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Estimating the number of new hepatitis C infections in Australia in 2015, prior to the scale-up of direct-acting antiviral treatment

Abstract

Background: The recent downward revision of the estimated number of people living with chronic hepatitis C in Australia means that the annual number of new hepatitis C infections should also be revised. We aimed to estimate the annual number of new hepatitis C infections among people who inject drugs (PWID) in Australia in 2015, prior to the introduction of direct-acting antiviral treatment (DAA) for hepatitis C, as an updated baseline measure for assessing the impact of DAAs on hepatitis C incidence over the next 10 years.

Methods: A systematic review identified articles estimating hepatitis C incidence rates among PWID between 2002 and 2015. Reported incidence rates were adjusted to account for unrepresentative needle and syringe program (NSP) coverage among study participants compared with PWID overall. The total number of PWID in Australia and the hepatitis C RNA prevalence among PWID were taken from published estimates. The annual number of new infections was estimated by multiplying the pooled NSP-coverage-adjusted incidence rate by the number of susceptible PWID in 2015.

Results: Five studies were included, with unadjusted incidence rates ranging from 7.6-12.8 per 100 person-years. The overall pooled incidence rate (after adjusting for NSP coverage) was 9.9 per 100 person-years (95% CI: 8.3-11.8). This led to an estimate of 4,126 (range 2,499-6,405) new hepatitis C infections in 2015.

Conclusions: Our updated estimate provides an important baseline for evaluating the impact of hepatitis C elimination efforts and can be used to validate outcomes of future modelling studies.

Keywords: elimination; hepatitis C; incidence; new infections; people who inject drugs.

Introduction

The advent of direct-acting antiviral (DAA) treatment for hepatitis C infection means that hepatitis C elimination has become a realistic goal (1). The World Health Organisation (WHO) has set 2030 global hepatitis C elimination targets of having 90% of cases diagnosed and 80% treated, as well as achieving an 80% reduction in new infections and a 65% reduction in mortality relative to 2015 levels (2). However, measuring progress towards these targets requires accurate baseline estimates from before DAA treatment became publicly available.

DAA treatments became publicly available in Australia in 2016, meaning that all Australians with hepatitis C can access treatment at a low out-of-pocket cost to the patient. As such estimates of the number of people living with hepatitis C in Australia around this time are important to measure the effect of making DAA treatments available to the Australian public. These estimates are typically calculated from hepatitis C notification data (i.e. recorded hepatitis C antibody positive diagnoses). However, a recent re-analysis of notification data has led to a major change in the estimated number of people with hepatitis C in Australia. By accounting for duplicate notifications and a new spontaneous clearance rate (~28% (3)), the previous estimate of 182,144 people living with hepatitis C (4) at the end of 2017 was revised down substantially to 143,580 (5). This adjustment means that estimates of the number of people with hepatitis C in Australia in 2016 and 2015 should also be revised downward and hence mathematical model projections, as well as other epidemiological factors derived from the estimated number of people with hepatitis C, should also be revised. A key estimate that warrants revision is the annual number of new hepatitis C infections, because (a) it is an important outcome for tracking progress towards elimination; and (b) it is difficult to measure directly from population based data and is typically derived from mathematical models.

Hepatitis C is a notifiable disease in Australia, meaning that positive tests are recorded in a national surveillance system with notification data being available online (6). While notifications can be classified as newly acquired if there is clinical evidence of symptoms consistent with acute hepatitis C or if there is evidence of a negative HCV antibody test within two years of the diagnosis, the vast majority do not have sufficient evidence to determine whether or not they are newly acquired and are therefore classified as “unspecified”.

Furthermore, low rates of annual testing among people who inject drugs (PWID) – a key risk population for hepatitis C in Australia – means that there is likely to be a substantial delay between infection and testing.

As a result, the system does not reliably reflect new hepatitis C infections (7). This means that estimating the number of new hepatitis C infections from notification data directly is challenging, and that mathematical models are typically used to derive this number. When epidemic models of hepatitis C are calibrated, four measures (parameters) are usually considered - population size, prevalence, time at risk and annual number of new infections. Data for three of these parameters are used as inputs to the model and these are then used to estimate the fourth (unknown) parameter. Typically, the inputs used are population size, hepatitis C prevalence and duration at risk of infection (i.e. the average length of injecting career), meaning that the number of new hepatitis C infections is the derived parameter. Previous models have resulted in generally declining estimates for new annual infections from 16,000 (11,000-19,000) new infections in 2001 (8), 10,300 (9,600-11,000) in 2003 (9), 9,700 new infections in 2005 (10), 6,300 (5,900-6,800) in 2008 (9) and 5,400 (range: 5,000-5,800) new infections in 2013 (9).

The revision to the estimated number of people chronically infected with hepatitis C in Australia is likely to directly affect the derived number of new infections in these models. Given this revision it is important to validate the likely annual number of new hepatitis C infections via other methods. We estimated the annual number of new hepatitis C infections among PWID in Australia prior to the introduction of publicly available DAA treatments in 2016 by combining estimates of PWID population size, prevalence amongst PWID and published incidence rates from longitudinal cohort studies of PWID.

Methods

Design:

Four steps were used to estimate the number of new hepatitis C infections in Australia prior to the introduction of publicly subsidised DAAs in 2016. First, estimates of hepatitis C incidence rates were identified from longitudinal studies of PWID in Australia. Second, these

incidence rate estimates were adjusted for needle and syringe program (NSP) coverage (see below). Third, the number of susceptible PWID in Australia was calculated based on published estimates of the total number of PWID and hepatitis C RNA prevalence. Fourth, the pooled NSP-coverage-adjusted incidence rate was multiplied by the number of susceptible PWID in Australia in 2015.

Calculation:

For the first step, a systematic review was conducted to identify longitudinal studies of PWID in Australia reporting hepatitis C incidence rates. We searched MEDLINE on 28th May 2020 for journal articles by combining the terms "hepatitis C" AND "Australia" AND "people who inject drugs" AND "incidence". Resulting studies were then screened for suitability. Eligible studies included estimates post-2002 (after the heroin 'glut' in Australia, (11)) and pre-2016 (when DAAs were introduced into the public health system). Studies which included estimates of reinfection following treatment, estimates of incidence amongst HIV-positive individuals only, estimates of incidence amongst prisoners only, or estimates among children were excluded. If incidence data were reported in studies published in 2002 or earlier, we searched Google for annual surveillance reports containing newer estimates (but prior to 2016) of incidence from the same cohort. We recorded the incidence estimate in person-years, as well as the number of seroconversions and person-years at risk used to calculate the incidence estimate for each study.

For the second step, the proportion of respondents who reported receptive syringe sharing (RSS) in each study was also recorded as an estimate of the proportion who experienced lack of NSP coverage (i.e. individuals who reported RSS were assumed to have insufficient NSP coverage). If RSS estimates were not available, estimates were taken from other published sources of the same cohort. High NSP coverage has been shown to reduce hepatitis C incidence (12), meaning that if the proportion of the PWID cohort with high NSP coverage is not equal to the proportion of PWID overall who have high NSP coverage, incidence estimates from the cohort will be biased. For each study i, the NSP-coverage-adjusted number of seroconversions among PWID, N_{ad_i}, was estimated from the reported number of seroconversions in the study, N_{study_i}, by:

$$N_{ad_i} = \frac{1 - NSP_{eff} \times NSP_{cov_{PWID}}}{1 - NSP_{eff} \times NSP_{cov_i}} N_{study_i}$$

where NSP_{eff} is the protective effect of high NSP coverage, $NSP_{cov_{PWID}}$ is the proportion of PWID with high NSP coverage generally and NSP_{cov_i} is the proportion of the study cohort who had high NSP coverage. The protective effect of NSPs was estimated from a Cochrane review (12), in which high NSP coverage (i.e. regular attendance at NSPs or all injections covered by new needle/syringe) was attributed to a 56% reduction in hepatitis C acquisition risk compared to low/no NSP coverage. NSP coverage among the entire population of PWID was defined as the percentage who had sufficient individual-level needle and syringe coverage for all of their injections, estimated at ~74% (13).

For the third step, the number of PWID in Australia was estimated to be 85,050 (range: 57,900-118,000) in 2015 – an average of the estimates in (14,15). The hepatitis C RNA prevalence among PWID was estimated to be 51% (95% CI: 48-54%) from the Australian National NSP Survey in 2015 (estimated by the proportion of participants with sufficient DBS samples for RNA testing who tested positive, weighted to account for gender and antibody status – since a higher proportion of antibody positive respondents had sufficient DBS for testing) (16). Therefore, we estimated the number of susceptible PWID in 2015, and hence the number of person-years susceptible to hepatitis C in 2015, to be 85,050 * (1-0.51) = 41,675.

For the final step, we combined the NSP-coverage-adjusted number of seroconversions and number of person-years at risk from each study to give an overall pooled estimate of incidence. The pooled incidence estimate was calculated using a generalised mixed effects linear model with a Poisson family, log link function. We then multiplied this estimate by the calculated number of susceptible PWID in 2015 to give the number of new hepatitis C infections in 2015. Upper and lower bounds were calculated by using the 95% CI for the pooled estimate of incidence, the 95% CI for RNA prevalence and the estimated range in the number of PWID. The 95% CI for the pooled incidence estimate was calculated using Poisson rate confidence intervals.

Results

Six longitudinal studies were found with estimates of hepatitis C incidence rates among PWID between the years 2003 and 2015; two were national studies, two were from Melbourne and two were from Sydney. Three of these studies (MIX, Networks 2 and HITS-c) drew on samples of community recruited PWID, one drew on PWID attending primary health services (KRC), one utilised sentinel surveillance of PWID attending NSPs (ANSPS), and one study (ACCESS) employed sentinel surveillance system data from individuals who attended primary healthcare clinics where services for PWID were available (17). Since we could not confirm that all individuals included in the study were PWID we excluded this final study, leaving five studies included in the analysis (Table 1).

Among the five included studies, unadjusted incidence rate estimates ranged from 7.6 per 100 person-years in MIX to 12.8 per 100 person-years in Networks 2 (Figure 1). In four of the studies, the proportion who engaged in receptive syringe sharing (RSS) was less than the overall average among PWID (26%).

The unadjusted pooled incidence rate across the five studies was 9.3 per 100 person-years (95% CI: 7.7-11.1), based on 118 new hepatitis C infections and 1,267.7 person-years at risk. After adjusting for NSP coverage, the number of new hepatitis C infections was inflated to 125.1, giving a pooled NSP-coverage-adjusted incidence rate of 9.9 per 100 person-years (95% CI: 8.3-11.8).

By multiplying the NSP-coverage-adjusted incidence rate (9.9 per 100 person-years) by the estimated number of susceptible PWID in 2015 (41,675), we estimated the annual number of new hepatitis C infections in 2015 to be 4,126 (range 2,499-6,405).

Discussion

Using incidence rate estimates from longitudinal studies of PWID, we estimated that 4,126 (range 2,499-6,405) new hepatitis C infections occurred in Australia in 2015. This figure is an important baseline for measuring the impact of DAA treatments on Australia's hepatitis C

elimination efforts. Our estimate is also useful for validating the outcomes of mathematical models as their calibrations are updated in line with new estimates of people with chronic hepatitis C infection in Australia.

Obtaining accurate estimates of new hepatitis C infections is important because new infections are one of two primary measures used for tracking progress towards the WHO's hepatitis C elimination targets. Between March 2016 and December 2019, 82,280 individuals living with hepatitis C infection were treated (24). Hepatitis C incidence is likely to be declining in response, but without accurate baseline estimates it is not possible to determine whether current levels of treatment will be sufficient to reach the WHO elimination targets. Prior to this study, the most recent estimate of annual hepatitis C infections was 5,400 cases in 2013. This figure was derived using a mathematical model based on the previous (higher) estimated number of people with hepatitis C. The recent downward revision to the number of people infected with hepatitis C in Australia in 2015 has meant that our estimate is slightly lower, suggesting previous mathematical models may have overestimated incidence, but there is a wide uncertainty. Given that our estimate is based on empirical data for incidence rates (as opposed to modelled estimates), and is adjusted for NSP-coverage biases, we believe that it more robustly reflects new hepatitis C infections in Australia. Moreover, this estimate can be used for validating future mathematical models of hepatitis C transmission because it was derived independently.

This study has limitations. First, the annual number of new hepatitis C infections probably changes over time, and it was not possible to capture this in the available data. Capturing such data is difficult and expensive, requiring longitudinal cohort studies that are sufficiently powered to estimate hepatitis C incidence at multiple time points. Despite this, incidence estimates across these studies are remarkably similar, suggesting minimal temporal variation in incidence prior to 2016 and that our pooled estimate of incidence is likely to be accurate for the year 2015. Second, this study only considers injection-drug-use-acquired infections, and does not consider infections acquired among other key populations such as HIV-positive men who have sex with men, although the number of new infections among this group is thought to be minimal by comparison (25). Finally, there is large uncertainty in the published estimates

of the number of PWID in Australia, but the wide confidence interval in this variable (57,900 – 118,000 PWID in 2015) is captured in our results.

Conclusion

Previous estimates of new hepatitis C infections in Australia were derived from modelling studies. The significant change in the estimated number of people with hepatitis C means that they may no longer be accurate. Based on reported incidence rates from longitudinal studies of PWID, we estimate that there were 4,126 (range 2,499-6,405) new hepatitis C infections in 2015. This finding is an important baseline estimate for determining whether hepatitis C elimination programs are on track and can be used to validate outcomes of future modelling studies.

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Tables

Table 1: Incidence data sources, description, incidence estimates and adjusted number of seroconversions

Study	Setting	Description	Years	RSS	Unadjusted incidence (/100py)	No. of new infections	Person-years at risk	Adjusted no. of new infections
Melbourne Injecting Drug User Cohort Study (MIX) (18)	Melbourne, Victoria	Community recruited PWID	2009-2014	9.9%	7.6 (95% CI: 4.8-11.9)	19	250.2	22.5
Networks 2 (19)	Melbourne, Victoria	Community recruited PWID	2005-2010	24.1%	12.8 (95% CI: 7.7-20.0)	19	148.0	19.4
HITS-c study (20)	Sydney, NSW	Community recruited PWID	2008-2011	13.2%	7.9 (95% CI: 4.9-12.7)	17	215.2	19.4
Australian Needle and Syringe Program Survey (ANSPS) (21)	National	PWID attending NSP	2004-2010	14.0%	9.7 (95% CI: 6.9, 13.7)	33	340.2	37.3
Kirketon Road Centre (KRC) (22)	Sydney, NSW	PWID attending primary healthcare service	2011-2015	40.0%*	9.6 (95% CI: 7.8-11.2)	30	314.1	26.5
Combined					**9.3 (95% CI: 7.7-11.1)**	**118**	**1267.7**	**125.1**

*Estimated from (23)

Figure Legends

Figure 1: Unadjusted and adjusted incidence (per 100 person-years) in each study included in the analysis

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