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, unregulated by a country’s level of development or location (figure 1). Additionally, injection drug use of opiates is a growing social burden, exacerbated by an increase in illicit opium production. 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. 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.

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. 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 humoral mediated in the form of neutralising antibodies. 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. 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.

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.

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. Thus, HIV vaccine strategies that have not been evaluated in the context of parenteral transmission might have limited use in much of the world.

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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.46–49 Like HCV infection, chronic HBV infection carries the risk of complications such as cirrhosis and primary liver cancer.49–52 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.43 However, studies have shown that vaccine uptake has been very low among IDUs, consistently remaining below 30%.46–49 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.46 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.7 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.19,50–51 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.52–55

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
child became a chronic hepatitis B surface antigen (HBsAg) carrier. Furthermore, a European consensus group have published a report indicating that vaccinated individuals without detectable antiHBs levels for many years still have retained the ability to mount protective immune responses upon in-vitro restimulation. Thus, solely using antibody seroconversion robust anamnestic immune responses upon in-vitro vaccination is not sufficient evidence with which to form accurate conclusions on the immunogenicity of vaccines. 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 HBV-infected; seroconversion rate 71.8%. Of note, the seroprevalence of protective antiHBs levels was only 71.9% in vaccinated individuals (230 out of 320 patients). 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.

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

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Vaccination schedule</th>
<th>Route/site</th>
<th>Drug user seroconversion* (%)</th>
<th>Control seroconversion* (%)</th>
<th>p value</th>
<th>Relevant conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schalm et al (1983)16</td>
<td>0, 1, and 6 months</td>
<td>Intramuscular/deltoid</td>
<td>34/34 (100%)</td>
<td>21/23 (91%)</td>
<td>-</td>
<td>Vaccine was immunogenic</td>
</tr>
<tr>
<td>Kunchess et al (1986)16</td>
<td>0, 1, and 6 months</td>
<td>Intramuscular/deltoid</td>
<td>9/0 (100%)</td>
<td>17/19 (95%)</td>
<td>-</td>
<td>Vaccine was immunogenic</td>
</tr>
<tr>
<td>Rumi (1991)17</td>
<td>0, 1, and 6 months</td>
<td>Intramuscular/deltoid</td>
<td>76% (13/27)</td>
<td>At 24 months follow-up 6/14 (43%)</td>
<td>p&lt;0·05</td>
<td>Vaccine was immunogenic</td>
</tr>
<tr>
<td>Rodrigue et al (1992)18</td>
<td>0, 1, and 2 months</td>
<td>Intramuscular/deltoid</td>
<td>50/86 (58%)</td>
<td>21/27 (80%)</td>
<td>p&lt;0·05</td>
<td>Vaccine was immunogenic</td>
</tr>
<tr>
<td>Lugoboni et al (1997)56</td>
<td>0, 1, and 6 months</td>
<td>Intramuscular/deltoid</td>
<td>34/38 (90%)</td>
<td>42/42 (100%)</td>
<td>p&lt;0·05</td>
<td>Vaccine was immunogenic</td>
</tr>
<tr>
<td>Borg et al (1999)53</td>
<td>0, 1, and 6 months</td>
<td>Intramuscular/deltoid</td>
<td>21/30 (70%)</td>
<td>No controls</td>
<td>NA</td>
<td>Vaccine was immunogenic</td>
</tr>
<tr>
<td>Quaglio et al (2002)28</td>
<td>0, 1, and 6 months; and 0, 1, and 2 months</td>
<td>Intramuscular/deltoid</td>
<td>0, 1, 6-month protocol 313/350 (89%); 0, 1, 2-month protocol 317/464 (68%)</td>
<td>No controls</td>
<td>p&lt;0·001</td>
<td>Vaccine was immunogenic</td>
</tr>
<tr>
<td>Lum et al (2003)39</td>
<td>0, 1, and 4–6 months</td>
<td>Intramuscular/..</td>
<td>38/49 (78%)</td>
<td>No controls</td>
<td>NA</td>
<td>Blunted immune responses in IDUs</td>
</tr>
<tr>
<td>Lugoboni et al (2004)40</td>
<td>0, 1, and 6 months (combined HBV/ HAV Twinrix vaccine)</td>
<td>Intramuscular/deltoid</td>
<td>HBV 33/34 (97.1%); HAV 35/35 (100%)</td>
<td>No controls</td>
<td>NA</td>
<td>Vaccine was immunogenic</td>
</tr>
<tr>
<td>Budd et al (2004)41</td>
<td>0, 1, and 2 months</td>
<td>Intramuscular/deltoid</td>
<td>55/74 (74%)</td>
<td>No controls</td>
<td>NA</td>
<td>HBV vaccination for IDUs is both feasible and effective</td>
</tr>
<tr>
<td>Lugoboni et al (2004)42</td>
<td>0, 1, and 6 months (prospective cohort study for 15 years)</td>
<td>Intramuscular/deltoid</td>
<td>Vaccinated 0/258 became HBV-infected; seroconversion rate 71.8%</td>
<td>Unvaccinated 13/45 (29%) became HBV-infected</td>
<td>p&lt;0·001</td>
<td>Vaccine provided clinical protection from HBV infection</td>
</tr>
<tr>
<td>Puvacic et al (2005)43</td>
<td>5 years post vaccination</td>
<td>-</td>
<td>18/28 (64%)</td>
<td>5 years post vaccination</td>
<td>p&lt;0·05</td>
<td>Booster vaccination for HBV is not necessary</td>
</tr>
<tr>
<td>.. = 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.</td>
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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.32 Additionally, a study completed in Washington state, USA, showed that targeted immunisation of IDUs was similarly able to mitigate a community-wide HAV epidemic.44 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.29 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).69 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.71 Tetanus is a vaccine. Although its use appears to provide lifelong immunity, booster vaccination is generally recommended for high-risk groups.31,72

In 1988, a cross-sectional study evaluating tetanus immunity in 319 IDUs was done in Spain.26 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).26 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.30 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.72 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.

**Influenza vaccination**

Annual influenza epidemics are a major cause of morbidity and mortality globally.7 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.39 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.39,80

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.51 Furthermore, the vaccination protocol must be safe as determined by the severity of adverse effects, both local and systemic.69 Using these standards, the studies evaluating influenza vaccination in IDUs have shown it to be both safe and effective.69,84 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.69,84
Potential HIV vaccination

The beginning of 2006 saw over 35 candidate HIV vaccines in clinical trials with new formulations being continually developed. 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. 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%. A phase 1/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. Using a variety of immunological assays, the results showed, in principle, that IDUs can generate effective neutralising HIV-1 antibodies in vitro.

Ultimately, a phase III trial of the AIDSVAX vaccine (VaxGen Inc, San Fransisco, 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.

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 infection. Among HBV vaccine studies, 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. 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.

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.

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, although using this site for immunisation was not ideal, since lower seroconversion rates were obtained compared with patients receiving intramuscular injections at the deltoid. As such, official recommendations were changed and current CDC guidelines advise intramuscular injections into the deltoid because of better access to the muscular layer. 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
schedule (0, 1, and 6 months) with the 2-month schedule (0, 1, and 2 months) in users of heroin. 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. 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.

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 AIDSVAX conferred protection in chimpanzees, but failed to do the same in human beings. It is known that human lymphocytes carry the μ, κ, and δ 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.

It has been suggested that immunomodulation in IDUs was responsible for decreased survival time from HIV infection until death. However, a recent report showed a longer survival time post-HIV exposure in IDUs compared with men who have sex with men. Moreover, another study showed that HIV-infected IDUs generate higher anti-HIV-1 titres compared with their sexually infected peers. 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. 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. 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.

Conflicts of interest
We declare that we have no conflicts of interest.

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