Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Predictors of hepatitis B vaccination completion among people who use drugs participating in a national program of targeted vaccination

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ARTICLE INFO

Article history:
Received 12 April 2018
Received in revised form 13 July 2018
Accepted 17 July 2018
Available online xxxx

Keywords:
Hepatitis B
Vaccination
High-risk group
People who use drugs

ABSTRACT

Background: Targeted vaccination strategies are necessary to prevent people who use drugs (PWUD) becoming infected with hepatitis B virus (HBV). The aims of this study were to provide an overview of the activities for PWUD in a decentralised vaccination program in the Netherlands and to explore the determinants associated with completing a standard hepatitis B vaccination series.
Methods: We used data for behavioural risk groups from the register of the national vaccination program. The data concerned PWUD who were immunised against hepatitis B in the Netherlands between 2002 and 2011. A standard series of three vaccinations (at 0, 1, and 6 months) was offered at inclusion and was continued if serological markers for past or chronic HBV infection were absent. Completion of a vaccination series (at least three vaccinations, irrespective of timing) was a dependent variable in our logistic regression analysis.
Results: The program reached 18,054 PWUD. Of the 15,746 participants eligible for vaccination (i.e. they were neither carriers of hepatitis B nor immune to hepatitis B), 9089 (58%) completed a series of three hepatitis B vaccinations. Factors associated with a higher completion rate of a vaccination series ($p < 0.01$) were: starting vaccination in the earlier years of the program, older age of PWUD, intravenous drug use, vaccine administration by addiction care centres, and flexibility in location of vaccine delivery.
Conclusion: Despite using a standard HBV vaccination schedule and no financial incentives, vaccination completion among PWUD was relatively high. Our results suggest that flexibility of vaccination location and administration of vaccines by healthcare workers with sustainable contact with PWUD could improve vaccination programs for this risk group.

1. Introduction

Western industrialised countries have implemented several vaccination strategies against hepatitis B to reduce the incidence of acute and chronic infection with hepatitis B virus (HBV). Universal vaccination, vaccination targeting specific high-risk groups, and a combination of both were strategies mostly implemented during the 1990 s [1,2]. Only the four Scandinavian countries have not yet included universal hepatitis B vaccination in childhood vaccination programs. The immunological effects of childhood programs will take several decades to protect an adult population against HBV infection because not all countries have augmented childhood vaccination with a catch-up program for youth and adolescents [2–5]. Incomplete coverage can limit the impact of starting targeted and universal vaccination programs 'early'. HBV transmission is ongoing in high-risk groups in the United States and Germany despite the introduction of targeted and universal vaccination in the 1980 s and the period 1990–1995 [6,7]. Consequently, targeted vaccination of adults at risk of HBV infection remains essential in many western countries to reduce further transmission [8,9–10].

In low endemic countries, virus transmission of acute hepatitis B cases occurs mainly through sexual contact in groups with high-risk behaviour such as men who have sex with men (MSM) or through the re-use of needles or other objects contaminated with infected blood either in a healthcare setting or among people who inject drugs (PWID). The latter is the fourth leading cause of

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https://doi.org/10.1016/j.vaccine.2018.07.045
0264-410X/

transmission and accounts for 11.3% of the acute cases in the European Union and the European economic area [4,11]. Despite strong regional differences, increasing evidence suggests that the prevalence of hepatitis B surface antigen (HBsAg) is considerably higher among PWID than in the general population. A recent German study reports a prevalence five times as great among PWID as in the general population [12,6,13]. Among people who use drugs (PWUD), the risk of infection with HBV is not only limited to people who inject drugs. Non-injecting PWUD have an increased risk of HBV infection as well, primarily via high-risk sexual behaviour [14–18]. Frequent co-infection in PWUD of HBV and HIV or HCV often results in more severe liver related morbidity [17,19]. The increased seroprevalence and disease burden urges for better prevention strategies against hepatitis B in this high-risk group.

Due to the low prevalence of HBV in the Dutch general population, the Netherlands implemented after a two-year pilot period a vaccination strategy targeting hepatitis B in high-risk behavioural groups in 2002, prior to implementing a universal childhood vaccination program in 2011. Initially, four groups were targeted: MSM, PWUD, commercial sex workers and heterosexuals with multiple sexual contacts. In 2007, heterosexuals with multiple sexual contacts were excluded due to their low prevalence of HBV infection. By the end of 2011, the program also stopped targeting PWUD because of the low prevalence of past and chronic HBV infection, no ongoing transmission of HBV strains associated with PWID, and a declining number of PWID in the Netherlands [20,21].

For this study we looked at PWUD in the targeted HBV-vaccination program. Participation of this high-risk group in vaccination programs can be poor because of possible debts, unstable housing situations, stigma related to drug use and hepatitis B [1,22–24] and opportunities that various organisations have missed [6,25]. Besides participation, as a measure of a program's reach, factors associated with improving vaccination series completion are equally important to effectively protect a high-risk population against hepatitis B.

This study presents an overview of one decade of the activities for PWUD in the national HBV vaccination program for Dutch risk groups and reports on factors associated with completing a standard series of three vaccinations against HBV.

2. Methods

2.1. Study population and data collection

Recruiting organisations entered participant and vaccination data in a national web-based database using a structured questionnaire. We extracted data for this observational retrospective study from this web-based database where vaccination data were stored anonymously. The web-based design enabled all participating organisations to access these data, which facilitated completing vaccination series for participants at various organisations (such as prisons and addiction care facilities). A person was categorised in this database as PWUD depending on his/her reported behavioural risk (at least drug use) and the location of received vaccinations. People who used any of the following drugs were eligible for vaccination: heroin, base coke/crack, cocaine, amphetamine or methadone regardless of the administration route (by injection and/or not). People using recreational drugs (e.g. ecstasy) were not eligible for hepatitis B vaccination in the program. If a person's behavioural risk was restricted to drug use, he/she was categorised as PWUD irrespective the location of vaccination. Anyone with other behavioural risk factors besides drug use was categorised as a PWUD if he/she received vaccinations at a prison or addiction care facility. All PWUD who met these criteria were included for analysis if their first vaccination visit was registered between 1 January 2002 and 31 December 2011.

The common database provided information about the location and region of vaccination, number of hepatitis B vaccinations, hepatitis B serology (antibodies to hepatitis B core antigen (anti-HBc) and/or HBsAg), and baseline characteristics: age, gender, method of drug use and previous or current activities in commercial sex work.

2.2. Recruitment sites

Addiction care in the Netherlands is characterised by low threshold care ranging from detection of substance abuse to treatment and rehabilitation. All public health services (PHS) in the Netherlands cooperated regionally with addiction care facilities, homeless shelters and prisons to offer a standard series of hepatitis B vaccination (0,1, and 6 months), free of charge at the locations mentioned. Local policy of organisations determined the extent of training of professionals for this program and cooperation between organisations. A yearly exchange of the program's best practices was nationally organised for all participating organisations. Outreach activities (e.g. vaccination at methadone outlets or syringe exchange programs) were included in the program to inform and vaccinate participants, as well as to optimise the uptake. The participants who finished the vaccination series could receive an incentive (such as a pocket radio; no financial incentives were given) depending on organisation's policy. For the aims of the study, the organisation *responsible* for administering vaccination was registered as the organisation of vaccine delivery. The *location* of vaccination was not necessarily a location of that same organisation. For example, a health worker from a PHS could administer a vaccine series at an addiction care facility.

2.3. Procedures

During the first visit, each participant received his/her first vaccination and health workers took a venous blood sample that was sent to a regional laboratory to assess the HBsAg and anti-HBc as serological markers of a possible hepatitis B infection. Evaluation of a serological profile of hepatitis B can be complex due to declining antibodies, false-positive results or an occult HBV infection [26]. In short, no further vaccination was offered to a person who was positive to anti-HBc and HBsAg (classified as carrier of hepatitis B) or who was anti-HBc positive and HBsAg negative (classified as immune to hepatitis B). Carriers of hepatitis B were referred to standard health care for evaluation of the chronic hepatitis B infection. The main purpose of this public health program was to increase immunity to HBV in PWUD and to stop possible spill over to other risk groups. Therefore antibodies against HBsAg from individual participants were not routinely tested after vaccination to assess HBV immunity.

2.4. Ethical approval

The data were obtained from anonymous digital records in a fully de-identified manner and none of the researchers had access to patient identifying information. The study protocol was therefore exempt from formal medical-ethical approval under the prevailing Dutch laws because this is a retrospective observational study using anonymous data only.

2.5. Statistical analysis

The primary outcome was successful vaccination against hepatitis B, defined as completion of a series of at least three vaccinations, irrespective of the timing of the vaccine administration. Vaccination completion rates were computed only for participants

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eligible for further vaccination (HBV carrier and those immune to hepatitis B were ineligible). The time between the first and third vaccinations was expressed in months with an interquartile range (IQR). Participant characteristics per onset year of vaccination were compared using a *t*-test or chi-square test. We used logistic regression analyses with completion of a vaccination series as a dependent variable for calculating the odds ratio (OR) and 95%CI of the independent variables. Variables that were significantly associated with the outcome variable (vaccination completion) at the p 0.10 level in a bivariate analysis were entered in a multivariable analysis. A significance level of a p value < 0.01 was considered significant in the multivariable analysis. We used SPSS version 22 (IBM, Armonk, NY, USA) for the statistical analyses.

3. Results

The program reached more than 18,000 people who use drugs. Table 1 shows their characteristics. Of the 18,054 participants, 2302 participants (12.8%) had positive anti-HBc blood tests. In this group, 134 persons had detectable HBsAg (5.8%; 0.7% overall). A total of 6.3% of the participants reported that they had injected drugs in the past or last 6 months.

More than half of the participants (N = 9592) started their vaccination series at the location of an addiction care facility. However, PHSs organised and administered most vaccination series (N = 9410), followed by addiction care (N = 5478) (Table 2). A total of 17,816 participants (98.7%) received their first vaccination. Of the 15,746 participants eligible for vaccination, 12,683 (80.5%) and 9089 (57.7%) received the second and third vaccinations, respectively. Only a minority (<100 participants) received more than three vaccinations.

The median time to completion was 7.1 months, (IQR 6.2–9.9) for a standard series. The vaccination completion rate gradually dropped from 74.7% in 2002–2003 to 41.3% in 2010–2011. The participants who started in 2002–2003 differed significantly from those who started in 2010–2011 in age, intravenous drug use, anti-HBc, and HBsAg serology. Over time the proportion of intravenous drug use (currently or in the past) declined from 12.9% to 3% (Table 3).

3.1. Factors associated with completion of a vaccination series

All the variables in univariate analyses were significantly associated with completion of a vaccination series against hepatitis B (Table 4), except for previous or present commercial sex work activities. In a multivariable logistic regression analysis the year starting a vaccination series, intravenous drug use, age, gender, and vaccination at different locations and organisation of vaccine delivery remained significantly associated with completion of the vaccination series (p < 0.01, Table 4).

Table 1
Characteristics of participants in the national vaccination program against hepatitis B virus in people who use drugs.

Variable	N = 18,054	
Gender		
Male	83.2%	
Mean age, (SD)	37.3 (10.0)	
Percentiles: 25–50–75	30 – 37 – 44	
Dutch nationality		
Yes	72.3%	
Anti-HBc (%)		
Positive	2,302	(12.8)
Negative	13,790	(76.4)
Unknown	1962	(10.9)
HBsAg (%)		
Positive	134	(0.7)
Negative	2,112	(11.7)
Not tested, anti-HBc negative	15,808	(87.6)
Not eligible for further vaccination*	2308	
Intravenous drug use (%)		
Yes, in the past	802	(4.4)
Yes, last 6 months	327	(1.8)
No (drug use, not IV)	16,925	(93.7)
Commercial sex work (%)		
Yes, in the past	1415	(7.8)
Yes, last 6 months	137	(0.8)
No	16,500	(91.4)
Unknown	2	(0.0)

* HBV carrier or immunity to hepatitis B. In addition to 134 HBsAg-positive and anti-HBc-positive participants (HBV carriers) 6 participants were HBV carriers and had an unknown anti-HBc status resulting in 2302 + 6 = 2308 participants.

4. Discussion

The hepatitis B vaccination program targeting PWUD succeeded in involving various organisations whose outreach activities took place close to the living environment of this high-risk group. To our knowledge this is the largest cohort (18,054 participants) seen in a period of ten years. In this program, 87.2% of the participants were eligible for further vaccination and 57.7% completed a regular vaccination series.

4.1. Improving vaccination series completion

Our results from the multivariable analysis suggest that a higher completion rate for vaccination series was associated with starting vaccination in the earlier years of the program, an older age of PWUD, women, intravenous drug use, vaccine administration by addiction care centres, and flexibility in location of vaccine delivery. An effect consistent with earlier studies was vaccination completion being more likely in an older population [27,28]. Additional efforts should therefore be made to encourage a younger population using drugs to complete a vaccination

Table 2
Organisation of vaccination delivery versus first consultation location in the vaccination program against hepatitis B virus for people who use drugs (N = 18,054).

Organisation of vaccination delivery	Number of locations	Location of first consultation						Total
		Addiction care facilities	PHS	Prison	Homeless shelter	Other#	Unknown	
Addiction care	43	4552	443	57	18	37	371	5478
PHS	29	4911	1788	1337	1014	223	137	9410
Prison	43	8	26	2456	0	88	195	2773
Other*	14	121	27	3	66	167	9	393
Total		9592	2284	3853	1098	515	712	18,054

PHS: public health services.
* e.g. psychiatric institution.
# e.g. sheltered accommodation.

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Table 3
Characteristics and vaccination completion rate of PWUD participating in the national vaccination program against hepatitis B virus over time per two-year period (N = 18,054).

Year starting vaccination series	2002–2003	2004–2005	2006–2007	2008–2009	2010–2011
N	2930	6069	4506	2707	1842
Gender male %	81.2	84.1	82.6	84.6	82.8
Age mean	37.6	37.0	37.2	36.6	38.7*
Anti-HBc %					
Yes	15.7	15.5	13.5	6.6	5.5*
No	76.6	75.9	77.3	75.1	77.6
Unknown	7.7	8.6	9.2	18.3	16.9*
HBsAg %					
Yes	0.7	0.8	0.7	0.7	0.4
No	14.7	14.5	12.5	5.6	4.8*
Not tested, anti-HBc Negative	84.6	84.8	86.8	93.7	94.8*
Intravenous drugs use %					
Yes, in the past	11.5	4.8	2.2	1.2	2.2*
Yes, last 6 months	1.4	3.3	1.1	0.8	0.8
No (drug use, not IV)	87.1	91.9	96.6	98.0	97.0*
Vaccination series					
Completed %	74.7	62.4	57.8	42.6	41.3*

Anti-HBc, antibody to hepatitis B core antigen; HBsAg, hepatitis B surface antigen.
* statistically significant difference compared to year 2002–2003 ($p < 0.05$).

Table 4
Univariate (unadjusted) and multivariable logistic regression model for variables with completion of a vaccination series as outcome variable.

	Univariate	n = 15,746		Multivariable n = 11,891*		
	n	p	OR	p	OR	95%CI
Period	15,746	<.001		<.001		
2002–2003	2469		Reference		Reference	
2004–2005	5129	<.001	0.56	<.001	0.68	0.59–0.77
2006–2007	3895	<.001	0.47	<.001	0.65	0.57–0.75
2008–2009	2522	<.001	0.25	<.001	0.40	0.34–0.47
2010–2011	1731	<.001	0.24	<.001	0.37	0.31–0.44
Gender	15,746					
Female	2656	<.001	1.20	0.009	1.16	1.04–1.30
Intravenous drugs	15,746	<.001		<.001		
No	14,776		Reference		Reference	
Yes, in the past	668	<.001	3.15		2.02	1.57–2.59
Yes, in the last 6 months	302	<.001	2.57		2.06	1.45–2.91
Age (continuous)	15,746	<.001	1.02	<.001	1.02	1.02–1.03
Commercial sex work	15,746					
Yes	1382	0.76	1.02	N.A.	N.A.	
Difference in location of vaccine delivery	11,891[1]					
Different locations	2184	<.001	2.19	<.001	2.10	1.86–2.38
Organisation of vaccine delivery	15,746	<.001		<.001		
Regional public health service	8172		Reference		Reference	
Addiction care facilities	4752	0.26	1.04	<.001	1.38	1.24–1.53
Prison	2513	<.001	0.61	<.001	0.77	0.68–0.87
Other	309	<.001	0.65	0.107	0.78	0.57–1.06

n = Number of participants eligible for vaccination (no hepatitis B carriers no immunity to hepatitis B).
N.A. not applicable.
[1] Difference in 'location of vaccine delivery' was available for participants with data who received at least 2 vaccinations given.
* Computed for 11,891 participants with data for all variables in the multivariable analysis.

schedule. Vaccination completion was also more likely if addiction care facilities administered the vaccination series, instead of the PHSs. This result confirms previous research that shows that more participants informed by drug service staff of addiction care facilities were vaccinated than participants informed by PHSs or flyers. A personal, sustainable contact between drug service staff and PWUD, facilitated by familiarity with substance abuse problems and higher frequency of working with PWUD, might explain this difference [29–31]. Vaccination completion was less likely if correctional facilities administered the vaccination series, rather than PHSs. This could be due to the many transfers of prisoners from prison to prison which results in a loss of vaccination information despite the use of a common database. A lost to follow up of people because of a shorter incarceration than the minimum time it takes to complete a standard series of hepatitis B vaccination is less likely as other organisations also have a lost to follow up for numerous reasons (such as moving house or stopping treatment). Moreover, the program facilitated completion of a vaccine series at a broad spectrum of organisations and locations that made it as convenient as possible to obtain a vaccination. Indeed, different locations of vaccination within a series were associated with better vaccine series completion. The multidisciplinary approach of this

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program, combined with a common database allowed flexibility in the location of vaccination regardless of the setting of first vaccination. This flexibility is likely to have improved the continuity of care for this highly mobile risk group.

In a Swedish study among PWID of whom 1142 initiated vaccination, a comparable 59.2% completed the standard vaccination series [32]. However, in our study the vaccination completion rates significantly decreased from 75% in the 1st year of the program to 41% in the final year. Participants in the earlier years of the program were probably more willing to be vaccinated and/or tested for HBV serology. The fundamental challenge of the last mile was to vaccinate the less willing and the harder to reach PWUD in the final years of the program. This circumstance probably led to a lower completion rate and a higher proportion of participants with an unknown anti-HBc status.

Financial incentives and an accelerated vaccination schedule had also proved helpful in prior studies to improve vaccination completion rates in an unstable drug-using population (vaccination completion between 31- and 83%) [27,28,33–37]. Compared to these studies we achieved a relatively high completion rate of 58% without any financial incentives or accelerated schedules. Offering earlier immunological protection in accelerated schedules (0,1, and 2 months) could also possibly prevent the HBV infection that is seen before completion of the intended standard schedule [32]. However, caution should be used with accelerated hepatitis B schedules because there is little validation of the long-term effectiveness of these alternative schedules in larger cohorts at high risk of hepatitis B. A booster dose is recommended after one year to improve long-term effectiveness in accelerated schedules [38]. The program did not choose an accelerated vaccination schedule because of the expected poor compliance with the booster dose.

In our study injection drug use was positively associated with completing the vaccination schedule in the multivariable analyses. It is difficult to explain this association because the results for injection drug use are conflicting for completion of the hepatitis B vaccination schedule [39–41]. In the program, self-reported past and/or current injection drug use decreased until 2005 and stabilised at about three percent from 2006- to 2011. In 2012, 1200 (8.6%) of the approximately 14,000 Dutch residents who were problematic opioid drug users, injected drugs, which corresponds to 0.11 PWID/1000 people (aged 15–64 years). This is a strikingly low prevalence compared to recent estimates of less than 1 to more than 9 cases per 1000 people (aged 15–64 years) in other European countries [42–44]. After 2002, an increase in immunisation coverage and referral to standard care of HBV carriers discovered in the program, could have altered further transmission dynamics of hepatitis B among PWUD. If indicated, antiviral agents can reduce infectivity by effectively reducing the viral load of HBV. Consequently, in 2012, the program no longer regarded PWUD, including PWID, as a risk group to be tackled in a national vaccination campaign against hepatitis B. An analysis confirmed that the program for PWUD was most cost-effective during the first half of the program (2002–2006) and was more expensive per protected individual in later years [45]. In 2012, vaccination of PWUD was recommended to be part of specialist addiction care in the Netherlands. Unfortunately, there are several barriers to implement this policy, but there is progress, albeit slow. The current most important barriers are financial regulations and local policy issues [46].

4.2. Limitations

We considered participants with anti-HBc to be immune to hepatitis B and therefore ineligible for further vaccination. However, immunity cannot be proven for a small proportion of people with ‘core-only’ antibodies against hepatitis B [47]. We may have falsely excluded some participants from receiving further immunological protection against hepatitis B. This observation will probably not have affected our study results, but should be considered in future prevention programs to effectively protect this population.

We defined a successful vaccination series to be at least three vaccinations given to increase immunity among PWUD. In contrast to the general population, PWUD have a suboptimal immunological response after vaccination [48]. An antibody titre below 10 IU/l against HBsAg is considered unprotective and necessitates additional booster vaccinations. Some participants might have remained unprotected from HBV after completion of a standard series. The additional cost and logistic effort versus the risk of infection and vaccine effectiveness should be considered before a decision is taken to include post-vaccination testing in a public health vaccination program against HBV [32,45,49].

The web-based database of the program was not primarily developed for research purposes. Some misclassification (1–2%) did occur in the ‘location’ variable. This could easily be corrected because of the additional information registered. Although this had no effect on the main results of our regression analysis, we cannot completely exclude some additional misclassification in the database. Risk behaviour was self-reported in this study. Because these questions are about sensitive personal information such as sexual behaviour and drug use, some participants might have been reluctant to answer all these questions honestly. This could have led to an underestimation of the risks reported.

5. Conclusion

Convenience is key to improve uptake and completion of a hepatitis B vaccination schedule among PWUD [29,37,50]. Despite using the standard vaccination schedule and no financial incentives, a relatively high completion rate of HBV vaccination was achieved for this risk-group. Our results suggest that convenience might consist of flexibility in the location of vaccination facilitated by the use of a common database. Further, the specific organisation that administers a vaccine series seems relevant for improving vaccination completion. These results inform public health services to optimise hepatitis B vaccination programs in countries with ongoing HBV transmission among people who use drugs.

Declarations of interest

SR, CH and JVS participated in an investigators initiated study on hepatitis B vaccination non-response in which two pharmaceutical companies (GSK and MSD) provided the vaccines in kind. ADG participated in a hepatitis C project in addiction care, unrelated to the present work, for which her organisation received a grant from pharmaceutical companies.

Acknowledgements

We thank all the participating organisations of the HBV vaccination program targeting groups at behavioural risk of hepatitis B for their efforts in collecting the data.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.07.045.

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Please cite this article in press as: Raven S et al. Predictors of hepatitis B vaccination completion among people who use drugs participating in a national program of targeted vaccination. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.07.045