Limited provision of diagnostic services to Victorians living with hepatitis C antibodies, 2001–2012: a multi-level modelling analysis

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Abstract

Objective: To determine what percentage of Victorians with a history of notified hepatitis C exposure received appropriate follow-up diagnostic services between 2001 and 2012.

Methods: Individual notification data and aggregate Medicare and supplementary testing data were entered into a compartmental transition model, which was used to estimate the percentage of people with a hepatitis C notification who were yet to receive either a negative diagnostic test for viral nucleic acid, or a test for viral genotype, at the end of 2012.

Results: We estimate that 58.2% (uncertainty interval: 42.2%, 72.4%) of Victorians with a hepatitis C notification between 2001 and 2012 did not receive either a negative test for viral nucleic acid or a viral genotyping test during the study period. At the end of 2012, we estimate there were approximately 20,400 Victorians living with hepatitis C antibodies who were yet to receive testing, of which approximately 9,300 would have been aged 45 years or older.

Conclusions: A majority of people living with HCV antibodies in Victoria had not received appropriate secondary diagnostic services as of the end of 2012.

Implications: As improved therapeutic options become available for people living with chronic hepatitis C, measures to support appropriate follow-up of people with suspected or confirmed chronic infections via primary care services will be required.

Key words: hepatitis C, health services, mathematical model, liver disease

Chronic hepatitis C virus (HCV) infection is a leading cause of liver-related mortality in Australia and around the world.[1,2] Of those exposed to the virus, 20–30% will clear it spontaneously without medical intervention; the remainder will develop chronic HCV infection.[3-4] Most chronic HCV infections are asymptomatic for many years, however prolonged infection poses a substantial risk of progression to advanced liver disease.[5]

Almost a quarter of a million Australians live with chronic HCV infection, of whom approximately 75,000 have progressed to moderate or advanced liver fibrosis, or to liver cirrhosis.[6] In Australia, HCV disproportionately affects people who inject drugs (PWID), with an estimated 55% of Australian PWID having been exposed to HCV,[7] and most new infections occurring through the sharing of contaminated injecting paraphernalia.[6]

Hepatitis C is a notifiable condition in Australia, with notification required upon detection of HCV antibodies (indicating a history of HCV exposure) or nucleic acid via blood test (which indicates active HCV infection).[8] Even after substantial decreases in the incidence of new infections over the past decade, there are approximately 10,000 new notifications for hepatitis C in Australia each year .[8]

Because a majority of HCV infections progress to chronicity, so long as the incidence of new infections substantially outpaces the rate of treatment with cure, the prevalence of chronic HCV infection in Australia will continue to rise. The uptake of treatment for hepatitis C has been persistently low, estimated at only 2,000–3,500 individuals annually, less than 2% of all chronically infected Australian residents.[9-12] Treatment uptake may be impeded by healthcare provider beliefs regarding exclusion criteria, particularly a perception that current injecting drug use is a contraindication, in spite of evidence that PWID can be treated successfully.[11,13]

Treatment for HCV infection is predominantly delivered through specialists either in private practice or through hospital-based liver clinics, although a small number of general practitioners are certified to administer treatment through the S100 Highly Specialised Drugs program.[14] Access is further impeded by poor knowledge of hepatitis C among some primary care providers,[14,15] mistaken or out-dated beliefs regarding exclusion criteria for treatment,[16] and recognition of the low efficacy and tolerability of historical interferon-based regimens.[9] A 2005 survey of individuals with a history of HCV infection in Victoria reported that only 37% of men and 52% of women had ever been referred to a hepatitis specialist regarding their infections.[17]

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The long-term consequences of the inadequate public health response to chronic viral hepatitis in Australia are now becoming apparent. Nationwide, the incidence of primary liver cancer has tripled since 1982, and liver cancer is now the 9th most common cause of cancer-related death in Australia.[18] Further increases are expected in the future.[19] In Victoria, one third of people diagnosed with hepatocellular carcinoma (HCC) die within a month, and median survival time is less than one year.[20]

On March 1 2016, several direct-acting antiviral (DAA) agents for hepatitis C were listed on the Pharmaceutical Benefits Scheme (PBS), meaning that shorter, more effective, and better-tolerated interferon-free treatment regimens are now available to Australians living with hepatitis C.[21] However, unless substantially increased numbers of people access treatment, the full public health benefit of these new therapies will not be realised.[9] In 2010, it was estimated that increasing the uptake of interferon-based therapy to 12,000 people per year from 2014 – only 5% of all those living with chronic hepatitis C – would result in cost savings of $9 million per year over three decades.[22] This has not been achieved; rather, it is estimated that the number of people accessing treatment for HCV infection did not exceed 3,500 in any year between 2009 and 2013.[6]

The clinical pathway from screening to treatment initiation involves several steps. After detecting HCV antibodies, it is recommended that clinicians order a qualitative or quantitative polymerase chain reaction (PCR) assay for viral RNA, to distinguish between resolved and active infection. If the PCR is positive, stage of liver disease and eligibility for treatment should be assessed and discussion with, or referral to a hepatitis specialist considered. Assessment for treatment requires a test for HCV viral genotype to determine the appropriate regimen.[8] In the present study, receipt of both a qualitative PCR confirming current infection status and, if PCR positive, a subsequent test for viral genotype was considered a "complete virological assessment" of a person with notified HCV exposure.

This study's primary objective was to determine the extent to which Victorians with a history of notified hepatitis C exposure have received adequate diagnostic services. We aimed to estimate the percentage of people with HCV exposure notified between 2001 and 2012 that had not received complete virological assessment by the end of 2012, and to describe the demographic composition of this group.

Methods

Data sources

De-identified data from notifiable disease surveillance notifications of individuals with HCV antibodies reported between 2001 and 2012 were obtained from the Victorian Department of Health and Human Services (DHHS). Variables included age, sex, and year of notification for each individual (duplicate notifications for the same individual are not entered into the surveillance database). Completeness of reporting on the relevant variables was high; age was reported for 99.6% of all individuals, sex for 99.0%, and year of notification for 100% of individuals. Individuals whose age or sex was unreported were not included in the model, which resulted in a final sample of 35,081 individuals with notified infections. As these data were permanently de-identified, no ethical approval for this study was required.

Qualitative PCRs may be reimbursed either through Medicare or through state-funded health services. Sex and age-group specific (categories 15–24, 25–34, 35–44, 45–54, 55–64, 65+ years) item reports on Medicare claims for qualitative PCR tests (MBS item 69499) claimed between 2001 and 2012 were retrieved from the public Medicare website.[23] This was supplemented with data on PCR tests provided through the Melbourne Sexual Health Centre (MSHC, the largest relevant state-funded service), obtained from the Victorian Infectious Diseases Reference Laboratory (VIDRL) for the same period. "Complete virological assessment" was defined as receipt of either a negative PCR, or both a positive PCR and a genotyping test.

Sex and age-group specific item reports on Medicare claims for genotype tests (MBS item 69491) claimed between 2001 and 2012 were retrieved from the public Medicare website.[22] Genotyping was not rebatable by Medicare prior to 2001, hence earlier data on testing are not available.

The estimated sex and age-specific risk of mortality each calendar year was based on all-cause mortality for 85,000 people notified with HCV antibodies in New South Wales (NSW) between 1998 and 2006,[1] as comparable Victorian data are not available. The median mortality risks between 1998 and 2001 were used for 2001, as this was prior to a substantial decline in drug-related mortality resulting from a national "heroin shortage", which began that year.[24] The sex and age-specific median risks between 2002 and 2006 were used for each year between 2002 and 2012.

Statistical methods

To estimate the accumulation of Victorians living with notified HCV infection who were yet to receive a complete virological assessment as of December 2012, a deterministic spread sheet model was developed and used to track the age of patients whose first HCV antibody notification was between 2001 and 2012 from the notification until further testing or death.

Children aged 0–14 years were excluded from the model due to the different diagnostic procedures required for this group.[25] As only 54 children in the sample (0.2% of the cohort) would have turned 15 by 2012, the effect of their exclusion from the next age stratum was minimal.

Each calendar year, patients were entered into the model in the appropriate age category, based on their age in the Victorian Department of Health and Human Services notification data. Individuals were removed based on: 1) the number of qualitative PCR tests received by each age group, with an assumption that a certain proportion of tests will return negative (meaning that a test for viral genotype is unnecessary); and 2) the number of genotyping tests provided by Medicare, assuming that receipt of this test represented a complete virological assessment for that individual.

Estimates of age and sex-specific all-cause mortality risks among people living with HCV antibodies were used to estimate the number of people in each age group who would have died prior to testing that year. After the removal of all those who received tests or died, ages were then incremented for the next year. Assuming homogeneous testing and mortality within each age-sex category, patients who had not been removed and would have turned 25, 35, 45, 55 or 65 years old during the year were moved to the next age bracket to start the following year. Those yet to receive a test or be removed from the model by the end of 2012 were assumed not to have received complete virological assessment.

Uncertainty intervals were estimated by varying the model's assumptions around two key parameters: 1) the proportion of tests given to people who are not contained in the notification dataset, 2) the proportion of people who test PCR negative.

With regard to the first assumption, individuals with infections notified during or after 2001 account for only 60% of the 56,280 Department of Health and Human Services notifications from 1995–2012. In addition to those living with infections reported from 1995–2000, there are likely to be individuals who screened positive but were not reported, as no surveillance system achieves perfect coverage. The combined effect of these factors is that a substantial proportion of tests after 2001 may have been provided to people whose infections were not included in the notification data for the analysis period. The point estimate assumes proportional receipt of testing by people within the notification dataset, while the lower bound estimate assumes that more tests were given to external individuals, which would decrease receipt of testing in our cohort (and vice versa with the upper bound estimate).

With regard to the second assumption, the probability of spontaneous clearance in people exposed to HCV is 20-30%.[3] As such, if PCR testing were performed at random, 20-30% of tests would be expected to return negative. However, in clinical practice, preferential antibody testing of individuals with clinical or biochemical features consistent with chronic infection would decrease this proportion. The point estimate assumes that 20% of PCRs return negative, consistent with the lower estimate of chronicity.

Table 1 shows the assumed percentage of tests in individuals not included in the notification dataset, as well as the variation in the PCR parameter for each model. Variation in mortality up to ±50% was initially included in the model, however the impact of this was negligible, and mortality was consequently held constant in the final analysis.

Results

Between 2001 and 2012, 35,081 individuals with HCV antibodies were notified to the Department in Victoria. During the same period in Victoria, there were 30,073 claims for HCV qualitative PCR tests through Medicare, and 16,373 claims for HCV genotyping tests for people of all ages. An additional 1,493 HCV PCR tests were provided through MSHC, as were 210 genotyping tests. We estimate that 58.2% of the cohort did not receive complete virological assessment during the study period (uncertainty interval: 42.2%, 72.4%).

Figure 1 shows the numbers of notifications and genotyping tests by sex and age group across the study period. The ratio of notifications to claims for genotyping tests ranged from 1.3:1 among men aged over 65 years to 6.2:1 among men aged 15-24 years. Ratios among women followed the same pattern across age groups, ranging from 1.2:1 among women aged over 65 years to 5.0:1 among women aged 15–24 years.

Under the best-guess model, the proportion of the cohort with an incomplete virological assessment at the end of 2012 was estimated at 58.2% (uncertainty interval: 42.2%, 72.4%), representing approximately 20,400 individuals who were alive at the end of 2012 and who had not yet received all recommended tests. We estimate that 2.9% of the cohort died prior to testing (Table 2).

Table 1: Values of key variable parameters in each model.

Model name	Tests for individuals external to the notification dataset	Percentage of PCR tests with negative results
Lower bound	20%	25%
Point estimate	40%	20%
Upper bound	60%	15%

Although variation in key parameters reveals substantial uncertainty, even under very conservative assumptions at least 42.2% of those with HCV exposure notified since 2001 would have had an incomplete virological assessment as of the end of 2012, a total of approximately 14,800 individuals (Table 2).

Receipt of testing was consistently lower among males than females, particularly in the younger age groups; only 14.6% of men who spent time aged 15–24 during the study period received a complete virological assessment before turning 25, compared to 34.2% of women in the same age group (data

Figure 1: Model schematic for first age group, 15–24-year-olds.

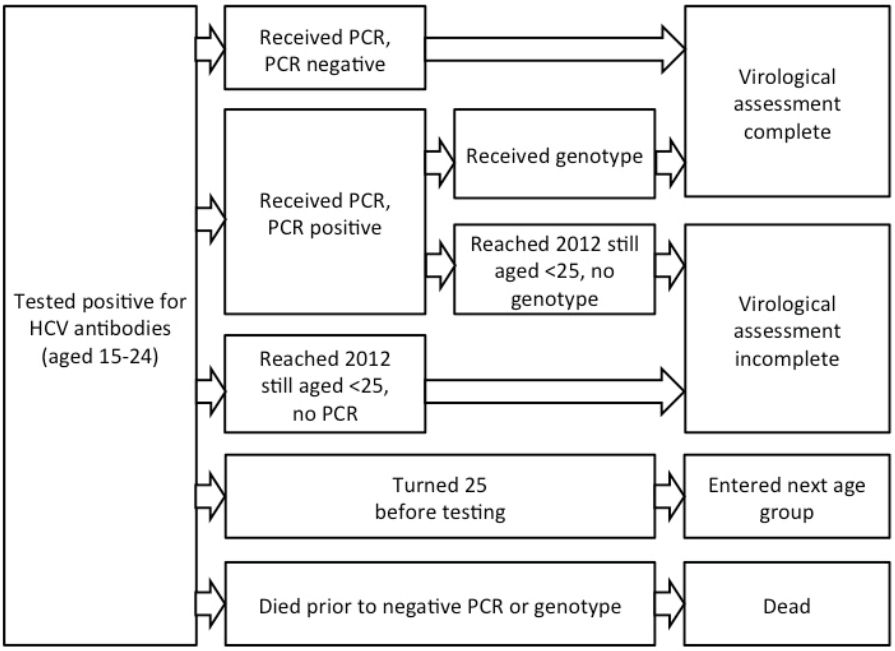


Table 2: Distribution of outcomes under each model.

Model	Notifications	Confirmed PCR –ve[a]	PCR positive & genotyped[b]	Died[c]	Incomplete virological assessment[d]
Lower bound	35,081	6,185 (17.6%)	13,276 (37.8%)	800 (2.3%)	14,820 (42.2%)
Point estimate	35,081	3,711 (10.6%)	9,957 (28.4%)	1,002 (2.9%)	20,411 (58.2%)
Upper bound	35,081	1,855 (5.3%)	6,638 (18.9%)	1,183 (3.4%)	25,404 (72.4%)

a: Received a PCR test which returned negative

b: Received a positive PCR followed by a test for viral genotype

c: Died prior to receiving either a negative PCR test or a positive PCR followed by a test for viral genotype

d: Still living at in December 2012, but yet to receive either a negative PCR test or a positive PCR followed by a test for viral genotype

not shown). Uptake improved marginally but consistently until age 45–54 years. Complete assessments appeared most common in this age group in both sexes, at 29.4% for males and 41.1% for females under the point estimate assumptions.

The age distribution of those with incomplete virological assessment in 2012 is shown in Figures 2 and 3, using estimates from the best-guess model. The age distribution under the other sets of assumptions was not materially different. Under the best-guess model there were an estimated 9,300 individuals aged 45 and over yet to receive a complete virological assessment in 2012; 45.8% of all those with incomplete virological assessments were in this age bracket.

Discussion

This analysis compared HCV notification data with PCR testing and viral genotyping data in Victoria between 2001 and 2012 to estimate the provision of diagnostic services to individuals who had been the subjects of a hepatitis C notification. Our analysis estimates that 58.2% of our state-wide cohort did not receive complete virological assessment during the study period.

This range was consistent with previous research in Victoria, which indicated that 63% of men and 48% of women surveyed had never been referred to a hepatitis specialist regarding their HCV infections.[17] At the end of 2012, the model estimated that approximately 20,400 individuals with a history of notified HCV exposure (UI: 14,800, 25,400) were yet to either receive a confirmation that their infection had cleared spontaneously, or have a chronic infection diagnosed and have the genotype of that infection identified to facilitate decision making about curative treatment.

In addition to the 35,081 individuals who were included in this analysis, a further 21,253 individuals were the subjects of notifications between 1995 and 2000, and an additional 4,391 notifications were recorded during 2013 and 2014.[26] If provision of diagnostic services to these individuals has been equally poor, the entire cohort of Victorians yet to receive appropriate follow-up for notified infections would be far larger than the 20,400 discussed here.

Tests for viral genotype have exceeded 80% of annual notifications only in the older age groups in recent years, indicating that chronically infected individuals who were diagnosed while they were younger may be catching up on diagnostic services after age 45, potentially as a result of long-term chronic infections becoming clinically apparent. This is concerning from both a clinical and a public health perspective; the risk of primary liver cancer is ten-fold higher in people aged 45–64 years than in those aged 25–44 years.[19] As such, this apparent failure to address chronic viral hepatitis acquired in youth before middle age is placing Victorians living with hepatitis C at avoidable excess risk of serious and potentially fatal sequelae. Although genotyping may not have been necessary for individuals who did not plan to pursue interferon-based therapy during the study period, the recent approval of interferon-free DAA regimens will provide these patients with much more tolerable and effective treatment options, should they wish to pursue treatment in the near future.

Limitations

There are some uncertainties about the number of individuals receiving follow-

Figure 2: Notifications and genotyping tests by sex and age group, 2001 to 2012.

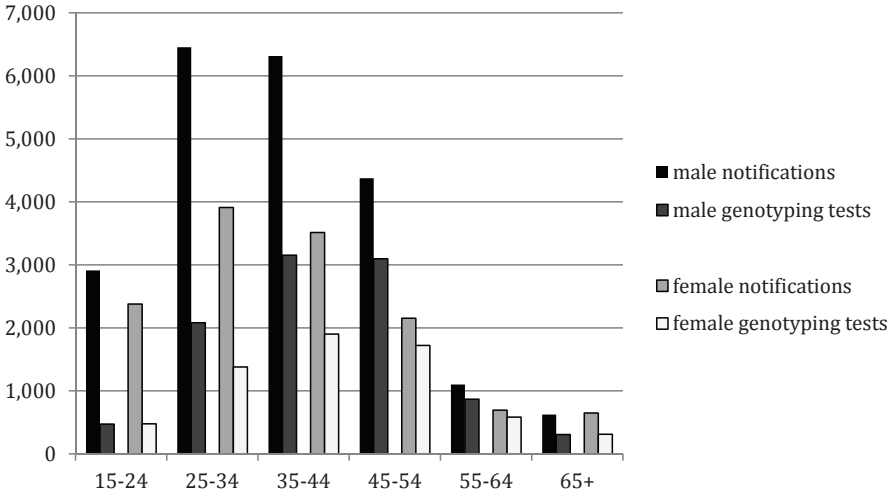


Figure 3: Age distribution of notifications and individuals with incomplete diagnostic assessments as of December 2012, males.

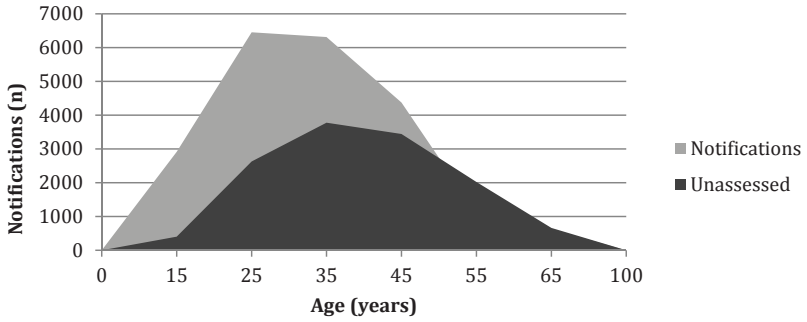
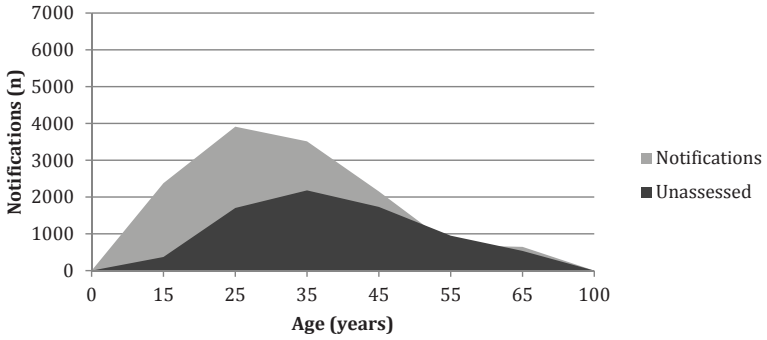


Figure 4: Age distribution of notifications and individuals with incomplete diagnostic assessments as of December 2012, females.



up testing. For example, the number of individuals engaged with care may be overestimated due to individuals who received multiple rebated tests, but underestimated due to some PCRs tests being administered through other state-funded providers (e.g. community-based health services, prison-based health services[27]) or through participation in clinical research. However, given that the Melbourne Sexual Health Centre is the largest relevant state-funded service and performed only 1,493 state-funded PCR tests compared to the 30,079 rebated by Medicare, the number and potential impact of tests performed by other state-funded providers is expected to be small. Genotyping tests are the more significant indicator, and these are only performed by three laboratories in Victoria, all of which are associated with public hospitals (Prof Scott Bowden, VIDRL, personal communication).

Some individuals may have received quantitative rather than qualitative PCRs – claims for quantitative tests to determine viral load (rather than the presence or absence of the virus) were not included in this analysis. The Medicare item number for quantitative tests (69488) does not distinguish between tests pre or post treatment. In addition, many individuals may receive an initial qualitative PCR to establish chronicity, followed by a quantitative PCR to establish replicative status (8), which would have led to over-estimation in the number of people receiving testing in the model.

Although there were 27,558 claims for quantitative tests during the study period, the material impact of excluding these tests is limited. Even in the ideal circumstance where all individuals had received PCRs, the low ratio of genotyping tests to notifications during the study period (16,595 vs. 35,081) indicates that, even assuming 30% of all people clear infection spontaneously and test PCR negative, no more than 67.5% of all chronically infected individuals can have received both a positive PCR and a genotyping test during the study period. For reasons described above with regard to tests for people outside the cohort and duplicate testing for some individuals, this percentage is likely to be lower in reality.

There is no way of estimating the number of people assessed for treatment prior to 2001 from the public data currently available, although the very low uptake of therapy nationally and the restrictive inclusion criteria prior to 2006 limits the probable impact of this earlier cohort on our results. The various versions of the model assumed between 0% and 60% of all tests were provided to individuals external to the notification data to which we had access (i.e. people with HCV infections notified prior to 2001, or detected but not reported). The upper limits of this range are consistent with the large number of individuals with histories of HCV exposure notified between 1995 and 2000, and with the greater clinical attention those with longer-term chronic infections should receive. The uncertainty around this parameter largely explains the substantial differences between the point estimate and the bounds – such uncertainties are unavoidable when working with these types of aggregate data.

Strengths

This analysis used complete, individual-level data on HCV notifications in Victoria covering the entire study period, and aggregate public Medicare data that constitutes the most complete record available of the relevant services, supplemented by additional data from the major community-based service in the state. The modelling approach used was simple and pragmatic and the model variants accounted for realistic potential variation in key parameters. This study is one of a small number examining the uptake of diagnostic services for HCV, a key intermediate step between initial identification of infection during screening and accessing treatment and avoids the biases inherent in studying these parameters in distinct clinical cohorts, particularly when considering the marginalised populations predominately affected by HCV.

A data linkage study similar to those performed to assess cancer incidence and mortality in New South Wales[1,28-29] could be used to validate the estimates in this analysis. Linkage of HCV notification data with Medicare records, the National Cancer Registry and the National Death Index would allow a direct estimate of the number of Victorians yet to receive clinical attention for notified HCV exposure, and a description of the demographic composition of this group, as well as the incidence of adverse outcomes.

Implications

Concerns have been raised repeatedly about the rising incidence of hepatitis C-associated advanced liver disease in Australia, and the resulting preventable and premature mortality.[1,13,16,28-31] Of particular concern in this analysis was the finding that almost half of those Victorians with incomplete virological assessments were aged over 45 years in 2012, highlighting the number of people living with chronic HCV infection who are at substantial risk of progression to advanced liver disease in the near future and who have apparently not yet been assessed for treatment.

The implications of our findings are twofold. Firstly, there is an urgent need to more proactively follow-up older Victorians living with chronic HCV infection, many of whom are likely already living with advanced liver disease, or at imminent risk of developing it.[6] Secondly, longer term strategies are required to ensure that complete virological assessment is achieved among young people with newly detected infections, to prevent the future burden of disease that will eventuate if they reach middle age with unmanaged chronic infection, as has happened with the previous generation. This is likely to require better engagement of young PWID in healthcare.[32] In general, there appears to be a substantial need for improved training for general practitioners and other clinicians engaged in HCV screening, which may include measures to address stigma associated with injecting drug use.

There is also a need for improved systems for tracking the care pathways of individuals, for example a dedicated registry for people living with chronic viral hepatitis. One such registry for viral hepatitis is under development in Portugal (Mr Ricardo Baptista Leite, Member of Parliament, Portugal, personal communication), while the Australian states and territories have maintained similar services to ensure appropriate follow-up of women with cervical abnormalities detected through pap smears since the 1990s, which could inform the development of similar services for people living with viral hepatitis.[33]

The development of more effective therapies presents an opportunity to substantially reduce the future burden of disease associated with chronic HCV infection in Victoria and around Australia. Modelling studies have shown that to achieve a significant impact nationally a large increase in treatment uptake will be required,[22-30] meaning that the current cascade of care for HCV treatment – which is particularly poor among PWID[34] – will need to be improved.[12,32] Our results identify diagnostic assessment as a significant bottleneck in the pathway to treatment, and investigation into

the precise reasons for this will be needed in order to determine the most appropriate interventions at both the primary care and health system levels. This issue will need to be addressed before the potential public health benefits of new HCV therapies can be fully realised.

Conclusion

We estimate that a majority of Victorians who tested positive for HCV between 2001 and 2012 were not provided with adequate diagnostic services during that period. At the end of 2012 almost half of these 20,400 individuals were aged over 45 years, and many of them will be at high risk of progression to advanced liver disease in the near future. Males were less likely to receive secondary diagnostic services than females and clinical follow-up of young men appears to be especially poor, placing them at particular risk of avoidable morbidity and mortality in future. In order to ensure that new, highly effective therapies for HCV achieve their full potential as a public health intervention, Australians living with hepatitis C must finally receive appropriate clinical and public health attention.

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