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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