Impact and effectiveness of a mass hepatitis A vaccination programme of preadolescents seven years after introduction

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Hepatitis A vaccine; Effectiveness; Herd immunity

Summary
Aim: To investigate the impact of a mass hepatitis A vaccination programme in preadolescents seven years after introduction in terms of its effectiveness and the prevented fraction.
Setting: The age distribution of notified cases and incidence rates in Catalonia (Spain) in the periods before (1992-1998) and after (1999-2005) introduction of the vaccination programme were compared.
Main results: The incidence rates in the whole population were 5.51 per 100,000 person-years in the 1992-1998 period and 2.98 in the 1999-2005 period. The rate reduction in the 10-19 years age group was 72.43% and was more than 45% in the 5-9 years and 20-29 years age groups. The effectiveness of the vaccination programme was 99.04 (95% CI: 93.11-99.88) and the prevented fraction in the 12-19 years age group was 90.13% (95% CI: 84.47-90.89).
Conclusions: The universal vaccination programme of preadolescents has had an important impact on hepatitis A in Catalonia, not only in vaccinated cohorts but also in non-vaccinated age groups due to a herd immunity effect.
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Introduction

Hepatitis A virus (HAV) infection is an acute self-limiting disease which is often asymptomatic in children. In adults, the clinical presentation is characterised by acute onset of malaise, anorexia and abdominal pain followed by jaundice. The disease lasts from two weeks to several months and
hospitalization is not infrequently required in people aged >50 years [1,2]. In 8-10% of cases, the disease relapses following an apparent recovery. In some cases, HAV may lead to extrahepatic complications (arthralgia, pancreatitis, vasculitis or glomerulonephritis). Fulminant hepatitis or death is not exceptional, especially in older people and patients with chronic liver disease [3].

Hepatitis A usually presents epidemic waves which are repeated at intervals that vary according to the circulation of the virus [4]. In Catalonia, as in other countries of low endemicity, seroprevalence studies show that hepatitis A infection has shifted to older age groups, which may imply a more severe clinical course [5].

In countries of low endemicity, the main high-risk groups include people travelling to endemic countries, male homosexuals, injecting and non-injecting drug users. However, infection is not limited to these groups and the source of infection is not determined in about half the cases [1,6].

The availability of an inactivated vaccine of proven immunogenicity and a protective efficacy [7,8] led to introduction of the vaccination of risk groups in Catalonia in 1995. This policy had a very limited impact on the incidence of the disease. Thus, at the end of 1998, universal vaccination with a combined hepatitis A + B vaccine manufactured by GlaxoSmithKline and containing 360 ELISA units of HAV antigen and 10 μg of HBV surface antigen was started in 12-year-old preadolescents. Three doses were administered subcutaneously at 0, 1 and 6 months. The effectiveness of the universal vaccination programme was 97% (95% CI: 78.5-99.6) in an evaluation made three years following its introduction [9].

The objective of this study was to investigate the impact of the hepatitis A vaccination programme in terms of its effectiveness and the prevented fraction, seven years after its introduction.

Materials and methods

The study was carried out in Catalonia, a region of 7 million inhabitants situated in the northeast of Spain, where reporting of all cases of viral hepatitis without regard to the aetiology has been mandatory since 1982; hepatitis A has been a separate notifiable disease only since 1991.

All cases of hepatitis A reported since 1992 were reviewed and confirmed cases, defined as a clinically compatible case with immunoglobulin M antibodies to the capsid proteins of HAV (anti-HAV IgM positive) or a clinically compatible case epidemiologically linked to an anti-HAV IgM positive case, were included in the study. In all cases the vaccination status was ascertained by reviewing school or paediatric registries.

The age distribution of cases and incidence rates in the 1992-1998 and 1999-2005 periods were analysed.

Incidence rates were calculated using census figures for each year [10] and their 95% confidence intervals (CI) were calculated assuming a Poisson distribution. Percent reductions between the two periods were compared by calculating a normal z statistic.

Statistical significance was established assuming an \( \alpha \) error = 0.05. The statistical analysis was carried out using the EPI-DAT (American Public Health Association, Washington DC) programme.

The effectiveness of the vaccination programme was calculated using the formula: \( \text{VE} = 1 - RR \), where \( RR \) is the relative risk resulting from the division of the incidence rate in the vaccinated cohorts by the incidence rate in the non-vaccinated cohorts. The 95% CI of the VE were calculated using the Taylor series [11]. For an effectiveness of 100%, the lower CI was calculated assuming a Poisson distribution [12].

The vaccinated cohorts were composed of children reaching 12 years of age during the years 1998-2005 (born in 1987-1993) and the non-vaccinated cohorts of children reaching 12 years of age during the 3 previous years (born in 1984-1986).

The numbers of children in the two cohorts were corrected according to the vaccination coverage of 91%, a value obtained from registers of vaccinations in schools and paediatric services.

A child was considered vaccinated if they had received three doses of vaccine with an interval of one month or more between the first and second dose and five months or more between the second and third dose.

The prevented fraction (PF) in the 12-19 years age group was calculated using the formula \( P_e (1 - RR) \), where \( P_e \) is the vaccine coverage in the population [13].

Results

Fig. 1 shows the overall hepatitis A incidence during the study period. Cases in the 10-19 years age group, which includes the vaccinated cohorts, accounted for 8.27% of the total in the study period, compared with 21.69% in the prevaccination period. The incidence rate of hepatitis A in the 1992-1998 period was 5.51 per 100,000 person-years, which fell to 2.86 per 100,000 person-years in the 1999-2005 period. The 10-19 years age group showed the greatest reduction (72.43%; \( p < 0.001 \)), while the reduction was >45% in the 5-9 years and 20-29 years age groups. The incidence rates were higher in the prevaccination period compared with the postvaccination period in all age groups up to 40 years of age but in people older than 40 years...
of age no statistically significant differences were observed (Table 1).

Twelve cases of hepatitis A were observed in children of the theoretically vaccinated cohorts (children born in 1987-1993), of which 11 occurred in non-vaccinated persons; the status of the remaining case could not be determined. In the non-vaccinated cohorts (children born in 1984-1986) there were 132 cases of hepatitis A that had received no dose of vaccine. The contribution of the vaccinated and non-vaccinated cohorts corrected by the assumed coverage was 1,591,366 person-years and 2,023,121 person-years, respectively (Table 2). This means that the Relative Risk (RR) was 0.0096 and vaccination effectiveness was 99.04% (95% CI: 93.11—99.88).

If the case where the vaccination status was not determined had not been vaccinated, vaccination effectiveness would be 100% and the lower 95% CI would be 96.46%.

According to these figures, the prevented fraction in the 12-19 years age group was 90.13% (95% CI: 84.47-90.89). If the effectiveness was 100%, the prevented fraction would be 91% (lower 95% CI: 87.78).

### Discussion

The results of this study carried out 7 years after the introduction of universal hepatitis A vaccination in Catalonia clearly show that the incidence of hepatitis A has declined more than 45% during the seven-year period after the introduction of universal vaccination.

The reduction observed cannot be attributed solely to vaccination, since some, but not all, studies carried out in Spain suggest that without universal vaccination hepatitis A incidence also decreases substantially, probably due to improvements in environmental and sanitation conditions [14,15].

Mathematical models indicate that an annual reduction of 4.5% should be expected without the use of the vaccine [16].

Samandari et al. [17] using a mathematical model to distinguish between the reductions in incidence attributable to vaccination and to the natural evolution of the disease found that a vaccination coverage of 10% in children aged 2-18 years prevented 51% of cases in this age group and 39% of all cases, probably due to herd immunity.

Wasley et al. [18] found that in US in states which recommended universal paediatric vaccination, incidence rates in the 10-18 years age group in 2003 fell by 90.62% compared with the 1990-1997 prevaccination period. In the 10-19 years age group the incidence rates fell by 72.43% in our study.

In Israel [19], after the introduction of universal vaccination of children with two doses at 18 and 24 months of age, an annual reduction of 98% was observed in the cohort of vaccinated children in the 2002-2004 period with respect to the 1993-1998 period and a reduction of 90% in non-vaccinated older children and adults.

However, as in our study, it is not easy to ensure that disease surveillance methods and environmental conditions in these studies are equal before and after the introduction of universal vaccination. In Catalonia, we consider that one year after the introduction of reporting hepatitis A separately, the surveillance system for the disease was consolidated. In a previous study, we estimated that underreporting of clinical cases is important, because only 20% of cases are reported [20]. Unfortunately, we did not study whether underreporting has changed over time, but we assume that there are no changes that limit the detection of cases of hepatitis A and therefore that the

### Table 1

<table>
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<td>30—39</td>
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<td>50—59</td>
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The fact that the greatest reduction in incidence rates (72.43%) occurred in the 10-19 years age group, which included the cohorts vaccinated after 1998, suggests that vaccination has played an important role.

Vaccination effectiveness in this study, calculated using cases occurring in vaccinated and non-vaccinated cohorts, was 99%, very similar to the 100% found by Werzberger et al. in vaccinated children during a nine-year follow-up in which many cases occurred in the non-vaccinated population [21]. The lack of cases in the vaccinated cohort over a nine-year period suggests that the hepatitis A vaccine confers long-term protection, either due to the persistence of protective antibodies or because an anamnesic response occurs after natural exposure to the wild virus [22]. It has been estimated that anti-HAV persist for 25 years in adults and 14-20 years in children [23].

The prevented fraction of hepatitis A in preadolescents and adolescents in Catalonia (90%) should be considered as a minimum level, as both the coverage and the effectiveness were estimated conservatively. If we assume that vaccine-induced protection lasts at least 9 years, but may be lifelong when an anamnesic response is generated following a new exposure [24], universal vaccination in the second year of life, where coverages reach 95-98% [25], would avoid practically all paediatric cases in Catalonia and would continue to protect these children in adolescence and adulthood [26]. In addition to the direct influence of the vaccine, indirect protection is produced by avoidance of cases in children, who transmit the disease more easily and are frequently asymptomatic, infecting non-vaccinated subjects [27,28].

The indirect protective effect in this study is suggested by the greater falls in disease incidence in non-vaccinated subjects from age groups most frequently in contact with the vaccinated cohorts.

A possible limitation of universal vaccination programmes is their cost [29]. However, some studies have found that universal hepatitis A vaccination is more cost-effective than vaccination with the conjugated pneumococcal vaccine, similar to the varicella vaccine and superior to that of viral hepatitis [16]. Enferm Infecc Microbiol Clin 2003;21:698—701.


References

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