Title: Hepatitis B virus exposure and vaccination in a cohort of people who inject drugs: What has been the impact of targeted free vaccination?

Running title: Hepatitis B virus in people who inject

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ABSTRACT

Background and Aim: Forty per cent of new hepatitis B virus (HBV) infections in Australia occur in people who inject drugs (PWID); long-term infection carries the risk of serious liver disease. HBV incidence among Australian PWID has not been measured since the advent of targeted (2001) and adolescent school-based 'catch-up' (1998) vaccination programs. We measured HBV incidence and prevalence in a cohort of PWID in Melbourne, Australia and examined demographic and behavioural correlates of exposure and vaccination.

Methods: Community-recruited PWID were surveyed about blood-borne virus risk behaviours and their sera tested for HBV markers approximately three-monthly over three years. Incidence was assessed using prospectively collected data. A cross-sectional design was used to examine prevalence of HBV exposure and vaccination at baseline. Poisson regression was used to identify correlates of HBV exposure and vaccination.

Results: At baseline 33.1% of participants (114/344) had been vaccinated against HBV, 40.4% (139/344) had been exposed (previously or currently infected) and 26.5% (91/344) were susceptible. HBV incidence was 15.7 per 100 person-years. Independent associations with HBV exposure included female gender, South-East Asian ethnicity, drug treatment in the past three months, injecting in prison, and prior exposure to hepatitis C virus. Independent associations with vaccination included being ≤25 years old, reporting HBV vaccination and never having been to prison.

Conclusions: HBV infection continues at high incidence among Australian PWID, despite the introduction of free vaccination programs. Innovative methods are needed to encourage PWID to complete HBV vaccination.

Keywords: hepatitis B virus, epidemiology, hepatitis B vaccination, drug users, illicit drugs

BACKGROUND

The hepatitis B virus (HBV) is the tenth leading cause of death worldwide and the leading cause of liver cancer, accounting for 60-80% of cases.[1] It is estimated that more than two billion people worldwide have been exposed to HBV, and 360 million are living with chronic infection and at risk of serious liver disease including cirrhosis and hepatocellular carcinoma.[1] In Australia, 187,000 people were estimated to be living with chronic infection in 2008.[2]

People who inject drugs (PWID) are at risk of HBV infection primarily through the sharing of contaminated injecting equipment and through unprotected sexual activity. Injecting drug use accounts for around 40% of new HBV infections in Australia each year.[3]

Despite the availability of an effective three-dose HBV vaccine since 1982, coverage among PWID is low, leaving them vulnerable to infection.[4-10] Many Australian PWID are unaware of the availability of hepatitis B tests or vaccination[6] and around half do not know their true HBV status.[11] Several studies have also identified multiple missed opportunities for vaccination during contact with prisons, drug treatment centres or other primary or tertiary health centres.[7,9,12]

Limited information exists about HBV incidence in either Australia or internationally. The literature that does exist demonstrates that PWIDs are infected at significantly higher rates than the general population.[13-22] However, no Australian community-based PWID HBV incidence data and only limited prevalence data[5,10,23] have been published since the introduction of school-based adolescent 'catch-up' programs and free hepatitis B vaccination for high risk groups, including PWID. These programs commenced in Victoria, Australia's second most populous state, in 1998 and 2001 respectively,[24] and their impact on PWID vaccination coverage and incident HBV infection has not been examined. In the US and Europe, evidence of the impact of universal and/or targeted HBV vaccination policies is mixed.[8,9,25-27]

This paper reports on the incidence and prevalence of HBV exposure and their correlates in a cohort of Australian PWID. The demographic and behavioural characteristics of PWID exposed to HBV were compared with those who remained unexposed. We also measured the incidence, prevalence and correlates of HBV vaccination.

METHODS

Data for this study were drawn from the *Networks II* study, a longitudinal study of PWID in Melbourne, Australia concentrating on the social, behavioural and immunological factors associated with viral hepatitis infection and clearance.[28]

Recruitment

Outreach workers trained in phlebotomy and pre and post-test counselling recruited PWID from five street-based drug markets distributed widely across metropolitan Melbourne, spanning four local government areas. Potential participants were approached by outreach workers on the street, referred by needle and syringe programs, or recruited through 'snowballing' (in this case meaning participants referred PWID with whom they had injected in the previous three months). In order to build a sample with a relatively high proportion of current PWID who had not been previously infected with blood-borne viruses (BBVs), we recruited people who fulfilled one or more of the following criteria: (1) aged 25 years or less, (2) injecting for less than three years, (3) reported HCV antibody negative status. These 'primary' participants became part of the actively followed cohort and were asked to refer their injecting networks to the research team. Injecting network members were defined as people with whom primary participants had injected in the same place and at the same time at least once in the previous three months. Referred injecting partners did not need to fulfil any of the three eligibility criteria listed above, but if they did fulfil one or more they

were regarded as a primary participant for the purposes of this study. If referred injecting partners did not satisfy any of the above criteria they were labelled 'secondary' participants and not actively followed up, but nevertheless formed part of the baseline sample for the purposes of calculating BBV prevalence.

Interviews and serology

Participants were interviewed and provided 50ml blood samples at three-month intervals between July 2005 and August 2008, and reimbursed AU$25 on each occasion. Demographic characteristics were collected along with information about BBV risk behaviours including injecting and sexual risk behaviours and history.

Data were collected on handheld computers and linked to serological results. Specimens were tested for HBV surface antibody, surface antigen and core antibody to determine participants' HBV status. Participants not previously exposed to or vaccinated against HBV (and therefore susceptible) were re-tested at follow-up. Screened participants received pre and post-test counselling; HBV susceptible individuals were encouraged and supported to attend a local primary health centre for free vaccination and those who tested positive for current infection were referred to an infectious disease specialist for further assessment.

Serology was performed at the Victorian Infectious Diseases Reference Laboratory (VIDRL). For venous blood samples, hepatitis B surface antigen was detected using an Abbott Murex HBsAg Version 3 and the bioMeriux VIDAS was used to detect hepatitis B core antibodies and surface antibodies. The Abbott Murex anti-HCV (version 4.0) assay was used to detect HCV antibodies and positive results were confirmed using the BioRad MONOLISA anti-HCV PLUS (version 2). A further confirmatory test, the CHIRON RIBA HCV 3.0 immunoblot assay (SIA) was also used to confirm positive HCV antibody status.

Exposure to HBV was classified by serological positivity to core antibody and/or surface antigen tests (indicating current or past infection). Vaccine-induced immunity was classified by serological positivity to isolated surface antibody where antibody titre was above 10 IU/L, consistent with current guidelines.[1]

Measures

Potential correlates of HBV exposure and vaccination (informed by the literature) were: age (≤ 25 years *vs.* > 25 years), gender, ethnicity (European, South-East Asian, other (including Aboriginal)), accommodation (stable *vs.* unstable), schooling (completed secondary school *vs.* did not), employment status (employed or studying *vs.* unemployed), age of first injection (≤ 17 years *vs.* >17 years), length of injecting career (≤ 7.5 years *vs.* > 7.5 years), injecting frequency (< daily *vs.* > daily), drug most frequently injected (methamphetamine, buprenorphine, heroin), drug treatment (never, *vs.* ever; treatment in past three months *vs.* none), sharing needles/syringes (never, *vs.* ever), previous incarceration (never, *vs.* ever), injecting in prison (never, *vs.* ever), number of injecting partners in the previous three months (≤ 2 *vs.* > 2) number of lifetime sexual partners (≤ 12 *vs.* > 12), number of new sex partners in the previous three months (0, 1, > 1), risky sex with regular or new sex partners in the previous three months (used condoms all of the time *vs.* did not use condoms all the time), tattooing history (ever *vs.* never), reported previous HCV test result (never tested/don't know/negative *vs.* positive), reported HBV vaccination status (vaccinated *vs.* not) and baseline HCV antibody serology (negative *vs.* positive). Vaccination status was not differentiated by the number of doses received.

Data analyses

Prevalences were obtained from the results of baseline serology (therefore including primary and secondary participants as described earlier), and corresponding survey data utilized to examine demographic and behavioural associations with HBV exposure and vaccination. Data for

vaccinated participants were removed from the analysis of exposed *vs.* non-exposed associations. Preliminary analyses indicated non-linear associations for continuous variables (age, age of first injection, length of injecting career, number of injecting partners in the previous three months, lifetime number of sex partners, number of new sex partners in the previous three months) and these were consequently categorized using the median as the cut-off point.

Using a stepwise backward elimination method, multivariable Poisson regression models with robust error variance[29, 30] were built using variables significant to $p<0.1$ in bivariable analysis and age and gender were forced into the model. Variables significant to $p<0.05$ were retained in the final, adjusted model.

Baseline and follow-up serology results were used to calculate incidences of HBV infection and vaccination (primary participants only). Incidences were calculated as the ratio of the number of cases (participants seroconverted or vaccinated) divided by the person-years at risk, determined using the date of each susceptible participant's first blood sample and the date of either the most recent sample or the midpoint between the most recent negative sample and the sample at which infection or vaccination was detected. Logistic regression was used to identify independent predictors of loss to follow-up.

Data were analysed using the Stata statistical software package, version 11.2 (Stata Corporation, Texas).

RESULTS

Sample characteristics

Baseline HBV test results and corresponding interview data were available for 344 participants (Table 1). There were 139 (40.4%) HBV-exposed, 91 (26.5%) unexposed and 114 (33.1%)

participants with markers of vaccine-induced immunity at baseline. Of the 139 exposed participants, 14 tested positive for HBV surface antigen, an indicator of current infection (an overall prevalence of 4.1%). One of these cases tested positive for surface antigen only, indicating acute HBV infection.

[insert Table 1 here]

Participants were predominantly male with a median age of 25.2 years. Most participants had not completed secondary schooling, less than one-quarter were currently employed or studying and almost a third reported unstable living arrangements. At first interview, participants had been injecting for a median of 7.5 years and almost half reported injecting at least daily in the week prior to interview. Two thirds reported having ever shared needles/syringes and 42.5% of these had done so in the three months prior to interview (overall three-month sharing rate: 28.2%, 97/344). Most participants named heroin as the drug they had most frequently injected in the three months prior to interview. Just over a third of participants reported a history of imprisonment; 38.7% (48/124) of these reported having injected in prison at least once. Eighty per cent had ever accessed drug treatment services, with 50% receiving treatment in the three months prior to interview, most (159/172) of whom were receiving methadone or buprenorphine/buprenorphine-naloxone combination.

HBV infection and vaccination incidence

Of the 91 HBV unexposed participants at baseline, 22 were secondary participants and therefore not eligible for follow-up according to our criteria. Of the remaining 69 primary participants, 40 (60%) provided at least one follow-up blood sample. Participants lost to follow up were more likely to be aged 25 years or less and to have completed secondary schooling than those

successfully followed. These 40 participants were interviewed and tested a median of four times (IQR: 2.8-5.0) over a median of 48.1 weeks of follow-up (IQR: 31.6-64.1 weeks). During the follow-up period six participants were newly infected with HBV, an overall incidence of 15.7 per 100 person-years (95% CI 7.1, 35.1). Twenty-four participants remained unexposed and ten participants were vaccinated, an overall vaccination incidence of 26.2 per 100 person-years (95% CI 12.8, 44.4) (Figure 1).

[insert Figure 1 here]

Characteristics of exposed *vs.* non-exposed participants

Demographic and behavioural associations with HBV exposure at baseline were examined; participants immune to HBV infection through vaccination (n=114) at baseline were removed from this analysis (Table 2). Significant bivariable correlates of HBV exposure for participants at baseline were: being of south-east Asian ethnicity, having stable living arrangements, injecting for longer than 7.5 years, ever having shared needles/syringes, currently or previously being in drug treatment, having a history of incarceration, ever having injected in prison, having had more than 12 sexual partners, reporting a previous positive HCV test, and testing positive to HCV antibody in the current study (HCV exposed). After adjustment, being female, of south-east Asian ethnicity, receiving drug treatment in the three months prior to interview, ever injecting in prison and HCV exposure were significantly associated with HBV exposure.

[insert Table 2 here]

Characteristics of vaccinated *vs.* non-vaccinated participants

Demographic and behavioural variables were tested for association with HBV vaccination in 114 vaccinated (determined by serology) and 230 non-vaccinated (including exposed and unexposed) participants. Being female, aged 25 years or younger, having initiated injecting before the age of 17 years, injecting for two years or less, reporting no prior incarceration history, never having injected in prison, having no tattoos, reporting a previous HBV vaccination, and testing positive for HCV antibodies in the current study were associated with vaccination on bivariable analysis (Table 3). After adjustment, being 25 years of age or younger, having no incarceration history, and reporting receiving an HBV vaccination remained significantly associated with HBV vaccination.

[insert Table 3 here]

DISCUSSION

HBV incidence

Few published reports of incident HBV infection in PWIDs exist, and only one from Australia. Previous research has shown HBV incidence in this population to range between 1.8 and 30.7 per 100 person-years.[13-16, 18-22] The HBV incidence observed in this cohort (15.7 per 100 person years) is comparable to rates observed overseas but is significantly higher than the 1.8 per 100 person years (95% CI 0.8, 4.3) last observed in a Melbourne cohort of PWID during the 1990s.[15] This high HBV incidence, combined with the low coverage of HBV vaccination in our cohort, suggests the current free vaccination program for at-risk groups (including PWID) in Victoria, which was implemented in the period between the two studies,[24] is failing to make significant inroads in preventing HBV transmission in PWID in Victoria.

High HBV incidence is a particular concern given the high rate of infection HCV in this cohort and other PWID cohorts[28, 31] and the complications that may occur with co-infection with both hepatitis viruses, including increased risk of progressive liver disease and cirrhosis.[32, 33]

HBV prevalence and correlates of exposure

The prevalence of HBV exposure in our cohort at baseline was 40.4%, higher than the 28% observed in a cohort of community-recruited PWID from Sydney[34] but similar to that measured in the aforementioned 1990s Melbourne cohort (45.2%).[15] An HBV exposure prevalence of 59% was recently reported in Sydney,[5] but the Sydney sample was considerably older (median 36 years) and was primarily recruited from drug treatment and primary health centres, suggesting a bias towards longer drug-using careers and therefore greater opportunity for HBV exposure.

The association between HBV exposure and South-East Asian ethnicity was expected due to the high prevalence of the virus in Asia and 15% of our cohort reporting South-East Asian ethnicity. The correlation with exposure to HCV was also anticipated due to the transmissibility of both hepatitis viruses via blood to blood contact. Both of these factors have previously been reported to be significantly associated with HBV exposure.[34]

Women were significantly more likely to be exposed to HBV than men (67.7% versus 57.4%) in our cohort. This finding is contrary to recent Victorian population-level research in which men were significantly more likely to have been exposed to HBV.[35] Most likely this was due to the greater BBV vulnerability of female PWID, with several studies demonstrating a greater BBV risk among women who inject due to factors such as earlier initiation to injecting, a greater reliance on others to assist with drug acquisition, preparation and injection, and borrowing needles/syringes and ancillary equipment from male partners.[36, 37]

Injecting in prison was also independently associated with HBV exposure in our cohort. Imprisonment has been previously identified as a risk for HBV infection,[34, 38, 39] and recent Australian research has also demonstrated BBV transmission within prisons.[40, 41]

Unlike some previous studies (e.g., Van Ameijden et al, 1993[22]), we did not identify an association between sexual risk behaviour and HBV exposure in our cohort. It is possible that HBV is more efficiently transmitted through unsafe injecting (direct blood to blood contact) than unprotected sexual activity, therefore masking the risk of this activity. Similar findings have been reported elsewhere.[42] Alternatively, participants may not have accurately reported their sexual risk behaviours.

Correlates of vaccination

Younger age was strongly associated with vaccination in these analyses; this is presumed to reflect the introduction of adolescent catch-up programs in secondary schools in the last decade, which is likely to have benefited younger PWID, and suggests that this program is having a positive impact, in contrast to targeted programs. After adjustment, incarceration was significantly associated with a lower likelihood of vaccination. Given that injecting in prison was associated with HBV exposure in our cohort and that one-third of our cohort had a history of imprisonment it would seem particularly pertinent to offer vaccination during periods of incarceration. The Victorian Department of Justice Primary Health Care Standards (2005) state that "immunisation services are promoted" in prisons[43] but the reality on the ground suggests the current level of "promotion" is currently far from adequate. These data indicate a significant missed opportunity for vaccination in prison. Modelling has demonstrated that providing HBV vaccination to 50% of prisoners in England and Wales could achieve immunisation coverage of 57-72% among community PWID and could reduce HBV incidence by up to 80% over 12 years from 2006.[44, 45]

Limitations

Cohort studies are useful in measuring disease incidence but one of their limitations is loss to follow up. Only 60% of our eligible HBV susceptible participants were available for follow up so our observed HBV incidence is reliant on a small subset. This means that the confidence intervals on our observed incidence are wide. Nevertheless, the rate of HBV infection among this subset was high. Cross-sectional data were utilised to describe associations with exposure and vaccination, but a limitation of cross-sectional design is the inability to infer causation.

Due to the marginalisation and stigmatisation of people who inject drugs, it is difficult to identify a clear participant sampling frame. Participants in this study were not randomly selected and therefore cannot be considered representative of the broader population of PWID. Participants were recruited from established street drug markets across Melbourne and thus may differ from cohorts recruited from drug treatment or other community settings in different jurisdictions.

The recruitment protocol was designed to maximise the proportion of PWID participants who were not yet exposed to blood-borne viruses in order to observe new infections over time. This may have introduced a selection bias and possibly resulted in a lower observed prevalence of HBV exposure (since HBV and HCV exposure are independently correlated in this and other cohorts[34]). However, this selection bias is potentially balanced by the recruitment of members of participants' injecting networks, who did not have to fulfil any eligibility criteria.

Sharing injecting paraphernalia (spoons, filters, etc.) has previously been identified as a risk for BBV transmission.[46] We did not collect these data and therefore could not assess the risk of HBV exposure posed by these behaviours.

CONCLUSION

Almost a third of our participants were susceptible to HBV infection at baseline, and incidence of HBV infection was around 16% per annum, despite the availability of free vaccination programmes for at-risk populations. While younger participants were more likely to have been vaccinated, it may be at least another decade before universal infant vaccination and adolescent catch-up programs achieve adequate coverage.[10] Therefore selective targeting of high-risk groups, including PWID, remains important in the medium term. Strategies to immunize this population are needed to prevent future infections and the risk of developing HBV-related liver disease. Given the low coverage of HBV vaccination among PWID and the transient lifestyles of many, innovative ways to attract and retain PWID in vaccination programs must be developed. Trials offering motivational incentives to PWID to complete HBV vaccination programs have achieved high completion rates;[47, 48] a similar trial is underway in Sydney.[49] In the absence of incentives, health services which target drug users need to routinely offer HBV vaccination to their clients and develop imaginative methods of engagement and delivery. The findings from this study support the 'don't ask, vaccinate' policies proposed by some public health advocates,[50] particularly targeted at new initiates to injecting.

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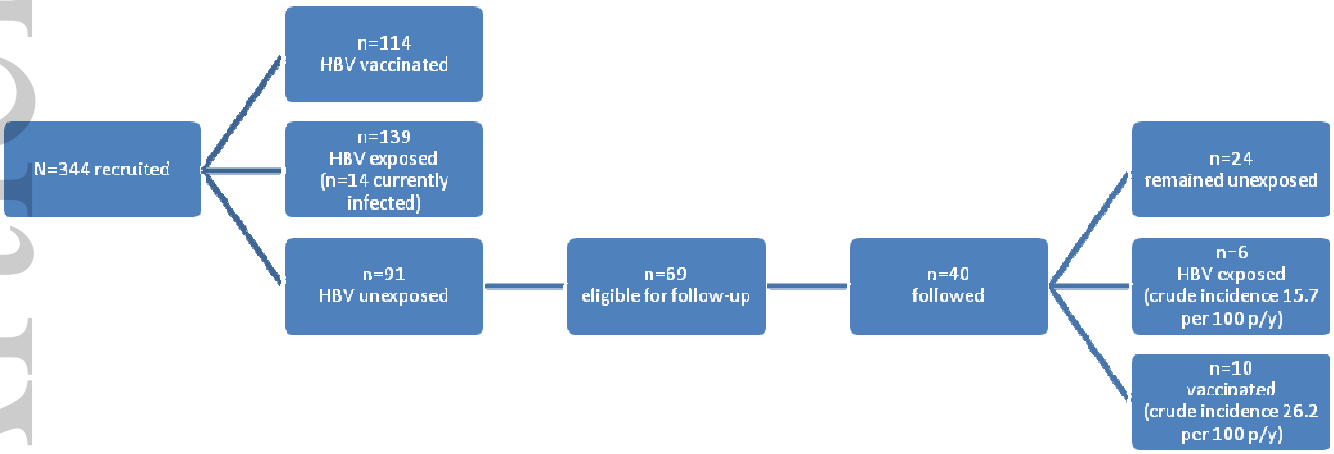
Figure 1: Flowchart of recruitment and HBV infection and vaccination status at baseline and follow-up



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