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SEROPREVALENCE OF HEPATITIS A ANTIBODIES IN TRAVELLERS AT THE EDMONTON TRAVELLERS' HEALTH CLINIC — ALBERTA

Introduction

International travel has become so routine that many Canadians travelling abroad do not always consider the health hazards associated with it. Such hazards are most frequently common infections such as hepatitis A (HAV) rather than exotic tropical diseases. Although the HAV has a worldwide distribution, it is particularly common in countries where poverty, crowding and lack of sanitation lead to poor personal, food and water hygiene.

Most residents in developing countries acquire immunity to HAV early in life so that by adulthood there is almost universal immunity to HAV[1]. In Canada and other industrialized countries, there is generally a low seroprevalence of hepatitis A antibodies (anti-HAV) in children and young adults. In the adult population in these countries, it is estimated that HAV seroconversion increases approximately 10% per decade so that by 60 years of age up to 80% of the adults may be immune to HAV[2].

The World Health Organization (WHO) recommends that all persons susceptible to HAV, who are travelling to high-risk areas with likelihood of exposure to HAV, should be offered immune globulin (IG) as a prophylaxis against hepatitis A infection[3]. Because most travellers do not know their anti-HAV status, implementing this recommendation presents a dilemma as to whether screening for HAV immunity should be considered. Screening all travellers for acquired immunity to HAV has not been considered to be practical or cost effective in Canada. Specific data related to anti-HAV prevalence rates in Canadian international travellers are not available.

The Edmonton Board of Health Travellers' Health Clinic provides pre-travel health services for the area. The majority of the travellers visiting the clinic are persons who have recently immigrated to Canada from high HAV-endemic areas, are over 30 years of age, and have extensive travel histories. At present, unless there is serologic evidence of previous hepatitis A infection, IG is offered to all persons who are thought to be at high risk of acquiring hepatitis A, based on their destination, duration of stay and mode of travel. IG is considered to have 80% to 90% effectiveness in suppressing or attenuating the hepatitis A infection[1]. Depending on the dose, protection from a single administration of IG lasts for only 3 to 6 months. Therefore, many frequent travellers have repeated administration of IG without any screening for anti-HAV. For persons who may have had a prior hepatitis A infection, this is an uncomfortable, unnecessary and costly intervention.

The purpose of this 3-month study was to determine the anti-HAV seroprevalence rates of travellers attending the Edmonton Board of Health Travellers' Clinic, and to investigate factors that might be associated with serologic evidence of immunity. Such data might identify groups for whom screening for immunity to hepatitis A would be cost effective.

Methods

Between November 1991 and February 1992, persons ≥ 16 years of age visiting the Edmonton Travellers' Health Clinic for whom IG would be recommended were requested to participate in this study.

The risk of susceptible travellers acquiring hepatitis A infection during international travel is influenced by a variety of factors, such as the incidence of hepatitis A in the area visited, the length of stay, the living conditions, and the prudence of the traveller in making safe food and water choices[4]. In this study, the following factors and assumptions were used to assess the risk of acquiring hepatitis A and the need for IG prophylaxis.

- *Serologic evidence of past hepatitis A infection*

  Life-long immunity was assumed.

- *Incidence of hepatitis A in the area*

All developing countries were considered high risk, particularly when the traveller's plans included staying in rural areas.

- *Length of stay*

A stay of ≥ 4 weeks in areas of high HAV endemicity was considered high risk. Short-term travel (< 4 weeks) was not usually considered to present a high risk requiring IG prophylaxis. However, when exposure was expected to be likely, e.g., camping/trekking in Nepal, IG was recommended for short periods of travel.

- *Living conditions/accommodation*

Travel beyond standard tourist itineraries or staying in substandard accommodation were considered high risk.

An informational sheet and an explanation of the study was provided to each traveller. Those who agreed to participate in the study were asked to sign a consent form, provide a blood sample and complete a short self-administered questionnaire. Information was obtained on age, sex, birthplace, extent of previous stay/travel in developing countries, history of or contact with hepatitis A infection, and number of siblings.

Verbal consent was obtained to record age and sex information on persons who did not wish to participate in the study and those who were excluded. The reasons for exclusion were insufficient English language comprehension, not enough time before departure to arrange for serologic screening, inability to obtain a blood sample, or a definite history of hepatitis A infection.

Public health nurses collected venous blood at the first visit or, if it was more convenient for the traveller, at a subsequent visit to the clinic. The blood samples were delivered to the Provincial Laboratory of Public Health for Northern Alberta in Edmonton on a weekly basis and were tested within 2 to 3 weeks of the procurement date.

All the sera were tested for anti-HAV using an enzyme immunoassay (EIA) kit supplied by ADI Diagnostics Ltd. Positive and negative controls were performed according to the manufacturer's instructions. Results were reported as positive or negative relative to a control-determined cut-off value.

All of the statistical analyses were carried out using the SPSS/PC + version 4.0.1 program.

All participants were informed of their serologic screening result by phone, mall or at the next appointment, and were provided with written documentation of their anti-HAV status. If the traveller was anti-HAV negative, appropriate information and IG prophylaxis was provided.

This study was reviewed and approved by the Edmonton Board of Health Research and Ethics Review Committee.

Results

Five-hundred and six people agreed to participate in the study and 202 declined (71% participation rate). The group who participated was not significantly different from the group who declined with respect to age or sex (Chi-square, p=0.17 and p=0.52, respectively).

Response rates for the questionnaire items were high, varying from 98% to 100%. Sera for anti-HAV were obtained from all 506 participants. One sample contained insufficient blood for analysis and, therefore, the results reported are based on 505 people. Of the 505 participants, 270 were male and 225 female. Gender was not recorded for 10 participants.

Seroprevalence of Anti-HAV

Overall, 47% of participants had antibody to hepatitis A, with similar rates in males and females (Table 1).

Table 1
Percentage of Males and Females with Immunity to Hepatitis A

Gender	Percentage
Males	47
Females	45

The number of participants with anti-HAV increased with age. Seropositivity was lowest in the 20 to 29 age group and increased to approximately 60% by age 50. After 50 years of age only modest increases were noted (Figure l).

Using the WHO's geographic grouping of countries, seropositivity by country of birth is shown in Figure 2. Approximately 50% of the study participants were born in Canada (n=279). Twenty percent of these travellers had immunity to HAV. In contrast, 80% of foreign- born participants were seropositive, the highest rate of immunity being reported in persons born in Middle-South Asia* and South East-Asia†.

There was a significant association between the number of siblings and positive serology results in both countries of high and low endemicity (Chi-square, $p < 0.001$). As the number of siblings increased, the rate of positive serology also increased (Table 2). However, regression analysis, which included age, number of siblings, country of birth, total time spent in countries of high HAV endemicity, and serology results, showed that the country of origin was the most important factor in predicting serology status. This variable accounted for 37% of the variance, while the other three variables accounted for only an additional 5% of the variance.

History was a poor predictor of serologic results. Seventy percent of those who said they had hepatitis had anti-HAV while 45% of those with no history of hepatitis were seropositive. There was no significant relationship between immunity to HAV and having lived with someone who had hepatitis A (Chi-square, p=0.08).

* Middle-South Asia includes Afghanistan, Bangladesh, Bhutan, India, Islamic Republic of Iran, Maldives, Nepal, Pakistan, and Sri Lanka.

† South-East Asia includes Brunei Darussalam, Cambodia, Indonesia, Laos People's Democratic Republic, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam.

Figure 1
Immunity to hepatitis A by age group

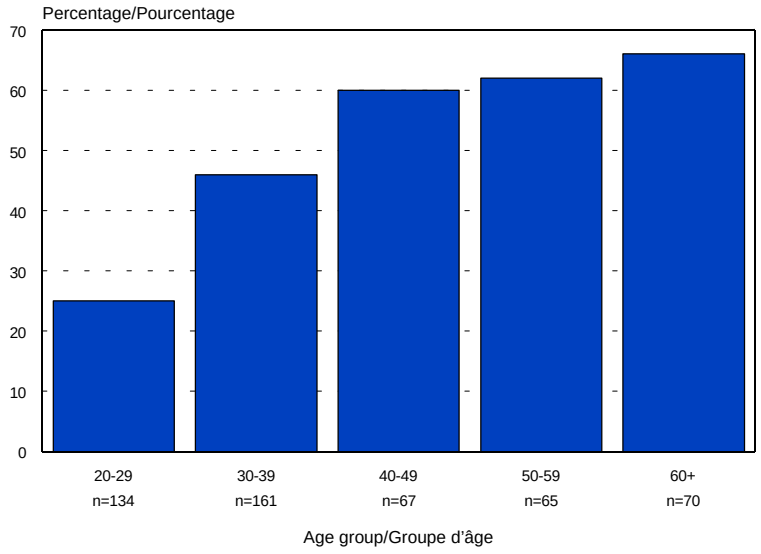


Table 2
Immunity to Hepatitis A by Number of Siblings

Number of Siblings	Number of Travellers	% Seropositive
0	18	28%
1 - 3	258	32%
4 - 5	100	52%
> 5	126	74%

Analysis of duration of time in countries of high HAV endemicity showed that spending ≥ 5 years in a high-risk area was associated with a much higher likelihood of being positive when compared to spending < 5 years.

Discussion

Hepatitis A is transmitted by the fecal-oral route. Hepatitis A infections frequently are asymptomatic, particularly when acquired during childhood. The HAV seroprevalence rate in this study was 47%. This is a rate somewhat higher than the observation made by Payment[2] who reported a 36% seropositivity rate in a randomly selected population in Montreal, Quebec. This higher rate may reflect the difference that exists between the populations who comprise the international travellers and the Canadian population at large with respect to immunity against HAV. As previously reported[2], and other observed results (Tuttle J, unpublished data), the prevalence of HAV antibodies is age-dependent. The most dramatic increase in the rate of seropositivity (from 25% to 46%) was noted between the 20 to 29 and 30 to 39 age groups. By 40 years of age, more than half (60% to 66%) of individuals have evidence of immunity.

Not unexpectedly, birthplace of the traveller was strongly associated with HAV seropositivity. Persons who were born in highly endemic areas, such as Middle-South Asia, South-East Asia and Africa had seropositivity rates of 97%, 93% and 72%, respectively, compared to 55% for Northern Europe and 20% for persons born in Canada.

Other factors considered in this study, such as history of hepatitis A or living with someone who had hepatitis A, did not show a significant association with being HAV seropositive. This indicates that these questions are not useful in assessing the need for IG. The lack of correlation between history and serologic status found in this study confirms that serologic testing is the only accurate method of determining immunity to HAV.

Green et al[5] noted that number of siblings was a strong predictor of HAV seropositivity, suggesting that in large families there was a greater opportunity to have an asymptomatic infected child who could infect other members of the family. In this study 74% of the travellers who had more than 5 siblings were HAV-antibody positive compared to 28% for travellers with no siblings. However, when several variables, such as age, number of siblings, place of birth and total time spent in high-risk areas, were included in a regression analysis, the place of birth was the most important in predicting seropositivity. Therefore, additional examination of this relationship would be useful.

Finally, the last factor considered in this study was extended travel histories of the traveller. Masterton et al[6] obtained travel-histories from over 1,000 British travellers and concluded that neither travel to nor the duration of stay in high-risk areas directly influenced the HAV seropositivity. Hall et al[7] suggested that the risk to the travellers is not necessarily related only to the high HAV endemicity in the area, but that the nature of travel and lifestyle while in the area may be more important or an equally important risk to the traveller.

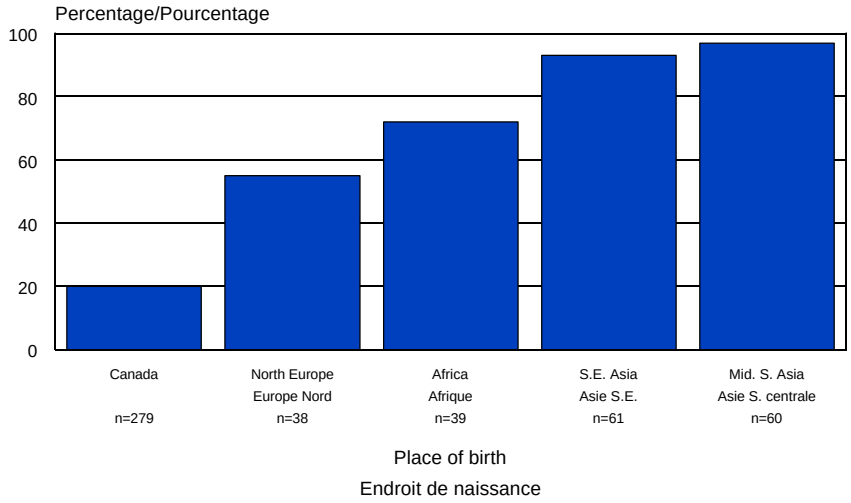
In this study, only the question of duration of stay/travel in high-risk areas was assessed. There was no significant difference in HAV seropositivity among travellers who spent < 5 years in areas of high HAV endemicity. For travellers with a stay > 5 years, a rate of 88% seropositivity was noted. However, in the absence of other information on confounding factors, such as place of birth, nature of travel and lifestyle, generalization of this observation should be made with caution.

Data from this study would suggest that a subset of travellers may exist who are most likely to have a high prevalence of HAV antibodies. The select groups could be defined as travellers ≥ 40 years of age, place of birth in area of high HAV endemicity, and a cumulative travel/residence history in a high-risk area > 5 years.

If the results of this 3-month survey can be generalized to the high-risk travel population visiting the travel clinic in Edmonton, it would suggest that at least 60% of travellers > 40 years of age would have immunity to HAV. Thus, a substantial number of persons receiving IG do not require it for protection against HAV.

Although advised of the benefit of determining their anti-HAV status, few travellers actually have a serologic screening done. For a one-time traveller this is of little consequence but frequent travellers may be subjecting themselves to unnecessary prophylaxis, discomfort, cost and risk. While reports of serious adverse reactions associated with IG are rare, no injection of a biological is without some risk.

Figure 2
Immunity to hepatitis A by place of birth



From an economic perspective, serologic screening as a cost- effective alternative to IG administration would be influenced by the rate of positivity in specific target groups, which could be identified by the frequency of travel to high-risk areas. The cost of providing a single injection of IG for a traveller is about $15.00, which would include the biological cost, handling charge and administration. The cost of anti-HAV serologic testing is in the range of $35.00, depending on the laboratory services used. Thus, routine anti-HAV screening would be cost effective for travellers who are likely to visit high-risk areas frequently and who are part of the subset of travellers identified in this study as likely to be seropositive. These criteria for selective serologic screening would greatly reduce the unnecessary use of IG.

Conclusion

The results of this survey would suggest that selective screening for anti-HAV immunity in the travel population should be considered. Because the rate of seropositivity varies from area to area, it would be advantageous to know the anti-HAV immunity profile of the population before establishing the screening criteria. To realize a higher degree of success in implementing this recommendation it would be necessary to provide convenient access to screening through the travel clinic and to provide a portable record of the anti-HAV status for each traveller screened.

Acknowledgements

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Editorial Comment

This study provides evidence that in Edmonton, at least, there are characteristics which indicate an increased risk of having acquired immunity to hepatitis A: age, country of birth and travel history. Since this report was written, a hepatitis A vaccine has been "licensed"in Canada. The cost of this vaccine, to a traveller, could be in the order of $106 (including dispensing fees). It would seem worthwhile to consider serologic testing for HAV immunity in those likely to be immune before embarking on a course of vaccine. However, age, at least, may become a less efficient indicator of immunity and, as the cost of the vaccine may decrease, a future study including a cost-benefit analysis would be worthwhile.

HEPATITIS A IN DOWNTOWN MONTREAL, QUEBEC, 1990-1992

Introduction

In 1991, the Community Health Department (CHD) of Hôpital Saint-Luc served a population of approximately 240,000 in an area that covered most of downtown Montreal, including a district with a large homosexual male population where businesses and medical clinics serving this population are concentrated.

Late in 1990, a hepatologist at the hospital informed the CHD that there had been a recent increase in clinical cases of hepatitis A that did not appear to involve the usual modes of transmission. After confirming that the number of cases reported to the CHD was a true increase, staff of the Public Health Unit of the Regional Board of Health and Social Services of Montreal Centre decided to conduct telephone interviews with cases to obtain additional information on their personal characteristics and possible modes of transmission involved.

Table 1
Percentage of Hepatitis A Cases in Males in 1990 and 1991

	1990	1991	Chi-square chi-carré	p =
Saint-Luc CHD	78% (47/60)	93% (187/201)	10.77	0.001
Montreal area (minus Saint-Luc)	65% (70/108)	74% (160/215)	3.23	not significant

Methods

Data on the number of reported cases of hepatitis A and other diseases at the Saint-Luc CHD and elsewhere were obtained from the computerized registry of the Quebec Public Health Laboratory. The registry was checked to eliminate duplication in reporting where cases had been notified by both the physician and the laboratory. All the cases of hepatitis A mentioned in this report were confirmed serologically, i.e., by detection of HAV IgM antibody.

The nurses who usually conduct case follow-up administered a standardized questionnaire to all those who could be reached by telephone. Only the results of the survey of notifications received in 1991 are presented here, i.e., from 1 January to 31 December, 1991.

Notifications of Hepatitis A

The number of reported cases per month remained unchanged among females, but notifications among males began to increase in August 1990 and peaked in September 1991 (Figure 1). There was a smaller increase in notifications from the rest of the Montreal area, i.e., l'Île de Montréal, and the Quebec City area but little or no increase in the rest of the province.

Table 1 indicates that the Saint-Luc CHD had a higher percentage of reported hepatitis A cases among males than the rest of the Montreal area in both 1990 and 1991, and that this percentage increased significantly between the two years at Saint-Luc CHD but not elsewhere. The cumulative incidence of the disease per 100,000 population for all ages shows the same phenomenon (Table 2).

The age distribution of cases at the CHD and in the rest of the province shows that the incidence begins to increase at age 20. In 1990, the proportion of cases among individuals ≥ 20 years was the same at the CHD and elsewhere in the province: 81% and 80%. In 1991, however, the proportion rose to 94% at the CHD and to 87% elsewhere, the difference having become significant (p= 0.01). This indicates that the increase affected primarily adults.

Table 2
Rate of Hepatitis A Cases per 100,000 Population, by Sex, Province of Quebec, 1990 and 1991

		1990	1991
All of the Montreal area	Males	13.7	41.7
	Females	5.7	7.5
Rest of the province	Males	3.6	7.5
	Females	2.1	2.6

Reports of Other Infectious Diseases

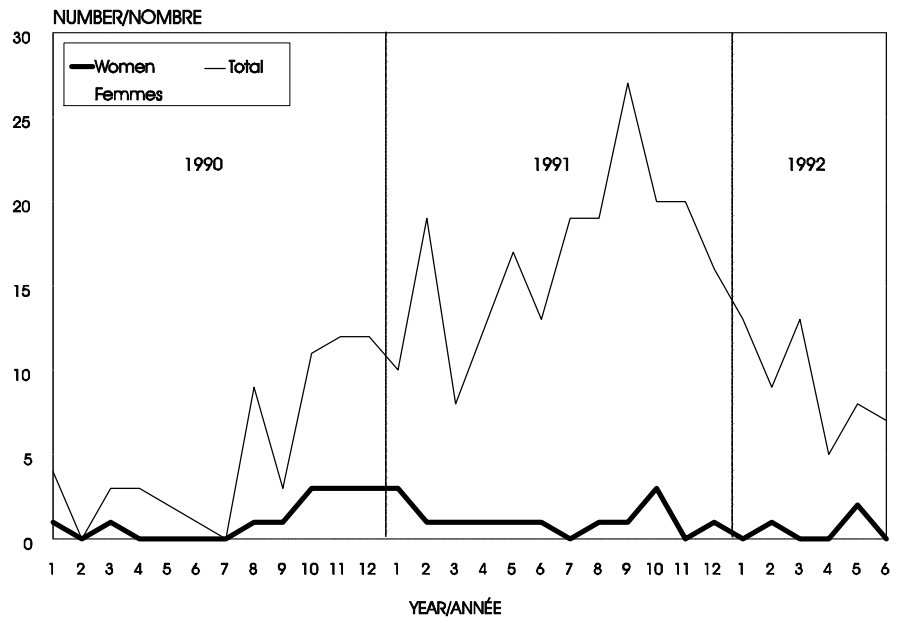
There was no increase in the number of notifications of other enteric infections (giardiasis, salmonellosis, shigellosis) or sexually transmitted diseases (STDs) (gonorrhea, syphilis) among males or females between 1990 and 1991.

Telephone Survey

Of the 201 cases reported in 1991, 126 included the patient's address; 109 of these could be reached, and 108 agreed to participate. One hundred and four of the 108 cases gave information that was sufficiently detailed to be analyzed.

The age distribution was essentially the same for survey participants as for all reported cases. However, there were fewer males among the participants than in the reported cases (88% vs 93%) because only 49% (92/187) of males compared with 86% (12/14) of females agreed to participate in the survey. This is due to the fact that physicians at clinics with a large homosexual male clientele do not record their patients' names on the notification and laboratory forms. As a result, it was not possible to reach a greater number of male cases. Of the males who did participate in the survey, 86% (69/80) said that they were homosexual, compared to 9% (1/11) of the females.

Figure 1
Number of hepatitis A notifications, by sex and reporting date, Saint-Luc Community Health Department, Montreal, 1990-1992



Modes of transmission

Table 3 shows the results of the telephone survey regarding modes of transmission.

Table 3
Presumed Modes of Transmission in Descending Order of Frequency

Same-sex sexual partner	77%	(70/91)
Oral-anal sex	38%	(29/76)
Contact with a known or suspected case	26%	(26/100)
Use of non-injectable drugs	19%	(18/96)
Consumption of shellfish	17%	(16/96)
Travel to countries with a high prevalence of hepatitis A	14%	(14/103)
Consumption of untreated water	5%	(5/100)
Use of injectable drugs	3%	(3/101)
Consumption of unpasteurized milk	1%	(1/100)
Contact with a day-care centre	1%	(1/102)

Role of oral-anal sex

Among the homosexual subjects, 73% responded to the question regarding oral-anal sex (51/70) and 53% of these (27/51) said that they had engaged in such activity recently. All of those who had oral-anal sex were homosexual men. None of the 21 of the 34 (62%) heterosexuals who answered this question replied affirmatively.

Normal modes of transmission among homosexual men

A history of travel to countries with a high prevalence of hepatitis A was quite significantly less frequent among the homosexual men than the other subjects: 3% (2/69) vs 48% (10/21), $p < 0.00001$. The same was true of a history of contact (other than oral-anal sex) with a known or suspected case: 4% (3/66) vs 35% (7/20), $p < 0.001$. These two modes of transmission accounted for 85% (17/20) of the cases among heterosexuals, but only 8% (5/66) of those among the homosexual men. The other possible modes of transmission are not associated with sexual orientation.

Discussion

Several facts suggest that this epidemic was affecting primarily homosexual men living in downtown Montreal:

1) The relative increase in the number of cases was greatest in the downtown area.
2) The increase occurred only among adult males.
3) Eighty-six percent of the males who responded to the questionnaire said that they were primarily homosexual. This figure obviously does not reflect reality because of those cases who were reported anonymously by clinics with a large homosexual clientele and could not be reached. Epidemics of hepatitis A have been previously reported in this population group[1].
4) Oral-anal sex appears to occur more frequently among homosexual men than among heterosexuals. It has been shown that such contact carries a risk of transmission of hepatitis A[2].
5) Although the opportunity for the normal modes of transmission, e.g., contact with a case, travel to a country with a high prevalence of the disease, etc., probably occurred more frequently in the study group than in the general population, this would not be sufficient to explain the epidemic.
6) Finally, the strong negative association between homosexuality and a history of contact with a case or travel to high-risk countries is an additional indication that transmission among homosexual men occurs differently than in the general population.

The fact that the number of cases of STDs and enteric diseases (other than hepatitis A) remained constant among males also indicates that it is unlikely that the increase in hepatitis A cases was due to an increase in risky sexual behaviour among homosexual men. This should have also resulted in an increase in the number of other STDs. For diseases other than hepatitis A, it is not known how many notifications came from homosexual men. It is, therefore, possible that a slight

increase in cases in this group is lost in the total cases among males. However, especially for syphilis and giardiasis, which are particularly common among homosexual men, at least a slight increase would have been expected since, whatever the cause of the epidemic, it was sufficient to quadruple the number of cases of hepatitis A among males.

Therefore, it seems more likely that the epidemic was due to a one or twofold increase in the introduction of the virus into the group of homosexual men from a human or non-human reservoir as a result of an unidentified environmental or behaviourial change, and not to increased transmission of the virus in the group. Once the virus is introduced in this group, conditions are favourable for its transmission, even in a non-epidemic period.

The increase in hepatitis A that was reported the same year in several other cities in Canada, the United States and Australia[3] leads us to the same conclusion: it is unlikely that sexual behaviour changed abruptly and at different times in different cities. It is easier to imagine that the hepatitis A virus was introduced more or less randomly into two geographically distinct populations.

In response to the epidemic, we alerted primary care physicians and gave them greater access to immune globulin. This was a situation where the recently licensed hepatitis A vaccine[4] could have been helpful, whether used in response to the epidemic (combined with immune globulin) or administered routinely to high-risk groups.

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Editorial Comment

From October 1994 to January 1995, the number of reported cases of hepatitis A for the whole region of Montreal began to increase again, from 6 to 21. In the months prior to this period the number had rarely exceeded 5. The majority of these cases are in men living in the downtown area, many of whom are homosexual. In January, a letter was sent to those physicians most likely to see new cases, to alert them to the outbreak and to remind them of the possible role of passive and active immunization in controlling it. Press releases were also sent to various periodicals to alert persons at high risk.

Announcement

14TH INTERNATIONAL PAPILLOMAVIRUS CONFERENCE

23-28 July, 1995
Quebec Hilton, Quebec City

The 14th International Papillomavirus Conference is a multidisciplinary meeting for scientists in the field of human and animal papillomavirus. The conference, presented in English, will focus on animal papillomaviruses, cell transformation, diagnosis/therapy, epidemiology, immunology, molecular pathogenesis, replication/transcription, virus-cell interactions and viral replication. A two-day preconference will be held on **22-23 July, 1995**.

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