

Marked decrease in the incidence and prevalence of hepatitis A in the Basque Country, Spain, 1986–2004

G. CILLA¹, E. PÉREZ-TRALLERO^{1,2*}, J. ARTIEDA³,
E. SERRANO-BENGOECHEA¹, M. MONTES¹ AND D. VICENTE¹

¹ *Servicio de Microbiología, Hospital Donostia, San Sebastián, Spain*

² *Departamento de Medicina Preventiva y Salud Pública, Facultad de Medicina, Universidad del País Vasco, San Sebastián, Spain*

³ *Servicio de Epidemiología, Subdirección de Salud Pública de Gipuzkoa, San Sebastián, Spain*

(Accepted 16 May 2006; first published online 20 July 2006)

SUMMARY

The aim of this study was to determine changes in the epidemiology of hepatitis A virus (HAV) infection in the Basque Country, Spain, and to evaluate their implications for vaccination strategies. A total of 1356 persons were enrolled in a study of the prevalence of anti-HAV in 2004 and compared with two previous studies (1986–1987 and 1992). The selection method and the characteristics of the population were similar in the three studies. A marked decline in the seroprevalence in all age groups ($P < 0.001$) and in the incidence of cases/100 000 inhabitants (from 38.0 in 1986–1988 to 2.9 in 2002–2004) were observed. The mean age of patients with hepatitis A increased from 17.7 years in 1986–1992 to 21.2 years in 1993–1998 and 25.3 years in 1999–2004 ($P < 0.001$). Between 1997 and 2004, 20% of patients were hospitalized. The changes observed have occurred rapidly causing a change in the epidemiological pattern from middle-high endemicity (1986) to low endemicity (2004).

INTRODUCTION

Hepatitis A has a worldwide distribution. Transmission is generally oro-faecal, whether from person-to-person or through contaminated water or food. It is estimated that each year there are ~1.5 million cases of symptomatic hepatitis A [1]. Although infections are usually self-limited, hepatitis A can be serious, especially in adults and individuals with chronic liver disease [2, 3]. Mortality, especially that due to fulminant hepatitis, is ~2% in adults aged >50 years [2]. Hepatitis A causes considerable economic losses in many countries of middle or low endemicity, in which

the infection frequently affects adults [1, 2]. Several highly effective vaccines against hepatitis A virus (HAV) are available, which generate long-term, and possibly lifelong, immunity [1, 4]. Recommendations on vaccination vary from country to country, oscillating from selective vaccination of at-risk groups to universal vaccination [1]. The vaccination strategies adopted depend mainly on the epidemiological pattern of hepatitis A and on the availability of economic resources. In a previous study of the incidence and prevalence of HAV infection in the Basque Country, Spain (1986–1992) [5] we observed a decline in HAV circulation as a result of economic and health-related improvements in our population. The epidemiological pattern observed in the Basque Country between the two previous study periods was considered representative of countries in transition between high and low

* Author for correspondence: E. Pérez-Trallero, M.D., Ph.D., Servicio de Microbiología, Hospital Donostia, Paseo Dr. Beguiristain s/n, 20014 San Sebastián, Spain.
(Email: mikrobiol@terra.es)

states of endemicity [6]. The main aims of the present study were to determine new changes in the epidemiology of HAV infection in the Basque Country and evaluate their implications for the choice of vaccination strategy.

METHODS

Gipuzkoa is one of the three regions comprising the Autonomous Community of the Basque Country, northern Spain. Its 1997 km² of territory is inhabited by 673 563 people. The hepatitis A vaccine has been recommended in Spain since 1998 in selected high-risk populations (travellers to endemic countries, injecting drug users, sewage workers in regular contact with raw sewage, patients with chronic liver disease or haemophilia, etc.).

Seroprevalence study

The population sample studied was composed of 1356 persons enrolled in 2004, obtained from two population groups: first, 482 children and adolescents attended as outpatients, randomly selected from 1- to 19-year-olds who underwent blood extraction for the diagnosis of non-serious diseases unrelated to liver disease (injuries, before minor surgery, etc.) in the regions of San Sebastián, Tolosa and Urola-Costa ($n=967$) and, second, 874 women aged 20–44 years randomly selected from women who gave birth in the Hospital Donostia ($n=4429$), which is part of the public health system and attends ~65% of the women who give birth in the region. These women came from throughout the region of Gipuzkoa and were from all social classes, including the most disadvantaged socioeconomic groups. Because of the substantial increase in the number of immigrants to Gipuzkoa since 1999 and to gain greater insight into the regional circulation of HAV, the presence of anti-HAV was studied in the total number of par-turient women selected and in the same population after excluding immigrant women. None of the persons included in the study had acute liver disease. Both population groups included persons from rural and urban regions representing the middle and low classes of Gipuzkoa. The sample size for each age group was calculated on the basis of the population census and on the prevalence of HAV antibodies (seroprevalence) in a previous study [5], with an accuracy of 5% and a confidence level of 95%. Serum samples were stored at -40°C until processing. The

results obtained were compared with those of two population samples of 1013 and 1211 persons selected in the same way and in the same geographical area in 1986–1987 and 1992 respectively [5], comprising a period of 19 years.

Incidence

The incidence of hepatitis A between 1986 and 2004 was obtained on the basis of the mandatory infectious disease reports sent each week to the Notifiable Disease Reporting System of the Basque Country by general practitioners, paediatricians and other specialists. Hepatitis A became a disease of numerical notification (anonymous cases) in 1982 and has been a disease of mandatory individual notification (identified cases) since 1997. In addition, each week the microbiology laboratories of the public health system of the Basque Country report all hepatitis A cases confirmed by specific IgM detection (>90% of the total number of cases confirmed in the region), which allows the age of patients with hepatitis A to be studied in distinct periods. In 2000 an active surveillance system was implemented. Laboratory-confirmed cases were contacted within 72 h of the serological diagnosis to detect new cases related to each index case. This measure facilitated the study of risk factors and possible sources of infection as well as the appropriate management of contacts of index cases. Between 1997 and 2004 hospital admissions due to hepatitis A in the public and private hospitals of the region were studied. To do this, the medical records of all admissions that took place within that period with a primary discharge diagnosis of viral hepatitis A were obtained from the hospitals' Clinical Documentation Services using the Minimum Data Set, an obligatory hospital admissions system for clinical information and surveillance. The diagnosis of viral hepatitis A corresponded to codes 07.00 and 07.01 of the ninth edition of the *International Classification of Diseases (Clinical Modification)*.

Serological methods

Qualitative detection of anti-HAV IgG was performed with a chemiluminescent microparticle immunoassay method (Architect HAVAb-IgG; Abbott, Wiesbaden, Germany). The diagnosis of acute hepatitis A was confirmed through detection of anti-HAV IgM using commercial kits [HAVAB M (Organon Teknika, Boxtel, The Netherlands) and

Table 1. Prevalence of antibodies against hepatitis A virus (anti-HAV) in relation to age in the population of Gipuzkoa (Basque Country, Spain) selected in 1986–1987, 1992 and 2004

Age (yr)	Anti-HAV positive											
	1986–1987*				1992*				2004			
	<i>N</i>	<i>n</i>	(%)	95% CI†	<i>N</i>	<i>n</i>	(%)	95% CI	<i>N</i>	<i>n</i>	(%)	95% CI
1–9	427	32	(7.5)	5.2–10.4	334	8	(2.4)	1.0–4.7	215	6	(2.8)	1.0–6.0‡
10–19	219	83	(37.9)	31.4–44.7	348	73	(21.0)	16.8–25.6	267	18	(6.7)	4.0–10.4
20–29	211	170	(80.6)	74.6–85.7	257	148	(57.6)	51.3–63.7	376	134	(35.6)	30.8–40.7
30–39	156	153	(98.1)	94.5–99.6	272	238	(87.5)	83.0–91.2	347	151	(43.5)	38.2–48.9
40–44									151	107	(70.9)	62.9–77.7
Total	1013				1211				1356			

* Data obtained in a previous study [5].

† Exact binomial 95% confidence interval.

‡ χ^2 with 2 D.F. for age groups 1–9, 10–19, 20–29 and 30–39 ($P \leq 0.001$).

IMX HAVAB-M (Abbott) until 1997 and AxSYM HAVAB-M (Abbott)] from 1997 onwards. Serological methods were performed according to the manufacturers' instructions.

Data analysis

The incidence of HAV infection was analysed using the corresponding population censuses of the Basque Institute of Statistics. The χ^2 test was used to compare prevalences or percentages. Analysis of variance (ANOVA) was used to compare the age of patients with acute hepatitis A. Values of $P < 0.05$ were considered significant. The statistical analysis was performed with the SPSS program, version 12.0.1 for Windows (SPSS Inc., Chicago, IL, USA). The study was approved by the Ethics Committee for Clinical Research of the Hospital Donostia.

RESULTS

Prevalence of anti-HAV IgG in the population sample

Throughout the study period (1986–2004), the seroprevalence of anti-HAV IgG progressively decreased in all the age groups studied, especially in the older groups (Table 1). In children aged < 10 years, the seroprevalence in 2004 (2.8%) was similar to that observed in 1992 (2.4%), although there was a significant decline between 1986–1987 and 1992 (7.5%). In children and adolescents aged 10–19 years, the decrease was pronounced, with a proportion of immune individuals of 6.7% in 2004, compared with

21.0% and 37.9% in 1992 and 1986 respectively. Notably in 2004, the 20–29 years age group had a prevalence of anti-HAV of 35.6%, compared with 57.6% and 80.6% in 1992 and 1986–1987 respectively. Moreover, $< 45\%$ of women aged 30–39 years had anti-HAV antibodies in 2004 while antibodies were detected in 87.5% and 98.1% of women of the same age studied in 1992 and 1986 respectively. The decrease in seroprevalence was statistically significant in the four age groups compared throughout the three study periods (χ^2 with two degrees of freedom, $P \leq 0.001$). When immigrant women were excluded, the percentage of women aged 20–29 years immune to HAV infection in 2004 was 24.3% (74/305, 95% CI 19.6–29.5) and this percentage was 41.3% (136/329, 95% CI 36.0–46.9) and 70.9% (105/148, 95% CI 62.9–78.1) in women aged 30–39 and 40–44 years respectively. The percentage of immigrants among all parturient women was higher in the 20–29 years age group (18.9%) than among women aged ≥ 30 years (4.8%) ($P < 0.001$).

Incidence

The mean annual incidence of hepatitis A substantially decreased throughout the study period, from 38.0 cases/100 000 inhabitants in the 3-year period from 1986 to 1988 to 2.9 cases/100 000 inhabitants in 2002–2004 (Fig. 1). Since 1995, the annual incidence has been low and has only been higher than 5 cases/100 000 inhabitants in 1997 and 2000–2001 (6.2, 12.0 and 10.8 cases/100 000 inhabitants respectively). In 2000 and 2001, the incidence increased, with 154

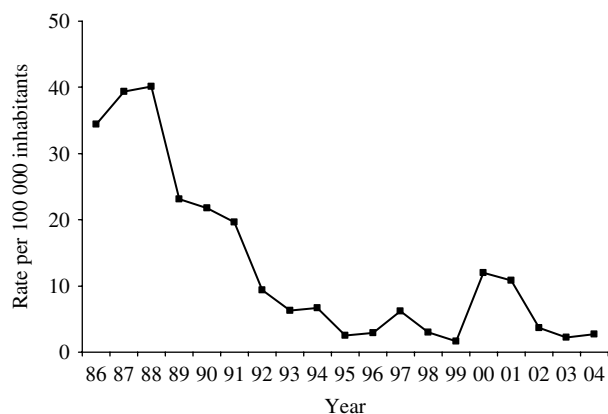


Fig. 1. Reported incidence of 'hepatitis type A' in Gipuzkoa (Basque Country, Spain).

reported cases. Of these, 49 were associated with intake of insufficiently cooked clams and most occurred in a winter outbreak in which HAV was detected in bi-valve molluscs from four of the five shellfish beds investigated in the affected region [7]. Another 44 cases had the antecedent of a contact with a recent case of hepatitis A (15 of which were from day-care centres), 14 with travel to a developing country, and 14 with drinking untreated water. In 33 cases no relation with any risk factor could be established. There were hardly any cases of hepatitis A in immigrants (four cases between 2000 and 2004).

Age of patients with hepatitis A

Throughout the study period, the mean age of patients with serologically confirmed hepatitis A increased, from 17.7 years during 1986–1992 to 21.2 years and 25.3 years in 1993–1998 and 1999–2004 respectively (ANOVA $F=38.83$, $P<0.001$) (Table 2). Likewise, the incidence of hepatitis A in persons aged <30 years decreased, while that in older individuals slightly increased (Fig. 2). In the last period studied (1999–2004), the mean annual incidence of hepatitis A per 100 000 inhabitants and by age group was similar in the first four decades of life (9.5–11.2 cases/100 000 inhabitants) and was lower in groups aged 40–49 (3.0) and ≥ 50 years (0.2).

Hospitalization

Between 1997 and 2004 there were 319 patients with confirmed hepatitis A in the population attended by public hospitals, of which 64 (20.1%) required hospitalization. Hospitalization was more frequent in patients aged ≥ 35 years (31.1%, 19/61) than in

younger age groups (17.6%, 45/255) ($\chi^2=5.55$, $P=0.018$). The mean length of hospital stay was 6.3 days (range 1–21 days). There were no deaths or liver transplantations due to hepatitis A.

DISCUSSION

The present study shows a decrease in the incidence and prevalence of hepatitis A in the Basque Country in the last two decades. The changes observed have been substantial and have occurred rapidly. In 2004, most of the population aged <40 years was susceptible to HAV infection and only 5% of the population aged <20 years showed HAV antibodies, strongly contrasting with the seroprevalence found in 1986–1987. The prevalence of HAV antibodies observed in 2004 in women aged 30–39 years was slightly lower than expected, probably because of the lower proportion of immigrant women that gave birth at the age of >29 years. In this study, there were no men in the population aged ≥ 20 years. However, in large seroepidemiological studies performed in Spain, the seroprevalence rates did not differ by gender [8, 9]. Although it is well known that children play an important role in HAV transmission and serve as a source of infection for the general population [2, 10], children are not currently a common source of infection as infection among them is rare. Although active surveillance of hepatitis A cases was introduced in 2000, the lower incidence was observed in the last 3-year period analysed (a mean incidence of 2.9 cases/100 000 inhabitants), and this figure is in line with those reported in countries with low endemicity [11–13]. Throughout the study period the age at presentation of HAV infection progressively increased. This tendency is not surprising in countries in which HAV circulation is decreasing [12, 14] and is due both to the growing susceptibility of the adult population and to the greater clinical expression of the infection in this population [1].

All together, the data in the present study confirm that the Basque Country is an area with low endemicity. Decreases in the seroprevalence and in infection rates are also currently observed in some countries and regions of southern Europe [8, 9, 15–18] and in economies in transition in other continents [18]. The speed at which this change has taken place in the Basque Country is marked and although susceptibility to HAV infection increased in the general population, no large outbreak has occurred. The small increase observed in incidence in 2000 and 2001

Table 2. Distribution by age and mean age of serologically confirmed cases of viral hepatitis A in Gipuzkoa (Basque Country, Spain) in three time periods: 1986–1992, 1993–1998 and 1999–2004

Age group (yr)	1986–1992*		1993–1998		1999–2004	
	No. of cases	(%)	No. of cases	(%)	No. of cases	(%)
0–9	139	(25.7)	59	(23.9)	32	(14.0)
10–19	194	(35.9)	47	(19.0)	36	(15.8)
20–29	153	(28.3)	89	(36.0)	71	(31.1)
30–39	49	(9.1)	38	(15.4)	68	(29.8)
≥40	6	(1.1)	14	(5.7)	21	(9.2)
Total†	541		247		228	
Mean age‡	17.7		21.2		25.3	

* Data obtained in a previous study [5].

† The ages of 80, 2 and 2 cases were unknown in 1986–1992, 1993–1998 and 1999–2004 respectively.

‡ ANOVA $F=38.834$, $P<0.001$.

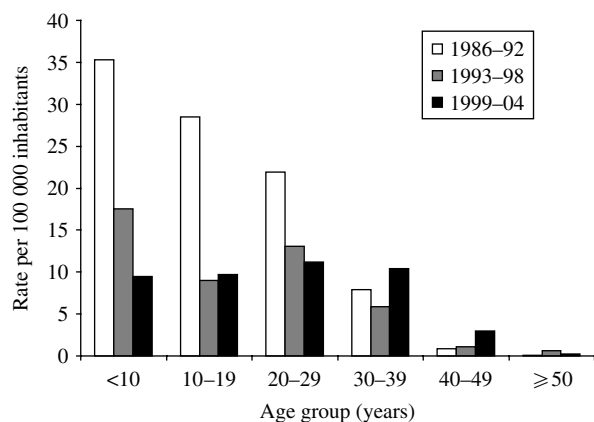


Fig. 2. Incidence of hepatitis A by age group in Gipuzkoa (Basque Country, Spain) in three time periods: 1986–1992 (□), 1993–1998 (■) and 1999–2004 (■) (serologically confirmed cases). Data from 1986 to 1992 were obtained from a previous study [5].

was mainly due to a small outbreak associated with consumption of raw or insufficiently cooked clams and to family clusters. The prolonged duration of this period of low incidence suggests that it is not the result of periodic tendencies in HAV circulation but is rather the result of a real change in the conditions that allow viral transmission. Socioeconomic development has been clearly associated with a decrease in HAV transmission among populations [19]. In Spain, significant social, sanitary and health-related advances have taken place since the mid-1960s, which are the main cause of the change in the epidemiological pattern of HAV [9, 20]. In the next few years, the incidence of HAV infection can be expected to remain low and therefore susceptibility among the population

will continue to rise. Paradoxically, this could increase the burden of the disease due to the greater severity of hepatitis A in adults [12, 14]. Indeed, in the present study the percentage of hospitalization in patients aged >35 years was 31% compared with 18% in those aged <35 years.

Several inactivated vaccines are available for the prevention of hepatitis A and are highly immunogenic and well tolerated. Application of these vaccines has the potential to drastically decrease the levels of circulating HAV and eliminate the virus altogether [2]. Since the end of the 1990s, universal vaccination has been implemented in some countries or regions where hepatitis A is a major public health problem. Such is the case in Israel [21], the United States [22] and Puglia (Italy) [23], and marked decreases in the incidence of HAV infection have subsequently been observed. In addition, in Catalonia (Spain), a region with similar social and health characteristics to those of the Basque Country, a pilot programme of universal vaccination in pre-adolescents (12-year-olds) was introduced in 1998, in which a combined vaccine against hepatitis A and B substituted vaccination against hepatitis B [23]. The mean annual incidence of HAV infection decreased from 6.2 cases/100 000 inhabitants in 1996–1998 to 2.6 cases/100 000 inhabitants in the following 3 years [24]. This tendency is similar to that observed in the Basque Country where there is no policy of universal vaccination. This observation underlines the difficulty of evaluating vaccination strategies against HAV, which require a prolonged period of surveillance. However, in Catalonia, every year a cohort of pre-adolescents

with high vaccination coverage is incorporated into the population [24], whereas in the Basque Country the susceptibility of the population to hepatitis A increases each year.

This study demonstrates that the epidemiological pattern of hepatitis can change rapidly. We believe that, in regions or countries showing this tendency, the main measures to control infection are implementation of active surveillance of new hepatitis A cases, reinforcement of good personal hygiene habits, and vaccination of high-risk groups. Similar strategies are being carried out in European countries with low endemicity [12, 17, 25]. However, because of the increasing vulnerability of the adult population, the potential severity of hepatitis A in this population [2, 12], and the difficulty of achieving high vaccination coverage in at-risk groups, universal vaccination strategies should be evaluated. Among the multiple possibilities currently available for scheduling universal vaccination against HAV infection, the two options more used to date are vaccination at 12–18 months of age or before adolescence [21–23]. Given the long-term possibility of eradicating this infection, we believe the first option to be preferable, especially if a combined vaccine is used.

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the help of the University of the Basque Country, Spain (grant GIU05/54), and Abbott Laboratories, who kindly donated their reagent kits for the seroepidemiological study performed in 2004.

DECLARATION OF INTEREST

None.

REFERENCES

1. **World Health Organization.** Hepatitis A vaccines. WHO position paper. *Weekly Epidemiological Record* 2000; **75**: 38–44.
2. **CDC.** Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *Morbidity and Mortality Weekly Report* 1999; **48**: 1–37.
3. **Almasio PL, Amoroso P.** HAV infection in chronic liver disease: a rationale for vaccination. *Vaccine* 2003; **21**: 2238–2241.
4. **Van Damme P, et al.** Hepatitis A booster vaccination: is there a need? *Lancet* 2003; **362**: 1065–1071.
5. **Pérez-Trallero E, et al.** Falling incidence and prevalence of hepatitis A in Northern Spain. *Scandinavian Journal of Infectious Diseases* 1994; **26**: 133–136.
6. **Begg NT, Gay NJ.** Theory of infectious disease transmission and herd immunity, chapter 10. In: Collier L, Balows A, Sussman M (eds). *Topley & Wilson's Microbiology and Microbial Infections, Vol. 3, Bacterial Infections*, Hausler WJ, Sussman M, eds. 9th edn. London, 1998, pp. 147–165.
7. **Departamento de Sanidad, Gobierno Vasco.** Brote de hepatitis A en Gipuzkoa. *Salud Pública* 2001; **10** (semestre 1): 4. (http://www.osasun.ejgv.euskadi.net/r52-478/es/contenidos/informacion/boletin_epidem/es_5482/adjuntos/10bolecast.pdf). Accessed 5 July 2006.
8. **Dal-Ré R, García-Corbeira P, García-de-Lomas J.** A large percentage of the Spanish population under 30 years of age is not protected against hepatitis A. *Journal of Medical Virology* 2000; **60**: 363–366.
9. **Bruguera M, et al.** Changes in the seroepidemiology of hepatitis A virus infection in Catalonia (Spain) from 1989 to 1996. Implications for a new vaccination strategy. *Medicina Clínica (Barcelona)* 1999; **112**: 406–408.
10. **Staes CJ, et al.** Sources of infection among persons with acute hepatitis A and no identified risk factors during a sustained community wide outbreak. *Pediatrics* 2000; **106**: e54.
11. **Wasley A, Samandari T, Bell BP.** Incidence of hepatitis A in the United States in the era of vaccination. *Journal of the American Medical Association* 2005; **294**: 194–201.
12. **Crowcroft NS, et al.** PHLS Advisory Committee on Vaccination and Immunisation. Guidelines for the control of hepatitis A virus infection. *Communicable Disease and Public Health* 2001; **4**: 213–227.
13. **Thierfelder W, et al.** Prevalence of markers for hepatitis A, B and C in the German population. Results of the German National Health interview and examination survey 1998. *European Journal of Epidemiology* 2001; **17**: 429–435.
14. **Di Giammarino L, Dienstag JL.** Hepatitis A – The price of progress. *New England Journal of Medicine* 2005; **353**: 944–946.
15. **D'Amelio R, et al.** Hepatitis A, Italy. *Emerging Infectious Diseases* 2005; **11**: 1155–1156.
16. **Antunes H, Macedo M, Estrada A.** Hepatitis A virus prevalence: Portuguese first results of low endemicity. *Acta Medica Portuguesa* 2004; **17**: 219–224.
17. **Franco E, Vitiello G.** Vaccination strategies against hepatitis A in southern Europe. *Vaccine* 2003; **21**: 696–697.
18. **Jacobsen KH, Koopman JS.** Declining hepatitis A seroprevalence: a global review and analysis. *Epidemiology and Infection* 2004; **132**: 1005–1022.
19. **Jacobsen KH, Koopman JS.** The effects of socio-economic development on worldwide hepatitis A virus seroprevalence patterns. *International Journal of Epidemiology* 2005; **34**: 600–609.
20. **Amela C, et al.** Trends in hepatitis A virus infection with reference to the process of urbanization in the greater Madrid area (Spain). *European Journal of Epidemiology* 1995; **11**: 569–573.

21. **Dagan R, et al.** Incidence of hepatitis A in Israel following universal immunization of toddlers. *Journal of the American Medical Association* 2005; **294**: 202–210.
22. **CDC.** Recommended childhood and adolescent immunization schedule: United States, 2006. *Morbidity and Mortality Weekly Report* 2006; **54**: Q1–Q4.
23. **Lopalco PL, et al.** Hepatitis A and B in children and adolescents – what can we learn from Puglia (Italy) and Catalonia (Spain)? *Vaccine* 2001; **19**: 470–474.
24. **Domínguez A, et al.** Prevalence of hepatitis A antibodies in schoolchildren in Catalonia (Spain) after the introduction of universal hepatitis A immunization. *Journal of Medical Virology* 2004; **73**: 172–176.
25. **Steenbergen JE, et al.** Two years' prospective collection of molecular and epidemiological data shows limited spread of hepatitis A virus outside risk groups in Amsterdam, 2000–2002. *Journal of Infectious Diseases* 2004; **189**: 471–482.