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Correlates of Susceptibility to Hepatitis B among People Who Inject Drugs in Sydney, Australia

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ABSTRACT *Despite a safe, effective vaccine, hepatitis B virus (HBV) vaccination coverage remains low among people who inject drugs (PWID). Characteristics of participants screened for a trial investigating the efficacy of financial incentives in increasing vaccination completion among PWID were examined to inform targeting of vaccination programs. Recruitment occurred at two health services in inner-city Sydney that target PWID. HBV status was confirmed via serological testing, and questionnaires elicited demographic, drug use, and HBV risk data. Multinomial logistic regression was utilized to determine variables independently associated with HBV status. Of 172 participants, 64% were susceptible, 17% exposed (HBV core antibody-positive), and 19% demonstrated evidence of prior vaccination (HBV surface antibody≥10 mIU/ml). Compared with exposed participants, susceptible participants were significantly more likely to be aged less than 35 years and significantly less likely to be receiving current opioid substitution therapy (OST) and to test hepatitis C antibody-positive. In comparison to vaccinated participants, susceptible participants were significantly more likely to be male and significantly less likely to report daily or more frequent injecting, current OST, and prior awareness of HBV vaccine. HBV vaccination uptake could potentially be increased by targeting younger, less frequent injectors, particularly young men. In addition to expanding vaccination through OST, targeting "at risk" youth who are likely to have missed adolescent catch-up programs may be an important strategy to increase coverage. The lack of an association between incarceration and vaccination also suggests increasing vaccination uptake and completion in adult and juvenile correctional facilities may also be important.*

KEYWORDS *Hepatitis B virus, Substance abuse, Intravenous, Immunization, Public health*

INTRODUCTION

While injecting drug use is the leading exposure category for notifications of newly acquired hepatitis B virus (HBV) infection in Australia[1] and vaccination is

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recommended for high-risk adults including people who inject drugs (PWID),[2] HBV immunization coverage in this group remains low.[3] This is despite the availability of a safe and effective vaccine being available free-of-charge for PWID in a range of clinical settings. Although the hepatitis B vaccine was included in Australia's infant vaccination schedule for 2000 with coverage reaching 86% of 1-year-old children in 2002,[4] universal infant vaccination will not impact on the immunity of Australia's adult populations for several decades.[5] School-based adolescent catch-up vaccination programs were implemented for 2002 and reach just over half of the target group.[4] In addition, migrants to Australia are often not vaccinated.[5] HBV infection during adulthood may result in fulminant acute hepatitis leading to liver transplantation or death and a significantly increased risk of liver cirrhosis and cancer among the 1–5% chronically infected after exposure.[6] High mortality in people coinfected with hepatitis C virus[7] (HCV) is of particular concern given 50–60% HCV antibody (HCV Ab) prevalence among PWID in Australia.[8] Identifying PWID who are susceptible to infection will therefore remain important in Australia for many years.

Between 28% and 59% of PWID in Australia are estimated to have been exposed to HBV (HBV core antibody (HBcAb)-positive), and a further 26–33% have evidence of vaccine-induced immunity (HBV surface antibody (HBsAb) $\geq$ 10 IU/mL and HBcAb-negative; Winter et al., submitted for publication).[9–14] Overall, these studies indicate that 14–46% of PWID in Australia are susceptible to HBV, yet many of this group believe that they are immune to infection.[10,15] A recent review found that 50–73% of PWID who reported prior vaccination had no evidence of vaccine-conferred immunity.[15] One study found that of those reporting susceptibility, 54% had been exposed and 22% vaccinated.[10] International studies comparing serological and self-reported HBV status indicate that 5–22% of PWID who reported susceptibility were in fact vaccinated; and 28–75% of those susceptible had been exposed.[16–22] Thus, reliability of self-reported HBV status in PWID is poor.[15]

Identifying PWID who are susceptible to infection is necessary to better target vaccination campaigns. As part of the Hepatitis B Acceptability and Vaccination Incentive Trial (HAVIT), a randomized controlled trial of the efficacy of incentive payments in increasing HBV vaccination uptake and completion among PWID,[23–25] potential participants were screened to determine their susceptibility to HBV. This paper describes the characteristics of three groups who presented to enrol in HAVIT, namely: (1) those confirmed as susceptible to infection ("susceptible") and those who were (2) previously exposed to ("exposed") or (3) previously vaccinated against ("vaccinated") HBV. Importantly, we identify the characteristics of the group who remain susceptible to HBV infection in order to provide an empirical basis from which to better target vaccination programs for PWID.

METHODS

Participants were screened at two health services in inner-city Sydney that target PWID. Both services provide low threshold walk-in access to a primary health care nurse with referral to a broad range of additional health care services as needed. Eligibility criteria included age 16 years and older, injected drugs in the preceding 6 months, and self-reported no previous HBV vaccination or infection, a maximum of one previous dose of HBV vaccination, or unknown infection and vaccination status. Exclusion criteria comprised evidence of natural or vaccine-induced HBV immunity, self-report of previous exposure to HBV or two+ vaccinations, serious

mental or physical illness or disability likely to impact on capacity to complete study procedures, and/or HIV infection.

Pre-test discussion and provision of the first dose of HBV vaccine (Engerix B 20mcg (1 ml) manufactured by GlaxoSmithKline) was undertaken by clinic staff consistent with clinical protocols designed to expedite HBV vaccine uptake and completion. Participants were also tested for HBsAb, HBcAb, HIV antibody (HIV Ab), and HCV Ab (unless the medical file already documented HCV Ab seropositive status). Assays used were the Abbott Architect assays HBsAb CMIA, HBcAb II, HIV Ag/Ab combo, and HCV Ab (with confirmatory test measured by BioRad Monolisa HCV Ag/Ab Ultra-assay), respectively.

Questionnaires were self-completed using Audio Computer-Assisted Self Interview (ACASI) software (from the Questionnaire Development System™ Nova Research Company) which has been shown to increase accurate reporting of illicit behaviors and to improve comprehension and completion by people with low literacy.[26,27] Domains assessed included demographics; lifetime and recent (preceding 6 months) injecting drug use; severity of dependence using the Severity of Dependence Scale (SDS);[28] binge drinking using the Alcohol Use Disorders Identification Test (AUDIT);[29] drug treatment (lifetime and recent); injecting risk behavior (lifetime and recent);[30] and knowledge of, attitudes towards, and barriers against HBV vaccination. The cutoffs chosen for SDS scores indicating clinically significant dependence on the main drug injected were 3 and above for participants reporting mainly injecting cocaine[31] and 4 and above for all other drugs.[28]

All participants who completed the screening assessment were reimbursed with an AU$20 store voucher. Ethical approval for the study was granted by the Sydney South West Area Health Service (Royal Prince Alfred Hospital Zone), South Eastern Sydney, and Illawarra Area Health Service Northern Hospital Network and the University of New South Wales human research ethics committees.

Statistical Analysis

The sample was divided into the three groups: susceptible to, exposed to, and vaccinated against HBV. Variables associated with HBV serological status at $p \leq 0.2$ in univariate analysis plus recruitment site as an a priori variable were entered into a backward stepwise multinomial logistic regression (MLR) model. Covariates that did not maintain significance at $p \leq 0.05$ with serological status when other factors were held constant were removed to derive the final model. To confirm the findings of the MLR model, each of the three HBV serological categories was dropped in turn and multivariate logistic regression performed on the remaining two categories. All analyses were conducted using STATA 10.0.

RESULTS

With one transgender participant excluded to permit analysis of gender as a binary variable, 172 participants were included in the current analysis. Of these, 110 (64%) were serologically confirmed as susceptible to HBV infection, 33 (19%) demonstrated evidence of prior vaccination, and 29 (17%) demonstrated evidence of prior exposure. Participants' median age was 34 years, and 78% were male (Table 1). Fifteen percent identified as Aboriginal and/or Torres Strait Islander; 16% were born outside of Australia, and 42% reported less than 4 years of secondary education. The median age at first injection was 19 years, and 55% reported injecting daily or more frequently in the preceding 6 months. Half (51%) reported that they had

TABLE 1 Demographic, drug use, and risk behavior characteristics by HBV serological status

	Susceptible	Exposed	Vaccinated	Total
	N = 110 (%)	*N* = 33 (%)	*N* = 29 (%)	*N* = 172 (%)
Recruitment site				
Site 1	47	61	55	51
Site 2	53	39	45	49
Male	81	79	66	78
Age (years, median)	33	42	31	34 (17–58)
Age (<35 years)	58	27	62	53
ATSI	13	21	14	15
Country of birth (overseas)	18	21	3	16
<4 years secondary education	45	39	34	42
Incarceration (ever)	48	67	41	51
Age first injected (years, median)	20	19	18	19 (10–52)
Age first injected (<20 years old)	48	55	62	52
Time injected (years, median)	11	22	10	11.5 (0–40)
Duration of injecting (<13 years)	60	30	59	54
Daily or more frequent injection	47	67	69	55
Main drug injected (last 6 months)				
Heroin	46	58	59	51
Methamphetamine	25	12	14	21
Other	28	30	28	28
Injected 3+ drugs (last 6 months)	51	61	69	56
Dependent on main drug according to SDS[a]	76	82	76	77
HCV Ab-positive	50	88	62	59
OST (ever)	52	85	62	60
OST (current)	27	55	52	37
Aware of HBV vaccine prior to enrolment	57	73	79	64

[a]Severity of Dependence Score

mainly injected heroin, and 21% mainly injected methamphetamine during that period.

Compared with exposed participants, univariate analysis demonstrated that the susceptible group was significantly more likely to be younger than 35 years of age and to have injected for 12 or fewer years (Table 2). The susceptible group was significantly less likely to report lifetime and current opioid substitution treatment (OST) and to test positive to HCV antibody. In comparison to the vaccinated group, the susceptible group was significantly less likely to report daily or more frequent injection, current OST, and prior awareness of the HBV vaccine.

Although associated with HBV status at the univariate level equal to or less than the cutoff of $p = 0.2$, country of birth was omitted from the regression model due to small cell sizes. In the final MLR model (Table 2) using exposed participants as the referent category and controlling for recruitment site, susceptible participants were significantly more likely to be younger than 35 years of age (adjusted odds ratio (AOR) 3.14; 95% confidence interval (CI) 1.20–8.26), less likely to report current OST (AOR 0.27; 95% CI 0.11–0.66) and to test HCV Ab-positive (AOR 0.21; 95% CI 0.06–0.68). With vaccinated participants as the referent group, susceptible

TABLE 2 Multinomial analysis of correlates of HBV status comparing susceptible to exposed and vaccinated groups

	Susceptible vs exposed[a]				Susceptible vs vaccinated[a]			
	Univariate		Multivariate		Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Male	1.14 (0.44, 2.98)	0.788	1.67 (0.56, 4.99)	0.362	2.23 (0.91, 5.48)	0.081	2.82 (1.05, 7.59)	0.040
Age (<35 years)	3.71 (1.58, 8.72)	0.003	3.14 (1.20, 8.26)	0.020	0.85 (0.37, 1.97)	0.705	0.83 (0.33, 2.10)	0.691
ATSI	0.54 (0.20, 1.48)	0.232	–	–	0.91 (0.28, 3.01)	0.879	–	–
Country of birth (overseas)	0.83 (0.31, 2.17)	0.697	–	–	6.22 (0.80, 48.46)	0.081	–	–
<4 years secondary education	1.28 (0.58, 2.83)	0.539	–	–	1.58 (0.67, 3.71)	0.291	–	–
Incarceration (ever)	0.46 (0.21, 1.05)	0.065	–	–	1.32 (0.58, 3.02)	0.514	–	–
Age first injected (<20 years old)	0.77 (0.35, 1.69)	0.522	–	–	0.57 (0.25, 1.31)	0.186	–	–
Duration of injecting (<13 years)	3.45 (1.50, 7.95)	0.004	–	–	1.06 (0.46, 2.43)	0.893	–	–
Daily or more frequent injection	0.45 (0.20, 1.01)	0.054	0.44 (0.17, 1.10)	0.079	0.40 (0.17, 0.96)	0.041	0.34 (0.13, 0.87)	0.025
Main drug injected (last 6 months)								
Heroin	0.64 (0.29, 1.40)	0.260	–	–	0.61 (0.27, 1.40)	0.243	–	–
Methamphetamine	2.48 (0.80, 7.66)	0.116	–	–	2.13 (0.68, 6.67)	0.192	–	–
Other	0.90 (0.39, 2.11)	0.813	–	–	1.03 (0.41, 2.57)	0.949	–	–
Injected 3+ drugs (last 6 months)	0.67 (0.31, 1.49)	0.329	–	–	0.47 (0.20, 1.12)	0.086	–	–
Dependent on main drug according to SDS[b]	0.72 (0.27, 1.93)	0.511	–	–	1.03 (0.39, 2.68)	0.955	–	–
HCV Ab-positive	0.14 (0.05, 0.42)	0.000	0.21 (0.06, 0.68)	0.009	0.61 (0.26, 1.41)	0.249	0.72 (0.28, 1.81)	0.483
OST (ever)	0.19 (0.07, 0.53)	0.002	–	–	0.66 (0.28, 1.52)	0.326	–	–
OST (current)	0.31 (0.14, 0.70)	0.005	0.27 (0.11, 0.66)	0.004	0.35 (0.15, 0.81)	0.014	0.31 (0.13, 0.77)	0.012
Aware of HBV vaccine prior to enrolment	0.50 (0.21, 1.18)	0.114	0.44 (0.17, 1.18)	0.102	0.35 (0.13, 0.93)	0.035	0.31 (0.11, 0.86)	0.024

[a]Controlling for recruitment site
[b]Severity of Dependence Score

participants were significantly more likely to be male (AOR 2.82; 95% CI 1.05–7.59) and less likely to report injecting daily or more frequently (AOR 0.34; 95% CI 0.13–0.87), current OST (AOR 0.31; 95% CI 0.13–0.77), and prior awareness of the HBV vaccine (AOR 0.31; 95% CI 0.11–0.86).

DISCUSSION

The present results suggest that PWID who are susceptible to HBV infection—the group that must be targeted for vaccination—are also the most challenging to identify. Current strategies to link this population into health care appear insufficient. Our data suggest that this group is not only younger than exposed PWID but significantly less likely than both exposed and vaccinated PWID to have accessed OST. Coupled with the absence of a significant difference in age between susceptible and vaccinated participants, our results suggest that OST provides an important opportunity to improve coverage in this group. However, the significantly higher prevalence of current OST in the vaccinated group compared with the susceptible group may also reflect the vaccinated group's higher rates of daily or more frequent injection, indicative of sustained and chronic opioid use,[32] an implicit requirement for initiation of OST. The collection of a range of detailed information during the screening phase of the HAVIT trial combined with serological testing provided an opportunity to systematically examine differences between three groups of PWID in Australia: those susceptible to, vaccinated against, and previously exposed to HBV infection.

As OST usually requires daily attendance at a health service and HBV vaccination is provided free of charge by public OST programs in NSW, higher levels of participation in OST by vaccinated participants may also reflect the benefit of repeated engagement with health services in augmenting HBV vaccination rates. Our data support the findings of an Australian study where 83% of enrolled HBV seronegative OST clients completed the vaccination course.[13] Increasing access to OST (where medically indicated) and expanding HBV vaccination within these programs has the potential to increase HBV vaccination coverage in this group. Nonetheless, many susceptible subjects were currently in OST, indicating that vaccination is incomplete within OST programs, consistent with a recent national survey.[33] Educational strategies regarding HBV vaccination may also be important in this population as, not surprisingly, susceptible participants were also least likely to have been aware of the existence of HBV vaccination.

Innovative models of service delivery are required to contact and engage susceptible PWID before they experience harms related to their injecting drug use, including the potential acquisition of HBV, HCV, and HIV. Both sites in the current study are well-established low-threshold services. Each provides clean injecting equipment at no cost as well as offering free and anonymous healthcare on a drop-in basis and conducting outreach in street-based drug environments.[34,35] Targeting young people at risk of injecting drug use may also require collaboration between these services and other organizations in contact with "at risk" young people, such as juvenile correctional facilities, refuges, and supported accommodation services and youth centers, as recommended by a recent Canadian study of street-involved youth.[36]

Susceptible participants were more likely than vaccinated participants to be male, suggesting that female PWID may be more likely to be vaccinated than their counterparts. This association has also been demonstrated among young PWID in

San Francisco[37] and may reflect men's generally lower levels of health-seeking behaviors.[38–40] Women injectors in our sample may have had higher levels of access to health services where opportunistic vaccination could be conducted. Targeting men who inject drugs for general health care may increase their rates of opportunistic vaccination.

Incarceration was not associated with vaccination, suggesting that opportunistic vaccination is not occurring among incarcerated PWID in Australia, a finding consistent with previous research.[41,42] With half of our susceptible participants reporting lifetime incarceration, targeting prisoners for vaccination has potential to increase vaccination coverage in PWID. Currently, the prison health service in NSW targets prisoners at risk of having or acquiring a blood-borne or sexually transmitted infection for HBV vaccination. While increasing HBV vaccination uptake and completion has been identified as a strategic direction,[43] expanding the current targeted program to all prisoners with no record of prior immunization or infection, combined with increasing completion of commenced vaccination courses, would assist in fulfilling this important public health objective.

The profile of participants previously exposed to HBV infection suggests that this was a group with longstanding involvement in injecting drug use. Exposed participants were significantly older than vaccinated and susceptible participants (41 years versus 31 and 33 years, respectively) with correspondingly longer injecting histories (22 years versus 10 and 11 years, respectively). The increased cumulative risk exposure constituted by a higher lifetime number of injections likely accounts for the increased exposure to HBV as well as the significantly higher HCV Ab prevalence observed in this group.

Limitations

Our sample may not be representative of PWID in general as participants were recruited from clinic populations. The characteristics of PWID not in contact with services may differ from those of this sample. Drug use and other stigmatized behaviors may have been under-reported by participants, although the use of ACASI has been shown to minimize social desirability bias.[26,27] This was a major study for its type, but nonetheless, a larger sample would have allowed for more statistical power and therefore a greater capacity to detect truly significant differences between groups.

Implications

HBV vaccination among PWID could potentially be increased by targeting younger PWID who inject less frequently and who are not enrolled in OST. Male injectors were also less likely to have been vaccinated. Previous vaccination was associated with enrolment in OST, suggesting that expanding entry to and maintaining opportunistic vaccination through OST is an important strategy in increasing HBV vaccination coverage among PWID. Targeting of at risk youth prior or concurrent with initiation of injecting drug use through youth-oriented services represents an additional opportunity for increasing uptake and completion. Our data also provide evidence of missed opportunities for vaccination with a substantial proportion of susceptible PWID reporting previous incarceration. Adult and juvenile correctional facilities are also well positioned to increase uptake and completion of hepatitis B vaccination in this vulnerable group.

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