Hospitalization rates associated with hepatitis B and HIV co-infection, age and sex in a population-based cohort of people diagnosed with hepatitis C

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SUMMARY
To determine the extent age, sex and co-infection affect morbidity in people infected with hepatitis C virus (HCV), we performed a population-based study linking HCV notifications in New South Wales, Australia with their hospital (July 2000 to June 2006), hepatitis B virus (HBV) and HIV notification, and death records. Poisson models were used to calculate hospitalization rate ratios (RRs) for all-cause, illicit drug and liver-related admissions. Co-infection RRs were used to estimate attributable risk (AR). The 86 501 people notified with HCV contributed 422 761 person-years of observation; 0.8% had HIV, 3.7% HBV, and 0.04% had both. RRs for males were equal to or lower than for females in younger ages, but higher in older ages (P for interaction ≤0.013). HBV/HIV co-infection resulted in ARs of over 70% for liver disease and 30–60% otherwise. However, at the cohort level the impact was minimal (population ARs 1.3–8.7%). Our findings highlight the importance and success of public health measures, such as needle and syringe exchange programmes, which have helped to minimize the prevalence of co-infection in Australia. The findings also suggest that the age of study participants needs to be considered whenever the burden of HCV-related morbidity is reported by sex. The results are likely to be representative of patterns in hospital-related morbidity for the entire HCV-infected population in Australia and the ARs generalizable to other developed countries.

Key words: Hepatitis B, hepatitis C, hospitalization, HIV/AIDS, record linkage.

INTRODUCTION
Infection with hepatitis C virus (HCV) is known to be associated with increased morbidity compared to the general population [1–6] and certain cofactors are thought to add to this burden. There is good evidence that age at infection, duration of infection, male gender, and co-infection with either HIV or hepatitis B virus (HBV) are predictors of liver disease progression in people with chronic HCV [7, 8]. However, this evidence has mostly come from clinic-based studies (usually cross-sectional), studies of small cohorts infected through transfusion of blood products or injecting drug use (IDU) [9, 10], or using a larger cohort of veterans in the USA [11] which may not be representative of the general HCV-infected population [7, 11, 12]. Recent population-based studies examining predictors of excess morbidity have been conducted in Scotland [13, 14]. However, they did not examine the excess burden associated with HBV co-infection and focused on all-cause morbidity.
[13] or first hospital admission (or death) due to decompensated liver disease only [14]. The aim of this study was, therefore, to determine the relative effect of age, sex and both HIV and HBV co-infection status on all-cause, as well as liver and illicit drug-related, hospitalization rates in all people notified with chronic HCV in New South Wales (NSW), Australia.

**METHODS**

**Data sources**

Our study cohort included all people notified with HCV infection in NSW (population 7 million), as recorded on the NSW Notifiable Diseases Database (NDD) between 1992 (when personal identifiers were first recorded) and 2006. HCV cases co-infected with HIV and HBV were identified by linkage to NDD notifications for HBV and to NSW data from the National HIV Registry (NHR) and National AIDS Registry (NAR). Under the Public Health Act 1991 all new HBV, HCV, HIV and AIDS diagnoses are notifiable to the NSW Department of Health. HIV infections have been notifiable since 1985 and NAR contains data on all AIDS diagnoses since 1982. The NDD, NHR and NAR records contain demographic information (including full name for NDD and name code (first two letters of surname and given name) for HIV and AIDS notifications) and variables for disease code and diagnosis date.

Hospital admissions for the cohort were obtained from the Admitted Patient Data Collection, a database which covers all in-patient admissions from all public (including psychiatric) and private hospitals in NSW. The data are collected by financial year (1 July to 30 June) of separation (discharge, transfer, death, or change in admission type within the same hospital). Each admission includes demographic and administrative information and diagnosis and procedure fields coded according to the 10th revision of the International Classification of Diseases – Australian Modification (ICD-10-AM). Up to 55 diagnostic codes can be recorded for each admission. For our analysis, admissions were categorized by their principal (first) diagnostic code (used to record the main condition responsible for the admission). Patient name has been recorded since 1 July 2000. For this reason, the study period was limited to separations from 1 July 2000 to 30 June 2006 (the most recent year data were available).

The Registry of Births Deaths and Marriages is a registry of all deaths (based on receipt of a medical certificate of cause of death) in NSW and includes the date of death. We used date of death to determine if and when a person died in order to censor their person-years at risk.

**Linkage process**

Data linkage was carried out by the Centre for Health Record Linkage (CHeReL) [15]. The NDD, hospitalization and death data were linked using probabilistic record-linkage methods and Choice-Maker software [16]. Full name on the NDD dataset was then recoded to name code before linkage with the AIDS/HIV registries using deterministic methods based on a 100% match on name code, date of birth and sex.

**Exclusions**

Cases were excluded if age or sex was missing, and were ineligible if they died before the start of the study period or within 14 days of their diagnosis date, or were diagnosed within 14 days of the end, or after, the study period. All hospital admissions before or beginning within 14 days of diagnosis were excluded to reduce the bias towards higher rates of admission around the time of diagnosis [6]. Duplicate and nested admissions (i.e. an admission wholly within the date range of another admission) were removed so that there was only one admission (and therefore one principal diagnostic code) for each time period. We also excluded admissions with a principal diagnostic code of extracorporeal dialysis (Z49.1). The high prevalence of HCV in patients undergoing dialysis is already known [17] and dialysis accounted for by far the highest number of admissions in our cohort (17% of all admissions, rate 9.9/100 person-years) [4] and could therefore subsume any other associations.

**Statistical analysis**

Rates of admission were calculated using person-years at risk as the denominator. This was calculated for each person as the time 14 days after diagnosis or from the start of the study period (whichever was later) until the end of the study period or death (whichever came first). Hospital admission rate ratios (RRs)
with 95% confidence intervals (CIs) were calculated using a random effects Poisson regression model to account for the correlation between hospitalizations for the same person [18]. Three outcomes were examined: admission rates for all causes, illicit drug-related, and HCV-related liver disease (non-alcoholic liver disease and liver cancer). Independent risk factors included in each model were age (time dependent, in 15-year age groups (collapsed to 30-year age groups where the number of admissions were small]), sex, and co-infection with HIV and HBV. Each model was also adjusted for calendar year (time dependent). The interaction between age and sex was also investigated as our previous study identified higher admission rates in females than males in young age groups but the opposite trend in older age groups [4]. There were too few people in the cohort with both HIV and HBV co-infection to investigate the interaction of these terms. The significance of each independent variable including the interaction term was determined using the likelihood ratio test.

The adjusted RRs for HIV and HBV co-infection obtained from the Poisson models were used to estimate the attributable risk per cent (AR%) and population attributable risk per cent (PAR%) using the following formulas [19]:

\[
\text{AR\%} = \frac{\text{RR} - 1}{\text{RR}} \times 100,
\]

\[
\text{PAR\%} = \frac{\text{Pe} \times (\text{RR} - 1)}{(\text{Pe} \times (\text{RR} - 1) + 1)} \times 100,
\]

where Pe is the proportion of the cohort co-infected with either HBV or HIV.

Ethics approval was granted by the University of NSW and the NSW Population and Health Services Research Ethics Committee.

### RESULTS

#### Study cohort

There were 91986 people notified with HCV in 1992–2006; 4731 (5.1%) were ineligible and 754 (0.9%) of those eligible were missing information for age or sex. The remaining cases comprised the study cohort, which is described in Table 1.

#### Age and sex

There was a significant interaction between age group and sex for all-cause \(\chi^2 (5 \text{ D.F.}) = 292.25, P < 0.001\), illicit drug-related \(\chi^2 (4 \text{ D.F.}) = 20.29, P < 0.001\] and HCV-related liver disease \(\chi^2 (4 \text{ D.F.}) = 12.65, P = 0.013\] admissions, and so results are presented by age and sex groupings combined (for details of added effect of interaction terms see Supplementary Table S1, available online).

RRs for all-cause hospitalizations were higher in females than in males for the \(<45 \text{ years age group}\) while the reverse was the case for those aged \(\geq 60 \text{ years} (\text{Fig. 1})\). RRs for males increased with age, while RRs for females showed a peak in 15- to 29-year-olds as well as increasing with age in those aged \(\geq 60 \text{ years}\).

RRs associated with illicit drug-related admissions were highest in the 15–29 years age group for both males and females (Fig. 2). Males and females had similar RRs in age groups <30 years, but in older age groups males had higher RRs.

RRs for HCV-related liver disease tended to increase with age for both males and females (Fig. 3).
However, in the ≥75 years age group the RR for males was significantly higher than for females.

**Hepatitis B and HIV co-infection**

Co-infection with HBV or HIV significantly increased the rate of hospitalization for all causes, illicit drug-related admissions, and especially HCV-related liver disease (Table 2). For all-cause admissions, the RR for HIV co-infection was significantly higher than for HBV co-infection, whereas within the illicit drug-related or HCV-related liver disease admissions the RRs for HBV and HIV were not statistically different. In members of the cohort who were co-infected with either HIV or HBV, a considerable proportion of admissions could be attributed to their co-infection (if it is assumed that co-infection causes the increased rates). For example, 61% of all admissions in the HIV co-infected group could be attributed to their HIV infection. Despite the high AR, however, due to the low prevalence of co-infection (Table 1), especially with HIV, only a small percentage of hospitalizations for the whole cohort could be attributed to co-infection. The exception was HBV co-infection, which was attributed to 8.7% of admissions for HCV-related liver disease in the cohort.

**DISCUSSION**

Within the NSW cohort of people notified with HCV, co-infection with HIV and HBV, as well as a person’s age and sex, impacted significantly on their rate of hospitalization. RRs for all-cause and liver-related morbidity increased with age, while the RR for illicit drug-related admissions was highest in the 15–29 years age group. However, for all three admission types examined there was a significant interaction between age and sex with RRs for males being equal to or lower than for females at younger ages, but higher in older ages. Individuals with HIV or HBV co-infection had significantly increased rates of hospitalization compared to those with HCV mono-infection, especially for liver disease. However, public health measures such as needle and syringe programmes (NSPs) [20] have helped to minimize the prevalence of co-infection in Australia’s HCV-infected population. Therefore the additional burden of morbidity attributable to co-infection in our HCV-infected cohort was minimal.
Over 70% of hospital admissions for liver disease and 30–61% of admissions for all-cause and illicit drug-related conditions in individuals with HBV or HIV co-infection could be attributed to their co-infection status. Hence, at an individual level, co-infection added significantly to the burden of morbidity either directly or because treatment is more difficult [21]. Therefore ongoing efforts to prevent co-infection, including increased HBV vaccination coverage in IDUs [22] and wider access to NSPs [23] are important public health measures.

Despite the high AR, at a population level fewer than 9% of liver-related, 4% of illicit drug-related and 2% of all-cause admissions in our cohort were attributable to HBV co-infection and the PARs for HIV were less than 3%. This is because of the low prevalence of co-infection in the HCV-infected cohort, which mirrors the low prevalence in Australia’s IDU population [22, 24] (who contribute most newly notified cases of HCV in Australia [25]), but is in contrast with estimates reported from many other countries. HIV has been estimated in population-based HCV cohorts in Denmark (4%) and Scotland (4%) [5, 26], but more widely in IDUs. High prevalence estimates among IDUs have been reported in Eastern Europe (especially Estonia) [27], Spain, and South East Asia [28, 29]. While the USA, China, Italy, India and France have prevalence estimates >10% [28, 29]. Many of these countries, particularly China, and parts of South East Asia, also have a high prevalence (≥8%) of chronic HBV in the community [30]. In such countries, the proportion of hospitalizations in the HCV-infected population attributable to co-infection and the overall burden of morbidity is expected to be considerably higher than in Australia.

The low prevalence of HIV and HBV co-infection in Australia’s IDU population could be explained by the fact that blood to blood transmission of HIV is less likely than for HCV [31] and that a high proportion of adults infected with HBV clear the infection. In addition, blood screening programmes for HIV and HBV have been in place longer than those for HCV, and HBV is preventable by vaccination. However, it is likely that the introduction of NSPs in Australia in the late 1980s (while the prevalence of HIV and HBV in IDUs remained low but the prevalence of HCV was already >50% [31]) contributed significantly to preventing HIV and HBV co-infection. HIV, HBV and HCV are all blood-borne viruses and therefore can be transmitted via sharing infected needles and other injecting equipment. It is therefore biologically plausible that providing clean syringes would reduce the transmission of these viruses in IDUs. Indeed many studies have shown an impact [32–34], although randomized trials have not been conducted due to logistical and ethical concerns. A

### Table 2. Effect of HIV and hepatitis B (HBV) co-infection on rates of hospitalization in people notified with hepatitis C, by type of admission

<table>
<thead>
<tr>
<th>Type of admission (ICD-10 codes)</th>
<th>Exposure</th>
<th>Person-years</th>
<th>Rate*</th>
<th>RR†</th>
<th>95% CI</th>
<th>P value</th>
<th>AR%</th>
<th>PAR%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All causes‡</strong></td>
<td>HBV</td>
<td>Neg. 133 808</td>
<td>407 586</td>
<td>32.8</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pos. 6634</td>
<td>15 175</td>
<td>43.7</td>
<td>1.43</td>
<td>1.32–1.54</td>
<td>&lt;0.001</td>
<td>30.1</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
<td>Neg. 138 206</td>
<td>419 493</td>
<td>32.9</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pos. 2236</td>
<td>3267</td>
<td>68.4</td>
<td>2.57</td>
<td>2.20–3.01</td>
<td>&lt;0.001</td>
<td>61.1</td>
</tr>
<tr>
<td><strong>Illicit drug-related</strong></td>
<td>HBV</td>
<td>Neg. 11 908</td>
<td>407 586</td>
<td>2.9</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>[F11-16, F19, T40 (excl. T40.2, T43.6)]</td>
<td></td>
<td>Pos. 864</td>
<td>15 175</td>
<td>5.7</td>
<td>2.04</td>
<td>1.74–2.39</td>
<td>&lt;0.001</td>
<td>51.0</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
<td>Neg. 12 597</td>
<td>419 493</td>
<td>3.0</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pos. 175</td>
<td>3267</td>
<td>5.4</td>
<td>1.53</td>
<td>1.10–2.13</td>
<td>0.009</td>
<td>34.6</td>
</tr>
<tr>
<td><strong>HCV-related liver disease</strong></td>
<td>HBV</td>
<td>Neg. 2291</td>
<td>407 586</td>
<td>0.6</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(C22, K71-77)§</td>
<td></td>
<td>Pos. 167</td>
<td>15 175</td>
<td>1.1</td>
<td>3.55</td>
<td>2.33–5.40</td>
<td>&lt;0.001</td>
<td>71.8</td>
</tr>
<tr>
<td></td>
<td>HIV</td>
<td>Neg. 2418</td>
<td>419 493</td>
<td>0.6</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pos. 40</td>
<td>3267</td>
<td>1.2</td>
<td>3.77</td>
<td>1.59–8.89</td>
<td>0.001</td>
<td>73.5</td>
</tr>
</tbody>
</table>

* Crude hospitalization rate per 100 person-years.
† Adjusted for calendar year, age and sex.
‡ Excludes admissions for extracorporeal dialysis.
§ HCV-related liver disease = liver cancer (C22) and non-alcoholic liver disease (K71–77).
large ecological study involving 99 cities from around the world found HIV prevalence decreased by 18% per annum on average in cities with NSPs compared to an 8% increase in those that did not [34]. However, modelling studies in Australia [35, 36] suggest that at current levels of needle sharing HCV transmission would not be controlled in IDUs due to the higher infectiousness of HCV [31] and its underlying prevalence (60%) [24].

Interestingly, co-infection with HIV or HBV significantly increased the rate of admission for illicit drug-related conditions by 1.5 (AR 35%) and twofold (AR 51%), respectively. Population-based linkage studies examining mortality associated with illicit drug use have also shown higher standardized mortality ratios (SMRs) in cases who were co-infected with HIV and HBV compared to mono-infected cohorts [2, 3, 5]. In addition, clinical studies also suggest an increase in psychiatric and substance-use disorders with HIV co-infection [37]. The additional hospital-related morbidity associated with co-infection may be partly a surrogate measure for riskier lifestyle behaviours (i.e. riskier IDU practices) which both increase the probability of infection with HIV and HBV (and HCV) and of hospitalization for illicit drug-related causes.

Co-infection with either HIV or HBV increased the rate of admission for liver disease by more than 3-5-fold. These findings are consistent with evidence from clinic-based studies and cohort studies of patients with haemophilia. In addition, a recent population-based study reported HIV co-infection more than doubled the risk of hospitalization for decompensated liver disease [14]. Co-infection with either HBV or HIV is associated with an increased rate of fibrosis progression and risk of cirrhosis [38–42]. In addition, hepatocellular cancer has been reported to occur more often, and follow a more aggressive course, than in HCV mono-infected individuals [43–45]. HIV co-infected individuals with low CD4 counts have been shown to have a worse prognosis [38, 39] but even in the era of highly active antiretroviral therapy (HAART) the risk of cirrhosis was reported to be 1.7 times higher than in HCV mono-infected individuals [41].

We found an interaction between age and sex for all three admission types examined. Females had similar or higher RRs than males in younger age groups, while in older age groups, where morbidity from all-cause and liver disease was greatest, males had significantly higher RRs than their female counterparts. Therefore, the age of study participants needs to be considered whenever the burden of morbidity is reported by sex. Individuals infected at an older age or for a longer duration have been shown to have a higher rate of fibrosis progression [8, 10, 46, 47]. We were unable to measure these risk factors separately. However, a large cross-sectional study showed that, regardless of the duration of infection, the risk of cirrhosis increased significantly after the age of 50 years [8], and our results are consistent with these findings. The divergence between males and females at older ages, especially for liver-related admissions, is consistent with previous studies showing that the RR of fibrosis progression in males is higher than for females, but mostly for developing severe fibrosis after 20 years of infection [8, 45].

The results of our study need to be interpreted in the context of some limitations. First, being a population-based study, there were only a few patient-specific risk factors available for analysis. Therefore, we were unable to control for potential confounders such as alcohol use and ethnicity. However, previous studies indicate that alcohol use is similar in mono-infected and HIV or HBV co-infected patients [26, 38], and in an Australian study there were no differences in fibrosis progression rates by ethnicity [48]. A second limitation is that not all cases of HBV and HIV co-infection in the cohort would have been identified. A high proportion of the cohort are likely to have been screened for HIV and HBV [49], but identifiers for matching HIV cases were not complete. However, unidentified co-infections would only lead to an underestimate of the true RR. Another limitation is that hospital data with identifiers for linkage were only available for a 6-year period from June 2000. A small proportion (2.3%) of the notified cases had died prior to this, so our ‘survivor cohort’ may have underestimated hospital-related morbidity for all notified cases. Finally, we were unable to exclude anti-HCV antibody-positive cases who cleared their infection. HIV co-infection is associated with an increased risk of chronic HCV infection [10]. However, it is estimated that more than 70% of HCV infections are chronic [50], regardless of their co-infection status, and therefore the additional risk due to co-infection is likely to be minimal. In addition, few patients are likely to have cleared their HCV infection following antiviral therapy; only 1.4% of those living with HCV were estimated to have received treatment in 2006 [25].

To conclude, in our population-based cohort of people with HCV, an individual’s age, sex and
HIV/HBV co-infection status impacted significantly on their rate of hospitalization. The low prevalence of co-infection meant that the overall contribution of HIV and HBV to morbidity in our cohort was minimal. However, the high RRs indicate efforts to minimize HIV and HBV transmission, and improve HBV vaccine uptake in people with chronic HCV, are important. We found an interaction between age and sex with RRs for all-cause and liver-related hospitalizations highest in older men. The findings suggest that the burden of HCV-related morbidity in NSW will increase as the predominantly middle-aged male cohort move into age groups with higher hospitalization rates.

NOTE
Supplementary material accompanies this paper on the Journal’s website (http://journals.cambridge.org/hyg).

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DECLARATION ON INTEREST
None.

REFERENCES


