Aus dem Robert Koch-Institut
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DISSERTATION

HIV, hepatitis B and C, risk behaviours and access to health and harm reduction services for people who inject drugs in Germany

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"Harm reduction is a set of principles and an evidence-informed package of services and policies that seek to reduce the health, social and economic harms of drug use."
Quote from the chapter "Harm Reduction: Linking human rights and public health" (1).

Table of contents

Abbreviations

AB – antibodies

BBI – blood-borne infections

CHC – chronic hepatitis C infection

CI – confidence interval

DAA – direct acting antivirals

DBS – dried blood spots

DCF – drug consumption facilities

DRUCK – Drogen und chronische Infektionskrankheiten (“drugs and chronic infectious diseases”)

FSU – former Soviet Union

GP – general practitioner

HBV – hepatitis B virus infection

HCV – hepatitis C virus infection

IDU – injecting drug use

LI – long-term injectors

MVA – multivariable analysis

NSP – needle and syringe programmes

NI – new injectors

OR – odds ratio

OST – opioid substitution therapy

PWID – people who inject drugs

RDS – respondent driven sampling

RKI – Robert Koch Institute

UVA – univariable analysis

WHO – World Health Organization

Abstract (English)

Background:
People who inject drugs (PWID) are at increased risk of acquiring and transmitting blood-borne infections (BBI) such as HIV, hepatitis B (HBV) and hepatitis C (HCV) through unsafe injecting practices and unprotected sex. In the six papers included in this doctoral dissertation, we aimed to examine BBI prevalence, risk behaviours and access to health and harm reduction services among PWID to inform and scale-up targeted prevention efforts in Germany.

Methods:
We performed several both descriptive and multivariable analyses based on a multicity bio-behavioural survey using respondent driven sampling conducted in eight German cities between 2011 and 2014. Inclusion criteria were age ≥16 years and having injected drugs in the last 12 months. All participants were interviewed using a standard questionnaire and provided a capillary blood sample which was tested for HIV, HBV and HCV.

Results:
Overall, 2077 PWID were recruited. Most (89%) participants had injected drugs for five years or more, 80% had detention experience, 49% were currently in opioid substitution therapy (OST) and the majority (86%) had recently visited a low threshold drug service. Prevalence was 4.8% for HIV, 41% for chronic HCV infection (CHC) and 1.1% had current HBV infection. Overall, 32% had vaccine-induced HBV antibodies and no detectable HBV antibodies indicating susceptibility to HBV infection were found in 43%. Overall, 17% of those with HIV and 27% of those with CHC did not know they were infected. We found a strong association of the study city with HBV vaccination, and no association between HBV vaccination and detention or OST experience. PWID born in the former Soviet Union had higher HCV seroprevalence and more often reported risky drug consumption behaviours compared to German PWID. The proportion of PWID positive for HCV increased with both frequency and duration of their detention experience. People injecting <2 years were less often tested for HCV despite frequently attending addiction therapy.

Conclusions:
HIV, HBV and HCV varied between the city samples. However, HCV was highly endemic among PWID and behaviours linked with increased infection risk were prevalent in all cities. We identified missed opportunities for linkage to services and the six papers included in this doctoral dissertation all contribute key findings useful for strengthening BBI prevention and control interventions among PWID in Germany.

Abstract (German)

Hintergrund:
Personen, die Drogen injizieren (IVD), haben ein erhöhtes Risiko, aufgrund gemeinsamen Gebrauchs von Injektionsutensilien und ungeschützten Sexualkontakten sexuell und durch Blut übertragene Infektionen wie HIV, Hepatitis B (HBV) und Hepatitis C (HCV) zu erwerben und weiterzugeben. In den sechs in dieser Dissertation enthaltenen Publikationen wollten wir HIV, HBV und HCV Seroprävalenzen untersuchen, sowie damit gekoppelte Daten zu Risiko- und Präventionsverhalten einschließlich Zugang zu Angeboten der Schadensminimierung, Suchttherapie und medizinischen Versorgung von IVD analysieren, um gezielt die Prävention zum Schutz vor HIV und Hepatitiden bei IVD in Deutschland zu informieren und zu stärken.

Methodik:
Für diese Publikationspromotion haben wir mehrere deskriptive und multivariable Analysen (MVA) durchgeführt, die sich alle auf einem multizentrischen Sero- und Verhaltenssurvey unter IVD basieren. Die Studie wurde zwischen 2011 und 2014 in acht deutschen Städten durchgeführt. Einschlusskriterien waren intravenöser Drogenkonsum in den letzten 12 Monaten und ein Mindestalter von 16 Jahren. Neben einem ausführlichen fragebogengestützten Interview wurden Kapillarblutproben von Teilnehmern anonym auf HIV, HCV und HBV untersucht.

Ergebnisse:
Insgesamt wurden 2077 IVD rekrutiert. Die meisten (89%) Teilnehmer hatten fünf Jahre oder länger Drogen injiziert, 80% hatten Hafterfahrung, 49% waren aktuell in Opioidsubstitutionstherapie (OST) und die Mehrheit (86%) hatte in den letzten 30 Tagen eine niedrigschwellige Drogenberatungsstelle besucht. Die Prävalenz von HIV war 4,8%, 41% hatten eine chronische HCV-Infektion (CHC), 1,1% hatten eine akute/chronische HBV-Infektion, 32% waren HBV-geimpft und bei 43% wurden keine HBV-Antikörper nachgewiesen. Insgesamt wussten 17% der HIV-Infizierten und 27% der Teilnehmenden mit CHC nicht, dass sie infiziert waren. Die MVA zeigte eine starke Assoziation zwischen HBV-Impfung und der Studienstadt jedoch keine zwischen HBV-Impfung und Inhaftierung oder OST-Erfahrung. Teilnehmende, die in Nachfolgestaaten der Sowjetunion geboren waren, hatten eine höhere HCV-Seroprävalenz und berichteten häufiger über riskantes Drogenkonsumverhalten im Vergleich zu deutschen IVD. Der Anteil von HCV-Infektionen nahm mit kumulativer Haftdauer und Anzahl der Inhaftierungen zu. Personen, die <2 Jahre injizierten, wurden -trotz häufiger Suchttherapieerfahrung- seltener auf HCV getestet.

Schlussfolgerungen:
Es gab deutliche Unterschiede in der Seroprävalenz von HIV, HBV und HCV zwischen den acht Studienstädten, jedoch waren HCV-Infektion sowie Verhaltensweisen, die mit einem erhöhten BÜI-Risiko verbunden sind, in allen Städten weit verbreitet. Eine bessere Kooperation zwischen u.a. niedrigschwelliger Drogenhilfe, dem Suchtmedizinsystem, Justizvollzugsanstalten und der Ärzteschaft kann hier helfen. Alle Publikationen in dieser Dissertation tragen wichtige Erkenntnisse zur Anpassung der Präventionsempfehlungen bei IVD in Deutschland bei.

1. Introduction

People who inject drugs (PWID) are at increased risk of being infected with blood-borne infections (BBI) such as viral hepatitis B and C (HBV and HCV) and HIV through sharing of injection paraphernalia and unprotected sex (2-5). In the past in Germany, few bio behavioural studies had been done among PWID to investigate the prevalence of HBV, HCV, HIV and the related risk- and protective factors for these infections (6-10). These previous studies had limited geographical coverage and were based on convenience sampling. There is no routine monitoring system in place in Germany to monitor infections or risk and preventive behaviours among PWID. German HCV notification data shows that injecting drug use is attributed to 75% of newly diagnosed cases with information on route of transmission (11).
The objective of the DRUCK-study ("DRUCK" is an acronym based on the German translation of "Drugs and chronic infectious diseases") was to estimate the prevalence of HBV, HCV and HIV among PWID as well as to gather information on risk and health seeking behaviours among this population in order to inform and scale-up prevention efforts for this group in Germany.
In total, six papers published between 2016-2020 are included in this doctorate by publication (12-17).

1.1 Research questions

With this dissertation research project, we aimed to address the following questions:

1. What are the key characteristics of PWID in Germany – in terms of socio-demographics, utilisation of health and harm reduction services, substance use patterns and risk behaviours related to drug use (12)
2. What is the prevalence of HBV, HCV and HIV among people who inject drugs in Germany (12, 14)
3. How well are people who inject drugs aware of their infection status - comparing the self-reported infection status with the serological markers of infection (13)

In addition, detailed analyses of the following topics were done:

4. Factors associated with HBV infection and HBV vaccination including recommendations for improving the uptake of HBV vaccination among people who inject drugs in Germany (14).
5. An investigation of HCV and HIV seroprevalence and related risk behaviours among migrants from the former Soviet Union who inject drugs in Germany in order to identify potential needs for targeted interventions in this sub-group (15).
6. The association between detention experience and HCV status among PWID including the role of duration and frequency of detention for HCV status and whether risk behaviours practiced in detention could explain an observed increase in risk (16).
7. Description of characteristics, HCV prevalence and estimated HCV incidence among people who recently started injecting drugs including recommendations for improved uptake of BBI testing and prevention efforts in this group (17).

2. Methods

A detailed explanation of the methodology used in the DRUCK-study is given in the published study protocol (18) and the Wenz et al paper (12). In the following a brief overview of the methods is provided.

Data was collected in the following eight German cities between May 2011 and May 2014: Berlin, Essen, Leipzig, Frankfurt, Cologne, Hanover, Munich and Hamburg with the aim of recruiting between 200-400 participants in each city. Eligible for participation were people aged 16 years or older who had injected drugs in the last 12 months, and who consumed drugs in one of the eight study cities. Participants could only participate in the study once and all had to provide informed consent (12, 18).

2.1 Sampling and recruitment

Participants were recruited using respondent driven sampling (RDS) – a "chain referral" and modified "snowball" sampling technique and analysis tool which was introduced in 1997 as an approach to study "hidden populations" (19). The RDS approach has since been used in hundreds of studies worldwide to assess e.g. HIV prevalence and associated risk behaviors in often stigmatized and criminalized populations who cannot be identified through a standard sampling frame but who are linked through social networks such as for example people who use drugs (20, 21).

Low threshold drop-in drug services were used as study sites in all study cities. In each city, between 8-12 initial participants (called "seeds") were identified through local study partners to start recruitment. The "seeds" were selected to represent a broad range of PWID in the local setting with respect to e.g. socio-demographic and behavioural characteristics. Study participation was reimbursed with 10 euros (in cash) and an additional 5 euros for each successful peer-recruitment, with a maximum of three recruitments per participant.

Recruitment expanded through so called "recruitment waves" where the "seeds" recruited the first wave of participants, who then recruited a second wave of participants and so on until the targeted sample size was reached or until the end of the scheduled recruitment period (12). Individual identification numbers on the coupons allowed monitoring of the recruitment process. When reporting the study results we followed the 2015 guidelines for reporting on epidemiological studies using RDS (22).

2.2 Collection of socio-demographic and behavioural data

A two-day training of the study staff in each study city was done prior to starting data collection to ensure standardisation and adherence to the study protocol (12).

Participants were interviewed by trained staff of the local low threshold drug services using a paper questionnaire which was based on a model questionnaire for bio-behavioural surveys in people who inject drugs developed by the European Monitoring Centre for Drugs and Drug Addictions (EMCDDA) (23, 24) and adapted to fit to the local settings as well as to ensure standardization with current global indicators in international reporting mechanisms such as the Global AIDS Response Progress Reporting (25). The questionnaire covered the following topics: socio-demographic characteristics, substances used, injecting behaviour, sexual risk behaviour, detention experience, use of health and addiction services including history of testing and knowledge related to HIV, HBV and HCV. Most interviews lasted 30-45 minutes. Minor modifications were made to the questionnaire throughout the study period and therefore some variables are not available for all cities. An example of the questionnaire can be found online at the RKI DRUCK-study website (26).

2.3 Laboratory testing for HIV, hepatitis B and C

Dried blood spots (DBS) from capillary blood were collected and tested for HIV, HCV and HBV markers. Samples reactive for HIV-1/-2 antibodies (AB) were confirmed by Western blot. All samples were tested both for HCV AB and by PCR. Chronic HCV infection (CHC) was defined as testing both HCV AB and HCV RNA positive whereas HCV positivity (used as outcome variable in the last three papers (15-17)) was defined as either HCV AB and/or HCV RNA positive. DBS were tested for the following HBV markers: HBsAg (only during the pilot phase in Berlin and Essen), HBV-DNA, antibodies to hepatitis B surface antigen (anti-HBs), and antibodies to hepatitis B core antigen (anti-HBc) (in all study cities) (14). The interpretation of HBV laboratory results was performed in accordance with the German clinical guidelines (14, 27). Participants who were positive for anti-HBs and negative for all other HBV markers were classified as having vaccine-induced antibodies. Past HBV infection was defined by testing positive for anti-HBc and negative for HBsAg or HBV-DNA and current HBV infection as positive for HBsAg. Further details on the DBS testing and lab procedures are described elsewhere (18, 28).

2.4 Key definitions implemented for the analyses

The use of stimulant drugs was defined as the consumption of amphetamine, methamphetamine, cocaine, crack, or 3,4-methylenedioxyme-thamphetamine (MDMA) during the last 30 days, regardless of the mode of consumption.

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 (14).

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. Migrants from the former Soviet Union (FSU) were defined as those born in Armenia, Azerbaijan, Belarus, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Moldova, Russia, Tajikistan, Turkmenistan, Ukraine, or Uzbekistan (15).

To explore the association between detention experience and HCV status among PWID we defined detention experience as having been in any of the following: juvenile arrest/prison, pre-trial custody, prison and forensic commitment (i.e. detention in a clinic for forensic psychiatric care following a criminal conviction) (16).

Finally for the last analyses presented in this dissertation, we defined people who had injected drugs for less than five years as “new injectors” (NI) in line with other studies (29-31) and estimated HCV incidence among NI using the following reported variables: date of study participation, month and year of birth and age when IDU was initiated. By assuming that all participants were HCV-negative when they began injecting drugs and that infection occurred at midpoint between initiation of IDU and participation in the study we used stochastic simulation to simulate the (unknown) month injection drug use was initiated and the (unknown) later time point HCV infection occurred based on 200 realisations in each case. For each realisation, we performed a bootstrap to account for the sampling error and characterised the resulting probability distribution by its mean and the 2.5 and 97.5 percentiles (17).

2.5 Statistical data analyses

Initially, descriptive analyses were performed, generating counts and frequencies for all variables including the overall HIV, HCV and HBV seroprevalence. Most variables had less than 5% missing values and missing data were excluded when calculating percentages.

Where appropriate, Chi^2- or Fisher exact test (i.e. when expected cell size <5) were performed to describe differences between groups. Univariable (UVA) and multivariable analysis (MVA) were performed using logistic regression and the odds ratio (OR) and 95% confidence interval (CI) for key variables of interest were calculated. 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 always adjusted for sex, age and study city. Other variables were retained only if the p-value was <0.05 in the likelihood ratio test. Interaction terms considered meaningful a priori were examined and added to the MVA models one by one, checking for significant improvement using the likelihood ratio test ($p < 0.05$). Data analyses were performed using Stata versions 13.1, 14.0, 14.1 and 15.1 for Windows.

2.6 Ethical approval, data protection and funding

Ethical approval for the study was granted by the ethics committee at the Charité University of Medicine (Berlin) in 2011 and with an amendment approved in 2012 (Number EA4/036/11). In 2012, the Federal Commissioner for Data Protection and Freedom of Information approved the study protocol (III-401/ 008#0035) (18). All participants provided informed consent allowing their anonymized data to be used for publication. No personal data allowing identification of study participants were collected. Informed consent forms and questionnaires were sent from the study sites to the RKI where data entry and analysis were performed. Informed consent forms were stored separately from questionnaires and these study materials were only accessible to a limited number of study personnel. In each of the study cities, referral structures were organized so that participants who received their HIV, HCV and HBV test result could be referred to medical care for further diagnostics and treatment, if necessary (14).

The pilot phase in 2011 (data collection in Berlin and Essen) was funded by the RKI. And the rest of the study (from April 2012 to January 2016) was funded by the German Federal Ministry of Health.

3. Results

In total, 2077 people who had injected drugs in the last 12 months were included in the study.

3.1 Socio-demographics, substance use and other characteristics of the study participants

The median age was 38 years and ranged between 29-41 years in the eight study cities, participants recruited in one study city (Leipzig) were markedly younger than the other participants (12). The majority of participants were male (77%) and the proportion of female participants ranged from 19 to 35% in the eight cities (12). Between 9-31% of participants were born outside of Germany. More than half (53-77%) reported ever having been homeless and 73-86% were ever in detention (12). Median duration of injecting was 10-18 years (12). Most participants (76-88%) had injected drugs in the last 30 days and 57-85% reported heroin consumption in this period (12). The type of substances consumed varied across the eight cities. Leipzig had a uniquely high proportion of participants reporting methamphetamine consumption (67%) (12). Cocaine consumption was high (reported by more than half of participants) in three cities (Hamburg, Hannover and Essen) whereas consumption of crack

was reported by more than half of participants in Frankfurt and Hanover (12). Sharing needles or syringes in the last 30 days was reported by between 5-22% of participants, while sharing unsterile paraphernalia such as spoons, filter or water was reported by 33–44% (12).

3.2 Contact with health care and harm reduction services

The proportion of people currently in opioid substitution therapy (OST) varied between 31-66% across the eight study cities and 55-89% had ever been in OST (12). Between 79-91% of participants had visited a low threshold drug service in the last 30 days. And 77-95% had been to see a doctor in the last year (12). The proportion of participants tested for HIV and HCV in the last 12 months was lowest in Leipzig (44% and 29%, respectively) and varied between 57%-70% and 42-75% respectively in the remaining seven study cities (12).
There were large differences between the eight study cities for several of the variables collected. Table 1 (below) presents selected key variables by study city. More details on the descriptive results from the study are presented in the Wenz et al paper (12).

3.3 Prevalence of HIV, HBV and HCV, treatment access and knowledge of infection status

In total, 100 participants (4.8%) tested positive for HIV (13). One additional sample was reactive for HIV AB, but had an indeterminate immunoblot result, and was not classified as HIV positive (13). The HIV prevalence varied between 0 in Leipzig and 9.1% in Frankfurt (12). Out of the 100 HIV positive participants, 56% reported currently receiving ART treatment (32). Chronic HCV infection (CHC) was found among 857 (41%) participants, cleared HCV infection among 457 (22%), acute HCV infection among 47 (2%) and 716 (34%) were found to be unexposed to HCV (13). CHC varied between 23%-54% in the study cities (see table 1 & (12)). Among the in total 1361 ever HCV positive participants, 1092 people were identified as ever being in need of HCV treatment (defined as current CHC or ever reporting HCV treatment) and among these 30% reported ever starting interferon-based HCV treatments (32).
Overall, 17% of those with HIV and 27% of those with CHC infection did not know they were infected (13).
A current HBV infection was found in 1.1% (city range: 0.3-2.5%), past HBV infection among 24% (city range: 2-31%) and 32% had vaccine-induced HBV antibodies (city range: 15-52%). No detectable HBV antibodies indicating susceptibility to HBV infection were found in 43% (city range: 16-69%) (see table 1 & (14)).

Table 1: Overview of socio-demographics, infection status, substance use behaviours, detention experience and access to health and harm reduction services among study participants in each of the eight study cities (N=2077)

	Berlin	**Essen**	**Leipzig**	**Frankfurt**	**Cologne**	**Hanover**	**Munich**	**Hamburg**	**Range**
Participants	N=337	N=197	N=130	N=285	N=322	N=252	N=235	N=319	197-337
% female	19%	20%	22%	26%	23%	20%	35%	22%	19-35%
Median age; range	35; 18-60	38; 19-55	29; 18-55	39; 20-64	41; 18-62	39; 19-64	39; 19-63	40; 17-65	29-41
% <25years	9%	5%	27%	2%	3%	6%	7%	4%	2-27%
% foreign-born	31%	19%	9%	21%	21%	23%	17%	26%	9-31%
% ever homeless [a]	65%	65%	77%	74%	68%	53%	59%	71%	53-77%
HIV, HCV and HBV infection status									
HIV+	3.9%	6.1%	0%	9.1%	1.6%	8.7%	3.0%	5.0%	0-9.1%
HCV+ [b]	55%	73%	42%	66%	71%	75%	63%	70%	42-75%
Chronic HCV [c]	37%	45%	23%	50%	48%	54%	36%	45%	23-54%
HBV vaccinated	15%	23%	26%	26%	25%	52%	51%	42%	15-52%
HBV acute/ chronic	0.3%	2.5%	2.3%	1.4%	1.2%	0.4%	0.9%	0.6%	0.3-2.5%
Past HBV	16%	30%	2%	27%	25%	31%	24%	27%	2-31%
HBV unexposed	69%	44%	69%	46%	49%	16%	24%	30%	16-69%
Use of health care services and testing history									
Visit to harm reduction service [d] (last 30d)	-	-	-	91%	81%	88%	79%	89%	79-91%
Ever in OST	73%	86%	55%	82%	87%	84%	89%	80%	55-89%
Current OST	40%	43%	31%	45%	66%	43%	55%	56%	31-66%
Tested for HIV (last 12m) [e]	57%	68%	44%	66%	70%	61%	70%	68%	44-70%
Tested for HCV (last 12m) [f]	49%	59%	29%	54%	59%	42%	75%	47%	29-75%
Substance use behaviours and detention experience									
Median years injecting (± SD)	13 (±9)	17 (±9)	10 (±6)	17 (±10)	18 (±9)	18 (±9)	17 (±9)	18 (±9)	10-18
Injecting <2 years	8%	5%	11%	5%	4%	3%	5%	6%	3-11%
Injecting in the last 30d	83%	86%	76%	84%	82%	80%	80%	88%	76-88%
Heroin use (last 30d)	83%	78%	69%	79%	85%	75%	57%	63%	57-85%
Cocaine use (last 30d)	37%	61%	18%	44%	47%	66%	21%	80%	18-80%
Shared needle/ syringes (last 30d)	15%	19%	18%	5%	20%	22%	13%	11%	5-22%
Shared equipment [g] (last 30d)	38%	34%	43%	44%	34%	33%	35%	33%	33-44%
Ever in detention [h]	77%	86%	83%	84%	82%	86%	73%	80%	73-86%

Footnotes for table 1: SD = standard deviation; 12m = 12 months; 30d = 30 days; "-" data not collected
[a] Main reported form of residence, included living on the street and in homeless shelters;
[b] HCV+: anti-HCV and/or HCV RNA positive; [c] Chronic HCV: anti-HCV and HCV RNA positive;
[d] Low-threshold harm reduction service; [e] Excluding those with a HIV diagnosis older than 12 months;
[f] Denominator includes participants never tested, never tested positive and those who had their first HCV diagnosis in the last 12 months; [g] Injection equipment: e.g. spoon, filter and water;
[h] Detention includes juvenile arrest/prison, pre-trial custody, prison, forensic commitment (i.e. detention in a clinic for forensic psychiatric care, following a criminal conviction).

3.4 Factors associated with HBV infection and HBV vaccination

The most frequently reported settings where participants had their last HBV vaccination were medical doctors not offering addiction therapy, e.g. general practitioners (34%), OST services (23%) and hospitals (17%) (14). Few participants reported having been vaccinated in prison, in low threshold drug services or during long-term addiction therapy. In our multivariable analysis (MVA), we found a strong association of the study city with HBV vaccination, and no association between having vaccine-induced HBV antibodies and having been in detention or in OST (14). HBV infection status was significantly associated with study city, age, years of injecting, use of stimulants, migration status and homelessness (14).

3.5 HCV, HIV and related risk behaviours among migrants from the former Soviet Union who inject drugs

Among the participants, N=208 were FSU-migrants and N=1318 were born in Germany. FSU-migrants were more often male (83% vs. 76%, p=0.022) and younger than Germans (median age: 33 vs. 39 years) (15). HCV seroprevalence was higher in FSU-migrants; 75% vs. 65% in Germans (p=0.006), but there was no significant difference in HIV seroprevalence 5.8% vs. 4.6% (p=0.443) (15). FSU-migrants more often reported risky drug consumption behaviours such as: injecting daily (39% vs 30%, p=0.015), injecting with friends (39% vs. 31%, p=0.038), cocaine use (33% vs. 24%, p=0.044), consuming more than one drug (18% vs. 10%, p=0.006), and sharing filters/cookers (36% vs. 28%, p=0.045) (15). We found no statistically significant differences in HIV/HCV testing rates (range: 51%–66%), opioid substitution treatment (44% vs. 51%) or access to clean needles/syringes (90% in both groups) (15). In the MVA we saw that the risk for HCV-infection was increased in male FSU-migrants compared to German males (OR 3.32, p=0.006), whereas no overall difference was identified between female FSU-migrants and German females (OR: 0.83, p=0.633) (15). However, the risk for HCV infection at a younger age was higher for females than for males (15).

3.6 The association between detention experience and hepatitis C among people who inject drugs

In total, 1998 participants had complete information about detention experience and were included in this analysis (16). Among these 20% reported no detention experience, 29% short and rare experience (meaning $\leq$3.5 years in total, $\leq$3 times in detention), 12% reported short but frequent experience, 7% long but rare experience and 32% long and frequent experience (16).

We found that the proportion of PWID positive for HCV increased with both frequency and duration of their detention experience (16). The association between detention experience and HCV status remained statistically significant after correcting for known HCV risk factors. By adjusting our MVA model for risk behaviours practised during detention[1], the ORs of detention experience were reduced but remained significant: OR 1.83 (95% CI 0.97–1.76) for short and rare experience, OR 1.83 (95% CI 1.25–2.67) for short but frequent experience, OR 2.68 (95% CI 1.62– 4.42) for long but rare experience, and OR 2.80 (95% CI 1.92–4.09) for long and frequent detention experience, compared to those with no detention experience (16).

[1] In-detention risk behaviours were defined as reporting either “ever injecting drugs in detention” or “ever having had a non-professional tattoo or piercing in detention” (16).

3.7 HCV prevalence and estimated HCV incidence among people who recently started injecting drugs

Among the study participants 11% had injected drugs for less than five years and were classified as NI (17). These participants were more often female and younger at study participation, but older at the time of initiation of IDU compared to long-term injectors (LI) (17). NI were less likely to be HCV antibody positive compared to LI (36% vs 70%), but among HCV antibody positives a higher proportion of NI had chronic HCV (76% vs 66%) (17). Among the NI who were HCV antibody positive, 41% were unaware of their HCV-status (17). The estimated HCV incidence was 20 infections/100 person years at risk among people injecting less than 5 years and 36 infections/100 person years at risk among people injecting less than 2 years (17). No previous HCV testing was reported by 27% of NI compared to 6% among LI and more than half of those never tested for HCV had been in contact with addiction therapy (17). More than 80% of NI had attended low-threshold drug services in the last 30 days and we did not find any significant differences in unsafe drug injecting behaviour practiced in the last 30 days between NI and LI (17).

4. Discussion

The six papers included in this doctoral dissertation all contribute key findings which are useful for informing and strengthening public health interventions aimed at improving the uptake of BBI prevention and control interventions among PWID in Germany. In the following the main outcomes from the six papers are discussed.

4.1 Risk behaviours, drug consumption patterns and access to health and harm reduction services

The majority of recruited participants were male, the median age was 38 and most had injected drugs for more than 10 years (12). We found that unsafe drug use behaviour such as sharing unsterile needles/syringes or other paraphernalia (such as spoons, filters or water) was reported in all study cities. This may be linked in part to knowledge gaps around transmission and preventive behaviours for HIV and viral hepatitis (33) as well as the fact that access to clean equipment is still insufficient in some areas (12). Like other studies we found that sharing of other paraphernalia was more common than sharing needles or syringes (34, 35) highlighting the need for intensified communication to PWID about the risk of BBI transmission through unsterile paraphernalia. Sharing of unsterile needles/syringes or other paraphernalia has been shown to be linked to the types of substances consumed with injection of shorter-acting drugs (such as new psychoactive substances and cocaine) requiring higher frequency of injection and thereby a higher supply of sterile injecting equipment (36-39).

In our study heroin was the mostly commonly consumed substance in all cities except for in Hamburg (where 80% reported consuming cocaine vs 63% reporting heroin consumption in the last 30 days) (12). Large sub-national variations in injecting behaviours are common in most countries (40).

The proportion of participants tested for HIV or HCV in the last 12 months also varied considerably between the study cities, but was overall higher than testing rates observed among other risk groups in Germany such as men who have sex with men (41) and higher than BBI testing rates among PWID reported from other countries (42-44).

The majority of participants (55-89%) had experience with ever being in OST and between 31-66% were currently in OST. This is on average slightly lower than a recent estimate of OST coverage in Western Europe (43). It is important to bear in mind that OST is a well-documented option for linking PWID to BBI prevention, testing and care interventions (45-48), but also that OST is not relevant for PWID who are injecting non-opioids.
Participants were asked about recent (last 30 days) visits to low threshold drug services (LTDS) in five of the eight study cities (12). A high proportion (79-91%) of participants reported attending a LTDS indicating that these drop-in harm reduction facilities reach a large proportion of PWID in Germany. LTDS are recommended as ideal settings to reach PWID with voluntary testing, counselling and linkage to care for BBI (49-51).

4.2 Prevalence of HIV, hepatitis B and C and need for treatment

The HIV prevalence among participants was much higher than the estimated 0.1% national HIV prevalence in Germany in end 2015 (52). An HIV prevalence of 5% or more was found in four of the study cities. These results are higher compared to reported data on the HIV prevalence in PWID in many other Western European countries, such as the United Kingdom, Denmark, Norway, Austria, or Luxemburg, but lower than in countries like Italy, Portugal and France (3, 12).
HCV was highly endemic among participants in all study cities and CHC prevalence varied between 23-54% (12). The prevalence of HBV among the study participants was about five times higher than the HBV prevalence in the general population in Germany (53), confirming PWID as an important risk group for HBV in Germany (14). Many factors are likely associated with the geographically heterogeneous BBI prevalence found: two key factors are likely to be age (which is closely linked with duration of injecting) and drug use patterns in each city (12). Cities with older participants, long-established drug scenes (e.g. Essen, Hanover and Frankfurt) and frequent cocaine consumption all had high levels of HIV, HBV and HCV (12). A recent systematic review found that HCV AB prevalence in the EU/EEA countries varied between 14-84% (54) and a global modelling study estimated CHC prevalence among PWID in Western Europe to be between 36-44% (4).
Several studies on HCV among PWID in Europe done around the same time as our study, only tested for HCV AB and did not include HCV RNA results (55, 56). This is a problem as HCV AB results alone does not give any information on the number of PWID with CHC in need of treatment. We found that nearly half of the HIV positive participants were not on ART treatment and only 30% of those ever in need of HCV had ever started treatment (32).

4.3 Awareness of infection status

We found that awareness of infection status was relatively high among PWID. Our results compare well with the estimated proportion of PWID with undiagnosed HIV in Germany from the Robert Koch Institute and indicate that awareness of HIV infection might be higher among PWID than among men who have sex with men and non-injecting heterosexuals who overall seem to be tested less regularly (13, 57).
The awareness rate of 73% among those with CHC, is high compared with similar studies of PWID from Europe and Australia (31, 55, 56, 58) and also higher than the estimated awareness among people with CHC in the general population in both Germany and most other European countries (59-62).
But despite high awareness, more than a quarter of those with chronic HCV and nearly one in five of those with HIV did not know their status, although they were often in OST or attending

other harm reduction services where BBI testing and counselling should be easily available (13). Not being aware of the infection status implies that they cannot access appropriate care and risk unknowingly transmitting the infection to others (13).

4.4 Improving the uptake of hepatitis B vaccination among PWID

Despite Germany having a clear recommendation to vaccinate PWID and people with detention experience as well as people with HCV infection against HBV since 1982, a large proportion of PWID remain at risk of HBV infection, as indicated by 43% of participants having no infection- or vaccine-induced antibodies (14). However, young study participants (<25 years) had a higher proportion of vaccine-induced immunity and a lower prevalence of HBV infection than those in the older age groups, suggesting that they had been covered by the routine infant vaccination recommendation implemented in Germany in 1995 (14).
In our MVA, we found no association between having vaccine-induced HBV antibodies and having detention experience or having been in OST although these are appropriate settings to target PWID for HBV vaccination (14). Also, few participants reported having been vaccinated in prison, low threshold drug services or during long-term addiction therapy indicating that all these settings could be better utilised to improve HBV vaccination rates among PWID (14). Further research is needed to better understand why more PWID are not vaccinated in these settings in Germany. The WHO guidance on prevention of viral hepatitis B and C among PWID from 2012 (63) highlights that both a rapid vaccine schedule (64-66) as well as providing cash incentives (67-69) and convenient access (70-72) significantly increases the uptake and completion of HBV vaccination among people who use drugs. The guidance also specifies that HBV vaccination should be provided at a location and a time convenient for PWID (63).
There is a need for intensifying efforts to ensure that HBV vaccination is routinely offered during OST and in prison settings in order to improve HBV vaccination coverage among PWID in Germany.

4.5 Recommendations for migrants from the former Soviet Union who inject drugs

The population of FSU-migrants in Germany has been described as heterogeneous in terms of integration, language skills and health-related risk patterns (73). We found that FSU-migrants who inject drugs were more often male, younger, were more likely to report risky drug consumption behaviours and more often had HCV compared with native Germans who inject drugs (15). This is in line with findings from a similar study among Russian-speaking drug users in Paris, France (74). A qualitative study among FSU-migrants in Germany with problematic drug and alcohol consumption also found high prevalence of risk behaviours and gaps in knowledge about HCV and the German health and addiction treatment system (75). Participants from the FSU were more likely to report injecting a combination of drugs or consumption of drugs that require a higher injecting frequency, such as cocaine, which has been associated with a greater infection risk in several studies (39, 40, 76, 77).
In both groups, 90% reported that they had easy access to clean needles and syringes, only around 50% were currently in OST and had been tested for HCV in the last 12 months (15). This indicates good access to clean injection equipment, but that scaling up access to addiction treatment services and HCV testing services for all PWID is needed.
The difference in overall the HIV prevalence between FSU-migrants and native Germans was not statistically significant (5.8% vs 4.6%). As German participants were older, and thereby

had longer time to get infected, this might have led to a similar total HIV prevalence in the two groups (15). We found a larger proportion of HIV infected FSU-migrants in the younger age-groups (<35 years), which could imply a recent higher HIV incidence in this groups, however the numbers are too small to derive strong conclusions (15). A main result from the MVA was that risk of HCV infection was higher in male FSU-migrants compared to male Germans also after taking known risk factors such as detention experience in to account (15).
Strategies to better reach (male) FSU-migrant PWID might include providing information regarding transmission routes and options for prevention in Russian and other languages of the region. As well as ensuring regular testing and linkage to care, particularly for HCV, by having Russian speaking staff and/or providing regular translations services including engagement of peer workers at low threshold drug services (15). As we do not know when participants migrated to Germany we cannot assess if HCV or HIV infection in participants from FSU occurred before or after their arrival in Germany. The high proportion of CHC among both FSU and German participants highlights the need for implementation of targeted interventions to prevent and treat BBI among all PWID in Germany.

4.6 Recommendations for reducing HCV transmission associated with detention experience

The majority (80%) of our participants reported detention experience. This is much higher than the overall estimated proportion of PWID with detention experience in Western Europe (36% (range: 30-41%)) (3). Detention facilities in Germany therefore offer an important opportunity to counsel, test and treat PWID for BBI. Our analyses showed that risk behaviours practiced during detention explained part of, but not all of the increased HCV risk among PWID with detention experience indicating that transfers between community and detention involves additional risks (16). This has also been found in other studies (78, 79). There is a high risk of returning to illicit drug use in the period following release from prison (78, 80-82) and individuals recently released from prison report syringe sharing more frequently than those without recent prison experience (83). A transition both into and out of detention may cause an interruption in OST for people in treatment, as specific arrangements for treatment continuation are often not in place and OST not being available in all German detention facilities (16, 84). Very few (<10) countries in the world offer needle and syringe programmes (NSP) in prison (85) despite clear international recommendations to do so (86, 87). In Germany, NSP is only available in one (female) prison (84). Difficulties in accessing sterile injecting equipment can lead to increased unsafe use, as equipment is then frequently shared between inmates (88-90).
The proportion of study participants who were HCV positive increased both with frequency and duration of their detention experience (16). An important strength of this analysis is that it considered the duration and frequency of detention simultaneously, thus allowing the independent effects of both aspects to be observed (16). There is a need for increased HCV prevention efforts throughout the detention process. NSP and evidence-based drug dependence treatment, including OST, are known to reduce the risk of transmission of BBI (48, 91-93) and should be made available along with regular BBI counselling, testing and linkage to care for PWID in all German detention facilities.

4.7 Missed opportunities for BBI testing among new injectors

The HCV incidence among participants who started injecting less than 5 years ago was similar to findings from other international studies (29, 31, 94). The markedly higher estimated incidence among the participants who had injected for less than 2 years supports that HCV infection often happens early after initiation of IDU when PWID are e.g. not yet linked to harm reduction services (17, 31).

We found that a relatively high proportion (27%) of NI had never been tested for HCV, despite more than 50% reporting having been in contact with addiction therapy (17). This indicates missed opportunities for integrated BBI testing in addiction services which are suitable settings to reach PWID with BBI prevention and linkage to care interventions (42, 50, 95-97). However, it is also important to offer BBI testing in other harm reduction services and settings where PWID are reached (17). Low threshold drug services are important venues for needle and syringe exchange in Germany and were frequented by a high proportion of both NI and LI (17). Until very recently it was required in Germany that a physician was on-site when HCV-testing is performed which greatly limited implementation of HCV testing in low-threshold settings. However, since March 2020 (with the introduction of the “Masernschutzgesetz”) non-physicians can perform rapid tests for BBI such as HIV and HCV. Allowing and training non-physician providers to perform testing is recommended by international organisations (50, 98) and has been shown to increase uptake of BBI testing among key risk groups such as PWID (99). Apart from increasing testing in addiction services and low threshold drug services, we found that also pharmacies, prisons and homeless shelters could be better utilised in Germany to reach both NI and LI with BBI testing, prevention and linkage to care interventions (17).

4.8 Limitations

Our study has a number of limitations which should be kept in mind when interpreting the results.

Due to the cross-sectional design of this study we cannot draw conclusions on causality (e.g. between potential risk factors and infection status). Minor alterations were made in the questionnaire throughout the study period meaning that some variables are not available for all eight cities (12).

Using DBS testing for HBV, HCV and HIV prevalence studies is a well-accepted and widely used methodology (42, 100, 101). However, weakly anti-HBs-positive samples could have been missed with the DBS technique, especially in HIV-positive persons (28). Therefore, our prevalence of anti-HBs antibodies, e.g. of HBV vaccinated individuals, should be considered a conservative estimate (14). Overall, the assessment of the serological test systems for HIV, HCV and HBV showed good accordance between directly tested serum samples in comparison to DBS (28).

Regarding representativeness, it is important to bear in mind that the selection of study cities was based on the availability of low-threshold drug services both interested and able to participate in the study (12, 18). We found large variations in the characteristics of the PWID recruited from the eight study cities highlighting the difficulty in drawing national conclusions and underlining the importance of tailoring interventions for PWID to the local context. Most seeds (initial participants) were identified through the low-threshold drug services which were used as study sites and this might have led to an overestimation of the proportion of PWID in contact with low-threshold drug services (12). A selection bias from including more people with good communication skills cannot be excluded (12). Some, but not all, study sites included

supervised drug consumption facilities (DCF) where pre-obtained illegal drugs can be injected or smoked under sanitary conditions and medical supervision. DCFs often attract long-term and higher risk PWID (102-104) and the characteristics of the PWID recruited for our study were similar to attendees of a German DCF (105). PWID recruited for our study may not be representative of all PWID in Germany.

Also, although data were anonymized, some participants may have been reluctant to report sensitive data such as unsafe drug injecting experiences and/or sexual behaviours correctly, and answers might have been influenced by social desirability bias (12).

Finally, it is important to keep in mind that our study was planned and carried out before the well-tolerated direct-acting antiviral (DAA) therapies for HCV infection became available. These drugs have revolutionised HCV care and are highly effective also among people who are injecting drugs (106-108). Hopefully HCV testing and treatment among PWID in Germany will have increased in recent years and new studies are needed to assess this.

5. Conclusion

The six papers included in this doctoral dissertation have focused on various risk groups within the population of PWID in Germany – including those not aware of their infection status, those not vaccinated against HBV, FSU-migrants, those with detention experience and those who recently started injecting. Such research to identify subgroups among PWID with a potential increased need for BBI prevention and linkage to care is important to successfully plan and target intervention strategies.

The DRUCK-study was the first large multicity bio behavioural study using RDS to recruit PWID in Germany. In the recruited sample of people predominantly with a long duration of injecting drug use, seroprevalence for HIV, HBV and HCV varied between the city samples. However, HCV was highly endemic among participants in all city samples and behaviours linked with increased risk of BBI were also prevalent in all cities. The DRUCK-study gathered information on the characteristics of PWID in Germany and identified a need to further intensify prevention strategies for BBI in this population. Several initiatives have been launched since the DRUCK-study, these include the publication of the integrated German strategy for controlling HIV, hepatitis B and C and other sexually transmitted infections (109), increased BBI testing among PWID in low-threshold settings and a strengthened focus on facilitating linkage to care such as through the project “HIV? Hepatitis? Das CHECK ich” implemented in 2017-2019 (110) as well as increased access to DAA treatment for CHC. Also following the DRUCK-study several awareness raising efforts regarding hepatitis aimed both at PWID as well as at medical doctors (GPs and OST doctors) and staff working in low threshold drug services have been carried out in Germany. All these initiatives have hopefully contributed to an improved access to prevention and treatment of BBI among PWID in Germany since the end of the DRUCK-study.

A major strength of the study was the establishment of a network of multiple stakeholders including the low-threshold drug service and harm reduction organisations across the country. A key challenge that still lies ahead is the implementation of an ongoing national monitoring system for infections among PWID and their access to preventive interventions including the package of essential public health harm reduction interventions (111-113). Efforts are underway led by the RKI to establish such an ongoing monitoring among PWID in 2020.

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7. Statutory declaration

"I, Stine Nielsen, by personally signing this document in lieu of an oath, hereby affirm that I prepared the submitted dissertation on the topic *"HIV, hepatitis B and C, risk behaviours and access to health and harm reduction services for people who inject drugs in Germany*" (HIV, Hepatitis B und C, Risikoverhalten und Zugang zu Gesundheitssystem und Suchthilfe Einrichtungen bei injizierenden Drogengebrauchenden in Deutschland), independently and without the support of third parties, and that I used no other sources and aids than those stated.
All parts which are based on the publications or presentations of other authors, either in letter or in spirit, are specified as such in accordance with the citing guidelines. The sections on methodology (in particular regarding practical work, laboratory regulations, statistical processing) and results (in particular regarding figures, charts and tables) are exclusively my responsibility.

Furthermore, I declare that I have correctly marked all of the data, the analyses, and the conclusions generated from data obtained in collaboration with other persons, and that I have correctly marked my own contribution and the contributions of other persons (cf. declaration of contribution). I have correctly marked all texts or parts of texts that were generated in collaboration with other persons.

My contributions to any publications to this dissertation correspond to those stated in the below joint declaration made together with the supervisor. All publications created within the scope of the dissertation comply with the guidelines of the ICMJE (International Committee of Medical Journal Editors; www.icmje.org) on authorship. In addition, I declare that I shall comply with the regulations of Charité – Universitätsmedizin Berlin on ensuring good scientific practice.

I declare that I have not yet submitted this dissertation in identical or similar form to another Faculty.

The significance of this statutory declaration and the consequences of a false statutory declaration under criminal law (Sections 156, 161 of the German Criminal Code) are known to me."

Date Signature

8. Declaration of own contribution to the published papers

Stine Nielsen was one of the scientific coordinators for the DRUCK study employed at the Robert Koch Institute from the beginning of the study. She was part of a small group of about 4 people, who as a team:

- planned the study concept, aim, design and execution
- applied for and received the ethical approval
- developed the study questionnaire and data collection forms

Stine Nielsen coordinated the data collection in two of the eight study cities. She led the double data entry of the 2077 collected questionnaires (using EpiData), performed data validation and merged the information from the laboratory results with the questionnaires creating a joint dataset in Stata with all the validated information which was used for the analyses presented in the six scientific papers included in this dissertation.

Stine Nielsen additionally contributed the following to the below listed publications:

Publication 1:
Wenz B, **Nielsen S**, Gassowski M, Santos-Hövener C, Wei C, Ross RS, Bock CT, Ratsch BA, Kücherer C, Bannert N, Bremer V, Hamouda O, Marcus U, Zimmermann R and the DRUCK study group: „*High variability of HIV and HCV seroprevalence and risk behaviours among people who inject drugs: results from a cross-sectional study using respondent-driven sampling in eight German cities (2011–14)*" BMC Public Health. Sept 2016. 16:927. Impact factor: 2.55
Contribution:

- Together with Wenz, Gassowski and Zimmermann, Stine Nielsen developed the plan of analysis and carried out all the data analyses and the interpretation of results.
- Specifically, Stine Nielsen performed the analyses related to use of health care services (presented in table 2, in the results on page 6 and discussed on page 10).
- She took an active part in developing all tables and figures included in the paper and in the supplementary material
- Assisted with the literature search and identified relevant publications to be used as references
- Provided input and revisions to the manuscript including assisting with responding to comments from the peer review process

Publication 2:
Nielsen S, Gassowski M, Wenz B, Bannert N, Bock CT, Kücherer C, Ross RS, Bremer V, Marcus U, Zimmermann R and the DRUCK study group: *„Concordance between self-reported and measured HIV and hepatitis C virus infection status among people who inject drugs in Germany"* BMC Hepatology, Medicine and Policy. Sept 2016. 1:8. Impact factor: none (The journal was new in 2016, it is indexed in pubmed)
Contribution:

- Stine Nielsen led the development of the plan of analysis, conducted the data analyses and led the interpretation of the results with input from especially Gassowski and Zimmermann
- Produced the three tables in the manuscript
- Performed the literature search and identified relevant publications
- Wrote the first draft and incorporated feedback from the co-authors
- Submitted the manuscript and took the lead in replying to comments from the peer reviewers

Publication 3:
Haussig JM, **Nielsen S**, Gassowski M, Bremer V, Marcus U, Wenz B, Bannert N, Bock CT, Zimmermann R and the DRUCK study group: *"A large proportion of people who inject drugs are susceptible to hepatitis B: Results from a bio-behavioural study in eight German cities"* International Journal of Infectious Diseases. Jan 2018. 66:5-13. (Epub: Oct 2017). Impact factor: 3.41
Contribution:

- Stine Nielsen did some of the initial descriptive analyses (presented in table 2, table 3 and Figure 2, described on page 7-10 and discussed on page 10-12)
- Contributed to the plan of analysis and the multivariable analyses (presented in table 4 and 6)
- Contributed to the interpretation of the results and writing of the first draft

- Assisted with the literature search and identified relevant publications to be used as references
- Took an active part in submitting the paper and in responding to comments from the peer review process

Publication 4:
Derks L, Gassowski M, **Nielsen S**, an der Heiden M, Bannert N, Bock CT, Bremer V, Kücherer C, Ross RS, Wenz B, Marcus U, Zimmermann R, On behalf of the DRUCK study group: *"Risk behaviours and viral infections among drug injecting migrants from the former Soviet Union in Germany: results from the DRUCK-study"* International Journal of Drug Policy. Sept 2018. 59: 54-62. Impact factor: 4.49
Contribution:

- Contributed to the data analyses and interpretation of results
- Assisted with the literature search and identified relevant publications to be used as references
- Provided input and revisions to the manuscript including assisting with responding to comments from the peer review process

Publication 5:
Gassowski M, **Nielsen S**, Bannert N, Bock CT, Bremer V, Ross RS, Wenz B, Marcus U, Zimmermann R and the DRUCK study group: "*History of detention and the risk of hepatitis C among people who inject drugs in Germany"* International Journal of Infectious Diseases. April 2019. 81:100-106. Impact factor: 3.33
Contribution:

- Together with Gassowski and Zimmermann, Stine Nielsen developed the analysis plan for this paper
- Supported the data analyses, interpretation of results and the development of all four tables
- Stine Nielsen wrote parts of the discussion where our findings are compared to other international studies on detention experience and hepatitis C
- Assisted with the literature search and identified relevant publications to be used as references
- Supported the submission of the paper

Publication 6:
Enkelmann J, Gassowski M, **Nielsen S**, Wenz B, Marcus U, Bremer V, Zimmermann R and the DRUCK study group: *"High prevalence of hepatitis C virus infection and low level of awareness among people who recently started injecting drugs in a cross-sectional study in Germany, 2011–2014: missed opportunities for hepatitis C testing"*. BMC Harm Reduction Journal. January 2020. 17:7. Impact factor: 2.94
Contribution:

- Stine Nielsen did parts of the descriptive analyses presented table 1 and contributed to the data analyses and interpretation of results
- Assisted with the literature search and identified relevant publications to be used as references
- Provided input and revisions to the manuscript including assisting with responding to comments from the peer review process

_____
Signature, date and stamp of first supervising university professor / lecturer

_____
Signature of doctoral candidate

9. Full text copies of the included six publications

Paper 1: *High variability of HIV and HCV seroprevalence and risk behaviours among people who inject drugs: results from a cross-sectional study using respondent-driven sampling in eight German cities (2011-14)*. BMC Public Health. September 2016.
Impact factor: 2.55

Paper 2: *Concordance between self-reported and measured HIV and hepatitis C virus infection status among people who inject drugs in Germany.* BMC Hepatology, Medicine and Policy. September 2016.
Impact factor: none (The journal was new in 2016, it is indexed in pubmed)

Paper 3: *A large proportion of people who inject drugs are susceptible to hepatitis B: Results from a bio-behavioural study in eight German cities.* International Journal of Infectious Diseases. October 2017.
Impact factor: 3.41

Paper 4: *Risk behaviours and viral infections among drug injecting migrants from the former Soviet Union in Germany: results from the DRUCK-study.* International Journal of Drug Policy. July 2018.
Impact factor: 4.49

Paper 5: *History of detention and the risk of hepatitis C among people who inject drugs in Germany.* International Journal of Infectious Diseases. January 2019.
Impact factor: 3.33

Paper 6: *High prevalence of hepatitis C virus infection and low level of awareness among people who recently started injecting drugs in a cross-sectional study in Germany, 2011–2014: missed opportunities for hepatitis C testing.* BMC Harm Reduction Journal. January 2020.
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Paper 1: High variability of HIV and HCV seroprevalence and risk behaviours among people who inject drugs: results from a cross-sectional study using respondent-driven sampling in eight German cities (2011-14). BMC Public Health. September 2016.

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RESEARCH ARTICLE Open Access

High variability of HIV and HCV seroprevalence and risk behaviours among people who inject drugs: results from a cross-sectional study using respondent-driven sampling in eight German cities (2011–14)

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Abstract

Background: People who inject drugs (PWID) are at increased risk of acquiring and transmitting HIV and Hepatitis C (HCV) due to sharing injection paraphernalia and unprotected sex. To generate seroprevalence data on HIV and HCV among PWID and related data on risk behaviour, a multicentre sero- and behavioural survey using respondent driven sampling (RDS) was conducted in eight German cities between 2011 and 2014. We also evaluated the feasibility and effectiveness of RDS for recruiting PWID in the study cities.

Methods: Eligible for participation were people who had injected drugs within the last 12 months, were 16 years or older, and who consumed in one of the study cities. Participants were recruited, using low-threshold drop-in facilities as study sites. Initial seeds were selected to represent various sub-groups of people who inject drugs (PWID). Participants completed a face-to-face interview with a structured questionnaire about socio-demographics, sexual and injecting risk behaviours, as well as the utilisation of health services. Capillary blood samples were collected as dried blood spots and were anonymously tested for serological and molecular markers of HIV and HCV. The results are shown as range of proportions (min. and max. values (%)) in the respective study cities. For evaluation of the sampling method we applied criteria from the STROBE guidelines.

(Continued on next page)

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Results: Overall, 2,077 PWID were recruited. The range of age medians was 29–41 years, 18.5–35.3 % of participants were female, and 9.2–30.6 % were foreign born. Median time span since first injection were 10–18 years. Injecting during the last 30 days was reported by 76.0–88.4 % of participants. Sharing needle/syringes (last 30 days) ranged between 4.7 and 22.3 %, while sharing unsterile paraphernalia (spoon, filter, water, last 30 days) was reported by 33.0–43.8 %. A majority of participants (72.8–85.8 %) reported incarceration at least once, and 17.8–39.8 % had injected while incarcerated. Between 30.8 and 66.2 % were currently in opioid substitution therapy. Unweighted HIV seroprevalence ranged from 0–9.1 %, HCV from 42.3–75.0 %, and HCV-RNA from 23.1–54.0 %. The implementation of RDS as a recruiting method in cooperation with low-threshold drop in facilities was well accepted by both staff and PWID. We reached our targeted sample size in seven of eight cities.

Conclusions: In the recruited sample of mostly current injectors with a long duration of injecting drug use, seroprevalence for HIV and HCV varied greatly between the city samples. HCV was endemic among participants in all city samples. Our results demonstrate the necessity of intensified prevention strategies for blood-borne infections among PWID in Germany.

Keywords: PWID, Sero- and behavioural survey, HIV, Hepatitis C, Respondent-driven sampling, Second generation surveillance, Injecting drug users, Germany, Europe

Abbreviations: CI, Confidence intervals; DRUCK-study, Drugs and chronic infectious diseases study (Studie zu "Drogen und chronischen Infektionskrankheiten"); ECDC, European centre of disease prevention and control; HCV, Hepatitis C virus; HCV RNA, Hepatitis C virus ribonucleic acid; HIV, Human immunodeficiency virus; IDU, Injecting drug users; NSP, Needle and syringe exchange programme; n/s, Needles and syringes; OST, Opioid substitution treatment; PWID, People who inject drugs; RKI, Robert Koch-Institute; UNODC, United Nations Office on Drugs and Crime; RDS, Respondent-driven sampling; VCT, Voluntary testing and counselling

Background

According to estimations 15 million people were living with the hepatitis C virus (HCV) in the WHO European Region in 2013 [1], and 2.2 million with the human immunodeficiency virus (HIV) [2]. In most European countries people who inject drugs (PWID) are a key transmission group for blood-borne infections, including HCV and HIV [3, 4]. Studies identified several risk factors to be associated with HCV [5–11] and HIV [12, 13] infections among PWID including years of injecting, sharing of needles, syringes and other equipment, imprisonment and unprotected sex.

HIV and HCV testing are common interventions for HIV and HCV surveillance and control. They increase knowledge of HIV and HCV status, and ought to be entry points to HIV- and HCV-related treatment and care. It has been shown that opioid substitution therapy (OST) reduces injecting drug use by lowering the frequency of injecting and related unsafe practices, thereby effectively decreasing the transmission of HIV [14–16] and in combination with needle and syringes programmes (NSP) also of HCV [17]. It furthermore facilitates regular medical care and adherence to HIV and HCV treatment [18–20].

Knowledge about HIV and HCV prevalence and related behaviour amongst PWID in Germany is currently based on outdated regional studies of convenience samples. Studies providing a clear and up-to-date picture of the epidemiology of HCV and HIV amongst PWID in Germany do not exist and ongoing monitoring of infections or risk behaviours among PWID is not established. Nevertheless, regional surveys from the last decades in Germany have indicated that HCV is hyperendemic in PWID [21–24]. While the prevalence of HCV infection in the most recent population-based survey in the adult population was 0.3 %, local surveys among PWID have found prevalence ranging from 50–80 % [22–25]. High rates of infection in the PWID population were also reported from other European countries with anti-HCV prevalence ranging from 13.8 to over 90 % [26]. National estimates in Germany show that PWID are also at-risk of HIV transmission. Nearly 10 % of all estimated HIV infections were attributed to injecting drug use as of end of 2014 [27]. According to Backmund, in 2007 HIV prevalence among PWID in Germany must have been between 4.3 and 6.5 % [28] and thus, significantly higher than in the general population, where HIV infections are below 0.1 % [29]. Although there are variations across Western European countries, prevalence above 5 % among PWID has been reported in France, Spain, Ireland, Greece, Portugal, and Sweden in recent years [26]. Due to preventive efforts the number of newly

diagnosed HIV infections among PWID in Germany has been declining since a peak in the late 1980ies. In 2014, an estimated 7.5 % of the 3,200 new HIV cases (240) were caused by transmission among PWID, including a sizeable proportion of approximately 25–30 % of these infections being diagnosed in Germany, but being originally acquired in Eastern or Central Europe [27]. Chronic co-infection with HCV and HIV is also common among PWID in some European countries, with a high prevalence of co-infection ranging between 15 and 70 % reported by Estonia, France, Latvia, Italy, Netherlands, Poland, Portugal and Spain [30].

To tackle the risk of blood-borne and sexually transmitted infections among PWID it is essential to combine behavioural, socio-demographic and serological data to inform the planning and implementation of effective prevention and intervention strategies [31]. By identifying knowledge gaps regarding the transmission and prevention of infections, and by revealing risky and preventive practices, factors that drive transmission among PWID can be identified and addressed. Based on such information, specific recommendations for reducing risk behaviours, scaling up prevention, treatment and care can be formulated. To obtain information on the prevalence of blood-borne infections and related behaviours for PWID in Germany, we conducted a sero-behavioural study using respondent driven sampling (RDS) in eight large cities across the country in cooperation with low-threshold drug services.

Sampling hard-to-reach populations

Standard probability methods are generally difficult to apply in hard-to-reach populations, where a sampling frame for the targeted population is not available. RDS was introduced by Heckathorn in 1997 as a modified snowball method to recruit hard-to-reach populations [32]. Globally, more than 460 studies from 69 countries applying RDS have been published, and several studies have used RDS to recruit PWID in recent years [33]. Due to their strong social networks and because PWID often buy from and inject drugs with other PWID, RDS worked well as a recruitment method in the majority of studies [34, 35]. RDS works effectively as a sampling method, when four requirements are met [32]: first, participants need to know one another through the network of the group under study. Second, the network needs to be dense enough to attain a sample with sufficient sociometric depth in order to reach equilibrium. The statistical rationale of RDS depends on the stabilization of the sample composition after a sufficient number of recruitment waves - the point at which the characteristic proportions remain stable, even if the recruitment continues is known, as the equilibrium [32]. The number of waves required to reach equilibrium is again linked to the third requirement: random recruitment must set in at some point to avoid that sampling is limited to a specific sub-group and only reflecting the characteristics of the seed with which the chain began. The tendency to recruit persons who are similar and thereby causing bias in the samples is termed homophily. Fourth, an enabling system to motivate participants to recruit other participants must be in place [36].

Objectives

In this paper we present descriptive results of the first sero-behavioural study of PWID using RDS performed in Germany. The objectives are to describe basic characteristics of participants in the respective study cities focusing on i) socio-demographic factors, ii) seroprevalence of HIV and HCV, including co-infections, iii) use of health services, and iv) injecting and sexual risk behaviours. Furthermore, we assess whether RDS was effective for sampling PWID in the study cities.

Methods

Detailed information about methodological issues has been described earlier [37].

Overview

From 2011 to 2014, we recruited PWID using RDS across eight cities in Germany targeting a sample of 200–400 PWID in each city. All cities have a relatively large PWID community and were selected for their geographic and demographic diversity as well as the availability of low-threshold drop-in facility services. Four of the cities - Berlin, Cologne, Munich and Hamburg - have more than one million inhabitants; the four others - Essen, Leipzig, Frankfurt on the Main (Frankfurt) and Hanover- between 500,000 and 700,000.

Study population

Eligibility for participation was defined as i) aged 16 or older, ii) self-reported injecting drug use within the past 12 months in the respective city, iii) willingness to take part in an questionnaire assisted-interview and to provide a capillary blood specimen for serological and molecular testing iv) willingness to give informed consent, and v) not having participated in the study previously.

Sampling method

Sampling started with a small number of initial recruits ('seeds') in each city, selected by local partners of low threshold drug services to represent a range of characteristics (gender, country of birth, residential area and preferred low-threshold drug service, self-reported HIV serostatus, mainly preferred substance, former experience of sex work and imprisonment). All seeds were selected based on an anonymous list of PWID and their

characteristics provided by the local partners. The recruitment expanded through so called 'recruitment waves' of peers; after the seeds recruited the first recruitment wave of participants the first recruitment wave continued to recruit the second recruitment wave of participants and so on until the targeted sample size was reached.

Recruitment process

In each city we established between one and four RDS study sites in local low-thresholds drop-in facilities, where participants enrolled in the survey and redeemed their coupons. The recruitment coupons were valid for two weeks. Each individual received 10 EUR for participating in the study, and was paid an additional 5 EUR for each eligible drug user they recruited. To ensure anonymity and to track the recruitment process we assigned a unique numeric identifier to each participant. If a seed turned out not to be productive additional seeds were selected if needed to keep the recruitment process ongoing. Recruitment and data collection was conducted by staff of low-threshold drug services who are trained to work with PWID. This recruitment process continued until the end of the scheduled recruitment period which was reached after 7 to 9 weeks.

Demographic, behavioural and serological data and network information

Staff of the Robert Koch Institute (RKI) conducted a two-day pre-survey training on study design, RDS methodology, standardised interviews, blood sample collection procedures and logistics for the staff of low-threshold drug services in the respective study cities. Eligible PWID had to undergo a questionnaire-assisted interview in German or Russian, wherever Russian-speaking staff was available. We asked questions regarding respondent's demographic characteristics, their knowledge, attitudes, behaviour and practices as well as their network. Minor modifications were made in the questionnaire throughout the four years while conducting the survey. Therefore, some variables are not available for all cities. The network size was determined by asking respondents how many PWID (fulfilling the inclusion criteria for the study) they know by name who would also know the respondent by name. We also asked how many of these persons they believed they could recruit for the study. The questionnaire was based on a model questionnaire developed by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), and additional indicators proposed by the European Centre of Disease Control (ECDC) and the Global AIDS response progress reporting (GARPR) [38–40]. Dried blood spots (DBS) on filter cards (Whatman #903) were obtained from participants' capillary blood.. During the pilot phase of the study (cities of Essen and Berlin), DBS testing was validated in the Institute of Virology, National Reference Centre (NRZ) for Hepatitis C, at the University of Duisburg-Essen, which subsequently also performed the regular analyses on serological and molecular markers of HIV and HCV. The Division for HIV and other Retroviruses and the Division for Viral Gastroenteritis and Hepatitis Pathogens and Enteroviruses in the Department for Infectious Diseases at the RKI were in charge of the laboratory testing for the remaining six cities. The study flow and laboratory procedures including possible shortcomings arising from DBS testing are described in detail elsewhere [37, 41]. Prevalence of infection was determined by detection of anti HIV or anti HCV antibodies and detection of molecular markers for HIV and HCV by nucleic acid amplification tests. Pre- and post-test counselling were offered to participants according to international and national recommendations [42].

Measures to assess the effectiveness of RDS

For evaluation of the sampling method we applied criteria following the guidelines for "Strengthening the Reporting of Observational Studies in Epidemiology for RDS Studies" (STROBE-RDS), a checklist of essential items to present in RDS publications [33]. We provide information about the relationship of respondents with their recruiters and calculated the equilibrium and the number of recruitment waves for five key variables: I. participants' mean age; II. proportion of male participants; III. proportion of PWID born in Germany; IV. HCV prevalence; and V. HIV prevalence. Furthermore, we describe the level of homophily among the study population. Homophily (Hx) was analysed for the following three outcomes: age, gender and HIV serology. As recommended a graphical representation of the entire recruitment network for all study cities is included. Finally, we assess whether the incentives could motivate PWID to participate in the study. Detailed material of this evaluation is attached in the Additional file.

Statistical analysis

For data entry we used EpiData 3.0. We applied descriptive statistics by using Stata version 14.0. The crude sample proportions are presented for all cities in Tables 1, 2 and 3. The results are shown as range of proportions (min. and max. values (%)) for the respective study cities. Based on the reported network size of each participant, we used the respondent driven sampling analysis tool RDSAT version 7.1 (http://www.respondentdrivensampling.org) to define population proportions and variance estimates of each dataset [43]. We included seeds in the analysis. The number of re-samplings to determine bootstrap 95 % confidence

Table 1 Socio-demographic variables, 2011-14[a]

		Berlin		Essen		Leipzig		Frankfurt		Cologne		Hanover		Munich		Hamburg		range
		n = 337		*n* = 197		*n* = 130		*n* = 285		*n* = 322		*n* = 252		*n* = 235		*n* = 319		(min-max)
		n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	%
Age	Mean ± SD; median; range	35.6 ± 8.8; 35.0; 18-60		37.9 ± 7.9; 38.0; 19-55		29.4 ± 7.0; 29.0; 18-55		39.6 ± 8.7; 39.0; 20-64		39.9 ± 8.4; 41.0; 18-62		39.0 ± 8.7; 39.0; 19-64		38.3 ± 8.5; 39.0; 19-63		39.8 ± 8.9; 40.0; 17-65		29-41
	<25 years	30	9.0	9	4.6	35	26.9	6	2.1	11	3.4	15	6.0	16	6.8	13	4.1	2.1-26.9
Gender	Female	62	18.5	39	19.8	29	22.3	73	25.8	73	22.7	50	19.8	83	35.3	71	22.3	18.5-35.3
Country of birth	Foreign-born	103	30.6	38	19.3	12	9.2	59	20.7	67	20.8	57	22.6	39	16.6	84	26.3	9.2-30.6
	Eastern Europe and Former Soviet Union[b]	83	24.7	20	10.2	8	6.3	34	11.9	22	6.8	40	15.9	23	9.8	62	19.5	6.3-24.7
Educational level	No school certificate	52	15.4	38	19.4	17	13.2	24	8.5	67	20.8	34	13.5	20	8.5	50	15.8	8.5-20.8
	Completed lower secondary - 9th grade	143	42.4	109	55.6	62	48.1	147	52.1	130	40.4	119	47.2	137	58.3	135	42.6	40.4-58.3
	Completed 10th grade	121	35.9	38	19.4	45	34.9	78	27.7	74	23.0	78	31.0	52	22.1	95	30.0	19.4-35.9
	High school graduate	21	6.2	11	5.6	5	3.9	33	11.7	51	15.8	21	8.3	26	11.1	37	11.7	3.9-15.8
Main source of income in the past 12 months	Regular job/ Unemployment benefit	56	16.8	29	14.7	25	19.4	67	23.8	59	18.3	61	24.2	67	28.6	84	26.8	14.7-28.6
	Social benefits/ pension	289	86.5	176	89.3	111	86.1	231	81.9	291	90.4	217	86.1	192	82.1	229	72.9	72.9-90.4
Homelessness	In the last 12 months[c]	29	8.6	28	14.2	28	21.5	79	28.7	48	15.3	17	6.8	27	11.5	55	17.3	6.8-28.7
	Ever	216	64.5	128	65.0	100	76.9	210	73.9	218	68.1	133	52.8	139	59.2	225	70.8	52.8-76.9

[a]Footnote (Table 1): Because not all participants replied to every variable, some variables include missing values. This means that the city-specific denominator for some variables might be lower than the n displayed at the top of the table
[b]Eastern Europe and Former Soviet Union: Includes PWID reporting being born in the following 24 countries: Azerbaijan, Bosnia & Herzegovina, Bulgaria, Croatia, Czech Republic, Estonia, Georgia, Hungary, Kazakhstan, Kosovo, Kyrgyzstan, Latvia, Lithuania, Montenegro, Poland, Romania, Russian Federation, Serbia, Slovakia, Slovenia, Tajikistan, Ukraine, Uzbekistan and Yugoslavia
[c]Main reported form of residence, includes living on the street and in homeless shelters

intervals (CI) was set to 15,000 to improve the accuracy of the variance estimates and the network size outliers pulled in by 5 %. The enhanced smoothing algorithm type was employed as recommended by Johnston [44]. The RDS estimated population proportions based on the reported network are provided in the (Additional file 1: Table S1). We used RDSAT 7.1 to calculate homophily for all eight data sets. The homophily (Hx) metric is between −1 und 1. In line with Heckathorn's suggestion we defined any value of Hx ≥ 0.3 as intermediate homophily and any value ≤ −0.3 as strong heterophily [45]. We applied Stata 14.0 to calculate equilibrium and the number of recruitment waves. Equilibrium was attained when the sample distribution from one recruitment wave to the next fell within a discrepancy of less than 2 % [46].

Results

Socio-demographic characteristics of participants

Overall, we recruited a total of 2,079 participants in the multicentre survey, of which two did not meet our eligibility criteria. Most of the interviews took around 45 min to 1 h to complete. In each city except Leipzig (*n* = 130) a sample size between 200–400 PWID was achieved (see Table 4). In all cities the proportion of female participants ranged between 18.5 and 35.3 %. The median age of participants varied between 35–41 years – except in Leipzig where the median age was 29 years. Accordingly, the proportion of PWID younger than 25 years was higher in Leipzig (26.9 %) compared to the remaining seven cities (2.1–9.0 %). Leipzig was also an exception with regards to country of origin of the participants. Foreign-born participants accounted for 9.2 % in Leipzig and ranged between 16.6 and 30.6 % in the other seven cities. The proportion of participants born in Eastern Europe and Former Soviet Union ranged between 6.3 in Leipzig and 24.7 % in Berlin.

The majority of participants in all cities had completed lower secondary school (40.4–58.3 %) and between 8.5 and 20.8 % had not completed any school. Between 72.3–90.4 % reported currently receiving social benefits/

Table 2 Serological and molecular findings for HIV and HCV and use of health care services, 2011-14[a]

	Berlin		Essen		Leipzig		Frankfurt		Cologne		Hanover		Munich		Hamburg		range
	n = 337		*n* = 197		*n* = 130		*n* = 285		*n* = 322		*n* = 252		*n* = 235		*n* = 319		(min-max)
Serological and molecular findings	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	%
HIV +	13	3.9	12	6.1	0	0	26	9.1	5	1.6	22	8.7	7	3.0	16	5.0	0.0-9.1
HCV seroprevalence; Anti-HCV + and/or HCV-RNA +	185	54.9	143	72.6	55	42.3	189	66.3	229	71.1	189	75.0	149	63.4	222	69.6	42.3-75.0
Cleared infection; Anti HCV+, HCV RNA -	60	17.8	54	27.4	25	19.2	46	16.1	76	23.6	53	21.0	64	27.2	79	24.8	16.1-27.2
Chronic infection; Anti HCV+, HCV RNA +	125	37.1	89	45.2	30	23.1	143	50.2	153	47.5	136	54.0	85	36.2	143	44.8	23.1-54.0
Seroconverters; Anti HCV-, HCV RNA +	4	1.2	3	1.5	7	5.4	5	1.8	15	4.7	5	2.0	2	0.9	6	1.9	0.9-5.4
Co-infections: Anti HIV+, Anti HCV + and/or HCV RNA+	12	92.3	12	100.0	-	-	21	80.8	3	60.0	19	86.4	6	85.7	11	68.8	60.0-100.0
Use of health care services and testing history																	
Use of harm reduction service (last 30d)	[b]	-	[b]	-	[b]	-	256	90.5	261	81.3	221	87.7	185	78.7	284	89.0	78.7-90.5
Currently in OST	135	40.3	85	43.2	40	30.8	129	45.3	213	66.2	109	43.3	129	55.1	179	56.3	30.8-66.2
Ever receiving OST	244	72.8	170	86.3	71	54.6	233	81.8	279	86.7	211	83.7	208	88.9	254	79.6	54.6-88.9
Ever tested for HIV	298	90.6	184	94.4	98	76.6	277	97.5	302	95.0	233	94.3	220	96.1	301	95.0	76.6-97.5
Tested for HIV (last 12 m)[c]	173	57.1	125	68.3	54	43.9	171	66.3	207	69.7	137	60.6	146	69.9	197	68.4	43.9-69.9
Ever tested for HCV	287	89.4	184	94.9	85	70.3	264	94.6	290	93.6	224	91.8	215	96.0	269	90.0	70.3-96.0
Tested for HCV (last 12 m)[d]	70	49.0	39	59.1	21	28.8	44	54.3	60	58.8	30	42.3	52	75.4	47	46.5	28.8-75.4

[a]Footnote (Table 2): Because not all participants replied to every variable, some variables include missing values. This means that the city-specific denominator for some variables might be lower than the n displayed at the top of the table
[b]data not collected
[c]Excluding those with a diagnosis older than 12 months
[d]Denominator includes those never tested, those never tested positive and those who had their first HCV diagnosis in the last 12 months

pensions. Furthermore, more than half of the participants in all cities had been homeless at least once in life (52.8–76.9 %). Between 6.8 (in Hanover) and 28.7 % (in Frankfurt) of the participants reported being homeless or staying in homeless shelters as their main residence in the past 12 months (Table 1).

Seroprevalence of HIV and HCV and use of health care services

HIV prevalence amongst participants varied between 0 % in Leipzig and 9.1 % in Frankfurt. HCV prevalence (Anti-HCV or HCV-RNA positive or both) ranged from 42.3 in Leipzig to 75.0 % in Hanover (Fig. 1), while HCV viremic infections (HCV-RNA positive) were found to range from 23.1 in Leipzig to 54.0 % in Hanover. HCV-RNA in the absence of anti-HCV antibodies was detected in 0.9 % of the cases in Munich and in 5.4 % of the cases in Leipzig, indicating recent HCV infections before seroconversion. HCV co-infections amongst the HIV positive participants were detected between 60.0 % of cases in Cologne and 100 % in Essen.

Use of health services and testing history

Data on utilisation of low-threshold drug services (in the last 30 days) was collected in five of the eight study cities. The proportion of PWID who visited a low-threshold drug service in the last 30 days ranged from 78.7 to 90.5 %. About three out of five participants in each of the eight cities (54.6–88.9 %) reported ever receiving opioid substitution therapy (OST). Currently receiving OST varied between 30.8 in Leipzig and 66.2 % in Cologne. In all cities the vast majority had been tested for HIV during their lifetime (76.6–97.5 %). Undergoing an HIV test in the last 12 month was reported by 43.9 % (Leipzig) to 69.9 % (Munich). The majority of the study population in each city reported ever being tested for HCV antibodies (70.3–96.0 %), while having been tested recently (12-month prevalence) was reported between 28.8 (Leipzig) and 75.4 % (Munich) (Table 2).

Recent substance use and risk behaviours

The median number of years since first injection was 10 years in Leipzig, 13 years in Berlin and between 16 and 18 years in the remaining cities. In seven cities, the proportion of participants who initiated injecting in the last two years ranged from 3.2 in Hanover to 7.8 % in Berlin. In Leipzig one out of ten (11.1 %) had started injecting in the last two years.

Injecting drugs in the last 30 days was reported by more than three out of four participants in all eight cities (76.0–88.4 %) and daily injection in the last 30 days varied between 17.2 in Munich and 39.1 % in Berlin. In the last 30 days Heroin was the most frequently used substance (all routes of administration) in five cities

Table 3 Substance use, sharing behaviours, sexual risks and incarceration experience, 2011-14[b]

	Berlin *n* = 337		Essen *n* = 197		Leipzig *n* = 130		Frankfurt *n* = 285		Cologne *n* = 322		Hanover *n* = 252		Munich *n* = 235		Hamburg *n* = 319		range (min-max)
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	%
Years of injecting (mean ± SD; median; range)	13.4 ± 8.8; 13.0; 0-43		16.9 ± 9.0; 17.5; 0-40		10.0 ± 6.1; 10.0; 0-30		17.4 ± 10.0; 16.0; 0-44		17.9 ± 9.0; 18.0; 0-42		17.6 ± 9.4; 18.0; 0-43		17.4 ± 9.1; 17.5; 0-45		18.0 ± 9.4; 18.0; 0-43		10.0-18.0
Injecting <2 years	26	7.8	10	5.1	14	11.1	14	4.9	13	4.0	8	3.2	12	5.2	19	6.0	3.2-11.1
Injected drugs (last 30d)	279	82.8	170	86.3	99	76.2	238	83.5	263	81.7	202	80.2	187	79.6	282	88.4	76.2-88.4
Injected daily (last 30d)	108	39.1	57	33.7	29	30.2	72	31.2	84	32.3	65	32.2	32	17.2	69	24.7	17.2-39.1
Heroin consumed (last 30d)	280	83.1	154	78.2	89	68.5	224	78.6	275	85.4	189	75.0	133	56.8	201	63.2	56.6-85.4
Cocaine consumed (last 30d)	125	37.1	120	60.9	23	17.7	125	44.0	150	46.7	166	65.9	49	20.9	255	79.9	17.7-79.9
Crack consumed (last 30d)	8	2.4	6	3.1	1	0.8	204	71.6	6	1.9	147	58.6	1	0.4	146	45.9	0.4-71.6
Methamphetamine (last 30d)	9	2.7	0	0.0	87	67.4	4	1.4	3	0.9	0	0.0	15	6.4	7	2.2	0.0-67.4
Unsafe Use behaviour																	
Shared needle/syringes (last 30d)	40	15.0	32	19.2	17	17.9	11	4.7	51	19.5	44	22.3	24	13.2	29	10.6	4.7-22.3
Shared equipment (spoon, filter, water) (last 30d)	99	37.5	56	33.5	40	42.6	99	43.8	84	33.6	64	33.0	61	34.5	87	33.0	33.0-43.8
Sexual risks																	
Sexual intercourse (last 12 m)	237	72.9	144	77.0	110	84.6	228	80.9	224	74.2	182	73.7	193	82.1	237	75.0	72.9-84.6
No condom use during last sexual intercourse	130	56.1	59	44.9	45	63.4	125	56.3	138	61.6	109	60.2	130	69.1	134	56.5	44.9-69.1
Last sex partner was IDU	134	57.5	73	51.4	70	68.6	139	65.6	120	56.1	105	64.4	127	69.4	118	54.1	51.4-69.4
Incarceration																	
Ever incarcerated[a]	257	76.5	169	85.8	108	83.1	239	84.2	262	81.9	214	85.6	171	72.8	254	79.6	72.8-85.8
Total duration of incarceration (yr) Mean ± SD; median; range	3.8 ± 4.5; 2.0; 0-26		5.3 ± 5.2; 4.0; 0-23		3.4 ± 4.3; 2.0; 0-24		5.1 ± 5.5; 3.0; 0-29		4.8 ± 5.0; 3.0; 0-23		6.5 ± 6.3; 5.0; 0-30		3.2 ± 3.6; 2.0; 0-15		5.0 ± 4.9; 4.0; 0-20		2.0-5.0
Injecting in prison (ever)	101	39.3	55	32.7	19	17.8	59	24.7	78	29.9	78	37.0	35	20.5	70	27.7	17.8-39.3
Shared needle/syringes/ equipment (among those injecting during their last imprisonment)	32	33.0	20	37.7	7	38.9	20	36.4	38	49.4	32	41.0	14	40.0	33	48.5	33.0-49.4
Unprofessionally tattooed/pierced in prison (ever)	81	24.2	67	34.5	39	32.2	79	27.8	97	30.2	76	30.3	45	19.4	71	22.3	19.4-34.5

[a]Including juvenile arrest/prison, pre-trial custody, prison, forensic commitment
[b]Footnote (for Table 3): Because not all participants replied to every variable, some variables include missing values. This means that the city-specific denominator for some variables might be lower than the n displayed at the top of the table

(Berlin: 83.1 %; Essen: 78.2 %; Cologne: 85.4 %; Hanover: 75.0 % and Munich 56.8 %); while in Leipzig methamphetamine was the most frequently reported substance (67.4 %). In the other seven cities methamphetamine was less common (0.0–6.4 %). Crack was used by a high proportion of participants in three cities (Frankfurt: 71.6 %; Hanover: 58.6 % and Hamburg: 45.9 %) while reported by much lower proportions in the remaining five cities (0.4–3.1 %). Cocaine use was lower in Berlin (37.1 %), Leipzig (17.7 %) and Munich (20.9 %) compared to Frankfurt (44.0 %), Cologne (46.7 %), Essen (60.9 %), Hanover (65.9 %) and Hamburg (79.9 %). Sharing of unsterile needles and syringes (n/s) in the last 30 days was reported by 10.6 % in Hamburg and up to 22.3 % in Hannover among participants who reported having injected during the last 30 days.; only in Frankfurt the proportion was lower (4.7 %). Recent sharing of unsterile equipment like spoons, filters or water for injection with other injectors was reported by 33.0 % in Hanover and Hamburg and by up to 43.8 % in Frankfurt among persons who injected during the last 30 days.

Table 4 Details of the recruitment procedures using RDS in eight German cities, 2011-14

	Berlin (*n* = 337)	Essen (*n* = 197)	Leipzig (*n* = 130)	Frankfurt (*n* = 285)	Cologne (*n* = 322)	Hanover (*n* = 252)	Munich (*n* = 235)	Hamburg (*n* = 319)
Target sample size	300-350	200	200	300	300	200-250	200	300
Month and year of recruitment	05-07. 2011	10-12. 2011	10-12.2011	01-03.2013	04-05.2013	07-09.2013	10-12.2013	03-05.2014
Time of recruitment	8 weeks	8 weeks	7 weeks	9 weeks	8 weeks	8 weeks	8 weeks	8 weeks
No. of study sites	4	1	2	2	1	1	1	1
No. of seeds in total	19	18	13	11	12	7	13	9
No. of unproductive seeds	4	6	4	2	0	4	3	0
Max. number of recruitment waves	13	10	8	20	13	14	14	20
Coupon received from partner	[a]	[a]	7 %	5 %	2 %	4 %	3 %	2 %
Coupon received from acquaintance	[a]	[a]	78 %	64 %	84 %	50 %	67 %	65 %
Coupon received from stranger	[a]	[a]	15 %	31 %	14 %	46 %	30 %	33 %

[a]data on the relationship to the recruiter was not collected in first two study cities

Sexual risk behaviours

Between 72.9 and 84.6 % of participants reported engaging in sexual intercourse in the last 12 months, of which 44.9 % in Essen and up to 69.1 % in Munich reported not having used a condom at last sexual intercourse. More than half of the participants reported that their last sexual partner was also injecting drugs (51.4 % in Essen and up to 69.4 % in Munich).

History of incarceration

Imprisonment (ever) was reported by the majority of participants in all cities (72.8–85.8 %) and median of total duration of incarceration ranged between 2.0 years in Leipzig, Berlin and Munich to 5.0 years in Hanover. Of those who had ever been in prison, between 17.8 % in Leipzig and 39.3 % in Berlin reported injecting drugs while incarcerated. Of these, between 33.0 and 49.4 % had shared n/s or other equipment when injecting during their last incarceration. Tattooing and piercing during imprisonment were reported by 19.4 % of the participants in Munich and up to 34.5 % of the participants in Essen.

The detailed data on substance use and risk behaviours in the last 30 days are shown in Table 3.

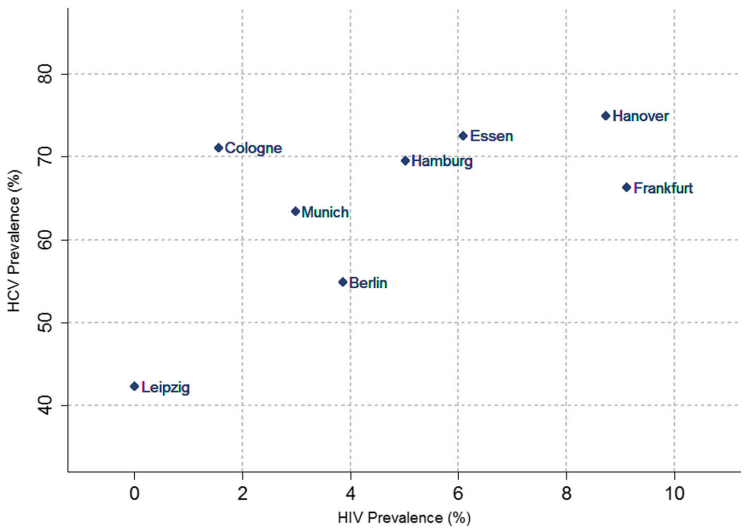

Fig. 1 HIV and HCV seroprevalence in the eight cities (%)

Evaluation of the sampling method: respondent driven sampling

Between 7 and 19 seeds started the recruitment process in the respective cities. The sample of Leipzig ($n = 130$) reached a maximum of eight recruitment waves, while the samples of Frankfurt and Hamburg reached a maximum of 20 recruitment waves (Table 4). Equilibrium and homophily were assessed after the recruitment process had been completed. We reached equilibrium for four of the following five key variables: I. participants' median age; II. proportion of male participants; III. proportion of PWID born in Germany; IV. HCV prevalence; and V. HIV prevalence in all study cities except in Leipzig. Equilibrium for HIV prevalence was not attained in our sample of Frankfurt, Hanover and Cologne. The results of these analyses are presented in the (See Additional file 2: Figure S1a, Additional file 3: Figure S1b, Additional file 4: Figure S1c, Additional file 5: Figure S1d, Additional file 6: Figure S1e and Additional file 7: Figure S2). Respondents and recruiters had the following relationships: Most participants (54–86 %) received their coupons from their partner or from an acquaintance. Between 14 % of the participants in Cologne and up to 46 % of the participants in Hanover received their coupons from a stranger (Table 4). The reported network size defined as "how many people who injected drugs in the last 12 months do you know (and they know you)" ranged from 0–1400 individuals. We did observe random recruitment among the participants. In Frankfurt, Cologne and Hamburg young participants (<25 years) demonstrated a strong negative homophily, indicating that younger participants only recruited older participants (Hx = −1). Among the female participants, only women in Leipzig demonstrated a negative homophily (Hx = −0.37). In Cologne and Munich HIV positive participants only recruited HIV negative participants (Hx = −1) while HIV negative participants in Cologne demonstrated intermediate homophily recruiting mostly other HIV negative participants (Hx = 0.67). The recruitment chains in Cologne and Hamburg show a very late recruitment of HIV positive PWID in the study sample (See Additional file 8: Figure S4e and Additional file 9: Figure S4h). In those two city samples the recruitment chains have often ended once HIV positive participants were recruited. A graphical representation of the recruitment networks (including HIV and HCV serostatus) in each study city is displayed in the (See Additional file 10: Figure S4a-b, Additional file 11: Figure S4c-d, Additional file 8: Figure S4e-f, Additional file 9: Figure S4g-h).

In all cities we observed a decreased interest in participation in the days following the monthly "social benefit"-payment. We did not experience recruitment challenges such as commercial exchange of coupons, imposters or duplicate recruits.

Discussion

This paper presents first findings of the first large bio-behavioural survey among PWID using RDS in Germany. With a study sample of 2,077 participants, the results of the study provide recent data on current HCV and HIV prevalence, socio-demographical factors and behaviours among PWID in Germany. Our results show that HCV is endemic among the study populations (42.3–75.0 %). This result is similar to estimations from available regional surveys and reported data from several European countries [47]. Viremic HCV infections among the participants were found to range between 23.1–54.0 %. In contrast to previous findings from sub-regional surveys in Germany [28], HIV prevalence varied widely between the city samples ranging from 0 % in Leipzig to 9.1 % in Frankfurt. HIV prevalence of more than 5 % was found in four of the city samples. These results are higher compared to reported data on the HIV prevalence in PWID in many other Western European countries, such as the United Kingdom, Denmark, Norway, Austria, or Luxemburg, but still lower than in countries like Italy, Portugal and France [48].

HIV and HCV seroprevalences were both found to be geographically heterogeneous. While Leipzig was the city sample with the lowest prevalences, participants in Essen, Hanover and Frankfurt had high levels of HIV and HCV infections. The differences between the locations might be due to several factors. We identified three characteristics that might be associated with the different levels of HIV and HCV prevalence across the cities: First, age (closely linked with duration of injecting), second, drug use patterns in each city and third, the history of intravenous drug use and the HIV epidemic in the region. In Essen, Hanover and Frankfurt (all city samples with high levels of HIV and HCV infections) study participants were generally older and duration of injecting was longer than in Leipzig. This is consistent with the trend of aging injecting drug user-populations in Germany and Europe at large. The longer a person has injected drugs, the more likely it is that this person will have been exposed to blood-borne pathogens [5]. The sample of Cologne seems to be an exception with an unexpected low HIV seroprevalence. However, as described, in this city HIV-positive persons were recruited only in a late stage of the recruitment process shortly before the end of the study. We therefore might underestimate the true HIV prevalence in this city sample. Further research will be needed to explain this discrepancy.

The different HCV and HIV prevalence might also be associated with the varying use of cocaine, crack and methamphetamines in the cities. Cocaine was found to be most common in Hamburg, Hanover and Essen while crack was mostly used in Frankfurt, Hanover

and Hamburg, all of which are cities with a high HIV and HCV prevalence. Cocaine and crack have a shorter biological half-life and need to be consumed more frequently than other substances in order to maintain their effect [49, 50]. PWID who use cocaine or crack may consequently be more exposed to unsafe use than PWID who use substances requiring less injections. Methamphetamine was found to be most common in Leipzig. This confirms an increasing trend of methamphetamine use in border regions to Czech Republic like Saxony reported in the last years [51–54]. Methamphetamine has a longer biological half-life than heroin and may thus be less frequently injected [55]. Furthermore, the distinct demographic characteristics and consumption patterns in Leipzig might be related to the division of Germany to East and West until 1990. A drug scene in the former East probably developed only after the German re-unification in 1990. While HIV incidence among PWID in West Germany peaked in the mid-1980s, in the Eastern part of Germany the spread of HIV was delayed in time [56]. The delayed epidemic of intravenous drug use and associated blood-borne infections in East Germany are reflected in our results. According to the national HIV case-reporting system HIV is present among PWID in Leipzig with two reported cases in 2012 and three in 2015 [57]. This indicates an ongoing HIV transmission, albeit on a low level [58]. In our sample of Leipzig, we found the highest proportion of new injectors and the highest proportion of participants testing HCV RNA-positive in the stage of seroconversion, likewise indicating ongoing transmissions. This result is consistent with evidence that HCV incidence is rapidly increasing among new injectors [7, 59].

Injecting and sexual risk behaviours

Risk behaviours (30-day prevalence) like using unsterile paraphernalia (spoons, filters or water), sharing of unsterile n/s and practicing unsafe sex, also with non-IDU (12-month prevalence), was reported in all city samples. In the last two decades, harm reduction interventions like NSP in high income countries, including Germany have led to a remarkable decline in the re-use of unsterile n/s and in HIV incidence among PWID [60–63]. From our findings we must conclude that either the access to clean n/s is still insufficient and/or that there are still knowledge gaps around transmission and preventive behaviour of HIV and HCV. In other studies, sharing of other paraphernalia still persists at higher levels than sharing n/s among PWID [64–66]. This was also reflected in our study: sharing other paraphernalia appeared much more common than sharing n/s which was most prevalent in the sample of Frankfurt. In this particular case, the high discrepancy might be related to the high number of crack users. Crack is generally linked to a high consumption frequency, and thus with an increased use of paraphernalia.

Several studies have demonstrated that HCV is more infectious than HIV and a prolonged survival of HCV in syringes and non-syringe injecting paraphernalia has been shown [67, 68]. Not surprisingly and in line with data from other Western European countries, HCV infections therefore appeared to be more prevalent within the study population than HIV [26].

High proportions of the participants reported that their last sexual intercourse was unprotected. The last sexual partner was frequently reported to be an injecting drug user as well, but it was also not uncommon that the sexual partner was a non-PWID. The reported sexual behaviours thus demonstrate the potential risk of spreading HIV through the sexual route. While other studies have demonstrated the higher risk of non-PWID to acquire HIV [69], in Germany, little is known about HIV prevalence among the non-injecting sexual partners of PWID and their potential risk of being a bridge population between PWID and the general population. Therefore further research is needed to better understand the HIV/HCV prevention needs of sex partners of PWID who do not inject drugs themselves.

The study found high rates of incarceration (at least once in lifetime) among the study participants. Unsafe drug use and tattooing/piercing in prison were reported as common practices while in prison, thus constituting important risk factors for the transmission of HIV and HCV. Several studies have shown that not only drug use but also HIV and HCV infections among people in prison are of major concerns in Germany [70, 71]. The provision of harm reduction services in the criminal justice system seems to be insufficient, only one of 186 prisons in Germany offers NSP [72], and there are large variations regarding the availability of OST in prisons across the federal states [70, 73].

Our study shows that HCV and HIV testing rates (12-month prevalence) remained moderate to high in the study populations in comparison to other risk groups, like men who have sex with men [74]. Especially the large variation in the HCV testing rates across the study cities may be linked to the variation of participants who reported undergoing OST at the time of participating, but this needs further investigation.

An important limitation of our study is that it only provides a snap shot of the HIV and HCV epidemiology among PWID in Germany but it does not allow determination of cause-effect relationships. Furthermore, the selection of our study cities was based on the availability of low-threshold drug services in the cities willing and able to participate in the study. Since national representative data on PWID in Germany are not available, we cannot claim that the PWID recruited in the chosen cities are representative for all PWID in Germany.

Respondent driven sampling

The application of RDS as a method to recruit PWID was successful. We reached the targeted sample size within the set time frames in all cities except in one, and our primary and secondary incentives seemed appropriate to motivate PWID to enroll in the study. This is in line with other studies, showing that RDS is an effective recruitment method among PWID [35, 75].

The choice of low-threshold drug services as study venues probably increased the willingness of participation. We observed long recruitment chains in seven of the eight city samples, indicating that PWID are well connected via social networks or through making use of the low-threshold drug services. However, we cannot exclude selection bias of the city samples due to oversampling of persons as initial seeds as well as participants who showed communicative competence, well understood the study flow and the background of the study, and who were willing to recruit others for participation. Persons with a lower bonding to the drug scene or less communicative skills might be underrepresented in the samples.

Due to the extensive questionnaire, we refrained from asking the participants how many PWID rejected their coupons during the recruitment process. Reasons for rejecting and the number of PWID who refused are therefore unknown. It is possible that unknown barriers restricted participation and potentially created a bias. Yet we assume that our samples mostly attained adequate socio-metric depth, given that equilibrium was reached for four out of five key variables while reaching up to 20 waves in our samples. However, not all city samples allow robust weighting of results, as equilibrium was not reached in all and the length of the recruitment chains was too short in the city of Leipzig. In this city we recruited PWID in two low-threshold drug services with alternating study operating hours. This seems to have confused some study participants and it is possible that further potential participants were lost due to this fact. Equilibrium could be reached in the other seven samples, showing that bias introduced by the initial non-randomly selected seeds could be eliminated in these samples.

Despite the popularity and the widely applied methodology of RDS as a sampling method it is not known whether RDS can generate unbiased estimates. The assessment of RDS as a method of data analysis (RDS inference) is challenging as it often fails to produce precise results due to the unknown underlying truth [76]. Also, the key variable used to generate the RDS-generated estimates is the reported network size of the participant which may not have been consistently addressed by all interviewers or not consistently understood by all participants, leading to a large range and thereby further uncertainty about the validity of the RDS estimates. In 2012 McCreesh et al. have performed a RDS study with known characteristics in order to assess the precision and relevance of RDS inference and found that RDS failed to reduce bias when it occurred, and even tended to overestimate biased adjusted results [77]. In case biases occur in practice the method is not designed to correct for the sources of biases. RDS-generated estimates should therefore be interpreted with caution and are only shown in the Additional file 1: Table S1.

Conclusions

To best of our knowledge this study is the first bio-behavioural study using RDS in Germany successfully recruiting members of the target population. This paper presents basic descriptive results for key variables in all of the eight study cities. HCV was found to be hyperendemic within the study population. HIV and HCV seroprevalence were geographically heterogeneous, although unsafe use behaviour, such as sharing n/s and other paraphernalia, unsafe sex, and incarceration was common among all city samples.

Based on our findings, efforts to reduce sharing of non-syringe paraphernalia and to further reduce the use of unsterile n/s are urgently needed in Germany. We furthermore recommend to scale up and increase the access to multilevel and combined HCV and HIV prevention, including antiviral treatment, OST and voluntary counselling and testing (VCT) for PWID. Our study suggests that there might be opportunities to better integrate VCT services in low-threshold drug services, as they were used by up to 90 % of the participants (30-day prevalence). Based on the large regional differences observed in our study, we suggest developing context specific interventions. Harm reduction programmes should particularly consider new injectors. Internationally, there is consensus in the scientific discourse about the need to provide prevention, treatment and care interventions for all, people living in freedom as well as for prisoners [78].

Further in-depth analyses of the collected data will reveal possible associations between infections and behavioural factors and other characteristics, to derive concrete recommendations for current prevention strategies for HCV and HIV among PWID.

Additional files

Additional file 1: Sample proportion and estimated population proportion estimates for all variables. (XLS 75 kb)

Additional file 2: HCV prevalence. (TIF 566 kb)

Additional file 3: HIV prevalence in all study cities except in Leipzig. (TIF 518 kb)

Additional file 4: Proportion of male participants. (TIF 535 kb)

Additional file 5: Proportion of participants born in Germany. (TIF 628 kb)

Additional file 6: Participants´ median age. (TIF 494 kb)

Additional file 7: Number of recruits per recruitment wave. (TIF 695 kb)

Additional file 8: Sample of Cologne (2013); n=322 (12 seeds) and sample of Hanover (2013); n=252 (7 seeds). (TIF 3197 kb)

Additional file 9: Sample of Munich (2013); n=235 (13 seeds) and sample of Hamburg (2014); n=319 (9 seeds). (TIF 3828 kb)

Additional file 10: Sample of Berlin (2011); n=337 (19 seeds) and sample of Essen (2011); n=197 (19 seeds). (TIF 2489 kb)

Additional file 11: Sample of Leipzig (2012); n=130 (13 seeds) and sample of Frankfurt (2013); n=285 (11 seeds). (TIF 2504 kb)

Additional file 12: Homophily (Hx) in eight city samples (age, gender, HIV seroprevalence). Cities: Berlin (B), Essen (E); Leipzig (L); Frankfurt (F); Cologne (C); Hanover (H); Munich (M); Hamburg (HH). The homophily Hx shows the tendency of individuals in a group having social bonds with other individuals similar to them. Hx = 0 means that the formation of social bonds is independent of group membership. Hx=1 mean no social bonds to outsiders exist. Hx= -1 means all social bonds are formed with people outside the group [44]. (TIF 690 kb)

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Availability of data and materials
All data generated or analysed during this study are included in this published article (Tables 1, 2, 3, 4 and Fig. 1) and in supplementary information files (Additional file 1: Table S1, Additional file 2: Figure S1a, Additional file 3: Figure S1b, Additional file 4: Figure S1c, Additional file 5: Figure S1d, Additional file 6: Figure S1e, Additional file 7: Figure S2, Additional file 12: Figure S3 and Additional file 10: Figure S4a-b, Additional file 11: Figure S4c-d, Additional file 8: Figure S4e-f, Additional file 9: Figure S4g-h).

Authors' contributions
BW drafted the manuscript and performed the RDS sample analysis. RZ and UM designed the study and were supported by CSH, D. Schaeffer (Deutsche Aids-Hilfe e.V.), A. Leicht (Fixpunkt e.V), K. Dettmer (Fixpunkt e.V.) and OH. BW and SN were scientific coordinators of the study. RSR validated laboratory procedures for DBS testing and analysed the samples during the pilot phase of the study in 2011. CK, CTB and NB validated and performed laboratory testing since 2012. WC supported the analysis of the laboratory testing data. The manuscript was critically revised by SN, MG, CSH, WC, RSR, CTB, BAR, CK, NB, VB, OH, UM, RZ. All authors participated in the critical discussion of the results, and contributed to and have approved the final manuscript. The DRUCK-Study group approved the final manuscript as well.

Competing interests
R.S. Ross in the past received honoraria from Abbott Diagnostics and Siemens Healthcare Diagnostics for delivering talks and conducting analytical evaluations of diagnostic kits. All other authors declare that they do not have any competing interests.

Consent for publication
Not applicable.

Ethical approval and consent to participate
Ethical approval was received from the ethics committee at Charité University Medicine, Berlin, Germany, in May 2011 (Number EA4/036/11) and in November 2012 (amendment; Number EA4/036/11).
The Federal Commissioner for Data Protection and Freedom of Information approved the study protocol on 29/11/2012 (III-401/008#0035).
All participants signed an informed consent form to allow their anonymous data to be used for publication.

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Concordance between self-reported and measured HIV and hepatitis C virus infection status among people who inject drugs in Germany

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Abstract

Background: People who inject drugs (PWID) are disproportionately affected by both HIV and hepatitis C infection (HCV). Awareness of infection status is essential to ensure linkage to appropriate healthcare for those infected, who need treatment and regular follow-up, as well as for uninfected individuals, who need access to targeted testing and counselling services. In this paper we compare self-reported HIV and HCV status with serological markers of infection among PWID recruited through respondent driven sampling.

Methods: From 2011 through 2014, biological and behavioural data was collected from 2,077 PWID in Germany. Dried blood spots from capillary blood samples were collected and screened for HCV antibodies, HCV RNA and HIV-1/-2 antibodies. HIV reactive samples were confirmed by Western blot.

Results: Laboratory testing revealed that 5 % were infected with HIV and 81 % were aware of being infected. Chronic HCV infection was detected in 41 % of the participants, 2 % had an acute HCV infection, 22 % had a cleared infection, and 34 % were unexposed to HCV. The concordance between self-reported and measured HCV status was lower than for HIV, with 73 % of those with chronic HCV infection being aware of their infection.

Conclusions: We found a relatively high awareness of HIV and HCV infection status among PWID. Nevertheless, access to appropriate testing, counselling and care services targeted to the needs of PWID should be further improved, particularly concerning HCV.

Trial registration: Ethical approval was received from the ethics committee at the medical university of Charité, Berlin, Germany in May 2011 and with an amendment approved retrospectively on 19/11/2012 (No EA4/036/11). The German Federal Commissioner for Data Protection and Freedom of Information approved the study protocol retrospectively on 29/11/2012 (III-401/008#0035).

Keywords: People who inject drugs, Germany, Hepatitis C, HIV, Testing, Knowledge, Self-report, Validity, Undiagnosed, Respondent driven sampling

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Background

Accurate knowledge of infection status is important as it gives infected individuals the opportunity to seek appropriate healthcare and may encourage people to engage in preventive behaviours, which can protect themselves and others from infections. People who inject drugs (PWID) have a high risk and burden of both HIV and Hepatitis C infection (HCV) [1–4]. Determining HIV infection status is relatively straightforward since there is no clearance or cure. In contrast, screening for HCV antibodies (anti-HCV) will identify if a person has ever been in contact with the virus, but this person may have cleared the infection either with treatment or spontaneously, or the person may have a chronic HCV infection, characterised by being both anti-HCV and HCV RNA positive. A person who has cleared the infection can later be re-infected with HCV. Since the acquisition of both HIV and HCV is often asymptomatic or the occurrence of non-specific symptoms may be attributed to other problems, and since serious sequelae may take several decades to develop, people infected with these two viruses may remain unaware of being infected for a long period of time. Annual routine unlinked anonymous monitoring (UAM) of HIV and hepatitis among PWID in England, Wales and Northern Ireland has shown that the proportion of infected PWID unaware of their infection varied between 4 %-15 % for HIV and 45 %-53 % for HCV in the period 2010–2014 [5]. In a recent systematic review including 11 studies from five EU countries the proportion of undiagnosed HCV infections among PWID varied between 24 %-76 % (IQR: 38 %-64 % and median: 49 %) [4]. Several previous studies only looked at anti-HCV status and did not include HCV RNA status, which is needed to assess current infection status [4–6].

With new, highly effective and well tolerable HCV therapy options being available as well as the potential of HIV-treatment as prevention also among PWID [7], it is of growing importance to increase awareness of infection status.

In order to assess the level of awareness of infection status among PWID in Germany, we used data from a recent, cross-sectional bio-behavioural survey of this population to compare self-reported HIV and HCV status with serological markers of infection.

Methods

The DRUCK-study collected biological and behavioural data from 2,077 PWID in eight large German cities in the years 2011–2014 [8]. The respondents were recruited using respondent driven sampling. Inclusion criteria were a minimum age of 16 years, having injected drugs in the given study city in the last 12 months, and providing informed consent for study participation. All participants went through a questionnaire-assisted interview and provided a capillary blood sample, collected as dried blood spots (DBS). Samples and questionnaires were marked with the same unique identifier. The study was piloted in two cities and then implemented in the remaining six. Before starting the data collection we trained interviewers to increase their understanding of HIV and HCV, and laboratory staff for collection of DBS and handling and shipping of the samples in each of the study cities to ensure the comparability of results. All samples were screened for anti-HIV-1/-2 by EIA, and reactive samples were confirmed by Western blot. In six of the eight study cities, all samples were screened for both anti-HCV by EIA and analysed for the presence of HCV-RNA using nested RT-PCR. Anti-HCV positive samples were confirmed by immunoblot. In the two pilot cities all samples were screened for anti-HCV by EIA and RT-PCR was performed on all anti-HCV positive samples and on anti-HCV negative samples if test results did not correspond to self-reported results. The test specificity was 100 % for all three markers: anti-HIV, anti-HCV and HCV RNA. The same was true for the sensitivity for HIV and HCV RNA, whereas the sensitivity for anti-HCV was 97.8 % [9]. Further information about study design, data collection and laboratory methods etc. has been published elsewhere [8, 9].

Defining self-reported HIV status

The self-reported HIV status was determined using two questions: if the participant had ever been tested for HIV and if yes, what the result of their latest test was. Based on the answers participants were categorised as HIV negative, HIV positive or never tested. Participant's self-reported HIV status were categorised as unclear when they were not sure if they had ever been tested or if they did not know their last test result. Participants who reported having been diagnosed with HIV were asked about month and year of their first positive HIV test in order to calculate how long they had been aware of being infected.

Defining measured HIV status

We defined samples as HIV positive if testing positive for anti-HIV with EIA and being confirmed by Western blot. EIA-reactive samples with indeterminate immunoblot pattern were excluded from this analysis. Anti-HIV negative samples were determined as HIV negative.

Defining self-reported HCV status

To determine the self-reported HCV status several questions were used. Participants were asked if they had ever been tested for anti-HCV. Those who had not were categorised as never tested. The participants who reported testing for HCV were further asked if they had ever

received a positive anti-HCV test result. Those who had not were categorised as uninfected. Participants reporting having ever received a positive anti-HCV test result were further asked if they had ever been successfully treated or had cleared the infection spontaneously. Those who responded no to both questions were categorised as infected, while those who responded yes to either of the questions were defined as previously infected. As for HIV, participants who were either not sure if they had ever been tested or did not know their last test result, were categorised as unclear.

Defining measured HCV status

We defined chronic HCV infection as testing anti-HCV and RNA positive, acute infection (HCV infection acquired within the last 4–6 weeks) as anti-HCV negative, but RNA positive, cleared infection as anti-HCV positive and HCV RNA negative, and unexposed as testing anti-HCV and RNA negative.

An example of the questionnaire used to guide the interviews can be found online [10].

Results

In total, 2,077 PWID from eight German cities were included in the study, with the proportion of female participants ranging between 19 %-35 % in the respective cities, and a median age ranging between 29–41 years.

HIV status

The laboratory testing revealed 100 participants (4.8 %) to be positive for HIV, and 1976 (95.2 %) to be negative. One sample had a reactive EIA result but an indeterminate immunoblot, and was thus excluded from the analysis. Of the 100 HIV positive cases, 81 % were aware of their infection while 16 % reported their last HIV test to be negative. One HIV positive participant reported no previous testing.

Among the participants testing negative for HIV, 90 % reported a negative test result at last test, while 7 % reported never having had an HIV test. Of the HIV negative participants, six individuals (0.3 %) reported having received a positive HIV-test result. Two HIV positive and one HIV negative participant declined to answer the question on HIV-status. The concordance of the self-reported HIV status and laboratory test results is displayed in Table 1.

Among the 81 self-reported HIV infected, 5 % reported receiving their diagnosis in the last year, 17 % 1–5 years ago, 22 % 6–10 years ago and 47 % more than 10 years ago. Seven cases (9 %) did not provide information on time of their HIV diagnosis.

Table 1 Concordance of self-reported and measured HIV status, *n*=2076 (excluding one sample with indeterminate HIV status)

	HIV laboratory test results	
Self-reported status	HIV negative (AB-)	HIV positive (AB+)
Concordant	1784 (90 %)	81 (81 %)
Discordant	6 (0,3 %)	16 (16 %)
Never tested	133 (7 %)	1 (1 %)
Unclear	52 (3 %)	0 (0 %)
Answer declined	1 (0,1 %)	2 (2 %)
Total	1976	100

Unclear means not sure if tested or did not get last test result.
AB antibodies

HCV status

The laboratory tests found 716 (34 %) participants to be unexposed to HCV, 857 (41 %) participants to have a chronic HCV infection and 457 (22 %) participants with a cleared HCV infection. In 47 (2 %) participants HCV-RNA but no anti-HCV was detected, indicating an acute infection. As the participants were only asked about anti-HCV test results, this group was excluded from the analysis.

The concordance between the self-reported HCV status and the laboratory test results was 47 % among those unexposed, while 27 % reported an HCV status discordant to the laboratory findings (Table 2). Of these, 56 % reported a current HCV infection and 44 % a previous one (Table 3). Of all unexposed individuals, 16 % reported never to have had a test for HCV. In the group with confirmed, chronic HCV infections, 73 % reported a status concordant to the laboratory test results, whereas 19 % reported a differing HCV status. In 37 % of these discordant cases, participants reported to be uninfected and in 63 % a cleared infection. Among participants positive only for anti-HCV but not HCV-RNA, i.e., with a cleared infection, 38 % correctly reported to have cleared the infection. Of those reporting a discordant status, 89 % reported to be currently infected and 11 % reported an uninfected status.

Discussion

In our study population of PWID, the concordance of self-reported and measured HIV status was relatively high. The proportion of HIV positive participants aware of their infection was 81 %. These data compare well with the data from both the UAM in England, Wales and northern Ireland from 2010–2014 where 85-96 % of HIV positive PWID were aware of their HIV infection [5] and the latest HIV modelling data from Germany, where it was estimated that 89 % (81-93 %) of all HIV infected PWID living in Germany in 2014 had received an HIV diagnosis [11]. According to the same HIV modelling data for Germany, the proportion of HIV infected individuals who are aware of their HIV status is higher

Table 2 Concordance of self-reported and measured HCV status, *n*=2030 (excluding cases with acute infection)

	HCV laboratory test results		
Self-reported status	Unexposed (AB-, RNA-)	Chronic infection (AB+, RNA+)	Cleared infection (AB+, RNA-)
Concordant	339 (47 %)	622 (73 %)	174 (38 %)
Discordant	194 (27 %)	163 (19 %)	254 (56 %)
Never tested	113 (16 %)	37 (4 %)	15 (3 %)
Unclear	69 (10 %)	35 (4 %)	14 (3 %)
Answer declined	1 (0,1 %)	0 (0 %)	0 (0 %)
Total	716	857	457

Unclear means not sure if tested or did not get last test result
AB antibodies

among PWID compared to other groups such as men who have sex with men (MSM) (82 % (79-85 %)) and non-injecting heterosexuals (74 % (66-80 %)). This might partly be explained by the fact that the majority of HIV infections among PWID in Germany were acquired in the 1980ies and 90ies, which is also seen by the high proportion of known HIV infections being diagnosed more than 10 years ago. This means that the majority of HIV infected PWID have had many years to get a diagnosis and begin therapy. Increasing treatment rates among PWID may have a relatively large impact on reducing potential sources of HIV transmission within this population [7]. A low rate of newly acquired HIV infections is also indicated by the fact that <1 % of PWID not yet tested for HIV were found to be anti-HIV positive in our study. The one sample with a reactive AB test and indeterminate immunoblot could be a recent infection in the stage of seroconversion. We tried to receive a second blood sample from this participant to repeat the testing, but the person did not show up in the drug service again.

The finding that 17 % of those positive for HIV reported a negative HIV status or to never have been tested, underlines the undiminished importance of ensuring access to targeted HIV testing and counselling services for PWID in Germany, e.g., in low threshold settings.

For the disconcerting finding of six self-reported infections in participants without measurable anti-HIV several possible explanations exist. One possibility is the failure to detect antibodies in excessively diluted samples if the original amount of capillary blood was inadequately small, resulting in a higher dilution of the antibodies as compared to the standardized and validated protocol. Further we cannot rule out the communication of false positive test results to study participants, in particular if reactive screening test results were not confirmed, which can happen if respondents were not linked into care. Processing mistakes during sample collection or during testing of DBS, or the disappearance of HIV antibodies if treatment has been started early and viral load has remained suppressed continuously are further, though in our view less likely possibilities.

The results of the HCV testing revealed that 34 % were unexposed to HCV, 2 % had an acute HCV infection, 41 % of participants had a chronic infection and 22 % had a cleared infection. It is possible that a few acute HCV infections might have been missed in the two first pilot cities where PCR was only done for anti-HCV negative respondents with a self-reported HCV diagnosis. The concordance between self-reported and actual HCV status was much lower than for HIV. Concordance was highest (73 %) among those with a chronic infection, 47 % among those unexposed to HCV and just 38 % among those with a cleared infection.

The somewhat surprising finding of 27 % of those with no markers of HCV infection reporting to be infected (chronic or cleared HCV), might partly be explained by confusion about the different types of hepatitis, e.g., participants may previously have received a positive test result for hepatitis B. Another explanation could be the failure to detect antibodies e.g., due to excessive dilution, as described above for HIV or a false negative anti-HCV

Table 3 Discordance of self-reported and measured HCV status, *n*=611

	HCV laboratory test results		
Self-reported status	Unexposed (AB-, RNA-)	Chronic infection (AB+, RNA+)	Cleared infection (AB+, RNA-)
Uninfected		61 (37 %)	29 (11 %)
Infected	109 (56 %)		225 (89 %)
Previously infected (cleared infection)	85 (44 %)	102 (63 %)	
Total	194	163	254

AB antibodies

test result which is not unlikely given the estimated sensitivity of 97.8 %.

Of the participants with a chronic HCV infection, 27 % falsely believed to be uninfected, to have cleared the infection or had never been tested or were not sure of their test result. This rate is much lower than what is reported from the UAM in England, Wales and northern Ireland where 45-53 % of anti-HCV positive were unaware of their HCV infection in the years 2010–2014 [5]. Also the recent systematic review on HCV in PWID in Europe found higher rates of undiagnosed HCV: 24-76 % (IQR: 38-64 % and median: 49 %) [4]. An Australian study of 352 active injectors under the age of 30, found rates of concordance similar to our study: 68 % among those with a chronic infection and 46 % among those with a cleared HCV infection [12]. Also data from a French study of HCV among PWID found that only 22 % of PWID were unaware of their HCV infection [13, 14]. A recently published study from Spain presents data on the proportion of undiagnosed HCV infection among PWID stratified by migration status and duration of injecting. This study reports rates of undiagnosed HCV from 15 % among Spanish long-term injectors up to 57 % among migrant new injectors [6]. All these data suggest that awareness of HCV infection status among PWID in Germany is relatively high. This is also true when comparing with data for the general population in Europe, where between 40 % and 80 % of people with chronic hepatitis are believed to be unaware of their infection [15]. However, the persons indicating a true positive anti-HCV test result often do not necessarily also know their PCR test result. In times of effective treatment options for HCV this will become increasingly important.

In our study, the majority (63 %) of those with a chronic HCV infection with a discordant self-reported status were aware of having been exposed to the virus but believed to have cleared the infection. These participants might have simply assumed to be healed (we did not collect data on whether the reported clearance had been laboratory confirmed) or they might indeed have cleared the virus but later become re-infected. These results show the need of special screening efforts of PWID who have once cleared their HCV infection, as re-infections can only be diagnosed by detecting the viral RNA.

From a public health point of view, the most undesirable discordant status is being infected and either not being aware of being infected or believing to be uninfected. This discrepancy between perception and reality limits the access to appropriate health care and may increase the risk of unknowingly transmitting infections. However, the evidence about the association between knowledge of HCV status and risk behaviours in PWID is conflicting. Some longitudinal studies have observed a reduction in risky injecting drug use following notification of HCV-positive status [16, 17], while other studies found either no reduction or even increased risky injection behaviours among PWID receiving a diagnosis of HCV infection [18, 19]. This means that believing to be infected, while actually being uninfected may turn out to become a self-fulfilling prophecy. As mentioned in the results, it was common among both unexposed participants, as well as participants with a cleared infection, to wrongly believe they were currently infected. It might be that those who have been at risk assume they are infected and/or do not believe their test results.

Studying HCV infection status and HCV test status is complicated and not only our study participants, but in our experience also both non-medical and medical staff often had difficulties in distinguishing between the two HCV tests (AB and RNA) and in interpreting the combination of the two test results. Our findings, as are those from other, similar studies, are limited by the lack of clarity regarding HCV test and infection status among both interviewers and respondents. Several qualitative studies among PWID have shown that confusion and uncertainty regarding the meaning of a positive HCV test and HCV risk exist in this group and that HCV is often perceived as an almost inevitable consequence of drug injecting [20–22].

Our data is collected from eight large cities in Germany, but is not likely to be representative for all PWID living in Germany. E.g. our study sample might be more knowledgeable about their infection status than PWID living in smaller cities due to better access to drug user services, testing and treatment in larger cities.

Conclusion

In our study, 17 % of HIV positive PWID and 27 % of those with chronic HCV infection were unaware of their infections. These results indicate that the majority of the study population is aware of their infection status, however still more than a quarter of those with infectious HCV and nearly one in five of HIV infected PWID in our study sample did not know their status, although they were often attached to opioid substitution therapy or other harm reduction services. Not being aware of the infection status implies that they cannot access appropriate health care and they risk unknowingly transmitting the disease to others.

In line with several other studies, we also believe that the quality of post-test counselling is crucial for increasing awareness of infection status as well as for ensuring a positive impact on risk behaviours and ensuring linkage to care and appropriate medical services for both infected and uninfected PWID. In the era of highly effective antiviral HCV-treatment options, the opportunity is there to clear infection in almost all HCV-infected PWID, if infected persons become aware of their status and are linked to care.

Abbreviations
AB, antibodies; DBS, dried blood spots; HCV, Hepatitis C infection; MSM, men who have sex with men; PWID, people who inject drugs; RKI, Robert Koch Institute; UAM, unlinked anonymous monitoring

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Availability of data and materials
All the data from which conclusions of this research are drawn are present in Tables 1, 2 and 3. Additional information about the study have been published in [8, 9] and can be found on the website of the Robert Koch Institute: http://www.rki.de/DE/Content/InfAZ/H/HIVAIDS/Studien/DRUCK-Studie/DruckStudie.html (accessed on 19 June 2016).

Authors' contributions
SN did the analyses and drafted the manuscript together with MG, UM and RZ. RZ and UM designed the study. SN and BW were scientific coordinators of the study during the data collection period. RSR validated laboratory procedures for DBS testing and analysed the samples during the pilot phase of the study in 2011. CK, CTB and NB validated and performed laboratory testing since 2012. The manuscript was critically revised by MG NB, CTB, CK, RSR, NB, BW, VB, UM and RZ. All authors participated in the critical discussion of the results, and contributed to and have approved the final manuscript.

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Competing interests
All authors declare that they have no competing interest.

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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

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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.

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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

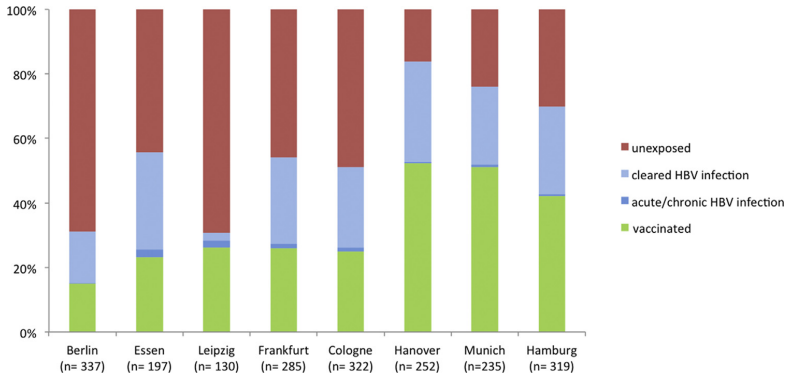

Figure 1. Serological and molecular findings for HBV status by study city.

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

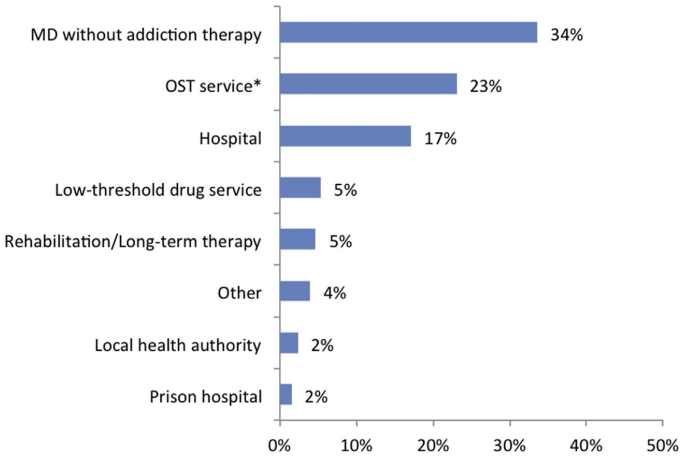

Figure 2. Place of last HBV vaccination ($n = 641$). Question not asked in Berlin, Essen, or Leipzig. MD, medical doctor; OST, opioid substitution therapy. *OST service includes medical doctors/outpatient clinics with OST or addiction therapy.

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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History of detention and the risk of hepatitis C among people who inject drugs in Germany

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ABSTRACT

Objectives: The aim of this study was to investigate the association between detention experience and hepatitis C virus (HCV) status, the role of duration and frequency of detention, and whether risk behaviours practiced in detention could explain an observed increase in risk.
Methods: Current drug injectors (injecting in the last 12 months) were recruited to participate in a sero-behavioural, cross-sectional survey using respondent-driven sampling in eight German cities during the years 2011–2014. Using multivariable logistic regression, the association between HCV status and reported detention experience was investigated.
Results: A total of 1998 participants were included in the analysis. Of these, 19.9% reported no detention experience, 28.6% short and rare experience (≤3.5 years in total, ≤3 times), 12.1% short but frequent experience, 7.1% long but rare experience, and 32.4% long and frequent experience. After correcting for HCV risk factors, the association between detention experience and HCV status remained statistically significant. By adjusting the model for intramural risk behaviours, the odds ratios of detention experience were reduced but remained significant.
Conclusions: The proportion of people who inject drugs positive for HCV increased with both frequency and duration of their detention experience. As intramural risk behaviours could not fully explain this increase, it appears that transfers between community and custody may confer additional risks.

Introduction

Hepatitis C (HCV) is a viral, blood-borne infection that becomes chronic in eight out of 10 cases, with the development of liver cirrhosis or liver cancer as possible long-term consequences (Te and Jensen, 2010). The use of contaminated injection equipment is an important mode of transmission, making the group of people who inject drugs (PWID) particularly vulnerable to HCV. In most countries, this group is disproportionately affected by the infection, and the global HCV prevalence among PWID has recently been estimated to be 52% (Degenhardt et al., 2016).

Prison experience is common among PWID, due to both drug-related crime and to acquisitive offending (Pierce et al., 2017). Individuals with a history of injecting drug use are overrepresented in prison populations across Europe and other developed countries (EMCDDA, 2012; Australian Institute of Health and Welfare, 2013). In Germany, it is estimated that 22–30% of sentenced inmates have a history of injecting drug use (Schulte et al., 2009; Eckert, 2008).

Despite prisons being highly controlled settings, drugs frequently find their way inside, making it possible for incarcerated PWID to continue their drug use. In the only existing, representative study of the German prison population from 2007, 33% of PWID reported injecting in prison (Eckert, 2008). Similar rates have been found in countries like Australia, Denmark, and Greece;

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however, the lifetime prevalence of injecting in prison has been reported at significantly higher rates (Dolan et al., 2010; Snow et al., 2014; Luciani et al., 2014; Christensen et al., 2000; Malliori et al., 1998). To a certain extent, prisons also serve as a place where injecting drug use is initiated (Eckert, 2008; Taylor et al., 1995; Butler et al., 2004).

Access to sterile injecting equipment, on the other hand, is very limited, as clean needles, syringes, and other injecting paraphernalia are rarely available. Despite the recommendations of the United Nations Office on Drugs and Crime and the World Health Organization to provide needle exchange programmes (NSP) for inmates, merely eight countries worldwide offered NSP in at least one prison in 2016 (Harm Reduction International, 2016; UNODC/ILO/UNDP/WHO/UNAIDS, 2013). To date, NSP is available in only one (female) prison in Germany. Difficulties accessing sterile injecting equipment lead to increased unsafe use, as the equipment must frequently be shared between inmates (Dolan et al., 2010; Luciani et al., 2014; Malliori et al., 1998; Taylor et al., 1995; Schäffler, 2012; O'Sullivan et al., 2003; Haber et al., 1999). In a paper on behavioural change amongst drug injectors in Scottish prisons, Shewan et al. described how the number of PWID sharing injecting equipment went up from 24% prior to imprisonment to 76% during imprisonment (Shewan et al., 1994).

At the same time, prison populations, especially those with a history of injecting drug use, often have a high prevalence of HCV. A meta-analysis of detained populations from 2013 estimated that two-thirds of detainees with a history of drug injection were positive for HCV antibodies (Larney et al., 2013). High HCV prevalence and multiple sharing among prisoners thus result in a high risk of infection. The same meta-analysis estimated the incidence rate among prisoners with a history of drug injection to be 16.4 per 100 person-years (Larney et al., 2013). The results of another meta-analysis by Stone et al. also suggest that recent incarceration among PWID is associated with a substantial increase in HCV acquisition risk (Stone et al., 2018).

Studies of PWID in the community have found previous imprisonment, multiple imprisonments, and the duration of imprisonment all to be associated with HCV infection; however, only one of these aspects is usually considered at a time (Macalino et al., 2016). Less is known about how the frequency and the duration of imprisonment each affect the risk of HCV. Thus, using data from a large sero-behavioural survey of PWID in Germany, this analysis was performed with the aim of investigating (1) the association between detention experience and HCV status, (2) the role of the duration and frequency of detention, and (3) whether risk behaviour practiced in detention could explain the observed increase in risk.

Methods

Participants and methods

A multicenter sero-behavioural survey was conducted in eight German cities between 2011 and 2014. Participants were recruited using respondent-driven sampling over a period of 8–10 weeks in each city. Study participation was reimbursed with €10 and another €5 for each successful peer-recruitment, with a maximum of three recruitments. Eligibility criteria for study inclusion were injecting drug use in the past 12 months, drug consumption in the surveyed city, and a minimum age of 16 years. All participants were asked to provide informed consent before being enrolled into the study.

Enrolled participants were interviewed face-to-face about their demographic characteristics, drugs used, injecting behaviour, sexual behaviour, detention experience, history of HIV, hepatitis B virus (HBV), and HCV testing, health status, and knowledge related to HIV, hepatitis B, and hepatitis C. An interview typically lasted 30–45 minutes. Each participant was also asked to provide a capillary blood sample on filter paper (i.e., dried blood spots), which was sent to the laboratory for analysis of serological and molecular markers for HBV, HCV, and HIV. If desired, participants could later pick up their test results. Ethical approval for the study was granted by the ethics committee of the Charité University of Medicine, Berlin.

A detailed description of the study protocol has been published elsewhere (Zimmermann et al., 2014).

Measures

The outcome variable used in this analysis was HCV status (negative/positive). A positive HCV status was defined as testing positive for antibodies, RNA, or both. Subsequently a negative HCV status was defined as having a negative result with both tests. Test results for both HCV antibodies and HCV RNA were available for all participants. The variable of interest in this analysis was detention experience. Having detention experience was defined as having ever been at least once in any of the following: juvenile arrest/prison, pre-trial custody, prison, forensic commitment (i.e., detention in a clinic for forensic psychiatric care, following a criminal conviction). Due to the way the data were collected, it was not possible to consider the various forms of detention separately. The variable was divided into five categories: none, short and rare, short but frequent, long but rare, and long and frequent. The duration (short vs. long) contained in the variable of interest was defined as the total duration of all detentions, where short was up to 42 months (3.5 years) and long was 43 months or longer. The frequency (rare vs. frequent) contained in the variable of interest was defined as the sum of all detentions, where rare was three times or less and frequent was four times or more. The two cut-off values were based on the median total detention duration and median detention frequency.

Risk factors for HCV previously described in the literature were identified in the dataset and those considered as possible confounders of the relationship between detention experience and HCV status were selected for analysis. The following variables were selected: age (<25 years, 25–39 years, ≥40 years), sex (male, female), region of birth (Germany, Western Europe, Central Europe, Former Soviet Union, Middle East, other), ever having been homeless (no, yes), duration of injecting drug use (≤2 years, 3–10 years, >10 years), typical number of injections on an average injection day (1, 2–4, ≥5), and ever had a non-professional tattoo/piercing while not in detention (no, yes). Known in-detention risk behaviours for HCV infection were also identified and those for which data were available were selected for the last step of the analysis: ever injected drugs in detention (no, yes), ever had a non-professional tattoo/piercing while in detention (no, yes).

If a question was answered with either "I don't remember" or "I don't want to answer", the response was re-coded as missing. Participants with incomplete data on detention experience and those in the stage of seroconversion (HCV antibody-negative, HCV RNA-positive) with last detention experience more than 12 months ago were excluded from the analysis.

Data analysis

A descriptive analysis was performed, generating counts and frequencies for all variables, as well as calculating the HCV seroprevalence for each variable category. To investigate the univariable associations between HCV status and each of the variables, logistic regression was used, reporting the odds ratio (OR) and 95% confidence interval (CI). As a next step, a multivariable model was built using stepwise forward selection.

The initial model included detention experience (the variable of interest), as well as age, sex, and study site. These variables were locked into the model throughout the selection procedure, regardless of their significance. The remaining variables were added in order of significance from the univariable analysis ($p < 0.2$). The model improvement was tested using the likelihood ratio test ($p < 0.05$). A backward stepwise elimination was also performed with the same set of variables. The same variables were locked in as in the forward selection and the 'p-value to remove' was set at 0.2. Upon completing the variable selection for the multivariable model, interactions considered meaningful a priori between detention experience and selected confounders were examined. The interaction terms were added to the multivariable model one by one, checking for significant improvement using the likelihood ratio test ($p < 0.05$). As a final step, the in-detention risk behaviour variables were added to the model in order to examine how this affected the effect of detention experience.

Missing data were excluded when calculating percentages, and list-wise deletion was applied in all logistic regression analyses described. All statistical analyses were performed using Stata version 13.1 for Windows (StataCorp LP).

Results

A total of 2077 participants were recruited for the study. Of these, 63 (3.0%) had incomplete data on detention experience and 16 (0.8%) were in the stage of HCV seroconversion with last reported detention experience more than 12 months ago and were thus excluded, resulting in a study sample of 1998 participants. Data were missing for 0.10–1.05% of observations, with the exception of the variable 'typical number of injections on an average injection day' for which data were missing for 4.7%. Of the individuals included in the analysis, 6.6% were younger than 25 years of age, 76.3% were male, and 22.2% were born outside of Germany (Table 1). The most common substances consumed in the last 30 days were heroin (74.7%), benzodiazepines (49.4%), and cocaine (48.4%). The majority (70.9%) reported more than 10 years of injecting drug use, most commonly injecting 2–4 times on an average injecting day (55.6%).

One fifth (19.9%) of the participants reported not having any detention experience, while 32.4% reported long and frequent and 28.6% short and rare detention experience. Short but frequent and long but rare detention experience were less common (12.1% and 7.1%, respectively). Four hundred and seventy participants reported ever having injected drugs while in detention, corresponding to 23.6% of the entire sample and to 29.4% of those reporting detention experience. The proportion of participants who had ever had a non-professional tattoo/piercing while in detention corresponded to 26.5% of the entire sample and to 32.9% of those ever detained. The proportion of participants reporting these risk factors increased significantly with both total duration and frequency of detention (Table 2). The overall HCV seroprevalence in the sample was 64.7%.

HCV seroprevalence increased along with the duration and frequency of detention experience, from 48.6% among those with no experience to 79.1% among those with long and frequent experience (Table 3). In the univariable analysis, all types of detention experience were significantly associated with HCV seropositivity: OR 1.35 (95% CI 1.04–1.74) for short and rare experience, OR 2.09 (95% CI 1.50–2.91) for short but frequent experience, OR 3.36 (95% CI 2.18–5.18) for long but rare experience, and OR 4.01 (95% CI 3.05–5.27) for participants

Table 1
Distribution of characteristics and behaviours of the study population.

Characteristic or behaviour ($N = 1998$)		n (%)
Age (years)	<25	132 (6.6)
	25–39	986 (49.4)
	≥40	878 (44.0)
Sex	Male	1523 (76.3)
	Female	472 (23.7)
HCV status	Negative	705 (35.3)
	Positive	1293 (64.7)
Detention experience	None	397 (19.9)
	Short and rare	571 (28.6)
	Short but frequent	241 (12.1)
	Long but rare	142 (7.1)
	Long and frequent	647 (32.4)
Region of birth	Germany	1553 (77.9)
	Western Europe	67 (3.4)
	Central Europe	80 (4.0)
	Former Soviet Union	203 (10.2)
	Middle East	73 (3.7)
	Other	18 (0.9)
Ever homeless	No	682 (34.2)
	Yes	1310 (65.8)
Duration of injecting drug use (years)	≤2	112 (5.7)
	3–10	466 (23.5)
	>10	1405 (70.9)
Typical number of injections on an average injecting day	1	446 (23.4)
	2–4	1059 (55.6)
	≥5	399 (21.0)
Ever had non-professional tattoo/piercing while not in detention	No	1473 (74.5)
	Yes	504 (25.5)
In-detention risk behaviour ($N = 1998$)		
Ever injected drugs in detention	No[a]	1525 (76.4)
	Yes	470 (23.6)
Ever had non-professional tattoo/piercing while in detention	No[a]	1454 (73.6)
	Yes	523 (26.5)

HCV, hepatitis C virus.
[a] Category also includes never detained individuals.

Table 2
Frequency of in-detention risk behaviours by type of detention experience.

	Ever injected drugs in detention			Ever had non-professional tattoo/piercing while in detention		
	No, *n* (%)	Yes, *n* (%)	*p*-Value[a]	No, *n* (%)	Yes, *n* (%)	*p*-Value[a]
Detention experience						
Short and rare	507 (89.3)	61 (10.7)	0.000	501 (88.7)	64 (11.3)	0.000
Short but frequent	191 (79.3)	50 (20.8)		188 (78.3)	52 (21.7)	
Long but rare	92 (64.8)	50 (35.2)		87 (61.3)	55 (38.7)	
Long and frequent	338 (52.2)	309 (47.8)		292 (45.3)	352 (54.7)	

[a] Chi-square test.

Table 3
HCV seroprevalence by risk factor—univariable associations.

Characteristic or behaviour (*N* = 1998)		HCV seropositive *n* (%)	OR	95% CI
Detention experience	None	193 (48.6)	Reference	
	Short and rare	320 (56.0)	1.35	1.04–1.74
	Short but frequent	160 (66.4)	2.09	1.50–2.91
	Long but rare	108 (76.1)	3.36	2.18–5.18
	Long and frequent	512 (79.1)	4.01	3.05–5.27
Age (years)	<25	46 (34.9)	Reference	
	25–39	609 (61.8)	3.02	2.06–4.42
	≥40	637 (72.6)	4.94	3.35–7.28
Sex	Male	982 (64.5)	Reference	
	Female	309 (65.5)	1.04	0.84–1.30
Region of birth	Germany	1004 (64.7)	Reference	
	Western Europe	48 (71.6)	1.38	0.80–2.37
	Central Europe	42 (52.5)	0.60	0.38–0.95
	Former Soviet Union	150 (73.9)	1.55	1.11–2.15
	Middle East	41 (56.2)	0.70	0.44–1.13
	Other	7 (38.9)	0.35	0.13–0.90
Ever homeless	No	415 (60.9)	Reference	
	Yes	873 (66.6)	1.29	1.06–1.56
Duration of injecting drug use (years)	≤2	30 (26.8)	Reference	
	3–10	243 (52.2)	2.98	1.89–4.70
	>10	1015 (72.2)	7.11	4.61–10.98
Typical number of injections on an average injecting day	1	243 (54.5)	Reference	
	2–4	710 (67.0)	1.70	1.36–2.13
	≥5	290 (72.7)	2.22	1.67–2.97
Ever had non-professional tattoo/piercing while not in detention	No	941 (63.9)	Reference	
	Yes	342 (67.9)	1.19	0.96–1.48
In-detention risk behaviour (*N* = 1998)				
Ever injected drugs in detention	No[a]	905 (59.3)	Reference	
	Yes	387 (82.3)	3.19	2.47–4.14
Ever had non-professional tattoo/piercing while in detention	No[a]	885 (60.9)	Reference	
	Yes	398 (76.1)	2.05	1.63–2.57

HCV, hepatitis C virus; OR, odds ratio; CI, confidence interval.
[a] Category also includes never detained individuals.

with long and frequent detention experience, compared to those with none. Other factors significantly associated with a positive HCV status in the univariable analysis were age, region of birth, ever being homeless, duration of injecting drug use, number of injections on an average injecting day, and ever having had a non-professional tattoo/piercing while not in detention. The two risk behaviours specific to the detention setting were also significantly associated with a positive HCV status: ever injected drugs in detention with OR 3.19 (95% CI 2.47–4.14) and ever had a non-professional tattoo/piercing while in detention with OR 2.05 (95% CI 1.63–2.57).

In the multivariable analysis, both selection procedures rendered the same model. Variables included in the final model to correct for confounding effects on the association between detention experience and HCV status were age, sex, region of birth, duration of injecting drug use, typical number of injections on an average injecting day, and having ever had a non-professional tattoo/piercing while not in detention (see Table 4). None of the tested interaction terms improved the model significantly. Correcting for these variables and study site did not lead to a loss of significance of detention experience, which remained associated with an increased risk of HCV with the following odds ratios: OR 1.39 (95% CI 1.04–1.86) for short and rare experience, OR 2.08 (95% CI 1.43–3.02) for short but frequent experience, OR 3.32 (95% CI 2.04–5.37) for long but rare experience, and OR 3.80 (95% CI 2.73–5.28) for participants with long and frequent detention experience, compared to those with none.

Adding the in-detention risk behaviours to the model, which are known to mediate the relationship between detention experience and HCV status as they are part of the causal pathway, decreased the ORs of detention experience but did not lead to a loss of significance. The ORs of detention experience in the model including the in-detention risk behaviours were as follows: OR 1.31 (95% CI 0.97–1.76) for short and rare experience, OR 1.83 (95% CI 1.25–2.67) for short but frequent experience, OR 2.68 (95% CI 1.62–4.42) for long but rare experience, and OR 2.80 (95% CI 1.92–4.09) for long and frequent detention experience, compared to those with none.

Table 4
Multivariable models excluding and including variables of in-detention risk behaviours.

Characteristic or behaviour		Model excluding in-detention risk behaviours[a]		Model including in-detention risk behaviours[a]	
		OR	95% CI	OR	95% CI
Detention experience	None	Reference		Reference	
	Short and rare	1.39	1.04–1.86	1.31	0.97–1.76
	Short but frequent	2.08	1.43–3.02	1.83	1.25–2.67
	Long but rare	3.32	2.04–5.37	2.68	1.62–4.42
	Long and frequent	3.80	2.73–5.28	2.80	1.92–4.09
Age (years)	<25	Reference		Reference	
	25–39	1.48	0.94–2.34	1.54	0.97–2.45
	≥40	1.98	1.20–3.28	2.01	1.21–3.33
Sex	Male	Reference		Reference	
	Female	1.75	1.34–2.28	1.75	1.34–2.28
Region of birth	Germany	Reference		Reference	
	Western Europe	2.23	1.18–4.22	2.27	1.20–4.29
	Central Europe	0.84	0.50–1.40	0.81	0.48–1.35
	Former Soviet Union	2.69	1.82–3.98	2.77	1.86–4.13
	Middle East	0.85	0.49–1.45	0.88	0.51–1.51
	Other	0.31	0.11–0.91	0.31	0.10–0.90
Duration of injecting drug use (years)	≤2	Reference		Reference	
	3–10	3.34	2.00–5.55	3.31	1.99–5.52
	>10	5.01	3.04–8.27	4.76	2.88–7.85
Typical number of injections on an average injecting day	1	Reference		Reference	
	2–4	1.68	1.31–2.16	1.64	1.27–2.11
	≥5	2.36	1.70–3.27	2.25	1.62–3.12
Ever had non-professional tattoo/piercing while not in detention	No	Reference		Reference	
	Yes	1.38	1.07–1.77	1.39	1.08–1.79
In-detention risk behaviour					
Ever injected drugs in detention	No[b]			Reference	
	Yes			1.78	1.30–2.44
Ever had non-professional tattoo/piercing while in detention	No[b]			Reference	
	Yes			1.16	0.86–1.56

OR, odds ratio; CI, confidence interval.
[a] Model adjusted for study site.
[b] Category also includes never detained individuals.

Discussion

Main findings

This analysis found an association between detention experience and HCV exposure in a sample of active injecting drug users. Individuals with longer and more frequent detention experience were more likely to be positive for HCV, suggesting both the duration and the frequency of detention to be relevant aspects for the risk of acquiring this infection. Self-reported in-detention risk behaviours, such as injecting drug use and having a non-professional tattoo or piercing, could only partially explain the higher probability of positive HCV status among those with detention experience.

An important strength of this analysis is that it considered the duration and frequency of detention simultaneously, thus allowing the independent effects of both aspects to be observed. The total time spent in detention was clearly associated with the likelihood of being HCV-positive in this sample. As the time spent in detention increases, so does the probability of having injected drugs or having a non-professional tattoo or piercing done at some point during detention (Koulierakis et al., 2000). Both of these practices are known routes of HCV transmission, and injecting drug use in particular is thought to be the main driver of intramural spread of HCV (Butler et al., 2004; Vescio et al., 2008; Kinner et al., 2012).

Not all detained PWID inject drugs during their detention, but studies have shown that those who do are more likely to share injecting equipment than are PWID in the community (Dolan et al., 2010; Shewan et al., 1994), thereby increasing their risk of HCV infection. In the present study, it was found that the practice of either of these risk behaviours became more likely with increasing detention experience. It was also possible to show that these two behaviours partly explain the detention-associated risk of HCV, supporting the idea of intramural transmission. This finding, together with the increase in risk associated with detention frequency, also suggests that the increased risk of HCV among ever-detainees is not only caused by risk factors inside the detention facilities, but that further risks are contained in the broader process of detention.

This hypothesis is also proposed in a paper by Stone et al., based on a modelling exercise of the impact of incarceration on HCV transmission among PWID in Scotland (Stone et al., 2017). As each detention episode, regardless of duration, entails a transition of the individual from the community into custody and back again, the additional risk may arise from these transitions. A transition in either direction may lead to interruption of opioid substitution therapy (OST) for individuals in treatment, as specific arrangements for treatment continuation are often not in place and OST is not available in all detention facilities in Germany (Schulte et al., 2017). In detention facilities that do offer OST, a short sentence is sometimes applied as an exclusion criterion for OST access (Schulte et al., 2009). Both community- and prison-based OST have been shown to reduce injecting frequency and syringe sharing, whereas a cessation of OST results in relapse and risky behaviour being more likely (Platt et al., 2017; Hedrich et al., 2012). In an Australian prospective cohort study of male heroin users, Dolan et al. found that particularly those serving short prison sentences (<2 months) were likely to drop out of OST, which increased their risk of HCV seroconversion (Dolan et al.,

2005). Additionally, factors such as withdrawal, lack of a social network, and dealing with emotions regarding the recent detention may all possibly make unsafe use during the first period in detention more likely.

The first period upon release may also make risk-taking more likely, as this can be a particularly chaotic time for PWID, with housing and financial arrangements often lacking. In Germany, health care in prison is covered by a separate prison health system, and when released, the transfer of the detainee back into the regular health insurance system should occur seamlessly. However, due to bureaucratic barriers this transfer is often delayed, leaving the newly released individual uninsured and without access to OST and other health care services immediately upon release. In addition, there may also be an aspect of 'celebration' following release, which may include more risky behaviour. A Canadian study observed that individuals recently released from prison reported syringe sharing more frequently than those without recent prison experience (Milloy et al., 2009). Overall, cycling between community and custody may increase the risk of HCV infection through less continuity and more interruptions of OST and access to other harm reduction measures.

Limitations

This study has several limitations. Due to the way the data were collected, it was not possible to analyse the different detention forms separately (juvenile arrest/prison, pre-trial custody, prison, forensic commitment). The effects of frequency and duration may vary between these forms, but it was not possible to account for this in the analysis. Data on access and utilization of OST and other harm reduction services during detention episodes and transition periods were not collected and it was therefore not possible to investigate the effect of these on the risk of acquiring HCV. Data on further intramural risk factors (e.g., sharing of snorting tubes, razors, bloody fights, etc.) were also not collected and could not be corrected for in the second multivariable model. It is also possible that not all participants answered the question on injecting drug use in prison truthfully due to social desirability. Finally, the possibility that individuals with a higher HCV risk behaviour in the community are also more likely to be detained could not be excluded; e.g. with an increasing severity of addiction, both the injection frequency and the likelihood of drug-related crime, in order to support the addiction, may increase.

Conclusions and recommendations

Efforts are needed to improve the prevention of HCV transmission occurring throughout the detention process. Prevention measures such as needle and syringe exchange programmes and evidence-based drug dependence treatment, including OST, are known to reduce the risk of transmission of blood-borne viruses and are broadly used in the community. On the basis of the equivalence of care principle, these effective measures of prevention should also be made available to PWID in all German detention facilities. Further research is needed, particularly in order to better understand the risk increase associated with the transitions between detention and the community. A cohort study of PWID entering a detention facility, including a follow-up period upon release, would improve our understanding of the risks of contracting HCV and other blood-borne viruses that PWID in Germany are potentially exposed to throughout the process of detention, including the period post release. It would also allow the impact of successfully maintained or interrupted OST on the risk of infection to be estimated.

Furthermore, considering the high HCV prevalence observed among the participants with detention experience, detention facilities offer an important opportunity to counsel, test, and treat PWID. Opt-out HCV screening should be offered upon entry and thereafter on a regular basis, with a positive test result leading to treatment while in detention. Appropriate linkage to care upon release must also be provided in order to make sure that the patients can progress through the continuum of care, regardless of whether they are in custody or in the community. Since the introduction of the directly acting antivirals, with their high clearance rates, limited side-effects, and reduced treatment times, this now appears more feasible than ever.

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Ethical approval and consent to participate

Ethical approval was received from the Ethics Committee at the Charité University of Medicine, Berlin (Germany) in May 2011 and with an amendment approved on November 19, 2012 (No EA4/036/11). Although all participants provided written informed consent, no personal data allowing identification of the study participants were collected. The Federal Commissioner for Data Protection and Freedom of Information approved the study protocol on November 29, 2012 (III-401/008#0035).

Conflict of interest

Prof. Dr N. Scherbaum has received honoraria for several activities (advisory boards, lectures, manuscripts) from Abbvie, Medice, Reckitt-Benckiser/Indivior, and Sanofi-Aventis. During the last 3 years he has participated in clinical trials financed by the pharmaceutical industry. Dr Bremer is an unpaid expert on the coordination committee for the implementation of the HIV/STI/hepatitis strategy of the German Government. The remaining authors declare no conflict of interest.

Author contributions

MG performed the analysis and drafted the manuscript. SN and RZ critically reviewed the manuscript draft. RZ and UM designed the study. BW, SN, and MG were scientific coordinators of the study. VB provided expertise and support throughout the study. SR validated laboratory procedures for dried blood spot testing and analysed the samples during the pilot phase of the study in 2011. CTB and NB validated and performed laboratory testing from 2012 onwards. All authors and the DRUCK Study Group approved the final manuscript.

Appendix A.

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BRIEF REPORT Open Access

High prevalence of hepatitis C virus infection and low level of awareness among people who recently started injecting drugs in a cross-sectional study in Germany, 2011–2014: missed opportunities for hepatitis C testing

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Abstract

Background: In Germany, risk of hepatitis C virus (HCV) infection is highest among people who inject drugs (PWID). New injectors (NI) are particularly vulnerable for HCV-acquisition, but little is known about health seeking behaviour and opportunities for intervention in this group. We describe characteristics, HCV prevalence, estimated HCV incidence and awareness of HCV-status among NIs and missed opportunities for hepatitis C testing.

Methods: People who had injected drugs in the last 12 months were recruited into a cross-sectional serobehavioural study using respondent-driven sampling in 8 German cities, 2011–2014. Data on sociodemographic characteristics, previous HCV testing and access to care were collected through questionnaire-based interviews. Capillary blood was tested for HCV. People injecting drugs < 5 years were considered NI.

Results: Of 2059 participants with available information on duration of injection drug use, 232 (11% were NI. Estimated HCV incidence among NI was 19.6 infections/100 person years at risk (95% CI 16–24). Thirty-six percent of NI were HCV-positive (thereof 76% with detectable RNA) and 41% of those HCV-positive were unaware of their HCV-status. Overall, 27% of NI reported never having been HCV-tested. Of NI with available information, more than 80% had attended low-threshold drug services in the last 30 days, 24% were released from prison in the last 12 months and medical care was most commonly accessed in hospitals, opioid substitution therapy (OST)-practices, practices without OST and prison hospitals.

Conclusion: We found high HCV-positivity and low HCV-status awareness among NI, often with missed opportunities for HCV-testing. To increase early diagnosis and facilitate treatment, HCV-testing should be offered in all facilities, where NI can be reached, especially low-threshold drug services and addiction therapy, but also prisons, hospitals and practices without OST.

Keywords: HCV, PWID, New injectors, Hepatitis C testing, Germany

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Background

Chronic hepatitis C virus (HCV) infection can lead to liver cirrhosis, liver failure and hepatocellular carcinoma. Currently, no effective vaccine exists but infections can be cured with antiviral treatment. The WHO aims at eliminating viral hepatitis as a public health threat by 2030 [1] and Germany has committed to this elimination agenda. A joint strategy for HIV, hepatitis B/C and other sexually transmitted infections was published by the German Ministry of Health in 2016 [2]. Major obstacles to overcome include a high proportion of people who are not aware of their infection and, linkage to care [3].

Germany is a low prevalence country for HCV infection. In a population-based survey of the general adult population living in Germany conducted in 2008–2011, HCV-antibody prevalence was 0.3% and HCV-RNA prevalence 0.2% [4]. People who inject drugs (PWID) are underrepresented in this survey and account for nearly 80% of newly diagnosed HCV infections notified in Germany with information on the mode of transmission [5].

Several studies have found HCV incidence to be highest in the first years of injection drug use (IDU) [6, 7], but little is known about the health seeking behaviour and opportunities for intervention in people who recently began injecting drugs, which in the following are referred to as "new injectors" (NI). Therefore, we analysed data from a cross-sectional study among PWID in Germany to describe HCV prevalence, estimated incidence and missed opportunities for HCV-testing and promotion of prevention measures in this group, with a focus on settings that could be used to reach NI in Germany and similar countries.

Methods

We analysed data from the DRUCK-study, a cross-sectional study conducted between 2011 and 2014 using respondent-driven sampling to recruit PWID that had injected drugs in the last 12 months in one of eight German cities (Berlin, Essen, Leipzig, Munich, Frankfurt, Hanover, Hamburg, Cologne). Data on sociodemographic characteristics, previous HCV testing and access to care were collected through questionnaire-based face-to-face interviews. Capillary blood was tested for HCV antibodies and RNA. More detailed methods and the full study protocol have been published elsewhere [8, 9]. To capture all participants who had been exposed to HCV, we defined participants with detectable HCV antibody and/or HCV-RNA as HCV-positive for this analysis.

We defined NI as people injecting drugs for less than 5 years and long-term injectors (LI) as people injecting drugs for 5 years or longer.

Stata version 15.1 was used to carry out statistical analyses. X^2-tests were performed and odds ratios using univariable logistic regression were calculated to compare groups.

Assuming that all participants were HCV-negative before they began injecting drugs, we estimated HCV incidence among NI as follows: date of study participation, month and year of birth and age when IDU was initiated was collected. Using stochastic simulation and assuming uniform distribution, we simulated the (unknown) month injection drug use was initiated and the (unknown) later time point HCV infection occurred based on 200 realisations in each case. For each realisation, we performed a bootstrap to account for the sampling error and characterised the resulting probability distribution by its mean and the 2.5 and 97.5 percentiles.

Results

Of 2077 participants that provided a blood sample, information on duration of IDU was available for 2059 of whom 232 (11%) were NI (range 8.1% in Cologne (former West Germany) - 19.8% in Leipzig (former East Germany)).

Of NI, 31% were female, 27% were first-generation migrants and 22% reported being homeless (defined as reporting living on the streets or in homeless shelters as main residence in the last 12 months).

Compared to LI, NI were significantly older at the time of initiation of IDU, were significantly less likely to have injected cocaine and significantly more likely to have injected methamphetamines (mainly in Leipzig) in the last 30 days. We did not find any significant differences in unsafe drug injecting behaviour in the last 30 days between LI and NI.

In study cities with syringe vending machines, NI were significantly more likely than LI to have used them to obtain sterile injecting equipment in the last 30 days (53% vs 38%, $p = 0.006$) and to mention them as their main source of sterile syringes and needles (28% vs 16%, $p = 0.004$).

For a detailed comparison of NI and LI see Table 1.

HCV-status, history of HCV-testing and awareness of HCV positivity

Of 2077 participating PWID, 66% ($n = 1361$) were HCV-positive: 22% ($n = 457$) were anti-HCV-positive and RNA-negative, 41% ($n = 857$) anti-HCV and RNA-positive, 2.3% ($n = 47$) anti-HCV-negative and RNA-positive. Prevalence of HCV-antibody and/or RNA positivity was 36% in NI and increased with duration of IDU, reaching 72% in participants injecting drugs for 10 years or longer. NI were less likely to be HCV-positive (36% vs 70%, $p < 0.0001$), but among HCV-positives, a higher proportion of NI had detectable HCV-RNA (76% vs 66%, $p = 0.06$); while proportions of NI and LI with chronic infection (anti-HCV-

Table 1 Sociodemographic characteristics, drug injection behaviour and HCV-status, awareness and testing experience of PWID participating in the German DRUCK-study 2011–2014 by duration of injection drug use

	Injecting drugs < 5 years (*N* = 232)		Injecting drugs ≥ 5 years (*N* = 1827)		*p*
	n	Proportion[k] (%)	*n*	Proportion[k] (%)	
Sociodemographic characteristics					
Female	73	31.5	403	22.1	0.001**
Age ≤ 25 years	71	30.6	62	3.4	< 0.001***
2nd-generation migrant[a]	26	11.2	273	14.9	0.128
1st-generation migrant[b]	63	27.2	393	21.5	0.051
Did not graduate from school	46	19.8	250	13.7	0.012*
A-level	23	9.9	182	10.0	0.982
Main place of residence in the last 12 months (max 2 entries)					
Own flat	111	48.1	1040	57.5	0.006**
With family or friends	57	24.7	297	16.4	0.002**
Homeless, staying in shelters	50	21.7	258	14.3	0.003**
Ever homeless[c]	132	57.1	1226	67.3	0.002**
Ever in prison	143	61.9	1518	83.3	< 0.001***
Released from prison in the last 12 months[d]	37	24.3	332	24.2	0.965
Sources of income in the last 12 months					
Job (including unemployment benefit I)	61	26.4	384	21.2	0.069
State benefits	171	74.0	1548	85.3	< 0.001***
Selling newspapers, begging, dealing	110	47.6	673	37.1	0.002**
Sex work	17	7.4	60	3.3	0.002**
Injection behavior					
Age at first injection < 18 years	19	8.2	623	34.1	< 0.001***
Injecting daily in the last 30 days	63	34.2	452	30.1	0.244
Substance injected in the last 30 days[f]					
Heroin	130	56.0	1109	60.8	0.165
Cocaine	73	31.5	752	41.2	0.004**
Crack	10	4.3	98	5.4	0.504
Speed (amphetamines)	11	4.7	60	3.3	0.254
Crystal (metamphetamines) [g]	17	7.4	64	3.5	0.005**
Substance consumed in the last 30 days					
Heroin	180	77.6	1355	74.3	0.217
Cocaine	95	41.0	908	49.8	0.011*
Crack	54	23.4	461	25.3	0.534
Speed (amphetamines)	49	21.1	234	12.8	0.001**
Crystal (metamphetamines)[g]	23	10.0	97	5.3	0.005**
Most common setting of drug injection in the last 30 days[h]					
Alone at home[e]	76	42.2	678	45.4	0.425
In consumption room[e,i]	24	27.6	195	31.9	0421
With good acquaintances[e]	75	41.2	484	32.4	0.017*

Table 1 Sociodemographic characteristics, drug injection behaviour and HCV-status, awareness and testing experience of PWID participating in the German DRUCK-study 2011–2014 by duration of injection drug use *(Continued)*

	Injecting drugs < 5 years (*N* = 232)		Injecting drugs ≥ 5 years (*N* = 1827)		*p*
	n	Proportion[k] (%)	*n*	Proportion[k] (%)	
With steady partner[e]	24	13.3	241	16.1	0.317
With hardly known or unknown people[e]	15	8.3	125	8.4	0.984
Unsafe use in the last 30 day[h]					
Used used needles or syringes	19	10.4	133	8.8	0.482
Used water from a shared container	45	24.7	316	21.4	0.302
Used used spoons or filters	40	22.1	280	18.7	0.268
Source for sterile needles and syringes in the last 30 days[h]					
Low threshold services	115	62.2	1069	70.2	0.025*
Syringe vending machine[j]	48	52.8	290	37.9	0.006**
Pharmacy (bought)	67	38.2	656	44.1	0.142
Access to addiction therapy					
Ever in detoxification	143	61.6	1517	83.2	< 0.001***
Ever in weaning/rehabilitation program	80	34.5	1004	55.1	< 0.001***
Ever in outpatient substitution therapy	126	54.3	1532	84.0	< 0.001***
Currently in outpatient substitution therapy	68	29.3	945	51.8	< 0.001***
HCV status, awareness and testing experience					
HCV positive	83	35.8	1270	69.5	< 0.001***
Detectable HCV-RNA	63	27.2	836	45.8	< 0.001***
Of HCV positive: Unaware of HCV positive status	33	40.7	157	12.6	< 0.001***
Ever tested for HCV	153	73.2	1653	93.6	< 0.001***
Report negative HCV test, last test > 12 months ago	32	36.8	135	38.8	0.730

[a]Born in Germany, mother and/or father born abroad
[b]Born outside of Germany
[c]Defined as reporting living on the streets or in homeless shelters as main residence in the last 12 months
[d]Not asked in Berlin, Essen
[e]Last 30 days
[f]Substance consumed in last 30 days and most common mode of consumption injection
[g]Methamphethamine use was concentrated in Leipzig (East Germany) and to a lower extent in Munich (South Germany), while it played almost no role in other study cities
[h]Only answered if participants injected drugs in the last 30 days
[i]Information available for Essen, Berlin, Hamburg; reported use of drug consumption rooms varied widely between cities: highest use in Hamburg (> 60% reported by NI and LI), lowest use in Berlin (< 10% reported by NI and LI)
[j]Exist in Berlin, Essen, Cologne, Munich
[k]of responding participants
*$p < 0.05$
**$p < 0.01$
***$p < 0.001$

positive, detectable RNA) were comparable (58% vs 63%, $p = 0.31$), the proportions of recent infections (anti-HCV-negative, detectable RNA) were significantly higher in NI (18.1% vs 2.4%, $p < 0.0001$).

HCV positivity among NI was lowest in Leipzig and Munich (both 20%) and highest in Hamburg (58%).

Estimated HCV incidence among NI was 19.6 infections/100 person years at risk (95% CI 16–24); if only participants injecting less than 2 years were considered, estimated incidence was 36.4 infections/100 person years at risk (95% CI 21–56).

NI were less likely to ever have been tested for HCV (73% vs 94%, $p < 0.0001$) and if HCV positive, more likely to be unaware of their HCV status (41% vs 13%, $p < 0.0001$). Reported testing experience among NI was lowest in Leipzig (38%) and in the other study cities ranged between 67% (Cologne) and 89% (Hamburg).

Uptake of medical care and addiction services: access points used by NI

In order to identify ways to reach NI, this part of the analysis focuses on NI.

Medical care was accessed by 82% of NI ($n = 192$) within the last 12 months. Most commonly mentioned last access points were practices without addiction services (31%, 58/186), practices offering opioid substitution therapy (OST, 30%, 55/186), hospitals (27%, 50/186) and prison hospitals (6.5%, 12/186).

Release from prison in the last 12 months was reported by 24% (37/152 with information, not asked in 2 study cities).

At the time of study, 75% of NI had already received at least one form of addiction therapy: 62% had ever received inpatient detoxification, 54% OST, thereof 29% currently and 34% had ever received long-term addiction therapy (93% as inpatient).

Information on last visit to low threshold drug services was collected in 5 study cities; in those 83% (105/127) reported attendance in the last 30 days.

Previous HCV testing among NI

Of NI that reported previous HCV-testing, 85% (130/153) provided details on the place where this was performed; the five most commonly mentioned places were practices providing OST (35%, 45/130), hospitals (33%, 43/130), practices without addiction services (14%, 18/130), low threshold drug services (8.5%, 11/130) and prisons (8.5%, 11/130).

Of 56 NI (27%) that reported never having been tested for HCV, 29% ($n = 16$) were HCV-positive. Previous access to addiction services was reported by 57%: 46% had been in inpatient detoxification, 27% in long-term addiction therapy programs and 27% in outpatient OST, thereof 18% currently (see Table 2). At least 21 NI without self-reported HCV testing experience had attended low-threshold drug services in the last 30 days (75%, 21/28 with information).

In the preceding 12 months, 24% (10/41 with information) were released from prison and 79% had sought medical care; most commonly mentioned points of contact were hospitals (40%) and practices without addiction services (37%).

Reported HCV testing experience was higher in females (78% vs 71%, $p = 0.33$), first-generation migrants (29% vs 21%, $p = 0.25$) and NI living in their own accommodation (52% vs 41%, $p = 0.16$); however, differences were not statistically significant (Table 2).

Significantly lower testing experience was reported from NI younger than 25 years (OR in univariable analysis 2.2, 95% CI 1.2–4.2) and those injecting amphetamines or methamphetamines (OR in univariable analysis 4.3, 95% CI 1.8–10.1).

Although low threshold drug services were the most commonly reported source of sterile needles and syringes, NI that denied previous HCV testing were significantly less likely to report them as source (46% vs 67%, $p = 0.01$) and were more likely than NI with testing experience to obtain their syringes and needles from syringe vending machines (36% vs 25%, $p = 0.3$) and pharmacies (26% vs 18%, $p = 0.2$) (Table 2).

NI without OST experience were less likely to ever have undergone HCV testing (56% vs 87%, $p < 0.0001$). They had a shorter duration of IDU (median 2 vs 3 years, $p = 0.02$), a lower HCV prevalence (27% vs 43% with OST, $p = 0.014$) and most commonly accessed medical care in practices without OST (51%), hospitals (26%) and prisons (10%).

HCV-positive NI that last accessed medical care in hospitals were more likely to be unaware of their HCV infection than those that last accessed care in OST-practices (OR 9.9, 95% CI 2.2–43).

Discussion

We found high HCV positivity and low awareness of HCV-positive status among participating NI. Among NI-estimated HCV incidence was 19.6/100 person years at risk, comparable to the estimated incidence among NI in New York 2000/2001 and slightly lower than in Catalonia 2010/2011 (18 and 25/100 person years at risk, respectively; both using a similar definition of NI, [10, 11]). Estimated HCV incidence was higher in study participants with IDU below 2 years (36/100 person years at risk), supporting that HCV infection often occurs early after initiation of IDU.

HCV prevalence was more than 100-times higher in NI than in a representative study of the "general adult population in Germany" and more than 220-times in LI [4]. Given that seroprevalence increases with time of IDU, it is especially important to reach NI with prevention measures and early HCV-testing.

Studies suggest that awareness of HCV positivity is associated with sustained protective behavioural changes, for example reducing injection risk behaviour [12, 13]. Awareness is a prerequisite for being linked into care and receiving antiviral treatment. Additionally it provides an opportunity for counselling around safer injection practices and linkage to effective prevention measures like OST, needle exchange and other harm reduction services.

In our study, more than 40% of HCV-positive NI were unaware of their HCV status, often with missed opportunities for HCV testing.

More than 50% of NI that reported never having been tested for HCV had previously been in contact with addiction therapy, many in an inpatient setting or in the form of OST, which involves regular engagement with services.

Table 2 HCV-status, awareness, injection behaviour and access to addiction and medical care of new injectors by self-reported HCV-testing experience prior to study

	Reported previous HCV-test (*N* = 153)		Reported no previous HCV-test (*N* = 56)		*p*
	n	%[i]	*n*	%[i]	
Sociodemographic characteristic					
Female	49	32.0	14	25.0	0.327
Age 25 years	39	25.5	24	42.9	0.015*
1st-generation migrant[a]	45	29.4	12	21.4	0.251
2nd-generation migrant[b]	13	8.5	6	10.7	0.621
Mainly homeless, staying in shelters[c]	31	20.4	17	30.4	0.130
Ever in prison	94	61.8	36	64.3	0.747
Released from prison in the last 12 months[d]	22	23.2	10	24.4	0.876
HCV status					
HCV-positive	64	41.8	16	28.6	0.081
Detectable HCV-RNA	47	30.7	14	25.0	0.421
Of HCV-positive: unaware of HCV-positive status	14	22.6	16	100.0	< 0.001***
Access to addiction therapy					
Drug addiction ever treated	128	83.7	32	57.1	< 0.001***
Ever in detoxification	105	68.6	26	46.4	0.008**
Ever in weaning/rehabilitation program	60	39.2	15	26.8	0.097
Ever in outpatient substitution	101	66.0	15	26.8	< 0.001***
Currently in outpatient substitution	52	34.0	10	17.9	0.024*
Sought medical care within the last 12 months	127	83.0	44	78.6	0.462
If accessed medical care within 12 months: last access point					
Hospital	25	20.2	17	39.5	0.012*
Practice without addiction services	37	29.8	16	37.2	0.371
Practice with OST	44	35.5	6	14.0	0.008**
Detention facilities (prison hospital)	11	8.9	1	2.3	0.152
Low threshold drug services	4	3.2	1	2.3	0.765
Rehabilitation	2	1.6	1	2.3	0.762
Local public health office	1	0.8	1	2.3	0.430
Main source for sterile needles and syringes in the last 30 days					
Low threshold services	80	67	21	46	0.011*
Bought in pharmacies	21	18	12	26	0.224
Syringe vending machine[e]	16	25	8	36	0.325
Visited low threshold drug services in the last 30 days[f]	77	88	21	75	0.112
Drug injection behaviour in the last 30 days[g]					
Injected drugs	126	82.4	47	83.9	0.789
Daily injection	46	36.8	13	27.7	0.260
Injection of heroin	93	60.8	26	46.4	0.063
Injection of cocaine	55	36.0	13	23.1	0.082
Injection of crack	8	5.3	2	3.6	0.613
Injection of amphetamines	7	4.6	4	7.1	0.462

Table 2 HCV-status, awareness, injection behaviour and access to addiction and medical care of new injectors by self-reported HCV-testing experience prior to study *(Continued)*

	Reported previous HCV-test (*N* = 153)		Reported no previous HCV-test (*N* = 56)		*p*
	n	%[i]	*n*	%[i]	
Injection of methamphetamines[h]	5	3.3	11	19.6	< 0.001

[a]Born in Germany, mother and/or father born abroad
[b]Born outside of Germany
[c]Defined as reporting living on the streets or in homeless shelters as main residence in the last 12 months
[d]Not asked in Berlin, Essen
[e]Substance consumed in the last 30 days and most common mode of consumption injection
[e]Exist in Berlin, Essen, Cologne, Munich
[f]Not asked in Berlin, Essen, Leipzig
[g]Substance consumed in the last 30 days and most common mode of consumption injection
[h]Consumption of methamphethamine was concentrated in Leipzig (East Germany) and to a lower extent in Munich (South Germany), while it played almost no role in other study cities
[i]of responding participants
$^{*}p < 0.05$
$^{**}p < 0.01$
$^{***}p < 0.001$

Engagement in addiction therapy is an important opportunity for HCV testing that should not be missed.

As could be shown in other studies, we found that NI engaged in OST were more likely to have been tested for HCV than those not receiving OST [14]. However, focusing on OST facilities, does exclude non-opioid dependent PWID and NI that are not (yet) linked to these services.

NI in our study often accessed medical care in hospitals or primary care without focus on addiction care and OST.

In the context of acute medical presentation in hospitals, HCV screening and discussion of test results are challenging. Although an American pilot study showed that emergency room-based HCV testing focused on PWID could be successfully integrated into clinical practice, finding a high prevalence of HCV, the study also encountered significant challenges linking those found to be HCV-positive to care [15]. Nevertheless, testing in emergency departments could at least help improve the level of awareness of one's HCV-status, a first step in the cascade of care. Opt-out testing for blood borne viruses including HCV reduces barriers and stigma around testing; in several emergency department-based studies, it was feasible and identified unknown HCV-infections [16, 17]. However, implementing routine screening policies in emergency rooms has rarely been attempted in Germany and will face considerable financial and logistical challenges.

Primary medical care is another setting that provides opportunities for HCV-testing. This should be enhanced for example through increasing awareness among physicians and decreasing barriers e.g. through on-site testing [18] or opt-out testing [19].

Low threshold drug services are important needle/syringe exchange sites in Germany. They were frequented by a high proportion of NI making them ideal places for integrated testing. Unfortunately—and in contrast to many other countries—in Germany, it is required that a physician is on-site when HCV-testing is performed and test results are given, which currently greatly limits feasibility for testing in this setting. Training non-physician providers to perform testing could increase feasibility and uptake of HCV-testing and has been successfully employed in other countries e.g. Scotland [20].

Other alternatives might be targeted distribution of HCV self-test kits in low threshold drug services or through vending machines, which would require legal changes (HIV self-tests are currently freely available, but HCV self-tests are not).

In the UK and in the USA, distribution of HIV self-tests through vending machines at venues frequented by gay men is being explored [21, 22]. To our knowledge, this has never been tested for PWID, but since they are used to vending machines for clean injection equipment, it might be worth studying acceptance and use of providing access to HCV self-test kits through vending machines for PWID.

Pharmacies, as the other important supplier of sterile injection equipment, currently play no role in other aspects of the HCV care cascade in Germany. However, studies from other countries suggest that they can be valuable and successfully offer and enhance HCV-testing, linkage to specialist care and even provide treatment [23–25]. Pharmacies could also be a source to access (free or subsidised) HCV self-tests.

In our study, if available, syringe vending machines were an important source for syringes and needles for NI and were more frequently used by NI with shorter duration of IDU.

This finding is in line with a previous study among PWID in Berlin, that users of vending machines often reported a shorter duration of IDU [26]. The authors suggest that in the first time after initiation of IDU, PWID might prefer to obtain their injection equipment anonymously and may not (yet) be willing to visit other

drug services [26]. French data showed that vending machines were used by younger PWID, that were hardly reached by other syringe programs [27]. Although they do not facilitate HCV-testing or support NI in other aspects of harm reduction, syringe vending machines are a valuable prevention measure, supplying sterile injection equipment around the clock.

Almost 25% of NI that reported no previous HCV testing had been in prison in the last 12 months. PWID are overrepresented in prison populations worldwide, making prisons suitable settings to deliver HCV prevention (and care) interventions, including HCV-screening [28–30]. According to a review and a cross-sectional survey, measures in European prisons are currently inadequate and need to be scaled up [28, 29]. Universal opt-out HCV-screening in prisons was found to be cost-effective and able to reduce HCV transmission in an American study [31]. It has been introduced in California [32] and has increased screening uptake among prisoners in England [33].

Homelessness was reported by more than 20% of NI in our study, comparable to the findings of a very similar study of NI in Catalonia [10]. Unstable housing has been found to be a risk factor for HCV infection among PWID in Vancouver [34], and in Puerto Rico, homeless PWID were significantly more likely to engage in high-risk injection behaviour than other PWID [35]. There is experience e.g. from London on how to reach the homeless population with HCV services [36, 37] .

Conclusion

It is important that HCV-counselling and testing are not restricted to medical addiction care, especially for NI. It should be offered in all facilities or settings where NI can be reached, including hospitals and primary medical care, prisons and needle/syringe exchange sites, especially low-threshold drug services. To reach HCV elimination goals and increase feasibility of HCV-testing in the setting of low-threshold drug services which are frequented by the majority of NI, consideration should be given to allow trained non-physician providers to conduct HCV testing. Feasibility and acceptability of HCV self-testing for PWID should be explored.

Limitations

The number of NI was small, so results have to be interpreted with caution. HCV-testing experience was self-reported; it is therefore possible that participants have been tested without their knowledge or that recall was incorrect. If participants reported no previous HCV-testing, reasons for this were not explored, so we cannot rule out that a test was offered but not accepted. Most seeds (initial study participants selected as recruiters/who "initiate sampling chains") were recruited through low-threshold drug services which were also used as study sites; this might have led to overestimation of contact with low-threshold drug services in some of the cities. As this was a cross-sectional study, we cannot draw conclusions on causality. There were regional differences in the size and characteristics of the population and as the population of NI is unknown, our sample might not be representative of all new injectors in Germany. Nevertheless the DRUCK study is the first large bio-behavioural study of current PWID in Germany and provides valuable information about characteristics of this group.

Abbreviations

HCV: Hepatitis C virus; IDU: Injection drug use; LI: Long-term injectors (injecting drugs for 5 years or more); NI: New injectors (injecting drugs for less than 5 years); OST: Opioid substitution therapy; PWID: People who inject drugs

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Authors' contributions

JE performed the analysis and drafted the manuscripts, supported by RZ, SN and MG. RZ and UM designed the study. BW, SN and MG were scientific coordinators of the study. VB provided expertise and support throughout the study. SR and team validated and tested samples from dried blood spots during the pilot study. All authors critically reviewed the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets generated and analysed during the current study are not publicly available to protect research participants' privacy.

Ethics approval and consent to participate

Ethical approval was received from the ethics committee at Charité University Hospital, Berlin, Germany, in May 2011 and with an amendment approved on 19 November 2012 (No EA4/036/11). All participants provided a written informed consent. No personal data allowing identification of study participants was collected. The Federal Commissioner for Data Protection and Freedom of Information approved the study protocol on 29 November 2012 (III-401/008#0035).

Consent for publication
Not applicable.

Competing interests
Prof. Dr. N. Scherbaum received honoraria for several activities (advisory boards, lectures, manuscripts and educational material) by the factories Abbvie, Hexal, Janssen-Cilag, Lundbeck, MSD, Medice, Mundipharma, Reckitt-Benckiser/Indivior and Sanofi-Aventis. During the last 3 years, he participated in clinical trials financed by the pharmaceutical industry. The other authors declare no competing interests.

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Publisher's Note

10. CV for Stine Nielsen

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

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11. Complete list of publications

Stine Nielsen ORCID ID: 0000-0002-5931-5379. Publications listed in reverse chronological order.

1. Nielsen S, Hansen JF, Hay G, Cowan S, Jepsen P, Omland LH, Krarup HB, Søholm J, Lazarus JV, Weis N, Øvrehus A, Christensen PB: *Hepatitis C in Denmark in 2016 - an updated estimate using multiple national registers*. PLOS ONE 15(9). Sept 2020. https://doi.org/10.1371/journal.pone.0238203
   Impact factor: 2.87
2. Sperle I, Nielsen S, Gassowski M, Naneva Z, Perchemlieva T, Amato-Gauci AJ, An der Heiden M, Bremer V, Golkocheva-Markova E, Hristov K, Kaneva E, Simeonova Y, Tenev T, Varleva T, Duffell E and Zimmermann R: *Prevalence of hepatitis C in the adult population of Bulgaria: a pilot study*. BMC Res Notes 13, 326. July 2020.
   Impact factor: 1.34
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4. Gassowski M, Nielsen S, Bannert N, Bock CT, Bremer V, Ross RS, Wenz B, Marcus U, Zimmermann R and the DRUCK study group: *History of detention and the risk of hepatitis C among people who inject drugs in Germany* Int. Journal of Infect Dis, vol 81; 100-106. Jan 2019
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5. Zimmermann R, Marcus U, Nielsen S, Wenz B, Gassowski M, Bremer V and the DRUCK-Study group: *Wissen und Informationsbedarfe von Drogengebrauchenden zu Hepatitis B, C und HIV*. Suchtmed 21(2): 111–117. 2019 [in German]
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