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Hepatitis A virus among drug users and the role of vaccination: a review

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In countries with advanced economies better health and hygiene conditions, along with the introduction, in some cases, of global vaccination, have relegated most viral hepatitis to marginal social groups and, in particular, drug users (DUs). The availability of safe and effective vaccines for hepatitis A virus (HAV) and B (HBV) may play a major role in combating this phenomenon. Despite the availability of a safe and effective vaccine for over a decade and the recommendations of international health organizations, vaccinations against HAV among DUs are not as widely known and available as are HBV vaccinations. The purpose of this review article is to present the most significant data in the literature on the prevalence of HAV among DUs and the role of targeted vaccination. To our knowledge, the present article is the first to solely deal with vaccination against HAV in DUs. Immunization after the administration of anti-HAV vaccine has been demonstrated in DUs even if they have responded significantly less than either the general population or carriers of chronic liver disease. All the vaccines were well tolerated and adherence to the vaccine schedule was good. Further studies are needed to optimize the timing and doses of vaccine to be administered to DUs, especially to assess adherence and antibody persistence. Vaccination campaigns are feasible among DUs and have proven to be highly cost–effective.

Keywords: adherence, drug users, hepatitis A vaccination, intravenous, immunization, HAV, vaccine, DUs

INTRODUCTION

Addiction and diffusion of viral hepatitis are two different phenomena but have long been closely correlated. Addiction is a global phenomenon, with geographic location having relatively little to do with its progress in a country, while there are large differences in the spread of viral hepatitis as related to its progression in different countries. Such differences tend to decrease significantly among drug users (DUs; United Nations Office on Drug, and Crime, 2006; Aceijas et al., 2004). In drug-addicted patients, in conjunction with the decrease of HIV-rate mortality, death from liver diseases have significantly increased (EMCDDA, 2003; Schaefer and Mauss, 2008). Counteracting this spread is a priority task, which has to involve all the structures that can interact with drug abusers.

Hepatitis C virus (HCV) is surely the most important hepatitis among DUs regarding both its diffusion and its high percentage of chronic disease. Currently, it is the most common cause of chronic hepatitis in developed countries (Centers for Diseases Control and Prevention, 2002; Schaefer and Mauss, 2008).

Health education and harm reduction policies (i.e., methadone or buprenorphine maintenance therapies and needle-exchange programs) are at the moment the only measure of prevention of HCV, since there is neither specific vaccination nor effective prophylaxis against exposure. Interventions using strategies that combined substance-use treatment and support for safe injection were most effective at reducing HCV seroconversion (Hagan et al., 2011). Vaccination campaigns targeted at high-risk groups and the introduction of mass vaccination in almost all developed countries has significantly reduced HBV prevalence among the youngest DUs (Baral et al., 2007; Brim et al., 2007). HBV infection through sexual transmission has an important role among non-injective DUs (Gyarmath et al., 2002; Rich et al., 2006).

Hepatitis D virus (HDV) is caused by a defective RNA-virus that requires the presence of the HBV Surface Antigen for transmission. HDV can be acquired both as a co-infection with HBV and as an overlap in a chronic HBV carrier. HDV infection can be effectively prevented with vaccination against HBV, while protection does not exist for chronic HBV carriers. In Europe and in the USA HDV infection has almost disappeared in the general population (GPOP), remaining confined almost entirely to DUs (Gaeta et al., 2000; Farci, 2003). Hepatitis A virus (HAV), the causative agent of type A viral hepatitis, is an ancient picornavirus virus, which was identified almost 40 years ago. Each year HAV affects 1.5 million people worldwide. The geography of infection is tightly linked to the quality of sewage water depuration systems. Improved living conditions and subsequent changes in HAV epidemiology have decreased the disease burden of hepatitis A in most developed countries (Martin and Lemon, 2006; Koslap-petraco et al., 2008; Jacobsen and Wiersma, 2010). The clinical manifestations of HAV infection range from asymptomatic to fulminant hepatitis. The severity of the disease is strongly dependent on the age of the host, being the asymptomatic disease typical of childhood while,

Abbreviations: CLD, chronic liver disease; DUs, drug users; GPOP, general population; HAV, hepatitis A virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus.

in adults, HAV infection causes severe manifestation of liver disease in 80% of cases. HAV rarely causes fulminant hepatic failure in the GPOP, generally less than 0.5% of cases (Crowcroft et al., 2001; Koslap-petraco et al., 2008; Jeong and Lee, 2010). Yet it is a cause of significant morbidity and mortality in patients with chronic liver disease (CLD). The pathogenesis of acute liver damage is thought to be mediated by host cytotoxic T-lymphocytes directed against virus-infected hepatocytes (Vento et al., 1998; Locarnini, 2000; Saab et al., 2005). Acute HAV super infection in carriers of chronic hepatitis C has been associated with a particularly high mortality rate, dozens of times higher than HAV infection in the GPOP (WHO, 2000; Keeffe, 2006; Kumar and Herrera, 2010).

Despite the recommendations of all the most important international public health associations and the existence of several scientific works that confirm the validity of such recommendations, HAV vaccination in DUs is still far too low (Brook, 2002; Quaglio et al., 2006b; Baral et al., 2007; Brim et al., 2007; Buxton and Kim, 2008; Lugoboni et al., 2009).

OBJECTIVES

The PubMed and Google Scholar database were searched for relevant publications between 1995 and 2010 using the following medical subject heading (MeSH) terms: "immunization," "immunogenic," "reactogenicity," "immunogenicity," "outbreak," "vaccine," "vaccination," "hepatitis A," "HAV infection," and "adherence." The MeSH terms were cross-referenced with articles containing the following keywords: "drug use," "DUs," "IDU," "substance abuse," "heroin dependence," "addiction," "intravenous": 84 potentially relevant studies were found. Thirteen studies evaluating epidemiological data and other five studies assessing vaccination strategies in DUs using epidemiological tools were retrieved. Only three studies evaluating seroconversion after vaccination were found. Four reviews were identified.

This is the first review full dedicated to the problem of HAV among DUs and to the specific prophylaxis with vaccination in this risk group.

The aims of the present paper were to review current literature regarding:

(a) epidemiology of HAV among DUs
(b) the efficacy, coverage, safety, and acceptance of HAV vaccine in DUs
(c) the role of co-infections on HAV vaccine
(d) targeted strategies (combined vaccinations, experimental schedules, emergency strategies).

HAV AND DRUG USERS

Even if HAV infection seems to be declining in much of the world as a result of better hygienic conditions, positive serology among DUs in non-endemic countries was reported as much higher than in the GPOP (**Table 1**).

Drug users are at risk of contracting the infection for at least three reasons: route of infection, by injection and sex, poor housing conditions, and the higher probability of being jailed. Possible HAV infection can have high clinical severity because of the frequent presence of chronic HCV infection, often being worsened by alcohol abuse.

ROUTE OF INFECTION

If fecal–oral contamination is by far the commonest way of transmission, it is possible to transmit the virus by injection, sexually (most of all, through oral–anal sex), and through vertical transmission (Brook, 2002; Martin and Lemon, 2006; Jeong and Lee, 2010). In a recent study, HAV viremia persisted for an average of 79 days after the liver enzyme peak. In addition, HAV-RNA was detected several days before IgM antibodies to HAV were detected. These results indicate that adults with HAV infection are viremic for as long as 30 days before the onset of symptoms and that the duration of viremia may be longer than previously described, suggesting that the opportunity for transmission may be greater than previously suspected (Bower et al., 2000; Crowcroft, 2003). Outbreaks, where it was possible to genetically demonstrate a common origin, have been repeatedly reported among DUs in non-endemic countries such as Norway, Holland, Great Britain, Italy, and the USA (Stene-Johansen et al., 1998; Hutin et al., 2000; O'Donovan et al., 2001; Granerød and Crowcroft, 2002; Syed et al., 2003; Roy et al., 2004; Spada et al., 2005; Tjon et al., 2005). Particularly, during an HAV outbreak among DUs in central Italy in 2002, mortality from hepatic failure was 6.4% compared to a national average of 0.01% (Spada et al., 2005). In such cases the role of mixed-use syringes can be crucial. By capture–recapture analysis, the suspicion has been reported that in England underreporting of HAV infection may be high and a number of outbreaks have occurred undetected by routine surveillance (Matin et al., 2006). Seroprevalence data indicate that, in non-endemic countries for HAV, positive levels among DUs are generally higher than among the GPOP (**Table 1**), even if there are some exceptions; in the areas, where there are data of lower social marginality among DUs (Quaglio et al., 2006a), the HAV seroprevalence among DUs and GPOP does not differ (Lugoboni et al., 2005).

LIVING CONDITIONS

Even if increasingly effective water sanitation and policies for targeted vaccination, in the most developed countries, have drastically reduced HAV incidence – between 1995 and 2007 the rate of acute hepatitis A was reduced by 92% in the United States (Daniels et al., 2009), HAV outbreaks have been frequently reported among the homeless. The homeless have an increased risk of HAV infection due to living conditions when compared with the GPOP (Tjon et al., 2005; Hagan et al., 2011). This increased risk has been demonstrated to be related to homelessness, independently of other known risk factors, such as injection of illicit drugs, sexual habits, and ethnicity (Hennessey et al., 2009). In fact, a recent study on HAV infection among DUs found that it was associated with low educational level and low-hygienic variables, factors found to be more decisive than needle-exchange (Luquero et al., 2009).

THE PRISON EXPERIENCE

Probably associated with many risk behaviors (common use of drugs by injection, anal sex, high presence of subjects coming from high HAV endemicity) or with crowded living conditions, prisons have been described many times as situations of high-risk for HAV infection even in the developed countries with low endemicity for HAV (Skidmore et al., 2001). Jail and facility incarcerations were

Table 1 | Hepatitis A virus: sero-epidemiological data among DUs.

Citation (country)	Population	SPr (%)	Route of infection	Mainly comments
Ochnio et al. (2001) (CAN)	DUs	42.6	IDU/MSM	Vulnerability to HAV outbreaks
Lugoboni et al. (2005) (I)	MMT/DUs	28.7	IDU/nIDU	Prevalence similar than the GPOP
Wells et al. (2006) (USA)	Dus	33	LC	DUs are targets for vaccination
Gerlich et al. (2006) (CH)	Dus	41.2	IDU	Need of vaccination
Latimer et al. (2007) (USA)	Jail DUs	36.9	JI	Vaccination within CF
Reimer et al. (2007) (D)	Dus	57.7	IDU/LC	Need for outreach vaccination programs
Poulos et al. (2007) (AUS)	DUs/HLs	48	–	Potential benefit from HAV vaccination
Campbell et al. (2007) (USA)	DUs	19	IDU	Low coverage with vaccination
Bart et al. (2008) (USA)	MMT	46.1	–	DUs pose a public health risk
Sunthornchart et al. (2008) (T)	DUs	60.1	IDU	Vaccination need
Luquero et al. (2009) (E)	Dus	35.5	LC	Vaccination recommended
Hennessey et al. (2009) (USA)	DUs/HLs	52	LC	HAV vaccine for homeless
Ramasamy et al. (2010) (AUS)	MMT	49	–	Further studies are needed
Removille et al. (2011) (L)	DUs	57.1	IDU/nIDU	Need for new immunization strategies

DUs, illicit drug users; HLs, homeless; MMT, methadone maintenance treatment; CF, correctional facility; SPr, seroprevalence; IDU, injecting drug use; nIDU, non-injecting drug use; LC, living conditions; MSM, men who have sex with men; JI, jail incarceration.

each independently associated with high HAV prevalence among DUs (Latimer et al., 2007; Reimer et al., 2007).

THE STATE OF CHRONIC LIVER DISEASE

The levels of prevalence of HCV antibodies are reported to be extremely high in all geographic areas; they are almost all over 70%, with few exceptions (United Nations Office on Drug, and Crime, 2006; Aceijas et al., 2004; Baral et al., 2007). We believe that the distinction between injective or non-injective use of illicit drugs is often limited: it is often hard to distinguish the manner of consumption even in the same subject; moreover, in a subject that had never used drugs by injecting, the risk of contracting typical injecting hepatitis has been demonstrated to be very high (Gyarmathy et al., 2002; Quaglio et al., 2003). It is most of all the carrier state of HCV (because of the high tendency of this virus to being chronic) to make DUs particularly at risk for the acute form of high lethality hepatitis A.

HEPATITIS A VACCINATION

For all these reasons both the WHO and the American Association for the Study of Liver Diseases have recommended HAV vaccine for people using illicit drugs, with or without chronic HCV infection. Furthermore, WHO recommends HAV vaccination for individuals with chronic HCV infection without specifying a different dose or schedule. The United States Advisory Committee on Immunization Practices cites a lack of evidence for anti-HAV vaccine administration on the basis of chronic HCV alone, but recommends that HAV-susceptible people with evidence of CLD or who are awaiting liver transplants, should be vaccinated (WHO, 2000; Crowcroft et al., 2001; Buxton and Kim, 2008).

Two effective vaccines have been available since 1995.

The former vaccination schedule for HAV consisted of 770 units; initially in three different doses, at 0, 1, 6 months. It has been made more rapid to meet the needs of travelers to exotic countries, who are the major purchasers of this vaccine. More recently, after an increased dose of vaccine (1440 units) was demonstrated to be effective after 1 month in almost all healthy young adults, a second dose of vaccine is proposed after a variable time of 6–18 months to get a longer-lasting vaccine coverage, since a lasting protection after the disappearance of specific antibody titer has not been demonstrated in HAV vaccination (in contrast to HBV vaccination; Andre et al., 2002; Baral et al., 2007). Such vaccination schedules have been demonstrated to be largely effective in seroconversion among the GPOP and adequate antibody levels were found after many years of vaccination, far beyond expectations. Vaccine-induced antibodies persist for more than 12 years in adults and there is good mathematical evidence that antibodies can persist for more than 25 years in more than 95% of vaccines (Nothdurft, 2008). Primary HAV vaccination failure in a healthy population has to be considered a rare event (Bonanni et al., 2005). Seroconversion after HAV vaccination has been defined by a particular neutralizing antibody level more than 20 mIU/mL. The immunogenicity of vaccine function has generally been identified by titring antibody levels. Even if recent studies have stressed the role of the cell-mediated immune response, in the protection against HAV infection the humorally mediated response, in the form of neutralizing antibodies, plays the main role (Baral et al., 2007; Nothdurft, 2008). Scientific literature reports a number of significant data on HAV vaccine coverage in the patients with CLD, most of all in HCV-carriers, regardless of their addictive status.

Even if sub-optimal response to vaccines has been reported in patients with CLD, more recent data seem to confirm that in the patients with CLD, the vaccine response to HAV vaccination is better than the response to the HBV one. The response in terms of seroconversion appears to be conditioned by the degree of fibrosis and by diabetes (Saab et al., 2005; Keeffe, 2006; Buxton and Kim, 2008; Kramer et al., 2009; Lugoboni et al., 2009). Generally, after two doses of HAV vaccine, seroconversion was achieved in a proportion between 75 and 98% of patients with CLD (Buxton and Kim, 2008; de Artaza Varaza et al., 2009; Kramer et al., 2009). Furthermore, there is a good level of evidence that the administration of three doses of combined HAV–HBV vaccine gives better

results even in the patients with advanced liver fibrosis (de Artaza Varaza et al., 2009; Kramer et al., 2009). However, it is not known to what extent the lower geometric mean anti-HAV concentrations demonstrated after vaccination in individuals with HCV is translated into a shorter duration of protection against HAV (Buxton and Kim, 2008).

Despite the encouraging responses in terms of immune response, the lack of serious side effects and cost–effectiveness, the supply, and the cover of HAV vaccine among patients with CLD are still sub-optimal (Shim et al., 2005; Daryani et al., 2007; Hernandez et al., 2009). Unlike HBV, where there are studies focused on DUs, to date there are still few studies that have evaluated HAV vaccination among DUs. After HBV vaccination, sub-optimal immunological responses (58–77%) have been reported among DUs despite the 95–99% proven in young adults from the GPOP (Baral et al., 2007; Brim et al., 2007).

HAV TARGETED TO DUs

In the literature, there are three types of studies on the validity of protection for HAV among DUs: the ones that have evaluated the response in terms of seroconversion and/or immunogenicity (also to predict the durability) of HAV vaccination, the ones that have evaluated the immune response after administration of HAV–HBV combined vaccination and the ones that have evaluated the effective protection in non-traditional settings such as accelerated vaccination campaigns during outbreaks of HAV and immunization blitz delivered to high-risk inner-city populations.

OFFER, COVERAGE, AND COMPLIANCE OF THE VACCINE FOR HAV

Hepatitis A virus vaccines have been widely shown to be safe, both the monovalent ones and the HAV–HBV combined ones. DU vaccination poses quite specific problems related not only to efficacy but also to supply and to compliance. There are very few studies that have evaluated these factors. The baseline study on supply and coverage of DUs with the HAV vaccine in addition to that for HBV, was performed in the USA and it evaluated more than 3000 DUs in five different cities. Although 83% of participants were willing to be vaccinated, only 36% of them received at least one dose of vaccine; coverage rate varied greatly from Baltimore (83%) to Chicago (2%). Adherence was highest when vaccine was available immediately on-site and lowest when offered only after receiving serological results. Monetary incentives bettered adherence when on-site vaccination was not available (Campbell et al., 2007). In a Swiss study that evaluated the HAV and HBV vaccination coverage in patients entering the heroin-assisted treatment between 2000 and 2002, only 10.3% of subjects received the vaccine despite the fact that 48.5% were susceptible to HAV (Gerlich et al., 2006).

Four other studies focusing on HAV vaccine compliance among DUs were found. Two groups performed the studies, the first (multicenter trial) in the northeast of Italy, and the second in Los Angeles, CA (USA). Both groups studied DU compliance with HAV vaccine and HBV as well. Many conclusions are similar, in the four studies, for the two vaccines. A good addiction therapy often means a good adherence to the vaccination programs. Multidisciplinary involvement by all the professionals of the services has proven successful in obtaining a good adherence to vaccination. Nurses have proven to be crucial in improving the acceptance and the adherence to vaccination in all the studies (Nyamathi et al., 2010a,b).

Programs designed for homeless DUs should include malleable psychosocial and health belief model variables; these aspects provide leverage points for interventions such as vaccine adherence (Stein and Nyamathi, 2010).

The vaccination programs directly charged by the services involved in the treatment of addiction are boast a lower drop-out rate. This aspect, strongly demonstrated in the biggest study that has evaluated compliance with vaccination among DUs (Quaglio et al., 2002, 2004b), seems to also be a crucial point in HAV vaccination, although assessed in a much smaller number of subjects (Quaglio et al., 2004a), and it has demonstrated a good adherence even to a more complex vaccination schedule as it is that of the HAV–HBV combine vaccine. The Addiction Services that vaccinate less are those with the worst results in terms of adherence to the programs (Quaglio et al., 2006a). Offering serologic screening in the absence of a concrete possibility of vaccination is inappropriate and illogical (Quaglio et al., 2006a). Rapid schedules, especially with combined HAV–HBV combined vaccine (0, 1, 2, 52 weeks), help in limiting the drop-out rate, but they have not been studied in terms of efficacy among DUs (Buxton and Kim, 2008).

Relying on the description that the DUs make of their serological hepatitis state is a source of error; in low threshold services, the following policy is recommended: *"Don't ask, take a blood sample, give a dose of vaccine, and try to schedule another visit"* (Kuo et al., 2004; Quaglio et al., 2006a; de La Fuente et al., 2007), but in the more structured services, it is more rational to keep an efficient data report to get the best solutions (Quaglio et al., 2004a; Lugoboni et al., 2009). Needle-exchange projects have proven effective in places that offer HBV vaccination and it is reasonable that it is the same thing for HAV vaccine (Des Jarlais et al., 2001; Altice et al., 2005). Prison facilities are other places that have a great opportunity to offer vaccination (Weinbaum et al., 2003). The difficulty of administering both doses of vaccine should not be discouraged from starting vaccination. There is not any risk to administering additional doses of vaccine (Quaglio et al., 2006a). Furthermore, immunizations delivered to high-risk inner-city populations in a blitz format can be successfully delivered (Weatherill et al., 2004).

REACTOGENICITY AND IMMUNOGENICITY OF MONOVALENT VACCINE AMONG DUs

Currently in the literature there are only two experimental studies that have evaluated such variables among DUs, both of them are multicenter studies conducted by Addiction Clinics in northern Italy. As already mentioned in the case of HBV vaccine, the response to the HAV vaccine has proved much weaker among DUs than among healthy adults. In the first study, which evaluated only seroconversion without calculating the geometric mean titer, only 60% of subjects (all HCV positive, HIV negative) showed seroconversion (HAV antibodies >20 mIU/L) after the first dose, while after the second dose all the subjects reached a protective antibody titer (Lugoboni et al., 2000).

In the second study, which consisted of dosing post-vaccine antibody concentration, in 36% of patients there was no seroconversion after the first dose and, even if after the second dose in

100% (43 on 43) of patients there was seroconversion, the antibody titer proved very low and short-lasting. The authors of both studies concluded by recommending administering the booster-dose after no more than 6 months from the first one because of the initial weak response among DUs. The HAV vaccination schedule currently proposed also for DUs proved ineffective because it has been studied only in the GPOP, where the first dose of vaccine led to seroconversion in almost all cases and where the booster-dose is required only to ensure lasting protection over time (Nothdurft, 2008; Kramer et al., 2009). Further studies are therefore required to optimize the timing and the doses to utilize among DUs to get adequate results.

There are different causes that explain this weak response to vaccination among DUs: immunity dysfunction, alcohol abuse, polydrug abuse, multiple bacterial infections, HCV infection, malnutrition, and cigaret smoking (Lemon and Thomas, 1997; WHO, 2000; Baral et al., 2007; Buxton and Kim, 2008).

Smoking status can be relevant because tobacco consumption is extremely prevalent among DUs and methadone-maintained patients but, despite this fact, substance abuse treatment programs too often ignore tobacco use (Baca and Yahne, 2008). All these factors should also be evaluated in the case of HAV vaccination for a better comprehension of immunogenicity and reactogenicity among DUs and for the development, if necessary, of a specific vaccine schedule.

HAV VACCINATION IN HIV-INFECTED PATIENTS

Hepatitis A virus vaccination is strongly recommended for HIV-infected patients, especially those with HCV co-infection or with CLD. An impaired immunogenicity of vaccines, including HAV vaccination, has been reported in patients with HIV infection (Baral et al., 2007). DUs are universally considered at high-risk of HIV infection, consequently immunological response of HAV vaccination is a relevant issue to consider.

The factor associated with better reactogenicity is the suppression of HIV replication at time of vaccination. A low viral load has been also associated with durable HAV response. There is less consent about the role of CD4 count and gender (Laurence, 2005; Weissman et al., 2006; Overton et al., 2007; Crum-Cianflone et al., 2011).

A schedule of vaccination with three doses of vaccine has been demonstrated more effective in HIV-infected adults (Crum-Cianflone et al., 2011).

However, no study evaluating the immunologic response among DUs with HIV has been found in the literature.

In all studies considered HAV vaccination has come out safe in HIV carriers.

COMBINED HAV–HBV VACCINATION

Since 1996 a combined vaccination against both viral forms has been marketed beyond the normal monovalent vaccines; it has been proposed with a schedule at 0, 1, 6 months and it has been demonstrated to be safe among the GPOP (Joines et al., 2001; Brim et al., 2007). As mentioned before, the vaccine gave better results, if compared to monovalent vaccine, among patients with CLD. Good tolerability and immunogenicity have prompted frequent trials aimed at reducing the administered doses and at accelerating the vaccination times (Beran et al., 2010; Burgess et al., 2010). Various accelerated schedules of combined vaccine have been proposed, generally targeted to last-minute travelers and, in some cases, to short-term correctional facility inmates.

This promising vaccine had been studied only once among DUs and it had been demonstrated to be well tolerated; the DUs study participants, however, responded with antibody levels significantly lower than that reported for the GPOP, even if, by the end of the study, all the DUs had developed a protective level. It must be emphasized that the antibody response to HAV was significantly greater than that found in DUs that had been vaccinated with monovalent vaccines: the combination of two antigens could therefore have an adjuvant effect as already reported in patients with CLD (Lugoboni et al., 2004; de Artaza Varaza et al., 2009).

EMERGENCY VACCINATION DURING OUTBREAKS

Many outbreaks of HAV involving DUs have been described. Although there have been no prospective observational studies evaluating clinical protection from HAV, four ecological studies have demonstrated that DUs, when vaccinated during an outbreak, retain the ability to mount protective immunological responses even after a single dose of vaccine.

The first experience of rapid vaccination of high-risk subjects (DUs and homeless) was performed in Bristol (United Kingdom) during an outbreak that involved a total of 123 subjects, most of whom were DUs and homeless. The strategy was described as effective in preventing further spread of infection (Syed et al., 2003).

In Rotterdam (the Netherlands), in 2004, there was an outbreak of HAV involving 30 homeless DUs. Contact tracing appeared very difficult in such a hard-to-reach group, so a mass vaccination campaign was performed over a 2-week period resulting in a single dose HAV vaccination. The immunization involved more than 1500 DUs and was effective in stopping the outbreak (Tjon et al., 2005). Other studies demonstrated that targeted vaccination campaigns, performed among DUs in all facilities, were able to mitigate a community-wide HAV epidemic (Gilbert et al., 2004) and an outbreak of HAV developed among prison inmates (Thorburn et al., 2001; **Table 2**).

THE COST–EFFECTIVENESS OF VACCINATION AGAINST HAV

Hepatitis B virus vaccination has proven to be extremely advantageous in terms of cost–benefits (Buxton and Kim, 2008; Lugoboni et al., 2009). There are no studies that have evaluated the cost–effectiveness of selective HAV vaccination among DUs as compared to other intervention models. Since most DUs are HCV infection carriers we will extrapolate some estimates made for this category of persons. Recent studies have evaluated the cost–effectiveness of two different vaccination strategies in patients with HCV: selective HAV vaccination and universal HAV–HBV combined vaccination. The selective HAV vaccination strategy proved to be the most cost–effective; however, the universal strategy would become more effective, thus it may be worth the additional cost (Weatherill et al., 2004; Jakiche et al., 2007).

However vaccination programs should be adapted to regional situations, according to differing epidemiology and disease burdens.

Table 2 | Hepatitis A virus vaccine among DUs.

Citation	Study population	Rewards/safety	Schedule	Maily comments
TRADITIONAL SCHEDULE: MONOVALENT ANTI-HAV VACCINE				
Lugoboni et al. (2000)	MMT, NE Italy	No/safe	0, 6 months	Sub-optimal response
Quaglio et al. (2004a)	MMT, ACs, NE Italy	No/safe	0, 6 months	Sub-optimal response
Civitelli (unpublished data)*	MMT, BMT, NE Italy	No/safe	0, 6 months	Seroconversion rate 96.8%
TRADITIONAL SCHEDULE: COMBINED ANTI-A/B VACCINE				
Lugoboni et al. (2004)	MMT, BMT, ACs, NE Italy	No/safe	0, 1, 6 months	Effective
ACCELERATED SCHEDULE FOR OUTBREAK CONTROL; MONOVALENT HAV VACCINE				
Thorburn et al. (2001)	Injailed DUs, ACs	No/safe	Single dose	Ecological, partial effective
Syed et al. (2003)	DUs and homeless	No/NS	Single dose	Ecological, effective
Gilbert et al. (2004)	Injailed DUs	No/safe	Single dose	Ecological, effective
Tjon et al. (2005)	DUs	No/NS	Single dose	Ecological, highly effective
Weatherill et al. (2004)	DUs and homeless	No/NS	Single dose	Ecological, effective

*MMT, methadone maintenance treatment; NE Italy, northeast Italy; ACs, addiction clinics; BMT, buprenorphine maintenance treatment; DUs, illicit drug users; NS, not stated. *Unpublished data.*

DISCUSSION

In developed countries, acute viral hepatitis decreased in the last decade. In the US, the acute HAV incidence was reduced by 92%, from 12 cases per 100,000 inhabitants in 1995 to 1 case in 2007, the lowest rate ever recorded (Daniels et al., 2009). In developed countries, HAV infection occurs in adulthood rather than in childhood. These changes may paradoxically enhance the disease burden, because the infection acquired during childhood can be largely asymptomatic while the opposite happens in adulthood. The increase in prevalence in young adults coincides with behavioral-related risk factors and disease importation.

Travel to high-risk areas in young people was associated with a significant increased risk of HAV infection (Diez Redondo et al., 2009). These aspects have a wide validity but they become crucial when DUs are considered. HAV rarely causes fulminant hepatic failure in the GPOP, but it is a cause of significant morbidity and mortality in subjects with CLD, a condition involving most DUs. Viral hepatitis is not the inevitable result. The availability of safe and effective vaccines for HAV and HBV can play a major role in stemming the phenomenon. The two vaccinations have partially different objectives and strategies and they find marked differences in attention and availability in the specialist facilities. HAV vaccination is less widely known and available than HBV vaccination, despite no lack of recommendations of international health organizations to vaccinate subjects at risk (Klevens et al., 2010). The low percentage of vaccinated DUs recognizes two causes: the absence of vaccination programs designed specifically for DUs and the low number of health workers able to vaccinate the DUs (François et al., 2002; van Steenbergen, 2002; Perrett et al., 2003).

There is good evidence that combined HAV/HBV vaccines have better immunogenicity than monovalent ones. However, many countries now immunize infants and/or adolescents against HBV and this raises the question whether to also immunize DUs with combined vaccine who had previously received HBV vaccine at an earlier age. At present, we do not really know if HBV vaccination received during adolescence and, even more, during infancy can protect these individuals once they become DUs. The lack of studies on this question is certainly a gap that should be filled.

Prevention of viral hepatitis among DUs may actually limit the spread of these diseases, not only in these subjects, but also in their relatives and in the health workers who deal with DUs. There is a clear need for definitive studies of vaccination strategies in DUs. As noted by other authors, there is a precise and disturbing finding in reviewing the scientific literature on vaccination in DUs: this group is at high-risk for vaccine-preventable hepatitis but it commonly receives the lowest immunization. This lack of attention occurs at all levels: not only in the management of clinical cases but also in terms of scientific speculation. It is hard to imagine other situations where live unanimous recommendations to vaccinate and a paucity of data, especially when applied to the specific group of DUs. Another paradox is that all the schedules of hepatitis vaccination are studied in young adults of the GPOP, whereas it has now been clear for at least 20 years that DUs respond very differently to immunization and the reasons for which this happens are not yet completely understood. People who have researched in the field of addiction know that DUs are not the ideal subjects on which to perform research and this is probably one of the reasons behind the lack of data in the literature. It is therefore crucial that more and more basic research on these topics be ongoing and that this research be possibly managed by the same health workers that offer and administer the hepatitis vaccinations to the DUs on a daily basis.

KEY LEARNING OBJECTIVES

1. HAV infection seems to be declining in much of the world, but the seroprevalence among DUs in non-endemic countries was reported as much higher than in the GPOP.
2. HAV outbreaks are still occasionally reported in low-endemic countries among inmates and inner-city high-risk populations.
3. Rapid immunization campaigns among DUs have been proved to be effective during HAV outbreaks.
4. Even if DUs are less responsive than the GPOP to HAV vaccination, as they are to HBV, it is feasible, safe, and immunogenic.

5. Vaccination programs with minor drop-out rates come to be those administered directly by addiction clinics personnel.
6. Vaccinating DUs, finally, is cost–effective.
7. A better understanding of immunizations among DUs may be crucial in the near future when, hopefully, anti-HCV and anti-HIV vaccines will be available.

FUTURE RESEARCH ISSUES

1. No study has ever been made on the duration of HAV antibody protection among DUs.
2. Even if studies have shown that persons with HIV respond less well to a first dose of HAV vaccination but fairly well to a second one, no study has ever been made to evaluate the immunologic response among DUs with HIV.
3. There is a clear need for more appropriate schedules for the DUs to be studied, especially the rapid schedules and the combined HAV–HBV vaccinations, that proved to have better immunogenicity than monovalent vaccines.
4. The co-factors associated to drug abuse should be studied more thoroughly.
5. The question of whether to also immunize DUs with combined vaccine who previously received HBV vaccine at an earlier age has not yet been answered.

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