Impact of the Single-dose Immunization Strategy Against Hepatitis A in Argentina

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Background: After a country wide outbreak occurred during 2003–2004, 1 dose of hepatitis A vaccine was introduced into Argentinian regular immunization schedule for all children aged 12 months in June 2005. The aim of this study was to assess the impact of this novel intervention.

Methods: A longitudinal analysis was done of hepatitis A virus (HAV) infection rates reported to the National Epidemiological Surveillance System from 2000 to 2011. Occurrence of fulminant hepatic failure (FHF) and liver transplantation cases up to 2011 were also assessed. Incidence rates and clinical impact were compared between pre- and postvaccination periods (2000–2002 vs. 2006–2011). Notification rates were also compared by age groups and geographical regions.

Results: Since 2006, an abrupt decline was observed in HAV infection rates, as well as in FHF and liver transplantation cases. The mean incidence rate of 7.9/100,000 in the postvaccination period represents a reduction of 88.1% ($P < 0.001$) when compared with the prevaccination period. Neither FHF nor liver transplantation due to HAV infection were observed since March 2007. Decline in incidence rates was evident in all geographical regions and all age groups but was higher in the prevaccination most affected areas and in young children. Although an absolute decrease was observed for cases and rates in all age groups, since 2006, a higher proportion of cases was observed in people >14 years of age.

Conclusions: The single-dose vaccination strategy has been highly effective for controlling HAV infection in all age groups till now in Argentina. Long-term surveillance will be critical to document the sustained success of this unique intervention.

Key Words: hepatitis A, Argentina, single-dose vaccination, toddlers, childhood immunization

(*Pediatr Infect Dis J* 2014;33:84–88)

Each year, hepatitis A, a disease preventable by vaccine, affects >200 million people worldwide.[1] Most of these cases, especially children <5 years of age, are mild or asymptomatic; however, in older children and adults, symptomatic disease is more frequent.[2] Fulminant hepatitis is rare but is associated with high morbidity, mortality and expense resulting from the need for a liver transplant.

The incidence is strongly correlated with socioeconomic indicators; with increasing income and access to safe water and adequate sanitation, the incidence of hepatitis A virus (HAV) infection decreases.[1] Declines in such infections have been reported in industrialized countries and associated with improvements in public health standards and with vaccination programs.[3–6]

Although vaccines against hepatitis A are safe, effective and cost effective when implemented universally in childhood, the high cost and a 2-dose schedule may explain the lack of widespread use of these vaccines.[7–14] Given the high immunological response to the first dose of vaccine and the expectation for longlasting protection induced by immunological memory, the use of a single-dose vaccination strategy could be an effective, easy-to-implement and affordable intervention in developing countries with high or intermediate rates of endemicity. However, this hypothesis has not been evaluated in clinical trials.

Since the early 1980s, when the differential diagnosis of hepatitis A and B became possible with serological tests, hepatitis A has been a major concern in Argentina. The disease has always been of intermediate to high endemicity based on seroprevalence, but during 2003–2004 there was a nationwide outbreak.[15] The rate of infection increased from 55.3 cases per 100,000 inhabitants in 2002 to 107.5 and 113.3 cases per 100,000 inhabitants in 2003 and 2004, respectively. The highest reported rates of infection were in children aged 5–9 and in the Northwest and Center West regions [*Sistema Nacional de Vigilancia de la Salud, Ministerio de Salud de la Nación*]. Hepatitis A was at that time the leading cause of fulminant hepatic failure (FHF) and liver transplantation (LT) in children.[16–18]

To reduce the high morbidity and mortality associated with this endemic disease, in June 2005, the National Ministry of Health, in agreement with national experts, introduced a single dose of inactivated hepatitis A vaccine (strains HM 175 720 EL.U, HAVRIX [GSK Biologicals, Rixensart, Belgium]; CR 326 25 U, VAQTA Merck Sharp & Dohme [Whitehouse Station, NJ]; GMB 80 U, AVAXIM [Sanofi-Pasteur, Lyon, France]; and RG-SB 12 UI, Virohep-A Junior [NOVARTIS, Buenos Aires, Argentina]) into the regular immunization schedule for all children 12 months of age.[19,20] This decision was based on the following factors:

- It was known, especially from outbreaks, that 85–95% of vaccinated individuals acquire protective antibody titers 10–14 days after the first dose and that almost 100% of these individuals acquire them after 4–6 weeks.[7–10]
- The age of 12 months was chosen based on serological prevalence surveys reporting that up to 84% of children of this age lacked anti-HAV antibodies in some provinces, meaning that this group was at high risk of infection.[15] It was also thought that the vaccine could be coadministered with other routine vaccinations, such as measles-mumps–rubella, with high coverage and was expected that this strategy would interrupt transmission in other age groups as well, as demonstrated abroad.[3–6]
- It was assumed that in addition to humoral response, immunological memory could be achieved with a single dose in children as had been described for adult travelers[21] and also that the natural booster induced by wild virus circulation in endemic areas could ensure longlasting protection.
- The economic situation was unfavorable at that time for including a booster dose, so a single-dose vaccination seemed to be an affordable and sustainable long-term strategy.

Accepted for publication August 16, 2013.

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The National Program for the Control of Immune Preventable Diseases which is part of the National Ministry of Health funded the complete study.

The authors have no other funding or conflicts of interest.

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ISSN: 0891-3668/14/3301-0084
DOI: 10.1097/INF.0000000000000042

At the time, the need for continuous and strict surveillance was noted to evaluate the outcomes of this novel intervention. Two Argentinean studies described a significant reduction in the incidence of hepatitis A and a decline in FHF and LT up to 2007 and 2008.[22,23] Recently, Gentile et al[24] briefly summarized the postvaccination epidemiological status of hepatitis A infection based on our preliminary data.[25–27] The current study describes in detail the impact of the universal single-dose vaccination on reported rates of hepatitis A infection by age and region. It also reports the change in the number of pediatric FHF and LT cases from the start of the single-dose vaccination strategy from 2005 to 2011.

MATERIALS AND METHODS

Viral hepatitis and other infectious diseases have been notifiable by law (No. 15465) since 1960 in Argentina. The surveillance system has improved and expanded in the past 2 decades. At the beginning of the 1990s, cases of hepatitis were differentiated as waterborne or blood borne. Since the mid-1990s, all laboratories have been able to make differential diagnoses of hepatitis A, B and C. The National Health Surveillance System provides informatics support for the National Epidemiological Surveillance System and uses 4 modules for the epidemiological surveillance of any reportable disease.

1. The Early Alert Module is based on passive clinical surveillance. Each week, physicians in all jurisdictions report individual cases to the public health authority to promptly initiate control measures. In the case of hepatitis A, a reportable case is defined as a person who tests positive for anti-HAV immunoglobulin M (IgM) or receives a clinical diagnosis of hepatitis A without serological confirmation, but with a strong epidemiological nexus with a confirmed infection. Vaccination status is assessed by checking the vaccination card. In the cases of hepatitis B (HBV), hepatitis C (HCV), hepatitis D (HDV) and hepatitis E (HEV), reportable cases are confirmed when serologic tests are positive for hepatitis core antibody IgM with or without HBV surface antigen, anti-HCV or HCV RNA, anti-HDV by enzyme immunoassay and anti-HEV IgM, respectively.
2. The Laboratory Surveillance System Module complements the clinical surveillance, adding specificity to the system by identifying the etiologic agent through laboratory tests.
3. Sentinel Surveillance is an intensified active surveillance module for high-incidence diseases. Laboratory technicians, clinicians and epidemiologists collect longitudinal data, which allows them to determine trends, direct surveillance and/or perform preventative interventions. Such information is collected in a geographically delimited area but can be generalized to other broader areas.
4. Specialized Surveillance collects data on diseases under national control programs such as tuberclosis, AIDS, etc. and combines this information with data from the rest of the modules. This administrative module focuses on specific topics in epidemiology, such as outbreaks, immune response, high-risk groups, close community, etc.

The information in these 4 modules is publicly accessible, although access is regulated and the subjects' identity is kept confidential. The *Manual of Standards and Proceedings for Surveillance and Control of Obligatory Reportable Diseases* regulates the whole system.[28]

For the purposes of this study, data on hepatitis A notifications and rates and pediatric FHF and LT cases were collected from January 2000 to December 2011. Notifications and rates of hepatitis A by age, region and year were determined per 100,000 inhabitants using data on hepatitis A cases reported through passive clinical surveillance (Early Alert Module) to the National Health Surveillance System. In this system, there is also an "unspecified hepatitis" reporting category, which includes all probable viral hepatitis cases without laboratory confirmation, but it is well known that hepatitis A accounts for >90% of the cases in this group, as it has a strong epidemiology nexus and the age distribution is highly coincident. Thus, these unspecified cases were also included in the analysis. Data were categorized into 5 age groups (0–4, 5–9, 10–14, 15–45 and >45 years) and 5 geographical regions (Northeast, Northwest, Center West, Center and South).

Data on cases of pediatric FHF and LT were obtained from 4 pediatric centers in Buenos Aires (Hospital Nacional de Pediatría Prof. Dr Juan P Garrahan, Hospital Universitario Fundación Favaloro, Hospital Italiano and Hospital Austral) and from the Unique Central National Institute of Ablation and Implant. These pediatric centers treated the most severe FHF and LT cases during the study period.

To assess the impact of the vaccination program, we compared rates of hepatitis A infection, pediatric FHF and pediatric LT during the 6-year period following the implementation of the program with the corresponding rates for the prevaccination period for the whole country. The period of the nationwide outbreak (2003–2004) as well as the year the vaccine was introduced (2005) were excluded from the analysis. Similar comparisons were done for specific age groups and regions.

Data on vaccine coverage were obtained from the National Program for the Control of Immune Preventable Diseases, which is part of the National Ministry of Health. Local immunization programs coordinate with the National Program and ensure that all vaccines are available for the target population in all 24 provinces. Each month, local programs report to national authorities the number of doses administered in order to calculate accurate coverage rates.

Statistical Analysis

Mean rates from the postvaccination period (2006–2011) were compared with mean rates from the prevaccination period (2000–2002) with the calculation of a normal z statistic in EpiInfo 3.5.1 (Centers for Disease Control and Prevention, Atlanta, GA). The same comparisons were made by age group and geographical region. $P < 0.001$ was chosen as statistically significant.

RESULTS

Before the single-dose mass vaccination against hepatitis A was implemented, national notifications increased from 66.5 per 100,000 inhabitants on average during 2000–2002 to 107.5 and 113.3 per 100,000 inhabitants, respectively, during the 2003 and 2004 outbreak (Fig. 1). The highest reported average rates between 2000 and 2002 were among 5–9 years of age (245.2/100,000) and in the Center West, South and Northwest regions (188.7, 168.5 and 136.2/100,000, respectively). These rates significantly exceeded the national average. The lowest rates were observed among individuals >45 years old (5.3/100,000) and in the Center region (31.0/100,000; Table 1). At that time, hepatitis A was the leading cause of FHF and LT in children.[16–18]

Vaccination coverage has been >90% since 2006, with a mean coverage nationwide of 96.8% for 2006–2011 (range, 77%–100%). Only 3 of 24 provinces did not achieve >90% coverage in this period. After the vaccination was implemented there was an abrupt decline in national hepatitis A infection rates. Similar results were found when unspecified hepatitis cases were added to the analysis (Fig. 1). The mean incidence of 7.9/100,000 in the postvaccination period represents a reduction of 88.1% ($P < 0.0001$) from the average annual rate of 66.5/100,000 in the prevaccination period (Table 1).

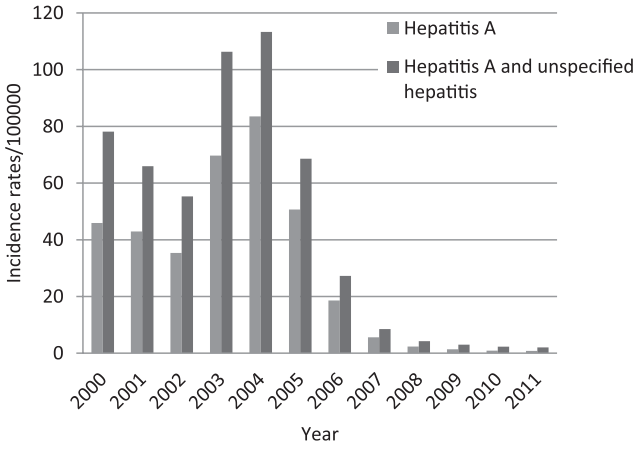

FIGURE 1. National hepatitis A incidence rates versus National hepatitis A and unspecified hepatitis incidence rates (per 100,000 inhabitants).

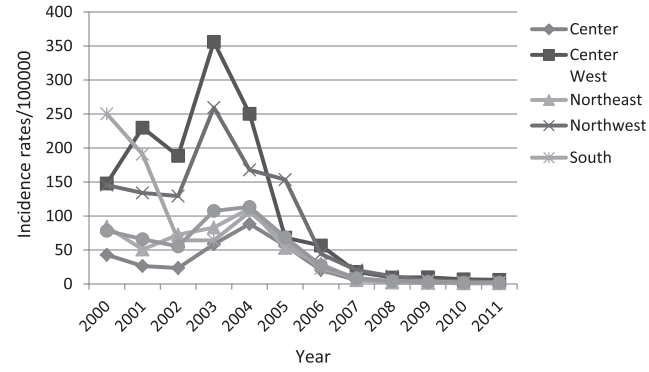

FIGURE 2. Yearly hepatitis A and unspecified hepatitis incidence rates by region (all age groups per 100,000 inhabitants).

This impressive decline was observed in all regions and among all age groups (Table 1). Regarding region, the greatest impact was seen in the Center West and Northwest areas, the regions most affected in the prevaccination period. Although differences in the Center and South regions were not statistically significant, they were clinically relevant (Fig. 2 and Table 1). Concerning age group, major reductions were observed in all pediatric populations (Fig. 3); individuals from the 15 to 44 group and those >45 years did not achieve a statistically significant decline (P = 0.0019 and P = 0.0033, respectively; Table 1). Moreover, although all groups experienced a reduction in hepatitis A rates, an increasing proportion of hepatitis A cases were observed in the postvaccination period among individuals >14 years (Fig. 4).

After the implementation of the universal immunization, cases of pediatric FHF and LT due to hepatitis A also decreased dramatically. Neither FHF nor LT due to HAV infection was observed between March 2007 and December 2011 (Fig. 5).

DISCUSSION

To control a nationwide outbreak, and decrease the incidence of hepatitis A and the prevalence of FHF and LT due to HAV infection, a single-dose HAV vaccine was implemented in 2005 for all Argentinean children 12 months of age. At the time, the Ministry of Health stressed the need for continuous and strict surveillance to evaluate the impact of this strategy as well as to recommend the need for a second dose.

The present report describes the epidemiological change in HAV in Argentina as a result of this universal mass vaccination. We compared rates of HAV infection from 2000 to 2011, before and after the implementation of the vaccination. We also examined the number of cases of FHF and LT as an indicator of the severity of the disease. Vaccine coverage has been high since 2006, and a dramatic decline in rates of hepatitis A has been observed. We included in the analyses cases of unspecified hepatitis on the assumption that most of these were in fact hepatitis A. Cases of hepatitis A and unspecified hepatitis had parallel declines over this same period, confirming this hypothesis. Moreover, the 2011 rates were the lowest recorded in the 12-year study period for both hepatitis A and unspecified hepatitis.

In the prevaccination period, hepatitis A was the leading cause of FHF and LT in the pediatric population. Following the introduction of the vaccine, there was a striking decrease in FHF and LT associated with hepatitis A: no new cases have been reported since March 2007. This achievement is vital not only in terms of disease and death averted but also in terms of costs, which are estimated to be around $40,000 for just 1 liver transplant (*Source: Unique Central National Institute of Ablation and Implant*).

Although the number of cases may decrease after an outbreak because of the absence of susceptible hosts, the fact that this decline in cases was sustained over time suggests a very low viral circulation associated with the new vaccination strategy.

TABLE 1. Hepatitis A and Unspecified Hepatitis Rates/100,000 (2000–2002 vs. 2006–2011 Period) by Age Group and Region

Hepatitis A and Unspecified Hepatitis Rates Per 100,000	Prevaccination 2000–2002 (Mean)	Postvaccination 2006–2011 (Mean)	% Decline	P value
National	66.5	7.9	88.1	<0.0001
Age group (years)				
0 to 4	162.2	15.5	90.5	<0.0001
5 to 9	245.2	26.6	89.1	0.0004
10 to 14	111.5	14.9	86.6	<0.0001
15 to 44	15.5	4.2	72.8	0.0019
>45	5.3	2.2	58.1	0.0033
Region (all age groups)				
Center	31.0	5.6	81.8	0.0039
Center West	188.7	17.8	90.6	<0.0001
Northeast	69.3	6.9	90.1	0.0003
Northwest	136.2	14.8	89.1	<0.0001
South	168.5	7.1	95.8	0.003

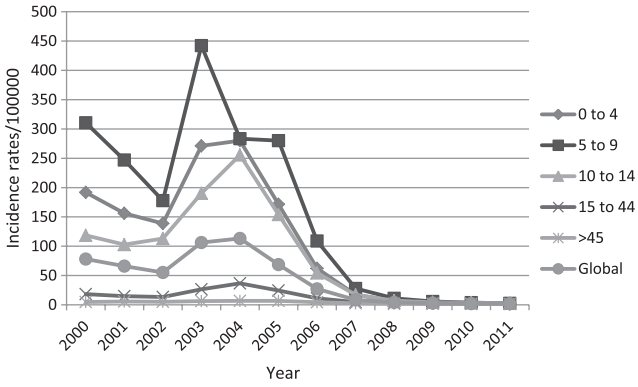

FIGURE 3. Yearly hepatitis A and unspecified hepatitis incidence rates by age group (per 100,000 inhabitants).

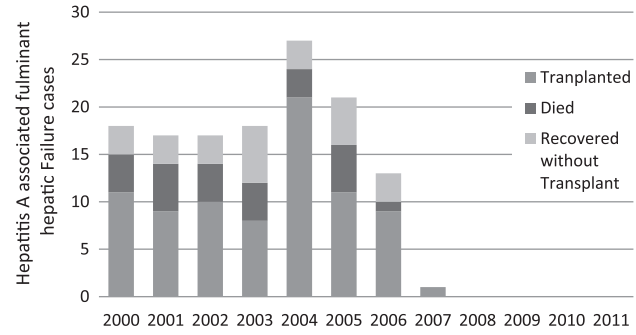

FIGURE 5. Hepatitis A associated pediatric FHF and LT cases by year.

Even so, the introduction of the vaccine may not be the only factor associated with the observed decline in the disease. Improvements in access to and supplies of safe water, as well as disposal of excrement, are associated with the circulation of hepatitis A and could help explain these differences.[29] However, a comparison of data from the National Census of Population and Housing for 2001 and 2010 shows that improvements in those practices have not been so significant, which demonstrates that the mass vaccination with sustained high coverage is the main cause for the reduced circulation of the virus.[30,31]

Similar abrupt reductions in rates have been reported by other countries after the implementation of universal mass vaccination. Israel and China showed a >95% and 92.7% reduction in rates, respectively, after the introduction of a vaccine; Puglia in Italy, Catalonia in Spain, Queensland in Australia and the United States have also reported a significant decline in hepatitis A rates after mass vaccination was implemented.[3–6,32–35] In contrast to these reports, Argentina achieved these results with a single-dose vaccination strategy.

Vaccination at 12 months was selected based on local serological studies that suggested that this age group was at high risk of infection. However, it was assumed, based on the experience of other countries, that transmission would be interrupted in older age groups as well.[3–6] The pre- to postvaccination drops in incidence from 162.2 to 15.5 among 0–4 years of age and from 245.2 to 26.6 among 5–9 years of age represent declines of 90.5% and 89.1%, respectively, and are the highest among all age groups. However, reductions of 58.1–86.6% were observed in older unvaccinated groups, reflecting the great impact of the herd immunity effect. Comparable results have been observed in other countries, where routine immunization of young children in communities with high rates of reported hepatitis A has led to a reduction in the disease in older populations.[3–6] In a similar way, although the highest rates of decline were observed in the most affected regions (Center West and Northwest), major reductions in cases and rates were evident in all regions.

Some questions arise following the introduction of toddler mass vaccination against hepatitis A in Argentina. Whether the disease will occur at a later age is still uncertain. Despite the dramatic decline in cases in all age groups, a greater reduction of cases was found among infants and young children. There was also an increase in the proportion of cases in the >14 years age group in recent years, although this still represents a small number of cases, and none of these cases were people who had received the vaccine. A similar setback was also observed in other countries after significant socioeconomic improvements were made or after hepatitis A vaccination was introduced with a 2-dose schedule. A marked decrease in incidence was associated with a paradoxical increase in icteric cases, which highlights the importance of continuous active, and passive surveillance as outbreaks in teenagers and susceptible adults may occur.[6,36]

Another unanswered question is how long the immunological response persists after the single-dose vaccination. A seroprevalence study conducted by Vizzotti et al[26] in 1139 vaccinated children found that more than 90% had protective antibodies 4 years after a single-dose vaccination. In addition, Espul et al[37] reported a seropositivity rate of 99.7% 3 years after 1 dose of vaccine in Argentinean children. Longer follow up is needed and is being planned by the National Ministry of Health (National Program for the Control of Immune Preventable Diseases), but for now these studies suggest that mid-term immunological protection can be achieved after a single-dose HAV vaccination.

In conclusion, Argentina is the only country in the world to not only incorporate a single-dose HAV vaccine into the national immunization schedule but also the first one to define the age of vaccination at 12 months. The significant decline in hepatitis A

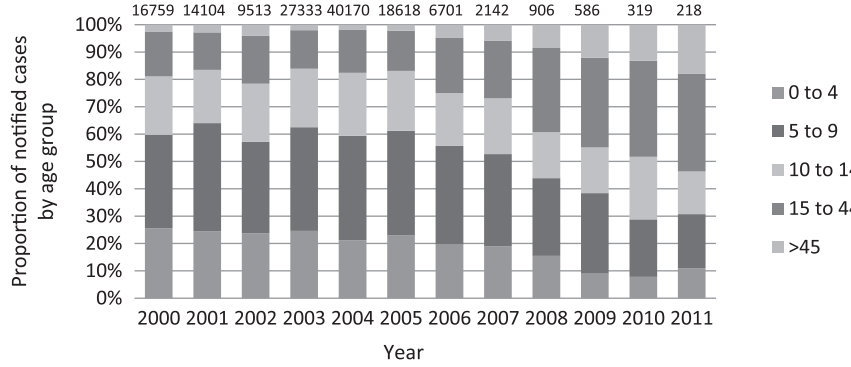

FIGURE 4. Proportion of hepatitis A and unspecified hepatitis notified cases by age group and by year. At the top of the bars are the reported cases by year.

notifications and rates nationwide and the absence of HAV-associated FHF and LT since 2007 suggest a strong decrease in the circulation of the virus and highlight the efficacy of the intervention.

Based on these findings, the World Health Organization Strategic Advisory Group of Experts on Immunization concluded in April 2012 that national immunization programs may consider the inclusion of single-dose inactivated hepatitis A vaccines in immunization schedules as a good alternative to the standard 2-dose regimen and that long-term protection from single- or 2-dose schedules should be regularly monitored by local health authorities.[1]

ACKNOWLEDGMENTS

The authors recognize the leadership of Dr. Ginés González García, former National Minister of Health (2002–2007), in making an innovative decision in a critical situation. They also recognize Dr. Juan Luis Manzur, current Minister of Health, for sustaining this policy to the present day. They are grateful to Ron Dagan (Pediatric Infectious Disease Unit, Soroka University Medical Center, Beer-Sheva, Israel) and Fernando Pollack (Fundación INFANT) for their suggestions.

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