# Enhanced case detection for newly acquired hepatitis C infection: epidemiological findings and health service implications

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## Abstract

Identifying newly acquired hepatitis C infections and describing their epidemiological characteristics has public health importance but can be resource intensive. We developed a new approach to conducting surveillance for newly acquired hepatitis C infection and analysed the epidemiological findings and health service implications. Doctors and laboratories in the Australian state of Victoria are required by law to notify all hepatitis C diagnoses to the Department of Human Services, but the routine report is limited to basic demographic information. For all cases reported as being aged 16–19 years or having clinical or laboratory indicators of newly acquired infection, during the period July 2004 to December 2005, additional information was sought from diagnosing doctors and used to classify cases as 'newly acquired' or 'unspecified' using a standard case definition. Of the 4,561 hepatitis C notifications received by the Department during the study period, 415 (9%) were selected for follow up and 148 of these (36%) were classified as newly acquired infections, compared with 4%–10% achieved from previous systems. Based on the enhanced data collection, the most common risk factor for transmission among newly acquired infections was injecting drug use (86%), the median age was 23 years, 59% were males and the predominant reason for testing was drug and alcohol screening (32%). This surveillance system was much more efficient at detecting newly acquired cases of hepatitis C infection than other approaches used in Victoria. Initial results show that injecting drug use continues to be by far the predominant mode of hepatitis C transmission in Victoria. *Commun Dis Intell* 2008;32:250–256.

Keywords: hepatitis C, surveillance, epidemiology, Australia

## Introduction

Identifying and characterising cases of newly acquired (or incident) hepatitis C infection (HCV) enables public health officials to determine who is at risk, and assess and improve prevention efforts. It also provides a mechanism for monitoring the occurrence of transmission whether due to injecting drug use, or rarer pathways such as sexual contact[1] and skin-piercing, medical or cosmetic procedures.[2] Finally, diagnosis of hepatitis C in its acute or early stages provides the opportunity for treatment with a very high likelihood of clearance.[3]

Although active surveillance of clinical viral hepatitis can detect incident hepatitis C infections,[4] the yield is generally quite low, because the vast majority of these infections are asymptomatic.[5] The most commonly used approach for epidemiological monitoring of hepatitis C infection in most countries has been passive surveillance, based on legislatively mandated case reporting by doctors and laboratories to health departments,[6] but in its basic form it also has a limited ability to systematically detect incident infections. Therefore enhanced surveillance, involving the collection of information on prior hepatitis C testing and clinical history, has been undertaken to enhance the yield of incident cases.[6,7]

Doctors and laboratories in the Australian state of Victoria have been required to notify all diagnoses of hepatitis C infection to the Department of Human Services (DHS) since 1991. In 2000, DHS implemented a system in which all notifying doctors were followed up, and asked to provide enhanced information on risk factors and recency of infection. Because this approach was highly resource intensive, it was replaced in 2001 with a 10% random sample strategy[8,9] and in 2002, by an approach that targeted individuals aged 20 years and under, prisoners and military personnel.[10] A further major revision to the system was introduced in June 2004. This paper describes the new system, uses its output to identify predictors of recent hepatitis C infection, and compares its attributes to those of alternative systems.

## Methods

### Notification process

Doctors complete a standard notification form used for all notifiable diseases, including patient demographics, the disease being notified and, for hepatitis C, whether the disease was acute or not, its onset date and clinical symptoms and doctor contact details. Laboratories send a copy of the pathology report. Testing is based on routine laboratory diag-

nostic methods, which would generally begin with an antibody test for hepatitis C, and may include tests for hepatitis C RNA.

A duplicate search is then conducted on the DHS notifiable disease database. Cases with a history of a previous HCV notification (which may include re-infections) will not be counted or followed up.

### Enhanced surveillance system

Cases of hepatitis C that were notified by a doctor or laboratory in people aged 16–19 years, or with specific indicators of recent acquisition, were selected for enhanced surveillance. The specific indicators that triggered enhanced surveillance were:

(a) doctor describes infection as acute;

(b) clinical indicator: any clinical suggestion of incident hepatitis C infection written on the doctor notification form i.e. bilirubin in urine, jaundice or elevated liver function tests;

(c) laboratory indicator: any evidence of a prior negative hepatitis C result or ALT 7 times the upper limit of normal.

The 16–19 years age group was selected to maximise the number of newly acquired infections detected, under the assumption that transmission among injecting drug users (IDUs), the primary hepatitis C risk group, is likely to occur most frequently within the first few years of initiation into injection,[11,12] an event that takes place at a median age around 18–19 years.[13,14]

For cases selected for enhanced data collection, surveillance officers contacted the doctor recorded on the notification form to obtain the information on reason for test, clinical indicators of acute hepatitis C, hepatitis C testing history (past negative and positive antibody and RNA tests), risk factors, results for hepatitis B serology and whether hepatitis A and B vaccines had been offered. The specific list of risk factors were consistent with those recommended as part of the National Hepatitis C Surveillance Strategy.[7] If the doctor could not provide the required information, permission to speak to the patient was sought and if obtained, the patient was contacted. Doctors were initially contacted by phone, however if repeatedly unavailable a letter and enhanced surveillance form were faxed. If the reported mode of transmission was other than injecting drug use, the case was referred for additional follow up.

A case was classified as either 'newly acquired' or 'unspecified' according to the Communicable Diseases Network Australia case definition for hepatitis C.[15] The Box shows the criteria used for the classification of hepatitis C newly acquired and unspecified cases.

No ethical approval was received for the enhanced surveillance as the activities were conducted on behalf of and in collaboration with DHS and the enhanced data collection procedures are covered under government legislation.

### Statistical analyses

When more than one risk factor was reported a nationally recommended hierarchy was employed and the case classified according to the risk factor recorded as the most common.[16]

Cases classified as newly acquired on the basis of the follow up data collection (from either doctor or patient) were compared with those not classified as newly acquired, with regard to demographic and risk factor variables. Univariate analysis was conducted to identify variables associated with being classified as newly acquired. Identified predictors were then analysed using a multiple logistic regression model.

**Box. Communicable Diseases Network Australia newly acquired hepatitis C case definition**

*Hepatitis C (newly acquired) – meets at least one of the following criteria*

- Detection of anti-hepatitis C antibody from a person who has had a negative anti-hepatitis C antibody test recorded in the past 24 months
- detection of hepatitis C virus by nucleic acid testing from a person who has had a negative anti-hepatitis C antibody test result within the past 24 months
- detection of anti-hepatitis C antibody from a child aged 18–24 months
- detection of hepatitis C virus by nucleic acid testing in a child aged 1–24 months
- detection of anti-hepatitis C antibody or hepatitis C virus RNA and clinical evidence (jaundice or bilirubin in urine or ALT 7 times upper limit of normal)

*Hepatitis C unspecified case*

- Has laboratory definitive evidence (antibody or nucleic acid testing) and does not meet any of the above criteria for newly acquired case and is aged more than 24 months

Based on the final classification of cases (newly acquired or unspecified) we assessed the positive predictive value of the criteria that had been used to select cases for follow up.

### Surveillance system attributes including resource utilisation

Attributes of various types of surveillance were compared. Calculation of resources used was based on an average 2.3 hours that was required to follow up each of the 415 notifications reported in this analysis. The number of staff days required per method was then calculated by multiplying the 2.3 hours per case by the expected number of cases followed up.

Data were managed and analysed using Stata Version 9.[17]

## Results

Between July 2004 and December 2005, 4,561 notifications of hepatitis C were reported. On the basis of the selection criteria for additional data collection, 415 (9%) were followed up. The diagnosing doctor could not be contacted for 37 (9%) cases of which 3 were subsequently classified as newly acquired based on the receipt of laboratory results indicating a prior negative test.

Of the 415 cases, most (n=260, 63%) were followed up on the basis of clinical or laboratory indicators, with over half of these being reported as acute at the time of notification (n=146, 56%). A further 163 were followed up due to the age being recorded in the range 16–19 years and 29 satisfied the follow up criteria on the grounds of both age and clinical or laboratory indicators.

### Newly acquired hepatitis C infection

Enhanced information allowed 148 of the 415 cases (36%) to be classified as newly acquired infections; the majority (70%, n=104) based on a record of having had a negative hepatitis C test within the 24 months prior to diagnosis and the remainder (30%, n=44) based on a record of clinical evidence consistent with the national case definition for acute hepatitis C infection.

A total of 182 hepatitis C notifications were followed up because they were recorded as being in a person aged 16–19, and of these cases, 27% (n=49) were ultimately classified as newly acquired. Based on clinical or laboratory indicators, 260 notifications were followed up with 44% (n=115) finally classified as newly acquired infections.

### Predictors of newly acquired hepatitis C infection

The median age of infections classified as newly acquired was 23 years (range: 16–52 years) compared with 19 years (range: 2–70 years) for unspecified infections. A lower proportion of acute cases were aged 16–19 years (33%) compared with unspecified infections (51%) but a higher proportion were aged less than 40 years (94%) compared with unspecified infections (85%). Being younger than 40 years was a significant predictor (OR=6.0, 95% CI= 2.1–16.9) in multivariate analysis.

A higher proportion of acute cases were born in Australia (82%) compared with unspecified infections (60%). In univariate analysis being born in Australia was predictive of newly acquired infection (OR=2.4, 95%CI=1.1–4.4) but was non-significant in the multivariate model.

Cases ultimately classified as acute were most often tested as part of a drug and alcohol screen (32%), or for clinical signs and symptoms of acute hepatitis C (27%); the corresponding proportions for unspecified infections were 23% and 4% respectively with the latter reason found to be an independent risk factor (OR=9.1, 95% CI=3.9–21.5) for newly acquired infection in the multivariate analysis.

The most frequently reported risk exposure in the previous 2 years among newly acquired hepatitis C infection was injecting drug use, reported by 86%, compared with 60% in unspecified infections. In multivariate analysis, this factor was predictive of newly acquired infection (OR=2.9, 95%CI=1.4–6.0). Other exposures were each reported at low levels (less than 3%) among newly acquired cases, but some were slightly more frequent than in unspecified infections; resulting in moderate associations in univariate analysis for tattooing (OR=1.9, 95% CI=1.1–3.3); piercing (OR=2.2, 95% CI=1.2–4.3) and being in prison (OR=1.8, 95%, CI, 1.01–3.2), that were all non-significant in the multivariate model. (Table 1).

### Positive predictive value of 'surveillance reason for follow up' for newly acquired infections

There was considerable variation in the degree to which the clinical and laboratory selection criteria were able to predict the likelihood of a case ultimately being classified as acute, and the positive predictive value of these criteria also varied with age. The predictive value of both clinical and laboratory criteria was high for those aged 16–19 years and then decreased sharply with age, whereas for cases followed up because the doctor had indicated that they were acute, the predictive value was generally lower and unrelated to age (Table 2).

## Table 1. Characteristics of hepatitis C infections and predictors of hepatitis C newly acquired infections

| Variable | Subgroup | Newly acquired | | Unspecified | | Univariate OR 95% CIs | Multivariate OR 95% CIs** |
|---|---|---|---|---|---|---|---|
| | | n=148 | % | n=267 | % | | |
| Age group | <40 years | 139 | 93.9 | 222 | 85.4 | **2.6 (1.2, 5.6)** | **6.0 (2.1, 16.9)** |
| | 40+ years* | 9 | 6.1 | 38 | 14.6 | – | |
| Sex | Female | 61 | 41.2 | 123 | 46.1 | 0.8 (0.6, 1.2) | |
| | Male* | 87 | 58.8 | 144 | 53.9 | – | |
| Region of birth | Australia | 122 | 82.4 | 161 | 60.3 | **2.4 (1.1, 4.4)** | |
| | Other* | 11 | 10.3 | 35 | 13.1 | – | |
| | Unknown | 15 | 17.4 | 71 | 26.6 | 1.5 (0.6, 3.9) | |
| Surveillance reason for follow up* | Doctor described infection as acute | 68 | 45.9 | 78 | 29.2 | **2.0 (1.3, 3.1)** | **2.1 (1.2, 3.7)** |
| | Aged 16–19 years | 49 | 33.1 | 135 | 50.6 | 0.3 (0.2, 0.5) | |
| | Clinical indicator | 32 | 21.6 | 30 | 11.2 | **2.2 (1.3, 3.7)** | **2.1 (1.01,4.5)** |
| | Laboratory indicator | 27 | 18.2 | 21 | 7.9 | **2.6 (1.4, 4.8)** | **4.3 (2.0, 9.2)** |
| Diagnosing clinic type | General practitioner | 83 | 56.1 | 155 | 58.1 | 0.9 (0.6, 1.3) | |
| | Other* | 62 | 42.0 | 100 | 37.4 | – | |
| | Unknown | 3 | 2.0 | 12 | 4.5 | 0.4 (0.11, 1.46) | |
| Reason for test* | Drug and alcohol screening | 47 | 31.8 | 62 | 23.2 | 1.3 (0.9, 2.1) | **1.8 (1.04, 3.2)** |
| | Symptoms and signs of acute hepatitis | 40 | 27.0 | 11 | 4.1 | **7.8 (3.9, 15.9)** | **9.1 (3.9, 21.5)** |
| | Patient request | 38 | 25.7 | 65 | 24.3 | 0.9 (0.6, 1.5) | |
| | Abnormal LFTs | 35 | 23.6 | 30 | 11.2 | **4.4 (2.4, 8.2)** | **2.5 (1.3, 5.0)** |
| | Other screening | 24 | 16.2 | 30 | 11.2 | **3.0 (1.6, 5.8)** | **2.6 (1.3, 5.2)** |
| | Other* | 37 | 25.1 | 166 | 62.2 | – | |
| Risk factor†,‡ | Injecting drug use | 127 | 85.8 | 161 | 60.3 | **3.9 (2.3, 6.5)** | **2.9 (1.4, 6.0)** |
| | Tattoo | 4 | 2.7 | 1 | 0.4 | **1.9 (1.1, 3.3)** | |
| | Piercing | 3 | 2.0 | 1 | 0.4 | **2.2 (1.2, 4.3)** | |
| | Sexual partner hepatitis C positive | 3 | 2.0 | 9 | 3.4 | 1.3 (0.8, 2.2) | |
| | Surgery | 3 | 2.0 | 6 | 2.2 | 1.2 (0.5, 2.6) | |
| | Household contact hepatitis C positive | 2 | 1.4 | 7 | 2.6 | 1.0 (0.5, 1.9) | |
| | Prison | 1 | 0.7 | 3 | 1.1 | **1.8 (1.01, 3.2)** | |
| | Other | 6 | 4.0 | 24 | 9.0 | 0.8 (0.4, 1.5) | |
| | Risk factor not determined | 3 | 2.0 | 11 | 4.1 | 0.4 (0.1, 1.3) | |

Significant variables are in bold type.

OR Odds ratio

* The reference group used to calculate the odds ratio.

† Not mutually exclusive, multiple responses could be ticked on the enhanced surveillance form. For the univariate and multivariate analysis, the 'yes' response was compared to the 'no' response.

‡ When injecting drug use was reported only injecting drug use was reported. For cases with non-injecting drug use risk factors all risk factors were reported

### Enhanced hepatitis C surveillance system attributes

We estimated that it would take 17.8 days per week (or more than 3 full time surveillance officers) to follow up all notifications received (Table 3). A 10% random sample would require 2.9 days per week for a yield of 14 cases per year. The strategy described in this paper of following up cases with clinical or laboratory indicators and all notifications in people aged 16–19 years would yield approximately 100 newly acquired infections per year with a surveillance officer working 2.5 days a week.

**Table 2. Positive predictive value of 'surveillance reason for follow up' for newly acquired hepatitis C infections, by age group**

| Surveillance reason for follow up* | Age group (years) | Positive predictive value (%) |
|---|---|---|
| Doctor described infection as acute | 16–19 | 54 |
| | 20–24 | 62 |
| | 25–29 | 53 |
| | 30+ | 36 |
| Clinical indicator | 16–19 | 100 |
| | 20–24 | 77 |
| | 25–29 | 38 |
| | 30+ | 38 |
| Laboratory indicator | 16–19 | 73 |
| | 20–24 | 60 |
| | 25–29 | 50 |
| | 30+ | 45 |

* Not mutually exclusive – multiple reasons may be selected.

Following up cases based on clinical or laboratory indicators only, produced a greater yield of newly acquired infections (44%) per case followed up, compared with the age-specific strategy alone (27%). It was estimated that it would require 2 days of work by the surveillance officer to detect 76 newly acquired infections per year. An age-specific strategy (16–19 years) would require 1.7 days work by the surveillance officer to follow up an estimated 33 newly acquired cases. A strategy based on a 22–24 years age group would yield an estimated 124 newly acquired infections, and widening the age group to 20–24 years would identify 186 cases per year and require an estimated 3.8 days per week.

## Discussion

The selection of hepatitis C notifications for follow up based on either young age or clinical or laboratory indicators identified newly acquired hepatitis C infections more frequently (36%) than systems that involved follow up of all cases (10%)[18] or a 10% random sample (4%).[8]

Among newly acquired infections, the median age of cases was 23 years. This finding is consistent with the expected average age of hepatitis C seroconversion for IDUs; the reported average age of onset of injecting among IDUs in Australia is between 18 and 19 years[13,14] and the average time to seroconversion after beginning to inject was estimated to be approximately 3 years in a study conducted in the United States of America.[19]

Injecting drug use continued to be by far the predominant mode of hepatitis C transmission in Victoria, as it has been in the rest of Australia and other Western countries.[1] A very low percentage of newly acquired

**Table 3. Specific attributes of different enhanced surveillance methods**

| Enhanced surveillance methods | Estimated cases per year | Estimated cases per week | Estimated surveillance days per week | Estimated proportion of cases identified as newly acquired infections (%) | Estimated Number of newly acquired infections per year | Demographically representative of newly acquired infections |
|---|---|---|---|---|---|---|
| 'Clinical or laboratory indicators' or 'aged 16–19' | 277 | 5.3 | 2.5 | 36 | 100 | No |
| 'Clinical or laboratory indicators' | 173 | 3.3 | 2.0 | 44 | 76 | Yes |
| Aged 16–19 years | 121 | 2.3 | 1.7 | 27 | 33 | No |
| Aged 19–21years | 237 | 4.6 | 2.3 | 37* | 81 | No |
| Aged 22–24 years | 336 | 6.5 | 2.8 | 37* | 124 | No |
| Aged 20–24 years | 504 | 9.7 | 3.8 | 37* | 186 | No |
| 10% random sample | 341 | 6.6 | 2.9 | 4† | 14 | Yes |
| All cases | 3,040 | 58.5 | 17.8 | 10‡ | 304 | Yes |
| Passive surveillance | 3,040 | | | none | 0 | No |

* Based on results from the 1996 New South Wales system.[1]

† Based on results from the 2001 Victorian system.[2]

‡ Based on the assumption that the proportion would be higher for those aged ≥19 years.

infections reported tattooing or sexual contact with a hepatitis C positive individual as a risk exposure; none of these individuals reported a history of IDU. It is possible that the reported occurrence of sexual risk may be an over-estimation because information on injecting drug use was not obtained from 2 of the 3 newly acquired cases. Although there are reports accumulating, which suggest that hepatitis C transmission can occur sexually among HIV positive men who have sex with men,[1] overall the occurrence of sexual transmission of hepatitis C remains rare.[20]

The enhanced surveillance system described here was not representative of all hepatitis C notifications, due to the incorporation of the age-specific strategy. The strength of this strategy is that it provides information on a well defined population that is at elevated risk of hepatitis C infection. The strategy could be extended to include a wider age range, but would require significantly more resources.

Although the follow up of cases with clinical or laboratory indicators of acute infection identified a higher proportion (44%) of newly acquired infections than the age-specific strategy it was somewhat surprising that more than half of these cases could not be confirmed as newly acquired. The confirmation rate would be substantially increased if follow up based on clinical or laboratory indicators was restricted to those aged less than 30 years. The lower positive predictive values in older cases may be due to the increase likelihood of chronic hepatitis infection with increasing age.[21]

There are several limitations that need to be considered when interpreting these findings. Firstly, a small number of doctors and laboratories were unable to be contacted to obtain enhanced surveillance information, resulting in these notifications being classified as unspecified. However, due to the small number it is unlikely that this 'loss to follow up' had any substantial impact on our results. Secondly, the assignment of risk factor is probably more accurate for newly acquired infections than it is for longer standing infections, as the risk occurred within a 2 year time frame and is hence less subject to recall bias.

Finally, any community wide surveillance system for hepatitis C has the inherent limitation that infections are rarely symptomatic in the early stages, and that most cases will therefore remain undetected.[5] Even if testing is conducted, it may be difficult to distinguish a newly diagnosed case as newly acquired, unless there is a history of a recent negative test prior to the positive diagnosis.

Considering the limitations of enhanced surveillance as a means of identifying and characterising newly acquired hepatitis C infections, alternative approaches to measuring hepatitis C incidence may also be necessary. Recruitment of people at risk of hepatitis into research cohorts is one option but it is very expensive and likely to be unrepresentative. Clinical services which offer regular testing to people at risk of hepatitis C provide another mechanism for monitoring incident cases.[16] The number of diagnoses detected in this way will be dependent on the regularity of client visits, but such cases may be more broadly representative of community patterns of infection than cases arising in a research cohort.

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