The shift in prevalence of hepatitis A immunity in Flanders, Belgium

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Abstract

The purpose of this study was to obtain data on the prevalence of hepatitis A in Flanders, Belgium, in order to analyse any change in the epidemiological pattern of hepatitis A virus (HAV) in the region, and to determine at which age pre-vaccination testing would be useful. To meet these goals, a sero-epidemiological survey was conducted : 4058 serum samples were collected from a random sample of the general population in 1993-94. The overall age-standardised prevalence was 51.3%. Among non-Belgians (N = 245), the age-standardised anti-HAV prevalence was 66.4%, significantly higher than the 49.6% anti-HAV prevalence found in Belgians (N = 3186). Among Belgians, seroprevalence increased with age : from 5.4% in the youngest age group (0-14 years) to over 80% in the two oldest age groups (55-64 years and ≥ 65 years). Prevalence rates were as high as 31.7% in the 25-34 year old age category, and 60.8% in the 35-44 year old age category.

The age-specific prevalence figures among Belgians and non-Belgians reflect two different epidemiological patterns : the epidemiological pattern of a low endemic region for Belgians and the epidemiological profile of an intermediate endemic region for non-Belgians. The age-specific prevalence figures in Belgians were compared with the 1979 and 1989 anti-HAV prevalence figures in Belgian first-time blood donors. A clear epidemiological shift showing decreasing HAV prevalence in the youngest age groups was found. If we accept that pre-vaccination screening is useful at a 35% prevalence rate, all persons over 35 years of age should be screened before vaccination. (Acta gastroenterol. belg., **1998**, 61, **4-7**).

Keywords : hepatitis A, prevalence, Belgium, epidemiology.

1. Introduction

1.1. *Epidemiology*

Faecal-oral transmission of hepatitis A virus (HAV) is facilitated by poor hygienic living and housing conditions, and is particularly common in developing countries (1-4). In these countries, HAV is mainly a childhood infection, whereas in industrialized nations, HAV infection occurs during adulthood as well as childhood. In the poorest developing countries, the pattern of very high endemicity (reported incidence 1-40/100,000) is characterized by rapid infection at a very young age ; over 90% of children become infected by the age of five (1). Very high endemic areas include Africa, and parts of South-America, the Middle East and South-East Asia. Western Europe, Australia and North America are low endemic areas (reported incidence 5-15/100,000) (1). In Western Europe, a gradient of low endemicity in Northern Europe increasing to moderate endemicity (reported incidence 15-150/100,000) in Southern Europe is found (1, 4).

Based on 1991-1992 results registered by sentinel general practices, the incidence of HAV in Belgium is 19/100,000 (5). This figure describes the epidemiology in terms of HAV disease and therefore reflects only clinical infection. To estimate the true number of infections, corrections for asymptomatic infections must be made (6, 7). Prevalence figures based on serological analysis therefore provide a more accurate epidemiological picture.

A 1979 prevalence study of regular blood donors (N = 312) in Belgium found a prevalence of HAV antibodies of 78.5% (95% C.I. : 74.0-83.3) (8). Among a group of first-time blood donors, prevalence was 48.5% (95% C.I. : 43.4-53.6). The first-time donors were slightly younger than the general blood donor population, which could explain the lower prevalence *. In 1989, the survey was repeated with a new sample of first-time blood donors and the results were compared with those from 1979 (9). These new data showed a high anti-HAV prevalence among older donors and a trend towards fewer HAV infections early in life. In 1979, 50% of 25-30 year-old first-time donors studied had HAV antibodies ; in 1989, among first-time donors, a 50% prevalence rate was not attained until the 35-40 age group.

1.2. *Objectives*

In 1993 and early 1994, a study of the prevalence of HAV antibodies was conducted at the request of the Health Administration of the Flemish Community. The purpose of this study was to obtain data on the prevalence of hepatitis A in Flanders and to analyse any change in the epidemiological pattern of HAV. In addition, these data could confirm the changing epidemiology already observed elsewhere in western Europe, and verify the decrease in anti-HAV prevalence among infants, children and young adults.

2. Materials and methods

2.1. *Study group*

The sample size calculation was performed with the aid of Epi Info (version 5.0, 1990). The sample size

* Age-standardised prevalence was not mentioned in this publication.

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per age stratum was calculated so that the results of the sample group agreed with that of the Flemish population with a probability of at least 95%.

Study participants were recruited from eleven hospitals in the five Flemish provinces. These participants were patients admitted to departments of general surgery, traumatology, orthopaedics and emergency units, and children admitted to the oto-rhinolaryngology department. In order to avoid a possible selection of hepatitis cases, only patients from these departments were included. During the study period (April 1993 to February 1994) 4058 serum samples were collected in ten hospitals, in accordance with the study protocol. The study group was similar in composition to the Flemish population in terms of age, sex and demographic distribution (10, 11).

2.2. *Serology*

The detection tests used were all commercial tests from Abbott Laboratories, based on radio immuno assay (RIA) techniques. The HAVAB kit was used to determine (total) anti-HAV antibodies. The interpretation of positive and negative results for all the tests was carried out as recommended by the test producer.

2.3. *Statistics*

For comparison between groups, chi-square and Fisher exact tests were used. If a p-value was below 0.05, the difference between proportions was considered statistically significant. Data were processed using CSS-(Complete Statistical System, Statsoft, Inc., 1991) and Epi-Info-Software (version 5.0, 1990). Age-standardised prevalence figures were used to adjust the prevalence data according to the age distribution of the Flemish population. The age-adjusted prevalence figures were calculated using the direct standardisation method (12).

3. **Results**

1993 data from the National Institute of Statistics (11) were used for comparison with the Flemish population and for standardisation of prevalence figures according to age, sex, nationality and demographic distribution. The mean age of the study group was 40.2 years (95% C.I. : 39.6-40.9) and the age distribution of the participants was similar to the age distribution of the Flemish population (10, 11).

Of 3479 participants the nationality was known : the study group comprised 92.8% Belgians (N = 3229), 2.7% non-Belgians of European nationality (N = 94) and 4.5% non-Europeans (N = 156). The number of participants of foreign nationality was thus 7.2%, significantly higher than the 4.7% ($X^2 = 47.96$; $p < 0.0001$) foreigner population in Flanders (11). This may possibly be explained by the urban location of the participating hospitals. As there was no significant difference in anti-HAV prevalence between the non-Belgians of European nationality and the non-Europeans, these two subgroups were grouped together for further analysis.

In the sero-epidemiological study, 3918 serum samples ** were screened for HAV antibodies (anti-HAV) and 2159 positives were found, representing a seroprevalence of 55.1% (95% C.I. : 53.5-56.7). In the non-Belgian group (N = 245) the anti-HAV prevalence was 62.4% (95% C.I. : 56.4-68.5), significantly higher ($X^2 = 8.05$; $p = 0.005$) than the 52.5% (95% C.I. : 50.8-54.3) found in Belgians (N = 3186). The difference between age-standardised anti-HAV prevalence was even greater : 49.6% in Belgians versus 66.4% in non-Belgians. The age-standardised prevalence of anti-HAV in the study group was 51.3%. The statistical analysis revealed no significant difference in anti-HAV seroprevalence between men and women in the total study group ($X^2 = 1.59$; $p = 0.207$). There was also no statistically significant difference in anti-HAV seroprevalence between men and women in the Belgian ($X^2 = 2.23$; $p = 0.136$) and non-Belgian group ($X^2 = 1.02$; $p = 0.312$).

The age-specific analysis of anti-HAV serology demonstrates a direct relationship between anti-HAV prevalence and age for the entire study group ($p < 0.0001$). Age-specific analysis in Belgians (N = 3186) showed an anti-HAV seroprevalence of 5.4% in the youngest age group (0-14 year) and a seroprevalence of over 80% in the two oldest age groups (55-64 year and 65 year) (table I). Prevalence becomes progressively higher in successive age groups : seroprevalence rates are 31.7% in the 25-34 year old group, and increase to 60.8% in the next age group (35-44 year) (table I, fig. 1). Clearly, non-Belgians (N = 245) have a different epidemiological profile than Belgians. The largest jump in prevalence occurs between 0-14 years (21%) and 15-24 years (63%). A prevalence of more than 80% is already attained in the 25-34 year old age group (table I).

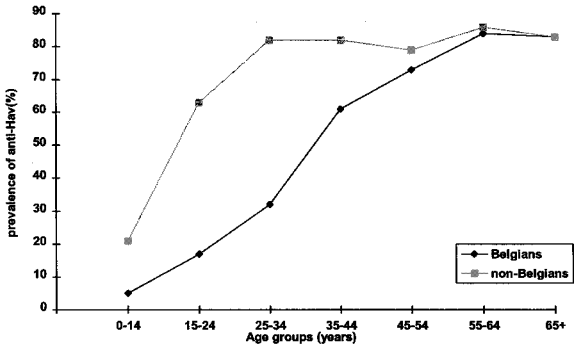

Fig. 1. — Age-specific anti-HAV seroprevalence plotted against nationality.

** The number of serum samples included in each statistical analysis differed from the total number of serum samples collected. For some samples data were missing (e.g. sex, nationality), while others contained too little serum to be properly tested.

Table I. — **Age-specific anti-HAV prevalence in Belgians and non-Belgians**

	Age (years)	0-14	15-24	25-34	35-44	45-54	55-64	≥ 65	**Total**
Belgians	Number	466	314	457	530	587	462	370	**3186**
	prevalence (%)	5.4	17.5	31.7	60.8	73.4	84.0	83.2	**52.5**
	95% C.I.	3.5-7.8	13.3-21.7	27.5-36.0	56.6-64.9	69.9-77.0	80.6-87.3	79.4-87.0	**50.8-54.3**
non-Belgians	Number	70	30	55	39	24	21	6	**245**
	prevalence (%)	21	63	82	82	79	86	83	**62.4**
	95% C.I.	12-33	44-80	69-91	66-92	58-93	64-97	36-100	**56-68**

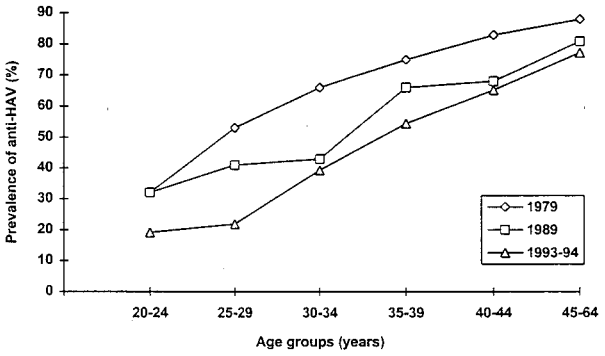

Fig. 2. — Age-specific anti-HAV prevalence in Flanders in 1979 (blood donors), 1989 (blood donors) and in 1993-94 (Belgians in general population).

Figure 2 compares the epidemiological profiles of first-time blood donors in 1979 and 1989 with that of Belgians in our total study group (8, 9). Although our study group was sampled differently, it was nevertheless worthwhile to compare these three groups, particularly since the majority of blood donors in 1979 and 1989 were Belgians. It is important to keep in mind, however, that HIV screening of all blood donors was instituted in 1985, and only then did selection of blood donors become very strict.

4. Discussion

It is assumed that there is a disproportionate number of study subjects living in urban areas. This is inherent in the choice of the participating hospitals and could explain why the study sample contained a higher proportion of non-Belgians than the general Flemish population. The age-specific prevalence figures per nationality reflect two different epidemiological patterns : for Belgians, the epidemiological pattern of low endemic regions ; for non-Belgians, an epidemiological profile comparable to that of regions of intermediate endemicity (fig. 1) (1).

Comparison of the three epidemiologcial profiles shown in Figure 2 provides a good indication of the changing HAV epidemiology in the Flemish population over the past fifteen years : a decreasing HAV prevalence in the youngest age groups is shown, as has been observed in other European countries (13, 14, 15). All results illustrate that HAV prevalence is linked to age and that the prevalence rates for all age groups have been decreasing. This may be due to improved hygienic living and housing conditions resulting in a decline in infections early in life. The higher prevalence rates in older age groups can be attributed to a cohort effect ; in the past, when hygienic living and housing conditions were poorer, infections were contracted during childhood and now the serological heritage for HAV is measured. The gradual decrease in the incidence of HAV infection during childhood is due to improvements in sanitary conditions (16). Our findings suggest there are fewer HAV infections in childhood in Flanders, and therefore a greater susceptibility to infection among adolescents and young adults than there was a decade ago. Since the expression of clinical disease is highly age-related, and since the age of infection has shifted to adolescence and adulthood, the number of clinical infections can be expected to increase. Furthermore, any lapse in hygiene could cause outbreaks particularly in closed communities, such as day care centres.

Significant changes in the epidemiological pattern of HAV have occurred throughout western Europe in the last 15 to 20 years. The rate of infection is decreasing and the age at infection is shifting from childhood to adolescence and adulthood, explaining the decline in age-specific prevalence data for younger generations of western Europe.

In Figure 3, the anti-HAV epidemiology of Flanders is compared with the anti-HAV epidemiology of other western European countries (4, 10, 17-19). Southern European countries still show an intermediate pattern of HAV endemicity, similar to that found among non-Belgians in the study group. Although one should consider that not all studies were conducted in the same year, an epidemiological gradient from North to South is clearly seen.

Studies in France show that in 1991 approximately 75% of the population under 25 years of age were not immune to HAV infection (4). France has shifted from moderate to low hepatitis A endemicity, similar to the shift already described for Flanders. In the current epidemiological situation in western Europe, HAV infection could easily be imported from endemic countries (by travellers and immigrants) and, because of the increased susceptibility of the population, could trigger outbreaks of overt hepatitis A cases.

There are three possible explanations for the higher anti-HAV prevalence among non-Belgians. First, most

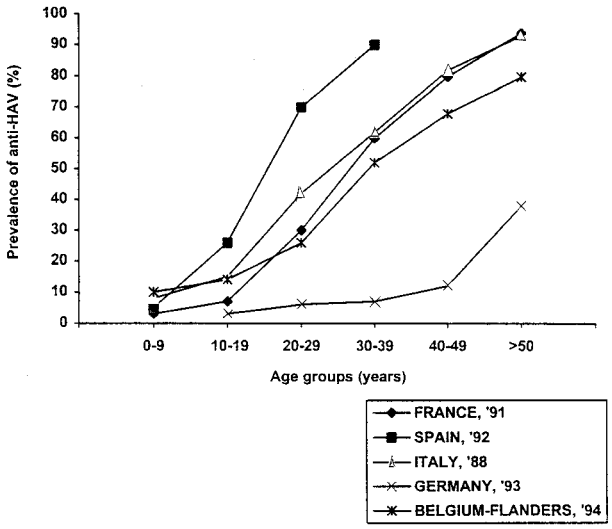

Fig. 3. — Age-specific anti-HAV prevalence in 5 Western European countries (based on ref. 4, 10, 17-19).

adult non-Belgians could have contracted HAV infection during childhood in their countries of origin. Second, immigrant children, still susceptible to HAV while in Belgium, could contract HAV during visits to their home countries, and could cause secondary morbidity on return to Belgium. These children represent a significant source of HAV infection. A similar source of HAV infection has also been described in the US among Mexican Americans, in the Netherlands (Van Steenbergen J., personal communication) and in Austria (13). Third, it is likely that the increased anti-HAV prevalence among non-Belgians is also due to differences in socio-economic situations : it is probable that the majority of non-Belgians belong to lower socio-economic classes, and have poorer hygienic living and housing conditions. Furthermore, the average number of siblings is expected to be greater among non-Belgians.

HAV epidemiology is similar among Belgians and non-Belgians in the two oldest age groups. This finding supports the hypothesis that the HAV epidemiology among the Flemish people changed relatively recently, with improved hygiene and sanitary conditions after the Second World War and general socio-economic improvements since the 1960's. One can assume that better living and housing conditions and fewer children per family play an important role in this epidemiological change.

Finally, according to this study, anti-HAV prevalence exceeds 35 percent among Belgians over 35 years old and among non-Belgians over 20 years old. As it was shown that pre-vaccination screening at a 35% prevalence rate is cost-effective in Belgium, these and older age-groups should be screened before vaccination (20).

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6. References

1. HADLER S.C. Global impact of hepatitis A virus infection : changing patterns. In : Hollinger F.B., Lemon S.M., Margolis H.S. (eds.) : Viral Hepatitis and Liver Disease. Williams & Wilkins, Baltimore, 1991 : pp 14-20.
2. PAPAEVANGELOU G. Epidemiology of hepatitis A in Mediterranean countries. *Vaccine*, 1992, **10** (suppl) : 63-66.
3. FORBES A., WILLIAMS R. Changing epidemiology and clinical aspects of hepatitis A. *Br. Med. Bull.*, 1990, **46** : 303-318.
4. DUBOIS F., THEVENAS C., CACES E., VOL S., DOCTORIARENA A., ECAULT J.L., GOUDEAU A., TICHET J. Séroépidemiologie de l'hépatite A dans six départements du Centre-Ouest de la France en 1991. *Gastroenterol. Clin. Biol.*, 1992, **16** : 674-679.
5. DEVROEY D., VAN CASTEREN V., VRANCKX R. Evolutie van de incidentie van klinische acute virale hepatitis in de Belgische huisartsenpraktijk — registratienet van de huisartsenpeilpraktijken — Resultaten van 1991 en 1992. Report, Institute of Hygiene and Epidemiology, Brussels, January 1997, 34 p.
6. MEHEUS A. Risk of hepatitis B in adolescence and young adulthood. *Vaccine*, 1995, **13** (suppl) : 31-34.
7. MATRICARDI P.M., D'AMELIO R., BISELLI R., RAPICETTA M., NAPOLI A., CHIONNE P., STROFFOLINI T. Incidence of hepatitis A virus infection among an Italian military population. *Infection*, 1994, **22** : 55-56.
8. VRANCKX R., DE DECKER H., COLE J., MUYLLE L., PEETERMANS M. Hepatitis A virus antilichamen in verschillende bevolkingsgroepen in de Antwerpse regio. *Arch. Pub. Health.*, 1981, **39** : 636-642.
9. VRANCKX R., MUYLLE L. Hepatitis A antibodies in Belgium : relationship between prevalence and age. *Infection*, 1990, **18** : 364-366.
10. BEUTELS M., VAN DAMME P., AELVOET W., DESMYTER J., DONDEYNE F., GOILAV C., MAK R., MUYLLE L., PIERARD D., STROOBANT A., VAN LOOCK F., WAUMANS P., VRANCKX R. Prevalence of hepatitis A, B and C in the Flemish population. *Eur. J. Epidemiol.*, 1997, **13** : 275-280.
11. Bevolkingsstatistieken 1993, N° 2 of the National Institute of Statistics, Ministry of Economic Affairs, Brussels, 1993, 2 : 111-159.
12. FLEISS J.L. Statistical methods for rates and proportions, 2nd ed. New York : John Wiley & Sons, 1981, 244-247.
13. PRODINGER W.M., LARCHER C., SÖLDER BM, GEIBLER D., DIERICH M.P. Hepatitis A in western Austria. The epidemiological situation before the introduction of active immunisation. *Infection*, 1994, **22** : 53-55.
14. JOUSSEMET M., BOURIN P., LEBOT O., FABRE G., DELOINCE R. Evolution of hepatitis A antibodies prevalence in young French military recruits. *Eur. J. Epidemiol., 1992,* **8** : 289-291.
15. NORDENFELT E. Hepatitis A in Swedish travellers. *Vaccine*, 1992, **10** : 873-874.
16. KOFF R. Seroepidemiology of hepatitis A in the United States. *The Journal of Infectious Diseases*, 1995, **171** (Suppl 1) : S19-S23.
17. BONANNI P., BANDETTINI R., PINTUS L., ALBERTI G., ICARDI G.C., CROVARI P. Changing pattern in the seroepidemiology of hepatitis A and B in Genoa. *J. Prevent. Med. Hyg.*, 1989, **30** : 29-36.
18. SALLERAS L., BRUGUERA M., VIDAL J., TABERNER J.L., PLANS P., JIMENEZ DE ANTA M.T., RODES J. Cambio del patrón epidemiológica de la hepatitis A en España. *Medicina Clínica*, 1992, **99** : 87-89.
19. BIENZLE U., BOCK H.L., MEISTER W., CLEMENS R., KRUPPENBACHER J.P. Anti-HAV seroprevalence in German travellers and hepatitis A vaccination in immune subjects. *Lancet*, 1993, **341** : 1028.
20. VAN DOORSLAER E., TORMANS G., VAN DAMME P. Cost-effectiveness analysis of vaccination against Hepatitis A in Travellers. *J. Med. Virol.*, 1994, **44** : 463-469.