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A large proportion of people who inject drugs are susceptible to hepatitis B: Results from a bio-behavioural study in eight German cities

J.M. Haussig[a,b,c], S. Nielsen[c,d,1], M. Gassowski[c], V. Bremer[c], U. Marcus[c], B. Wenz[c], N. Bannert[e], C.T. Bock[e], R. Zimmermann[c,*], on behalf of the DRUCK study group

[a] Postgraduate Training for Applied Epidemiology (PAE), Robert Koch Institute, Berlin, Germany
[b] European Programme for Intervention Epidemiology Training (EPIET), European Centre for Disease Prevention and Control, Stockholm, Sweden
[c] Department for Infectious Disease Epidemiology, Robert Koch Institute, Berlin, Germany
[d] Charité University Medicine, Berlin, Germany
[e] Department of Infectious Diseases, Robert Koch Institute, Berlin, Germany

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ABSTRACT

Background: People who inject drugs (PWID) are at high risk of hepatitis B virus (HBV) infection by sharing needles and drug use paraphernalia. In Germany, no routine surveillance of HBV prevalence and vaccination coverage among PWID exists.
Methods: Socio-demographic and behavioural data were collected between 2011 and 2014 through face-to-face interviews, during a bio-behavioural survey of PWID recruited in eight German cities. Dried blood spots (DBS) prepared with capillary blood were tested for HBV markers. Factors associated with past/current HBV infection and vaccination status were analysed by univariable and multivariable analysis using logistic regression. The validity of self-reported HBV infection and vaccination status was analysed by comparison to the laboratory results.
Results: Among 2077 participants, the prevalence of current HBV infection was 1.1%, of past HBV infection was 24%, and of vaccine-induced HBV antibodies was 32%. No detectable HBV antibodies were found in 43%. HBV infection status was significantly associated with study city, age, years of injecting, use of stimulants, migration status, and homelessness; HBV vaccination status was significantly associated with study city, age, and level of education. Correct infection status was reported by 71% and correct vaccination status by 45%.
Conclusions: HBV seroprevalence among PWID was about five times higher than in the general population in Germany, confirming PWID as an important risk group. Targeted information campaigns on HBV and HBV prevention for PWID and professionals in contact with PWID need to be intensified. Routinely offered HBV vaccination during imprisonment and opioid substitution therapy would likely improve vaccination rates among PWID.

Research in context panel

Evidence before the study

People who inject drugs (PWID) are at risk of blood-borne and sexually transmitted infections, such as hepatitis B virus (HBV) infection. There have been no recent studies providing up-to-date information on HBV among PWID in Germany, and routine monitoring of infections or risk behaviours among PWID has not yet been established. Knowledge on HBV prevalence and vaccination coverage in this population in Germany is based on outdated regional studies, which found markers of former HBV infection in 35–62% of study participants and low vaccination coverage. HBV vaccination has been recommended and implemented in Germany for PWID since 1982, and for all children since 1995, but the coverage among PWID is largely unknown. Several studies from other countries that have included smaller numbers of participants have suggested limited validity of self-reported HBV infection and vaccination status for PWID.

* Corresponding author at: Robert Koch Institute, Department of Infectious Disease Epidemiology, Seestr. 10, 13353 Berlin, Germany.
E-mail address: ZimmermannR@rki.de (R. Zimmermann).
[1] SN is currently a PhD student at the Charité University Medicine, Berlin, Germany.

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Added value of this study

The seroprevalence of current HBV infection among 2077 PWID in this study was found to be about five times higher than that in the general population in Germany, indicating that PWID are an important group at risk of HBV infection. Despite a clear national vaccination recommendation, a large proportion of PWID remains at risk of infection, as suggested by the absence of infection- or vaccine-induced antibodies. Settings in which PWID could easily be reached for vaccination (opioid substitution treatment (OST) or prisons) were found not to be associated with higher proportions of vaccinated PWIDs, hinting at missed opportunities for vaccination. The in-depth analysis of key factors associated with HBV infection and vaccination among this key risk group makes this study highly relevant for public health practitioners and policy-makers working on improving the health of PWID. Furthermore, the limited validity of self-reported HBV infection and vaccination status among PWID argues for pre-emptive vaccination of PWID if no vaccination record is available.

Implications of all the available evidence

This study shows the need for targeted information campaigns for PWID and professionals in contact with PWID on HBV and HBV prevention, despite national vaccination recommendations including both the recommendation of universal infant and child vaccination (since 1995) and risk group vaccination (starting in 1982) in Germany. The authors recommend intensifying efforts to ensure that HBV vaccination is routinely offered during OST and imprisonment in order to improve HBV vaccination coverage among PWID. The strong association of the study city particularly with HBV vaccination status, and less so with infection status, indicates an effect of the local setting. Further studies to evaluate local differences, e.g., in practices and efforts of medical doctors offering OST and local HBV vaccination and on information campaigns/programs and their impact, might identify additional effective measures and good practices to improve vaccination coverage.

Introduction

People who inject drugs (PWID) are at high risk of hepatitis B virus (HBV) infection through blood-borne transmission by sharing needles and drug use paraphernalia, as well as through unsafe sex. Worldwide, an estimated 12.7 million people inject drugs (United Nations Office on Drugs and Crime, 2014), and 6.4 million PWID are hepatitis B core antigen antibody (anti-HBc)-positive and 1.2 million are hepatitis B surface antigen (HBsAg) positive (Nelson et al., 2011). National estimates of HBsAg prevalence among PWID from seven European countries range from 0.5% to 6.3% (European Centre for Disease Prevention and Control, 2016). In Germany, data from routine reporting suggest that PWID constitute one of the main groups affected by HBV, in addition to migrants and men who have sex with men (Robert Koch-Institut (RKI), 2016). HBV outbreaks among PWID have been repeatedly reported in Europe over the past years (Andersson et al., 2012; Christensen et al., 2001). Studies have identified several risk factors associated with HBV infections among PWID, including age >25 years, sharing needles/syringes, history of needle/syringe sharing in prison, long duration of injecting drug use, homelessness, and unemployment (Andersson et al., 2012; Removille et al., 2011; Stark et al., 1997; Brack, 2002).

International recommendations of the European Centre for Disease Prevention and Control (ECDC), the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), and the World Health Organization (WHO) on the prevention of HBV among PWID emphasize the importance of vaccination (World Health Organization, 2012; European Centre for Disease Prevention and Control and European Monitoring Centre for Drugs and Drug Addiction, 2011). An effective, affordable, and safe subunit vaccine against HBV has been available since 1982. The WHO recommends vaccinating all infants after birth with the first of three to four vaccination doses (World Health Organisation (WHO), 2009). Since 1995, the German Standing Committee on Vaccination (STIKO) has recommended vaccinating all infants. Data collected between 2008 and 2011 indicated that 23% of adults in Germany had been vaccinated against HBV, with an increasing proportion in the younger age groups (57% among the 20–29-year-olds) (Poethko-Muller et al., 2013). Since 1982 (West Germany) and 1984 (East Germany), HBV vaccination of groups at increased risk, such as PWID and prisoners, has been recommended. Worldwide, several studies have found low HBV vaccine coverage among PWID (Quaglio et al., 2006).

There have been no recent studies providing up-to-date information on HBV among PWID in Germany, and routine monitoring of infections or risk behaviours among PWID has not yet been established. Knowledge on HBV prevalence and vaccination coverage among PWID in Germany is based on outdated regional studies, which found markers of former HBV infection in 35–62% of the study participants and low vaccination coverage (Stark et al., 1997; Brack, 2002; Ridder et al., 2004).

This analysis is based on data from a bio-behavioural survey of PWID recruited in eight large German cities, performed between 2011 and 2014. The objective of this analysis was to describe the HBV infection status and vaccination status of PWID and to identify factors associated with current or past HBV infection, as well as for not being vaccinated against HBV. Whether self-reported HBV infection status and HBV vaccination status were supported by serological test results was also investigated. This was done in order to develop recommendations for improved HBV vaccination coverage and HBV prevention among PWID.

Methods

Sampling and recruitment

Biological and behavioural data were collected from 2077 PWID in eight large German cities between 2011 and 2014 (Zimmermann et al., 2014). Study participants were recruited through respondent-driven sampling (RDS) in up to four local low-threshold drug services in each of the eight study cities (Berlin, Essen, Leipzig, Cologne, Munich, Frankfurt am Main, Hanover, and Hamburg). Inclusion criteria were age ≥16 years, having injected drugs in the given study city in the last 12 months, and providing informed consent for study participation. The study was piloted in Berlin and Essen. All participants attended a questionnaire-assisted interview and provided a capillary blood sample. Detailed information on the study design and recruitment process has been published previously (Zimmermann et al., 2014; Wenz et al., 2016).

Socio-demographic and behavioural data

Face-to-face-interviews included questions on socio-demographic factors, substances consumed, risk and preventive behaviours, and HBV infection and vaccination. Minor modifications to the questionnaire were made throughout the survey. Therefore, certain variables are not available for all cities. In the first three cities (Berlin, Essen, and Leipzig), participants were not asked whether they had ever been offered HBV vaccination. The setting of the last vaccination was not queried in Berlin and Essen.

Migration status was defined by country of birth: first-generation migrants were not born in Germany and second-

generation migrants were born in Germany, but one or both parents were not born in Germany. The level of education was categorized following the International Standard Classification of Education (ISCED). This was determined by querying the highest school education and highest professional formation. If the highest level of professional formation was missing, the highest school education was used as the highest education level. The use of stimulant drugs was defined as the consumption of amphetamine, methamphetamine, cocaine, crack, or 3,4-methylenedioxymethamphetamine (MDMA) during the last 30 days, regardless of the mode of consumption. Unsafe use was defined as using shared needles/syringes or spoons/filters, or sharing water for intravenous drug consumption in the past 30 days. Condom use during the last vaginal or anal intercourse was queried among participants who reported sex in the past 12 months.

Defining correct knowledge of own HBV infection and vaccination status

The self-reported HBV infection status was determined by asking whether the participant had ever been tested for HBV and if yes, what the result of the latest test was. Based on the answers, participants were categorized as HBV-negative, HBV-positive, or 'don't know'. The self-reported HBV vaccination status was determined by asking if the participant had ever been vaccinated against HBV. Participants with laboratory-confirmed current or past HBV infection were excluded from this analysis. The validity of the self-reported HBV infection and vaccination status was determined by comparing self-reported and laboratory tested status.

Biological data collection and laboratory analysis

Capillary blood samples were collected from each participant by finger prick and spotted on filter cards to prepare dried blood spots (DBS). DBS testing for this study was validated during the pilot (Ross et al., 2013). DBS were tested for HBsAg (only during the pilot study in Berlin and Essen), HBV-DNA, hepatitis B surface antigen antibodies (anti-HBs), and hepatitis B core antigen antibodies (anti-HBc) (all study cities); genotypes were determined as described previously (Zimmermann et al., 2014; Al Baqlani et al., 2014).

The interpretation of HBV laboratory results was performed according to German clinical guidelines (Cornberg et al., 2011) (Table 1). Samples with exclusive detection of anti-HBs antibodies with a detection limit of 10 IE/l were interpreted as HBV vaccinated. HBV seroprevalence was defined as current or past HBV infection. Samples negative for all tested HBV markers were interpreted as unexposed to HBV.

Table 1
Classification of serological and molecular markers for HBV diagnostics.[a]

HBV status	HBV marker		
	anti-HBs	anti-HBc	HBV-DNA/HBsAg
Unexposed	–	–	–
HBV vaccinated	+	–	–
Current HBV infection	(+)	(+)	+
Past HBV infection	(+)	+	–

HBV, hepatitis B virus; anti-HBs, hepatitis B surface antibody; anti-HBc, hepatitis B core antibody; HBsAg, hepatitis B surface antigen.

[a] '+' indicates detection of HBV marker; '(+)' indicates detection of HBV marker irrelevant for classification of HBV infection status; '–' indicates no detection of HBV marker.

Statistical analysis

Results are shown as the range of proportions (minimum and maximum values (%)) in the study cities. Univariable and multivariable analysis (UVA and MVA) were performed using logistic regression. To analyse the effect of the study city, a city with a medium prevalence was chosen as reference. For the MVA, models were built using stepwise forward selection by adding factors with a p-value lower than 0.2 in the UVA. Multivariable models were adjusted for sex and were retained only if the p-value was <0.05 in the likelihood ratio test. For the analysis of factors influencing HBV infection, HBV vaccinated participants were excluded. For the analysis of factors influencing HBV vaccination, participants with current/past HBV infection were excluded. All data analyses were performed using Stata version 14.0.

Ethics approval and data protection

Ethical approval was received from the Ethics Committee at Charité University Medicine, Berlin, Germany, in 2011 (Number EA4/036/11) and in 2012 (amendment; Number EA4/036/11). The Federal Commissioner for Data Protection and Freedom of Information approved the study protocol in 2012 (III-401/008#0035). All participants provided informed consent allowing their anonymized data to be used for publication. Participants were also allowed to give oral informed consent, which was then certified by the study manager's signature on the informed consent form. Informed consent forms and questionnaires were sent to the Robert Koch Institute where data entry and analysis were performed. Informed consent forms were stored separately from questionnaires, with restricted access only to study personnel. Participants were offered the option to receive their test results by consenting on a personal code word. In such cases, post-test counselling was provided. In each of the study cities, referral structures were organized so that persons who voluntarily received their test result could be referred to medical care for further diagnostics and treatment, if necessary.

Results

Among the 2077 participants, the proportion of women among the study cities ranged from 19% to 35%; the median age of participants was 29–41 years and median duration of injecting drugs was 10–18 years. Between 76% and 88% of participants reported injecting in the last 30 days, and 57–85% reported heroin consumption in this period. Other characteristics and drug consumption practices of the study population have been published elsewhere (Wenz et al., 2016).

HBV seroprevalence and prevalence of vaccine-induced HBV antibodies

The prevalence of current HBV infection was 1.1% ($n=22$) (city range 0.3–2.5%) and the prevalence of cleared HBV infection was 24% ($n=494$) (city range 2.3–31%). HBV seroprevalence among all study participants was 25% ($n=516$) (city range 4.3–32%). Similar to HBV seroprevalence, prevalence of HBV vaccination-induced HBV antibodies varied between study cities (city range 15–52%), with an average of 32% among all study participants. Across all study cities, 43% of study participants (city range 16–69%) had no antibodies against HBV through vaccination or natural immunity after HBV infection (Figure 1, Table 2).

HBV seroprevalence increased with age and was 3%, 17%, and 37% in the age groups <25 years, 25–39 years, and ≥ 40 years, respectively. Current HBV infections were detected in 0.7% within the age group of 25–39 years and in 1.6% of those ≥ 40 years old. No

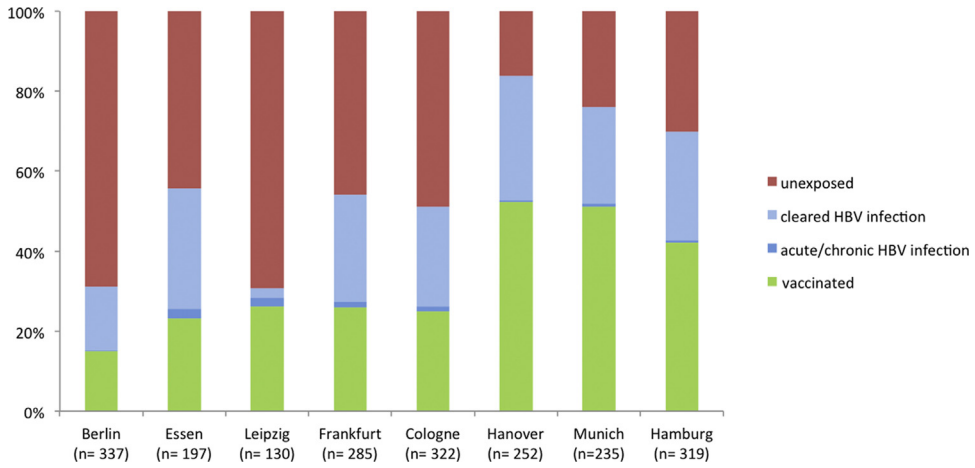

Figure 1. Serological and molecular findings for HBV status by study city.

Table 2
HBV status (according to laboratory findings) by age group, sex, and HIV and HCV status.

		Unexposed	Vaccinated	Current HBV infection	Past HBV infection
Age group	<25 years (n = 135)	63 (47%)	68 (50%)	0 (0.0%)	4 (3.0%)
	25–39 years (n = 1018)	503 (49%)	341 (34%)	7 (0.7%)	167 (16%)
	≥40 years (n = 922)	323 (35%)	261 (28%)	15 (1.6%)	323 (35%)
Sex	Male (n = 1594)	690 (43%)	493 (31%)	17 (1.1%)	394 (25%)
	Female (n = 480)	198 (41%)	178 (37%)	4 (0.8%)	100 (21%)
HIV status	Negative (n = 1977)	855 (43%)	639 (32%)	19 (1.0%)	464 (23%)
	Positive (n = 100)	35 (35%)	32 (32%)	3 (3.0%)	30 (30%)
HCV status	Negative (n = 716)	376 (53%)	253 (35%)	2 (0.3%)	85 (12%)
	Positive (n = 1361)	514 (38%)	418 (31%)	20 (1.5%)	409 (30%)
	Total (n = 2077)	890 (43%)	671 (32%)	22 (1.1%)	494 (24%)

HBV, hepatitis B virus; HIV, human immunodeficiency virus; HCV, hepatitis C virus.

current HBV infections were detected in those aged <25 years. Among all study participants, the HBV seroprevalence was higher among men than women (26% vs. 22%) (Table 2).

HBV genotypes

HBV genotyping was performed on 16 samples with active HBV infection (no genotyping was performed in Berlin or Essen). The most frequently identified genotype was D (n = 12), followed by A (n = 3) and G (n = 1). Other HBV genotypes were not detected.

Knowledge of correct HBV infection status

Self-reported and laboratory-tested HBV infection status were concordant in 71% (n = 1463), indicating correct knowledge of their own HBV infection status. Among study participants, 9.3% (n = 190) stated that they did not know their HBV infection status. Among the participants who had a past or current HBV infection, 41% (n = 209/511) were unaware of their infection. Among all study participants, 11% (n = 233) thought they had been or were currently infected with HBV, although their laboratory results indicated neither previous vaccination nor contact with HBV (Table 3).

Factors associated with HBV infection status

In the UVA, participant age ≥25 years (reference: <25 years), injecting drugs for more than 10 years, using stimulant drugs in the past 30 days, and ever having been incarcerated or in opioid substitution therapy (OST), were significantly associated with current/past HBV infection (Table 4). Furthermore, the HBV

Table 3
Self-reported HBV infection status and comparison to laboratory tested HBV infection status among patients with a valid answer on infection status (n = 2051).

	Self-reported HBV infection status			
HBV laboratory test result	Not infected	Infected	Don't know	Total
Unexposed	663 (32%)[a]	117 (5.7%)	98 (4.8%)	878 (43%)
Current/past infection	165 (8.0%)	302 (15%)[a]	44 (2.2%)	511 (25%)
Vaccinated	498 (24%)[a]	116 (5.7%)	48 (2.3%)	662 (32%)
Total	1326 (65%)	535 (26%)	190 (9.3%)	2051 (100%)

HBV, hepatitis B virus.
[a] Concordant results.

Table 4
Univariable and multivariable analysis of factors associated with HBV infection ($n = 1406$).

		Current/past HBV infection	Univariable analysis		Multivariable analysis	
			OR	95% CI	aOR	95% CI
Study city	Frankfurt	38%	Ref.		Ref.	
	Leipzig	6.3%	0.1 ***	0.0–0.3	0.2 ***	0.1–0.4
	Berlin	19%	0.4 ***	0.3–0.6	0.5 **	0.3–0.8
	Cologne	35%	0.9	0.6–1.3	0.8	0.6–1.3
	Hamburg	47%	1.5	1.0–2.2	1.2	0.8–1.8
	Essen	43%	1.2	0.8–1.8	1.4	0.9–2.2
	Munich	51%	1.7 *	1.1–2.6	1.9 *	1.1–3.1
	Hanover	67%	3.2 ***	2.0–5.2	3.2 ***	1.9–5.3
Sex	Male	34%	Ref.		Ref.	
	Female	37%	0.9	0.7–1.2	1.1	0.8–1.5
Age (years)	<25	6.0%	Ref.		Ref.	
	25–39	26%	5.4 **	2.0–15	2.2	0.7–6.4
	≥40	51%	16.5 ***	5.9–46	5.3 *	1.8–16
Duration of IV drug use	<10 years	15%	Ref.		Ref.	
	>10 years	44%	4.6 ***	3.3–6.4	2.8 ***	1.9–4.0
Use of stimulant drugs (past 30 days)	No	31%	Ref.		Ref.	
	Yes	40%	1.5 **	1.2–1.9	1.6 **	1.2–2.1
Migrant status	Non-migrant	38%	Ref.		Ref.	
	2nd generation	32%	0.8	0.6–1.1	0.9	0.6–1.2
	1st generation	37%	1.0	0.7–1.3	1.5 **	1.1–2.0
Ever been homeless	No	34%	Ref.		Ref.	
	Yes	38%	1.2	0.9–1.5	1.4 *	1.1–1.8
Ever incarcerated	No	29%	Ref.			
	Yes	38%	1.5 **	1.1–2.1		
Ever in opioid substitution therapy	No	24%	Ref.			
	Yes	40%	2.1 ***	1.5–2.8		
Unsafe use (past 30 days)	No unsafe use	40%	Ref.			
	No IV drug use	30%	0.6 **	0.5–0.9		
	Unsafe use	34%	0.8 *	0.6–1.0		
Condom use during last vaginal/anal intercourse	Yes	36%	Ref.			
	No sex past 12 months	42%	1.3	1.0–1.8		
	No	35%	0.9	0.7–1.2		

HBV, hepatitis B virus; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; IV, intravenous.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

infection status differed significantly between the study cities. Participants injecting drugs in Munich and Hanover more often had a current/past HBV infection compared to participants from the other cities. Migrant status, ever having been homeless, and condom use during the last vaginal/anal intercourse were not associated with HBV infection status in the UVA. Participants who stated either unsafe use or no intravenous drug use in the past 30 days (reference: no unsafe use) had significantly lower odds of having a current/past HBV infection.

In the MVA, study participant age ≥40 years (reference: <25 years), injecting drugs for more than 10 years, having used stimulant drugs in the past 30 days, being a first-generation migrant (reference: non-migrant), and having ever been homeless was associated with higher odds of having a current/past HBV infection. As in the UVA, the study city was also significantly associated with the HBV status.

Incarceration, unsafe use, OST experience, and condom use during the last vaginal/anal intercourse were not significantly

Table 5
Self-reported and laboratory tested HBV vaccination status among patients with a valid answer on vaccination status and with no laboratory-confirmed current/past HBV infection ($n = 1553$).

	Self-reported HBV vaccination status			
HBV laboratory test result	Not vaccinated	Vaccinated	Don't know	Total
Unexposed	353 (23%)[a]	407 (26%)	125 (8.1%)	885 (57%)
Vaccinated	239 (15%)	349 (22%)[a]	80 (5.2%)	668 (43%)
Total	592 (38%)	756 (49%)	205 (13%)	1553 (100%)

HBV, hepatitis B virus.
[a] Concordant results.

associated with being or having been infected with HBV in the MVA (Table 4).

Knowledge of correct HBV vaccination status

Among participants with no laboratory-confirmed current/past HBV infection, 45% ($n = 702$) of self-reported and laboratory-tested HBV vaccination status results were concordant, indicating correct knowledge of their HBV vaccination status. Among participants, 13% ($n = 205$) stated that they did not know their HBV vaccination status. Falsely assuming not being vaccinated against HBV was the case for 15% ($n = 239$) of participants. Among participants with neither vaccine-induced nor infection-induced detectable antibodies against HBV, 26% ($n = 407$) stated that they had been vaccinated against HBV (Table 5).

Setting of last HBV vaccination

Among participants who reported having been vaccinated against HBV ($n = 938$), 641 answered the question about the setting or place of their last vaccination. The most frequently reported settings were medical doctors without addiction therapy, e.g. general practitioners (34%), OST services (23%), and hospitals (17%) (Figure 2).

Factors associated with HBV vaccination status

The UVA showed that injecting drugs in Berlin, belonging to age group 25–39 years, having a high education level, ever having been incarcerated, and never having been in OST, were significantly associated with testing negative for vaccine-induced HBV antibodies (Table 6). In the MVA, participants who injected drugs in Berlin, belonged to the age group 25–39 years (reference: <25 years), and had a high education level (reference: low education level) were significantly associated with not having vaccine-induced HBV antibodies. No association was found in the MVA for incarceration and OST (Table 6).

Discussion

The HBV seroprevalence among PWID in this study was about five times higher than that in the general population in Germany, confirming PWID as an important risk group for HBV (Poethko-Muller et al., 2013). Furthermore, despite the existing recommendations of STIKO for the vaccination of PWID against HBV, neither vaccine-induced antibodies nor any natural immunity from past HBV infection were detected in 43% of participants, therefore leaving them at risk of infection. This suggests that the German vaccination recommendation for PWID and other groups at increased risk of HBV infection has not been reaching this group sufficiently. It is noteworthy that the study participants often had several indications for HBV vaccination besides intravenous drug use, e.g. HIV infection, hepatitis C virus (HCV) infection, or incarceration experience. However, young study participants (<25 years of age) showed a higher proportion of vaccine-induced immunity and a lower prevalence of HBV infection than those in the older age groups, indicating that they had already been covered by the general vaccination recommendation for infants implemented in 1995. Catch-up campaigns for older children were conducted to immunize children <19 years of age, but they were not systematically implemented and conducted on a large scale. In line with this, a higher proportion of vaccine-induced immunity among those aged 25–39 years was not observed; this age group represents a population that might have benefited from the general vaccination recommendation in childhood.

In this study, age ≥40 years and duration of intravenous drug use of more than 10 years was significantly associated with current/past HBV infections. This finding is biologically plausible, as it correlates with longer lifetime exposure to HBV and is in good agreement with several other studies (Removille et al., 2011; Edeh and Spalding, 2000). Further, first-generation migrants have higher odds of current/past HBV infection than non-migrants, similar to the results of the national German children and adolescents survey (Cai et al., 2011). This could be explained either by a higher prevalence of HBV or less effective HBV vaccination programmes in the country of origin, or limited access to HBV vaccination in Germany due to language or other barriers or lack of health insurance (Lutgehetmann et al., 2010).

Ever having been in OST was not significantly associated with HBV infection status in the MVA and indicates that opportunities to vaccinate OST recipients against HBV are currently not optimized. Reasons might be that awareness is low, because medical doctors offering OST are often not trained in infectious diseases and the dogma that people receiving OST are supposed to stop their

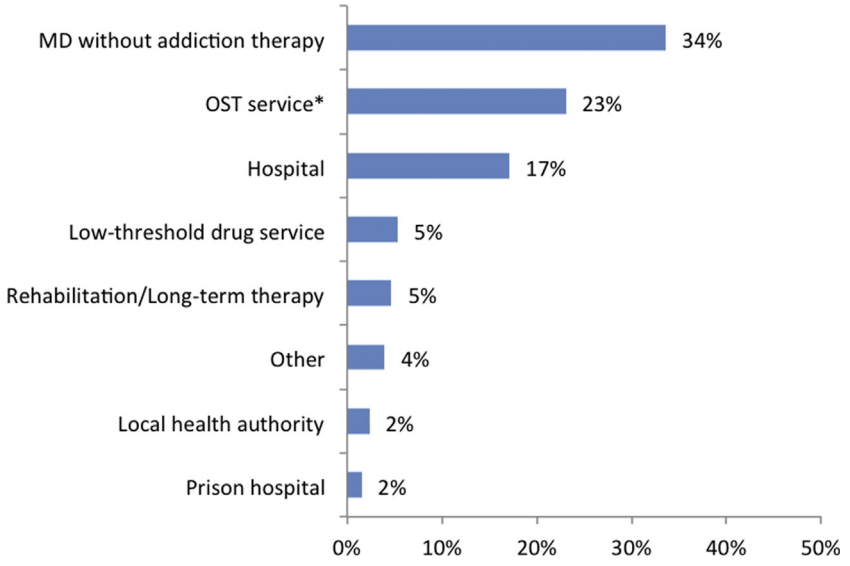

Figure 2. Place of last HBV vaccination ($n = 641$). Question not asked in Berlin, Essen, or Leipzig. MD, medical doctor; OST, opioid substitution therapy. *OST service includes medical doctors/outpatient clinics with OST or addiction therapy.

Table 6
Univariable and multivariable analysis of factors associated with not having HBV vaccine-induced antibodies ($n = 1561$).

		No vaccination-induced HBV antibodies detected	Univariable analysis		Multivariable analysis	
			OR	95% CI	aOR	95% CI
Study city	Frankfurt	64%	Ref.		Ref.	
	Hanover	23%	0.2 ***	0.1–0.3	0.2 ***	0.1–0.3
	Munich	32%	0.3 ***	0.2–0.4	0.3 ***	0.2–0.4
	Hamburg	42%	0.4 ***	0.3–0.6	0.4 ***	0.3–0.6
	Cologne	66%	1.1	0.7–1.6	1.1	0.8–1.7
	Essen	66%	1.1	0.7–1.6	1.1	0.7–1.8
	Leipzig	73%	1.5	0.9–2.4	1.8 *	1.1–3.0
	Berlin	82%	2.5 ***	1.7–3.8	2.7 ***	1.8–4.1
Sex	Male	58%	Ref.		Ref.	
	Female	53%	0.8	0.6–1.0	1	0.7–1.2
Age (years)	<25	48%	Ref.		Ref.	
	25–39	60%	1.6 *	1.1–2.3	1.9 **	1.2–2.9
	≥40	55%	1.3	0.9–2.0	1.7 *	1.1–2.8
Education	Low	55%	Ref.		Ref.	
	Middle	58%	1.1	0.9–1.3	1.2	0.9–1.5
	High	75%	2.4 **	1.3–4.7	2.8 **	1.4–5.6
	Other	59%	1.2	0.6–2.3	1.7	0.8–3.5
Ever incarcerated	No	51%	Ref.			
	Yes	58%	1.3 *	1.0–1.7		
Ever in opioid substitution therapy	Yes	55%	Ref.			
	No	63%	1.4 *	1.1–1.8		

HBV, hepatitis B virus; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval.
* $p < 0.05$.
** $p < 0.01$.
*** $p < 0.001$.

injecting drug use. The use of stimulant drugs in the past 30 days might be associated with riskier sexual and unsafe use behaviours (Tavitian-Exley et al., 2015); however, not using a condom during the last sexual intercourse did not seem to be associated with HBV infection status. This might indicate that the last intercourse is not a good proxy for life-time sexual risk behaviour or that sexual transmission is not the main route of HBV transmission in this group.

PWID aged ≥25 years or with a higher education level were less likely to have detectable vaccine-induced HBV antibodies. An association with high education level was not expected, although scepticism towards vaccination has been observed in persons with higher levels of education in other studies (Wei et al., 2009). However, due to the cross-sectional design of this study, drawing strong conclusions regarding whether different socio-demographic and behavioural factors are the cause or effect of HBV infection and vaccination is not possible.

Neither having been incarcerated nor being in OST was significantly associated with showing vaccine-induced HBV antibodies in the MVA, although these could be appropriate settings to target PWID for HBV vaccination. Most participants had received their last HBV vaccination from medical doctors not offering addiction therapy, and few had been vaccinated at low-threshold drug services, during rehabilitation/long-term addiction therapy, or in prison, indicating that these settings should be better utilized to improve HBV vaccination rates among PWID in Germany. The completion of a vaccination schedule would be easily feasible, e.g. during OST, due to the regular contact with medical staff.

The MVA revealed a strong association of the study city particularly with HBV vaccination, and less with infection status, indicating an effect of the local setting. In a setting where the proportion of HBV-infected PWID is low (and the proportion of vaccinated PWID high), the transmission of HBV is less likely to occur. Furthermore, local differences in practices of medical doctors offering OST, local HBV vaccination, and information campaigns/programmes, e.g. in low-threshold drug services, may also play a role here and need to be examined in further studies to evaluate the differences in the study cities and their impact.

Options to increase vaccination coverage among PWID, as recommended by the WHO and EMCDDA, include the immediate availability of on-site vaccination during information and vaccination campaigns targeting PWID, prison-based vaccination programmes, cash incentives, and accelerated immunization schedules (Campbell et al., 2007; Sutton et al., 2006; Weaver et al., 2014; Shah et al., 2015); however, these are not routinely implemented in Germany. Integrating vaccination campaigns into needle exchange programmes may also be a cost-effective option (Hu et al., 2008).

The self-reported HBV infection and vaccination status had limited validity, with 71% of participants reporting their HBV status and only 45% reporting their HBV vaccination status in concordance with the laboratory tests. This discordance between self-reported and tested results has been reported in previous studies among PWID (Topp et al., 2009). Similarly, among those with a chronic HCV infection, 73% reported their correct HCV status (Nielsen et al., 2016). Discordant results also included participants falsely assuming an HBV infection, probably due to confusing HBV with HCV. About 20% of study participants assumed that they were vaccinated against HBV, but showed neither vaccine- nor infection-induced antibodies, most probably leaving them at risk of HBV infection. Explanations for this might be confusing HBV vaccination with other vaccinations, or insufficient protection due to incomplete vaccination schedules. Furthermore, primary (non-response) or secondary (waning of antibodies) vaccination failure cannot be excluded as possible explanations for the lack of detection of vaccine-induced HBV antibodies. This would lead to an underestimation of the vaccination prevalence, but might also reflect the problem of inadequate immune response to HBV

vaccination previously described among PWID (Kamath et al., 2014).

Although all methodologies were validated, a limitation in the direct comparability of test results from the pilot cities and the remaining six cities cannot be excluded due to the change of the laboratory and the methodologies used for testing (Zimmermann et al., 2014). The assessment of all serological test systems for HBV showed good accordance between directly tested serum samples in comparison to DBS, except for anti-HBs in weakly positive sera. Weakly anti-HBs-positive samples could have been missed with this procedure. Thus the prevalence of anti-HBs antibodies, e.g. of HBV vaccinated individuals, based on the DBS technique must be considered as a conservative estimate, especially in HIV-positive persons (Ross et al., 2013). However, the anti-HBc results demonstrated high accuracy of the test systems and yielded comparable validation results. Furthermore, natural boosting with HBV can be expected among PWID, and choosing a low threshold for the detection of anti-HBs should help minimize the underestimation of HBV vaccination.

Although data were anonymized, participants might have been reluctant to report sensitive data such as unsafe use and sexual behaviours correctly, and answers might have been influenced by social desirability bias. RDS is an adequate sampling method to reach PWID. However, after evaluating the method in this study, it was decided against presenting RDS-weighted results, as some of the necessary assumptions for weighting were not fulfilled in all study cities (Wenz et al., 2016). Selection bias due to oversampling of persons with communicative competence and who understood the study flow cannot be excluded.

This study indicates that despite national vaccination recommendations including both the recommendation of universal infant and child vaccination (since 1995) and risk group vaccination (starting in 1982), many PWID are still at risk of HBV in Germany. Targeted information campaigns on HBV and HBV prevention for healthcare and community workers and medical doctors in contact with PWID, as well as for the PWID themselves, need to be intensified. PWID should be tested and counselled regularly for HBV, and if tested positive, linked to clinical care to assess the indication for treatment. Testing should be followed by a discussion of the results in more detail with the patients, and differences between HBV and HCV should be elucidated. Knowledge of the exact status is further important to avoid risk-taking behaviours. As the self-reported HBV vaccination status is not reliable, pre-emptive HBV vaccination should be considered if no vaccination record is available. Other options with promising results in other countries and recommended by the WHO and EMCDDA include a contingency management approach (Weaver et al., 2014), a 'don't ask, vaccinate' strategy (Day et al., 2010), and the importance of on-site availability of the vaccination being critical for uptake in a low-threshold setting (Campbell et al., 2007).

In order to avoid primary vaccination failure, the STIKO recommends control testing of anti-HBs antibody titres at 4–8 weeks after the last vaccination dose, and if titres remain too low (<100 IU/l), further booster vaccinations should be applied (Robert Koch-Institut (RKI), 2014).

Many study participants had been incarcerated (city range 73–86%) or were currently or previously in OST (city range 55–89%) (Wenz et al., 2016). Ensuring routinely offered HBV vaccination to PWID in these settings would likely improve HBV vaccination rates among PWID in Germany. An additional advantage of vaccinating during OST and incarceration is that in these settings, the completion and documentation of a vaccination course are more feasible than in the low-threshold system. Nonetheless, vaccination campaigns in low-threshold drug services are important to raise awareness and to reach those people not in contact with medical services, and should also be scaled-up.

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Conflict of interest

All authors declare that they have no conflicts of interest.

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'The DRUCK Study group' includes the following people (all in Germany):

Andreas Hecht (Sozialdienst Katholischer Männer e.V.; Andreas.Hecht@skm-koeln.de); Werner Heinz (Jugendberatung und Jugendhilfe e.V.; werner.heinz@jj-ev.de); Jürgen Klee (Aids-Hilfe Frankfurt e.V.; Juergen.Klee@frankfurt.aidshilfe.de); Astrid Leicht (Fixpunkt Berlin e.V.; A.Leicht@fixpunkt.org); Dr Claudia Kücherer (Robert Koch Institute; KuechererC@t-online.de); Dr Claudia Santos-Hövener (Robert Koch Institute; santos-hoevenerC@rki.de); Prof. Dr Norbert Scherbaum (Klinik für abhängiges Verhalten und Suchtmedizin, LVR-Klinikum Essen, Kliniken/Institut der Universität Duisburg-Essen; norbert.scherbaum@uni-due.de); Dirk Schäffer (Deutsche Aids-Hilfe e.V.; dirk.schaeffer@dah.aidshilfe.de).

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