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Research paper

Reaching hepatitis C virus elimination targets requires health system interventions to enhance the care cascade

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ABSTRACT

Background: Modelling suggests that achieving the World Health Organization's elimination targets for hepatitis C virus (HCV) is possible by scaling up use of direct-acting antiviral (DAA) therapy. However, poor linkage to health services and retention in care presents a major barrier, in particular among people who inject drugs (PWID). We identify and assess the cost-effectiveness of additional health system interventions required to achieve HCV elimination targets in Australia, a setting where all people living with HCV have access to DAA therapy.

Methods: We used a dynamic HCV transmission and liver-disease progression mathematical model among current and former PWID, capturing testing, treatment and other features of the care cascade. Interventions tested were: availability of point-of-care RNA testing; increased testing of PWID; using biomarkers in place of liver stiffness measurement; and scaling up primary care treatment delivery.

Results: The projected treatment uptake in Australia reduced the number of people living with HCV from approximately 230,000 in 2015 to approximately 24,000 by 2030 and reduced incidence by 45%. However, the majority (74%) of remaining infections were undiagnosed and among PWID. Scaling up primary care treatment delivery and using biomarkers in place of liver stiffness measurement only reduced incidence by a further 1% but saved AU$32 million by 2030, with no change to health outcomes. Additionally replacing HCV antibody testing with point-of-care RNA testing increased healthcare cost savings to AU$62 million, increased incidence reduction to 64% and gained 11,000 quality-adjusted life years, but critically, additional screening of PWID was required to achieve HCV elimination targets.

Conclusion: Even with unlimited and unrestricted access to HCV DAA treatment, interventions to improve the HCV cascade of care and target PWID will be required to achieve elimination targets.

Introduction

The advent of highly effective direct-acting antiviral (DAA) therapies for the treatment of hepatitis C virus (HCV) is a game-changer for the disease. With cure rates >90% (Lawitz et al., 2014; Poordad et al., 2011), DAAs are highly tolerable, require only short-duration (8–12 weeks) therapy, have simple dosing (once-daily) and are effective even in advanced liver disease. This advancement from interferon-based therapies, which had only moderate (40–70%) success rates, required prolonged therapy (6–12 months), and had considerable side-effects (Gane et al., 2011; Manns, Wedemeyer, & Cornberg, 2006; Poordad et al., 2011), means that elimination is now firmly on the agenda (Burki, 2014). In response, the World Health Organization (WHO) have released elimination targets aiming for a 65% reduction in HCV-related mortality and a 90% reduction in combined HCV and hepatitis B virus (HBV) incidence by the year 2030—further specified as a 95% reduction in HBV incidence and an 80% reduction in HCV incidence (World Health Organisation, 2016). However, for many countries a

Abbreviations: AU$, Australian dollar; APRI, AST to platelet ratio index; DAA, direct-acting antiviral; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; NSP, needle and syringe program; OST, opioid substitution therapy; PBS, Pharmaceutical Benefits Scheme; POC, point-of-care; PWID, people who inject drugs; QALY, quality-adjusted life year; SVR, sustained viral response; WHO, World Health Organisation.

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significant barrier to achieving these goals will be the high cost of DAA treatments. In the USA, a single DAA course can be as much as US$80,000 (Hepatitis C Online, 2015), and even in countries like Egypt where a DAA treatment course costs approximately US$1000 (Hill & Cooke, 2014), the high prevalence (~10%) of HCV in the general population (Egypt Ministry of Health, El-Zanaty and Associates, & Macro International, 2009; Sievert et al., 2011) means that restrictions on treatment access are required to limit government expenditure.

Overcoming cost barriers to DAA access is a necessary first step to achieving elimination but there are many others that need to follow. Health system limitations in the HCV cascade of care means many people will remain chronically infected. Currently between infection and cure individuals must undergo: (1) a blood test to detect HCV antibodies (which could be present due to either acute, chronic or resolved infection); (2) a polymerase chain reaction (PCR) test to detect HCV RNA (to distinguish current infections from previous infections); (3) a genotype and viral load test to determine the correct treatment protocol; (4) an assessment of liver fibrosis through either an aspartate aminotransferase-to-platelet ratio index (APRI), other serum fibrosis biomarker, or transient elastography (e.g. FibroScan (Echosens), HepaScore); and in most settings (5) a further consultation with a specialist to commence treatment. There is a need to consolidate or remove some of these steps as each one represents a point of loss to follow-up (Yehia, Schranz, Umscheid, & Re, 2014).

Australia provides an important case study because it represents a situation with unrestricted treatment access but similar health system barriers to other developed settings. Since March 2016, DAA treatments for HCV have been listed on the Australian Pharmaceutical Benefits Scheme (PBS) (Commonwealth of Australia Department of Health, 2015; Pharmaceutical Benefits Advisory Committee (PBAC), 2015) as a result of the Australian government committing AU$1 billion over 5 years for an unlimited number of treatment courses, with no restrictions on access according to disease stage, treatment history or drug use status (Australian Government Department of Health, 2015; Hepatitis C Virus Infection Consensus Statement Working Group, 2016; Thompson, 2016). This listing on the PBS means that patient co-payments for treatment are under US$30 per month (or under US $5 for concession holders), minimizing cost barriers. Treatments in Australia now can also be prescribed by primary care doctors in the community (Australian Pharmaceutical Benefits Scheme, 2016), further improving access. However, at the end of 2012 (before DAAs were seen on the horizon) more than 58% of people who tested HCV antibody positive had not completed a PCR and genotype test, let alone progressed to treatment (Snow, Scott, Clothier, MacLachlan, & Cowie, 2017). This sub-optimal care cascade is compounded by limited access to FibroScan machines, which are expensive and normally based at hospital clinics, not in community settings.

Modelling has shown that the elimination targets can be achieved in Australia if treatments are targeted to people who inject drugs (PWID) (Scott, McBryde, Thompson, Doyle, & Hellard, 2017)—the group at greatest risk of infection and transmission. Since the listing of DAAs on the PBS, approximately 30,000 people (13% of all people living with HCV) were successfully treated in 2016 (the first ten months) (The Kirby Institute, 2016). However, this reflects a large backlog of people with advanced liver disease who have already been engaged in care, waiting for DAA treatment, and treatment numbers among PWID are likely to be significantly lower. Maintaining high treatment rates will be a challenge, and increasing testing rates is likely to be necessary to meet global HCV elimination targets. As the number of cured individuals with HCV antibodies increases, standard antibody tests will also become less useful and biomedical advances such as point-of-care (POC) RNA tests, which have already been successfully trialled (Grebely et al., 2017; Gupta, Agarwala, Kumar, Maiwall, & Sarin, 2017; McHugh et al., 2017; Rahamat-Langendoen, Kuijpers, & Melchers, 2015), may be required.

Previous models of HCV transmission have been used to project the HCV epidemic and associated disease burden in many countries (Razavi et al., 2014), as well as to consider the cost-effectiveness of DAAs (Martin et al., 2012; Scott, Iser, Thompson, Doyle, & Hellard, 2016; Visconti, Doyle, Weir, Shiell, & Hellard, 2013), the potential impact of DAA treatment scale-up (Cousien et al., 2015, 2017; Hellard et al., 2012; Martin et al., 2013) and to estimate the treatment numbers required to achieve global targets (Scott et al., 2017); however it remains unclear how enough treatment demand can be generated among PWID to enable this to occur. In this paper we expand an existing mathematical model of HCV transmission, liver disease progression and treatment to include the complete cascade of care. The model is calibrated to epidemic and clinical conditions in Australia and used to estimate the cost and impact of: scaling up primary care treatment services; using APRI < 1 to triage for risk of cirrhosis and bypass the need for further hepatic fibrosis assessment; introducing POC RNA testing; and recommending annual testing of PWID through drug treatment services. We therefore determine the total cost and combination of additional policy interventions that will be required to achieve the WHO elimination targets in Australia.

Methods

Model description

We extended the dynamic compartmental model from Scott et al. (2017) to include the complete cascade of care (Fig. 1). In brief, METAVIR scores (Bedossa & Poynard, 1996) were used to classify stages of liver disease, and individuals were distinguished as either: susceptible (S—infection naïve or previously achieving spontaneous clearance or SVR through treatment); acutely infected (A); chronically infected with liver fibrosis (in stage F0–F4); chronically infected with decompensated cirrhosis (DC); chronically infected with hepatocellular carcinoma (HCC); first year or more than one year post liver transplant (LT1 and LT2 respectively); or chronically infected and in treatment achieving sustained viral response (SVR) (T0–T4—treated from liver fibrosis stage F0–F4 respectively). The model was stratified by: injecting drug use status (current, former or never, with people in the model able to move between current and former classifications due to cessation or relapse into injecting drug use); age (categories 20–24, 25–29, 30–34, 35–44, 45–54, 55–64, 65–74, 75–84, 85+ years, with 59% of mixing assumed to occur within the same age category and 41% outside (Dombrowski et al., 2013)); and stage of engagement along the HCV cascade of care (undiagnosed, infected and tested positive for HCV antibodies, infected and tested positive for HCV RNA, infected and had a genotype test, infected and undergone a liver fibrosis test, on DAA treatment, failed initial treatment, on second round treatment, and cured).

Susceptible PWID became acutely infected at a rate proportional to: the proportion of PWID who were currently infected, a relative incidence function capturing changes to Australian drug markets (see below), and a calibration constant. Newly infected PWID with no prior liver fibrosis spent an average 12 weeks (Mondelli, Cerino, & Cividini, 2005) in the acute stage of infection before 26% (Micallef, Kaldor, & Dore, 2006) spontaneously cleared and again became susceptible to infection, while the remaining 74% became chronically infected and entered liver fibrosis stage F0. Chronically infected PWID who were successfully treated could become re-infected (Simmons, Saleem, Hill, Riley, & Cooke, 2016). In the absence of local epidemiological studies in the DAA treatment era suggesting otherwise, re-infection was modelled

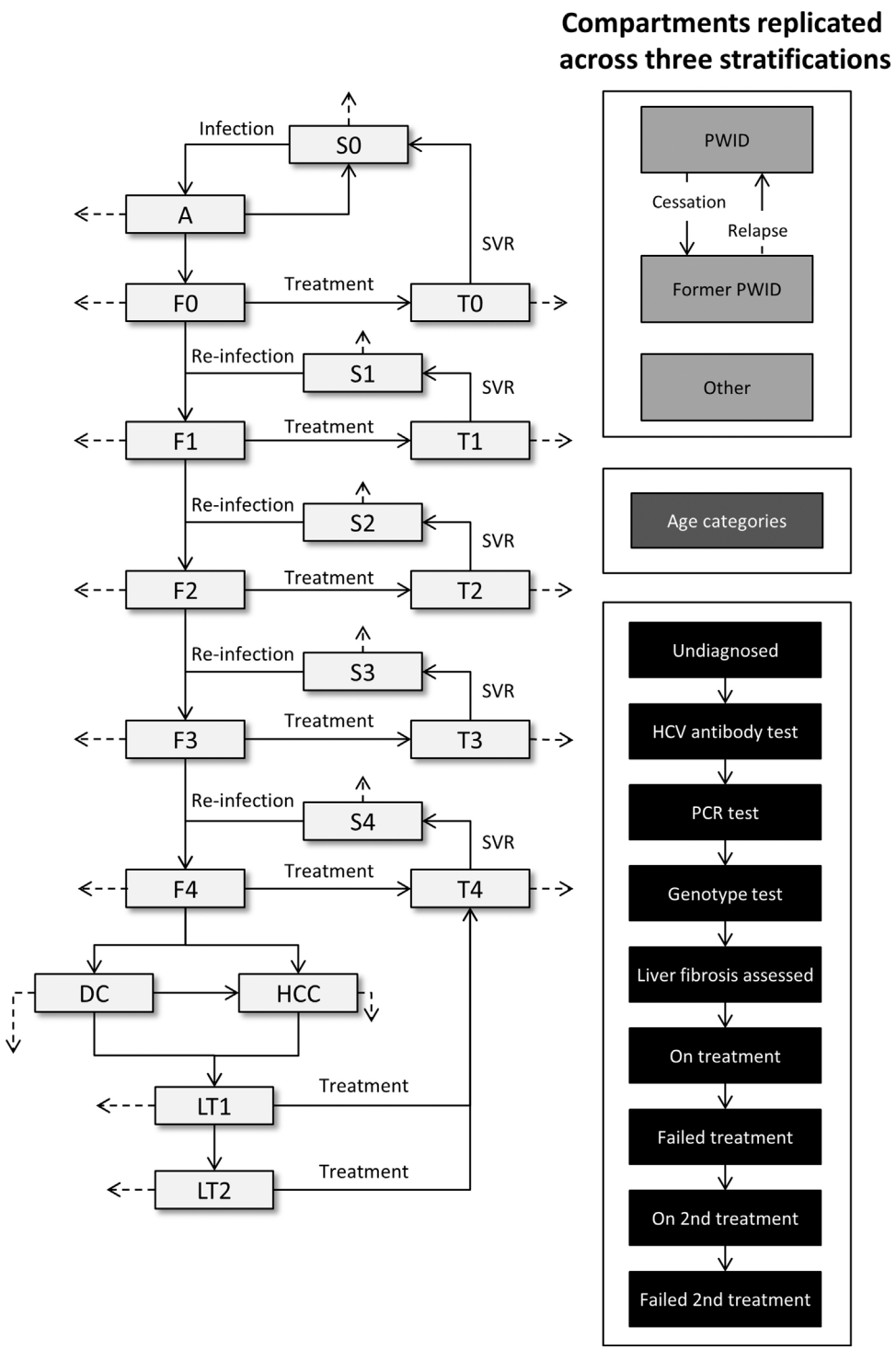

Fig. 1. Model schematic.

to occur at the same rate as initial infection. If PWID who had previously been cured were re-infected then they re-entered the furthest disease stage they had progressed to, and were assumed to not spontaneously clear infection. Both the re-infection and spontaneous clearance assumptions are likely to lead to conservative estimates of epidemiological impact. Liver disease progressed at rates obtained from the literature (Supplementary Table B2), and liver transplant could occur from the DC and HCC stages respectively (National Centre in HIV Epidemiology and Clinical Research, 2010).

The model had a burn-in period starting in 1950 with a population of 1000 PWID (10% infected), which increased linearly to 100,000 PWID in 2000 (Ministerial Advisory Committee on AIDS Sexual Health and Hepatitis, 2006) and then decreased to 80,000 PWID from 2005 onwards (Razali et al., 2007). PWID entered the model at 20 years old (Horyniak et al., 2013), assumed to be susceptible with no prior liver disease.

Further details on the model, assumptions and methodology are provided in the Supplementary material.

Calibration

The model has previously been calibrated to reproduce epidemiological and clinical data from Australia (Scott et al., 2017) based on a range of available literature, government reports and surveillance data. This included calibrating a time-varying incidence rate to fit the epidemic, which consisted of a background incidence rate (the calibration found to be 11.9% per annum) that was scaled by a relative incidence factor to approximate the effects of changes in drug market activity and associated risks (Day et al., 2003; Miller, Fry, & Dietze, 2001; Topp, Day, & Degenhardt, 2003): the relative incidence factor was assumed to linearly increase between 1950 and 2000, when it linearly reduced until 2005 and remained constant. Further details are in the Supplementary material.

Outcome measures

Alongside the epidemiological impact of each scenario (reductions in the number of people living with HCV, incidence and mortality), the total cumulative (2016–2030) healthcare costs associated with HCV disease management and treatment were calculated, based on the frequency of specialist and general practitioner consultation as well as the frequency of tests and procedures that would be requested for a typical patient (including additional support services for PWID). Health utilities associated with each liver disease stage were obtained from the literature (National Centre in HIV Epidemiology and Clinical Research, 2010; Thein, Yi, Dore, & Krahn, 2008) and used to estimate to total quality-adjusted life years (QALYs) accumulated by the model population between 2016 and 2030—this included the estimated 80,000 PWID in Australia (Ministerial Advisory Committee on AIDS Sexual Health and Hepatitis, 2006) (approximately 50% who had HCV (Iversen & Maher, 2013)) plus the remainder of people living with HCV in 2016 (i.e. non-PWID who were living with chronic HCV in 2016). A summary of demographic, HCV infection and HCV treatment model parameters are provided in Table 1, with further details, including health-related and cost parameters provided in the Supplementary material. Costs and health utilities were discounted at 3% per annum as recommended by the WHO (World Health Organization, 2016).

Harm reduction scale-up

For this analysis a modest scale-up of needle and syringe programs (NSPs) and opioid substitution therapy (OST) was assumed, in line with recent trends (Australian Institute of Health and Welfare, 2016; Iversen, Linsen, Kwon, & Maher, 2017), which would reduce the risk of new infections by 10%. Alternate values were tested in the sensitivity analysis.

Treatment scale-up

Since becoming available in March 2016, initial estimates suggest that approximately 40,000 individuals will be treated in the first year (The Kirby Institute, 2016). This includes an initial wave after which monthly treatment numbers appear to have

Table 1
Demographic, HCV infection and HCV treatment model parameters.

Parameter	Estimate	References and comments
Demographic parameters		
PWID population size	80,000	The population size was modelled to change over time, increasing to 100,000 in 2000 and then decreasing to 80,000 from 2005 onwards (Ministerial Advisory Committee on AIDS Sexual Health and Hepatitis, 2006; Razali et al., 2007)
Mean age at first injection	20 years	Horyniak et al. (2013)
Duration of injecting career	17 years	Fazito, Cuchi, Mahy, and Brown (2012)
Annual probability of drug relapse to IDU	0.027	Price, Risk, and Spitznagel (2001); Wong, Sylvestre, and Siebert (2004)
Infection parameters		
Annual probability of PWID infection	11.9%	Calibrated parameter. Varies over time due to risks associated with drug market changes (see Supplementary material)
Spontaneous clearance	0.26	Range 0.22–0.29. Uniform distribution assumed for uncertainty analysis (Micallef et al., 2006)
Genotype distribution in Australia		
Genotype 1	55%	McCaw, Moaven, Locarnini, and Bowden (1997)
Genotype 2	7%	McCaw et al. (1997)
Genotype 3	38%	McCaw et al. (1997)
Treatment parameters		
Probability of PWID completing treatment	0.892	Hellard, Sacks-Davis, and Gold (2009)
Treatment effectiveness		
Mild chronic HCV	0.90	For Genotype 1: (Gane et al., 2011, 2014; Lawitz et al., 2014; Poordad et al., 2013) assumed equally efficacious across genotypes
Moderate chronic HCV	0.90	Assumed equally efficacious for mild and moderate liver disease stages
Treatment duration		
Genotype 1 and 2	12 weeks	Chen et al. (2013); Gane et al. (2014); Lawitz et al. (2014); Poordad et al. (2013)
Genotype 3	24 weeks	
Australian weighted average	16.56 weeks	
Treatment numbers		
Between 1980 and 2015	2% of infected population per year	Dore (2012); Grebely, Oser, Taylor, and Dore (2013); Robaeys et al., 2013; Walsh, Lim, and Hellard (2008)
2016	40,000	Approximately 40,000 individuals will be treated in the first year of treatment scale-up (The Kirby Institute, 2016). Alternate values tested in sensitivity analysis
2017 onwards (per annum)	24,000	After an initial wave monthly treatment numbers appear to have plateaued at approximately 2000 per month (The Kirby Institute, 2016). Alternate values tested in sensitivity analysis

plateaued at approximately 2000 per month (The Kirby Institute, 2016). Therefore, we project a base scenario where 40,000 treatments are delivered in the first year and 24,000 in subsequent years. These values were varied in the sensitivity analysis.

Scenarios

HCV service delivery in Australia broadly fits into two categories. The first is traditional tertiary-based care, where a GP performs HCV antibody, RNA and genotype tests before referring the patient to a specialist for hepatic fibrosis assessment, treatment and follow-up. This is most suitable for people with cirrhosis, special populations (people with HIV or HBV co-infection, renal failure or decompensated liver disease), a second liver disease or failure of first line DAA therapy. The second category is entirely primary care, where recent Australian criteria (Australian Pharmaceutical Benefits Scheme, 2016) permits patients to have hepatic fibrosis assessment using APRI performed by their GP and treatments prescribed with no patient-specialist interaction required. In practice this has only been occurring approximately 30% of the time (Wade et al., 2017), with the majority of patients still being unnecessarily referred to specialists when their GPs are able to prescribe treatment.

Unpublished data from a randomized controlled trial of HCV service delivery in Australia and New Zealand (the "Prime study", with 41% current PWID) was used to parametrize the rates of cascade progression for each service delivery category (Wade & Hellard, 2016). Details are provided in the Supplementary material.

For each scenario in Table 2, the total discounted cost to the healthcare system, total discounted QALYs, total deaths and reduction in mortality and incidence due to treatment scale-up between 2016 and 2030 were estimated. Anyone progressing through the cascade was eligible for treatment regardless of liver disease stage or injecting drug use status, reflecting the current Australian situation. The requirement of an HCV RNA level and genotype test was removed from post-2016 projections due to implementation of pangenotypic DAA regimens.

Sensitivity and uncertainty analysis

A Monte Carlo uncertainty analysis was conducted to obtain 95% confidence intervals (95%CIs) around model estimates. Uncertainties of health utilities and annual disease transition probabilities were taken from previously published values (see Supplementary material).

While the uncertainty analysis considered parameter ranges from the literature, a variety of alternate scenarios were tested in one-way sensitivity analyses. This included scenarios with: initial prevalence among PWID either 40% or 60% compared to 50%; an estimated 60,000 or 100,000 PWID instead of 80,000; an average length of injecting career of 8.5 years instead of 17 years; harm reduction scale-up of 0%, 20%, 30% or 40% instead of 10%; six monthly or two yearly testing of PWID on OST instead of annually; 99% treatment adherence among PWID instead of 90%; average times between positive RNA diagnosis, liver assessment and treatment commencement being double those of the Prime Study; 48,000 DAAs courses commenced annually instead of 24,000; 8 weeks or 24 weeks duration of therapy for everyone; and DAAs being 95% effective rather than 90%.

Results

Impact on cascade of care and incidence

Unlimited and unrestricted treatment access is projected to lead to a dramatic decline in the number of people living with HCV (Fig. 2). Even in the base scenario (Fig. 2, top-left), the number of

Table 2
Modelled scenarios, assumptions made and model implementation strategy.

Name	Description and comments	Scenario implementation/parameters affected
Baseline	Current standard of care but with DAAs available for everyone progressing through the care cascade	
Scenario 1: scaled up primary care	A five-year period (2016–2021) to scale-up primary-based care from 30% (Wade et al., 2017) to 80% of all uncomplicated, non-cirrhotic patients (with scale-up to 60% tested in the sensitivity analysis)	The time between genotype and liver assessment was changed from a median 65 days to 0 days for primary care patients, based on Prime study data (see Supplementary material)
Scenario 2: scaled up primary care + APRI	Scenario 1 plus a five-year period to scale-up the use of APRI < 1 to exclude patients from requiring further hepatic fibrosis assessment	The additional step of liver assessment (including costs) was removed from the care cascade for people in the F0–F2 disease stage (used as a proxy for APRI < 1)
Scenario 3: scaled up primary care + APRI + annual testing of PWID on OST	Scenario 2 plus annual testing of PWID on OST (or on enrolment into OST). In 2015, 47% of Australian NSP survey respondents (Stafford & Breen, 2015) were currently accessing treatment, however most PWID (73%; Memedovic, Iversen, Geddes, & Maher, 2016) have done so previously. Given the documented cycling of PWID into and out of treatment (Burns et al., 2009), it is plausible that under this policy testing coverage would be high, but testing frequency may be less than annually for many individuals	The average time from infection to antibody positive diagnosis was decreased to six months for the estimated 47% of PWID who are reached by OST (assuming on average infection occurs at the mid-point of tests)
Scenario 4: scaled up primary care + APRI + point-of-care RNA	Scenario 2 plus a POC RNA test available (Rahamat-Langendoen et al., 2015)	The antibody diagnosis step in the care cascade was removed. Diagnosis costs were also changed: individuals in the model required only one diagnostic test, with an estimated test cost of AU $70 (Howell & Hellard, 2016), plus one fewer appointment cost. This is compared to the lab-based costs of $19 per antibody test and AU $92 per qualitative RNA test (Commonwealth of Australia Department of Health, 2016)
Scenario 5: all health system interventions	All health system interventions (i.e. Scenario 3 + Scenario 4). This scenario also considered achieving the mortality target by managing people post-SVR to minimize the probability of developing DC or HCC from the S4 stage (i.e. following treatment from F4 onwards)	As per scenarios 3 and 4, with the addition that the annual probability of developing DC or HCC from the S4 stage incrementally reduced (from 2% per annum) until the mortality target was reached

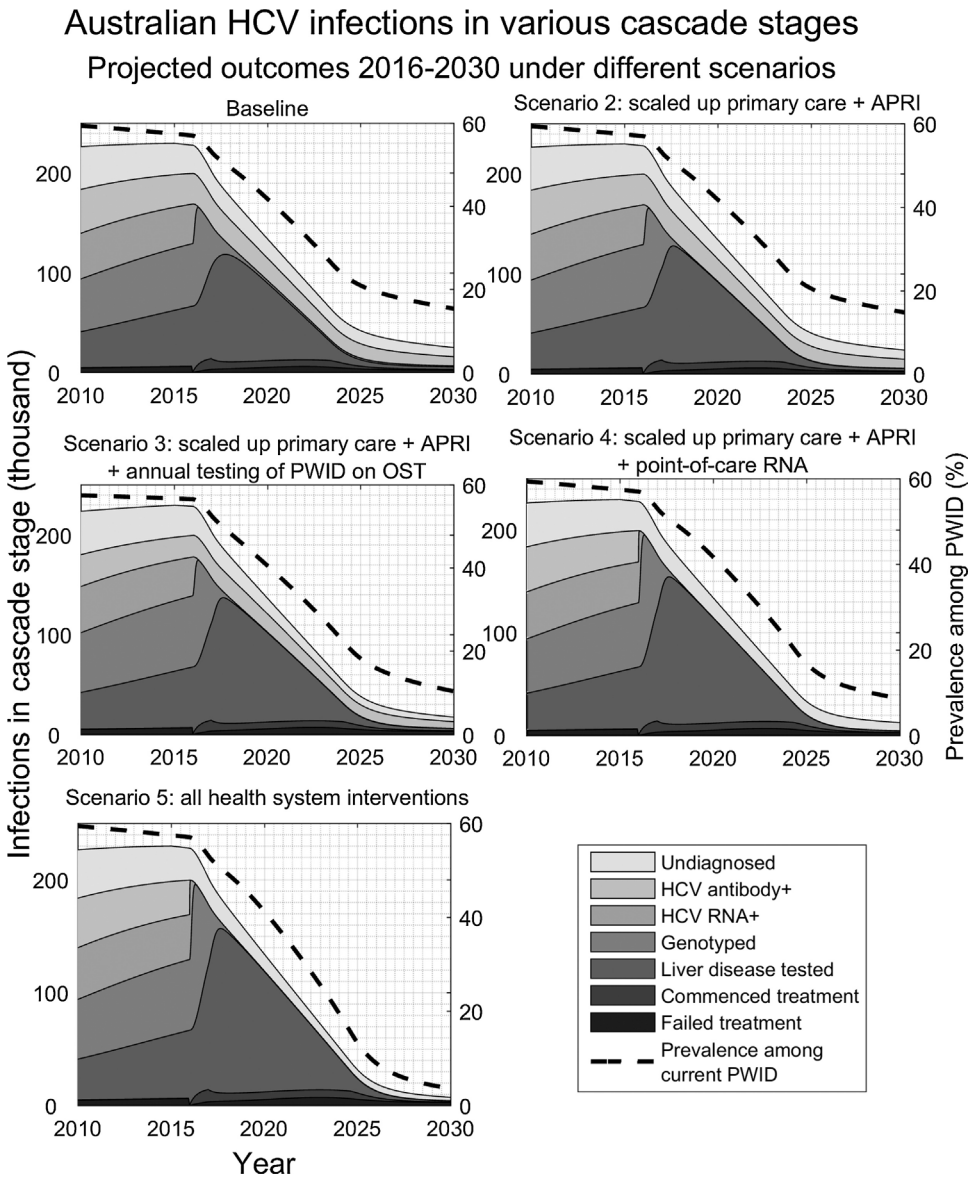

Fig. 2. Modelled cascade of care 2010–2030. Baseline: current standard of care. Scenario 2: scale up from 30% to 80% of people with early (F2 or less) liver disease accessing all treatment services through primary care networks, plus FibroScans not required for APRI < 1. Scenario 3: Scenario 2 but with annual HCV antibody testing among PWID on OST. Scenario 4: Scenario 2 but with a point-of-care RNA test available. Scenario 5: Scenario 3 but using a point-of-care RNA test and with additional management of patients post-SVR.

people with living with HCV in the model was reduced to approximately 24,000 by 2030. However, the majority (74%) of remaining infections were undiagnosed PWID, who could continue to transmit HCV to others. The base scenario reduced incidence in 2030 by 45% compared to 2015 levels.

Scenario 1 and Scenario 2 had little impact on the number of people living with HCV in 2030 or the HCV incidence in 2030 compared to the base scenario (Figs. 2 and 3 and Table 3). Scenario 3 and Scenario 4 led to fewer people living with HCV in 2030 compared to the base scenario (18,000 and 12,000 respectively; Fig. 2 and Table 3), and increased the 2030 incidence reduction (to 62% and 64% respectively; Fig. 3 and Table 3); however both scenarios were insufficient to reach the elimination targets. Scenario 5, combining scaled-up primary care, use of APRI < 1 to triage for risk of cirrhosis and implementing annual RNA testing of PWID on OST, was the only scenario that achieved the incidence reduction target (Fig. 3).

Impact on mortality

A 65% reduction in HCV-related mortality was not achieved in the model unless the annual probability of individuals developing DC or HCC after achieving SVR from stage F4 was reduced from 2.0% to 0.93%. This level of post-SVR management was included and projected as part of Scenario 5 (Fig. 3, right-panel).

Cost-effectiveness

Scenario 1 and Scenario 2 produced healthcare cost savings of AU$2 million and AU$32 million respectively with no changes in total QALYs (Table 3); however compared to the baseline estimated total healthcare costs of AU$1.052 billion, these savings were modest. Scenario 3 and Scenario 4 led to cost-savings of AU $3 million and AU$62 million respectively and health gains of 3000 and 11,000 QALYs respectively (Table 3). Scenario 5 cost an

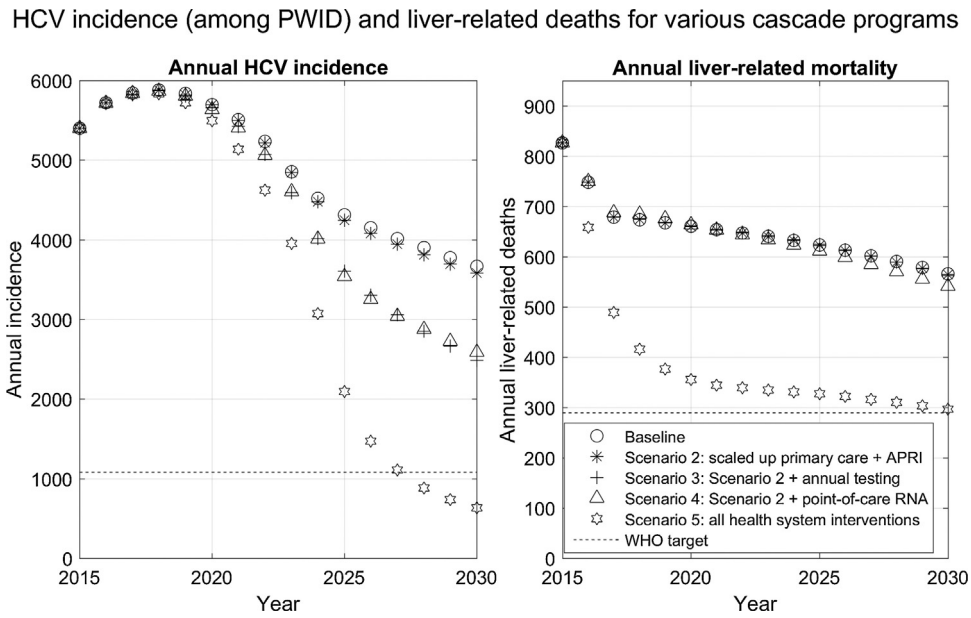

Fig. 3. Estimated annual HCV incidence and liver-related deaths 2015–2030. Baseline: current standard of care. Scenario 2: scale up from 30% to 80% of people with early (F 2 or less) liver disease accessing all treatment services through primary care networks, plus FibroScans not required for APRI < 1. Scenario 3: Scenario 2 but with annual HCV antibody testing among PWID on OST. Scenario 4: Scenario 2 but with a point-of-care RNA test available. Scenario 5: all health system interventions (including management of patients post-SVR).

additional AU$1 million but gained 21,000 QALYs, giving an incremental cost-effectiveness ratio of AU$47 per QALY gained.

Sensitivity analysis

Aside from when more or less people required treatment, the largest variations in outcomes occurred when harm reduction scale-up was varied (scaling up harm reduction was cost-saving and produced large reductions in 2030 incidence), or when the length of injecting career was halved, consistent with other modelling work (Scott, Hellard, & McBryde, 2015; Scott et al., 2017) (Table 4).

Of particular importance is that even six-monthly antibody testing of PWID on OST was insufficient to reach the incidence

Table 3
Cumulative model outcomes 2016–2030 under various scenarios. 95% confidence intervals (95%CIs) are the 2.5–97.5 percentiles of the Monte Carlo uncertainty analysis.

Point estimate (95%CI)	Current but with DAAs	Scenario 1: scaled up primary care	Scenario 2: scaled up primary care + APRI	Scenario 3: scaled up primary care + APRI + annual testing of PWID on OST	Scenario 4: scaled up primary care + APRI + point-of-care RNA	Scenario 5: all health system interventions
Treatments numbers						
Treatments given to current PWID (thousand)	44 (41–46)	44 (41–47)	45 (41–47)	50 (46–52)	50 (47–53)	58 (56–61)
Treatments given to former PWID (thousand)	60 (57–62)	60 (57–62)	60 (57–62)	61 (58–63)	63 (60–64)	62 (60–64)
Treatments given for non IDU-acquired infections (thousand)	135 (127–138)	135 (127–138)	135 (127–138)	135 (127–138)	138 (129–141)	138 (129–140)
Total treatments (thousand)	239 (230–243)	239 (230–243)	240 (231–244)	246 (237–250)	251 (241–255)	257 (249–263)
Model outcomes						
Total discounted cost (billion AU$)	1.052 (1.014–1.321)	1.050 (1.012–1.320)	1.020 (0.985–1.293)	1.049 (1.018–1.318)	0.990 (0.953–1.253)	1.053 (1.008–1.308)
Total discounted QALYs (million)	3.419 (3.257–3.442)	3.419 (3.257–3.444)	3.420 (3.257–3.444)	3.422 (3.260–3.447)	3.430 (3.268–3.453)	3.440 (3.279–3.462)
Reduction in incidence by 2030 (%)	45 (13–51)	45 (12–51)	46 (10–52)	62 (14–67)	64 (21–71)	91 (76–93)
Reduction in mortality by 2030 (%)	33 (21–53)	34 (21–53)	34 (21–53)	34 (21–54)	37 (24–57)	65 (64–65)
Prevalence among PWID in 2030 (%)	16 (15–20)	15 (15–20)	15 (14–19)	10 (10–14)	10 (8–13)	2 (2–4)
Cumulative deaths 2015–2030	8984 (9107–15,640)	8981 (9110–15,633)	8978 (9106–15,630)	8984 (9120–15,628)	8895 (9035–15,508)	5269 (5191–10,989)
Number of people living with HCV in 2030 (thousand)	24 (23–29)	23 (22–28)	23 (22–28)	18 (17–22)	12 (12–17)	7 (6–13)

Table 4
Results of sensitivity analysis. Total discounted costs, discounted QALYs, treatment numbers and incidence reduction under different model assumptions.

Scenario (percent difference *from base scenario*)	Total discounted cost (billion AU$)	Total discounted QALYs (millions)	Total treatments (thousand)	Incidence reduction by 2030 (%)
Base	1.052 (0%)	3.419 (0%)	239 (0%)	45%
Scenario 1: scaled up primary care	1.050 (0%)	3.419 (0%)	239 (0%)	45%
Scenario 2: scaled up primary care + APRI	1.020 (−3%)	3.420 (0%)	240 (0%)	46%
Scenario 3: scaled up primary care + APRI + annual testing of PWID on OST	1.049 (0%)	3.422 (0%)	246 (3%)	62%
Scenario 4: scaled up primary care + APRI + POC RNA	0.990 (−6%)	3.430 (0%)	251 (5%)	64%
Scenario 5: scaled up primary care + APRI + annual testing of PWID on OST + POC RNA + disease management post SVR	1.053 (0%)	3.440 (1%)	257 (7%)	91%
Base scenario but with				
40% initial prevalence rather than 50%	1.057 (0%)	3.675 (7%)	240 (0%)	62%
60% initial prevalence rather than 50%	1.087 (3%)	3.472 (2%)	245 (2%)	51%
60,000 PWID rather than 80,000	1.020 (−3%)	3.095 (−10%)	234 (−2%)	55%
100,000 PWID rather than 80,000	1.095 (4%)	3.718 (8%)	247 (3%)	23%
Half injecting career from 17 years to 8.5 years	1.115 (6%)	4.772 (28%)	257 (7%)	24%
0% scale-up of harm reduction rather than 10%	1.056 (0%)	3.417 (0%)	240 (0%)	33%
20% scale-up of harm reduction rather than 10%	1.048 (0%)	3.421 (0%)	238 (0%)	56%
30% scale-up of harm reduction rather than 10%	1.043 (−1%)	3.423 (0%)	238 (0%)	65%
40% scale-up of harm reduction rather than 10%	1.039 (−1%)	3.426 (0%)	237 (−1%)	74%
Testing of PWID on OST (47% of PWID) every six months	1.078 (2%)	3.425 (0%)	248 (4%)	69%
Testing of PWID on OST (47% of PWID) every two years	1.027 (−2%)	3.420 (0%)	242 (1%)	51%
Testing of PWID on OST (47% of PWID) every six months with POC RNA	1.251 (16%)	3.441 (1%)	258 (7%)	93%
Testing of PWID on OST (47% of PWID) every two years with POC RNA	1.010 (−4%)	3.438 (1%)	253 (6%)	74%
99% treatment adherence among PWID rather than 90%	1.036 (−2%)	3.422 (0%)	236 (−1%)	48%
Double the time from liver assessment to treatment	1.052 (0%)	3.419 (0%)	239 (0%)	45%
Double the maximum number of treatments delivered per year from 16,000 to 32,000	1.009 (−4%)	3.441 (1%)	240 (0%)	46%
8 weeks DAA treatment length for all patients	1.054 (0%)	3.421 (0%)	239 (0%)	45%
24 week DAA treatment length for all patients	1.047 (0%)	3.415 (0%)	239 (0%)	45%
SVR rate increased from 90% to 95%	1.003 (−5%)	3.431 (0%)	229 (−4%)	47%

reduction target without a POC RNA test being available. Conversely, if POC RNA testing were available, at least annual testing of PWID on OST was required, since two-yearly RNA testing of PWID on OST was insufficient to meet the incidence reduction target.

Discussion

By modelling the complete HCV epidemic in Australia, including transmission, liver disease progression and the cascade of care from infection to cure, we have shown that even in a setting with unlimited and unrestricted treatment access, achieving global HCV elimination targets will require policy and health system interventions to ensure that priority populations have access to testing, care and DAA therapy. In particular, to achieve the target of an 80% reduction in incidence by 2030, HCV RNA testing rates will need to increase among PWID, either by using new interventions such as POC RNA tests, or through increased engagement in care for those with HCV antibodies detected.

The model shows that without improvements to the cascade of care, treatment scale-up in Australia could reduce the number of people with HCV from approximately 230,000 in 2015 to approximately 24,000 by 2030, producing substantial reductions in incidence and liver-related deaths. However, this alone was insufficient to reach the WHO elimination targets because the remaining infections were primarily among PWID who were unaware of their HCV RNA status and could therefore continue to transmit infection. Introducing a policy of annually RNA testing PWID in drug treatment would be practical and our model predicts that it would be enough to reach the incidence target. Importantly, this initiative required both an annual testing frequency and a POC RNA test, since without a POC RNA test current rates of loss to follow-up from care meant that even six-monthly antibody testing was insufficient, while with a POC RNA test available (and hence no loss to follow-up from care at this stage) two-yearly testing was not frequent enough. Achieving a 65% reduction in liver-related mortality also required additional intervention to prevent people treated from late stage liver disease (F4 or worse) developing and dying from DC or HCC. For example, in 2015 there were estimated to be 45,000 people in Australia with HCV whose liver disease was stage F3 or worse (The Kirby Institute, 2015), meaning that even with treatments available the management of these people post-SVR will remain an issue into the future. The model estimates that if the annual probability of individuals achieving SVR from stage F4 developing DC of HCC could be reduced from 2.0% to 0.93%, then the 65% mortality reduction elimination target could be reached.

We found improvements to the cascade of care to be cost-saving even when they only provided marginal impacts on the epidemic. Delivering services through primary care networks and mandating that patients with APRI < 1 do not require a FibroScan was estimated to save AU$32 million by 2030, with no decrease in health outcomes. However these interventions produced minimal impact on the overall epidemic as they only saved an average 60 and 30 days per patient respectively, which are relatively short times compared to the advancement of liver disease or the transmission dynamics of HCV. These are likely to be conservative estimates, since shifting testing and treatment of patients from tertiary to primary care settings may have additional benefits that were not included in the model due to a lack of data; for example GPs may also become more proactive in identifying and screening PWID, thereby increasing diagnosis rates. However even without capturing these benefits both policies are recommended given that they would be cost-saving, easy to implement and have been found to be acceptable to patients, GPs and liver specialists (Wade et al., 2015).

A consequence of treatment scale-up is that the number of uninfected people carrying HCV antibodies from cleared infections will also increase. This could make the detection of re-infections difficult due to increased loss to follow-up after initial HCV antibody screening, highlighting the need for simple and accessible RNA testing. The use of POC RNA tests, combined with service

delivery through primary care networks and the use of ARPI, was estimated to save AU$62 million in healthcare costs by 2030, improve the 2030 incidence reduction from 45% to 64% and gain 11,000 QALYs, and should therefore be considered for use. The additional incidence reduction was the result of patients requiring one fewer step to know their HCV infection status, decreasing opportunity for loss to follow-up. We would therefore expect similar novel tests, such as a POC HCV antigen test, to produce similar results. Further work is required to develop testing guidelines, comparing the various available or in-production tests while accounting for their different properties.

A major element of the WHO's elimination strategy was for countries to provide adequate coverage of harm reduction (World Health Organisation, 2016). Although Australia already has high levels of NSP and OST coverage compared to many other countries, these programs have been shown to be cheap and extremely effective (Kwon et al., 2012). Our base scenario included a 10% scale-up of harm reduction, however increasing this to 20%, 30% or 40% produced additional cost-savings of AU$4 million, AU $9 million and AU$13million by 2030 respectively, as well as increasing the 2030 incidence reduction from 45% to 56%, 65% and 74% respectively. Harm reduction services should therefore be expanded to maximize coverage among PWID. Further work could consider their current availability geospatially to identify specifically where gaps in coverage could be filled or how high risk populations such as prisoners could be better serviced.

This model has limitations chiefly based around uncertainties of assumptions. To overcome this, we used model parameters and cost estimates from a range of sources and settings, including academic papers, meta-analyses, government reports and the Medicare Benefits Scheme and Pharmaceutical Benefits Scheme listings. To attempt to account for inherent uncertainty in each of these parameters, the multivariate uncertainty analysis was conducted, which resulted in modest and acceptable confidence intervals. We have also considered re-infection and initial infection to occur at the same rates, when in reality there may be behavioural differences between PWID who have achieved an SVR and infection naïve PWID. This is likely to make our results for the total costs, treatment numbers and incidence reduction conservative. Finally, this model has not considered the implementation costs of each intervention, such as the costs of educating GPs and OST service providers to change their testing practices, however recent trials of these policies have shown success with minimal implementation costs (Wade et al., 2015).

Conclusions

Treatment scale-up in Australia could reduce the number of people living with HCV from 230,000 in 2015 to 24,000 by 2030 and reduce incidence by 45%, but without improvements to the cascade of care Australia is unlikely to reach the WHO elimination target for new infections. Delivering services through primary care settings and using APRI to bypass hepatic fibrosis assessment produced only modest impacts but saved AU$32 million by 2030, with no decrease in health outcomes, and are therefore recommended. Adding to this POC RNA testing increased the healthcare cost savings to AU$62 million, gained 11,000 QALYs and further reduced the number of HCV infections; however additional testing of PWID, such as annual RNA testing as part of drug treatment services, was required to achieve WHO HCV elimination targets.

Conflict of interest

JD, MH, AT, AW and the Burnet Institute receive investigator-initiated research funding from Gilead Sciences, AbbVie and BMS. JD's institution has received honoraria from Merck, Gilead and BMS. No pharmaceutical grants were received in the development of this study.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.drugpo.2017.07.006.

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