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## Hepatitis A vaccine administration: comparison between jet-injector and needle injection

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### Abstract

**Introduction:** Type A hepatitis virus (HAV) is a serious health problem throughout the world and can be spread via fecal–oral contact. Both immune globulin and an HAV vaccine provide protection, but the vaccine gives complete protection. Efficacy of methods of vaccination in relation to the formation of anti-HAV antibodies is unclear; thus, this study seeks to determine if significant differences exist between the syringe as compared to the jet injection technique.

The purpose of this study was to compare in a randomized trial Bioject jet-injection system to a needle-syringe method. To determine if a significant difference between these two methods in seroconversion rates or geometric mean titers of anti HAV antibody occurs at day 15, 30, and 210 days after vaccination.

**Method:** Anti-HAV IgG(-) adult hospital employees were randomized to receive 1440 EL.U of hepatitis a vaccine (HAVRIX<sup>®</sup>) in 2 doses by either needle or jet-injector (Biojector<sup>®</sup>) system at month 0 and 6. HAV seroconversion titer results were measured by the Boehringer–Mannheim method.

**Results/discussion:** A higher proportion of persons who received HAV vaccine via the Biojector<sup>®</sup> seroconverted with anti-HAV level  $\geq 20$  mIU at day 15, 30, and month 7 when compared with a needle injection.

Side-effect profiles reported by participants in both methods were below those identified in current published and insert information, but the Biojector<sup>®</sup> had greater local reactivity in all categories when compared to the needle method. © 2000 Elsevier Science Ltd. All rights reserved.

**Keywords:** Hepatitis A antibody formation; Biojector<sup>®</sup>; HAVRIX<sup>®</sup> vaccine

### 1. Introduction

Type A hepatitis virus (HAV) is a serious health problem with the highest rates in under developed regions. HAV is a very stable enterovirus that withstands extreme climatic conditions. HAV has an incubation period of 20–50 days, replicates in the liver, and live virus is shed through the intestinal tract, and is transmitted via the fecal–oral route [1].

Early infection symptoms occur in more than 50% of adults and include malaise, fatigue, nausea, vomiting, and right upper quadrant abdominal pain [1]. Recovery takes 3–6 weeks; although, symptoms can last 6 months and are more severe in those with pre-existing liver disease. Once HAV infection runs its course, symptoms resolve and immunity occurs [2]. Immune globulin and HAV vaccines provide protection from infection but protection from immune globulin is temporary and incomplete [3]. HAV vaccine, made of whole formalin-inactivated virus particles [4], affords lasting protection with high antibody titers [5–9].

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Jet-injected vaccine has been shown to be as effective in eliciting a protective antibody response as a syringe injection [10–12]. Jet-injection requires less apparatus manipulation, allows medicine preparation ahead of time, reduces accidental puncture risk, and decreases administration time [13]. These are all important cost and time saving considerations when vaccinating large populations under time constraints.

The purpose of this study was to determine in a randomized trial if there is a significant difference between the Biojet jet-injection system and the needle-syringe method in seroconversion rates or geometric mean titers of anti-HAV antibody at day 15, 30, and 210 days after vaccination.

## 2. Method

The participants were adult employees from the Alaska Native Medical Center (ANMC). ANMC is a referral center for rural Alaska, which experiences 5–7 year epidemic cycles of HAV. The ANMC Hepatitis Program, on US Indian Health Service recommendation that health facilities at risk for HAV, offered

Table 1  
Z-scores and geometric mean antibody titers for each blood draw

Blood draws	Biojector <sup>®</sup>			Needle			z
	n	M	SD	n	M	SD	
15 days	151	42.86	2.181	149	28.56	2.169	2.39*
30 days	141	142.03	2.028	148	58.98	2.493	4.19**
7 months	126	1633.7	1.520	126	1344.53	1.186	2.37*

\*  $P < 0.02$ ; \*\*  $P < 0.0001$ .

vaccines to hospital employees. The Alaska Area IRB approved the study protocol. All self-referred subjects who were 18 years of age or older and signed informed consents prior to enrollment were eligible. Participants were screened for anti-HAV by commercial assay (HAVAB Abbott Laboratories, Abbott Park, IL, USA) at the ANMC laboratory. Seronegative participants were randomized to receive vaccines by a jet injector (Bioject) or by a traditional needle-syringe method which was accomplished using a computer generated randomization code. Each participant received 2 doses of HAVRIX<sup>®</sup> (1440 EL.U) vaccine in the deltoid muscle with either a 1"/23 G needle or a

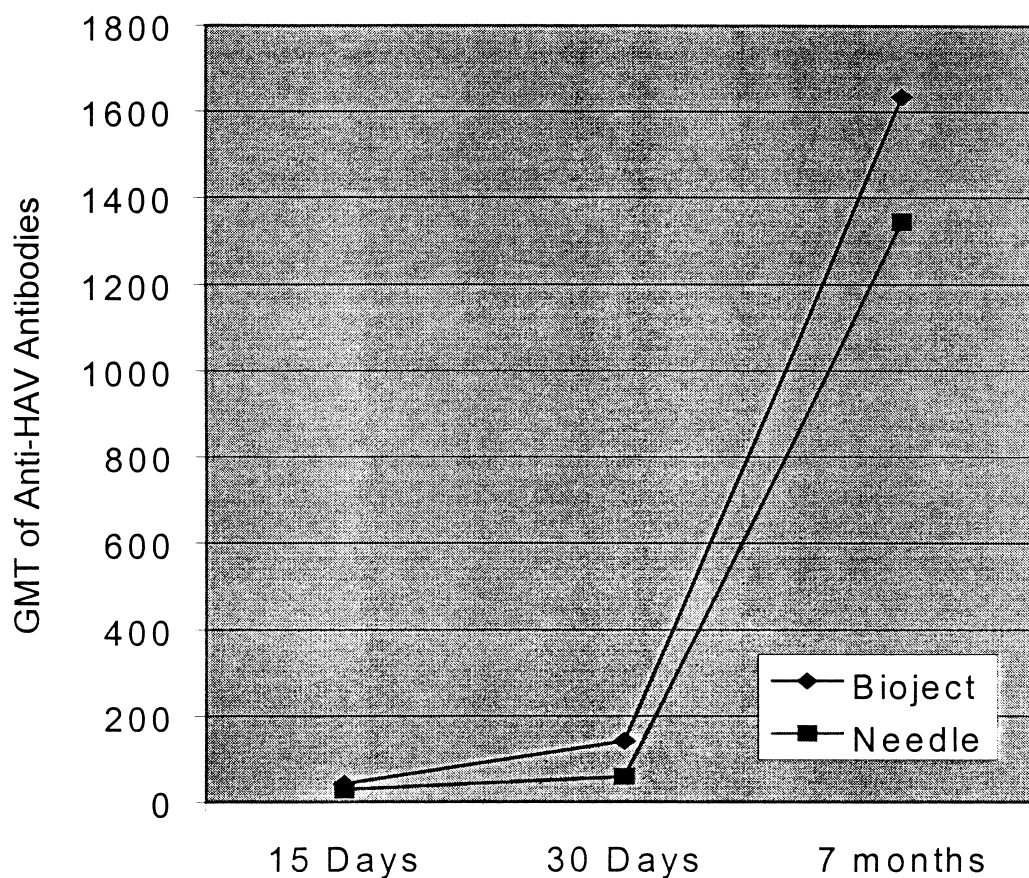


Fig. 1. A comparison of the mean HAV antibody titers for Bioject<sup>®</sup> and syringe injection methods.

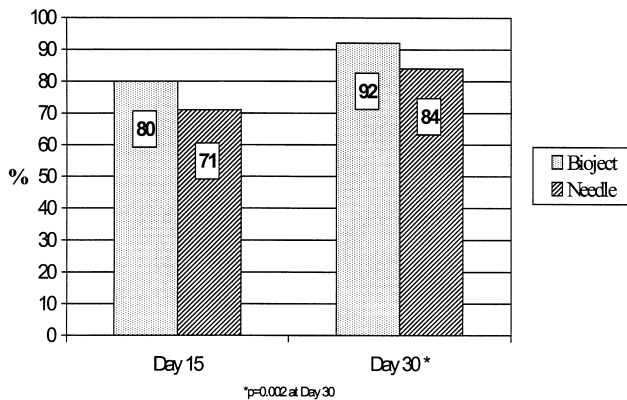


Fig. 2. % comparison of HAV seroconversion  $\geq 20$  mIU by Biojector<sup>®</sup> method and needle method at 15 and 30 days post vaccine.

jet-injector (Biojector<sup>®</sup>) system at months 0 and 6. Those with acute febrile illness were excluded from the study. There were two non-responders; one on transplant rejection medications was excluded while the other, taking multiple medications for chronic illnesses, was included in analysis.

To assess differences in HAV IgG titers between the 2 groups, blood was drawn on day 15, 30 and month 7 post-vaccine. Anti-HAV post vaccine titers by the Boehringer–Mannheim method at SmithKline Beecham contract laboratory in Miami, Florida were expressed in milli-International Units per milliliter (mIU/ml). A level of  $\geq 20$  mIU was defined as seroconversion to anti-HAV positive. Of the 321 enrollees, 151 Biojector<sup>®</sup> vs 149 needle method participants were drawn at day 15, 141 to 148 at day 30, and 126 for both at month 7.

Side effect data was collected in the form of a diary card. Individuals were instructed to complete the card for each of the 3 days after receiving the vaccine and return it by mail. In event the card was not received in a timely fashion (within 2 weeks), contact was made to complete the information by telephone or by interview.

### 3. Results

Mean age of participants in this study was 41 years, with a median of 40 years old in the Biojector and 42 in the needle group. In each group ethnic distribution was comparable with 55% of the participants Caucasian, 20% Alaska Native, <1% Black or Hispanic, 3% other ethnicity and 20% unknown. There was almost 2:1 female to male representation overall with a total of 206 females to 115 males: 109–52 in the Biojector<sup>®</sup> group and 97–63 in the needle group.

Analysis of data showed that in participants who received biojet, a significant increase in HAV antibody GMT on days 15, ( $z = 2.39$ ;  $P < 0.02$ ) 30, ( $z = 4.19$ ;  $P < 0.0001$ ) and month 7 ( $z = 2.37$ ;  $P < 0.02$ ) was noted when compared to those who received a needle injection (Table 1, Fig. 1). Participants in the Biojector<sup>®</sup> group had a greater proportion of persons with an anti-HAV level  $\geq 20$  15 (day) and 30 (day) than the needle method (Fig. 2) and this was significant ( $P = 0.002$ ) at 30 day. There was no significant effect of injection type on HAV GMT related to age or gender.

Diary cards were returned from 151 Biojector<sup>®</sup> and 150 needles for doses one and 133 Biojector<sup>®</sup> and 131 needles for dose 2. Local reactions reported on the diary cards were greater in the Biojector<sup>®</sup> group for both doses (Table 2).

### 4. Discussion

Our results demonstrate that the administration of the HAV vaccine by Biojector<sup>®</sup> resulted in a higher anti-HAV GMT when compared to needle injection at day 15, 30, and month 7 in this study population. The results are consistent with findings from Parent du Chatelet et al., who found jet injections produce significantly greater HAV antibodies when compared to the syringe method of medication delivery [13]. Regarding seroconversion of the HAV titer  $\geq 20$  mIU, as defined as the minimum level conferring immunity, the Biojector<sup>®</sup> resulted in about a 9% greater serocon-

Table 2  
Side effects comparing Biojector<sup>®</sup> vs needle/syringe

	Dose #1		Dose #2	
	Biojector <sup>®</sup>	Needle/syringe	Biojector <sup>®</sup>	Needle/syringe
Fever <sup>a</sup>	6% (10/156)	6% (9/157)	3% (4/133)	2% (2/131)
Tired <sup>a</sup>	32% (50/156)	23% (36/157)	34% (45/133)	25% (33/131)
Red <sup>b</sup>	24% (37/156)	2% (3/157)	16% (21/133)	2% (3/131)
Swollen <sup>b</sup>	22% (34/156)	2% (3/157)	17% (23/133)	5% (6/131)
Bruised <sup>b</sup>	26% (40/156)	1% (2/157)	26% (35/133)	4% (5/131)

<sup>a</sup> Participant reported having a fever or feeling tired within 3 days of injection.

<sup>b</sup> Participant reported injection site was either red, swollen or bruised within 3 days following the injection.

version rate advantage over the needle method at day 15 and at day 30. This advantage is statically significant ( $P = 0.002$ ) [4]. However in a study by Mathei, slightly lower HBV antibody titers were seen with the jet injection with the hepatitis B vaccine compared to the needle syringe method [15].

The HAV vaccine is usually given intramuscularly by the needle injection method. Although other methods of injection exist (i.e. jet-injection and intradermal), the efficacy of these methods in relation to the formation of anti HAV antibodies is unclear. Initial research indicates that the hepatitis A vaccine via the intradermal route is poor and should not be used [12].

The differences between the jet-injection and the syringe method extend beyond physical differences in the apparatus. When giving an intramuscular vaccination by the needle method, the vaccine deposited forms a pool within the muscle, which is gradually absorbed and then circulated. When the jet-injection is used, the “needle-free pressure mechanism administration of vaccine probably follows the paths of least resistance to disperse more widely in the injected tissue than the needle method which may affect the uptake by antigen presenting cells [16]”. This may account for some of the Biojector<sup>®</sup>'s greater local reaction: redness, swelling, and bruising. The characteristic of the jet-injection methods resulting in greater inflammation at the site of injection may mean greater contact with immune-competent inflammatory cells, thus, increasing the systemic response and earlier development of immunity supported by the earlier, higher titers [17]. Local reactions to the hepatitis A vaccine in previous studies were reported at 56% which is considerably greater than any of the solicited effects reported by participants in this study [14].

The jet-injection creates multiple openings into the tissue so blood and serous fluid seepage are of greater cross-contamination concern. However, the Biojector<sup>®</sup> eliminates this problem and practitioner needle injury worry while encouraging efficiency, early preparation and safety in the design of a single-use, pre-fillable cartridge. A needle is used initially to draw up medication then discarded, the aperture of the cartridge is held firmly against the skin, contact with only one patient and disposed of immediately. The cartridge aperture size is chosen according to individual body mass and fat distribution. Most errors with jet-injection systems lie in choosing inadequate aperture size denoted in this system by the number of the cartridge, number 4 being of average adult size. This error can result in depositing medication in subcutaneous tissue rather than in deep muscle. In this study we used only number 3 syringes on small adults with no or little fat/muscle mass and adults <110 lb and number 4 for all other participants.

In conclusion, the jet-injection method of HAV vaccine delivery provided a significantly higher anti-HAV GMT at the three points in time (day 15, 30, and month 7), and significantly higher seroconversion of  $\geq 20$  mIU at day 30. However it is uncertain whether significant differences in seroconversion rates and GMT equate with actual differences in protection. The Biojector<sup>®</sup> may provide a significant advantage to travelers needing accelerated vaccine schedules due to time constraints and may prove invaluable in an outbreak situation when quick protection is needed. While there is still controversy surrounding the administration of the vaccine by jet-injection, this study supports the advantages in the use of the Biojector<sup>®</sup> in persons receiving hepatitis A vaccine. More research on the use of the Biojector<sup>®</sup> system with regards to other immunizations is needed.

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