

EPIDEMIOLOGICAL SURVEY FOR INCIDENCE OF SHIGELLOSIS AND HEPATITIS  
TO EVALUATE POTENTIAL FIELD TEST SITES FOR VACCINE TRIALS

PART II - VIRAL HEPATITIS

Final Report

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Epidemiological Survey for Incidence of Shigellosis and Hepatitis to Evaluate Potential Field Test Sites for Vaccine Trials: Part 2: Hepatitis

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HAV infection is highly endemic in Israel and extensive use of immunoglobulin is used to prevent the disease in the military. With the recent advances in the new HAV vaccine development, it has become necessary to evaluate the possibility of a vaccine trial in the IDF. In order to identify candidate populations for the trial, 2 groups were evaluated in this study. The 1st study group comprised of a selected group of soldiers completing compulsory military service and believed to be at increased risk of contracting the disease. The soldiers were evaluated for HAV antibodies at the end of their 3-year compulsory service and an attempt was made to ascertain their antibody status at conscription, in order to estimate seroconversion rate. The prevalence of anti-HAV antibodies in this group at discharge was 45.3%. In addition 3.2% were HBs antigen positive and 7.6% had anti-HBs antibodies. The 2nd group comprised members of the permanent force in which the prevalence of anti HAV antibodies was found to be 81.3%. These findings describe basic seroepidemiologic data on two populations in whom the new HAV vaccines can be tested.

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## SUMMARY

Hepatitis A virus (HAV) infection is highly endemic in Israel and extensive use of immune serum globulin is used to prevent the disease in the military. With the recent advances in the development of the new HAV vaccines, it has become necessary to evaluate the possibility of a vaccine trial in the IDF. In order to identify candidate populations for the trial, two groups were evaluated in this study. The first study group comprised of a selected group of soldiers completing compulsory military service and believed to be at increased risk of contracting the disease. The soldiers were evaluated for HAV antibodies at the end of their three year compulsory service and an attempt was made to ascertain their antibody status at conscription, in order to estimate seroconversion rate. The prevalence of anti-HAV antibodies in this group at discharge was 45.3%. In addition 3.2% were hepatitis B surface antigen positive and 7.6% had anti-hepatitis B surface antibodies. The second group comprised members of the permanent force in which the prevalence of anti-HAV antibodies was found to be 81.3%. These findings describe basic seroepidemiologic data on two populations in whom the new HAV vaccines can be tested.

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## FOREWORD

The development of new vaccines against shigellosis and hepatitis A, has necessitated the planning and execution of clinical trials of the vaccines. In order to improve the efficiency of these trials, and in order to effectively evaluate their efficacy, it was felt that serologic markers of evidence of previous disease and of susceptibility to future disease should be studied. The current study on the seroepidemiology of shigellosis and hepatitis A was carried out as a collaborative effort between the the Medical Corps of the Israel Defence Force and the Walter Reed Army Institute of Research. For the protection of human subjects, the investigator(s) have adhered to policies of applicable Federal Law 45CFR46. Citations of commercial organizations and trade names in this report do not constitute an official Department of the Army endorsement or approval of the products or services of these organizations.

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## 1.0 BACKGROUND

Hepatitis A virus (HAV) infection is highly endemic in Israel and recently the incidence was reported to be about ten times as high as that of the United States (4,15). By the age of 18 years, more than 50% of the population have anti-HAV antibodies (10) as compared with about 20% in the USA, indicating that there is a high rate of infection during childhood. Ethnic differences in the prevalence of anti-hepatitis A antibodies within the Jewish population have been described, with those originating from Asia and Africa having a much higher prevalence than those from Europe and North America (7,10). These ethnic differences have in part been ascribed to variations in socioeconomic status, although they persist even after controlling for education level (7,10). This phenomenon contrasts with findings in other parts of the world, where racial differences have not been observed after taking into account socioeconomic status (3,16). Thus factors other than socioeconomic status may account for the ethnic differences in hepatitis A virus infection in Israel. There is a declining trend in the incidence of the disease among children and the proportion of the adult population which is susceptible is increasing (10). Consequently the problem of HAV infection in the military population may well increase in the future.

Studies in the Israel Defence Force have shown HAV infection to be the cause of more than 80% of all clinical cases of infectious hepatitis (11). Passive immunization with immune serum globulin (ISG) is used liberally in the military, both as post-exposure prophylaxis and, in a large section of this population, as annual pre-exposure prophylaxis. Controlled studies have demonstrated that this policy is highly effective in reducing the incidence of the disease among soldiers and markedly reduces the occurrence of epidemics of hepatitis (8).

An inactivated whole virus vaccine is currently undergoing laboratory and safety tests (1). Such a vaccine would clearly be of great value in the prevention of the disease in the IDF and would eliminate the need for repeated immunisation with ISG.

## 2.0 SPECIFIC AIMS

### Objectives

1. To determine the prevalence of anti-hepatitis A and B antibodies in subpopulations of conscripts in the IDF and to estimate the incidence of clinical and subclinical hepatitis A and B in subpopulations in the IDF.
2. To determine the prevalence of anti-hepatitis A antibodies among members of the permanent force of the IDF.

### 3.0 METHODS

#### 3.1 Study design

Prevalence and historical prospective studies.

#### 3.2 Study population characteristics

Blood samples are routinely drawn from a random sample of recruits each year and the serum stored at  $-20^{\circ}\text{C}$ . Repeat samples are drawn from the same recruits at the time of their discharge from the army, usually 3 years later. A sample of soldiers conscripted between 1983-4 were selected from this standard sample and their blood samples were used to determine both clinical and subclinical hepatitis A and B. Clinical hepatitis incidence was determined from the reports to the epidemiology branch of the IDF. A further sample of members of the IDF permanent force were selected and blood samples were drawn to determine the prevalence of anti-HAV antibodies.

#### 3.3 Sample sizes

##### a. Conscripts

472 male soldiers recruited between 1982-4

##### b. Permanent force

529 males

#### Note

The prevalence of antibodies against hepatitis A among recruits to the IDF differs markedly by ethnic group and educational status. In the 1984 survey (10), the prevalence of anti-HAV antibodies in the IDF was 54.0%. The prevalence among those of Western origin was 28.0% and the prevalence among those of Eastern origin was 71.1%. When broken down into groups according to educational status the picture was as follows:

|                              |                        |         |
|------------------------------|------------------------|---------|
| For those of Eastern origin: | <12 years of schooling | - 79.4% |
|                              | >=12 years             | - 65.1% |

|                              |                        |         |
|------------------------------|------------------------|---------|
| For those of Western origin: | <12 years of schooling | - 56.0% |
|                              | >=12 years             | - 22.0% |

In this study it was decided that the incidence of HAV infection be determined for the highest risk group which comprises those of

Western origin with  $\geq 12$  years of schooling. In this way the maximum incidence of the disease could be determined.

### Hepatitis serology

The antibody studies were performed at the central IDF laboratories. Sera was separated from the whole blood and frozen at  $-20^{\circ}\text{C}$  until tested. Qualitative evaluation of anti-HAV antibodies was determined by means of solid phase radioimmunoassay (HAVAB - Abbott Laboratories, N. Chicago, IL). HBsAg and anti-HBs were assayed by AUSRIA-II radioimmunoassay (Abbott Laboratories, North Chicago, IL).

### Interview data

Data available included demographic data (including age, country of origin, education, number of siblings and number of children) and details of military service were obtained. Country of origin was defined by the fathers birth place (or where this was Israel, the paternal grandfathers birthplace). Three broad areas of origin, Israel, East and West, were defined. West included Europe (excluding Turkey), the Americas, Australasia and Southern Africa. All others countries (mainly from the Middle East and North Africa) were classified as East.

### 3.5 Statistical analysis

The chi-square tests for difference between percentages and for trend were used to evaluate statistical significance in the univariate analysis. Multiple logistic regression analysis, a technique similar to multiple linear regression analysis when the dependent variable is dichotomous, was used to determine correlates of anti-HAV antibodies while controlling for other potentially confounding factors.

## 4.0 RESULTS

### Conscripts

The distribution of anti-HAV antibody status at conscription and at the end of military service three years later is given in Table 1. The prevalence of anti-HAV antibodies at discharge was 45.3% and at conscription was 35.8%. However, there was some doubt regarding the matching of some of the discharge and conscript sera and this may have overestimated the seroconversion rate.

The prevalence of anti-HBs antibodies and HBsAg at conscription

is given in Table 2. While the prevalence of HBsAg seems high the absolute number is small and the estimate is unstable. Overall, hepatitis B infection comprises a small proportion of viral hepatitis infections in Israel.

#### Permanent Force

The distribution of anti-hepatitis A antibody status by region of origin and age is given in table 3. Among both Easterners and Westerners, prevalence increased significantly with age although this was more marked among Westerners. The distribution by region of origin and education is given in table 4. The distribution by region of origin and number of siblings is given in table 5. Among Easterners, the prevalence of anti-hepatitis A antibodies ranged from 83.1 per cent among those with one sibling to 97.2 per cent among those with four or more. Among those from the West, the prevalence increased from 56.3 per cent with no siblings to 100 per cent with five or more. In both groups, there was a statistically significant association between number of siblings and presence of anti-hepatitis A antibody. In the same table it can be observed that there was a strong association between ethnicity and sibship size, with those from the East having significantly more siblings than those from the West. Results of the multiple logistic regression analysis are shown in table 6. The strongest correlate of anti-hepatitis A antibody was number of siblings followed by age, ethnic origin and number of children. Years of education was no longer significant after controlling for the other variables.

#### 5.0 DISCUSSION

This study demonstrated that the proportion of susceptibles to HAV infection in selected groups of recruits is high. The age-related changes in the prevalence of anti-HAV antibodies in the permanent force members appears to be a cohort effect (5) and there is evidence of a declining rate of infection among children in Israel (10). The prevalence of markers for previous HBV infection is relatively low although ethnic differences persist.

The seroconversion rate among conscripts in the study was relatively high. However, there was some doubt as to the identification of some of the subjects when linking conscript and discharge serum samples and this may be a source of bias.

The association of sibship size with hepatitis A antibodies may partly be explained by transmission of the disease among children. The fact that hepatitis A virus infection is largely asymptomatic in children (12), makes its transmission to close contacts more likely, since appropriate isolation would not be

carried out. For example, in a study in Peru, 27 per cent of asymptomatic children aged 1-4 were anti-hepatitis A IgM positive (9) and were believed to be a potent source of infection to others. It has been noted that hepatitis A virus infection is proportionately more common in employees of day-care centers and household contacts of children (particularly diapered) aged 1-2 years at daycare centers (2,6). Thus in large families there is an increased likelihood that there will be an asymptomatic infected child in the household, with the attendant risk of spread to the other siblings. Where the older children assist in caring for the younger children the risk of infection may be considerably enhanced.

It could be questioned as to whether sibship size itself is simply a marker of socioeconomic status and level of sanitation. In several studies prevalence of anti-hepatitis A antibodies has been related to social class and education (7) and improved living conditions have been associated with a decline in infection (12). In the present study all subjects were full-time members of the permanent military force and represent an employed, stable population. It does not seem likely that a significant number of the subjects live under conditions of compromised sanitation although one cannot exclude the possibility that some subjects experienced such conditions during childhood. It should be noted that ethnic differences in the prevalence of anti-hepatitis A antibodies among Israeli children were observed as recently as 1980 (13).

The age-related changes in the prevalence of anti-hepatitis A antibodies observed in the present study most probably reflect a cohort effect and not continuing infection in adulthood. Reported cases among adults represent only a small proportion of the cases of hepatitis in Israel and cannot explain the large increase in anti-hepatitis A antibody prevalence with age. Furthermore a decline in the prevalence of anti-hepatitis A antibodies among young adults has been documented in Israel between 1977 and 1984 (10). The cohort effect has been well-described in a number of European countries and Australia (5).

## 6.0 CONCLUSIONS

These findings have demonstrated that a large proportion of the military population are susceptible to HAV infection. The age-related changes observed in the permanent force members suggest the presence of a cohort effect and this would point to a decline in the incidence of infections in childhood and an increase in the proportion of the adult population who will be susceptible in the future. This would make the need for an active vaccination for the military even more essential.

These findings provide strong evidence of inter-sibling spread of HAV infection and suggests that one of the most important factors that will affect the prevalence of antibodies in sub-groups of the population will be changes in family size. When the new active HAV vaccines become available, they could be used in small children both to prevent the disease in these children and to reduce a major source of infection to siblings and adult contacts.

Because of the dynamic nature of the trends in the incidence of HAV infection in the Israeli population, there is a need to carry out regular seroepidemiologic studies in the military population. In this way planning of future HAV vaccine trials would be greatly improved.

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TABLE 1

Serology for hepatitis A total antibodies

|     | First blood at<br>conscription | Second blood at<br>discharge | Seroconversion<br>over 3 years |
|-----|--------------------------------|------------------------------|--------------------------------|
| n   | No. Positive (%)               | No. Positive (%)             | No. (%)                        |
| 472 | 169 (35.8)                     | 214 (45.3)                   | 45 (9.5)                       |

TABLE 2

Hepatitis B serology at discharge

| n   | HBsAg positive (%) | HBsAb positive (%) |
|-----|--------------------|--------------------|
| 472 | 15 (3.2%)          | 36 (7.6%)          |

TABLE 3

Prevalence of anti-hepatitis A antibody by age and ethnic origin  
in the permanent force IDF population

| Age group            | Easterners |          |          | Westerners |          |          |
|----------------------|------------|----------|----------|------------|----------|----------|
|                      | Tested     | Positive | Positive | Tested     | Positive | Positive |
|                      | N          | n        | %        | N          | n        | %        |
| 25-29                | 79         | 69       | 87.3     | 57         | 24       | 42.1     |
| 30-34                | 75         | 72       | 96.0     | 60         | 33       | 55.0     |
| 35-39                | 67         | 65       | 97.0     | 62         | 47       | 75.8     |
| 40-44                | 78         | 78       | 100.0    | 51         | 42       | 82.4     |
| Total                | 299        | 284      | 95.0     | 230        | 146      | 63.5     |
| Chi-square for trend |            |          | 12.5     |            |          | 24.0     |
| P                    |            |          | 0.0004   |            |          | < 0.0001 |

TABLE 4

Prevalence of antibody against hepatitis A virus by ethnic origin  
(by father) and years of education in the permanent force IDF  
population

| Years of<br>education | Easterners |          |          | Westerners |          |          |
|-----------------------|------------|----------|----------|------------|----------|----------|
|                       | Tested     | Positive | Positive | Tested     | Positive | Positive |
|                       | N          | n        | %        | N          | n        | %        |
| <12                   | 125        | 123      | 97.6     | 33         | 29       | 87.9     |
| 12                    | 95         | 88       | 92.6     | 63         | 36       | 57.1     |
| >12                   | 79         | 74       | 93.7     | 134        | 81       | 55.5     |
| Total                 | 298        | 284      | 95.0     | 230        | 146      | 63.5     |

TABLE 5

Prevalence of anti-hepatitis A antibody by ethnic origin and number of siblings in the IDF permanent force population

| Number of<br>siblings | Easterners |          |          | Westerners |          |          |
|-----------------------|------------|----------|----------|------------|----------|----------|
|                       | Tested     | Positive | Positive | Tested     | Positive | Positive |
|                       | N          | n        | %        | N          | n        | %        |
| 0                     | 2          | 2        | 100.0    | 16         | 9        | 56.3     |
| 1                     | 12         | 10       | 83.3     | 110        | 65       | 59.1     |
| 2                     | 26         | 22       | 84.6     | 59         | 37       | 62.7     |
| 3                     | 39         | 36       | 92.3     | 23         | 15       | 65.2     |
| 4                     | 41         | 40       | 97.6     | 8          | 6        | 75.0     |
| ≥ 5                   | 179        | 174      | 97.2     | 14         | 14       | 100.0    |
| Total                 | 299        | 284      | 95.0     | 230        | 146      | 63.5     |
| Chi-square for trend  |            |          | 9.3      |            |          | 7.7      |
| P                     |            |          | 0.0023   |            |          | 0.0054   |

TABLE 6

Variables associated with the presence of anti-hepatitis A antibodies in multiple logistic regression analysis in an adult population in Israel

| Variable           | Beta   | SE     | Chi-square | P        |
|--------------------|--------|--------|------------|----------|
| Number of siblings | 0.5935 | 0.1253 | 22.43      | < 0.0001 |
| Age                | 0.1566 | 0.0365 | 18.44      | < 0.0001 |
| Ethnic origin      | 1.3098 | 0.3829 | 11.70      | 0.0006   |
| Number of children | 0.2975 | 0.1441 | 4.26       | 0.0389   |
| Years of education | 0.0616 | 0.0442 | 1.94       | 0.1636   |

## 10.0 QUESTIONNAIRE

### Demographic information

1. Age
2. Sex
3. Country of origin
4. Years of education
5. Number of siblings

### Laboratory results

|       | <u>First blood</u> | <u>Second blood</u> |
|-------|--------------------|---------------------|
| HA    | -----              | -----               |
| HBsAb | -----              | -----               |
| HBAg  | -----              | -----               |

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