International Journal of Drug Policy 103 (2022) 103655

Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo

Research Paper

Hepatitis C incidence among patients attending primary care health services that specialise in the care of people who inject drugs, Victoria, Australia, 2009 to 2020

Anna Lee Wilkinson[a,b,*], Daniela K van Santen[a,b,c], Michael W Traeger[a,b], Rachel Sacks-Davis[a,b], Jason Asselin[a], Nick Scott[a,b], Brendan L Harney[a,b,d], Joseph S Doyle[a,d], Carol El-Hayek[a,b], Jessica Howell[a,b,e,f], Fran Bramwell[g], Hamish McManus[h], Basil Donovan[h], Mark Stoové[a,b], Margaret Hellard[a,b,d,i,1], Alisa Pedrana[a,b,1]

[a] Disease Elimination Program, Burnet Institute, Melbourne, Australia
[b] School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia
[c] Department of Infectious Diseases, Research and Prevention, Public Health Service of Amsterdam, Amsterdam, the Netherlands
[d] Department of Infectious Diseases, The Alfred and Monash University, Melbourne, Australia
[e] Department of Gastroenterology, St Vincent's Hospital, Melbourne, Australia
[f] Department of Medicine, University of Melbourne, Melbourne, Australia
[g] cohealth, Melbourne, Australia
[h] Kirby Institute, UNSW Sydney, Sydney, Australia
[i] Doherty Institute and Melbourne School of Population and Global Health, University of Melbourne, Melbourne 3000, Australia

ARTICLE INFO

Keywords:
Hepatitis C
Incidence
People who inject drugs
Direct-acting antivirals

ABSTRACT

Background: Monitoring trends in hepatitis C virus (HCV) incidence is critical for evaluating strategies aimed at eliminating HCV as a public health threat. We estimate HCV incidence and assess trends in incidence over time among primary care patients.

Methods: Data were routinely extracted, linked electronic medical records from 12 primary care health services. Patients included were aged ≥16 years, tested HCV antibody negative on their first test recorded and had at least one subsequent HCV antibody or RNA test (January 2009–December 2020). HCV incident infections were defined as a positive HCV antibody or RNA test. A generalised linear model assessed the association between HCV incidence and calendar year.

Results: In total, 6711 patients contributed 17,098 HCV test records, 210 incident HCV infections and 19,566 person-years; incidence was 1.1 per 100 person-years (95% confidence interval (CI): 0.9 to 1.2). Among 559 (8.2%) patients ever prescribed opioid-related pharmacotherapy (ORP) during the observation period, 135 infections occurred during 2,082 person-years (incidence rate of 6.5 per 100 person-years (95% CI: 5.4 to 7.7)). HCV incidence declined 2009–2020 overall (incidence rate ratio per calendar year 0.8 (95% CI: 0.8 to 0.9) and among patients ever prescribed ORT (incidence rate ratio per calendar year 0.9, 95% CI: 0.75 to 1.0).

Conclusion: HCV incidence declined among patients at primary care health services including among patients ever prescribed ORP and during the period following increased access to DAA therapy.

* Corresponding author.
E-mail address: anna.wilkinson@burnet.edu.au (A.L. Wilkinson).
[1] Equal contribution

https://doi.org/10.1016/j.drugpo.2022.103655

Introduction

Australia has committed to achieving the elimination of the hepatitis C virus (HCV) as a public health threat by 2030 (Australian Government, b). While Australia has had a longstanding approach to hepatitis C involving increasing access to prevention and harm reduction services, the public health response to HCV in Australia was catalysed by a commitment from the Australian government in 2016 to make direct-acting antiviral (DAA) therapy for the treatment of HCV highly subsidised and universally available. The availability of highly-effective DAA therapy led to a renewed elimination strategy focused on increasing treatment uptake, particularly for those with a history of injecting drug use (Scott, McBryde, Thompson, Doyle, & Hellard, 2017). DAA therapy in Australia is publicly subsidised, can be prescribed in primary care settings, and for people who inject drugs (current and previous injecting) and prisoners, of whom a disproportionate number have a history of injecting drug use (Doyle, Scott, & Sacks-Davis, 2019; Hepatitis C Virus Infection Consensus Statement Working Group, 2020; Thompson, 2016). To monitor progress towards elimination, Australia's Fifth National Hepatitis C Strategy outlines indicators and targets, including a reduction in new HCV infections by 60% by 2022 compared to 2015 levels. The National Strategy also provides guidance on the public health response to HCV among priority populations; people who inject drugs and/or are accessing drug treatment programs are priority populations and are disproportionately affected by hepatitis C infection in Australia (Australian Government, b).

Estimating HCV incidence, the rate of new infections, is key in monitoring progress towards HCV elimination as a public health threat. In Australia, as with many other countries, annual notifications of hepatitis diagnoses, provided to jurisdictional health departments, are often used as an approximation of incidence rates over time. Depending on the jurisdiction, notifications are classified as "unspecified" (most notifications) or newly acquired. In Australia, unspecified notifications (that is, not classified as newly acquired), were stable 2009–2015 at ~40 per 100,000 population, peaked in 2016 to 47 per 100,000, then declined to 29 per 100,000 population, or ~7400 notifications, in 2020 (Australian Government, a). Importantly the vast majority of positive HCV antibody or HCV RNA tests which constitute notifications do not reflect incident infections; negative tests are not collated by health departments and detailed clinical and test history are not routinely collated for people notified as a hepatitis C diagnosis. More reliable estimates of incidence rates are derived from longitudinal cohort studies in which participants are well-characterised and confirmed as being HCV antibody or RNA negative prior to having an infection identified. A recent review of HCV incidence rate estimates from Australian-based cohort studies conducted among people who inject drugs people who inject drugs between 2004 and 2015, reported HCV incidence estimates ranging from 7.6 to 12.8 per 100 person-years among people who inject drugs across five studies (Palmer, Wilkinson, & Aitken, 2021). However, because cohort studies are resource intensive, they are limited to specific time periods and populations.

Automated extraction of routinely collected clinical and laboratory data is an efficient and sustainable method of collating data from priority populations and includes positive and negative HCV tests, allowing for the construction of retrospective patient cohorts. Using data collated by the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance of Sexually Transmissible Infections (STIs) and Blood Borne Viruses (BBVs, ACCESS), a sentinel surveillance system that automatically extracts and collates electronic medical record data from a range of health services and pathology laboratories, we aimed to estimate HCV incidence and incidence trends over time. We estimate HCV incidence among patients accessing opioid-related pharmacotherapy (ORP); people accessing ORP are a priority population in the response to HCV in Australia therefore represent an important to include in measurements of trends in incidence.

Methods

Setting

The key purposes of ACCESS are to monitor the testing, diagnosis and management of BBVs and STIs in Australia, evaluate the impact of relevant health interventions, and provide data to inform Australia's strategic response to BBVs and STIs (Callander, Moreira, & El-Hayek, 2018). Primary care health services that offer specialised services to people who currently inject or previously injected drugs participate in ACCESS; these sites provide general health services and targeted services such as an onsite needle and syringe program, have one or more prescribers of ORP, and/or promote and provide viral hepatitis testing and treatment.

Data collection

Details of the ACCESS system has been previously described; (Callander et al., 2018) in brief data are extracted from databases at participating services using specialised software known as GRHANITE™. GRHANITE was developed by the Health and Biomedical Informatics Centre's Unit at the University of Melbourne (www.grhanite.com) (Liaw & Boyle, 2008). All data are de-identified prior to extraction and patient records are allocated an anonymous hash code, generated from patient identifying information in such a way as to allow probabilistic anonymous linkage of patient records both between and within ACCESS services. GRHANITE extracts sociodemographic, BBV and STI testing and treatment records from patient management systems, including records of electronic prescriptions of methadone or buprenorphine (Nguyen, Stoove, & Boyle, 2020). Analysis included HCV antibody and HCV RNA test records, age and sex of patients, and ORP prescription data extracted from 12 primary health services located in Victoria, Australia. Three clinics were in inner metropolitan Melbourne, five were in outer metropolitan Melbourne, and four were in regional Victoria. ACCESS data is processed so that multiples of the same HCV test (e.g., multiple antibody) conducted within seven days are considered a single test record. Only HCV test records with a valid result (positive or negative, and either HCV antibody or RNA) were included.

Analysis population

Eligible patients were ≥16 years, attended a clinic/s within the network of 12 primary care health services between 1 January 2009 and 31 December 2020, had a negative HCV antibody test as their first HCV test recorded in the analysis period, and had at least one subsequent HCV antibody and/or HCV RNA test during the analysis period. Patients were assigned as having 'ever' been prescribed ORP if an electronic script for medicines known to be used for ORP (methadone or buprenorphine) were recorded in ACCESS between 1 January 2009 and 31 December 2020.

Analysis

Summary statistics of age and sex recorded at the time of patients' first HCV antibody test, number of HCV test records and whether there was evidence of ORP ever (yes/no) were described. These characteristics were also stratified by patients that were subsequently identified as having an incident infection and those who were not. Age recorded at the time of the positive HCV antibody or HCV RNA test was also described.

For calculation of HCV incidence, follow-up time began on the date of the first recorded negative HCV antibody test and continued until an assigned incident HCV infection date or the last recorded negative HCV antibody or HCV RNA test on or before 31 December 2020. An incident HCV infection was defined as a positive HCV antibody or HCV RNA test following a previous HCV antibody negative. Incidence was then defined

as total number of incident HCV infections divided by total person-years of follow-up.

As the HCV infection date is unknown (that is, occurred in the unobserved interval between the HCV antibody negative test and positive HCV antibody or HCV RNA test, known as the negative-positive interval), we assigned the infection date of individuals as the midpoint of the negative-positive interval. Midpoint assignment is a method previously used in the estimation of incidence, including HCV incidence (Ang, Choy, Ng, Leo, & Wong, 2021). To explore if using a random-point in the negative-positive test interval, a second known method to assign HCV infection date, (Sobrino-Vegas, Monge Corella, & Serrano-Villar, 2014) produced substantially different trends in HCV incidence estimates over time, we used a 'random point' assignment of the infection date. Using this method, date of infection was assigned as a random date between positive test date and the previous negative antibody test date for each incident infection. We then examined annual trends in incidence where infection date was assigned to a random point in the negative-positive interval (Vandormael, Dobra, Barnighausen, de Oliveira, & Tanser, 2018).

To assess trends in incidence over time, annual incidence was defined as number of cases per annum divided by person-years of observation, and we used a generalised linear model (negative binomial distribution to account for overdispersion) to estimate the association between incidence rate and calendar-time (year as a continuous variable). Also, we estimated incidence among a subset of patients who have ever been prescribed ORP. It is unknown if patients in the study had a history of injecting drug use, therefore ORP prescription was used to approximate annual incidence among people who inject drugs and assess trends among this population.

HCV incidence estimates using data with interval censoring are influenced by the testing patterns, and this influence is amplified when using retrospective clinical data which has irregular and potentially long negative-positive test intervals. Unlike data from a research study, which has structured and active follow-up, prompts for testing are unobserved; testing may be driven by patient, clinician, clinic operation or environmental factors (that is, health promotion campaigns) and therefore test intervals vary between and within individuals. This analysis included all patients regardless of the length of their test intervals. Therefore, to explore how the test intervals were distributed annually, we use summary statistics to describe the distribution of the time since the individuals' previous HCV tests (test interval) in years. To illustrate how interval censoring, and methods of assigning an infection date to overcome unknown survival time may change the interpretation of trends in HCV incidence over time, we compared the number of assigned HCV incident infections to each calendar year when the midpoint and the random-point of the negative-positive interval was used to assign an infection date. The number of infections per year using the date of the positive test (diagnosis date) is also shown alongside each method of assigning the infection date.

Analysis was performed in Stata version 17 (StataCorp, College Station, Texas) and R (version 4.0.2).

Ethics

Ethics approval for the ACCESS was provided by the Alfred Hospital Human Research Ethics Committee (Project 248/17). As our study analyses de-identified data collected under the auspices of public-health surveillance, individual patient consent was not required.

Results

A total 38,677 patients were tested for HCV between 2009 and 2020 within a network of 12 primary care health services participating in ACCESS. Among these patients, 30,847 (79.7%) had an HCV antibody negative test as their initial test recorded and had a negative HCV RNA test (where HCV RNA testing was conducted at the same test event). Of these patients, 6711 (21.7%) had at least one further HCV antibody and/or HCV RNA test on or before 31 December 2020 (Fig. 1). Of the 6711 patients included in the analysis population, 61.1% were women, 38.0% men and 0.9% were 'Other' sex or sex was not recorded (unknown sex). Average age at the time of first recorded HCV antibody negative test was 32.6 years (standard deviation (SD)=11.6). Patients had a median of two HCV test records (interquartile range (IQR) 2.0, 3.0; Table 1). Compared to patients included, those excluded were older (mean age 34.9 vs 32.6, $p<0.000$), more likely to be male (45.7% vs 38.1%, $p<0.000$) and less likely to have a history of ORP (3.3% vs 8.3%, $p<0.000$, Supplementary Table 1). To illustrate the number of patients excluded and included over time, Supplementary Fig. 1 shows the annual number of patients excluded (first test observed a positive HCV antibody) and included, with more patients excluded in the 2009 and 2010 as expected because ACCESS commences in 2009.

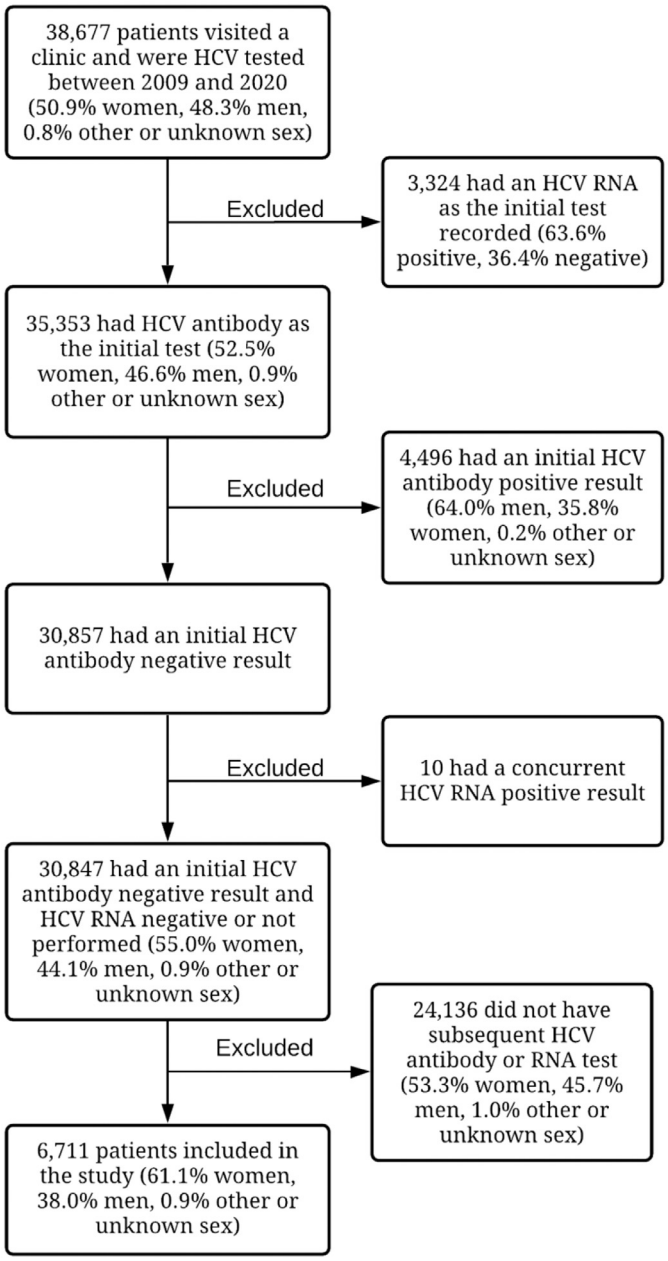

Fig. 1. Study flowchart of patients ≥16 years age eligible for estimation of HCV incidence, 1 January 2009 to 31 December 2020, Victoria, Australia.

Table 1
Characteristics of patients attending primary health services, who were negative HCV antibody on their first test and had at least one further HCV test (antibody or RNA), Victoria, Australia, 2009–2020.

	Overall $N = 6711$	Incident infections $n = 210$	No incident infection $n = 6501$
Age at first negative HCV antibody test (years), mean (SD)	32.6 (11.6)	31.2 (8.1)	32.7 (11.7)
Age at positive HCV (RNA or antibody) test date, mean (SD)	–	31.2 (8.8)	–
Sex, n (%)			
Men	2549 (38.1)	122 (58.1)	2427 (37.4)
Women	4100 (61.0)	87 (41.4)	4013 (61.6)
Other/unknown	62 (0.9)	1 (0.5)	61 (1.0)
HCV tests, median (IQR)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)	2.0 (2.0, 3.0)
History of at least one electronic prescription for ORP			
Yes n (% of column n)	559 (8.3)	135 (64.3)	424 (6.4)
Men n (% of ORP history Yes)	352 (63.0)	77 (57.0)	275 (64.9)
Women n (% of ORP history Yes)	207 (37.0)	58 (43.0)	149 (35.1)
Other/unknown n (% of ORP history Yes)	0	0	0

Table 2
Annual incidence of HCV infection among patients attending primary health services, who were negative HCV antibody on their first test and had at least one further HCV test (antibody or RNA), Victoria, Australia, 2009–2020. $N = 6827$.

Year	HCV tests ($n = 17,098$)	Individuals first HCV negative test ($n = 6711$)	HCV incident infections* ($n = 210$)	Person-years x 100	Incidence rate/100 PY (95% CI)
2009	778	647	6	3.2	1.9 (0.8 to 4.2)
2010	899	594	17	8.2	2.1 (1.3 to 3.3)
2011	1020	573	18	12.3	1.5 (0.9 to 2.3)
2012	1272	660	27	15.8	1.7 (1.2 to 2.5)
2013	1529	816	34	19.7	1.7 (1.2 to 2.4)
2014	1669	762	39	23.4	1.7 (1.2 to 2.3)
2015	1691	668	31	24.9	1.2 (0.9 to 1.8)
2016	1697	595	15	25.2	0.6 (0.4 to 1.0)
2017	1693	498	13	23.8	0.5 (0.3 to 0.9)
2018	1811	476	7	20.3	0.3 (0.2 to 0.7)
2019	1767	332	3	14.1	0.2 (0.1 to 0.7)
2020	1272	90	0	4.7	0 (0 to 0.7)†

* Midpoint of negative-positive test interval assigned as infection date.
† Poisson exact method for upper confidence limit (Ulm, 1990).

The 6711 patients included had a total of 17,098 HCV test records for the study period. There were 210 incident HCV infections and 19,566 person-years of follow-up; the overall incidence rate was 1.1 per 100 person-years (95% confidence interval (CI): 0.9 to 1.2). Of the 6711 patients, 559 (8.2%) had been prescribed ORP at any point in the study period and these patients had a total of 1517 HCV tests for the study period. There were 135 HCV incident infections and 2082 person-years of follow-up among patients ever prescribed ORP; the overall incidence rate was 6.5 per 100 person-years (95% CI: 5.4 to 7.7).

Annual trends in HCV incidence showed a decline each year from 2015 through to 2020 (Table 2 and Fig. 2). The generalised linear model with year as a continuous variable, estimated that incidence declined on average by 18% per year over the 12 years (incidence rate ratio 0.81, 95% CI: 0.76 to 0.87). Among patients ever prescribed ORP, annual incidence increased 2010 to 2013, was generally stable 2013 to 2015, then markedly declined after 2015 through to 2020. Among patients ever prescribed ORP, incidence declined on average by 14% per year over the 12 years (incidence rate ratio 0.86, 95% CI: 0.75 to 1.0). Notably, there were no incident infections detected in 2019 and 2020, however in 2020 considerably fewer patients were tested (Fig. 3, Table 3).

Summary statistics showed two-thirds of the analysis population were women, and women in the study may have been tested as part of antenatal screening as opposed to a specific HCV risk (therefore contributing to person-years but have fewer incident infections). To explore if there were differences in HCV incidence, a post-hoc analysis of HCV incidence stratified by sex was conducted and results included in Supplementary material. There were 122 HCV incident infections among 2549 men who contributed 7591 person-years. The overall rate among men was 1.6 per 100 person-years (95% CI: 1.3 to 1.9). There were 87 infections among 3893 women who contributed 11,892 person-years of follow-up. The overall rate among women was 0.7 per 100 person-years (95% CI: 0.6 to 0.9). Annual incidence declined among men and women from 2014 onwards (Supplementary Table 1, Supplementary Fig. 2).

The time since previous test (test intervals, in years) were calculated for each follow-up HCV test of individuals and overall median time between tests was 2.3 years (IQR 1.0, 4.3). The distribution of the test interval within calendar years of the follow-up tests was estimated, stratified by whether the follow-up test was positive or negative. The overall median time since previous tests for follow-up tests which were negative was 1.3 years (IQR 0.5, 2.6) and the annual time between tests remained relatively stable over the study period. For follow-up tests that were positive (incident infection identified), the overall median time since previous test was 3.0 years (IQR 0.9, 5.0) and increased over the study period, peaking at >6 years for tests conducted in 2019 (Fig. 4).

To illustrate how methods of assigning HCV infection date distributed the number of infections (thus potentially changing the interpretation of the trend in HCV incidence over time), the number of infections in each calendar year using the midpoint and random point methods of assignment, and the diagnoses date were plotted. The number of incident infections assigned to each calendar year using the midpoint of the negative-positive interval for assigning infection date places the peak in the number of incident infections in 2014. The approach of using a random point in the negative-positive test interval places the peak in 2012. Using the date of the first positive HCV antibody or RNA test, 2015 had a notable increase in the number of positive tests, with high numbers 2016–2017 and fewer positive tests in 2018–2020. As expected, both approaches to assigning the infection date placed the peak in HCV incidence infections before the peak in positive tests (Supplementary

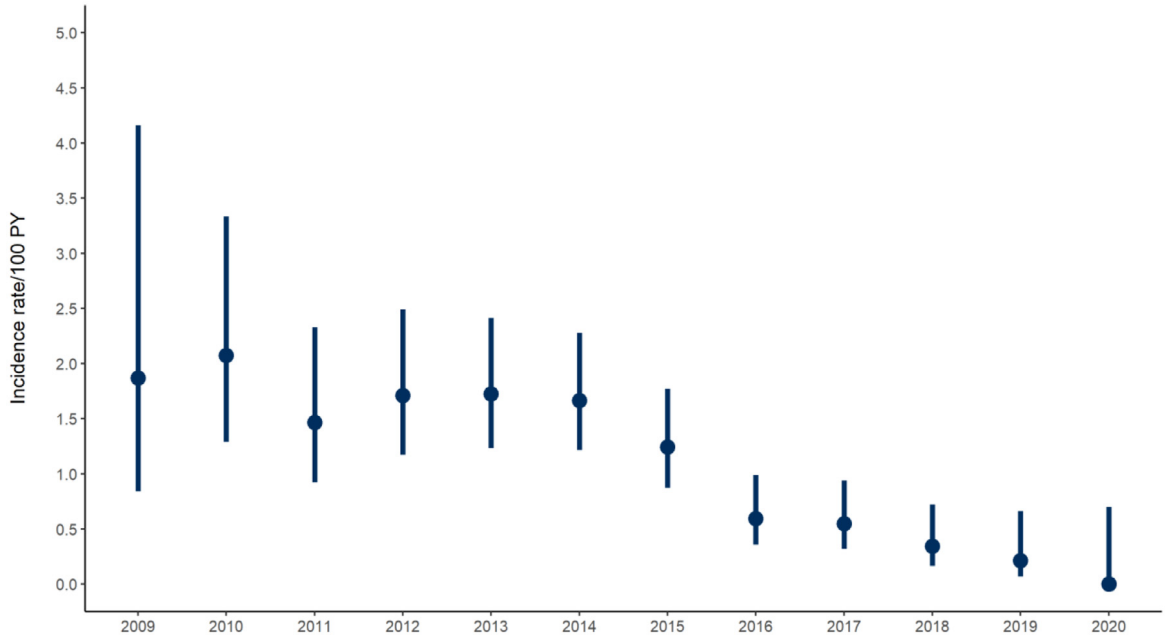

Fig. 2. Annual incidence of HCV infection among patients attending primary health services, who were negative HCV antibody on their first test and had at least one further HCV test (antibody or RNA), using midpoint to assign infection date, Victoria, Australia, 2009–2020, *N* = 6870.

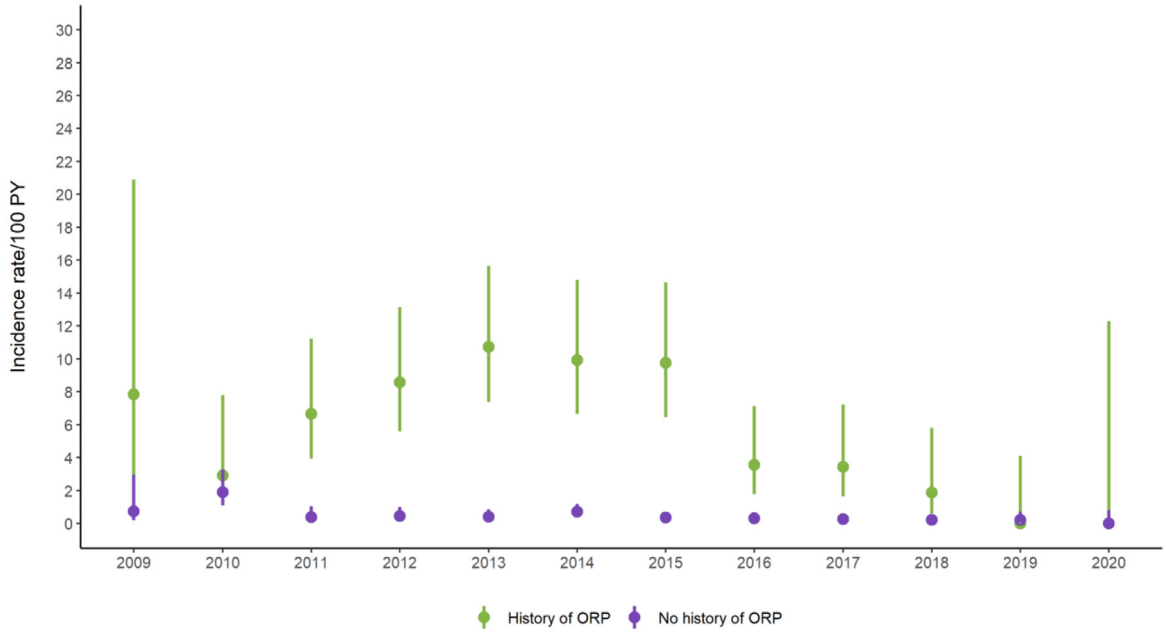

Fig. 3. Annual incidence of HCV infection among patients attending primary health services, who were negative HCV antibody on their first test and had at least one further HCV test (antibody or RNA), by history of ORP prescription, using midpoint to assign infection date, Victoria, Australia, 2009–2020, *N* = 6858.

Fig. 3). Both approaches to assigning an infection date show a declining trend in HCV incident infections over time (Fig. 1 and Supplementary Fig. 4).

Discussion

Among this retrospective cohort of approximately 7000 patients attending primary health care services participating in a sentinel network in Australia, we observed a decline in hepatitis C incidence following the introduction of widely accessible DAA treatments in 2015. Overall HCV incidence was highest among individuals ever prescribed ORP; however, declines were also observed in this group from 2015 onwards. This study provides contemporary estimates of HCV incidence, including for those most at risk of HCV in Australia and indicates that prevention efforts, particularly increased access to DAAs for the treatment of HCV have been effective in reducing HCV transmission.

Access to DAAs for the treatment of HCV increased in 2015 through early access programs and clinical trials, and then markedly expanded in 2016 through subsidization of the cost by the universal healthcare system in Australia with an estimated 22,000 people treated in Victoria in the early period of access to subsidised DAAs (2015–2016) (The Kirby Institute). The decline in HCV incidence observed in our clinical population is consistent with declines in incidence recently reported among Australian HIV-positive GBM (Doyle et al., 2020) and peo-

Table 3
Annual incidence of HCV infection among patients attending primary health services, who were negative HCV antibody on their first test and had at least one further HCV test (antibody or RNA), and had at least one prescription for ORP between 1 January 2009 and 31 December 2020, Victoria, Australia, 2009–2020, $N = 559$.

Year	HCV tests ($n = 1517$)	Individuals first HCV negative test ($n = 559$)	HCV incident infections* ($n = 135$)	Person-years x 100	Incidence rate/100 PY (95% CI)
2009	108	92	4	0.5	7.8 (2.9 to 20.9)
2010	156	112	4	1.4	2.9 (1.1 to 7.8)
2011	128	69	14	2.1	6.7 (3.9 to 11.2)
2012	146	59	21	2.5	8.6 (5.6 to 13.1)
2013	130	53	27	2.5	10.7 (7.4 to 15.6)
2014	135	44	24	2.4	9.9 (6.7 to 14.8)
2015	128	42	23	2.4	9.7 (6.5 to 14.7)
2016	127	28	8	2.2	3.6 (1.8 to 7.1)
2017	140	32	7	2.0	3.4 (1.6 to 7.2)
2018	129	14	3	1.6	1.9 (0.6 to 5.8)
2019	119	11	0	0.9	0 (0 to 4.1)†
2020	71	3	0	0.3	0 (0 to 12.3)†

* Midpoint of negative-positive test interval assigned as infection date.
† Poisson exact method for upper confidence limit (Ulm, 1990).

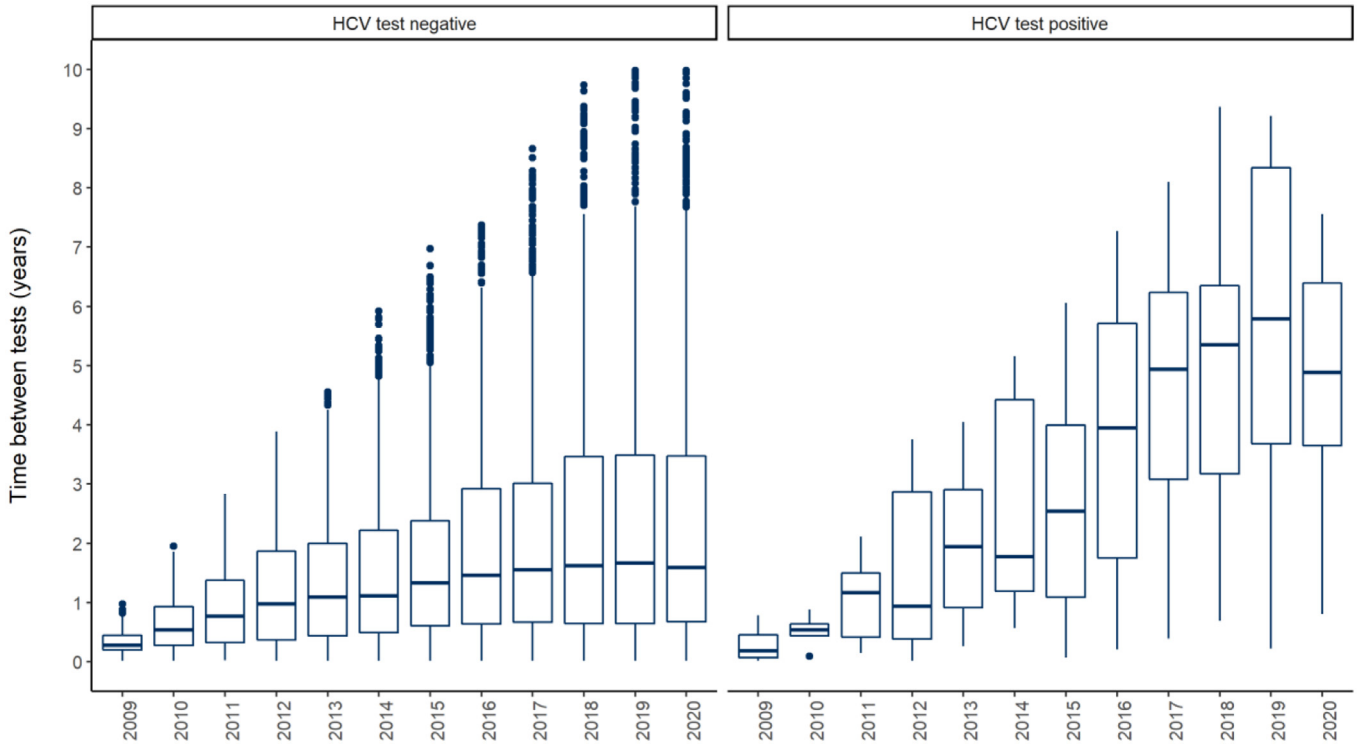

Fig. 4. Time (years) since previous HCV test (antibody or RNA), by year in which HCV test occurred, stratified by whether HCV test result is negative (left panel) or positive (right panel). Time since previous test summarised as median (solid line within the box), interquartile range (top (75th percentile) and bottom (25th percentile) of box), and outliers (dots), $N = 10{,}387$ HCV test intervals.

ple in prison (Hajarizadeh, Grebely, & Byrne, 2021), as well as declines in HCV RNA positivity in cross-sectional samples of people attending needle and syringe programs (Heard, Iversen, & Maher, 2021) and declining notifications of hepatitis C (Australian Government, a). Monitoring trends in new infections among all populations at risk of hepatitis C is critical to evaluating strategies aimed at eliminating HCV in Australia. Our data provide incidence estimates among a large population of individuals accessing care at a range of primary care health services across Victoria. Previous analysis of patients attending the same sites included in this analysis, showed that post-DAAs subsidization, there was a marked increase in the number of individuals treated for hepatitis C (Traeger, Pedrana, & van Santen, 2020). The increase in HCV treatment uptake, alongside the declining trends in incidence reported in this study strongly suggest a 'treatment-as-prevention' effect is occurring among this population, and reaffirm the importance of treatment uptake in eliminating HCV.

The overall incidence rate during the study period of 1.1 per 100 person-years was comparatively lower than incidence rates reported from studies of people who inject drugs, (Palmer et al., 2021) suggesting clinic attendees reflected a more general-population of individuals seeking primary care beyond those at specific risk of acquiring HCV. For example, women constituted two-thirds of clinic attendees but had an incidence rate half that of males, suggesting testing among low-risk females, potentially related to antenatal care HCV testing, was occurring at these health services. However, HCV incidence among a subset of patients ever prescribed ORP (a proxy for patients currently or with a history of injection drug use) was much higher at 6.5 per 100 person-years overall, with incidence increasing to a peak of 10.7 per

100 person-years in 2013. The overall HCV incidence estimate is largely consistent with previous estimates of incidence among Australian people who inject drugs. (Palmer et al., 2021) though it should be noted our estimate includes more recent years, including years following DAA roll-out therefore was expected to be lower than previous estimates which are all prior to 2016. A reduction in new infections among patients ever prescribed ORP further suggests that increased access to DAAs has reduced the number of people viremic and therefore the number of onward transmissions. However, substantial declines in DAA initiations in Australia have occurred since 2016 and an increase in testing is now critical to facilitate sufficient diagnosis of people who inject drugs in Australia, to maintain levels of treatment that can outpace transmission (Scott, Sacks-Davis, & Wade, 2020).

This study utilised the extraction of routinely collected clinical data to estimate HCV incidence, which allows for semi-automated, repeated measurement of HCV incidence; this system therefore provides important indicators for monitoring progress towards HCV elimination, with minimal cost and time delay. Importantly, the length and variation in test intervals resulting from risk-based and opportunistic testing within these health services, introduces methodological challenges when using electronic medical record data to monitor incidence outcomes, as opposed to data from a well-controlled setting like a cohort study. Further, testing can be influenced by clinic factors, as well as changes in policy or guidelines. In particular, the availability of DAAs in 2015–2016 likely motivated testing (or re-testing) among patients and clinicians; we observed a peak in the number of infections identified in 2015–2017. An increase in the mean test interval was also observed in 2016, suggesting patients who were tested some years earlier were reengaged in testing and care in 2016. As the mean test interval (time since last test) among patients who test positive was 3.9 years in 2016, use of the midpoint method (taking the midpoint between the negative-positive interval as infection date) placed a relatively large number of infection dates, and subsequently the peak in incidence estimates, in 2014. Changing trends in testing frequency and analysis methods used must be considered when interpreting the timing in the peak in incidence and the start of the decline. We note that the declining trend in incidence was also seen when assigning the infection date using a random point, and taken together, these data provide an indication that HCV incidence, and absolute number of identified infections, has declined over time, and since increased access to DAAs. Finally, the study included data from 2020, a period in which Victoria, where the health services where located, underwent >100 days of COVID-related restrictions and consequently, there is considerably less testing among the cohort in 2020 and the estimate of incidence must be interpreted with caution.

There are limitations to consider when interpreting the study findings. Whilst ACCESS links patients between participating health services, episodes of HCV testing undertaken by patients at health services that do not participate in ACCESS cannot be accounted for. The specific reason for HCV testing of patients, including a history of injecting drug use is unknown, meaning the overall estimate of incidence includes both those at high and low risk of HCV, that is patients with a history of injecting drug but not on ORP may be included in the overall incidence estimate but so were those with no history of injecting drug use. Estimating incidence among patients ever prescribed ORP, and stratification by sex does provide insight however into the sub populations within the analysis population and how they may be contributing to the overall estimate of incidence. It should be noted though that this study assigned patients as 'ever being prescribed ORP' based on an electronic health record (prescriptions) that had evidence of a methadone or buprenorphine prescription; the clinical indication for the prescription, the dose, and formula of medicine was unknown. Patients may have been misclassified as receiving ORP if the medicines were for a purpose other than ORP, however the extent of misclassification is unknown. We note the relatively small sample size of patients receiving ORP eligible for inclusion in the incidence analysis, compared to the overall sample. Further work is warranted to investigate patterns of hepatitis C testing among patients accessing ORP at these sites to understand this further. The analysis population reflects a population that is engaged with primary healthcare. Lastly, we highlight that because the ACCESS data commences in 2009, less person-time being accumulated in these years and more individuals were excluded because their 'first test observed' was a positive HCV antibody (Supplementary Fig. 1) therefore incidence could be under or over-estimated in the early years of the study. This study provides the first estimates of HCV incidence among attendees of primary care health services since DAAs were made widely available in Australia and does so using routinely collected data. The challenge from here will be to further investigate methods to estimate HCV incidence using routine clinical data particularly in the context of systematic changes in policy and practice leading to changes in test frequency and incidence over time (McManus, Callander, & Asselin, 2021).

Declines in HCV incidence since DAA therapy was made widely accessible in Australia in 2016 confirm the importance of access to treatment, and the role of treatment-as-prevention in eliminating HCV as a public health threat in Australia. The challenge now in Australia is to facilitate access to testing and diagnosis, to ensure sufficient levels of treatment are maintained.

Funding

This is the funding statement provided in the document. ACCESS receives core funding from the Australian Department of Health with the aim to monitor Australia's progress in the control of blood borne viruses and sexually transmissible infections. In addition, the governments of New South Wales, Victoria, Northern Territory, Western Australia, and the Australian Capital Territory provide funding for state level outcomes. Funding support from the Blood borne virus and sexually transmissible Research, Intervention and Strategic Evaluation Program (BRISE), an NHMRC Project Grant (APP1082336), a NHMRC Partnership Grant (GNT1092852), and the Prevention Research Support Program, funded by the New South Wales Ministry of Health, provided support for the generation of some outcomes presented in this paper.

Ethical approval

Ethics approval for the ACCESS was provided by the Alfred Hospital Human Research Ethics Committee (Project 248/17). As our study analyses de-identified data collected under the auspices of public-health surveillance, individual patient consent was not required.

Declarations of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors also acknowledge all clinics participating in ACCESS. ACCESS is a partnership between the Burnet Institute, Kirby Institute and National Reference Laboratory. The authors gratefully acknowledge the contribution to this work of the Victorian Operational Infrastructure Support Program received by the Burnet Institute.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2022.103655.

References

Ang, L. W., Choy, C. Y., Ng, O. T., Leo, Y. S., & Wong, C. S. (2021). Hepatitis C virus infection in HIV-infected men in Singapore, 2006-2018: Incidence and associated factors. *Sexual Health, 18*(3), 221–231.

Australian Government. Department of health. National Notifiable Disease Surveillance System. http://www9.health.gov.au/cda/source/cda-index.cfm Accessed 28 July, 2020.

Australian Government. Fifth National Hepatitis C Strategy: 2018-2022. https://www1.health.gov.au/internet/main/publishing.nsf/Content/ohp-bbvs-1/$File/Hep-C-Fifth-Nat-Strategy-2018-22.pdf Accessed 18 May, 2020.

Callander, D., Moreira, C., El-Hayek, C., Asselin, J., van Gemert, C., Watchirs Smith, L., et al. (2018). Monitoring the control of sexually transmissible infections and bloodborne viruses: Protocol for the Australian Collaboration for Coordinated Enhanced Sentinel Surveillance (ACCESS). *Journal of Medical Internet Research Protocols, 7*(11), e11028.

Doyle, J. S., Scott, N., Sacks-Davis, R., Pedrana, A. E., Thompson, A. J., Hellard, M. E., et al. (2019). Treatment access is only the first step to hepatitis C elimination: Experience of universal anti-viral treatment access in Australia. *Alimentary Pharmacology & Therapeutics, 49*(9), 1223–1229.

Doyle, J. S., van Santen, D. K., Iser, D., Sasadeusz, J., O'Reilly, M., Harney, B., et al. (2020). Micro-elimination of hepatitis C among people with HIV coinfection: Declining incidence and prevalence accompanying a multi-center treatment scale-up trial. *Clinical Infectious Diseases, 73*(7), e2164–e2172. 10.1093/cid/ciaa1500.

Hajarizadeh, B., Grebely, J., Byrne, M., Marks, P., Amin, J., McManus, H., et al. (2021). Evaluation of hepatitis C treatment-as-prevention within Australian prisons (SToP-C): A prospective cohort study. *Lancet Gastroenterology & Hepatology, 6*(7), 533–546.

Heard, S., Iversen, J., & Maher, L. (2021).Australian needle syringe program survey national data report 2016-2020: Prevalence of HIV, HCV and injecting and sexual behaviour among NSP attendees; https://kirby.unsw.edu.au/report/australian-nsp-survey-national-data-report-2016-2020 Accessed 20 July 2020.

Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: A consensus statement (June 2020). https://www.hepcguidelines.org.au/ Accessed 5 June 2020.

Liaw, S.-T., & Boyle, D. (2008). Secure data linkage and information sharing with GRHANITE. *Gran, H, editor HIC 2008 Australia's Health Informatics Conference; The Person in the Centre, Augsut 31 - September 2, 2008 Melbourne Converntion Centre Australia: Health Informatics Society of Australia Ltd (HISA); 2008:159-165.*

McManus, H., Callander, D., Asselin, J., et al. (2021). A new method for estimating the incidence of infectious diseases. *American Journal of Epidemiology, 190*(7), 1386–1395.

Nguyen, L., Stoove, M., Boyle, D., Callander, D., McManus, H., Asselin, J., et al. (2020). Privacy-preserving record linkage of deidentified records within a public health surveillance system: Evaluation study. *Journal of Medical Internet Research, 22*(6), e16757.

Palmer, A. Y., Wilkinson, A., Aitken, C., Dietze, P., Dore, G. J., Maher, L., et al. (2021). Estimating the number of new hepatitis C infections in Australia in 2015, prior to the scale-up of direct-acting antiviral treatment. *Journal of Gastroenterology and Hepatology, 36*(8), 2270–2274.

Scott, N., McBryde, E. S., Thompson, A., Doyle, J. S., & Hellard, M. E. (2017). Treatment scale-up to achieve global HCV incidence and mortality elimination targets: A cost–effectiveness model. *Gut, 66*(8), 1507–1515.

Scott, N., Sacks-Davis, R., Wade, A. J., Stoove, M., Pedrana, A., Doyle, J. S., et al. (2020). Australia needs to increase testing to achieve hepatitis C elimination. *Medical Journal of Australia, 212*(8), 365–370.

Sobrino-Vegas, P., Monge Corella, S., Serrano-Villar, S., Gutierrez, F., Blanco, J. R., Santos, I., et al. (2014). Incidence of hepatitis C virus (HCV) in a multicenter cohort of HIV-positive patients in Spain 2004-2011: Increasing rates of HCV diagnosis but not of HCV seroconversions. *Plos One, 9*(12), Article e116226.

The Kirby Institute. Monitoring hepatitis C treatment uptake in Australia (Issue 11). https://kirby.unsw.edu.au/report/monitoring-hepatitis-c-treatment-uptake-australia-issue-11-july-2021 Accessed 31 August, 2021.

Thompson, A. J. (2016). Australian recommendations for the management of hepatitis C virus infection: A consensus statement. *Medical Journal of Australia, 204*(7), 268–272.

Traeger, M. W., Pedrana, A. E., van Santen, D. K., Doyle, J. S., Howell, J., Thompson, A. J., et al. (2020). The impact of universal access to direct-acting antiviral therapy on the hepatitis C cascade of care among individuals attending primary and community health services. *Plos One, 15*(6), Article e0235445.

Ulm, K. (1990). A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). *American Journal of Epidemiology, 131*(2), 373–375.

Vandormael, A., Dobra, A., Barnighausen, T., de Oliveira, T., & Tanser, F. (2018). Incidence rate estimation, periodic testing and the limitations of the mid-point imputation approach. *International Journal of Epidemiology, 47*(1), 236–245.