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Interventions to Increase Completion of Hepatitis B Vaccination in People who Inject Drugs: A Systematic Review and Meta-analysis

Stacy Tressler
West Virginia University, sriffee@mix.wvu.edu

Ruchi Bhandari
West Virginia University

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REVIEW ARTICLE

Interventions to Increase Completion of Hepatitis B Vaccination in People who Inject Drugs: A Systematic Review and Meta-analysis

Stacy Tressler and Ruchi Bhandari

Department of Epidemiology, West Virginia University, Morgantown, West Virginia, USA

Increases in opioid misuse and injection drug use have resulted in a rise in acute cases of hepatitis B. We conducted a systematic review and meta-analysis of randomized studies to determine the effect (pooled odds ratio) of interventions to increase hepatitis B vaccination completion in people who inject drugs (PWID). Odds ratios from the included studies were combined to create a pooled odds ratio (OR) using the Inverse Heterogeneity Model. Eleven studies met the eligibility criterion of having a randomized intervention to increase hepatitis B virus vaccination completion among PWID. The odds of vaccine completion in the intervention group were greater than in the control/comparison group (pooled OR, 2.53; 95% confidence interval [CI], 1.07–5.99). Subgroup analysis indicated that financial incentives were most effective (OR, 7.01; 95% CI, 2.88–17.06), followed by accelerated vaccine schedules (OR, 1.90; 95% CI, 1.14–3.14). Interventions using financial incentives and accelerated vaccine schedules are moderately effective at increasing hepatitis B vaccination completion in PWID.

Keywords. hepatitis B; meta-analysis; people who inject drugs; vaccination.

Globally, ~90% of the world's population lives in countries with a high or intermediate prevalence of hepatitis B [1]. Worldwide, ~240 million people are chronically infected with hepatitis B virus (HBV), and in the Unites States, an estimated 2.2 million people are chronic carriers of the virus [2, 3]. It is estimated that chronic hepatitis B (CHB) infection is responsible for 50% of all cases of hepatocellular carcinoma, and 25% of people with CHB will die prematurely from complications of the disease [1].

Major risk factors for HBV infection in the United States include sexual exposure and injection drug use (IDU) [4]. Since 2009, opioid misuse and IDU in the United States have resulted in an increase in acute cases of hepatitis B [2]. In 2015, 30.3% of newly HBV-infected people reported IDU as a risk factor [4]. Adults with compromised immune systems are more likely to develop chronic infection (20%) compared with those with a healthy immune system (5%) [1]. People who inject drugs (PWID) have a higher risk of developing chronic infection due to altered immune function and co-infections with hepatitis C virus (HCV) and HIV [5].

The rise in opioid misuse and IDU has highlighted the need to provide education and harm reduction services to PWID, including HBV vaccination [2, 6]. Survey data from 2013 indicate that only one-third of adults have completed the 3-dose HBV vaccination series, and this number is estimated to be even lower in PWID [2]. PWID can be a difficult population to reach, and completion of the standard 3-dose series at 0, 1, and 6 months in this population can be challenging. For this reason, different strategies have been used to increase vaccination rates, including accelerated vaccine schedules, financial incentives, case management, peer coaching, and motivational interviewing [7–17]. In 2014, The World Health Organization (WHO) published guidance on preventing HBV and HCV in PWID. Using a systematic review approach, the authors graded the quality of evidence for using an accelerated vaccine schedule, financial incentives, and peer-based strategies to improve health outcomes for people with substance use disorders [3]. Although the quality of the evidence supporting these strategies was low, the WHO recommends their use to prevent the transmission of HBV and HCV in PWID [3].

Objective

The primary objective of this study was to conduct a systematic review and meta-analysis of randomized controlled trials and randomized studies to determine the overall effect of strategies to increase HBV vaccination in PWID.

METHODS

Study Eligibility

The eligibility criteria for inclusion in this systematic review with meta-analysis were established a priori. Each study was

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Correspondence: Stacy Tressler, MPH, Department of Epidemiology, West Virginia University, P.O. Box 9190, Morgantown, WV 26506 (sriffee@mix.wvu.edu).

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required to meet the following eligibility criteria: (1) randomized controlled trial or randomized study with at least 1 intervention group and 1 control/comparison group, (2) intervention aimed at increasing adherence to completion of the HBV vaccine series as either a primary or secondary outcome, (3) outcome data available on completion of the 3-dose HBV vaccination series, and (4) a study sample that included PWID (representing either all or a percentage of the overall study sample). The gray literature was not searched, and only studies published in English were included.

Data Sources

An electronic search of PubMed, Web of Science, and Cochrane Library was performed on February 20, 2018. Search terms included "inject*," "drug use*," "hepatitis B vacc*," and "hepatitis B vaccine*." MESH terms included "hepatitis B vaccines" and "substance abuse, intravenous." There were no time restrictions placed on the search, and each database was searched from its inception through February 20, 2018. Hand-searching of references was performed when reviewing relevant studies to identify randomized controlled trials (RCTs) not found during the electronic search. An additional search of the 3 databases was performed on June 19, 2019, to search for studies meeting the inclusion criteria that were published between February 20, 2018, and June 19, 2019. No additional studies were identified.

Study Selection

Studies obtained from the search results were imported into EndNote (VXE; Thomas Reuters, New York, NY, USA). Duplicates were identified and removed. Titles and abstracts were reviewed to identify studies meeting the inclusion criteria. A flowchart detailing the exclusion process and the reasons for exclusion can be found in Figure 1. For studies using the same sample, the study with the data most relevant to the review topic was selected.

Data Extraction

Microsoft Excel (version 2010; Richmond, WA, USA) was used to develop a codebook for data extraction before article selection. Each study was coded on 51 items, including the following major categories of variables: (1) study characteristics, (2) intervention characteristics, (3) participant characteristics, and (4) outcome characteristics. For studies with >1 intervention group, outcome data for the most intensive intervention were selected. If a true control group did not exist, the comparison group selected by the study authors was used. Data were included in the meta-analysis even if studies reported outcome data for a PWID subpopulation.

Risk of Bias Assessment

Risk of bias was assessed for each included study using the Cochrane Risk of Bias tool [18]. Study bias was assessed as high,

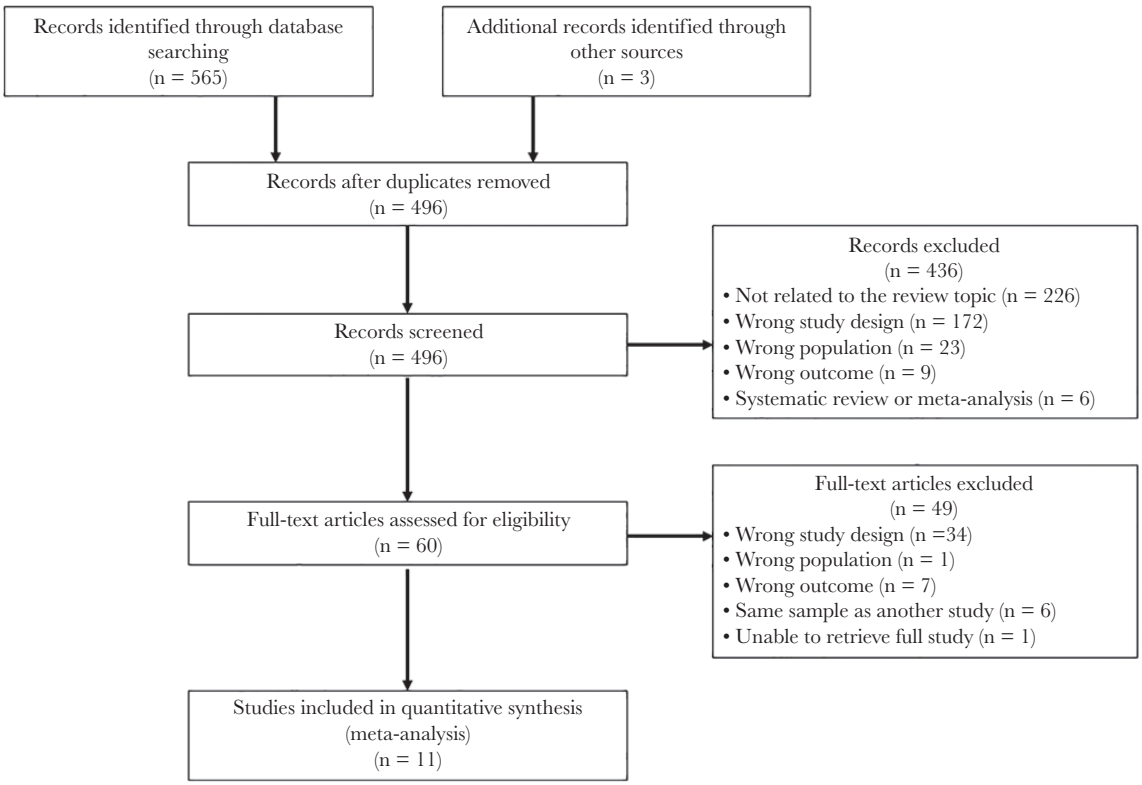

Figure 1. Flowchart of study selection.

low, or unclear on the following measures: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome data, (5) incomplete outcome data, (6) selective reporting, and (7) other major sources of bias.

Statistical Analysis

All analyses were completed in Meta XL using the Inverse Heterogeneity Model (IVhet). Data on studies reporting adjusted and crude odds ratios (ORs) of completion of the 3-dose HBV vaccination series in the intervention group compared with the control/comparison group were entered into Meta XL. Adjusted and crude odds ratios were pooled to create an overall effect size. Pooled ORs with 95% confidence intervals (CIs) were calculated using the IVhet in Meta XL. Heterogeneity and inconsistency were assessed using the Q statistic (based on the chi-square test statistic) and I^2. For the Q statistic, a P value <.10 was indicative of statistically significant heterogeneity between studies. I^2 scores of 25% (low), 50% (moderate), and 75% (high) were used to determine the amount of inconsistency between studies. Small-study effects were assessed using a funnel plot. Cumulative, influence, and subgroup analyses were conducted. Subgroup analyses included intervention type (accelerated, financial, and case management or enhanced services) and reported OR (adjusted vs crude).

RESULTS

Study Characteristics

A flowchart depicting the search strategy and study selection process can be found in Figure 1. A total of 565 studies were identified through electronic database searches. An additional 3 studies were identified through hand-searching references during review of full articles, for a total of 568 studies. Using both electronic and manual searching methods, 72 duplicates were identified and removed. A total of 496 studies were screened for eligibility, resulting in the removal of 485 studies.

Eleven studies, representing 4027 participants, met the selection criteria and were included in the meta-analysis. All of the studies included adherence to the 3-dose HBV vaccine series as their primary outcome. Countries where the studies were conducted included the United States (n = 7) Iran (n = 1), Denmark (n = 1), Australia (n = 1), and the United Kingdom (n = 1). Study settings included prison (n = 2), syringe exchange program (n = 2), methadone maintenance program (n = 2), drug treatment program (n = 2), community (n = 1), streets in an urban area (n = 1), and a combination of shelters, drug treatment facility, and streets (n = 1). An overview of study characteristics can be found in Table 1.

Participant Characteristics

The mean age of participants ranged from 34 to 46.3 years. Studies had a greater proportion of males compared with females, with a range of 55% to 100% males. The studies varied on the percentage of participants who reported IDU and ranged from 8.9% to 100%. Five studies included only participants who reported IDU, and the other 6 studies included participants who reported IDU and other alcohol/drug use. Ten studies based IDU on self-report, and each study differed on whether the IDU was classified as current, recent, ever/lifetime, or future risk. The only common variables reported for all 11 studies were percent IDU and percent males. Participant characteristics can be found in Table 1.

Intervention Characteristics

Interventions were classified into 3 main categories: (1) HBV vaccine schedule (n = 4), (2) monetary/financial incentives (n = 3), and (3) case management/enhanced services (n = 4). Four studies focused on schedule-based interventions using a variety of accelerated vaccine schedules for the intervention group and all controls/comparisons assigned to the standard schedule of 0, 1, and 6 months. Three studies used monetary or financial intervention, and incentives included cash and vouchers in both fixed and escalating amounts. Details of the amounts used in each study can be found in Table 1. The case management/enhanced services interventions included motivational interviewing, case management, coaching, and hepatitis care coordination. Study characteristics can be found in Table 1.

Risk of Bias Assessment

The Cochrane Risk of Bias assessment tool was used to rank the studies as having high, low, or unclear risk of bias on 7 domains (Supplementary Figure 1). Due to the nature of the interventions, almost all studies were ranked as having a high risk of bias, based on 3 criteria: allocation concealment, blinding of participants and personnel, and blinding of outcome assessment. For all studies, the risk of bias for selective outcome reporting was low. The risk of bias varied among studies for the other 3 criteria, namely random sequence generation, incomplete outcome data, and other issues.

Data Synthesis

Results of the OR for vaccine completion in the intervention group compared with the control/comparison group can be found in Figure 2. An overall pooled OR of 2.53 (95% CI, 1.07–5.99) indicated a statistically significant (P = .04) increase in the odds of completing the 3-dose vaccine in the intervention groups compared with the control/comparison group. Study heterogeneity was statistically significant (P < .0001), and inconsistency was categorized as high (I^2 = 89%). An influence analysis with each study excluded once revealed that results did not remain statistically significant when 4 of the 11 studies were individually removed from the model once. The results of the influence analysis can be found in Supplementary Table 1. A cumulative meta-analysis of the studies by year (Supplementary Figure 2) showed that the ORs in the studies

Table 1. Study and Participant Characteristics of the 11 Studies Included in the Meta-analysis

Study	Country	Setting	Study Design	Randomized & Vaccine Eligible, No.	Type of Intervention	Intervention	Control	Mean Age, y	Male, %	IDU, %
Asli et al. 2011 [9]	Iran	Prison and corrections facility	RCT	169	Vaccine schedule	0, 1, 4, 8 wk	Standard vaccine schedule	34	100	8.9 (history of)
Bowman et al. 2014 [10]	United States	Syringe exchange program	Randomized	461	Vaccine schedule	0, 1, 2 mo	Standard vaccine schedule	40.4[a]	73[a]	100 (past 30 d)
Christensen et al. 2004 [8]	Denmark	Prison	Randomized	34	Vaccine schedule	0, 1, 3 wk	Standard vaccine schedule	[b]	[b]	100 (IDU ever)
Hwang et al. 2010 [11]	United States	Community	RCT	1260	Vaccine schedule	0, 1, 2 mo	Standard vaccine schedule	[c]	77	30 (IDU ever)
Masson et al. 2013 [12]	United States	Methadone maintenance treatment program	RCT	300	Case management/ enhanced services	Enhanced care coordination 2-session counseling with MI, on-site testing & vaccination, enhanced case management	2-session counseling, on-site testing, off-site vaccination and evaluation	44.85[d]	68	70 (IDU ever)
Nyamathi et al. 2009 [13]	United States	Homeless shelters, residential drug treatment programs, and outdoor areas	Randomized	865	Case management/ enhanced services	Nurse case management, $5 incentive per dose, and tracking	Standard hepatitis training with $5 incentive per dose	42.3	76.7	16.7 (lifetime) 6.7 (recent)
Nyamathi et al. 2015 [14]	United States	Residential drug treatment facility (urban)	RCT	345	Case management/ enhanced services	Intensive peer coaching and nurse case management	Usual care	42	100	32.5 (lifetime)
Nyamathi et al. 2010 [15]	United States	Methadone maintenance treatment programs (urban)	RCT	148	Case management/ enhanced services	1-on-1 MI	Nurse-led hepatitis health promotion	46.3	55	34.4 (recent)
Seal et al. 2003 [7]	United States	Community—recruited from the streets	RCT	96	Monetary	$20 monthly for 6 months	Maintain weekly contact with an outreach worker	43	72	100 (current)
Topp et al. 2013 [16]	Australia	Inner-city health service clinic in a syringe exchange program	RCT	139	Monetary (voucher)	AU $20 at first visit, AU $30 at dose 2, AU $30 at dose 3, and AU $30 cash at study follow-up visit	Standard care plus AU $20 voucher at first visit and AU $30 cash at study follow-up visit	33.1	77	100 (previous 6 mo)
Weaver et al. 2014 [17]	United Kingdom	Drug treatment centers	Cluster RCT	210	Monetary (voucher)	Fixed amount: £10 with each dose; escalating amounts: £5 1st dose, £10 2nd dose, £15 3rd dose	Treatment as usual with no incentive	36.2	80	100 (previous, current, or at-risk for future)

Abbreviations: IDU, injection drug use; MI, motivational interviewing; RCT, randomized controlled trial.

[a]For the total study (n = 1964), retrieved from Heimer et al. paper [22].

[b]Did not report demographic information for the randomized study. Only reported demographic information for the nonrandomized follow-up study that took place in Estonia.

[c]Not reported.

[d]Calculated from the mean age of the intervention and control groups.

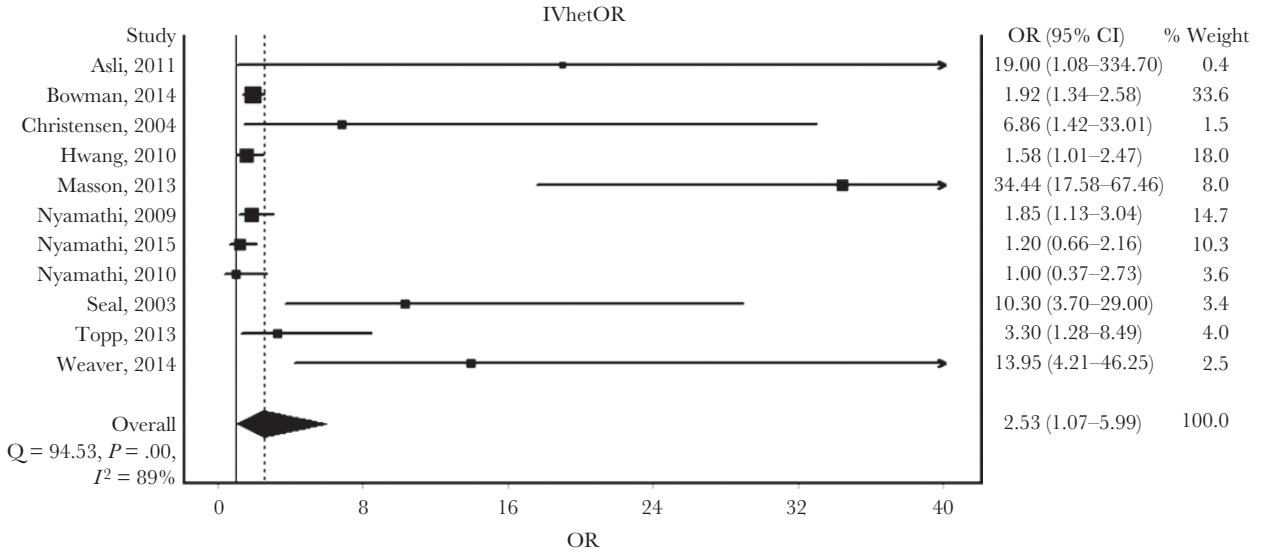

Figure 2. Forest plot of overall meta-analysis results using the Inverse Heterogeneity Model. Abbreviations: CI, confidence interval; IVhet OR, Inverse Heterogeneity Model odds ratio; OR, odds ratio.

have decreased since 2003 and have not remained statistically significant. Small-study bias was assessed using a funnel plot (Supplementary Figure 3), plotting the natural log OR for each study against its precision. Asymmetry in the funnel plot indicated potential small-study effects or other sources of bias such as true heterogeneity between studies. Two subgroup analyses

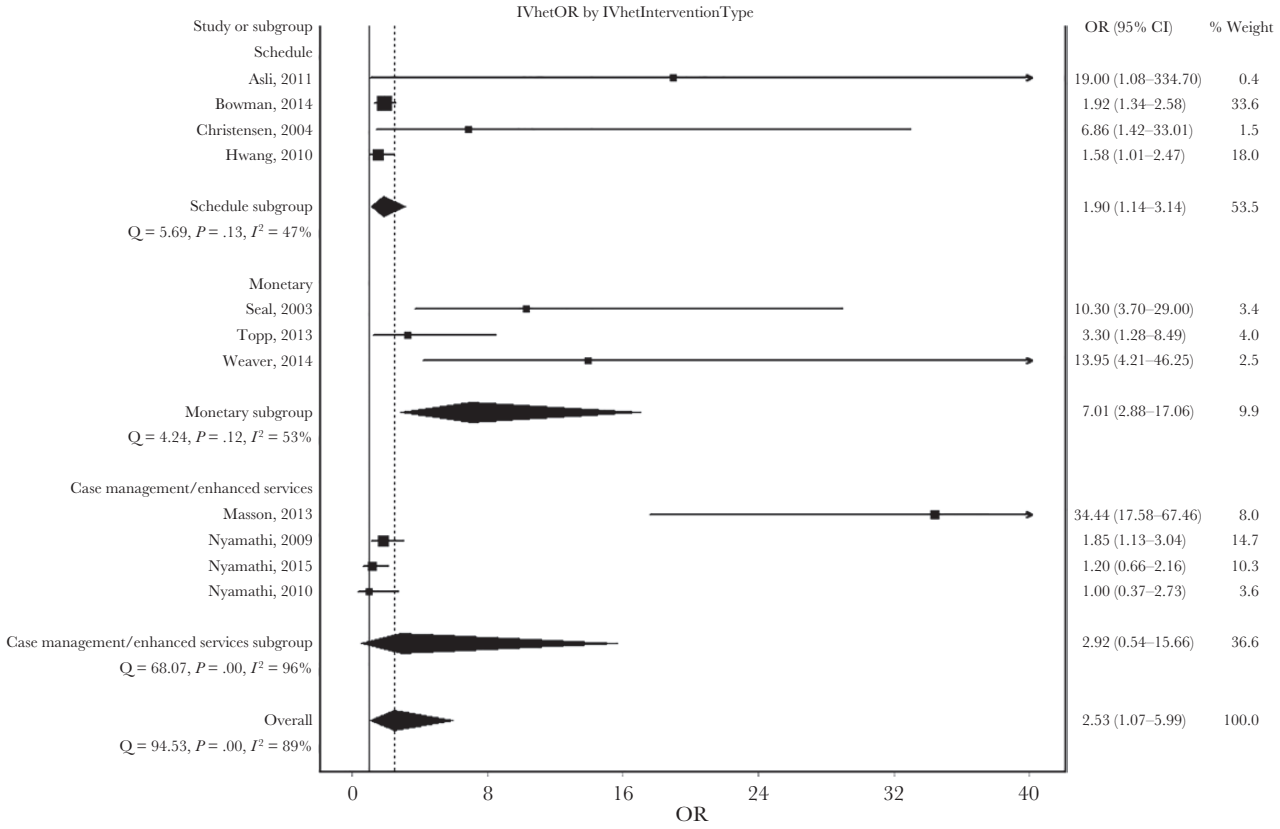

Figure 3. Forest plot of subgroup analysis by intervention type using the Inverse Heterogeneity Model. Abbreviations: IVhet OR, Inverse Heterogeneity Model odds ratio; OR, odds ratio.

comparing results by type of intervention and type of OR were included in the analysis. Intervention types were categorized as vaccine schedule, monetary/financial incentives, and case management/enhanced services (Figure 3). For the vaccine schedule subgroup, the pooled OR was 1.90 (95% CI, 1.14–3.14), heterogeneity was not statistically significant ($P = .13$), and inconsistency was moderate ($I^2 = 47\%$). The pooled OR for the monetary subgroup was 7.01 (95% CI, 2.88–17.06), heterogeneity was not statistically significant ($P = .12$), and inconsistency was moderate ($I^2 = 53\%$). The case management/enhanced services subgroup pooled OR was not statistically significant (OR, 2.92; 95% CI, 0.54–15.66), heterogeneity was statistically significant ($P < .0001$), and inconsistency was high ($I^2 = 96\%$). Finally, the subgroup analysis of crude vs adjusted OR yielded the following results: the pooled OR for studies that reported adjusted ORs was 2.26 (95% CI, 1.02–4.97), heterogeneity was statistically significant ($P < .0001$), and inconsistency was high ($I^2 = 77\%$); the pooled OR for studies that reported crude ORs was 3.04 (95% CI, 0.49–18.88), heterogeneity was statistically significant ($P < .0001$), and inconsistency was high ($I^2 = 94\%$) (Figure 4).

DISCUSSION

This systematic review and meta-analysis included 11 RCTs or randomized studies that implemented strategies to increase completion of the 3-dose HBV vaccine series in PWID. The pooled OR for all 11 studies indicated a statistically significant increase in the odds of completing all 3 doses in the intervention group compared with the control/comparison group (OR, 2.53; 95% CI, 1.07–5.99; $P = .04$). Subgroup analyses comparing the interventions by type indicated that the odds of vaccine completion in those who received financial incentives was the highest, followed by receipt of an accelerated vaccine schedule. Subgroup analysis of the case management/enhanced services group yielded an OR that was not statistically significant. These findings are consistent with WHO recommendations from 2014 that were based on previous research to increase compliance with HBV vaccination in PWID [3].

Hepatitis B is a vaccine-preventable disease that remains problematic in certain at-risk groups. Since 2009, the increase in IDU in the United States has highlighted the importance of providing harm-reduction services to PWID, including access to HBV vaccine. However, making the vaccine available does not always translate to increased HBV vaccination rates in PWID. Strategies are needed to increase the vaccine uptake among this at-risk group. The cost of the vaccine is minimal compared with the savings from improved quality of life and reduced health care costs. In 1 study, the cost of providing financial incentives to increase vaccine compliance was $220 per participant compared with the cost of increasing compliance through outreach methods, which equaled $590 per participant [7]. Combining financial incentives with an accelerated vaccine schedule represents a low-cost and effective method for increasing compliance.

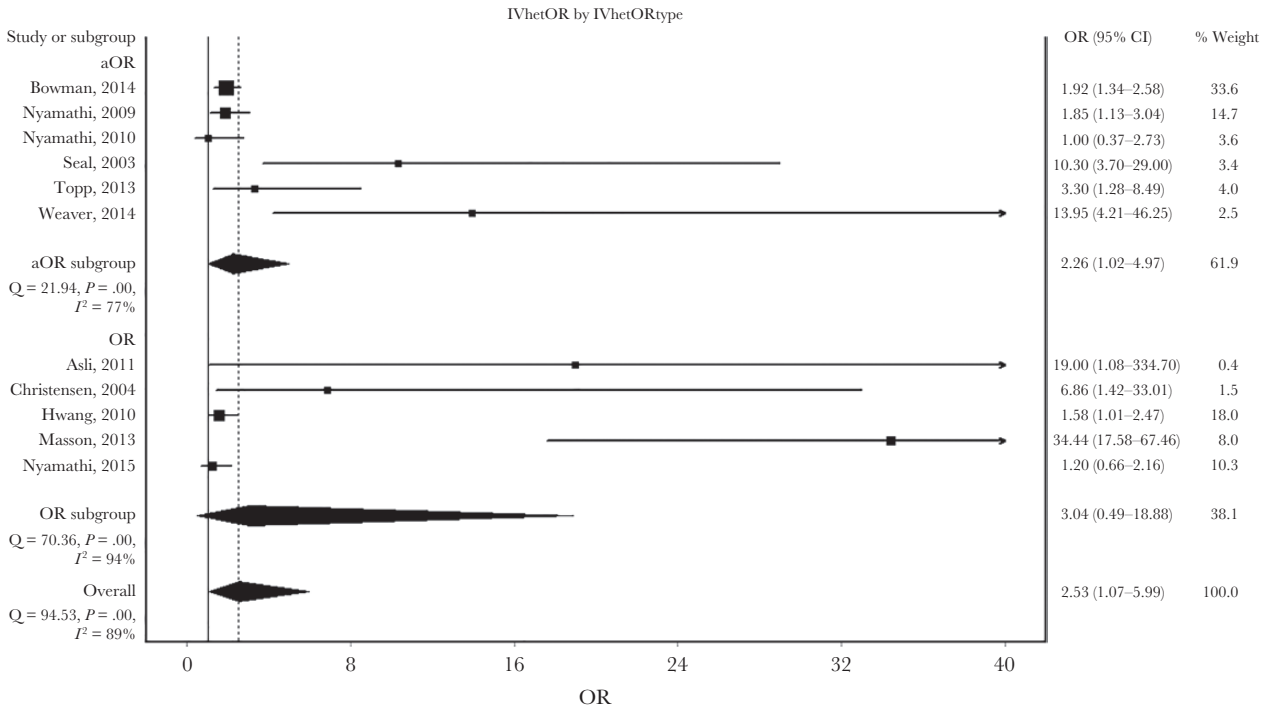

Figure 4. Forest plot of subgroup analysis by type of reported odds ratio using the Inverse Heterogeneity Model. Abbreviations: aOR, adjusted odds ratio; IVhet OR, Inverse Heterogeneity Model odds ratio; OR, odds ratio.

In 2017, the Food and Drug Administration approved Heplisav-B, a new 2-dose, highly immunogenic hepatitis B vaccine [19]. The new 2-dose series is administered at 0 and 30 days, compared with the traditional series administered at 0, 1, and 6 months. Use of the 2-dose series in future vaccine interventions among PWID may increase adherence and result in a higher immune response compared with the traditional 3-dose series. However, results from a recent study indicated that the percentage of at-risk people completing the second dose of the traditional HBV vaccine series was only 40.4%, suggesting a need to incorporate strategies to increase HBV vaccine schedule adherence even for a 2-dose series [20].

More randomized controlled studies are needed to examine the effectiveness of interventions specifically in PWID. Based on findings from the Hu et al. (2008) study, administering the first dose of HBV in conjunction with testing for HBV is both cost-saving and effective and should be considered when conducting future research [21]. Additionally, combining different strategies, for example, accelerated vaccine schedules with financial incentives, may confound the association and make it difficult to determine the effectiveness of the individual intervention. Therefore, future studies should compare only 1 intervention strategy with 1 control group.

A potential limitation of this study was the significant amount of heterogeneity between the 11 studies. However, this limitation was addressed through subgroup analysis of intervention type, which indicated that heterogeneity was not significant within 2 of the 3 subgroups. For this reason, the interpretation of the results from the intervention subgroup analysis may be more appropriate than the pooled OR. Additionally, the 11 studies varied greatly on the percentage of people who reported IDU. Ten of the 11 studies relied on self-reported drug use and may have been influenced by bias. There was substantial variation in how and when people were randomized to the intervention and control groups. All of the studies took place in either prison or urban areas, which may affect generalizability, especially to PWID living in rural areas. Generalizability to females may also be problematic due to the majority of participants being males. Some of the studies were part of larger studies, and data for the vaccine-eligible population were not always reported. Publication bias and small-study effects may have influenced the overall findings of the study, resulting in statistically significant results. Finally, coding studies proved problematic due to the quality of reporting. Several of the studies reported conflicting information in the text, charts, and tables, making it difficult to determine the true numbers.

CONCLUSIONS

Increasing HBV vaccination is a cost-effective way of preventing both primary and secondary infections in PWID. Using accelerated vaccine schedules and financial incentives has been shown to increase compliance to the 3-dose vaccine schedule. As IDU continues, more research is needed to find strategies to improve health outcomes in this at-risk group.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of interest. The study authors have no conflicts of interest to declare. The authors of the 11 studies included in the meta-analysis had no conflicts to declare, with the exception of 1 study that did not provide a conflict of interest statement but reported that the study was funded by GlaxoSmithKline [8]. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. S.T. performed the initial study search, selection of studies for inclusion in the systematic review and meta-analysis, and served as the primary coder, with R.B. as a second coder. Both S.T. and R.B. contributed to the interpretation of results, contributed to major revisions, and worked on the final manuscript.

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