Original Article

Single-Dose Universal Hepatitis A Immunization in Argentina: Low Viral Circulation and High Persistence of Protective Antibodies Up to 4 Years

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Background. Single-dose hepatitis A virus (HAV) vaccination was implemented in all Argentinean children aged 12 months in 2005. Between 2005 and 2011, a dramatic decline was observed in HAV infection rates, fulminant hepatitis, and liver transplantation. This study assessed current viral circulation and estimated protective antibody persistence 4 years after vaccination.

Methods. Prevalence of prevaccination anti-HAV antibodies in 12-month-old children was evaluated as an indirect estimation of viral circulation (Group A). Seroprevalence was also measured in 5-year-old children who received 1 dose of HAV vaccine at 1 year of age (Group B). Blood samples were tested for immunoglobulin (Ig)G anti-HAV antibodies (seroprotection = ≥10 mIU/mL). All Group A-positive samples were tested for IgM anti-HAV antibodies to identify recent infections. Logistic regression analysis was done to evaluate associations between demographic and socioeconomic variables and seroprotection.

Results. Of 433 children from Group A, 29.5% (95% confidence interval [CI], 25.2–33.8) were positive for IgG anti-HAV antibodies with a geometric mean concentration (GMC) of 6.17 mIU/mL (95% CI, 5.33–7.15 mIU/mL); all IgM anti-HAV were negative. From 1139 in Group B, 93% (95% CI, 91.7–94.6) maintained seroprotection with a GMC of 97.96 mIU/mL (95% CI, 89.21–107.57 mIU/mL). Kindergarten attendance was associated with seroprotection in Group B (odds ratio [OR], 2.0; 95% CI, 1.26–3.3). In contrast, high maternal educational level was associated with a lack of seroprotection in this group (OR, .26; 95% CI, .09–.8).

Conclusions. Single-dose, universal hepatitis A immunization in infants resulted in low HAV circulation and persistent immunologic protection up to 4 years in Argentina. Variables associated with presence or absence of seroprotection in vaccinated children could be related to differences in hygiene habits in settings with residual viral circulation.

Key words. Argentina; hepatitis A; immunogenicity; single-dose vaccination; viral circulation.

Hepatitis A is one of the most frequently reported vaccine-preventable diseases worldwide, and affects more than 200 million people annually [1]. In Latin America, the incidence is approximately 250 000 cases per year (rate: 20–40 cases per 100 000). Although complications from hepatitis A are rare, fulminant hepatic failure (FHF) occurs in 0.3%–0.4% of affected children [2].

Hepatitis A virus (HAV) is typically transmitted by the fecal-oral route, generally through human transmission in areas with poor sanitation and scarce access to safe water. In populations with higher socioeconomic status or better hygienic conditions, most infections occur through contamination of fresh produce or foods [3]. However, in countries such as Argentina, these 2 sanitary conditions coexist and transmission occurs in both ways. Considering that the virus may persist in feces and soil for prolonged periods of time, and that in Argentina, only approximately 50% of the population has sewers, high viral circulation

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resulted in recurrent outbreaks of hepatitis A [4, 5]. Seroepidemiology studies conducted in the 1990s showed that by the age of 1 year, children from higher socioeconomic areas in Buenos Aires city had a 5% seropositivity rate for HAV compared with 73.1% of children from poor sanitation areas at the Northwest region of the country [6].

Vaccination against hepatitis A has been shown to be safe and effective and results in sustained high levels of protection [7–10]. When implemented universally, vaccination has also proved to rapidly decrease hepatitis A incidence rates and control the disease [11–14]. However, the high cost and need of a 2-dose schedule has limited its widespread use in most low- and middle-income countries.

In June 2005, Argentina introduced a single dose of inactivated HAV vaccine (strains: HM 175 720 EI.U, Havrix, GlaxoSmithKline; CR 326 25 U, Vaqta, MSD; GMB 80 U, Avaxim, sanofi pasteur; RG-SB 12 UI, Virohep-A Junior, Novartis) as part of the routine immunization schedule for all children 12 months of age, after a nationwide outbreak in 2003 to 2004 [15, 16]. At that time, hepatitis A was the leading cause of FHF and liver transplantation (LT) in children [17–19].

The single-dose vaccination strategy at 12 months of age was decided based on the following: (1) previous data demonstrating that 85%–95% of vaccinated individuals achieve protective antibody titers 10–14 days after the first dose, and almost 100% seroconvert after 4–6 weeks [7–10, Tregnaghi et al., unpublished data]; (2) the experience from other countries where transmission was interrupted even in older age groups as a result of vaccinating the younger cohorts (herd protection) [11–14]; (3) the expectation that in addition to the humoral response, immunological memory recall could be elicited after a single dose in children, as had been demonstrated in adult travelers, and that the natural booster induced by wild virus circulation in endemic areas could ensure long-lasting protection [20]; and (4) the economic limitations in Argentina at the time to include a 2-dose series; so, if 1 dose was sufficient, it would make for an affordable and sustainable long-term vaccination strategy. To evaluate the effectiveness of the 1-dose HAV program, a continuous and strengthened surveillance was implemented by the Ministry of Health of Argentina [21].

Although epidemiological data demonstrated a dramatic decline in HAV infections, several questions arose after the introduction of mass vaccination against hepatitis A in Argentinean infants [22–24]. The decline of viral circulation was difficult to assess. The prevalence of antibodies against HAV immediately before vaccination in toddlers could correlate with HAV circulation and could be an indirect surrogate indicator [25]. Another concern was whether a booster dose will be needed in the future. After immunization, it is expected that anti-HAV titers will decrease in the next several years after [26, 27]; even though immunity wane is expected to be gradual, and it has been estimated that HAV vaccine-induced protective antibodies could persist for more than 20 years in adults, and up to 14 and 24.5 years in children from China and Taiwan, respectively [26–28]. However, these estimations were done after a 2- or 3-dose schedule and in a different epidemiological context than Argentina; thus, the length of protection remained uncertain after a single-dose vaccination in our country. In this study, we aimed to assess the prevalence of anti-HAV antibodies immediately before vaccination in infants as a surrogate indicator of viral circulation, and we estimate the prevalence of protective antibody titers 4 years after single-dose HAV vaccination.

METHODS

Study Population

Participants were enrolled from March to November 2011 from historically low, middle, and high endemic hepatitis A regions of the country. The following regions were selected based on past seroprevalence data: Hospital de Niños Ricardo Gutierrez (Buenos Aires city), Hospital de Niños de San Justo and Hospital Nacional Profesor Dr Alejandro Posadas (Buenos Aires province), Hospital de Niños de la Ciudad de Tucumán (Tucumán city), and Hospital de Niños Orlando Alassia (Santa Fe city). Both Buenos Aires and Santa Fe provinces are located in the central region, and Tucumán is in the Northwestern region of Argentina. Children who visited these healthcare centers for routine well child visits were screened to participate in the study. To determine the prevalence of anti-HAV antibodies before vaccination, healthy 12-month-old (±1 month) children who had not received any HAV vaccine were recruited for the study (Group A). To estimate the prevalence of anti-HAV protective antibodies, 5-year-old children who had received a single dose of HAV vaccine at 1 year of age and had not received any additional HAV vaccination were recruited as the vaccinated cohort (Group B). Children with a history of hepatitis A, primary or secondary immunodeficiency, chronic disease, or any active illness at the time of enrollment, as well as those who were participating in other trials, or whose parents did not give written informed consent to participate in this study were excluded. Immune response results shortly after vaccination were not available for the children in Group B for comparison with the samples collected 4 years later. The study was approved by each hospital's Ethics Committee and by the Ministry of Health of Argentina.

Data Collection and Laboratory Assessments

Demographic and socioeconomic data were collected using a standardized questionnaire completed by the children's parents. Hepatitis A seronegativity was associated with a higher socioeconomic status in a previous Argentinean study [29]. Thus, some variables included in this analysis such as educational level, number of people per room, excretal disposal type, and access to tap water aimed to reassess this finding. On the other hand, the variable "breastfeeding" was included assuming this might correlate with seroprotection. Finally, attendance to nursery (3–24 months of age) or kindergarten (usually 3- to 5-year-old children) was considered as enabling environments for viral circulation among infants or young children.

Blood sample analysis was performed at the Hepatitis and Gastroenteritis Service, Virology Department, National Reference Laboratory at the National Institute of Infectious Diseases ANLIS "Carlos Malbrán" in Buenos Aires. Serum was tested for immunoglobulin (Ig)G anti-HAV antibodies using the commercially available AxSYM HAVAB 2.0 microparticle enzyme immunoassay ([MEIA] Abbott Laboratories, Abbott Park, IL). Seropositivity was defined as antibody titers ≥10 mIU/mL [30]. All positive samples in Group A were also tested for IgM anti-HAV antibodies using the commercially available AxSYM HAVAB M 2.0 MEIA system to further distinguish between recent HAV infections and maternal antibodies. Immunoglobulin M anti-HAV can be detected in nearly 100% of patients with acute hepatitis A infection and remains positive in most of them for 3–6 months and for 12 months in up to 25% of patients [31]. Children in Group B with antibody titers <10 mIU/mL were offered to receive a second dose of vaccine because immediate postvaccination response was not known to rely on immunological memory recall. No additional measurement of antibodies was performed thereafter.

Statistical Analysis

Descriptive statistics and seroprevalence results were obtained using Epi Info 3.5.1 program (Centers for Disease Control and Prevention, Atlanta, GA). Means and standard deviations and median values and interquartile ranges with their confidence intervals (CIs) were estimated for continuous variables. Proportions (with 95% CIs) were estimated for categorical data. To evaluate the association between demographic and socioeconomic variables and antibody seropositivity, *t* test or Wilcoxon rank-sum test and χ^2 test were used; adjusted odds ratios (ORs) with their 95% CIs were also used. Multivariate analysis was performed for significant variables from the previous bivariate analysis using logistic regression analysis.

RESULTS

A total of 433 infants were recruited in Group A and 1139 children in Group B. The distribution of children was similar by hospital and region in both groups, and the demographic and general characteristics of the studied population were similar between groups (Table 1). In general, there was a similar proportion of males and females, the great majority lived in urban areas, and most had been breastfed and had access to safe water. Nearly half of the studied population had sewers, and the rest had cesspools or septic tanks for excreta disposal. A few mothers had tertiary or university education levels. The major differences between the groups were age, exposure to HAV vaccination, and attendance to nursery school or kindergarten (Group A: 7.4% vs Group B: 68.2%).

Of the children in Group A, 305 (70.4%) were susceptible to HAV infection before vaccination and 128 (29.6%) (95% CI, 25.2–33.8) had anti-HAV IgG titers ≥10 mIU/mL. The mean geometric anti-HAV IgG concentration (GMC) was 6.17 mIU/mL (95% CI, 5.33–7.15 mIU/mL) for this group. Figure 1 shows the cumulative distribution of antibody titers in Group A. Positive samples were analyzed for the presence of IgM anti-HAV antibodies, and all (100%) tested negative. Logistic regression analysis of Group A showed that none of the following were associated with seroprotection: age, gender, hospital, network water access, type of excreta disposal, attendance to nursery school, breastfeeding, maternal age, or type of housing and location.

Table 1. Basic Characteristics of the 2 Study Groups in Argentina. Group A (Unvaccinated 12-Month-Old Infants), Group B (Vaccinated 5-Year-Old Children)

	Group A	Group B
Population Characteristics	n = 433	n = 1139
Age in months (median-range)	12 (11–13)	65 (61–70)
Gender (%female)	195 (45)	513 (45)
Attend nursery (Group A)/ kindergarten (Group B) (%)	32 (7.4)	777 (68.2)
Breastfeeding (%)	388 (89.5)	1011 (88.8)
Gets water by public net (%)	351 (81)	931 (81.7)
Urban location (%)	426 (98.4)	1121 (98.4)
Excreta disposal type (%)	0	3 (0.3)
does not have		
Septic tank	7 (1.6)	24 (2.1)
sewers	201 (46.4)	551 (48.4)
cesspool	224 (51.8)	558 (49)
Others	1 (0.3)	2 (0.2)
Mothers' instruction level (%)		
1°	160 (36.9)	420 (36.9)
2°	191 (44.2)	524 (46)
3°	39 (8.9)	84 (7.4)
Mother's age (median and interquartile range)	26 (22–32)	31 (26–36)
Number of people per room (mean)	3.5	2.9

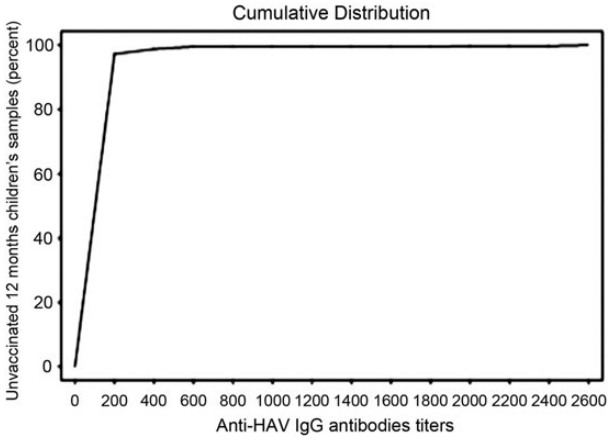

Figure 1. Cumulative distribution curve of anti-hepatitis A virus (HAV) antibody titers (mIU/mL) in unvaccinated 12-month-old children (Group A). Ig, immunoglobulin.

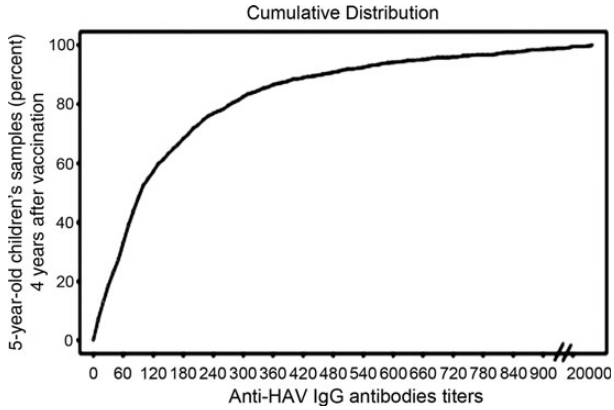

Figure 2. Cumulative distribution of anti-hepatitis A virus (HAV) antibody titers (mIU/mL) in 5-year-old children, 4 years after single-dose HAV vaccination (Group B). Ig, immunoglobulin.

Of the children in Group B, 1059 (93%) (95% CI, 91.7–94.6) had anti-HAV IgG >10 mIU/mL. Anti-HAV IgG GMC was 97.96 mIU/mL (95% CI, 89.21–107.57 mIU/mL). Figure 2 shows the cumulative distribution of antibody titers in Group B. Multivariate analysis showed that attendance to kindergarten was the only independent variable associated with seroprotection in this group with an OR of 2.0 (95% CI, 1.26–3.3). High maternal education level was associated with a decrease probability of seroprotection (OR, .26; 95% CI, .09–.8).

DISCUSSION

The introduction of a single-dose HAV vaccine in the national immunization schedule in Argentina since 2005 has resulted in (1) persistence of seroprotection up to 5 years of age and in (2) a dramatic decline in country-wide HAV-related outbreaks and almost elimination of HAV-associated FHF and LT. The success of this strategy was first assessed by Vacchino [22] in a study that analyzed HAV cases and infection rates that were reported to the National Epidemiological Surveillance System (SNVS) between 2005 and 2007 [22]. In this study, vaccine coverage for a single dose was over 95% since 2006, resulting in an abrupt decline in hepatitis A cases and infection rates. An incidence rate of 10.2/100.000 in 2007 was observed, which represented an 88.0% reduction compared with the prevaccination period (1998–2002). This decline was observed in all age groups and regions reflecting the impact of herd protection on HAV circulation and transmission. In addition, Cervio et al [23] assessed the impact on HAV-associated FHF and LT in the pediatric population until 2008, and they observed the disappearance of HAV-associated FHF and LT cases since November 2006 and March 2007, respectively [23]. As of 2011, the National Ministry of Health confirmed the continued decline in HAV incidence rates and the absence of FHF and LT HVA-associated cases [24].

Although cases may decrease after an outbreak due to the absence of susceptible hosts, the fact that this decline has been sustained over time suggests a decrease in viral circulation associated with this novel vaccination strategy. This finding is reflected in our study because <30% of infants had protective antibodies against HAV before vaccination. In addition, all positive samples tested negative for anti-HAV IgM antibodies, indicating no recent infection among the infant group in this study. These results were similar in all geographic areas assessed, and they contrast with previous seroprevalence reports, which showed diverse positivity rates ranging from 5% in Buenos Aires city to 73.1% in the Northwest region for a similar age group [6]. The low exposure to viral circulation in this age group after the implementation of universal single-dose vaccination against HAV is also supported by the decline in the notified hepatitis A cases to the SNVS in children under 1 year of age, which decreased from 1087 cases between 2000 and 2005 to 156 in the period from 2006 to 2013. (Source: National Epidemiological Surveillance System. Hepatitis A and unspecified hepatitis cases in children less than 1 year of age. 2000–2013.)

Seroprevalence studies are important to determine the optimal age for vaccination, and, in our case, these studies demonstrate the effectiveness of immunizing children at 12 months of age, because a great proportion of children at this age become susceptible to HAV as maternal antibodies decline. Moreover, these studies remark that the optimum immunization age for HAV vaccination should

be separately determined for each country according to its endemicity, sanitary conditions, and estimated transmission.

Most of the 5-year-old children in this study achieved and maintained protective antibody levels up to 4 years after single-dose HAV vaccination. Our results extend the findings of Espul et al [32] who examined the seroprevalence of anti-HAV at 3 years after vaccination and reported a seropositivity rate of 99.7% after 1 dose of vaccine in Argentinean children.

The prevalence of protective antibodies in our study was similar between regions, and it was significantly associated with kindergarten attendance. This finding seems logical considering the difficulties in implementing adequate hygienic habits in younger children and suggests that there is a residual viral circulation. In accordance with this finding, Blanco et al [33] and Yanez et al [34] have documented HAV circulation from environmental surveillance conducted in rivers and sewage samples from different regions of the country in the postuniversal vaccination era. We also observed that children born to mothers with tertiary or university educational level were less likely to maintain protective antibody titers than children born to mothers with only a primary level of education. This result could be related to better hygiene and sanitation and therefore lower exposure to residual circulating virus, and again it agrees with the results of Yanez et al [34] who found a lower prevalence of anti-HAV in the high-income population.

This study has some limitations. The period of time for wild virus circulation exposure in the group of unvaccinated infants was not so long considering the half-life of maternal antibodies. However, this is the only group in which this assessment could be done because vaccination in Argentina is recommended at 12 months. Another limitation is that immune response results shortly after vaccination were not available for the children in Group B. Thus, comparison with the samples collected 4 years later was not possible in this group. Finally, we could not correlate the rate of seroprotection with the type of vaccine received because these data were not recorded.

Moreover, several questions remain to be answered. It needs to be determined whether the effectiveness of this strategy will be long-lasting given the potential of waning immunity. It is possible that even when long-term antibody protection is not maintained, the anamnestic response could be rapid and robust enough to prevent HAV disease in the vaccinated population. Anamnestic response has been demonstrated in adult travelers after a booster dose up to 11 years after a single-dose vaccination, and in infants when challenged by a booster vaccination 15 months after a single dose of vaccine, or even 6 years after a 3-dose vaccination series [20, 35–39]. Thus far, international experts agree that HAV vaccine boosters are not needed after a full 2-dose primary vaccination course in healthy individuals [40]. Whether that conclusion could be extended to 1-dose schedules is still a question to be answered. It is also unknown whether HAV infection and disease could be shifted to older age groups as it has been shown in other countries after significant socioeconomic improvements were made, or after hepatitis A vaccination was introduced with a 2-dose schedule among children [41, 42]. In recent years, there has been an increase in the proportion of cases in the >14-year-old age group in Argentina; however, this result still represents a small number of cases, and none of these cases had received HAV vaccine [24]. Undoubtedly, the universal 1-dose HAV vaccination of toddlers in Argentina led to an impressive decline in the number of HAV cases in all age groups, with the highest reduction of cases in young children. The societal value of innovative schedules in low- and middle-income countries should be weighed against the original proven schedules that are challenging to introduce and nonsustainable where resources are scarce. We believe that these strategies should be accompanied by active and passive surveillance systems that allow the continuous monitoring of the immunization program's effectiveness and anticipate corrective measures if outbreaks arise in nonvaccinated populations. In this sense, Argentina is committed to making decisions based on local evidence and to share its experiences in order to promote cost-effective strategies. The present study is part of this policy. Further studies are being carried out by the National Ministry of Health to monitor and periodically evaluate this single-dose vaccination strategy.

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