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Effectiveness and impact of the hepatitis B vaccination program in preadolescents in Catalonia 21 years after its introduction

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ABSTRACT

Hepatitis B is a viral disease of global importance. In Catalonia in the 1980s, the seroepidemiological pattern of HBV infection was low-intermediate. In 1990, the Expert Committee on Vaccinations of the Department of Health of the Generalitat of Catalonia evaluated the systematic introduction of hepatitis B vaccination in preadolescents, maintaining the vaccination of risk groups. The objective of this study was to estimate the effectiveness and impact of the systematic hepatitis B vaccination programme in preadolescents in Catalonia 21 years after its introduction. A retrospective cohort study was conducted, comparing the disease incidence in vaccinated and unvaccinated cohorts. Cases of hepatitis B were defined as those reported by the General Subdirectorate of Surveillance and Response to Public Health Emergencies between 2000 and 2014. The incidence rate was 2.5 per 100,000 persons in 1991 and 1.2 per 100,000 persons in 2014, a reduction of 52%. During the study period, 388 cases of hepatitis B infection were notified, of which three were classified as vaccine failures. Vaccine effectiveness was 99.30% (95% CI: 97.83–99.78) and the population prevented fraction in the cohorts of preadolescents studied was 64.56% (95% CI: 60.45–68.66). The effectiveness and impact of the hepatitis B vaccination program in preadolescents in Catalonia is high, with the consequent benefits for the population.

1. Introduction

Hepatitis B is a viral disease of worldwide importance due to its morbidity and mortality and its high chronicity in children. Chronicity increases the lifelong risk of cirrhosis or hepatocellular carcinoma, and patients are continuing transmitters of the hepatitis B virus (HBV) [1].

In Catalonia in the 1980s, the seroepidemiological pattern of HBV infection was low-intermediate: 20% of adults had infection markers and the prevalence of chronic carriers was 1.5–2% [2]. Perinatal and horizontal transmission in infancy was rare, and there was little risk of developing hepatitis B before puberty: 9.3% persons aged 15–24 years had positive HBsAg antibodies [3], indicating that the infection was acquired from 14 years of age onwards: it was estimated that 97% of persons aged 14 years were susceptible. Infection in adolescence and young adults is explained by transmission through sexual behaviour and injection drug use.

In Catalonia, hepatitis B has been a notifiable disease since 1991 and data on the incidence of acute cases are available [4].

Hepatitis B vaccination in Catalonia began in 1984 with the vaccination of the children of HBsAg-positive mothers and priority risk groups (health workers, haemophiliac patients and haemodialysis patients) in accordance with the CDC Expert Committee on Vaccinations recommendations [5]. In 1988, the risk groups included were expanded to include children of HBsAg-positive mothers, which was strongly supported by obstetricians and neonatologists and, in 1986, the subprogramme of active-passive immunization of children born to HBs Ag-positive mothers was created [6].

However, it was found that the vaccination of risk groups was not an optimal strategy for achieving a marked reduction in incidence rates, as was also the case in the USA [7,8], mainly due to

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the difficulty in accessing some groups or in protecting them before exposure to the virus.

In December 1990, the Expert Committee on Vaccinations of the Department of Health of the Government of Catalonia evaluated the introduction of routine hepatitis B vaccination, and found the best population strategy was to vaccinate in preadolescence, while maintaining the vaccination of risk groups [9]. Catalonia was the first autonomous community in Spain to include hepatitis B vaccination in the routine vaccination schedule [10].

Universal vaccination began in October 1991 in schools at the age of 11–12 years with three vaccine doses at 0, 1 and 6 months. Between 1992 and 2014, the Catalan vaccination calendar has been modified three times. The first modification [11] responded to the increased susceptibility to hepatitis A infection in childhood-adolescence and the appearance of a new combined hepatitis A + B vaccine, allowing the prevention of the two infections with the greatest risk in adolescence. Therefore, the monovalent vaccine was replaced by the combined vaccine as part of a pilot program. In 2002, hepatitis B vaccination with the hexavalent vaccine was introduced in infants at 2, 4 and 6 months [12], with two cohorts, infants and preadolescents, being vaccinated simultaneously. This situation lasted until July 2014, when the vaccination of preadolescents was suspended because the first infants vaccinated had reached the preadolescent vaccination age [13].

The objective of this study was to estimate the effectiveness and impact of the systematic hepatitis B vaccination programme in preadolescents in Catalonia 21 years after its introduction.

2. Materials and methods

A retrospective cohort study was carried out in vaccinated and unvaccinated cohorts according to the year of birth. The unvaccinated cohort was defined as persons born between 1976 and 1979 who were followed for 15 years, from 2000 to 2014. The vaccinated cohort was defined as persons born between 1981 and 1994, who were followed from 2000 to 2014. The cohort born in 1980 was not included as the vaccination age occurred in the year the programme was initiated. The vaccinated cohort was considered until 2001, since in 2002 vaccination of infants began and this could be added to the effect in the estimation of vaccine effectiveness (VE).

Cases of hepatitis B were defined as those reported to the Department of Health of the Generalitat of Catalonia (General Subdirectorate of Surveillance and Response to Public Health Emergencies) between 2000 and 2014.

Cases included in the study met the confirmed case criteria for hepatitis B positivity (acute symptoms consistent with viral hepatitis and hepatitis B core antigen [anti-HBc] IgM antibodies) [14]. Data on the vaccination coverage of preadolescents with three doses of vaccine from 1992 until 2013, the last year in which this programme functioned, was obtained from Catalan Vaccination Programme records.

The date of birth, date of symptom onset and the vaccination status were collected for recorded cases. The variables of the vaccination status were checked by reviewing the epidemiological records and, if necessary, the medical record.

Vaccination failure was defined as a case that had received three doses at 0, 1 and 6 months, or a correct alternative regimen, with symptom onset 6 months after the last dose of vaccine [15].

We estimated incidence rates in the vaccinated and unvaccinated cohorts, eliminating cases in which symptom onset preceded vaccination. Based on the incidence rates obtained, the rate ratio (RR) and 95% confidence intervals (CI) were estimated, as was the vaccine effectiveness (VE) using the formula: $VE = (1-RR) \times 100$ and the 95% CI were estimated using the Taylor series.

The population prevented fraction of hepatitis B in the cohorts of preadolescents studied was estimated using the formula: Prevented fraction = incidence in the unvaccinated cohort–incidence in all cohorts studied (vaccinated cohort and unvaccinated cohort)/incidence in the unvaccinated cohort) [16].

3. Results

Fig. 1 shows the number of cases in unvaccinated and vaccinated cohorts reported between 2000 and 2014. The incidence rate in 1991 was 2.5 per 100,000 persons, which decreased to 1.2 per 100,000 persons in 2014. By age group, the highest incidence rate in 1991 was in the 20–29 years age group, followed by the 30–39 years age group (Fig. 2). A substantial reduction was observed in the 20–29 and 30–39 years age groups (83.4% and 42.1%, respectively). The reduction in the global incidence rate between 1991 and 2014 was 52%. Vaccination coverage estimated by vaccination records during 1992–2013 fluctuated between 80 and 90% (Fig. 3).

During the study period, 388 cases were notified. Of these, 232 (59.8%) occurred in the unvaccinated cohort (born between 1976 and 1979), and the rest in the vaccinated cohort. There were 9 cases (2.32%) in people who had received ≥ 1 vaccine dose: of these, 6 cases were classified as incomplete vaccination (although some did not meet the criterion of the maximum range of the incubation period) and three cases fulfilled the criterion of vaccine failure.

Of the 232 notified cases in the unvaccinated cohort, four had received the vaccine, but did not meet the criteria for vaccine failure and were classified as incomplete vaccination, although one had received three doses, but the time between the last dose and symptom onset was two months. In this cohort, no case of vaccination failure was detected.

In the vaccinated cohort, 156 cases were notified, of which three were classified as vaccine failures, two did not meet the vaccine failure criteria (incomplete vaccination schedule) and 11 cases became ill before receiving the vaccine. The three vaccine failures were male; two were vaccinated as preadolescents, with a time between the date of the last dose and symptom onset of 9 years in both cases. The third vaccine failure was vaccinated at 0, 1, and 4 months of age with a fourth dose at 5 years of age, and with symptom onset 12 years, 8 months after the last dose.

The incidence rate was 4.06 per 100,000 person-years in the unvaccinated cohort and 0.03 per 100,000 person-years in the vaccinated cohort (Table 1), with an RR of 0.0069 (95% CI 0.0022–0.0217). The estimated vaccination effectiveness (VE), considering as vaccination failures only cases that had received three doses at 0, 1 and 6 months, or a correct alternative regimen, with a symptom onset 6 months after the last dose of vaccination, was 99.30% (95% CI: 97.83% −99.78%).

Table 1 shows the incidence rates including the two vaccinated cases with an incomplete vaccination schedule as vaccine failures; the RR was 0.0116 (95% CI: 0.0047–0.028). In this case, the VE was 98.84% (95% CI: 97.19%–99.52%).

The benefit attributed to the vaccination program in the cohorts of preadolescents studied by estimating the population prevented fraction was 64.56% (95% CI: 60.45–68.66) when the two cases with incomplete vaccination were not considered vaccination failure and 64.28% (95% CI: 59.02–69.49) when they were.

4. Discussion

Our results show that the introduction of systematic hepatitis B vaccination in Catalonia in preadolescents, with vaccination coverage rates of around 85%, has evidently had favourable effects in decreasing the incidence rate in the whole population, and in the

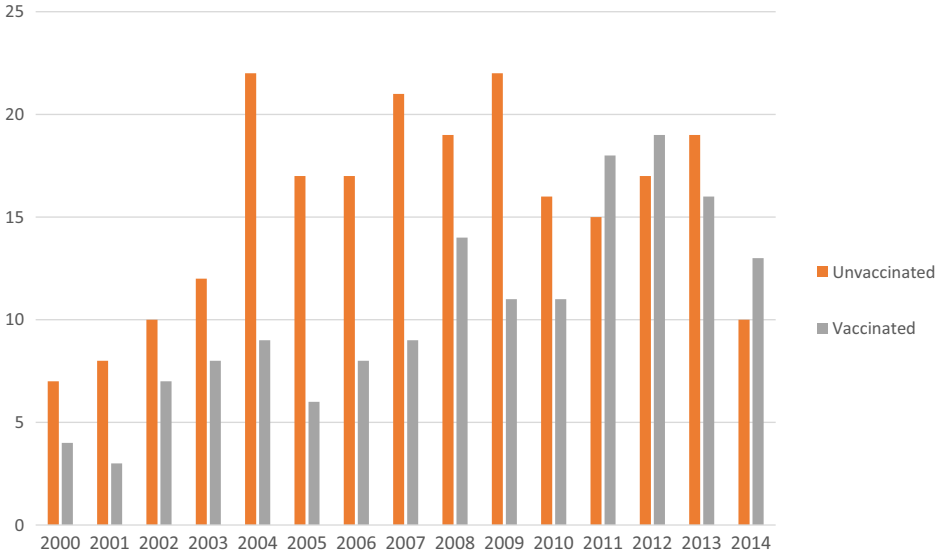

Fig. 1. Number of cases in non-vaccinated and vaccinated cohorts* reported between 2000 and 2014. *The non-vaccinated cohort was composed of subjects born between 1976 and 1979 and the vaccinated cohort of subjects born between 1981 and 1994.

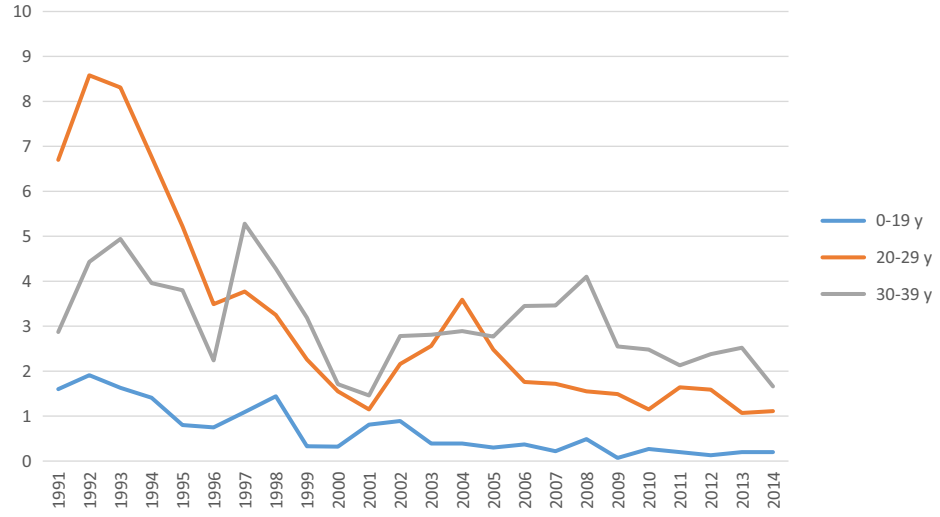

Fig. 2. Evolution of incidence rates of notified hepatitis B cases by age group in Catalonia, 1991–2014.

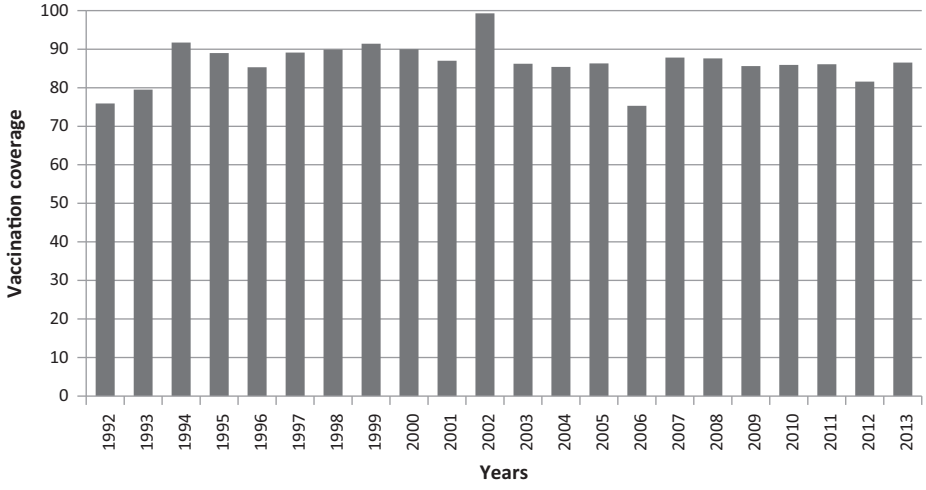

Fig. 3. Evolution of vaccine coverage with 3 doses of hepatitis B vaccine. Catalonia, 1992–2013.

Table 1
Distribution of hepatitis B cases in vaccinated (1981–1994) and unvaccinated (1976–1979) cohorts considering vaccine failure in those receiving 3 doses at 0, 1 and 6 months or an alternative schedule and including the two cases with an incomplete schedule as vaccine failures.

	Cases	Person-years	Incidence rate[a] (95% CI)
Considering as vaccination failures only			
Unvaccinated cohorts	232	5,714,625	4.06 (3.56–4.61)
Vaccinated cohorts	3	10616823,89	0,028 (0.007–0.077)
Considering vaccination failures and incomplete schedule			
Unvaccinated cohorts	232	5,714,625	4.06 (3.56–4.61)
Vaccinated cohorts	5	10616823,89	0,047 (0.002–0.104)

[a] Per 100,000 person-years.

age groups in which infection was more frequent, including the 20–29 years and 30–39 years age groups (reductions of 52%, 83.4% and 42.1% between 2000 and 2014, respectively).

The estimated effectiveness of the vaccination program was over 98%, regardless of whether the more stringent definition of vaccine failure (99.30%; 95% CI 97.83–99.78) or a more flexible definition (98.84%; 97.19–99.52) was used.

Our results are consistent with those found in Italy, the first country in the world in which systematic vaccination was introduced, in 1991 in adolescents aged 12 years [17], where hepatitis B rates decreased from 5.1 per 100,000 in 1991 to 1.3 in 2005 [18].

Our results are also aligned with the objectives adopted by the WHO in May 2016 in the first Global Health Sector Strategy on Viral Hepatitis which proposed to reduce chronic infections due to viral hepatitis by 90% and mortality by 65% by 2030 [19].

The most marked reduction in age groups with the highest risk was also observed in the Italian study by Mele et al., in which the decrease was especially evident in the 15–24-years age group (a 24-fold decrease from 1991 to 2005) and the 0–14-years age group (a 50-fold decrease from 1991 to 2005), even if, for the latter group, the 1991 incidence was already low, because a trend to a decreasing incidence had started before 1991 [18]. The program contributed to the reduction of hepatitis B infection in persons aged 15–24 years, a group at increased risk of infection associated with the onset of sexual activity.

In areas with high endemicity, systematic vaccination has reduced the prevalence of HBsAg by more than 90% [20].

In addition, although not evaluated in the present study, the hepatitis B vaccine was the first to prevent cancer by reducing the incidence of hepatocellular carcinoma by up to 80% in young adults [21]. Likewise, 85–90% of other deaths related to HBV are vaccine preventable [22].

Hepatitis B infection in correctly-vaccinated persons, taking into account the time from the end of vaccination to the onset of symptoms, may be due to mutations in the virus. This has been studied in high endemicity countries in which vaccination was introduced in childhood. These vaccination programs achieved significant reductions in the disease, but cases in vaccinated persons were observed, which may be due to variations in the escape of the hepatitis B vaccine due to selection pressure. Several studies have evaluated this hypothesis, and have found mutations mainly in one of the determinants of HBsAg [23–27].

The hepatitis B vaccine is highly effective and, in our study, vaccine failures were less frequent than those observed by other authors [17]. As vaccine escape mutants do not seem to play an important role in vaccine failure, these cases should be traced to the percentage of healthy vaccinees (5%−10%) who do not mount an adequate antibody response [28].

Economic benefit of routine hepatitis B vaccination might also be considered. An analysis of a systematic vaccination program in Italy showed that vaccination involves clear savings from both the societal and health service provider perspectives [29].

One limitation of the study is that the coverage estimated by the vaccination program records is probably underestimated, since some people are vaccinated in primary care centres and there are also areas of Catalonia where private paediatric care is considerable. Another possible limitation is the lack of data on the vaccination history in the notification cards of the cases, but this was solved by searching for information in other data sources, so the impact of this limitation was minimized. A final limitation might be the under-reporting of hepatitis B cases: however, we think this is unlikely because no changes in the reporting or recording system were introduced in Catalonia during the study period and the systems were the same for vaccinated and unvaccinated cohorts.

In conclusion, the results of this study show that the effectiveness of the hepatitis B vaccination programme in preadolescents that was introduced in Catalonia in 1991 has been very high in the vaccinated cohort (>98%) and that the population prevented fraction in the cohorts of preadolescents studied was also relevant (>64%).

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Conflict of interest statement

The authors have no conflict of interests.

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