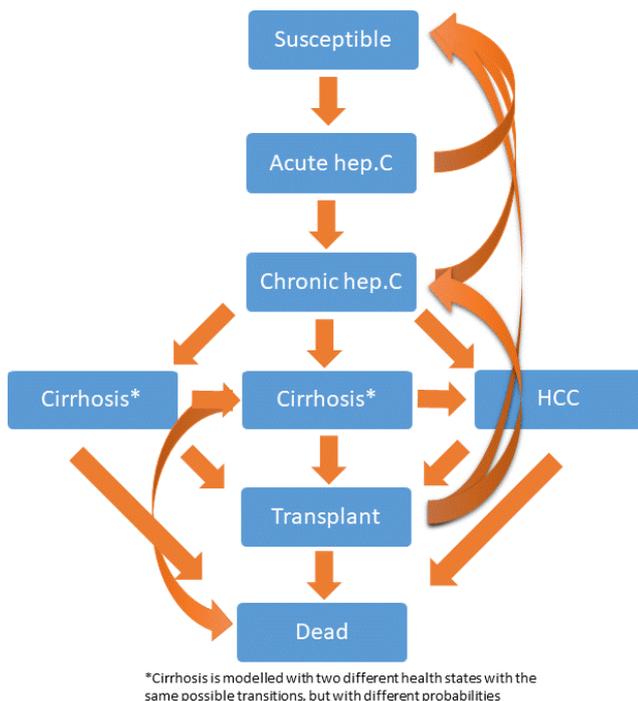
Table A3 Utility weights and decrements

Health states in the model	Utility ^a	SE	References
HCV susceptible	+0.090	0.030	McDonald et al (2012) ⁴⁶
HCV infection	0.747	0.014	McLernon et al (2008) ²³
Cirrhosis	-0.014	0.017	McLernon et al (2008) ²³
HCC	0.380	0.184	Townsend et al (2011) ⁴⁷
Transplanted	-0.038	0.017	McLernon et al (2008) ²³

^aAll values with plus or minus are increments or decrements compared to HCV infected, others are health state weights.

Table A4 Intervention parameters

	Estimate	Source
Screen among PWID		
Increased proportion taking test	RR = 3.2 (2.6-3.9)	Hickman et al (2008) ³¹
Screen by asking everyone attending GP office		
Increased cases of hepatitis C detected	RR = 1.4 (0.6-3.1)	Roudot-Thoraval et al (2000) ³³
Price per letter sent to GPs (including salary etc.)	23.39	Difi (http://www.difi.no/sites/difino/files/gevinstkalkulator-digital-post_1.xlsx)
Number of GPs in Norway	4531	Helsedirektoratet
Change recommendations to treat all with hepatitis C		
Estimated relative increase in patients treated with new recommendations	2.72	Average between estimate from Olav Dalgard (2.0) and Oslo Economics (3.7)
Increase clean needles and syringes programme		
Number of needles handed out in Norway	2 296 411	Norwegian Directorate of Health (Personal communication: Thomas Anton Sandøy)
Number of injections per year	4 072 500 (2 814 750-5 959 250)	SIRUS (Ellen Amundsen)
Decrease in number of PWID due to increase in clean needles	OR = 0.76	Turner et al (2011) ²⁸
Cost of syringes and other clean equipment in Oslo	3 690 000	Oslo Municipality (email)
Number of syringes in Oslo	1 212 990	Oslo Municipality (document)
Substitution from illicit drugs to opioid substitution therapy		
OR of effect of OST on HCV incidence	OR = 0.41	Turner et al (2011) ²⁸
Cost per year for OST treatment (2001)	217 655	Melberg et al (2003) ⁴⁸
Adjustment for inflation from 2001 to 2015	1.2861	http://www.ssb.no/kpi

**Figure A1** Simplified model structure as presented in published article: Wisløff et al¹⁰ <https://doi.org/10.1007/s40273-017-0604-3>

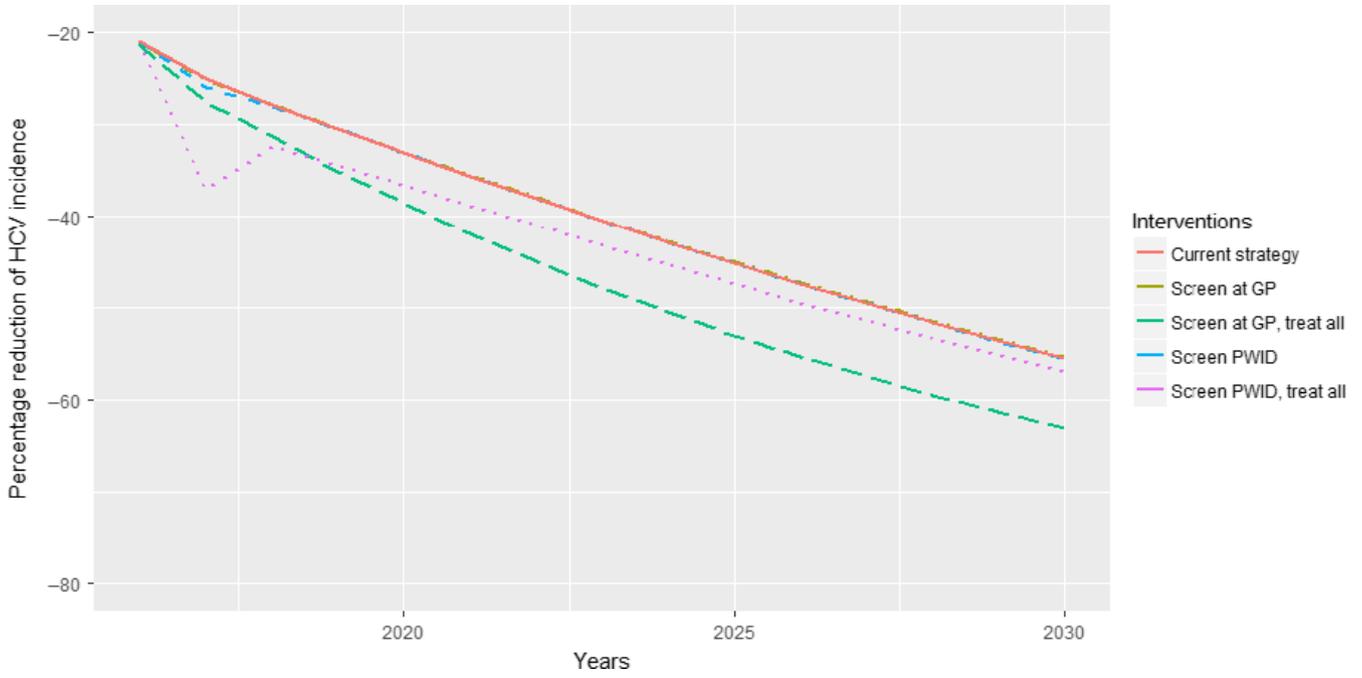


Figure A2 Reduction in incidence of hepatitis C with different screening strategies

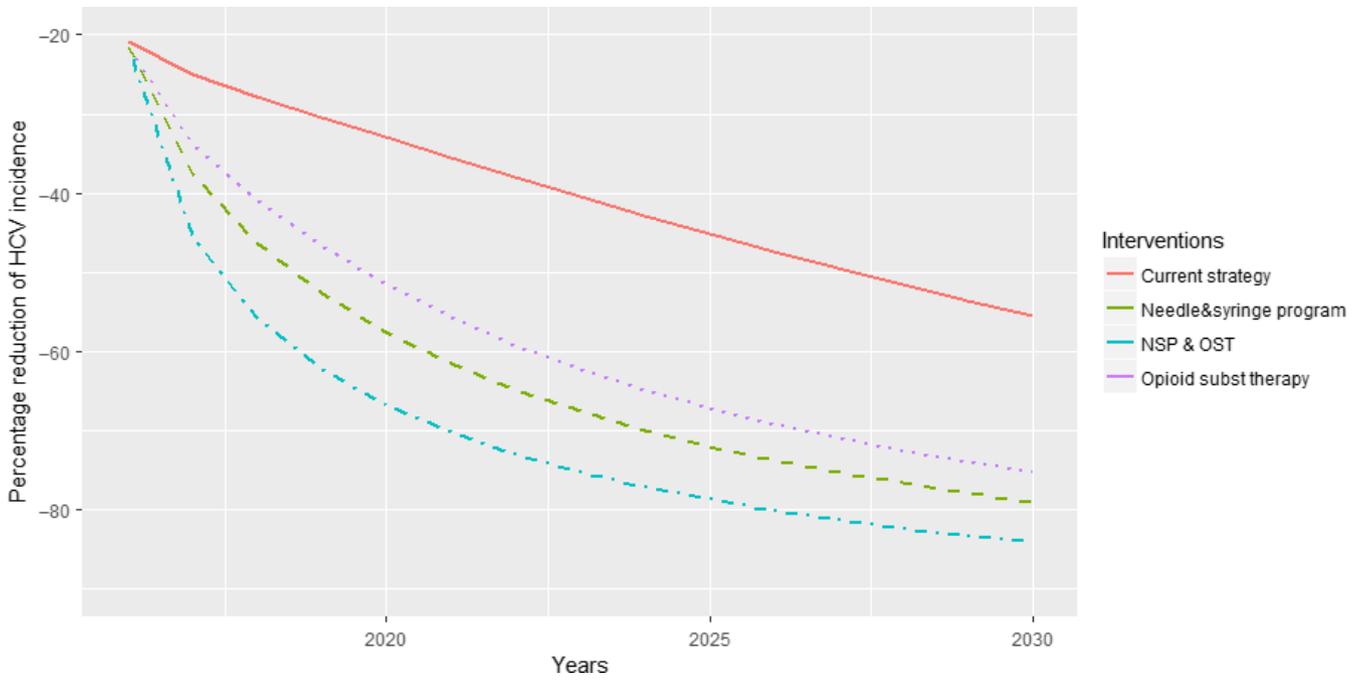


Figure A3 Reduction in incidence of hepatitis C with different harm reduction initiatives

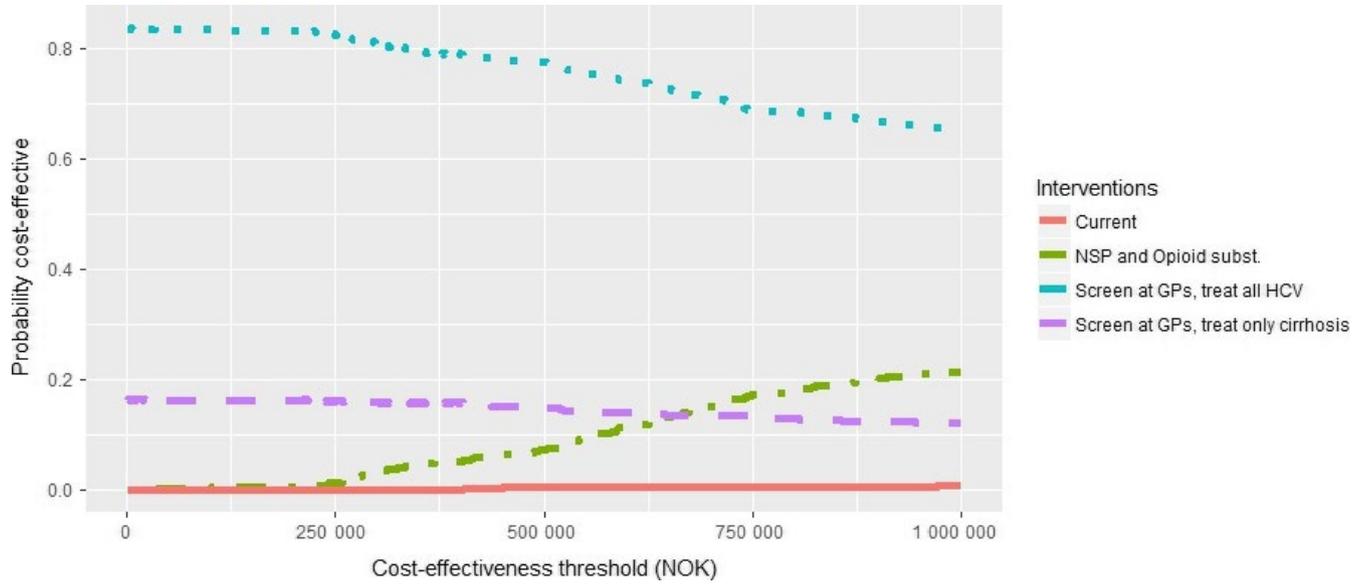


Figure A4 Cost-effectiveness acceptability curve combining all strategies (only strategies with positive probability shown). GP, general practitioner; HCV, Hepatitis C virus positive; NSP, Needle and syringe programme; NOK, Norwegian kroner