European Monitoring Centre
for Drugs and Drug Addiction

TECHNICAL REPORT

Evidence for the effectiveness of interventions to prevent infections among people who inject drugs

Review of mathematical modelling studies of opioid agonist treatment and needle and syringe programmes for preventing hepatitis C transmission

From the package of technical documents published to accompany the joint ECDC and EMCDDA update of the guidance, 'Prevention and control of infectious diseases among people who inject drugs' (2023)

Legal notice

PDF ISBN 978-92-9497-890-5 doi:10.2810/124224 TD-07-23-337-EN-N

Luxembourg: Publications Office of the European Union, 2023

Suggested citation:

European Monitoring Centre for Drugs and Drug Addiction (2023), *Evidence for the effectiveness of interventions to prevent infections among people who inject drugs: Review of mathematical modelling studies of opioid agonist treatment and needle and syringe programmes for preventing hepatitis C transmission*, Technical report, EMCDDA, Lisbon.

About this report

This report was commissioned by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) through contract CT.19.EU4MD.0099.1.0 and was produced by Lara Gordon (University of Bristol [UoB]), Jack Stone (UoB), Hannah Fraser (UoB), Peter Vickerman (UoB), Matthew Hickman (UoB), Sharon Hutchinson (Glasgow Caledonian University [GCU] and Public Health Scotland [PHS]), Norah Palmateer (GCU and PHS).

This technical report is complemented by a second technical report, commissioned by the EMCDDA, entitled *Evidence for the effectiveness of interventions to prevent infections among people who inject drugs: Drug treatment, needle and syringe programmes and drug consumption rooms for preventing hepatitis C, HIV and injecting risk behaviour.*

European Monitoring Centre
for Drugs and Drug Addiction

Praça Europa 1, Cais do Sodré, 1249-289 Lisbon, Portugal
Tel. +351 211210200
info@emcdda.europa.eu | www.emcdda.europa.eu
twitter.com/emcdda | facebook.com/emcdda

Contents

Abbreviations

CI	Confidence interval
DAAs	Direct-acting antivirals
ECDC	European Centre for Disease Prevention and Control
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
HCV	Hepatitis C virus
NSP	Needle and syringe programme
OAT	Opioid agonist treatment
PWID	People who inject drugs
WHO	World Health Organization

Executive summary

This report describes the methods and findings of a systematic review of mathematical modelling studies of the population-level impact of opioid agonist treatment (OAT) and needle and syringe programmes (NSPs) on hepatitis C virus (HCV) transmission among people who inject drugs (PWID). This review is one component of a series of systematic reviews of the literature undertaken to update the European Centre for Disease Prevention and Control (ECDC) and European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) 2011 joint guidance on 'Prevention and control of infectious diseases among people who inject drugs'. Previous guidance did not consider evidence from mathematical modelling studies. The aim of the work was to assess the evidence from mathematical modelling studies relevant to a wide range of European settings of the population-level impact of OAT and NSPs on HCV transmission among PWID.

Methods

We systematically searched PubMed, Web of Science and Embase databases for mathematical modelling studies evaluating the impact of current and/or scaled-up coverage of OAT and NSPs. The search was conducted on 3 December 2020 with no restrictions on language or publication date. The modelling studies identified were included if they presented the impact, in terms of change in HCV prevalence or incidence or new HCV infections averted, of current or scaled-up levels of OAT and/or NSPs. Studies were also included if they considered the impact of HCV treatment with direct-acting antivirals (DAAs) alongside OAT and NSPs. Only studies relevant for European settings were included for this review, that is, modelling studies focused on a European setting or those that did not focus on a specific geographic setting. All references were screened by a second researcher, with discrepancies resolved through discussion with a third reviewer. Each of the included studies was graded based on the model type used in the study and on the quality of the parameterisation of the model with regards to the data sources used to obtain estimates for the efficacy of interventions. Model projections from studies were synthesised descriptively and, where possible, quantitatively using linear regression.

Findings

Primarily due to the number of studies found for each intervention, the evidence from mathematical modelling studies for the individual interventions, that is, OAT and NSPs separately, is not as strong as for the combined interventions. However, the available evidence suggests that the scaling up of OAT and NSPs individually can lead to moderate-to-substantial decreases in HCV incidence at the population level. For example, 50 % OAT coverage could see a reduction in incidence > 31 % at the end of a 14-year study period compared to 0 % OAT coverage, with results of a similar scale observed for NSPs. Although there is uncertainty in the size of the projected impact of OAT in prison settings, studies suggest that a beneficial impact of prison OAT can be achieved on the overall (community and prison) HCV incidence among PWID. The evidence suggests that the combination of OAT and NSPs can have a substantial impact on HCV transmission among PWID. Our quantitative synthesis suggests that, for every 10 % relative reduction in the gap to 100 %, OAT and NSP coverage could reduce HCV incidence by 12 % (95 % confidence interval = 11-13 %). In other words, moderate scale-ups, such as a 40 % reduction in the gap to full (i.e. 100 %) coverage of both OAT and NSPs would lead to substantial reductions in

incidence in the range of 43-52 %. Where available, the evidence suggests that the combination of OAT and NSPs has greater beneficial impact at the population level than would be expected from either intervention on its own. The impact of the scaling up of OAT and NSPs may be greater in settings where HCV incidence is already declining, such as through HCV treatment. While studies suggest the greatest impact would be achieved through the combination of OAT, NSPs and DAA treatment, analyses suggest that OAT and NSPs play a major role in the impact achieved.

Conclusions

Although there is variation in the projected impacts of OAT and NSPs, their scaling up can achieve moderate-to-substantial population-level impacts on HCV transmission among PWID, especially if implemented in combination, and should be recommended alongside DAA treatment. Our quantitative syntheses provide a report of the impact that can be expected of the scaling up of OAT and NSPs and suggest that, regardless of existing coverage, further scale-ups can meaningfully reduce HCV incidence.

Background

The elimination of viral hepatitis as a public health threat has been defined by the World Health Organization (WHO) as a 90 % reduction in the number of new chronic hepatitis B and C infections and a 65 % reduction in the number of deaths by 2030, with milestones for 2020 set at 30 % and 10 % reductions, respectively. The baseline is 2015. The indicators proposed by the WHO to monitor the impact of the elimination strategy include the incidence of hepatitis C virus (HCV) and hepatitis B virus infections and deaths from hepatocellular carcinoma, cirrhosis and chronic liver diseases attributable to HCV and hepatitis B virus infections (WHO, 2017).

In October 2011, the European Centre for Disease Prevention and Control (ECDC) and European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) published joint guidance on 'Prevention and control of infectious diseases among people who inject drugs' (ECDC & EMCDDA, 2011). Seven key interventions were recommended based on a combination of scientific evidence with expert opinion and models of best practice of prevention within the EU/European Economic Area. The guidance was supported by two technical reports (ECDC & EMCDDA, 2011a, 2011b) summarising the evidence for the effectiveness of needle and syringe programmes (NSPs) and of drug treatment, respectively, for preventing HCV, HIV and injecting risk behaviour. A stakeholder survey conducted in 2018 by the ECDC and EMCDDA suggested the need to update the evidence base underpinning the guidance recommendations in order to capture new evidence and to take cognisance of emerging public health topics and new regional/global infectious disease strategies. The ECDC and EMCDDA initiated the update process in 2019 and commissioned an update of the evidence base and a collection of evidence for several new areas.

In order to update the guidance, five packages of work were undertaken:

- an updating of the review of reviews on the effectiveness of NSPs (existing intervention), drug treatments (existing intervention) and drug consumption rooms (new intervention),
- a literature review of modelling studies of the population-level impacts of drug treatments and NSPs (new component),
- a systematic review of interventions that can improve linkage to care and adherence to treatment for hepatitis B virus, HCV, HIV and tuberculosis (new component of the infectious disease treatment intervention),
- a collection of models of practice about linkage to care, adherence to treatment, community-based testing and health promotion (new accompanying report)
- updates to infectious disease testing, infectious disease treatment and health promotion (existing interventions)

The present technical report describes the literature reviews that were undertaken to identify and synthesise the evidence for the second work package listed above. Closely related to this report is another technical report 'Evidence for the effectiveness of interventions to prevent infections among people who inject drugs: Drug treatment, needle and syringe

programmes and drug consumption rooms for preventing hepatitis C, HIV and injecting risk behaviour', which describes a review of empirical studies undertaken to address the first work package. The evidence generated from these two work packages was presented at a meeting of multidisciplinary experts, appointed by the ECDC/EMCDDA, who appraised the evidence, voted on draft recommendations and provided considerations based on practice. A summary report of the discussions from the expert panel meeting and the proposed changes to the draft recommendations arising from these discussions are presented in a separate report (Summary report of discussions and proposed changes to the draft recommendations on interventions to prevent infections among people who inject drugs from the Expert Panel Meeting, 7-8 June 2021).

Methods

Research question

This literature review aims to answer the following research question:

What is the population-level impact from mathematical modelling studies of a) opioid agonist treatment (OAT), b) NSPs and c) the combination of OAT and NSPs with and without direct-acting antiviral (DAA) treatment for HCV on the prevention of HCV transmission among people who inject drugs (PWID)? ([1])

The studies being used for this literature review form a subset of studies for a larger systematic review. A protocol was developed for the larger systematic review, which has been published on PROSPERO (https://www.crd.york.ac.uk/prospero, registration no.: CRD42020224201). Thus, details pertaining to literature searching will refer to those used for the larger systematic review.

PICO and inclusion/exclusion criteria

The research question was formulated according to the Population, Intervention, Comparison and Outcome (PICO) model, as specified below (Table 1).

([1]) This component was not part of the 2011 guidance. The rationale for its inclusion is that mathematical modelling evidence can provide information on the coverage and targeting of an intervention that is required to produce a change in the outcome, which is particularly relevant in the context of the WHO elimination strategy, as policymakers require guidance on how to achieve HCV elimination. Studies were restricted to Europe to accommodate what was feasible with resource and time constraints.

TABLE 1
PICO criteria for the literature review of modelling studies

Population	People who inject drugs (PWID)
Interventions	1. Opioid agonist treatment (OAT) in the community and in prison 2. Needle and syringe programmes (NSPs) 3. OAT (in the community) + NSPs 4. OAT (in the community) + NSPs + direct-acting antiviral (DAA) treatment for hepatitis C virus
Comparators	Pairs of modelled scenarios in which OAT and/or NSP coverage differ
Outcomes	Hepatitis C virus (incidence, prevalence, cases averted)

Inclusion and exclusion criteria are detailed in Table 2.

TABLE 2
Inclusion and exclusion criteria for the literature review of modelling studies

	Inclusion criteria	**Exclusion criteria**
Publication date	No date restrictions	N/A
Language	No language restrictions	N/A
Publication type	Full study publication available	Conference abstracts, repeated/duplicated results
Study design/type	Mathematical modelling studies. These may include cost-effectiveness studies if a mathematical model was used	Statistical modelling studies, reviews of mathematical modelling studies
Geographic region	Studies focusing on countries/regions in Europe were included, as well as studies not focusing on a specific geographic region	Studies only focusing on countries/regions outside of Europe
Study population	People who inject drugs (PWID). This includes former PWID due to the varying definitions of 'currently injecting' used by the studies. This may include subpopulations of PWID, such as incarcerated PWID, young PWID, migrant PWID, homeless PWID, poly-drug injectors and people who inject synthetic opioids	Non-injecting drug users (unless results were presented separately for the PWID subset of the study population)

	Inclusion criteria	Exclusion criteria
Intervention	Interventions as stated in the PICO criteria. If a study considered the effect of needle/syringe sharing by changing the proportion of the population who are sharing, this was considered to be a proxy for an NSP as it is modelled in a similar way	Supervised injection facilities that also supply needles/syringes (unless the effect of the NSP alone can be isolated). Studies that only examined hepatitis C virus treatment scale-up
Study outcomes	Hepatitis C virus incidence/prevalence/percentage cases averted	Studies using other measures of effect. For example, studies examining how interventions affect the reproductive ratio or those only examining the cost-effectiveness of interventions
Study setting/mode of delivery of intervention	All settings for the delivery of interventions were considered, unless a setting constituted an intervention in its own right, where the effects could not be isolated, such as in supervised injection facilities (see the 'Intervention' row above)	N/A

Abbreviation: N/A, not available.

Data sources and search methods

The following databases were searched: PubMed, Web of Science and Embase (via the Ovid platform). The search was conducted on 3 December 2020.

Study selection

Results of searches were stored in EndNote and de-duplicated according to the guide by Bramer et al. (2016). Title/abstract and full-text screening were performed independently by two researchers, with discrepancies resolved through discussion with a third reviewer. One reviewer selected the relevant studies for the EMCDDA literature review from the list of studies accepted for the larger review; one reviewer extracted relevant data from these studies.

Critical appraisal

In the absence of a validated tool to critically appraise mathematical modelling studies, a brief critical appraisal of the studies was designed and undertaken. This process examined the type of model used in the study and assessed the quality of the parameterisation of the model with regards to the data sources used to obtain estimates for the efficacy of interventions. Based on these attributes, studies were graded as 'low' quality (neither model type nor quality of parameterisation were adequate, or they were unclear), 'medium' quality (either model type or quality of parameterisation was adequate) or 'high' quality (both model type and quality of parameterisation were adequate).

Methods for data synthesis

Two key methods were used to synthesise the evidence from the review of mathematical modelling studies: descriptive synthesis and quantitative synthesis.

Descriptive synthesis involves the extraction of key conclusions from each study involved in the review and comparing them in a qualitative manner to get an overall picture of the effect of each intervention at the population level.

Quantitative synthesis uses linear regression analysis to combine results from a large number of intervention scale-up scenarios to gain understanding of how the impact of each intervention varies as the coverage of the intervention is scaled up.

Description of the linear regression analysis

Background

Each data point used in the linear regression analysis considers a comparison between a baseline scenario and a comparison scenario. The baseline scenario does not necessarily refer to the 'status quo' scenario, where all interventions are at the current levels for the relevant location. Rather, the comparison scenario is defined to be one where the relevant interventions are scaled up relative to a specified baseline. For example, for the OAT+NSP intervention, the baseline scenario may have treatment scaled-up relative to the status quo and the comparison scenario will have the same treatment scale-up (i.e., as in the baseline scenario), plus increased OAT+NSP coverage.

For a data point to be eligible, the incidence/prevalence must be reported for a baseline scenario where the coverage of the intervention (e.g. OAT/NSP) is provided and for a comparison scenario where the coverage of the intervention is scaled up.

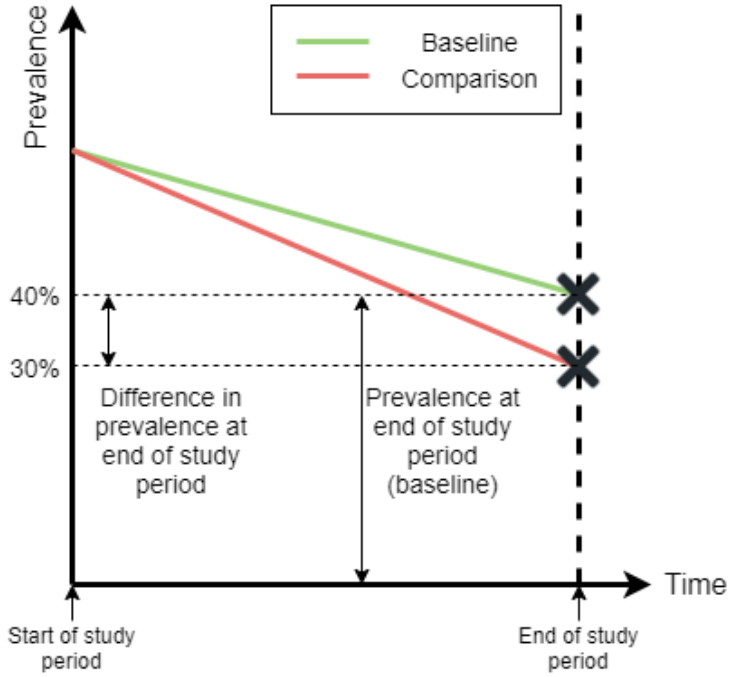
The number of data points included in the quantitative synthesis is not equal to the number of studies. This is because some studies examine many different scale-up scenarios across different locations, leading to multiple data points. The tables in Appendix 1 provide the number of data points that each study contributes to the quantitative synthesis.

Explanatory and response variables

For this analysis, the response variable is the 'relative reduction in incidence/prevalence at the end of the study period between the baseline and comparison scenarios'. For example, if the baseline scenario predicts that HCV prevalence will be 40 % at the end of the study period and the comparison scenario predicts that it will be 30 %, then this corresponds to a reduction of $\frac{(40 - 30) \times 100}{40}$ = 25 %. This is illustrated in Figure 1.

FIGURE 1

Illustrative example of the 'relative reduction in incidence/prevalence at the end of the study period between the baseline and comparison scenarios



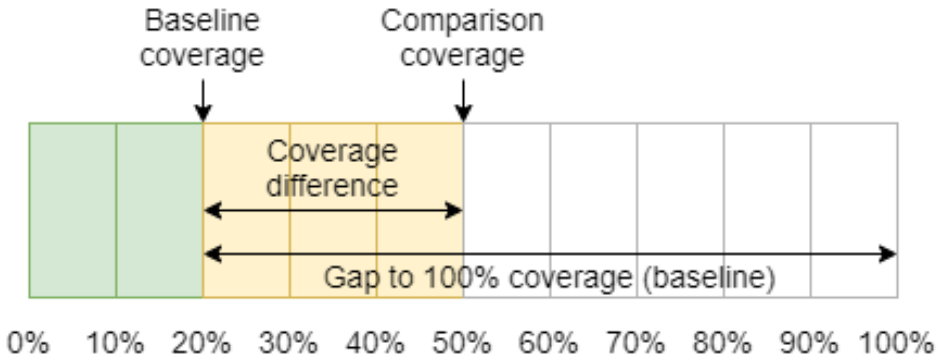
The key explanatory variables in the analysis are measures of the change in coverage of OAT and NSPs and the increase in DAA treatments. Specifically, the OAT and NSP coverages are measured by considering the 'gap to full (100 %) coverage' ([2]). For example, if OAT coverage is at 20 %, then there is a coverage gap to full coverage of 80 % (=100 % − 20 %). To compare the scale-up in coverage between a baseline scenario and a comparison scenario, the 'relative reduction in the gap to full coverage' is used. For example, consider a baseline coverage of 20 % and a comparison scenario where the coverage increases to 50 %, as shown in Figure 2. To calculate the relative reduction in the coverage gap, we examine the coverage increase as a percentage of the coverage gap in the baseline scenario. For this example, this corresponds to a relative reduction in the gap of $\frac{(50 - 20)}{100 - 20} \times 100 = 37.5$ %. Similarly, if the intervention scenario increased the coverage of OAT from 20 % to 60 %, then the coverage gap would be halved: $\frac{(60 - 20)}{100 - 20} \times 100 = 50$ %.

The relative reduction in the gap to full coverage is a useful measure because its value stays between 0 and 100, making comparisons straightforward. Additionally, the measure accounts for both the baseline coverage level and the absolute change in coverage between the baseline and comparison scenarios. This means that the same relative reduction in the gap to full coverage can be achieved with different changes in coverage if the baseline coverage is different. For instance, a 50 % relative reduction in the gap starting from a baseline coverage of 20 % requires a scale-up to 60 % coverage, which is a 40 % absolute

([2]) Note: this measure has been chosen for ease of comparison, not because we advocate 100 % coverage as a goal.

increase. However, the same relative reduction in the gap (i.e. 50 %) starting from 60 % coverage requires a scale-up to 80 % coverage, which is only a 20 % absolute increase. If this variable is linearly associated with the impact on incidence and prevalence (which appears to be the case for the regression models presented here), then this attribute could mean that a fixed increase in the coverage of an intervention could have different levels of impact depending on the baseline coverage.

FIGURE 2
Example explaining 'relative reduction in the gap to full (100 %) coverage'



In this analysis, the regression models have been kept simple, which means that other variables possibly affecting how OAT and NSP coverage impact incidence/prevalence have not been included. However, it is important to be aware that additional factors likely explain some of the variation in the data points. One of these variables is discussed briefly in the Results.

The time horizon (length of the study period) varied across the studies used. This was not taken into account in the models presented here because most data points used similar time horizons of 10-14 years. Possibly due to the small amount of variation in time horizons, there did not appear to be a strong relationship between the outcomes of interest and the time horizon.

The assumed efficacies of interventions at the individual level were also not taken into account in the quantitative synthesis because they were deemed to be sufficiently similar across studies and they were all within the 95 % confidence intervals (CIs) for the estimates found in overview of reviews and primary literature review (Technical report-Evidence for the effectiveness of interventions to prevent infections among people who inject drugs - Drug treatment, needle and syringe programmes and drug consumption rooms for preventing hepatitis C, HIV and injecting risk behaviour). A key point is that the relative risk of HCV infection is lower for OAT than for NSPs, that is, OAT is assumed to have a greater efficacy in the mathematical modelling studies ([3]). This underpins the results presented in Section 3. For information on the time horizons and the intervention efficacies assumed by each study, refer to Appendix 1.

([3]) Across all studies included in the review, the range for the relative risk of HCV transmission for OAT was 0.41-0.48. For NSPs, the range was 0.43-0.59. For both OAT and NSPs, the range was 0.18-0.26.

Results

Fifteen relevant studies were identified (Figure 3).

FIGURE 3
PRISMA flow diagram for the review of mathematical modelling studies

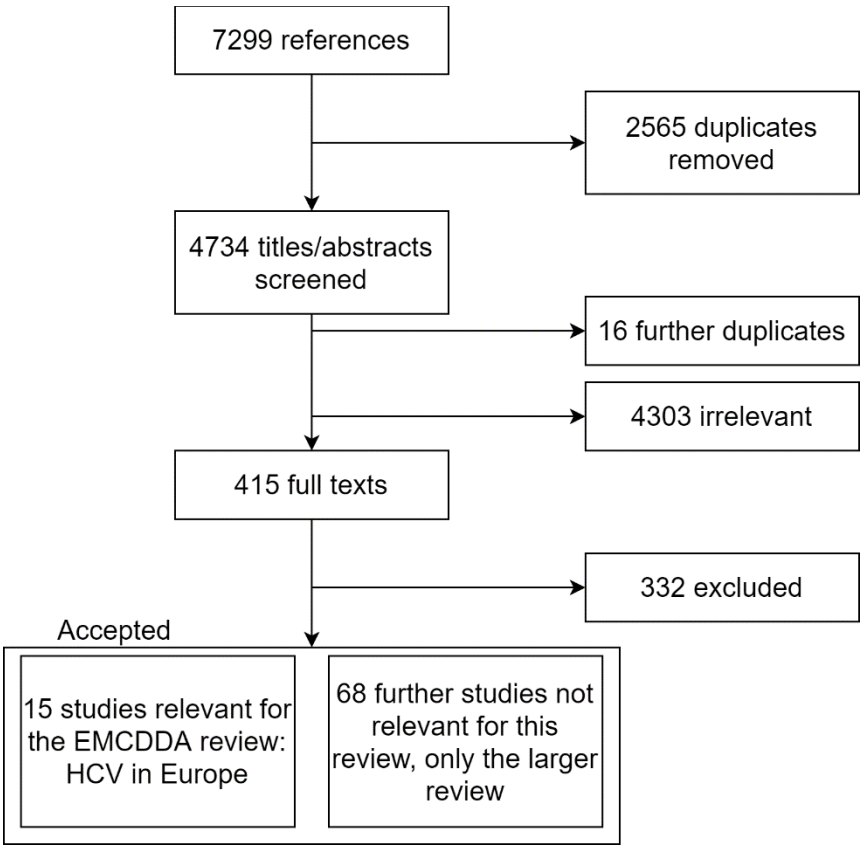


Table 3 summarises the number of studies at each quality grade found for each intervention and the method of data synthesis used to investigate that intervention. Note that descriptive synthesis is always used to supplement quantitative synthesis because not all studies can be included in the quantitative synthesis. For more information on the individual studies included in the review, refer to Appendix 1. This includes reasons for ineligibility for quantitative synthesis, if applicable.

For the purposes of this review, OAT coverage is defined as the percentage of PWID receiving OAT. NSP coverage is defined as the percentage of PWID receiving more than 100 % of their needles/syringes from an NSP service. Note that NSP coverage is defined differently in one study (Borges et al., 2020) and the definition is unclear in another (Wisløff et al., 2018) (Appendix 1). DAA treatment coverage is given as the number treated with DAAs per 1000 PWID per year, independent of the HCV status of the PWID.

TABLE 3
Summary of the studies and data synthesis methods for each intervention

Intervention	Studies and quality grades	Data synthesis method
Opioid agonist treatment (OAT)	Three studies in total: two 'high' grade (Platt et al., 2017; Ward et al., 2018) and one 'low' grade (Wisløff et al., 2018)	Descriptive synthesis
OAT in prisons	Two studies in total, both 'medium' grade (Csete et al., 2016; Stone et al., 2017)	Descriptive synthesis
Needle and syringe programmes (NSPs)	Seven studies in total: three 'high' grade (Fraser et al., 2018a; Platt et al., 2017; Ward et al., 2018), two 'medium' grade (Sweeney et al., 2019; Vickerman et al., 2007) and two 'low' grade (Borges et al., 2020; Wisløff et al., 2018)	Quantitative synthesis with linear regression analysis + descriptive synthesis
OAT+NSPs	Nine studies in total: six 'high' grade (Cousien et al., 2018; Fraser et al., 2018a; Fraser et al., 2018b; Platt et al., 2017; Vickerman et al., 2012; Ward et al., 2018), two 'medium' grade (Gountas et al., 2017; Mabileau et al., 2018) and one 'low' grade (Wisløff et al., 2018)	Quantitative synthesis with linear regression analysis + descriptive synthesis
OAT+NSPs+ direct-acting antiviral (DAA) treatment	Five studies in total: four 'high' grade (Cousien et al., 2018; Fraser et al., 2018a; Martin et al., 2013; Ward et al., 2018) and one 'medium' grade (Gountas et al., 2017)	Quantitative synthesis with linear regression analysis + descriptive synthesis

Throughout the next sections, the linear regression coefficients are referred to simply as 'coefficients'. A coefficient value of 0.8 indicates that an increase of 10 units in the respective explanatory variable leads to an 8 % decrease in incidence/prevalence at the end of the study period ([4]). Similarly, if an explanatory variable has a coefficient of 0.3, then an increase

([4]) In terms of units for the explanatory variables, a 10-unit increase would correspond to a 10 % reduction in the coverage gap for the OAT and NSP measures, or 10 additional treatments per 1000 PWID per year for the DAA measure.

of 10 units in that variable would lead to a 3 % decrease in incidence/prevalence at the end of the study period.

Full details of the regression models discussed in this section can be found in Appendix 2. For information on the key statistics (e.g. mean and standard deviation of coverage measures), refer to Appendix 3.

Opioid agonist treatment

Three studies were identified for the OAT-only intervention. There was an insufficient number of data points for quantitative synthesis (seven for the incidence regression model and six for the prevalence regression model). Therefore, we rely on descriptive synthesis for this intervention.

Two of the studies examined the effect of removing the intervention. The same three UK settings were used in both of these studies (Bristol, Walsall and Dundee), where increasing OAT coverage was assumed. The most recent data for coverage estimates prior to the study period ranged from 70 % to 81 % across settings. Using a model that included both PWID and former PWID, Platt et al. (2017) suggested that, across three UK settings, the current levels of OAT intervention would avert at least 46 % (46-56 % between settings) of new HCV infections compared to a scenario with no OAT over a 15-year period. Ward et al. (2018) presented qualitatively similar results using a model that considers currently injecting PWID only: the current OAT intervention would avert 48-83 % of new HCV infections across settings over a 14-year study period. Additionally, Ward et al. (2018) also reported beneficial impacts of OAT on both incidence and prevalence. In particular, they found that the current levels of OAT would lead to a > 60 % decrease in incidence by the end of the 14-year study period compared to no OAT. The third study, from Wisløff et al. (2018), was based in Norway and reported that the scaling up of OAT from 0 % to 50 % would result in a 69 % decrease in incidence over a 14-year study period, compared to a 55 % decrease with no OAT. This corresponded to an approximate 31 % decrease in incidence at the end of the study period.

Evidence statement: Three mathematical modelling studies project that the scaling up of OAT from 0 % coverage to at least 50 % coverage among PWID would lead to moderate-to-substantial decreases in HCV incidence at the end of the study period (>31 %) and/or in new infections (>46 %) at the population level.

Opioid agonist treatment in prison

Two studies were found to model OAT in a prison setting. Both studies reported the effects of OAT in prison on HCV transmission among all PWID, not just those in prison. Stone et al. (2017) reported that removal of prison OAT at 57 % coverage resulted in a 9.3 % increase in overall incidence among PWID at the end of a 15-year study period, a large effect given that incarcerated PWID make up only 9 % of the overall PWID population. In contrast, Csete et al. (2016) reported much larger effects: going from 57 % OAT coverage to 19 % coverage in prison resulted in a 56 % increase in incidence in the overall PWID population at steady state (i.e. when the epidemic has stabilised).

The results of these studies suggest that there is uncertainty in the projected impact of OAT in a prison setting on overall HCV incidence among PWID. This uncertainty is due to the different assumptions each study makes of the effect of OAT on prison-based transmission, as well as differences in incarceration dynamics and levels of transmission within prison ([5]). However, both studies reported a beneficial impact of prison OAT for coverage levels > 50 % at the level of the whole PWID population.

Evidence statement: While there is uncertainty in the size of the projected impact of OAT in a prison setting on overall HCV incidence among PWID, two mathematical modelling studies reported a beneficial impact of prison OAT coverage levels > 50 % at the level of the whole PWID population.

Needle and syringe programmes

Seven studies were identified for the NSP-only intervention. Of these, three (Fraser et al., 2018a; Ward et al., 2018; Wisløff et al., 2018) had results that could be used for quantitative analysis, with 10 eligible data points for the incidence analysis and 8 for the prevalence analysis. The linear model examining the effects of NSPs on incidence did not obtain a sufficiently good fit to deduce meaningful results about coefficients. However, removal of the data points from low-grade studies (leaving eight data points) resulted in an adequate fit, as illustrated in Figure 4 ([6]). The black line represents the linear model. All studies assume that NSPs have a positive impact at the individual level, which we would expect to extend to the population level. Indeed, this is illustrated by the positive gradient on the graph. This indicates that increasing coverage of NSPs reduces the incidence at the end of the study period compared to what would have happened without the increase in NSP coverage. The gradient of the linear model suggests that, for every 10 % reduction in the NSP coverage gap, there should be a reduction in incidence at the end of the study period of 9.5 % (95 % CI = 7.1-12 %). For example, a reduction in the gap to full NSP coverage by 40 % could lead to reductions in incidence at the end of the study period in the range of 28 % to 48 %. Caution should be taken when interpreting these results due to the small number of data points used to produce the model fit, especially given that the data points from low-grade studies were removed.

There were no eligible data points for prevalence from low-grade studies. Therefore, these data points did not need to be removed (Appendix 2: Figure 9). A comparison of the models suggested that NSPs have an approximate 1.5 times greater effect on incidence than on prevalence for the same decrease in the coverage gap ([7]).

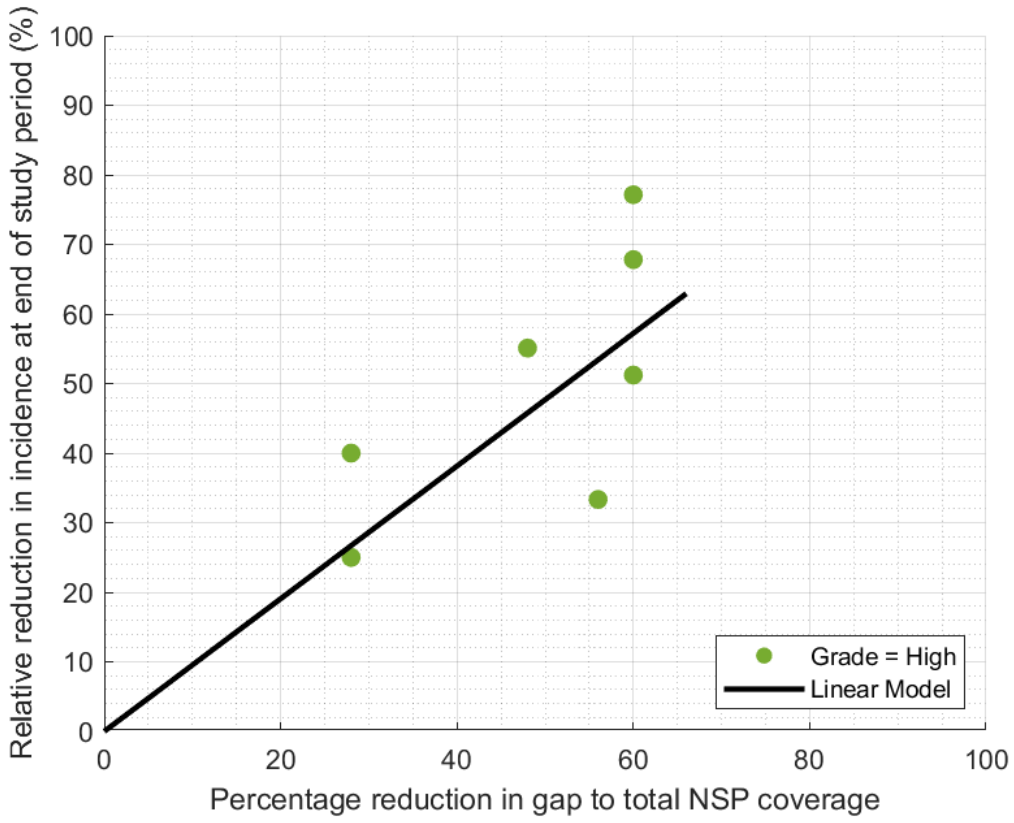
([5]) The impact of prison OAT is also likely to depend upon levels of retention following release from prison (Stone et al., 2021).

([6]) Note that the linear model has been fixed to pass through the origin so that no increase in coverage corresponds to no impact on HCV transmission.

([7]) The incidence model has coefficient = 0.95 (95 % CI = 0.71-1.2, $p = 4.1 \times 10^{-5}$) while the prevalence model has coefficient = 0.64 (95 % CI = 0.35-0.93, $p = 1.2 \times 10^{-3}$). The ratio of the coefficients gives 0.95/0.64 = 1.5 (2 significant figures).

FIGURE 4

Relative reduction in incidence at the end of the study period for various levels of NSP scale-ups. For this linear model, low-grade data points have been removed



Qualitatively, if we use all of the evidence from the NSP evidence table (see Appendix 1), we can see that all studies find that increased NSP coverage reduces HCV transmission. NSPs appear to have the potential for large incidence reductions. For example, two studies (Fraser et al., 2018a; Wisløff et al., 2018) reported more than 50 % reductions in HCV incidence for scale-up coverage levels of 100 % (from 75 %) and 80 % (from 50 %) over time horizons of 14 and 10 years, respectively. The effects on HCV prevalence and the relative reduction appear to be weaker. For example, Vickerman et al. (2007) reported that large and sustained reductions in syringe sharing would be required to reduce prevalence for all PWID. Sweeney et al. (2019) determined that, across three UK settings (Bristol, Walsall and Dundee), 8-40 % of infections could be averted over a 10-year time horizon with current NSP coverage (range, 30-57 % across settings), suggesting a small-to-moderate impact.

Evidence statement: Seven mathematical modelling studies reported beneficial impacts of NSPs on HCV transmission at the population level, although the predicted impact at the population level varies across studies. Limited quantitative evidence suggests that a moderate reduction in the relative gap to full NSP coverage (40 %) would lead to moderate reductions in incidence at the end of the study period (range, 28-48 %). NSPs are likely to have a larger impact on incidence than on prevalence.

Combination OAT+NSPs

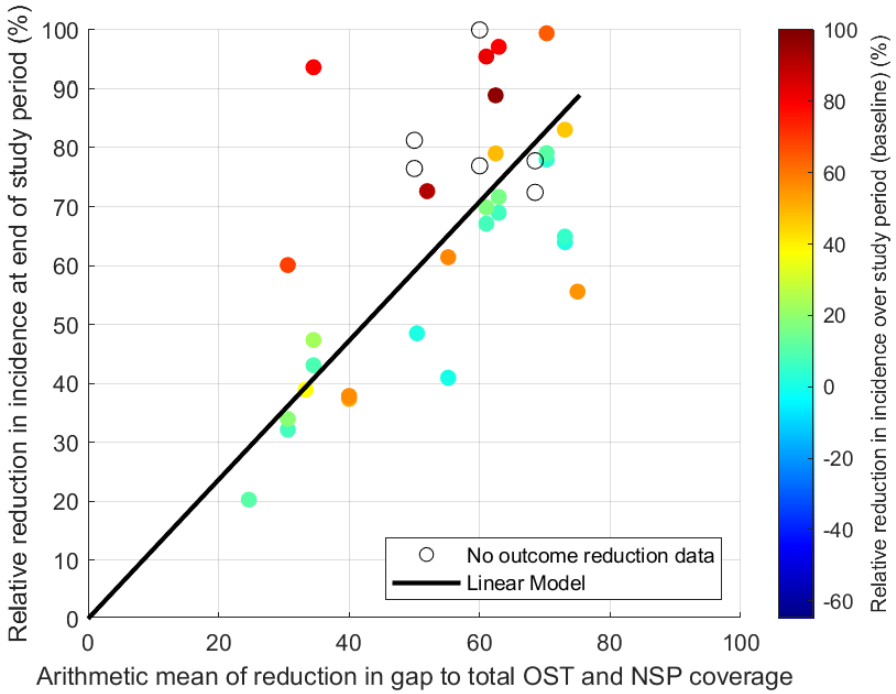
Nine studies were identified for combined OAT+NSPs. Of these, four (Fraser et al., 2018a; Vickerman et al., 2012; Ward et al., 2018; Wisløff et al., 2018) were eligible for inclusion in the quantitative analysis, contributing 36 data points for the incidence analysis and 42 for that of prevalence.

Figure 5 illustrates the relationship between the average reduction in the coverage gap for OAT and NSPs and the relative reduction in HCV incidence achieved. The linear model suggests that, for every 10 % reduction in both the OAT and NSP coverage gaps, there should be a reduction in incidence at the end of the study period of 12 % (95 % CI = 11-13 %). In other words, moderate scale-ups, such as a 40 % reduction in the gap to full coverage of both OAT and NSPs, could lead to substantial reductions in incidence in the range of 43-52 % at the end of the study period.

The data points in Figure 5 are colour coded according to the 'relative reduction in outcome (incidence/prevalence) over the study period in the baseline scenario'. The red points are towards the top of the graph and the blue points are towards the bottom. This suggests that the baseline epidemic trajectory (i.e. changes in incidence/prevalence that are not attributable to increases in intervention coverage) affects the reduction in incidence that can be achieved when OAT and NSPs are scaled up, with OAT and NSPs having greater impact on incidence when incidence is already declining. Similar trends for prevalence are shown in Figure 14 in Appendix 2. These findings underscore the possible effects of additional variables on the relationship between the OAT and NSP scale-up and the impact on incidence/prevalence.

FIGURE 5

Relative reduction in incidence at the end of the study period for various levels of OAT+NSP scale-ups. Data points are colour coded according to the reduction in incidence over the study period in the baseline scenario



We also considered linear regression models that use two explanatory variables, that is, the reduction in coverage gap for both OAT and NSPs separately. Unfortunately, this combined relationship cannot be easily viewed on a two-dimensional graph. In both the incidence and prevalence regression models, OAT has a larger coefficient than NSPs (Appendix 2: Figures 11 and 13). For example, the incidence model predicts that OAT could be 2.6 times more effective than NSPs at the population level ([8]). While it is interesting to try to understand the individual contributions of OAT and NSPs to the combination intervention, we urge caution in interpreting the results here. The result can partially be explained by the fact that studies assume that the relative reduction in the risk of HCV infection is lower with OAT than NSPs (Appendix 1). Additionally, the studies typically explore larger reductions in the coverage gap for OAT than NSPs (on average, 59.8 % versus 49.1 % for incidence and 58.3 % versus 45.5 % for prevalence), which could affect the linear regression coefficients.

All linear regression models analysed for the OAT and NSP combination intervention suggest that the combination intervention will have a larger impact on incidence than on prevalence ([9]).

In terms of the descriptive synthesis of all studies, it is difficult to decipher the relationship between intervention coverage and the effect from separate summaries of the individual studies. However, it is clear that all studies included in the review agree that the combination intervention of OAT and NSPs is associated with reductions in HCV transmission at the population level, with most studies reporting large effects. Additionally, studies (Platt et al., 2017; Ward et al., 2018; Wisløff et al., 2018) examining the OAT and NSP interventions on their own as well as their combination suggest that the combination has more beneficial impacts at the population level than would be expected from either intervention on its own.

Evidence statement: Even with moderate reductions in the coverage gap (40 %), the combined scale-up of OAT and NSPs can have substantial impact on incidence (43-52 % at the end of the study period) at the PWID population level, although the impact on prevalence is smaller. The intervention may have greater impact when HCV incidence/prevalence is already declining.

As discussed above, we found that the reduction in incidence/prevalence over the study period in the baseline scenario was associated with incidence/prevalence reductions at the end of the study period between the baseline and comparison scenarios. Furthermore, we found that the reduction in incidence/prevalence over the study period in the baseline scenario was strongly associated with the baseline coverage of DAA treatment (correlation coefficient = 0.751 for the incidence data points). Therefore, it was deemed appropriate to also investigate the impact of the combination interventions of OAT, NSPs and DAA treatment. This will be explored in the next section.

([8]) The coefficient for OAT is 0.82 (95 % CI = 0.65-1.0, $p = 2.5 \times 10^{-11}$), while the coefficient for NSPs is 0.32 (95 % CI = 0.12-0.52, $p = 0.27 \times 10^{-3}$).

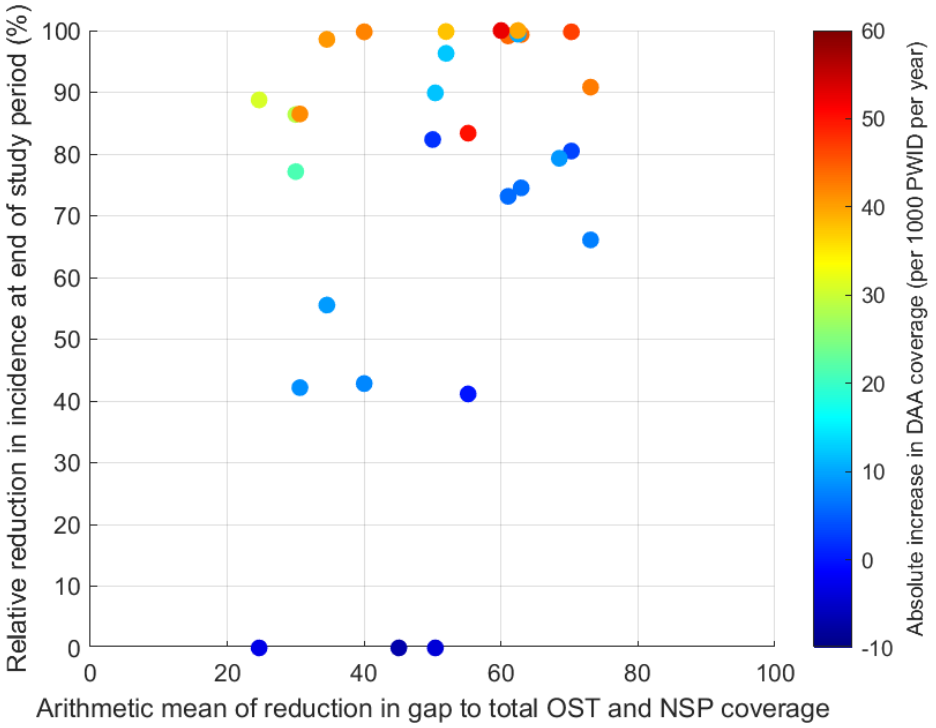
([9]) The incidence model has coefficient = 1.18 (95 % CI = 1.07-1.29, $p = 1.2 \times 10^{-22}$), while the prevalence model has coefficient = 0.82 (95 % CI = 0.70-0.95, $p = 1.5 \times 10^{-16}$). The ratio of the coefficients gives 1.07/0.82 = 1.4 (2 significant figures).

Combination OAT+NSPs+DAAs

Five studies were eligible for the OAT+NSP+DAA combined intervention. Of these, three (Fraser et al., 2018a; Martin et al., 2013; Ward et al., 2018) were eligible for quantitative synthesis. Linear model fitting was restricted to three explanatory variables at most due to the limited number of data points. A linear model was fit for incidence reduction (%) with a relative reduction in the gap (%) for OAT (coefficient = 0.50, 95 % CI = 0.24-0.75, $p = 4.9 \times 10^{-4}$) and NSPs (coefficient = 0.43, 95 % CI = 0.17-0.68, $p = 1.9 \times 10^{-3}$) and an absolute increase in DAA treatments per 1000 PWID per year (coefficient = 1.2, 95 % CI = 0.77-1.6, $p = 3.9 \times 10^{-6}$) as explanatory variables ([10]). The p-values show that all explanatory variables are significant at the 5 % significance level. The effects of OAT and NSPs appear to be weaker for prevalence reduction than for incidence reduction, which is consistent with the results for the OAT+NSP intervention. This is not true for treatment, which has similar coefficient values for both the incidence and prevalence models.

FIGURE 6

Data points used for linear models considering the combination OAT+NSP+DAA intervention, with reduction in incidence as the outcome of interest. Note that there is a strong association with an increase in DAA coverage, as indicated by the colour coding



([10]) Note that the value of the regression coefficient for DAA treatment should not be compared with the value of the regression coefficient for the reduction in the coverage gap for OAT and NSPs because the treatment measure is not a percentage, unlike the OAT and NSP measures. Nonetheless, the p-values are useful for gauging the relative importance of the explanatory variables.

Figure 6 indicates that an absolute increase in DAA coverage of > 20 treatments per 1000 PWID per year and a > 30 % reduction in the gap to full coverage of both OAT and NSPs could result in at least a 70 % decrease in incidence at the end of the study period. Similar results were found for prevalence (Appendix 2: Figure 17).

Caution should be taken when comparing linear model results for OAT+NSPs+DAAs with those from OAT+NSPs because different studies are used to produce the linear models and the nature of the coverage scale-up is different (see Appendix 3).

By reviewing the evidence from all of the studies, we can see that all mathematical models hypothesise that the use of DAA treatment as part of a combined intervention with OAT and NSPs has the potential to substantially reduce both HCV incidence and prevalence, in agreement with the quantitative synthesis. Moreover, studies (Fraser et al., 2018a; Gountas et al., 2017; Martin et al., 2013; Ward et al., 2018) that examined both the OAT+NSP and OAT+NSP+DAA combination interventions concluded that the OAT+NSP+DAA intervention would have the most beneficial impact on HCV transmission.

Evidence statement: The combination intervention with OAT, NSPs and DAA treatment appears to be the most effective intervention examined in this review for reducing HCV transmission. However, OAT and NSPs clearly play a major role and should therefore be recommended for scale-up alongside treatment.

Discussion

Summary of evidence

Table 4 below shows the evidence statements for each intervention considered in this review. Notably, the evidence statement is stongest for the combination of OAT and NSPs, where the number of modelling studies allowed us to quantatively synthesise the evidence, providing estimates of the expected impact from the scaling up of these interventions. Notably, no studies were found to model the impact of NSPs in prison settings.

TABLE 4
Summary of the modelling evidence

Intervention	Evidence statement
Opioid agonist treatment (OAT)	Three mathematical modelling studies project that the scaling up of OAT from 0 % coverage to at least 50 % coverage among people who inject drugs (PWID) would lead to moderate-to-substantial decreases in hepatitis C virus (HCV) incidence at the end of the study period (>31 %) and/or in new infections (>46 %) at the population level
OAT in prisons	While there is uncertainty in the size of the projected impact of OAT in a prison setting on overall HCV incidence among PWID, two mathematical modelling studies reported a beneficial impact of prison

Intervention	Evidence statement
	OAT coverage levels > 50 % at the level of the whole PWID population (community and prison)
Needle and syringe programmes (NSPs)	Seven mathematical modelling studies reported beneficial impacts of NSPs on HCV transmission at the population level, although the predicted impact at the population level varies across studies. Limited quantitative evidence suggests that a moderate reduction in the relative gap to full NSP coverage (40 %) would lead to moderate reductions in incidence at the end of the study period (range, 28-48 %). NSPs are likely to have a larger impact on incidence than on prevalence
OAT+NSP	Even with moderate reductions in the coverage gap (40 %), the combined scale-up of OAT and NSPs can have a substantial impact on incidence (43-52 % at the end of the study period) at the PWID population level, although the impact on prevalence is smaller. The intervention may have greater impact when HCV incidence/prevalence is already declining
OAT+NSP+direct-acting antivirals (DAAs)	The combination intervention with OAT, NSPs and DAAs was the most effective intervention examined in this review for reducing HCV transmission. However, OAT and NSP clearly play a major role and should therefore be recommended for scale-up alongside DAAs

Largely due to the number of studies found for each intervention, the evidence from mathematical modelling studies for the individual interventions (OAT and NSPs separately) is not as strong as for the combined interventions. However, the available evidence suggests that the scaling up of OAT and NSPs individually can lead to moderate-to-substantial decreases in HCV incidence at the population level. Although there is uncertainty in the size of the projected impact of OAT in prison settings, studies suggest that prison OAT can have a beneficial impact on the overall (community and prison) HCV incidence among PWID.

The evidence from modelling studies suggests that the combination of OAT and NSPs can have substantial impact on HCV transmission among PWID. Our quantitative synthesis suggests that every 10 % relative reduction in the gap to 100 % OAT and NSP coverage could reduce HCV incidence by 12 % (95 % CI = 11-13 %). In other words, moderate scale-ups, such as a reduction in the gap to full coverage of both OAT and NSPs by 40 %, could lead to substantial reductions in incidence in the range of 43 % to 52 %. As well as informing coverage levels, a key added benefit of the modelling evidence is its ability to provide information on combination interventions, for which there is less empirical evidence.

Where available, the evidence suggests that the combination of OAT and NSPs has greater beneficial impacts at the population level than would be expected from either intervention on its own. The impact of the scaling up of OAT and NSPs may be greater in settings where HCV incidence is already declining, such as through HCV treatment. While studies suggest that the greatest impact will be achieved through the combination of OAT, NSPs and DAA treatment, analyses suggest that OAT and NSPs play a major role in the impact achieved.

Strengths and limitations

The qualitative synthesis of multiple modelling studies is challenging because each study makes different assumptions and uses different levels of intervention scale-ups. Therefore, quantitative synthesis was used in an attempt to gain clarity on how levels of intervention scale-ups relate to population-level impacts. This novel approach to the synthesis of evidence from modelling reviews allows us to obtain information on the scale-up in intervention coverage levels required to achieve specific reductions in HCV incidence. However, this approach has not been validated and the findings are thus also presented with descriptive syntheses.

Primarily because of the number of studies found for each intervention, the evidence from mathematical modelling studies for the individual interventions (OAT and NSPs separately) is not as strong as for the combined interventions. Due to the heterogeneity among studies and the associated complexities this creates when data synthesis is being conducted, the recommendation based on the modelling evidence is informed by what can be directly interpreted from only the strongest of the quantitative syntheses, that is, analyses of the impact of the combination of OAT and NSPs.

Conclusions

Although there is variation in the projected impacts of OAT and NSPs, a moderate-to-substantial population-level impact on HCV transmission among PWID can be achieved through their scale-up, especially if implemented in combination. Our quantitative syntheses provide a guide of the impact that can be expected of the scaling up of OAT and NSPs and suggest that, regardless of existing coverage, further scale-ups can result in meaningful reductions in HCV incidence. Future work is required to validate the findings of our quantitative synthesis, which could further aid coverage target setting for OAT and NSPs both individually and in combination. Because the existing evidence is limited, further modelling evaluating the population impact of prison-based interventions is needed.

References

Borges, M., Gouveia, M., Fiorentino, F., Jesus, G., Cary, M., Guerreiro, J. P., Costa, S. and Carneiro, A. V. (2020), 'Costs and consequences of the Portuguese needle-exchange program in community pharmacies', *Canadian Pharmacists Journal* 153, pp. 170-178. doi:10.1177/1715163520915744.

Bramer, W. M., Giustini, D., de Jonge, G. B., Holland, L. and Bekhuis, T. (2016), 'De-duplication of database search results for systematic reviews in EndNote', *Journal of the Medical Library Association* 104, pp. 240-243. doi:10.3163/1536-5050.104.3.014.

Cousien, A., Tran, V. C., Deuffic-Burban, S., Jauffret-Roustide, M., Mabileau, G., Dhersin, J. S. and Yazdanpanah, Y. (2018), 'Effectiveness and cost-effectiveness of interventions targeting harm reduction and chronic hepatitis C cascade of care in people who inject drugs: the case of France', *Journal of Viral Hepatitis* 25, pp. 1197-1207. doi:10.1111/jvh.12919.

Csete, J., Kamarulzaman, A., Kazatchkine, M., Altice, F., Balicki, M., Buxton, J., Cepeda, J. et al. (2016), 'Public health and international drug policy', *Lancet* 387, pp. 1427-1480. doi:10.1016/S0140-6736(16)00619-X.

European Centre for Disease Prevention and Control (ECDC) and European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) (2011), *Prevention and control of infectious diseases among people who inject drugs*, Stockholm, ECDC. Available at: https://www.ecdc.europa.eu/en/publications-data/ecdc-and-emcdda-technical-guidance-prevention-and-control-infectious-diseases-0

ECDC and EMCDDA (2011a), Evidence for the effectiveness of interventions to prevent infections among people who inject drugs. Part 1: Needle and syringe programmes and other interventions for preventing hepatitis C, HIV and injecting risk behaviour, Stockholm, ECDC.

ECDC and EMCDDA (2011b), Evidence for the effectiveness of interventions to prevent infections among people who inject drugs. Part 2: Drug treatment for preventing hepatitis C, HIV and injecting risk behaviour, Stockholm, ECDC.

Fraser, H., Martin, N. K., Brummer-Korvenkontio, H., Carrieri, P., Dalgard, O., Dillon, J., Goldberg, D. et al. (2018a), 'Model projections on the impact of HCV treatment in the prevention of HCV transmission among people who inject drugs in Europe', *Journal of Hepatology* 68, pp. 402-411. doi:10.1016/j.jhep.2017.10.010.

Fraser, H., Mukandavire, C., Martin, N. K., Goldberg, D., Palmateer, N., Munro, A., Taylor, A. et al. (2018b), 'Modelling the impact of a national scale-up of interventions on hepatitis C virus transmission among people who inject drugs in Scotland', *Addiction* 113, pp. 2118-2131. doi:10.1111/add.14267.

Gountas, I., Sypsa, V., Anagnostou, O., Martin, N., Vickerman, P., Kafetzopoulos, E. and Hatzakis, A. (2017), 'Treatment and primary prevention in people who inject drugs for chronic hepatitis C infection: is elimination possible in a high-prevalence setting?', *Addiction* 112, pp. 1290-1299. doi:10.1111/add.13764.

Mabileau, G., Scutelniciuc, O., Tsereteli, M., Konorazov, I., Yelizaryeva, A., Popovici, S., Saifuddin, K. et al. (2018), 'Intervention packages to reduce the impact of HIV and HCV infections among people who inject drugs in Eastern Europe and Central Asia: a modeling and cost-effectiveness study', *Open Forum Infectious Diseases* 5, ofy040. doi:10.1093/ofid/ofy040.

Martin, N. K., Hickman, M. Hutchinson, S. J., Goldberg, D. J. and Vickerman, P. (2013), 'Combination interventions to prevent HCV transmission among people who inject drugs: modeling the impact of antiviral treatment, needle and syringe programs, and opiate substitution therapy', *Clinical Infectious Diseases,* 58 Suppl2, pp. S39-S45. doi:10.1093/cid/cit296.

Platt, L., Sweeney, S., Ward, Z., Guinness, L., Hickman, M., Hope, V., Hutchinson, S. et al. (2017), *Assessing the impact and cost-effectiveness of needle and syringe provision and opioid substitution therapy on hepatitis C transmission among people who inject*

drugs in the UK: an analysis of pooled data sets and economic modelling. Public Health Research, 5.5. doi:10.3310/phr05050.

Stone, J., Fraser, H., Young, A. M., Havens, J. R. and Vickerman, P. (2021), 'Modeling the role of incarceration in HCV transmission and prevention amongst people who inject drugs in rural Kentucky', *International Journal of Drug Policy* 88, pp. 102707. doi:10.1016/j.drugpo.2020.102707.

Stone, J., Martin, N. K., Hickman, M., Hutchinson, S. J., Aspinall, E., Taylor, A., Munro, A. et al. (2017), 'Modelling the impact of incarceration and prison-based hepatitis C virus (HCV) treatment on HCV transmission among people who inject drugs in Scotland', *Addiction* 112, pp. 1302-1314. doi:10.1111/add.13783.

Sweeney, S., Ward, Z., Platt, L., Guinness, L., Hickman, M., Hope, V., Maher, L. et al. (2019), 'Evaluating the cost-effectiveness of existing needle and syringe programmes in preventing hepatitis C transmission in people who inject drugs', *Addiction* 114, pp. 560-570. doi:10.1111/add.14519.

Vickerman, P., Hickman, M. and Judd, A. (2007), 'Modelling the impact on Hepatitis C transmission of reducing syringe sharing: London case study', *International Journal of Epidemiology* 36, pp. 396-405. doi:10.1093/ije/dyl276.

Vickerman, P., Martin, N., Turner, K. and Hickman, M. (2012), 'Can needle and syringe programmes and opiate substitution therapy achieve substantial reductions in hepatitis C virus prevalence? Model projections for different epidemic settings', *Addiction* 107, pp. 1984-1995. doi:10.1111/j.1360-0443.2012.03932.x.

Ward, Z., Platt, L., Sweeney, S., Hope, V. D., Maher, L., Hutchinson, S., Palmateer, N. et al. (2018), 'Impact of current and scaled-up levels of hepatitis C prevention and treatment interventions for people who inject drugs in three UK settings-what is required to achieve the WHO's HCV elimination targets?', *Addiction* 113, pp. 1727-1738. doi:10.1111/add.14217.

Wisløff, T., White, R., Dalgard, O., Amundsen, E. J., Meijerink, H. and Kløvstad, H. (2018), 'Feasibility of reaching world health organization targets for hepatitis C and the cost-effectiveness of alternative strategies', *Journal of Viral Hepatitis* 25, pp. 1066-1077. doi:10.1111/jvh.12904.

WHO (2017), *Action plan for the health sector response to viral hepatitis in the WHO European Region*, World Health Organization, Geneva.

Appendix 1. Tables summarising the evidence from each study

Three articles use the same basic model (Platt et al., 2017; Sweeney et al., 2019; Ward et al., 2018) but with slight differences in implementation. For example, Platt et al. (2017) includes former PWID, unlike Ward et al. (2018). Moreover, the results are reported over different time periods and for different outcome measures. Therefore, they are treated separately in this review.

Data points were considered ineligible for inclusion in the linear regression analysis if the incidence/prevalence reduction over the study period in the baseline scenario exceeded 99 %, the incidence was less than 0.1 per 100 person-years at the end of the study period or the prevalence was less than 0.1 % at the end of the study period. This is because accurate results for the relative reduction in incidence/prevalence at the end of the study period between a baseline and comparison scenario cannot be calculated when baseline incidence/prevalence is very low. These data points were removed after the data point count for each study was made.

OAT

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
First author and year: Platt et al., 2017 **Location:** Bristol, Dundee, Walsall (United Kingdom) **Time period(s) modelled:** 15 years (2016-2031) **Outcome(s):** Percent reduction in new cases **Study grade:** High	Dynamic deterministic model of HCV transmission and disease progression	Relative risks of HCV transmission of 0.41 (0.22-0.75) for OAT, 0.59 (0.36-0.96) for NSPs and 0.26 (0.09-0.64) for OAT+NSPs	No. There were not enough data points suitable for the OAT analysis; therefore, quantitative analysis was not performed	Under the baseline scenario, OAT coverage increased in all settings. The most recent data for coverage estimates prior to the study period ranged from 70 % to 81 % across settings. Across the three settings, removal of OAT would result in at least an 86 % (range, 86-125 % between settings) increase in the number of new infections by 2031. Note that the effects of OAT are more marked than those of NSPs (refer to NSP sections for more details). The authors' overall conclusions relate to the interaction of OAT with NSPs. Refer to the table on the combined OAT+NSP intervention for details

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
				Note: the modelled population includes former PWID
First author and year: Ward et al., 2018 **Location:** Bristol, Dundee, Walsall (United Kingdom) **Time period(s) modelled:** 14 years (2016-2030) **Outcome(s):** Incidence, prevalence, percent reduction in new cases **Study grade:** High	Dynamic deterministic model of HCV transmission and disease progression	Relative risks of HCV transmission of 0.41 (0.22-0.75) for OAT, 0.59 (0.36-0.96) for NSPs and 0.26 (0.09-0.64) for OAT+NSPs. DAA efficacy sampled from a uniform distribution (0.86-0.92)	No. There were not enough data points suitable for the OAT analysis; therefore, quantitative analysis was not performed	Under the baseline scenario, OAT coverage increased in all settings. The most recent data for coverage estimates prior to the study period ranged from 72 % to 81 % across settings. Removal of OAT would increase the number of new HCV infections over the time period by 92-483 % across locations. However, the scaling up of OAT to 80 % coverage would result in a 49 % decrease in new infections in Walsall and Bristol, with even more substantial decreases in Dundee due to existing levels of treatment Note that the effects of OAT are more marked than those of NSPs (refer to the NSP section for more details)
First author and year: Wisløff et al., 2018 **Location:** Norway **Time period(s) modelled:** 14 years (2016-2030) **Outcome(s):** Incidence **Study grade:** Low	Compartmental Markov model	Odds ratio for the effect of OAT of 0.41 (0.21-0.82); adjusted odds ratio for the effect of NSPs of 0.48 (0.24-0.93). Appears to compare > 100 % coverage with < 100 % for NSPs	No. There were not enough data points suitable for the OAT analysis; therefore, quantitative analysis was not performed	This study was primarily a cost-effectiveness study that also included impact projections The modelling suggested that the scaling up of OAT from 0 % to 50 % would result in a 69 % decrease in incidence over the study period. Note that this is less than the reported incidence reductions for NSPs (see the NSP section for more details)

OAT in prison

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
First author and year: Csete et al., 2016 **Location:** Scotland, Australia, Ukraine and Thailand **Time period(s) modelled:** Not specified **Outcome(s):** Incidence **Study grade:** Medium	Dynamic deterministic HCV transmission model	Efficacy of OAT not specified	No. There were not enough data points suitable for the analysis of OAT in prison; therefore, quantitative analysis was not performed	Rather than directly comparing various levels of prison OAT, the modelling compares four scenarios similar to Scotland, Australia, Ukraine and Thailand, which have varying levels of prison OAT, as well as other changes in risk. The authors note that Australia has similar incarceration rates and durations to Scotland but that a lower level of prison OAT (19 % coverage in Australian prisons versus 57 % in Scotland) correlates with a high HCV incidence among incarcerated PWID. This corresponds to an incidence of 12.3 per 100/year in Scotland and 19.2 per 100/year in Australia, a 56 % increase
First author and year: Stone et al., 2017 **Location:** Scotland **Time period(s) modelled:** 15 years (2015-2030) **Outcome(s):** Incidence, prevalence **Study grade:** Medium	Dynamic deterministic model of incarceration and HCV transmission	Efficacy of OAT not specified – comparison made by considering HCV in scenarios where OAT was and was not implemented	No. There were not enough data points suitable for the analysis of OAT in prison; therefore, quantitative analysis was not performed	With existing treatment and OAT coverage in prison (57 %), incidence and chronic prevalence could be reduced among all PWID by 10.7 % and 9.7 % over the study period, respectively. However, without prison OAT, these figures become 3.1 % and 4.7 %, respectively The authors note that, although their projections 'suggest that existing prison OAT may be having little impact on the overall epidemic due to the low proportion (9 %) of PWID in prison at any point in time, it is still likely to be cost-effective because of the large reduction in HCV incidence and other benefits achieved'

NSPs

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
First author and year: Borges et al., 2020 **Location:** Portugal **Time period(s) modelled:** 2015-2019, results reported in 1-year increments **Outcome(s):** Percent reduction in new cases (over 5 years), cases averted **Study grade:** Low	Equation for number of new infections as a function of disease prevalence, probability of effective cleaning of drug injecting equipment, number of needles in circulation, sharing rate, probability of infection per single injection with infected needle, number of individuals sharing the same needle	Sharing rate in status quo scenario taken in range of 1 % to 9 %. Change in sharing rate in intervention scenario taken in range of −7.7 % to 3.7 %. Note that coverage between baseline and comparison is provided as the percent increase in needles exchanged	No. Results were not reported for incidence/prevalence	Over the 5-year study period, there was a 6.8 % reduction in new HCV infections due to the participation of community pharmacies in the national needle exchange programme. In 1 year, the intervention was estimated to increase the number of needles in circulation by 7 %. For subsequent years, a stable 14 % increase from baseline was assumed. The focus of this study was cost-effectiveness; therefore, the authors' conclusions do not focus on impact. However, they recognise that the inclusion of community pharmacies in the needle exchange programme reduces HCV (and HIV) infections while saving money for their health system
First author and year: Fraser et al., 2018 **Location:** France (study considers other countries, but only France is relevant for NSPs)	Dynamic deterministic HCV transmission model	Relative risks of infection of 0.42 (0.3-0.53) for OAT, 0.43 (0.15-0.70) for NSPs and 0.18 (0.04-0.32) for OAT+NSPs	Yes. Three data points were used for the analysis of incidence and three for the	This study does not focus on the NSP as an intervention on its own but on the combinations OAT+NSPs and OAT+NSPs+DAAs. Refer to these sections for more details. The OAT+NSPs scenarios examine the impact of the scaling up of both of these interventions to 80 % coverage

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
Time period(s) modelled: 10 years (2016-2026) **Outcome(s):** Incidence, prevalence **Study grade:** High			analysis of prevalence	There are scenarios for France where only NSPs are scaled up to 80 % because OAT is already at the desired 80 % coverage at baseline Under scenarios where treatment coverage is at the status quo level (with DAAs), no NSP scale-up would result in incidence and prevalence reductions of 5.9 % and 6.7 %, respectively. Conversely, with an NSP scale-up from 50 % to 80 %, there would be reductions of 54.1 % and 35.5 %, respectively. Results with varying levels of underlying treatment coverage are included in the quantitative analysis
First author and year: Platt et al., 2017 **Location:** Bristol, Dundee, Walsall (United Kingdom) **Time period(s) modelled:** 15 years (2016-2031) **Outcome(s):** Percent reduction in new cases **Study grade:** High	Dynamic deterministic model of HCV transmission and disease progression	Relative risks of HCV transmission of 0.41 (0.22-0.75) for OAT, 0.59 (0.36-0.96) for NSPs and 0.26 (0.09-0.64) for OAT+NSPs	No. Results were not reported for incidence/prevalence separately for each location	Under the baseline scenarios, NSP coverage remained stable in Bristol and Walsall but increased in Dundee. Prior to the study period, the most recent coverage estimates ranged between 38 % and 60 % across settings. Removal of NSPs would result in at least a 22 % (range, 22-59 % between settings) increase in the number of new infections by 2031. The authors' overall conclusions relate to the interaction of NSPs with OAT. Refer to the table on the combined OAT+NSP intervention for details. Note that the effect of NSPs is not as significant as the effect of OAT (refer to OAT sections for more details)
First author and year: Sweeney et al., 2019 **Location:** Bristol, Dundee, Walsall (United Kingdom)	Dynamic deterministic model of HCV transmission	Relative risks of HCV transmission of 0.41 (0.22-0.75) for OAT, 0.59 (0.36-0.96) for	No. Results were not reported for incidence/prevalence	This study compared the current NSP provision with a scenario in which NSPs were removed for 10 years. The model predicts that 8 % of infections in Bristol and Walsall and 40 % of infections in Dundee could be averted by continuing the current

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
Time period(s) modelled: 10 years (2016-2026) **Outcome(s):** Percent reduction in new cases **Study grade:** Medium	and disease progression	NSPs and 0.26 (0.09-0.64) for OAT+NSPs		NSP provision, with a range of 30-57 % across settings. This study focused on cost-effectiveness and the conclusions thus do not focus on impact. However, NSPs are deemed to be a 'highly effective low-cost intervention to reduce hepatitis C transmission'
First author and year: Vickerman et al., 2007 **Location:** London (United Kingdom) **Time period(s) modelled:** 8 years **Outcome(s):** Prevalence **Study grade:** Medium	Dynamic deterministic model of HCV transmission	Transmission rate per syringe sharing event in the chronic phase – varied between scenarios	No. The scenarios modelled could not be compared in a way compatible with the quantitative analysis	Rather than directly examining NSPs, this article examined prevention strategies that would reduce syringe sharing. The study also examined the relationship between the duration of injecting and the efficacy of these prevention strategies. The results showed that 'modest reductions in syringe sharing frequency (<25 %) will reduce the HCV seroprevalence in newly initiated [PWID] (injecting less than four years) but much larger and sustained reductions (>50 %) are required to reduce the HCV seroprevalence in long-term [PWID] (injecting more than 8 years)'. The authors stress that it is important for these intervention strategies to target all PWID, not just longer-term injectors, to achieve substantial reductions in HCV seroprevalence
First author and year: Ward et al., 2018 **Location:** Bristol, Dundee, Walsall (United Kingdom) **Time period(s) modelled:** 14 years (2016-2030)	Dynamic deterministic model of HCV transmission and disease progression	Relative risks of HCV transmission of 0.41 (0.22-0.75) for OAT, 0.59 (0.36-0.96) for NSPs and 0.26 (0.09-0.64) for OAT+NSPs. DAA efficacy sampled from a	Yes. Six data points were used for the analysis of incidence and six for the analysis of prevalence	In the baseline scenarios, NSP coverage ranged between 28 % and 56 % across study settings prior to the study period. Removal of NSPs would increase the number of new HCV infections over the study period by 23-64 % across locations. However, the scaling up of NSPs would reduce new infections by about 29 % in Bristol and Walsall, with more significant reductions in Dundee due to existing levels of treatment. Note

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
Outcome(s): Incidence, prevalence, percent reduction in new cases **Study grade:** High		uniform distribution (0.86-0.92)		that the effect of NSPs was not as significant as the effect of OAT (refer to OAT sections for more details)
First author and year: Wisløff et al., 2018 **Location:** Norway **Time period(s) modelled:** 14 years (2016-2030) **Outcome(s):** Incidence **Study grade:** Low	Compartmental Markov model	Odds ratio for the effect of OAT of 0.41 (0.21-0.82); adjusted odds ratio for the effect of NSPs of 0.48 (0.24-0.93). Appears to compare > 100 % coverage with < 100 % for NSPs	Yes. Two data points were used for the analysis of incidence	This study is primarily a cost-effectiveness study that also includes impact projections The modelling suggested that the scaling up of NSPs to more than 100 % coverage from 75 % would result in a 74 % decrease in incidence over the study period. Note that this is more than the reported incidence reductions for OAT (see OAT sections for more details)

OAT+NSPs

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
First author and year: Cousien et al., 2018 **Location:** France **Time period(s) modelled:** 20 years **Outcome(s):** Cases averted **Study grade:** High	Dynamic, individual-based, stochastic model of HCV transmission, , cascade of care and health outcomes	Relative risks of infection of 0.5 for NSPs and 0.21 for OAT+NSPs. Efficacy of 0.95 for DAAs	No. Results were not reported for incidence/prevalence	Rather than directly examining changing coverage of OAT and NSPs, this study examined the effect of a reduction in the time to initiation of these interventions from injecting initiation. We can calculate that the model predicts that improved access to OAT and NSPs corresponds to a 4.1 % reduction in new HCV infections The article is a cost-effectiveness study that primarily focuses on the combination of OAT and NSP interventions with improved access to HCV treatment. Refer to the table on the combined OAT+NSP+DAA intervention for details
First author and year: Fraser et al., 2018a **Location:** Amsterdam (Netherlands), Belgium, Czechia, Denmark, Finland, Hamburg (Germany), Norway, Scotland, Slovenia, Sweden **Time period(s) modelled:** 10 years (2016-2026) **Outcome(s):** Incidence, prevalence **Study grade:** High	Dynamic deterministic HCV transmission model	Relative risks of infection of 0.42 (0.3-0.53) for OAT, 0.43 (0.15-0.70) for NSPs and 0.18 (0.04-0.32) for OAT+NSPs	Yes. Thirty data points were used for the analysis of incidence and thirty for the analysis of prevalence	The scaling up of OAT and NSPs to 80 % coverage could achieve reductions in incidence of 37.2-89.2 % over the study period across scenarios and in prevalence of 17.6-78.6 %, with underlying treatment at the status quo level (with DAAs). Without the scale-up of OAT and NSPs, these figures are 0.1-52.6 % and 0.1-51.8 %, respectively Results for different underlying treatment rates are included in the quantitative analysis

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
First author and year: Fraser et al., 2018b **Location:** Scotland **Time period(s) modelled:** 7 years (2008-2015) **Outcome(s):** Incidence **Study grade:** High	Dynamic deterministic HCV transmission model	Relative risks of infection of 0.48 (0.17-1.33) for OAT, 0.5 (0.22-1.12) for NSPs and 0.21 (0.08-0.52) for OAT+NSPs	No. The coverage data were not compatible for comparison with the other studies	Rather than comparing fixed coverages of interventions, this study examined the historical scale-up of various interventions and identified how each individual intervention contributed to the observed decrease in HCV transmission. This involved comparing scenarios where there is no intervention scale-up with scenarios where individual and combination interventions are scaled up. No change in the intervention scale-up would have led to a 27.4 % decrease in incidence over the study period, whereas the scaling up of OAT and NSPs only would lead to a 47.3 % decrease in incidence. This corresponds to a 27.4 % decrease in incidence at the end of the study period, using no intervention scale-up as the baseline Additionally, the authors attribute most of the observed decline in HCV incidence to the scale-up of OAT and NSPs Note: The study also examines HCV treatment, but this is with pegylated interferon and ribavirin rather than DAAs, so it is not relevant for this review
First author and year: Gountas et al., 2017 **Location:** Athens (Greece) **Time period(s) modelled:** 14 years (2016-2030)	Dynamic, discrete time, stochastic, individual-based HCV transmission model	Relative risk of HCV infection while in a harm reduction programme of 0.41. Harm reduction programme defined ambiguously but	No. The coverage data were not compatible for comparison with the other studies	This study focuses on the combination of harm reduction (OAT and NSPs) with HCV treatment, but the effect of increasing harm reduction is isolated for some constant treatment coverages. Under a moderate treatment coverage (4 % PWID/year), increasing harm reduction by 2 %/year for the duration of the study period would

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
Outcome(s): Incidence, prevalence **Study grade:** Medium		suggests OAT or a high-coverage NSP		result in a 5.1 % absolute decrease in chronic HCV prevalence and a 19.2 % lower incidence in 2030 compared to constant harm reduction. Under high treatment coverage (8 % PWID/year), the figures are 1 % and 38 %, respectively. For conclusions regarding the combined effect of harm reduction and treatment, refer to the table on the combined OAT+NSP+DAA intervention
First author and year: Mabileau et al., 2018 **Location:** Belarus, Georgia, Kazakhstan, Republic of Moldova, Tajikistan **Time period(s) modelled:** 20 years (2013-2033) **Outcome(s):** Percent reduction in new cases **Study grade:** Medium	Dynamic deterministic model of HCV and HIV transmission and the natural history of these diseases	Relative risk of transmission of 0.5 for a 100 % NSP; relative risk of injection of 0.17 (0.15-0.85) for OAT	No. Results were not reported for incidence/prevalence	This is a cost-effectiveness study that also reports the impact of interventions. Compared to the other interventions examined (increasing NSPs only, increasing HCV treatment), it was found that increasing OAT and NSP coverage (OAT increased to 20 %, NSPs increased to 60 %) had a 'high impact' among PWID, with infections averted among locations ranging from 42 % (in Tajikistan) to 55 % (in Republic of Moldova)
First author and year: Platt et al., 2017 **Location:** Bristol, Dundee, Walsall (United Kingdom) **Time period(s) modelled:** 15 years (2016-2031) **Outcome(s):** Percent reduction in new cases	Dynamic deterministic model of HCV transmission and disease progression	Relative risk of HCV transmission of 0.41 (0.22-0.75) for OAT, 0.59 (0.36-0.96) for NSPs and 0.26 (0.09-0.64) for OAT+NSPs	No. Results were not reported for incidence/prevalence separately for each location	Across the three settings, removal of OAT and NSPs would increase the number of new infections by 2031 by at least 125 % (range, 125-166 % between settings). Removal of OAT would result in at least an 86 % (86-125 %) increase and removal of NSPs would result in at least a 22 % (22-59 %) increase. The scaling up of NSPs to 80 % coverage was predicted to reduce the number of new infections by at least 10 % (10-26 %). The authors conclude that current levels of

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
Study grade: High				interventions are 'preventing considerable transmission of HCV infection in these cities'. Furthermore, the benefits of the combined OAT and NSP interventions increase the impact more than would be expected from each intervention on its own
First author and year: Vickerman et al., 2012 **Location:** General locations with 20 %, 40 % and 60 % baseline prevalence, as well as the United Kingdom **Time period(s) modelled:** Various, from 5 to 20 years **Outcome(s):** Prevalence **Study grade:** High	Dynamic deterministic HCV transmission model	Relative risks of infection of 0.48 (0.17-1.33) for OAT, 0.5 (0.22-1.12) for NSPs and 0.21 (0.08-0.52) for OAT+NSPs	Yes. Nine data points were used for the analysis of prevalence. Only results for time periods of 10 and 20 years could be extracted for inclusion in the quantitative analysis	For a 40 % baseline prevalence, the scaling up of OAT and NSPs from 0 % to 20 %, 40 % or 60 % would result in prevalence reductions of 13 %, 24 % and 33 %, respectively, over 10 years. For higher prevalence settings, there is less impact In the United Kingdom, no OAT and NSPs would result in a prevalence of 65 % compared to the reported 40 % The authors suggest that OAT and NSPs can reduce HCV prevalence among PWID. However, scale-up needs to be sustained at high levels for long periods of time for substantial reductions (over half), such as the scaling up of OAT and NSP coverage from 50 % to 80 % for at least 20 years
First author and year: Ward et al., 2018 **Location:** Bristol, Dundee, Walsall (United Kingdom) **Time period(s) modelled:** 14 years (2016-2030)	Dynamic deterministic model of HCV transmission and disease progression	Relative risks of HCV transmission of 0.41 (0.22-0.75) for OAT, 0.59 (0.36-0.96) for NSPs and 0.26 (0.09-0.64) for OAT+NSPs. DAA efficacy sampled from a	Yes. Nine data points were used for the analysis of incidence and six for the analysis of prevalence	Removal of both OAT and NSPs would result in an increase in new infections over the study period of 132-878 % across locations, corresponding to approximately 350 % and 433 % increases in incidence at the end of the study period in Bristol and Walsall, with more substantial relative increases in Dundee due to low incidence in the baseline scenario. If OAT and NSPs were scaled up to 80 %, this would reduce incidence at the end

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
Outcome(s): Incidence, prevalence, percent reduction in new cases **Study grade:** High		uniform distribution (0.86-0.92)		of the study period by approximately 20 % and 49 % in Bristol and Walsall, with decreases in Dundee less clear due to low baseline incidence. These results emphasise the importance of OAT and NSPs for reducing HCV transmission
First author and year: Wisløff et al., 2018 **Location:** Norway **Time period(s) modelled:** 14 years (2016-2030) **Outcome(s):** Incidence **Study grade:** Low	Compartmental Markov model	Odds ratio for the effect of OAT of 0.41 (0.21-0.82); adjusted odds ratio for the effect of NSPs of 0.48 (0.24-0.93). Appears to compare > 100 % coverage to < 100 % for NSPs	Yes. One data point was used for the analysis of incidence	This study is primarily a cost-effectiveness study that includes impact projections Regarding harm reduction strategies, the authors conclude 'combining an increase in the current clean [NSP] with OAT was clearly the most cost-effective options'. This strategy, which involves the scaling up of OAT from 0 % to 50 % coverage and an increase in NSPs to more than 100 % coverage, would result in an 80 % reduction in incidence over the study period

OAT+NSPs+DAAs

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
First author and year: Cousien et al., 2018 **Location:** France **Time period(s) modelled:** 20 years **Outcome(s):** Cases averted **Study grade:** High	Dynamic, individual-based, stochastic model of HCV transmission , cascade of care and health outcomes	Relative risk of infection of 0.5 for NSPs and of 0.21 for OAT+NSPs. Efficacy of DAAs of 0.95	No. Results were not reported for incidence/prevalence	This is a cost-effectiveness study that primarily focuses on strategies to improve access to HCV treatment but also examines the effect of combining these strategies with improved access to OAT and NSPs The authors conclude that the combination of HCV treatment interventions with improved access to OAT and NSPs was the most effective strategy, compared to either the treatment strategies alone or the OAT and NSP strategy alone We refrain from reporting a quantitative value for the reduction in new infections because the HCV treatment interventions included improved testing, which is not featured in the other studies included in this review
First author and year: Fraser et al., 2018a **Location:** Amsterdam (Netherlands), Belgium, Czechia, Denmark, Finland, Hamburg (Germany), Norway, Scotland, Slovenia, Sweden	Dynamic deterministic HCV transmission model	Relative risks of infection of 0.42 (0.3-0.53) for OAT, 0.43 (0.15-0.70) for NSPs and 0.18 (0.04-0.32) for OAT+NSPs. Efficacy of 0.9 for DAAs	Yes. Twenty-two data points were used for the analysis of incidence and twenty-two for the analysis of prevalence	The scaling up of OAT and NSPs to 80 %, as well as a doubling of DAA treatment, could result in reductions in incidence over the study period of 41.2-99.7 % across sites and a reduction in prevalence of 17.9-99.5 %. Without these increases, these figures are 0.1-52.6 % and 0.1-51.8 %, respectively The scaling up of OAT and NSP coverage to 80 % in all sites decreased the treatment scale-up needed to reduce incidence to 2 per 100/year in 10 years or less by 20-80 %

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
Time period(s) modelled: 10 years (2016-2026) **Outcome(s):** Incidence, prevalence **Study grade:** High				The authors conclude that a reduction in HCV in Europe to minimal levels 'will require scale-up of both HCV treatment and other interventions that reduce injecting risk (especially OAT and provision of sterile injecting equipment)'
First author and year: Gountas et al., 2017 **Location:** Athens (Greece) **Time period(s) modelled:** 14 years (2016-2030) **Outcome(s):** Incidence, prevalence **Study grade:** Medium	Dynamic, discrete time, stochastic, individual-based HCV transmission model	Relative risk of HCV infection while in a harm reduction programme of 0.41. Harm reduction programme defined ambiguously but suggests OAT or a high-coverage NSP	No. The coverage data were not compatible for comparison with the other studies	Under moderate treatment regimens (2 % or 4 % PWID/year) and with an increase in harm reduction (OAT and NSP) coverage of 2 %/year, there would be relative reductions in chronic HCV prevalence of 26.5 % and 46.2 %, respectively, over the study period. The corresponding figures for incidence were 14 % and 21 %. If more than 8 % PWID/year are treated, prevalence would reduce by almost 94.8 % and incidence by 88 % With reference to the results in the OAT+NSP intervention table, the authors conclude that, as treatment coverage is increased, the benefits of harm reduction in reducing prevalence are reduced, but it has a significant impact in terms of reducing incidence In summary, the authors conclude that the combined OAT+NSP+DAA intervention 'could achieve major reductions in HCV incidence and prevalence among [PWID] by 2030'
First author and year: Martin et al., 2013	Dynamic deterministic HCV	Relative risks of infection of 0.48 (0.17-1.33) for OAT,	Yes. Three data points were used for	The authors examined the treatment rates required to reduce HCV prevalence to specific levels, alongside an increase in OAT and NSP

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
Location: General locations with 20 %, 40 % and 60 % baseline prevalence **Time period(s) modelled:** 10 years **Outcome(s):** Prevalence **Study grade:** High	transmission model	0.50 (0.22-1.12) for NSPs and 0.21 (0.08-0.52) for OAT+NSPs	the analysis of prevalence	coverage. With DAAs, if OAT and NSP coverage were increased from 0 % to 40 %, then 7, 16 or 29 treatments per 1000 PWID/year could halve prevalence for baseline chronic HCV prevalence of 20 %, 40 % and 60 % The authors highlight the importance of the combination treatment with OAT and NSPs to achieve 'substantial reductions (>50 %)' in HCV prevalence over the study period
First author and year: Ward et al., 2018 **Location:** Bristol, Dundee, Walsall (United Kingdom) **Time period(s) modelled:** 14 years (2016-2030) **Outcome(s):** Incidence, prevalence, percent reduction in new cases **Study grade:** High	Dynamic deterministic model of HCV transmission and disease progression	Relative risks of HCV transmission of 0.41 (0.22-0.75) for OAT, 0.59 (0.36-0.96) for NSPs and 0.26 (0.09-0.64) for OAT+NSPs. DAA efficacy sampled from a uniform distribution (0.86-0.92)	Yes. Nine data points were used for the analysis of incidence and three for the analysis of prevalence. Note that there are more scenario comparisons reported in the article that would be relevant here, except reporting inconsistencies meant that quantitative comparisons between baseline and comparison scenarios were not	The numbers of treatments required to reduce incidence by 90 % over the study period if OAT and NSPs are scaled up to 80 % were 40, 22 and 14 treatments per 1000 PWID in Bristol, Dundee and Walsall, respectively. Contrast this with the current coverage (81 %, 72 % and 72 % on OAT; 56 %, 48 % and 28 % on an NSP; 9, 52.5 and 2 treatments per 1000 PWID), which would lead to approximate reductions in incidence of 11 %, 99.97 % and 1 %, respectively The authors note that, although their analyses show that OAT and NSPs are important for reducing HCV transmission, a combined approach that uses HCV treatment is required to reduce HCV to low levels of incidence

Key information	Model details	Assumed intervention efficacy	Used in quantitative analysis?	Key results/conclusions
			possible for all scenarios	

Appendix 2. Linear regression models

Note that all linear models have been derived under the assumption that a zero scale-up of the intervention corresponds to a zero change in incidence/prevalence.

Adjusted R squared statistics are reported for each linear regression model.

Definitions of variables used in the linear regression models

Variable	Meaning
OAT_gap	Relative reduction in the gap to full OAT coverage (see Figure 3)
NSP_gap	Relative reduction in the gap to full NSP coverage (similar to OAT_gap)
Arith_OSTNSP_gap	The arithmetic mean of OAT_gap and NSP_gap
DAA_inc	Absolute increase in the number of DAA treatments per 1000 PWID per year between the baseline and comparison scenarios
Outcome_red_rel	Relative reduction in the outcome (incidence or prevalence) at the end of the study period between the baseline and comparison scenarios
Outcome_red_base	The relative reduction in the outcome (incidence or prevalence) over the study period for the baseline scenario

Black = 'explanatory variables', blue = 'response variables'

NSPs

FIGURE 7

Linear model for the NSP intervention that uses 'gap to full NSP coverage' as an explanatory variable and 'relative reduction in incidence at the end of the study period' as the response variable

Incidence

```
  --> Model name: NSP_inc

 Explanatory vars = NSP_gap, ; Response var = Outcome_red_rel.

 Number of data points = 10.
Linear regression model:
  Outcome_red_rel ~ NSP_gap

Estimated coefficients:
        Estimate      95 % CI       pValue
        ________  _________________  __________

  NSP_gap   0.6775   (0.4165, 0.9385)  0.00023712

Adjusted R squared statistic: -0.979.
```

.

FIGURE 8

Linear model for the NSP intervention that uses 'gap to full NSP coverage' as an explanatory variable and 'relative reduction in incidence at the end of the study period' as the response variable

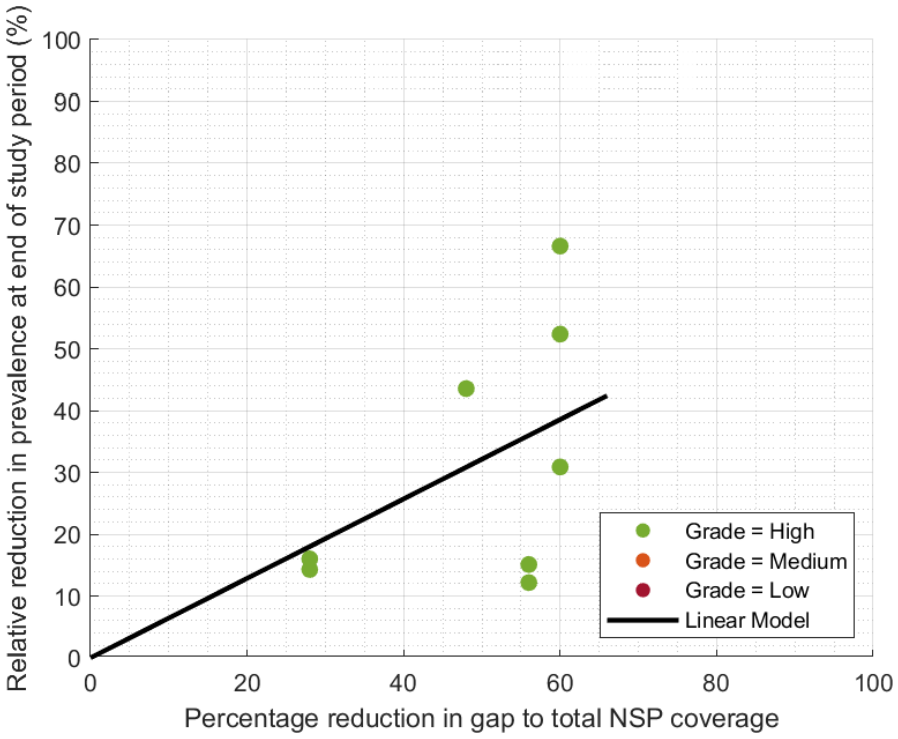
```
 --> Model name: NSP_inc_nolowgrade

 Explanatory vars = NSP_gap, ; Response var = Outcome_red_rel.

 Number of data points = 8.
Linear regression model:
  Outcome_red_rel ~ NSP_gap

Estimated coefficients:
        Estimate      95 % CI       pValue
        ________   _________________   __________

  NSP_gap  0.95345   (0.7051, 1.2018)  4.0358e-05

Adjusted R squared statistic: 0.305.
```

Points from studies graded as 'low' have been removed. This is the model illustrated in Figure 4.

FIGURE 9

Relative reduction in prevalence at the end of the study period for various levels of NSP scale-ups

Prevalence



Data points are colour coded according to the grade of their respective study.

FIGURE 10
Linear model for the NSP intervention that uses 'gap to full NSP coverage' as an explanatory variable and 'relative reduction in prevalence at the end of the study period' as the response variable

```
 --> Model name: NSP_prev

 Explanatory vars = NSP_gap, ; Response var = Outcome_red_rel.

 Number of data points = 8.
Linear regression model:
  Outcome_red_rel ~ NSP_gap

Estimated coefficients:
        Estimate     95 % CI       pValue
        ________  _________________  __________

  NSP_gap   0.6424   (0.3515, 0.9333)  0.0012241

Adjusted R squared statistic: 0.258.
```

This is the model illustrated in Figure 9.

OAT+NSPs

FIGURE 11
Linear model for the OAT+NSP intervention that uses 'gap to full OAT coverage' and 'gap to full NSP coverage' as explanatory variables and 'relative reduction in incidence at the end of the study period' as the response variable

Incidence

```
 --> Model name: OSTNSP_inc

 Explanatory vars = OAT_gap, NSP_gap; Response var = Outcome_red_rel.

 Number of data points = 36.

Linear regression model:
  Outcome_red_rel ~ OAT_gap + NSP_gap

Estimated coefficients:
        Estimate     95 % CI       pValue
        ________  _________________  __________

  OAT_gap  0.82335   (0.6510, 0.9957)  2.492e-11
  NSP_gap  0.31771   (0.1184, 0.5171)  0.0026805

Adjusted R squared statistic: 0.452.
```

FIGURE 12

Linear model for the OAT+NSP intervention that uses the arithmetic mean of 'gap to full OAT coverage' and 'gap to full NSP coverage' as an explanatory variable and 'relative reduction in incidence at the end of the study period' as the response variable

```
 --> Model name: OSTNSP_inc_arith

 Explanatory vars = Arith_OSTNSP_gap, ; Response var = Outcome_red_rel.

 Number of data points = 36.

Linear regression model:
  Outcome_red_rel ~ Arith_OSTNSP_gap

Estimated coefficients:
                Estimate      95 % CI       pValue
                ________  __________________  __________

  Arith_OSTNSP_gap   1.1803   (1.0756, 1.2850)  1.2082e-22

Adjusted R squared statistic: 0.339.
```

This is the model illustrated in Figure 5.

FIGURE 13

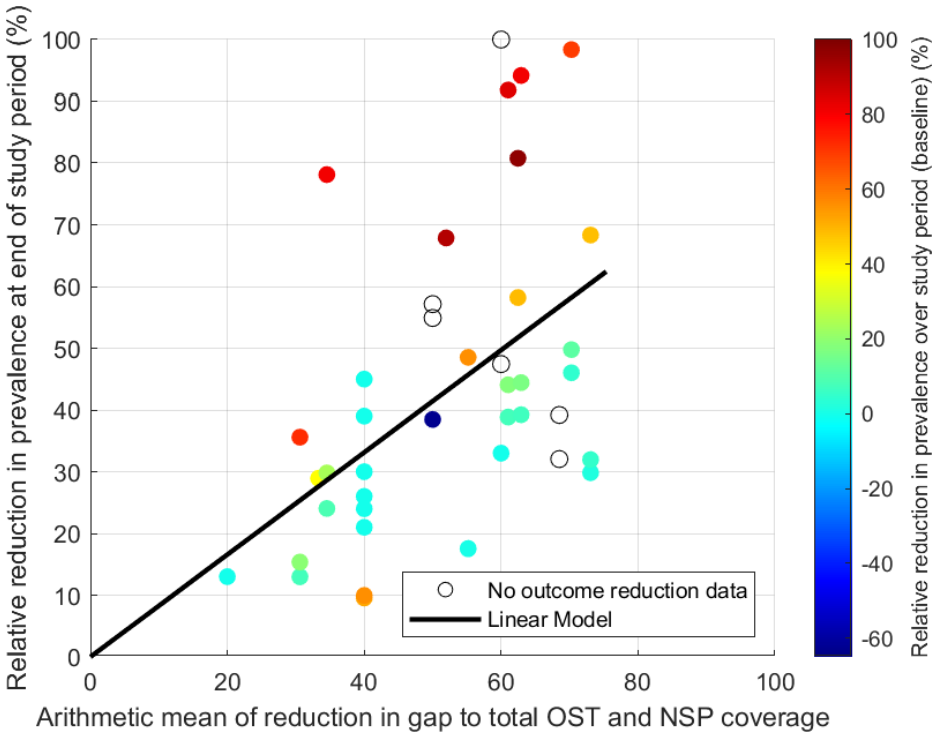
Linear model for the OAT+NSP intervention that uses 'gap to full OAT coverage' and 'gap to full NSP coverage' as explanatory variables and 'relative reduction in prevalence at the end of the study period' as the response variable

Prevalence

```
 --> Model name: OSTNSP_prev

 Explanatory vars = OAT_gap, NSP_gap; Response var = Outcome_red_rel.

 Number of data points = 42.

Linear regression model:
  Outcome_red_rel ~ OAT_gap + NSP_gap

Estimated coefficients:
          Estimate      95 % CI       pValue
          ________  __________________  __________

  OAT_gap    0.5857   (0.3160, 0.8554)  8.0833e-05
  NSP_gap   0.20308   (-0.1258, 0.5320)  0.21929

Adjusted R squared statistic: 0.236.
```

FIGURE 14

Relative reduction in prevalence at the end of the study period for various levels of OAT+NSP scale-ups



Data points are colour coded according to the reduction in prevalence over the study period in the baseline scenario.

FIGURE 15

Linear model for the OAT+NSP intervention that uses the arithmetic mean of 'gap to full OAT coverage' and 'gap to full NSP coverage' as an explanatory variable and 'relative reduction in prevalence at the end of the study period' as the response variable

```
 --> Model name: OSTNSP_prev_arith

 Explanatory vars = Arith_OSTNSP_gap, ; Response var = Outcome_red_rel.

 Number of data points = 42.
Linear regression model:
  Outcome_red_rel ~ Arith_OSTNSP_gap

Estimated coefficients:
              Estimate      95 % CI       pValue
              ________  __________________  __________

  Arith_OSTNSP_gap  0.82834   (0.7032, 0.9535)  1.5599e-16

Adjusted R squared statistic: 0.222.
```

This is the model illustrated in Figure 14.

OAT+NSPs+DAAs

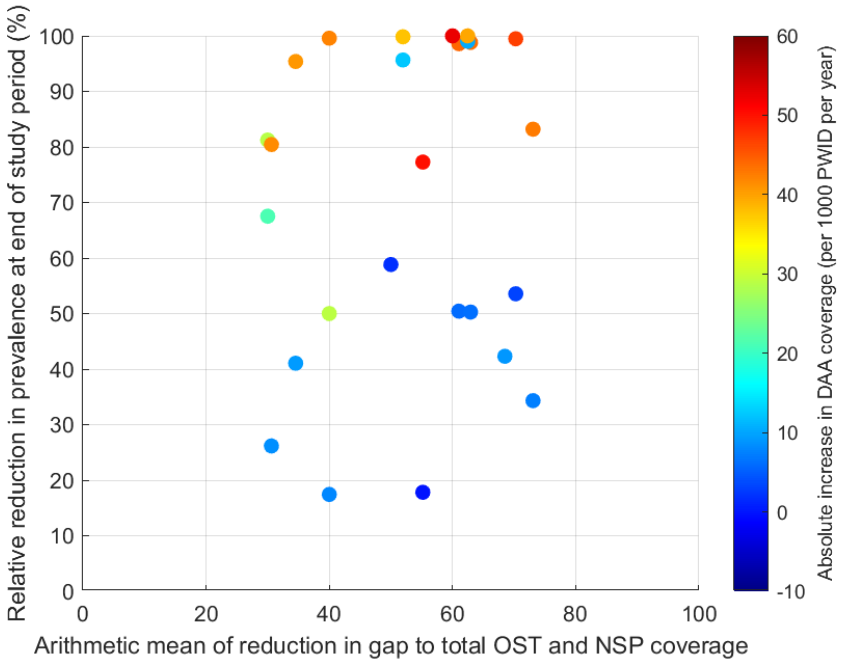
FIGURE 16
Linear model for the OAT+NSP+DAA intervention that uses 'gap to full OAT coverage', 'gap to full NSP coverage' and 'absolute increase in number of DAA treatments per 1000 PWID per year' as explanatory variables and 'relative reduction in incidence at the end of the study period' as the response variable

Incidence

```
  --> Model name: OSTNSPDAA_inc_DAAinc

  Explanatory vars = OAT_gap, NSP_gap, DAA_inc; Response var = Outcome_red_rel.

  Number of data points = 30.
Linear regression model:
  Outcome_red_rel ~ OAT_gap + NSP_gap + DAA_inc

Estimated coefficients:
        Estimate      95 % CI        pValue
        ________  __________________  __________

  OAT_gap  0.49515   (0.2385, 0.7518)  0.00049288
  NSP_gap  0.42813   (0.1729, 0.6834)  0.0018991
  DAA_inc   1.2013   (0.7738, 1.6288)  3.9297e-06

Adjusted R squared statistic: 0.494.
```

FIGURE 17
Data points used for linear models considering the combination OAT+NSP+DAA intervention, with the reduction in prevalence as the outcome of interest

Prevalence



Note that there is a strong association with an increase in DAA coverage, as indicated by the colour coding.

FIGURE 18

Linear model for the OAT+NSP+DAA intervention that uses 'gap to full OAT coverage', 'gap to full NSP coverage' and 'absolute increase in number of DAA treatments per 1000 PWID per year' as explanatory variables and 'relative reduction in prevalence at the end of the study period' as the response variable

--> Model name: OSTNSPDAA_prev_DAAinc

Explanatory vars = OAT_gap, NSP_gap, DAA_inc; Response var = Outcome_red_rel.

Number of data points = 28.

Linear regression model:
Outcome_red_rel ~ OAT_gap + NSP_gap + DAA_inc

Estimated coefficients:

	Estimate	95 % CI	pValue
OAT_gap	0.33432	(0.0757, 0.5930)	0.013379
NSP_gap	0.3514	(0.0488, 0.6540)	0.024621
DAA_inc	1.3267	(0.9101, 1.7434)	7.1848e-07

Adjusted R squared statistic: 0.511.

Appendix 3. Key statistics for data used in linear regression analysis

Please refer to definitions of variables in table in Appendix 2 (page 44). All values are taken to 3 significant figures up to an order of 0.001.

NSPs

Incidence models

Variable	Mean	Standard deviation
NSP coverage in the baseline scenario (%)	30.0	32.9
NSP coverage in the comparison scenario (%)	65.6	26.5
Reduction in the gap to full NSP coverage (%)	59.6	24.5

Variable	Mean	Range
Time horizon (years)	12.8	(10.0-14.0)

Prevalence models

Variable	Mean	Standard deviation
NSP coverage in the baseline scenario (%)	18.8	25.9
NSP coverage in the comparison scenario (%)	57.0	21.9
Reduction in the gap to full NSP coverage (%)	49.5	13.8

Variable	Mean	Range
Time horizon (years)	12.5	(10.0-14.0)

OAT+NSPs

Incidence

Variable	Mean	Standard deviation
OAT coverage in the baseline scenario (%)	37.8	23.7
OAT coverage in the comparison scenario (%)	78.3	5.50
Reduction in the gap to full OAT coverage (%)	59.8	18.7
NSP coverage in the baseline scenario (%)	45.1	27.0
NSP coverage in the comparison scenario (%)	74.6	15.1
Reduction in the gap to full NSP coverage (%)	49.1	23.2

Variable	Mean	Range
Time horizon (years)	11.0	(10.0-14.0)

Correlation coefficients	**Reduction in the gap to full OAT coverage**	**Reduction in the gap to full NSP coverage**	**Relative reduction in incidence over the study period in the baseline scenario**
Reduction in the gap to full OAT coverage	1	0.008	0.022
Reduction in the gap to full NSP coverage	0.008	1	−0.033
Relative reduction in incidence over the study period in the baseline scenario	0.022	−0.033	1

Correlation coefficient between ‘relative reduction in incidence over the study period in the baseline scenario’ and ‘DAA treatment rate in the baseline scenario’ = 0.751.

Prevalence

Variable	Mean	Standard deviation
OAT coverage in the baseline scenario (%)	28.8	24.5
OAT coverage in the comparison scenario (%)	71.0	16.6
Reduction in the gap to full OAT coverage (%)	58.3	16.3
NSP coverage in the baseline scenario (%)	34.9	30.5
NSP coverage in the comparison scenario (%)	66.5	19.4
Reduction in the gap to full NSP coverage (%)	45.5	20.1

Variable	Mean	Range
Time horizon (years)	11.5	(10.0-20.0)

Correlation coefficients	**Reduction in the gap to full OAT coverage**	**Reduction in the gap to full NSP coverage**	**Relative reduction in prevalence over the study period in the baseline scenario**
Reduction in the gap to full OAT coverage	1	0.274	0.162
Reduction in the gap to full NSP coverage	0.274	1	0.021
Relative reduction in prevalence over the study period in the baseline scenario	0.162	0.021	1

Correlation coefficient between ‘relative reduction in prevalence over the study period in the baseline scenario’ and ‘DAA treatment rate in the baseline scenario’ = 0.749.

OAT+NSPs+DAAs

Incidence

Variable	Mean	Standard deviation
OAT coverage in the baseline scenario (%)	47.3	24.3
OAT coverage in the comparison scenario (%)	79.5	2.05
Reduction in the gap to full OAT coverage (%)	50.5	27.0
NSP coverage in the baseline scenario (%)	46.9	23.0
NSP coverage in the comparison scenario (%)	76.4	11.6
Reduction in the gap to full NSP coverage (%)	50.7	20.4
DAA treatment rates in the baseline scenario (treatments per 1000 PWID per year)	9.57	9.30
DAA treatment rates in the comparison scenario (treatments per 1000 PWID per year)	31.0	18.5
Increase in DAA treatment rates between baseline and comparison scenarios (treatments per 1000 PWID per year)	21.4	19.1

Variable	Mean	Range
Time horizon (years)	11.1	(10.0-14.0)

Correlation coefficients	**Reduction in the gap to full OAT coverage**	**Reduction in the gap to full NSP coverage**	**Increase in the DAA treatment rate**
Reduction in the gap to full OAT coverage	1	−0.188	0.164
Reduction in the gap to full NSP coverage	−0.188	1	−0.086
Increase in the DAA treatment rate	0.164	−0.086	1

Prevalence

Variable	Mean	Standard deviation
OAT coverage in the baseline scenario (%)	37.1	25.0
OAT coverage in the comparison scenario (%)	75.2	12.6
Reduction in the gap to full OAT coverage (%)	55.7	22.0
NSP coverage in the baseline scenario (%)	42.5	27.5
NSP coverage in the comparison scenario (%)	71.9	16.4
Reduction in the gap to full NSP coverage (%)	47.3	20.2
DAA treatment rates in the baseline scenario (treatments per 1000 PWID per year)	6.65	5.84
DAA treatment rates in the comparison scenario (treatments per 1000 PWID per year)	30.4	19.2
Increase in DAA treatment rates between baseline and comparison scenarios (treatments per 1000 PWID per year)	23.8	17.8

Variable	Mean	Range
Time horizon (years)	10.4	(10.0-14.0)

Correlation coefficients	**Reduction in the gap to full OAT coverage**	**Reduction in the gap to full NSP coverage**	**Increase in the DAA treatment rate**
Reduction in the gap to full OAT coverage	1	−0.046	0.003
Reduction in the gap to full NSP coverage	−0.046	1	0.051
Increase in the DAA treatment rate	0.003	0.051	1