Epidemiol. Infect. (2000), **124**, 459–466. Printed in the United Kingdom

The prevalence of antibodies to hepatitis A virus and its determinants in The Netherlands: a population-based survey

F. TERMORSHUIZEN[1], J. W. DORIGO-ZETSMA[2], H. E. DE MELKER[1], S. VAN DEN HOF[1] AND M. A. E. CONYN-VAN SPAENDONCK[1]*

[1] *Department of Infectious Diseases Epidemiology, National Institute of Public Health and the Environment, P.O. Box 1, 3720 BA Bilthoven, The Netherlands*
[2] *Diagnostic Laboratory for Infectious Diseases and Perinatal Screening, National Institute of Public Health and the Environment, P.O. Box 1, 3720 BA Bilthoven, The Netherlands*

(*Accepted 10 January 2000*)

SUMMARY

The prevalence of antibodies to hepatitis A virus was assessed in a Dutch nationwide sample ($n = 7367$). A questionnaire was used to study the association with various sociodemographic characteristics. Overall, 33·8% (95% CI 31·6–36%) of the population had hepatitis A antibodies. The seroprevalence was less than 10% in people under 35; it increased from 25% at 35 years to 85% at 79 years. For those 15–49 years of age, Turks (90·9%) and Moroccans (95·8%) had greater seroprevalence than autochthonous Dutch (20·2%) and other Western people (25%). Low or middle socio-economic status, as indicated by the highest educational level achieved, was associated with greater seroprevalence, independently of age and reported immunization (OR 2·11 and 1·45; 95% CI 1·67–2·67 and 1·11–1·89, respectively). These data suggest autochthonous Dutch and other Westerners born after World War II were exposed to hepatitis A during childhood less frequently than older birth cohorts. Thus, more susceptibility is likely in the coming decades. Since this means a greater risk of outbreaks in future years, and since morbidity and mortality are more frequent in older persons, studying the cost effectiveness of selective and general vaccination might be worthwhile.

INTRODUCTION

The incidence of hepatitis A virus (HAV) infection in The Netherlands decreased substantially when socio-economic and sanitary conditions improved after World War II [1]. A declining incidence of HAV infection results in fewer immune subjects. As a consequence, the population becomes more susceptible to HAV infections imported from abroad, and there may be an increased risk for local outbreaks and community-wide upsurges [2, 3]. The majority of HAV infections occur in young children in whom the infection is mostly asymptomatic, and who may transmit the virus to adults [4]. If these adults are susceptible to HAV, they may develop clinical hepatitis [4]. Since adults, and in particular, older adults often experience a more severe clinical course and higher case-fatality rates, vaccination may be considered in order to reduce the overall public health burden of hepatitis A. This is an issue that is currently a matter of debate [5–7].

We describe the prevalence of antibodies to HAV (anti-HAV) in The Netherlands as determined in a population-based survey [8, 9]. The data will provide insight into the protection of the Dutch population against HAV infection. The results will be helpful for the health authorities in targeting hepatitis A vaccination and to define the most cost effective vaccination strategy [7, 10–13].

* Author for correspondence.

METHODS

Study group and data collection

The National Institute of Public Health and the Environment (RIVM) has established a serum bank with specimens from a sample of the Dutch population that were taken in a population-based cross-sectional study carried out from October 1995 to December 1996. The aim of this Pienter Project was to facilitate sero-epidemiological studies, mainly for the evaluation of the National Immunisation Programme (NIP). Persons were recruited by drawing a sample from the registry office in 40 municipalities, which were selected with a probability proportional to their population size. An age-stratified sample (age cohorts 0, 1–4, 5–9, …, 75–79 years) of 380 individuals was randomly selected from each municipality. Subjects were asked to give a blood sample, fill out a questionnaire (by themselves or for a young child by one of the parents) and bring their certificates of the NIP, military service and travel vaccinations. The questionnaire contained questions on age, sex, ethnic origin, household members, education, occupation, religion, countries ever visited, vaccination, medical history, smoking and alcohol consumption. The overall response (for both the questionnaire and the serum) was 55·0% (8359 out of 15189 persons invited). The study design is described in detail elsewhere [8, 9].

Information relating to all participants and non-participants about age, sex, marital status, nationality, degree of urbanization, region, and whether they had been reminded by telephone or mail was available. The effect of differential probabilities of response for these variables on the sample estimate amounted to less than one standard error and was therefore ignored. Information regarding all participants and a subgroup of non-participants who were willing to fill out a questionnaire about the highest educational level obtained was available. No independent association with non-participation was found for this variable. No information was available for non-participants regarding the other variables included in this hepatitis A serosurvey.

Serology

We were able to determine the presence of total anti-HAV in 7367 (88·1%) serum samples. A commercially available Microparticle Enzyme Immunoassay (MEIA) (Abbott Laboratories, North Chicago, Ill) was used according to the manufacturer's instructions for detection of total anti-HAV. We refer to the percentage of serum samples positive for the anti-HAV test as seroprevalence or prevalence of anti-HAV.

Data analysis

The prevalence of anti-HAV by age group within each municipality was weighted by the proportion of the age group in the population of the municipality concerned to yield the age-weighted seroprevalence for each municipality. As each of the 40 participating municipalities was sampled with a probability proportional to its population size, an estimate for the national seroprevalence was obtained by averaging the seroprevalences over the 40 municipalities without weighting [8, 9]. In addition, the seroprevalence was estimated by age, sex and ethnic origin. If one or both of the participant's parents were born in a specified foreign country, the participant was considered to belong to that ethnic minority.

To establish associations with educational level as indicator of socio-economic status (SES), visits to HAV-endemic countries, risk in household, occupation, military service and reported immunization, uni-, bi- and multivariate analyses were performed by logistic regression.

Educational level was defined on the basis of the highest educational level achieved and was classified as low (primary school or lower general secondary education), high (higher vocational education or postgraduate) or intermediate (all other levels). The highest level achieved by one of the parents was used for participants younger than 17 years.

Turkey, Greece and other countries in Africa, Asia, Central and South America and the Middle East were considered HAV-endemic countries.

Whether child-to-child and child-to-adult transmission within the household may play a role in the risk of contracting an HAV infection was explored by considering the associations between the seroprevalence and the number of persons in the household as well as the presence in the household of children who attend a day-care centre or a primary school. This analysis was restricted to participants aged 49 years or less because only they were likely to belong to a household with young children at the time they answered the questionnaire.

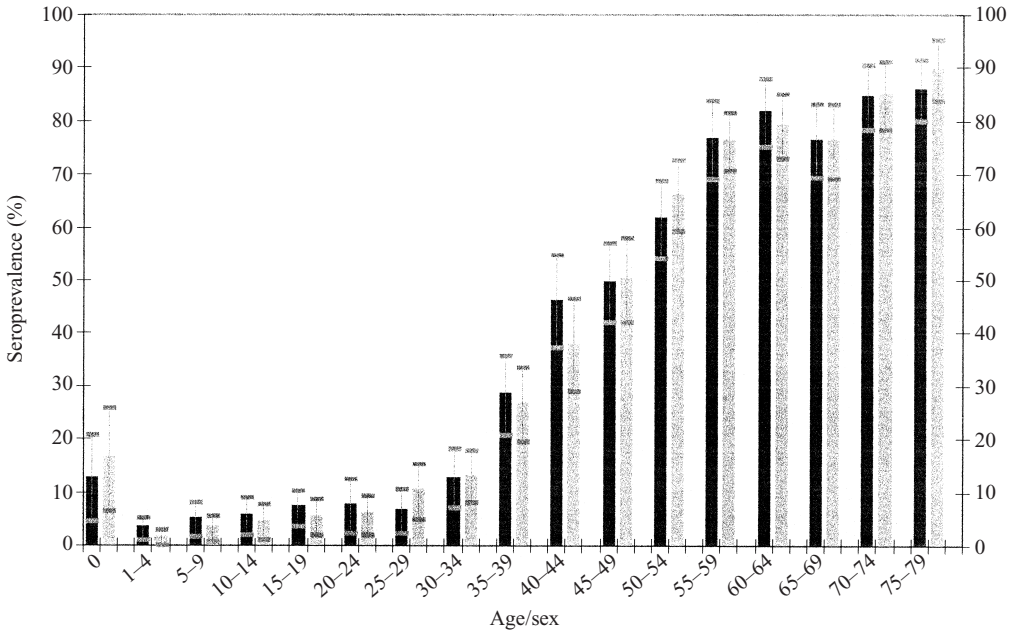

Fig. 1. Prevalence of anti-HAV (and 95% CI) by age and sex (black bars, men; grey bars, women).

Table 1. *Prevalence* (*in percentages*) *of anti-HAV by ethnic origin and age* (*n* = *7367*)

	Prevalence of anti-HAV (%)							
	0 years		1–14 years		15–49 years		⩾50 years	
Ethnic origin	*n*	%	*n*	%	*n*	%	*n*	%
Autochthonous Dutch	133	13·5	1456	1·7	2649	20·2	2331	77·3
Turkey	5	40·0	31	16·1*	33	90·9*	8	100·0*
Morocco		—	38	29·0*	24	95·8*	5	100·0*
Other Western countries	4	25·0	27	3·7	84	25·0	119	69·8
Indonesia		—	27	0·0	62	21·0	47	76·6
Surinam and The Netherlands and Antilles	3	0·0	32	12·5	34	38·2*	11	72·7
Other non-Western countries	7	14·3	77	7·8	61	50·8*	25	76·0
Unknown	3	66·7	9	0·0	13	30·8	9	88·9

(Prevalences shown with * are statistically significantly different from the percentage in autochthonous Dutch people in the same age group.)

Occupations possibly associated with HAV transmission were occupations with frequent contact with children (teachers at nursery and primary schools, staff of day-care centres), occupations in health care (nurses, medical doctors, paramedical staff) and others (military staff, charwomen, geriatric assistants) [14, 15].

Statistical analyses were performed with SAS software, version 6.12 for Windows. Whether a difference in seroprevalence or an odds ratio (OR) reached the level of statistical significance was evaluated by the 95% confidence interval (95% CI).

RESULTS

Prevalence of anti-HAV, overall and by age and sex

The age-weighted prevalence of anti-HAV in our sample was 33·8% (95% CI 31·6–36·0%). The seroprevalence was similar for men (34·4%, 95% CI 31·9–36·9%) and women (33·6%, 95% CI 31·4–35·8). The seroprevalence has been broken down by age and sex in Figure 1. The seroprevalence increased from 2 to 3% in the 1- to 9-year-olds to 86% in the 75- to 79-year-olds. A comparatively large seroprevalence was observed (14%) among infants.

https://doi.org/10.1017/S0950268899003842 Published online by Cambridge University Press

Table 2. *Age-adjusted odds ratios (OR) for associations between different variables and the prevalence of anti-HAV. Only persons from The Netherlands, other Western countries and Indonesia were included; infants (⩽1 year) were excluded (n = 6802).*

	n	OR	95% CI
Educational level			
Low	3451	1·97	1·64–2·37
Middle	1927	1·29	1·03–1·60
High	1380	1·00	
Unknown	44	2·97	1·11–7·98
Ever visited an HAV-endemic country?			
Never	4605	1·00	
Once or more	2197	0·73	0·63–0·84
Number of persons in the household (age ⩽ 49 years)			
1–2	842	1·00	
3–5	3129	1·13	0·89–1·44
> 6	303	1·29	0·80–2·09
Unknown	31	0·82	0·17–4·40
Children attending a day-care centre for primary school present in the household (age ⩽ 49 years)			
No	2264	1·00	
Yes	1955	0·95	0·76–1·18
Unknown	75	1·07	0·56–2·05
Occupational risk (age ⩾ 17 years)			
No	4062	1·00	
Staff in day-care centres/primary school	42	0·80	0·37–1·71
Staff in health care	152	0·74	0·48–1·15
Others (military staff, charwomen, etc.)	103	0·67	0·40–1·12
Unknown	735	0·99	0·80–1·21
Military service (male, age ⩾ 18 years)			
No	802	1·00	
Yes	607	0·83	0·63–1·09
Unknown	870	0·79	0·55–1·13
Immunization against HAV (as reported)			
Never immunized	5408	1·00	
Immunized – actively	59	4·51	2·25–9·04
Immunized – passively	352	0·67	0·51–0·89
Immunized – unknown how	94	0·98	0·58–1·64
Unknown	889	1·11	0·92–1·34

Seroprevalence by ethnicity and age

The seroprevalence is given both by ethnic origin and age in Table 1. Age has been broken down in four broad categories: infants (0 years), children (1–14 years), young and adult persons born after World War II (15–49 years), and older (⩾ 50 years). The age-specific seroprevalence of people from Turkey and Morocco (except infants) was statistically significantly higher than that of autochthonous Dutch people in the same age groups. In contrast, the age-specific seroprevalence for those from other Western countries and Indonesia did not differ significantly from the seroprevalence for autochthonous Dutch people in the same age groups. For people from Surinam, the Netherlands Antilles and other non-Western countries, the seroprevalence in the intermediate age group (15–49 years) was statistically significantly greater than the seroprevalence in Dutch people of the same age group.

Association with sociodemographic variables and vaccination status

The ORs for the associations between different variables and the prevalence of anti-HAV are pre-

https://doi.org/10.1017/S0950268899003842 Published online by Cambridge University Press

Table 3. *Logistic regression model for independent associations between age, educational level and having visited an HAV endemic country on one hand and the prevalence of anti-HAV on the other. This analysis was further restricted to participants who reported never to have received any immunization against HAV* ($n = 5408$).

	OR adjusted	95% CI
Age (years)		
1–14	1·00	
15–24	1·39	0·73–2·68
25–34	4·51	2·65–7·68
35–39	16·05	9·91–25·97
40–49	42·40	27·42–65·56
50–54	92·28	57·54–147·99
55–79	205·37	133·52–315·87
Educational level		
Low	2·11	1·67–2·67
Middle	1·45	1·11–1·89
High	1·00	
Unknown	2·47	0·78–7·83
Ever visited an HAV-endemic country?		
Yes	1·00	
Once or more	0·87	0·72–1·03

Hosmer and Lemeshow goodness-of-fit statistic = 9·21 ($P = 0·24$).

sented in Table 2. The ORs were adjusted for the possible confounding effect of age. For this analysis we combined the data of autochthonous Dutch people, people from other Western countries and from Indonesia because of the similarity in age-specific seroprevalence (see discussion and Table 1). Furthermore, we excluded the data of infants aged 0 years from this analysis because their large seroprevalence reflects the presence of maternally-derived antibodies (see Fig. 1). A lower educational level was associated with a greater seroprevalence (OR > 1). Having ever visited an HAV-endemic country was associated with a smaller seroprevalence (OR < 1).

The reporting of active immunization against hepatitis A was associated with a greater seroprevalence, whereas the reporting of passive immunization was associated with a smaller seroprevalence.

No associations with the number of persons and the presence in the household of children who were attending a day-care centre or primary school, occupational risk and military service were established.

No association with homosexual behaviour of men was established, which might be due to the very small number of participants reporting this possible risk factor ($n = 20$, data not shown) [16].

The OR of the association with the variable 'having ever visited a HAV endemic country' was 0·83 (95% CI 0·72–0·96) when the variable 'educational level' was introduced simultaneously in the logistic model. This association subsided when the analysis was restricted to persons who reported never to have received any immunization against HAV: OR = 0·87 ($n = 5408$, 95% CI 0·72–1·03) (Table 3).

DISCUSSION

This is the first study in which the prevalence of anti-HAV and various sociodemographic determinants are assessed in a nationwide sample of the general Dutch population. In our sample, 33·8% of the Dutch population had antibodies to HAV in 1995–6. Increasing age was associated with increasing seroprevalence, particularly among participants aged 30 years or more. Because only a small part of the participants (7%) reported active or passive immunization against HAV, we may assume that the seroprevalence mainly reflects prior exposure to HAV. As the greatest part of the notified cases of hepatitis A in The Netherlands concerns young children, the steep rise in prevalence in the age range of 35–54 years (Fig. 1) may be regarded as a cohort effect [4]. The younger birth cohorts are exposed to HAV less frequently because of a declining force of infection [17]. A similar cohort effect has been described in a number of Western countries [6, 12, 17–20]. High and fluctuating notification rates of hepatitis A were observed in The Netherlands in the 1950s and 1960s, probably reflecting the transition from high to low endemicity [4, 21, 22]. From the 1970s onward, a low yearly incidence has been observed (approximately 6 notified cases per 100000 inhabitants) [4]. Thus, the seroprevalence in people younger than 30 at the time of the survey (1995–6) may reflect the low incidence of the last decades, whereas the seroprevalence in people 30–49 years of age in 1995–6 may reflect the higher incidence of the 1950s and 1960s. The greater seroprevalence in people born during and before World War II (older than 49 in 1995–6) probably reflects the high incidence of HAV infection during their childhood before the improvement of hygienic and sanitary conditions started to hamper the transmission [1, 17, 22].

An overall prevalence of anti-HAV of 52% and an increase with age was found in the sera of 505

https://doi.org/10.1017/S0950268899003842 Published online by Cambridge University Press

volunteer blood donors in The Netherlands in 1977. At that time, the seroprevalence in participants aged 20–29 years was 36%, whereas the seroprevalence in participants aged 10–19 years was only 7% [18]. In comparison, the age-specific seroprevalence in our study (Fig. 1) appears to have shifted approximately 20 years to the older age groups, which is in agreement with the postulated cohort effect [12]. The consequence of a diminished force of infection is that the immunity of the Dutch population against HAV will decrease further in the decades to come.

We found a comparatively large age-specific seroprevalence in people from non-Western countries. In people from Turkey and Morocco in the age group 15–49 years, the seroprevalence exceeded 90%. This suggests that the cohorts of people born after World War II in these ethnic minorities were exposed to an invariably strong force of infection.

The small age-specific seroprevalence in autochthonous Dutch people, people from other Western countries and people from Indonesia who are very well assimilated into Dutch society, suggests a similarity in their exposure to HAV.

To get insight into the transmission of HAV, we evaluated the effects of various sociodemographic characteristics on the prevalence of anti-HAV [19, 23]. We excluded the data of participants from Turkey, Morocco, Surinam, The Netherlands Antilles and other non-Western countries because of their greater age-specific seroprevalence, which suggest different epidemiological patterns.

A low educational level was independently associated with a greater seroprevalence. We regard the highest educational level achieved as an indicator of SES, although this is a matter of debate. The relationship between educational level and SES depends on age because of a cohort effect in educational participation [24, 25]. On the other hand, information on educational level has the advantage of being available for all participants, whether they are in paid employment or not. Furthermore educational level is stable during adult life and can be measured with high validity and reliability [26]. We took the possible confounding effect of age into account when examining the relationship between education and seroprevalence. The association with seroprevalence we found then is in agreement with other reports [23, 27]. A lower SES may be associated with substandard housing conditions and less knowledge of sanitary practices, which are known to be correlated with HAV transmission [2, 23]. Independently of age, participants who have visited a HAV-endemic country appeared to have a smaller seroprevalence, which contrasts with our expectations [28–31]. The effect of educational level seems to be partly responsible for this negative association, which is understandable if we consider that participants with a high educational level are probably more inclined to travel to distant countries and a high educational level is associated with a smaller seroprevalence. No positive association appeared when we took immunization into account. We may hypothesize that some participants did not give valid information on immunization against hepatitis A. Many participants reporting immunization against HAV were not able to distinguish active from passive immunization. Furthermore, many of the participants who reported active immunization (24 out of 59) appeared to have no antibodies to HAV. In view of the high sensitivity of the test used and the efficacy of the vaccine [32], this is probably due to the inability of these participants to give valid information on the exact nature of the immunization received. Still, we would expect a greater seroprevalence among participants who had visited a HAV-endemic country. In the period 1993–7, approximately 14% of the 2579 notified cases among autochthonous Dutch people (on average, 74 per year) concerned infections contracted abroad, which suggests that many travellers do not receive protection against HAV before departure and are at risk of HAV infection [4]. Even when assuming a considerable degree of underreporting (60% [1]), this yearly number of infections contracted abroad by autochthonous Dutch people is probably too small to give a difference in seroprevalence in a sample such as that described in this study, being a random selection from 16 million inhabitants. The presence in the household of children attending a day-care centre or primary school was not associated with a greater seroprevalence. This finding also differs with our expectations and other studies from which it appears that day-care centres/primary schools and household contacts may play an important role in the spread of hepatitis A [14, 29, 30, 33, 34]. Although the risk of HAV infection for the staff of day-care centres, nursery schools and primary schools is also known to be greater, we did not find a greater seroprevalence among participants reporting such an occupation [14, 15]. This last finding might be due to the small number of participants reporting such an occupation ($n = 42$, Table 2). Furthermore, transmission at day-care centres and schools manifests itself often in

outbreaks, which may imply that many parents, household members and nursery and primary school teachers never encounter HAV, and as a consequence, samples like the one described in this study may fail to define them as a risk group [33].

In conclusion, approximately one-third of the Dutch population is currently immune to HAV infection. Being born before 1960 and being of non-Western origin, especially Turkish or Moroccan, appears to be strongly associated with the prevalence of anti-HAV due to greater prior exposure to HAV. Furthermore, there was a weak and negative association between a higher SES, as indicated by the educational level, and the seroprevalence. On the basis of our current results, we may expect an increase of the number of HAV-susceptible subjects in the Dutch population in the decades to come. This implies potential outbreaks and the desirability of vaccination, either selective or general. An analysis of the cost effectiveness of different vaccination policies might be valuable.

ACKNOWLEDGEMENTS

We acknowledge the Public Health Services, the Pienter project team, H. Kooy and W. Westerhoff for their very useful contributions to the realisation of this study.

REFERENCES

1. Leentvaar-Kuijpers A. Wie komt in aanmerking voor immunisatie met een geïnfecteerd hepatitis A-vaccin? Ned Tijdschr Geneeskd 1994; **138**: 941–2.
2. Papaevangelou G. Epidemiology of hepatitis A in Mediterranean countries. Vaccine 1992; **10** (S1): S63–6.
3. Termorshuizen F, Laar MJW van de. Upsurge of hepatitis A in the Netherlands – early 1998. Eurosurveillance 1998; **3**: 110–2.
4. Termorshuizen F, Laar MJW van de. De epidemiologie van hepatitis A in Nederland: 1957–1998. Ned Tijdschr Geneeskd 1998; **142**: 2364–8.
5. Forbes A, Williams R. Increasing age – an important adverse prognostic factor in hepatitis A virus infection. J R Coll Phys Lond 1988; **22**: 237–9.
6. Lemon SM, Shapiro CN. The value of immunisation against hepatitis A. Infect Ag Dis 1994; **3**: 38–49.
7. Shapiro CN, Coleman PJ, McQuillan GM, Alter MJ, Margolis HS. Epidemiology of hepatitis A: seroepidemiology and risk groups in the USA. Vaccine 1992; **10** (S1): S59–S62.
8. Melker HE de, Conyn-van Spaendonck MAE. Immunosurveillance and the evaluation of national immunisation programmes: a population-based approach. Epidemiol Infect 1998; **121**: 637–43.
9. Hof S van den, Melker HE de, Suijkerbuik AWM, Conyn-van Spaendonck MAE. Pienter Project: description of serum bank and information on participants from the questionnaires. RIVM Report No. 213675005, Bilthoven, 1997.
10. Zaaijer HL, Lelie PN. De kosten van hepatitis A-profylaxe bij reizigers. Ned Tijdschr Geneeskd 1997; **138**: 948–9.
11. Buma AH, Beutels P, Damme P van, Tormans G, Doorslaer E van, Leentvaar-Kuijpers A. An economic evaluation of hepatitis A vaccination in dutch military personnel. Mil Med 1998; **163**: 564–7.
12. Beutels M, Damme P van, Vranckx R, Meheus A. The shift in prevalence of hepatitis A immunity in Flanders, Belgium. Acta Gastro Enterol Belg 1998; **LXI**: 4–7.
13. Schwartz E, Raveh D. The prevalence of hepatitis A antibodies among Israeli travellers and the economic feasibility of screening before vaccination. Int J Epidemiol 1998; **27**: 118–20.
14. Hoebe CJPA. Hepatitis-A-epidemie in Heerlen, eind 1996; het belang van immunisatie van migrantenkinderen. Ned Tijdschr Geneeskd 1998; **142**: 521–5.
15. Hofmann F, Wehrle G, Berthold H, Köster D. Hepatitis A as an occupational hazard. Vaccine 1992; **10** (S1): S82–4.
16. Leentvaar-Kuijpers A, Kool JL, Veugelers PJ, Coutinho RA, Griensven JP van. An outbreak of hepatitis A among homosexual men in Amsterdam, 1991–1993. Int J Epidemiol 1995; **24**: 218–22.
17. Schenzle D, Dietz K, Frösner GG. Antibody against hepatitis A in seven European countries. II. Statistical analysis of cross-sectional surveys. Am J Epidemiol 1979; **110**: 70–6.
18. Frösner GG, Papaevangelou G, Bütler R, et al. Antibody against hepatitis A in seven European countries. I. Comparison of prevalence data in different age groups. Am J Epidemiol 1979; **110**: 63–76.
19. Green MS, Tsur S, Slepon R. Sociodemographic factors and the declining prevalence of anti-hepatitis A antibodies in young adults in Israel: implications for the new hepatitis A vaccines. Int J Epidemiol 1992; **21**: 136–41.
20. Gust ID, Lehmann NI, Lucas CR. Relationship between prevalence of antibody to hepatitis A antigen and age: a cohort effect? J Infect Dis 1978; **138**: 425–6.
21. Shapiro CN, Margolis HS. Worldwide epidemiology of hepatitis A virus infection. J Hepatol 1993; **18** (S2): S11–4.
22. Gust IA. Epidemiological patterns of hepatitis A in different parts of the world. Vaccine 1992; **10** (S1): S56–7.
23. Redlinger R, O'Rourke K, VanDerslice J. Hepatitis A among schoolchildren in a US-Mexico border community. Am J Public Hlth 1997; **87**: 1715–7.
24. Reijneveld SA, Gunning-Schepers LJ. Age, socioeconomic status, and mortality at the aggregate level. J Epidemiol Comm Hlth 1999; **48**: 146–50.

25. Rossum CTM van, Mheen H van de, Witteman JCM, Mackenbach JP, Grobbee DE. Socioeconomic status and aortic atherosclerosis in Dutch elderly people. The Rotterdam study. Am J Epidemiol 1999; **150**: 142–7.
26. Droomers M, Schrijvers CTM, Stronks K, Mheen D van de, Mackenbach JP. Educational differences in excessive alcohol consumption: the role of psychosocial and material stressors. Prevent Med 1999; **29**: 1–10.
27. Szmuness W, Dienstag JL, Purcell RH, Harley EJ, Stevens CE, Wong DC. Distribution of antibody to hepatitis A antigen in urban adult populations. N Engl J Med 1976; **295**: 755–9.
28. Steffen R. Risk of hepatitis A in travellers. Vaccine 1992; **10** (S1): S69–72.
29. Maguire HC, Handford S, Perry KR, et al. A collaborative case control study of sporadic hepatitis A in England. C D R 1995; **5**: R33–40.
30. Mele A, Stroffolini T, Palumbo F, et al. Incidence of and risk factors for hepatitis A in Italy: public health indications from a 10-year surveillance. J Hepatol 1997; **26**: 743–7.
31. Moschen ME, Floreani A, Zamparo E, et al. Hepatitis A infection: a seroepidemiological study in young adults in north east Italy. Eur J Epidemiol 1997; **13**: 875–8.
32. Chen XQ, Bülbül M, Gast GC de, Loon AM van, Nalin DR, Hattum J van. Immunogenicity of two versus three injections of inactivated hepatitis A vaccine in adults. J Hepatol 1997; **26**: 260–4.
33. Hadler SC, Webster HM, Erben JJ, Swanson JE, Maynard JE. Hepatitis A in day-care centers. N Engl J Med 1980; **302**: 1222–7.
34. Benenson MW, Takafuji ET, Bancroft WH, Lemon SM, Callahan MC, Leach DA. A military community outbreak of hepatitis type A related to transmission in a child-care facility. Am J Epidemiol 1980; **112**: 471–81.