

# Vaccine immunogenicity in injecting drug users: a systematic review

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Injection drug use is a prevalent global phenomenon; one not bound by a country's level of development or geographical location. Injection drug users (IDUs) are at high risk for a variety of parenterally acquired and transmitted infections. Licensed vaccines are available for some of these infectious diseases, such as tetanus, influenza, and hepatitis A and B viruses; however, there have been conflicting reports as to their immunogenicity in IDUs. We summarise the lessons learned from studies evaluating the immunogenicity of vaccination strategies in IDUs. A common theme across these diseases is that although there is a tendency towards decreased antibody responses after immunisation, there is no conclusive evidence linking these observations to a decrease in clinical protection from infection. There is a clear need for definitive studies of vaccination strategies in IDUs; however, a synthesis of the available published evidence suggests that immunisation does result in effective clinical protection from disease in this population. The inclusion of IDUs as a high-risk study population in future trials evaluating HIV and hepatitis C virus vaccines will help to assess the immunogenicity of candidate vaccines against parenteral exposure, and also to evaluate the efficacy of candidates as promising antigens become available.

## Introduction

With the worldwide population of injection drug users (IDUs) reaching an estimated 13 million, the problem has become a prevalent global concern, unrestricted by a country's level of development or location (figure 1).<sup>1,2</sup> Additionally, injection drug use of opiates is a growing social burden, exacerbated by an increase in illicit opium production.<sup>2-4</sup> IDUs are at high risk for a variety of parenterally acquired and transmitted infections including HIV, hepatitis C virus (HCV), hepatitis B virus (HBV), hepatitis A virus (HAV), tetanus, syphilis, and malaria.<sup>5-17</sup> Since effective treatment exists for only a subset of these diseases, it is important to focus on the development and use of effective prevention strategies, such as needle and syringe exchange, education, opioid replacement therapy, and vaccination.<sup>18-25</sup> Among these infectious diseases, there are licensed vaccines for HBV, HAV, and tetanus; however, there have been conflicting reports as to the immunogenicity of the vaccines in IDUs.<sup>26-29</sup> The immunogenicity of a substance is the level or potency of the immune response elicited when that substance encounters the host immune system. Laboratory markers of immunogenicity include antibody titres, cytotoxic T-cell responses, cytokine production, and many other novel techniques. The immunogenicity of vaccine function has traditionally been identified by measuring antibody levels because it is assumed that postvaccination protection is generally humorally mediated in the form of neutralising antibodies.<sup>30</sup> Seroconversion has been defined by a particular neutralising antibody level for each disease: more than 10 mIU/mL for HBV, more than 20 mIU/mL for HAV, and more than 0.15 IU/mL for tetanus.<sup>31-33</sup> However, recent studies have consistently suggested that the cell-mediated immune response also has an important role in protecting the vaccinated host from viral infection.<sup>34</sup>

The importance of antigen immunogenicity in the vaccination of IDUs is underscored by the fact that there is a growing consensus that a preventive HIV vaccine would

be a key component in the global control of HIV spread.<sup>35</sup> A common concern with ongoing and past HIV vaccine trials is how to evaluate the potency of immune responses in current or former IDUs. Specifically, if faced with a trial failure, there is conjecture as to whether the vaccine itself is ineffective or whether the population in which it was tested was unable to mount protective immune responses against HIV challenge. That said, the epidemiology of HIV tells us that it is crucial to include IDUs in vaccination trials and other prevention interventions, because although injection drug use accounted for an estimated 10% of global HIV infections in 2005, it accounted for one-third of HIV infections outside sub-Saharan Africa.<sup>36</sup> Thus, HIV vaccine strategies that have not been evaluated in the context of parenteral transmission might have limited use in much of the world.<sup>1</sup>

Hepatitis C is hyperendemic in IDUs, with worldwide average prevalence rates hovering around 80–90%.<sup>37,38</sup>

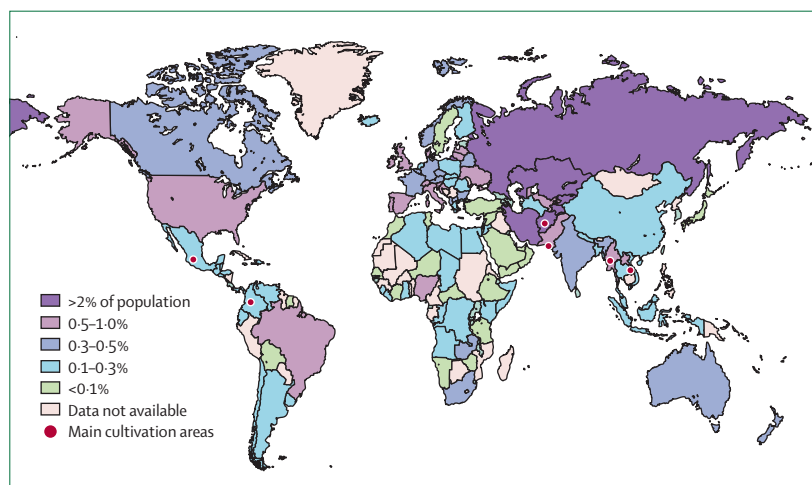


Figure 1: Worldwide use of opiates (including heroin) 2003-05

The level of opiate use (annual prevalence) is depicted as percentage of population using opiates. Adapted with permission from United Nations Office on Drugs and Crime World Drug Report, 2006.<sup>2</sup>

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Hence, in addition to assessing this population's suitability for examining the efficacy of HIV vaccines, it is equally important to determine the suitability of IDUs for HCV vaccines, because they are the predominant at-risk population for this disease.

We undertook a systematic review of the published work in an effort to summarise current knowledge regarding the immunogenicity of vaccination strategies in IDUs. Additionally, we speculate whether this at-risk population is an appropriate study group in which to further test HIV and HCV vaccines.

## Methods

### Search strategy and selection criteria

We searched PubMed, Embase, Ebsco, and the Cochrane Central Register of Controlled Trials using the following medical subject heading (MeSH) terms: "substance abuse, intravenous", "substance-related disorders", and "heroin dependence", limiting the results to studies published between Jan 1, 1980, and Feb 1, 2006. Only studies published in English language and on human research were included. The MeSH terms were then cross-referenced with articles containing the following keywords: "vaccination" (210 articles, 17 reviews), "immunization" (234 articles, 30 reviews), "vaccine" (323 articles, 54 reviews), "immunogenic" (26 articles, six reviews), "immunize" (four articles, one review), "immunogenicity" (16 articles, one review), and "immunized" (26 articles, three reviews). These search strategies were cross-referenced so as to identify unique articles and reviews (82 articles, eight reviews; figure 2). Based on abstract and title alone, 11 articles were excluded because these studies concentrated on vaccines to prevent drug use and vaccination immunogenicity in alcoholic cirrhosis. The full texts of the remaining 71 articles were retrieved and the reference list of each primary study was searched for additional relevant publications. Owing to the limited availability of research

concentrating on vaccination strategies in IDUs, all relevant studies whether retrospective, cross-sectional, ecological, or prospective were reviewed here.

There were 22 studies evaluating vaccination strategies in IDUs using epidemiological tools: 12 for HBV, four for HAV, two for tetanus, two for influenza, and two for HIV. Abstraction was done by one of the authors (SB) and abstraction methods and data extraction were independently validated by a second author (CB). Abstractors were not blinded to the purpose of the study. The validity of each study in terms of methodology and conclusions was critically assessed by two of the authors (SB, CB).

### Hepatitis B virus vaccination

Current estimates suggest that HBV has infected nearly 2 billion people worldwide, of whom between 350 and 400 million have evidence of chronic infection.<sup>39-42</sup> Like HCV infection, chronic HBV infection carries the risk of complications such as cirrhosis and primary liver cancer.<sup>39-42</sup> HBV is unique among the group of infectious diseases traditionally associated with injection drug use because an effective vaccine has been available for more than two decades.<sup>43</sup> However, studies have shown that vaccine uptake has been very low among IDUs, consistently remaining below 30%.<sup>44,45</sup> A comprehensive review exploring the dearth in knowledge regarding HBV in IDUs and the perspectives of health-care providers on HBV vaccination in IDUs has recently been published; therefore, we will not elaborate on these topics here.<sup>46</sup> Rather, we will focus on the reports that give insight into the immunogenicity of the HBV vaccine and other licensed vaccines in IDUs.

The HBV vaccine has long been the most studied of all vaccines in IDUs (table). Most studies have relied on the seroprevalence of HBV surface antigen specific antibodies (antiHBs) as a marker for protective immunity, whereas only one study so far has evaluated clinical protection in a prospective fashion.<sup>47</sup> We retrieved 12 studies that evaluated seroconversion proportions or geometric mean titres of antiHBs, or both, among drug users (table).<sup>15,28,47-56</sup> In three of these studies, lower seroconversion rates in IDUs led to the study authors concluding that former and current IDUs have blunted immune responses secondary to opioid-mediated immunomodulation.<sup>15,50,51</sup> In the other nine studies, including one evaluating a combined HBV/HAV vaccine (Twinrix; GlaxoSmithKline Biologicals, Rixensart, Belgium), the investigators concluded that HBV vaccine was both safe and immunogenic in this population.<sup>28,47-49,52-56</sup>

Although it is useful to know the seroprevalence of protective levels of antiHBs in immunised IDUs, of greater importance is the clinical protection that such a vaccine affords. A cohort study completed in Taiwan—a country hyperendemic for HBV—evaluated HBV incidence in a paediatric population immunised for HBV during infancy. Even with an antiHBs seroprevalence of only 37.4% (260 out of 696 patients) among the study population, no

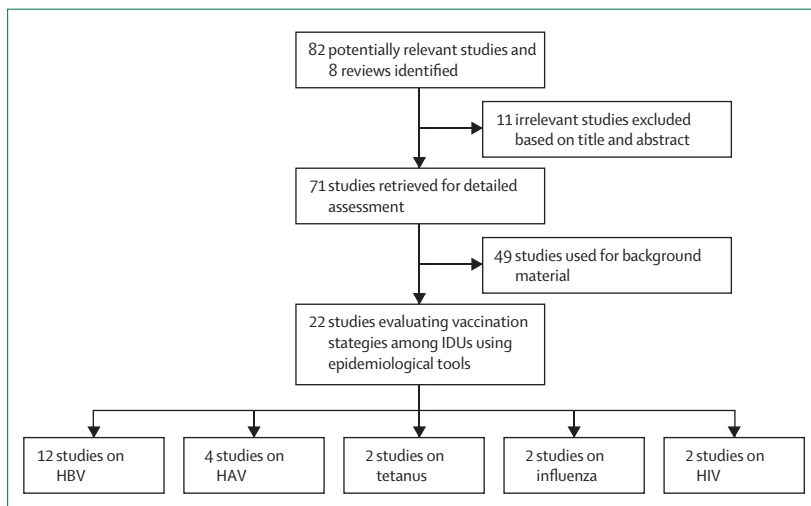


Figure 2: Flow diagram for study selection

IDUs=injection drug users. HBV=hepatitis B virus. HAV=hepatitis A virus.

	Vaccination schedule	Route/site	Drug user seroconversion* (%)	Control seroconversion* (%)	p value	Relevant conclusions
Schalm et al (1983) <sup>48</sup>	0, 1, and 6 months	..	34/34 (100%)	21/23 (91%)	..	Vaccine was immunogenic
Kunches et al (1986) <sup>49</sup>	0, 1, and 6 months	Intramuscular/deltoid	9/9 (100%)	No controls	NA	Vaccine was immunogenic
Rumi (1991) <sup>50</sup>	0, 1, and 6 months	Intramuscular/deltoid	76% (13/17). At 24 months follow-up 6/14 (43%) retained response	40/41 (98%). At 24-months follow-up 32/37 (86%) retained response	p<0.05	Blunted immune responses in IDUs
Rodrigo et al (1992) <sup>51</sup>	0, 1, and 2 months	Intramuscular/deltoid	50/86 (58%)	217/271 (80%)	p<0.05	Vaccine was less immunogenic among IDUs
Lugoboni et al (1997) <sup>52</sup>	0, 1, and 6 months	Intramuscular/deltoid	34/38 (89%)	42/42 (100%)	p>0.05	Vaccine was immunogenic
Borg et al (1999) <sup>53</sup>	0, 1, and 6 months	..	21/30 (70%)	No controls	N/A	Vaccine was immunogenic
Quaglio et al (2002) <sup>58</sup>	0, 1, and 6 months; and 0, 1, and 2 months	..	0, 1, 6-month protocol 313/350 (89%); 0, 1, 2-month protocol 317/464 (68%)	No controls	p<0.001 (between 0, 1, 6- month and 0, 1, 2-month groups)	Vaccine was immunogenic
Lum et al (2003) <sup>15</sup>	0, 1-2, and 4-6 months	Intramuscular/..	38/49 (78%)	No controls	NA	Blunted immune responses in IDUs
Lugoboni et al (2004) <sup>54</sup>	0, 1, and 6 months (combined HBV/ HAV Twinrix vaccine)	Intramuscular/deltoid	HBV 33/34 (97.1%) HAV 35/35 (100%)	No controls	NA	Vaccine was immunogenic
Budd et al (2004) <sup>55</sup>	0, 1, and 2 months	Intramuscular/deltoid	55/74 (74%)	No controls	NA	HBV vaccination for IDUs is both feasible and effective
Lugoboni et al (2004) <sup>47</sup>	0, 1, and 6 months (prospective cohort study for 15 years)	Intramuscular/deltoid	Vaccinated 0/258 became HBV-infected; seroconversion rate 71.8%	Unvaccinated 13/45 (29%) became HBV-infected	p<0.001	Vaccine provided clinical protection from HBV infection
Puvacic et al (2005) <sup>56</sup>	..	..	5 years post vaccination 18/28 (64%)	5 years post vaccination 54/68 (79%)	p>0.05	Booster vaccination for HBV is not necessary

..=not reported. NA=not applicable. IDUs=injection drug users. HBV=hepatitis B virus. HAV=hepatitis A virus. \*Data presented as number of patients seroconverted/total number of vaccinated patients.

**Table: HBV vaccine immunogenicity studies in injection drug users**

child became a chronic hepatitis B surface antigen (HBsAg) carrier.<sup>57</sup> Furthermore, a European consensus group have published a report indicating that vaccinated individuals without detectable antiHBs levels for many years still have robust anamnestic immune responses upon in-vitro restimulation.<sup>58</sup> Thus, solely using antibody seroconversion post vaccination is not sufficient evidence with which to form accurate conclusions on the immunogenicity of vaccines.<sup>59</sup> So far, there has only been one published prospective cohort study evaluating the clinical benefit of HBV vaccination in IDUs. This was completed in northeast Italy over a 15-year period. The study showed that among IDUs who had received at least three doses of vaccine, none of 258 patients seroconverted to being positive for the antibody to HBV core antigen (antiHbC), which is representative of infection, by contrast with 13 of 45 antiHbC seroconversions among those who refused vaccination (p<0.001).<sup>47</sup> Of note, the seroprevalence of protective antiHBs levels was only 71.9% in vaccinated individuals (230 out of 320 patients).<sup>47</sup>

### Hepatitis A virus vaccination

HAV is a well-documented public-health problem, generally limited to low-income and middle-income countries with transmission usually caused by faecal-oral contact or ingestion of contaminated food or water.<sup>60</sup>

Although incidence of HAV is decreasing in many parts of the developing world because of improved water sanitation facilities, there have been several recent epidemics in IDUs caused by parenteral transmission and poor sanitary practices in this population.<sup>29,60-65</sup>

Since 1995, there have been two effective HAV vaccines on the market and although IDUs are officially recommended targets of HAV vaccination, this population has low vaccination rates and remains at risk of infection.<sup>66,67</sup> Similar to experimental observations with HBV vaccination, IDUs generate decreased antibody geometric mean titres in response to vaccination compared with the general population.<sup>29,68</sup> In the general population, 95% of vaccinated patients will seroconvert after a single HAV vaccine dose, whereas a study in northeast Italy showed that it took two doses to achieve a similar seroprevalence of protective levels of HAV antibody in IDUs.<sup>29</sup> Although there have been no prospective observational studies evaluating clinical protection from HAV, there have been a few ecological studies indicating that as a population, IDUs retain the ability to mount protective immune responses after vaccination.<sup>61,62,64</sup>

In Rotterdam, Netherlands, in early 2004, there was an outbreak of HAV resulting in 30 genotypically linked (subtype 3a) cases in homeless IDUs.<sup>62</sup> Contact tracing was difficult because of the ephemeral nature of this group's

living arrangements and there was concern that the epidemic might be bridged to the general population. Consequently, a mass immunisation campaign was initiated over a 2-week period resulting in the single-dose vaccination of more than 1500 IDUs, which was effective in ending the HAV outbreak. Genotypically, the subtype of virus had not been observed in the area before the outbreak and has not returned since, giving further credibility that the targeted vaccination strategy was effective.<sup>62</sup> Additionally, a study completed in Washington state, USA, showed that targeted immunisation of IDUs was similarly able to mitigate a community-wide HAV epidemic.<sup>64</sup> These studies show that only evaluating seroconversion after vaccination is not sufficient to draw conclusions and lend support to the need for observational studies. In the only study evaluating immunogenicity of HAV vaccine in IDUs, single-dose immunisation resulted in only a 36% (16 of 44 patients) seroconversion, whereas all IDUs (43 of 43) seroconverted after the 6-month booster.<sup>29</sup> Notably, single-dose immunisation targeting IDUs has been able to potentiate enough protection to help prematurely end HAV outbreaks in different settings.

### Tetanus vaccination

The association between tetanus and IDUs was first recorded in 1876 in the UK, and was further elucidated in the 1950s in Chicago (IL, USA).<sup>69,70</sup> Tetanus is caused by an infection of *Clostridium tetani*, which belongs to the family of obligate anaerobes Clostridiaceae. Infections by the Clostridiaceae family are traditionally associated with ingestion or high-force crush injuries, but when IDUs use contaminated needles to inject into areas of devitalised tissue, they are at high risk of self-inoculation.<sup>71</sup> Tetanus is the only member of the *Clostridium* genus for which there is a vaccine. Although its use appears to provide lifelong immunity, booster vaccination is generally recommended every 10 years for the healthy population and every 5 years for high-risk groups.<sup>31,72</sup>

There has been no cohort, case-control, or experimental study to evaluate the immunogenicity of tetanus vaccine in IDUs. As such, inferences surrounding the immunogenicity of this vaccine in IDUs are based on a small number of cross-sectional and case-series studies.

A study in Italy that evaluated tetanus mortality suggested that in individuals less than 40 years of age, the single group with the highest risk was IDUs. Among cases of tetanus mortality in this study, vaccine coverage was very low.<sup>73</sup> These findings corroborate other studies showing higher incidence of tetanus-related mortality among IDUs compared with the general population.<sup>69,74,75</sup>

In 1988, a cross-sectional study evaluating tetanus immunity in 319 IDUs was done in Spain.<sup>26</sup> This study used two correlates of immunity; the first was a specific antibody geometric mean titre and the second was a tetanus toxin neutralisation assay. Whereas the overall immunity in this population was 49.2%, immunity levels varied significantly when stratified by age. Individuals

between the ages of 16 and 20 years had an overall immunity of 83.7% (36 of 43 patients), whereas only 27.5% of people (11 of 40 patients) over the age of 30 years were immune ( $p < 0.001$ ).<sup>26</sup> The authors deduced that the significant change in immunity levels was related to the introduction of an infant immunisation campaign in 1965. IDUs young enough to have been immunised at birth remain protected, whereas older unvaccinated IDUs were not protected from tetanus infection. Other than in emergent care, IDUs generally have irregular interaction with the health-care system and, unless vaccinated as infants, are unlikely to be immunised.<sup>76</sup> The aforementioned values correlate almost exactly with a study in Spain that investigated the immunogenicity of the tetanus vaccine. In that study, the serostatus of tetanus immunity of two healthy populations, one between the ages of 18 and 30 years (201 patients) and the other older than 45 years (147 patients), was evaluated.<sup>72</sup> Seroprevalence of protective antibodies was 90.5% in the 18–30-year age-group and 30.6% in the older group ( $p < 0.001$ ). The researchers postulated that the difference in baseline immunity was related to different vaccine coverage during infancy.<sup>72</sup>

### Influenza vaccination

Annual influenza epidemics are a major cause of morbidity and mortality globally.<sup>77</sup> With the current threat of an avian influenza (H5N1) pandemic, there has been a resurgence of interest in a universal vaccination programme for this disease.<sup>78</sup> Since many IDUs lack stable housing arrangements, they are more readily exposed to harsh environments experienced in winter months, and spend more time in overcrowded conditions such as shelters. Therefore, IDUs are at high risk for influenza infection and bacterial pneumonia secondary infections. Additionally, IDUs are at increased risk for bacterial endocarditis, which is an indication for influenza vaccination.<sup>79,80</sup>

There have been no observational studies evaluating efficacy of influenza vaccination in IDUs. However, there have been a limited number of studies evaluating seroconversion with antibodies specific to a given year's strain of influenza. According to the European Committee for Proprietary Medicinal Products, for the annual relicensure of influenza vaccines, vaccination must result in a seroprotection rate of more than 70% to be considered effective.<sup>81</sup> Furthermore, the vaccination protocol must be safe as determined by the severity of adverse effects, both local and systemic.<sup>82</sup> Using these standards, the studies evaluating influenza vaccination in IDUs have shown it to be both safe and effective.<sup>83,84</sup> The reports describing serostatus post-influenza vaccination were done in a population of IDUs living in the rehabilitation centre in northeast Italy previously discussed in the context of HBV vaccination. The results indicated that injection drug use did not result in any retained immunomodulation and therefore immunisation of IDUs was recommended unanimously by the investigators.<sup>83,84</sup>

## Potential HIV vaccination

The beginning of 2006 saw over 35 candidate HIV vaccines in clinical trials with new formulations being continually developed.<sup>34,85,86</sup> A collaboration between the US Centers for Disease Control and Prevention (CDC) and Bangkok Metropolitan Administration has resulted in several clinical efficacy trials for some of these candidate vaccine formulations.<sup>87-92</sup> In 1988, there was an explosive spread of HIV in Bangkok, when in 1 year the seroprevalence of HIV in IDUs went from 0% to 40%.<sup>93</sup> A phase I/II safety and immunogenicity trial was initiated in Bangkok IDUs after animal experiments indicated that the vaccine could induce protective immunity from HIV-1 and was likely to be safe in human beings.<sup>94,95</sup> Using a variety of immunological assays, the results showed, in principle, that IDUs can generate effective neutralising HIV-1 antibodies *in vitro*.<sup>88</sup> Ultimately, a phase III trial of the AIDSVAX vaccine (VaxGen Inc, San Francisco, CA, USA) showed no protection from HIV-1 infection in IDUs, with equivalent HIV incidence in treated and placebo arms. There was no evidence, however, that vaccine failure was caused by the inability of vaccinees to generate immune responses, because the vaccine failed to protect other high-risk populations from HIV infection as well.<sup>96,97</sup>

## Discussion

To our knowledge, this is the first paper to review literature regarding the immunogenicity of vaccination strategies in IDUs for which there are licensed vaccines, including HBV, HAV, tetanus, and influenza. The most important finding of this Review is that there is a dearth of definitive studies evaluating vaccination strategies in this population, a disappointing finding since the prevalence of the diseases reviewed are universally high among IDUs. We found only two prospective studies evaluating clinical protection from any of the reviewed diseases: one studying HBV and the other HIV. Although the logistical challenges in studying IDUs were not discussed here, the aforementioned studies as well as substantial research on the efficacy of intervention strategies that target IDUs show that this population is amenable to being studied in a variety of prospective settings.<sup>19,22,98-101</sup>

In a Review such as this, there are many potential limitations. First, although we aimed to use systematic search strategies, it is possible that relevant studies were missed. Second, the study was limited to English language publications, which could have served as a source of language bias in the results. That said, using informal searches of non-English language databases, we found no sources of primary data that had not been reported in English journals and indexed in PubMed. Finally, no studies were excluded on the basis of poor or poorly described methodology, meaning that some of the results may lack accuracy and may not be generalisable to all IDUs. With these caveats in mind, we believe that this Review is an accurate representation of the current knowledge regarding immunogenicity of vaccines in IDUs.

Most vaccine immunogenicity studies in IDUs have evaluated the HBV vaccine. Synthesising the results from these seroprevalence studies and one prospective cohort study suggests that there is no apparent relation between antiHBs serostatus and clinical protection from infection. In the evaluation of the HAV vaccine, studies have shown the targeted single-dose immunisation of IDUs to be effective in prematurely ending a community-wide HAV epidemic, even though single-dose immunisation is only marginally effective in potentiating HAV-antibody specific seroconversion in IDUs.<sup>61,62,64</sup> Because incidence significantly declined even though not all IDUs were immunised because of logistic limitations, the results suggest that herd immunity had a role in the outbreak dynamics. Thus, active immunisation of IDUs with hepatitis virus vaccines might be able to potentiate herd immunity, possibly decreasing transmission rates and preventing outbreaks.<sup>101</sup>

The only two studies to evaluate tetanus vaccination in IDUs present no evidence to show that IDUs retain less of a memory immune response to tetanus immunisation by comparison with the general population.<sup>26,72</sup> Because IDUs have infrequent contact with the health-care system, CDC guidelines suggest that any opportunity to provide them with tetanus vaccination should be used, because this is a cost-effective way of minimising tetanus-related morbidity and mortality.<sup>31,73,76</sup>

IDUs are at risk for influenza because of inadequate housing, malnutrition, and poor hygiene and injection practices, and should receive yearly influenza shots. In view of current speculation about a possible H5N1 pandemic, it is especially prudent to build the necessary infrastructure for delivering influenza vaccine to this at-risk population, because there is no evidence that this vaccine is not immunogenic in IDUs.<sup>83,84</sup>

Between studies, we found substantial variability of seroconversion rates and geometric mean titres among vaccinated IDUs. Reasons for this variability include factors associated with the vaccination protocol and factors associated with the host. For example, early recommendations for HBV vaccination called for either intradermal or intramuscular immunisation at the site of the buttock.<sup>102</sup> However, a consensus was later reached that using this site for immunisation was not ideal, since lower seroconversion rates were obtained compared with patients receiving intramuscular injections at the deltoid.<sup>103,104</sup> As such, official recommendations were changed and current CDC guidelines advise intramuscular injections into the deltoid because of better access to the muscular layer.<sup>105</sup> Although most of the studies we reviewed indicated the route of immunisation, few indicated the specific site of injection. As such, variable seroconversion rates of IDUs could partly be attributed to different immunisation techniques.

Another possible factor affecting seroconversion rates is the timing of vaccine doses. Among HBV vaccine studies, we only found one that compared the 6-month vaccination

### Search strategy and selection criteria

These are described in detail in the Methods section on page 668.

schedule (0, 1, and 6 months) with the 2-month schedule (0, 1, and 2 months) in users of heroin.<sup>28</sup> In that study, the participants assigned to the 6-month schedule had three times the odds of seroconverting compared with those on the 2-month schedule (adjusted odds ratio 3.1, 95% CI 2.06–4.68). Corroborating this finding are the results of other studies, which suggest that the 6-month schedule results in higher seroconversion rates.<sup>15,48,51,55</sup> Current HBV vaccine recommendations by the CDC are that the vaccination schedule for adults should be no shorter than 4 months, which also lends credence to these results.<sup>33</sup>

Host factors that could have caused variability in the results include being an injection drug user, smoking tobacco, concurrent use of alcohol or other drugs, and HCV and HIV infection status. The studies reviewed here that postulate a blunted immune response in IDUs base their inferences on research completed *in vitro* or in transgenic animal models with results that may or may not be generalisable to human beings. Although there are many examples of results in animal models differing from results from human clinical trials for several diseases, a relevant one here is that AIDS-VAX conferred protection in chimpanzees, but failed to do the same in human beings.<sup>95</sup> It is known that human lymphocytes carry the  $\mu$ ,  $\kappa$ , and  $\delta$  classic opioid receptors on their cell surface; however, it is unclear what concentration of opiates reaches these receptors in active IDUs *in vivo*, and whether that level is sufficient to cause downregulation of the immune response.<sup>106–108</sup>

It has been suggested that immunomodulation in IDUs was responsible for decreased survival time from HIV infection until death.<sup>109</sup> However, a recent report showed a longer survival time post-HIV exposure in IDUs compared with men who have sex with men.<sup>110</sup> Moreover, another study showed that HIV-infected IDUs generate higher anti-HIV-1 titres compared with their sexually infected peers.<sup>111,112</sup> These reports, in tandem, tend to refute earlier work indicating that IDUs have shorter post-HIV infection survival times secondary to immunomodulation.

### Conclusions

A consistent and disturbing finding in reviewing the published work on vaccination in IDUs is that they are at high risk for vaccine-preventable infections, but generally have among the lowest immunisation coverage rates. This finding was identified in studies of HBV, HAV, tetanus, and influenza immunisation, which strongly suggests that targeted immunisation strategies and novel approaches to immunisation delivery are likely to be needed for this vulnerable group. Although there is a need for further prospective observational studies and evaluative research of vaccination strategies among IDUs, a synthesis of the available published evidence implies that immunisation can result in effective clinical protection from disease in this population. Since vaccination series are increasingly being provided at infancy or during adolescence, observing disease incidence in the next

generation of IDUs will give a more accurate representation of vaccine immunogenicity.<sup>38</sup> However, for this future generation of IDUs, linking immunisation to valued services including needle and syringe exchange, drop-in counselling, and treatment and legal services might help to increase coverage for existing vaccines and facilitate the design of vaccine trial strategies for novel candidates.<sup>113</sup> IDUs should be included as a high-risk study population in future HIV and HCV vaccine trials to assess the efficacy of candidates and to assess the immunogenicity of these candidates against parenteral exposure.<sup>90,96,114</sup>

### Conflicts of interest

We declare that we have no conflicts of interest.

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