Impact of Hepatitis A vaccination with a two-dose schedule in Panama: Results of epidemiological surveillance and time trend analysis

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\textbf{A B S T R A C T}

\textbf{Purpose:} In April 2007, Panama introduced Hepatitis A universal vaccination using a two-dose schedule (HAVrix\textsuperscript{®} junior; GSK Vaccines, Belgium). We assessed the impact of this hepatitis A vaccine three years after it was recommended for universal mass vaccination in Panama.

\textbf{Materials and methods:} Hepatitis A vaccination impact was assessed using two different approaches. The first approach used retrospective data (incidence and number of cases for all age groups), collected from the passive surveillance of the Epidemiologic Surveillance System of the Ministry of Health of hepatitis A and unspecified hepatitis before (2000–2006) and after (2008–2010) introduction of hepatitis A vaccine. The second approach was a prospective hospital-based active surveillance for hepatitis cases conducted in subjects (0–14years) during 2009–2011 at three sentinel hospitals in Panama.

\textbf{Results:} Overall, the annual incidence of hepatitis A and unspecified hepatitis in 2008, 2009 and 2010 were 13.1, 7.9 and 3.7 per 100,000 subjects, lower than the baseline incidence of 51.1 per 100,000 subjects. In comparison to the mean baseline period (2000–2006), there was an 82% mean reduction in the overall hepatitis-related outcomes (hepatitis A and unspecified hepatitis) after vaccine introduction (2008–2010) in all age groups.

In the hospital-based surveillance (2009–2011), of the 42 probable viral hepatitis A cases, nine cases were confirmed as acute hepatitis A (8 in 2009, 1 in 2010). Of these confirmed cases, two belonged to the targeted vaccine group (1–4 years) but were not vaccinated.

\textbf{Conclusions:} Our study suggests that the introduction of two-dose hepatitis A vaccines in Panama has contributed to the reduction in the incidence of overall hepatitis-related outcomes for all age groups, suggesting herd protection. Additional monitoring is required to document a sustained long-term effect.

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1. Introduction

Hepatitis A (HepA) is one of the most common forms of acute viral liver infection and results in approximately 1.5 million clinical cases annually worldwide [1–3]. This self-limiting disease accounted for 34,000 deaths globally in 2005 [4] but was three times higher in 2010, when 102,000 deaths occurred [5]. HepA was reported to be highly endemic in regions such as South and Central America, the Middle East, South-East Asia and Africa [6,7]. However, a shift in the endemicity towards intermediate was observed in many regions including Asia, Latin America, Eastern Europe and Middle East [7,8]. This shift may increase the probability of
acquiring HepA infection in older susceptible individuals, which may lead to outbreaks and higher severity; therefore, the World Health Organisation (WHO) recommends widespread vaccination [6–9].

The inactivated hepatitis A vaccines (HAV); Havrix® (GSK Vaccines, Belgium) and Yfavax® (Merck) are licensed in Europe and the United States, Epaxal® (Crucell) in Switzerland and Argentina and Healivax is licensed in China [6,10]. Havrix® (1440 ELISA units per millilitre [ml] suspension) and Havrix® junior (720 ELISA units in 0.5 ml suspension) are two variants of the same vaccine with varying viral antigen content. Havrix® junior is a two-dose inactivated vaccine that was implemented for the first time in Latin America in 2007 and administered to children in Panama since then, through a Universal Mass Vaccination (UMV) programme [11]. The first dose is recommended between 12–18 months of age and the second dose, 6–12 months after the first dose [11]. Previous studies suggest that national immunization programmes with one or two-dose vaccination schedules resulted in reduction of HepA rates [12–17].

Our aim was to assess the impact of HAV when given as a two-dose schedule. Further, we assessed the trend in the incidence and frequency of HepA cases over time to describe the characteristics and clinical outcomes of acute hepatitis cases during the post-vaccination period.

2. Methods

Assessment of vaccine impact in terms of reduction in the HepA burden of disease was conducted using two different methodologies. The first method (time-trend analysis) employed a passive surveillance system using the retrospective national hospital admission data to assess the direct and indirect impact of HepA vaccination over a 10-year period (2000–2010), including the impact of the vaccine in different regions. The second methodology (descriptive analysis) was an active hospital-based surveillance for prospective data collection on the occurrence of confirmed cases of acute HepA cases during the post-vaccine introduction period (2009–2011). Both methods were used to describe the vaccine impact in various age groups (first method: all age groups; second method: <15 years).

2.1. Time-trend analysis

The national Epidemiologic Surveillance System of the Ministry of Health (MoH) databases indicated that HepA and unspecified hepatitis are notifiable diseases in Panama [18]. Reported number of HepA and unspecified hepatitis cases was collected using this database. It was considered that most of the unspecified hepatitis cases would correspond to HepA cases. A systematic analysis was performed on Panamanian population data (characterised by year, age and region) during 2000–2010. Aggregated data for HepA and unspecified hepatitis with vaccine dose information were analysed for three time periods: baseline period (2000–2006), transition year (2007) and post-vaccine introduction period (2008–2010).

Serological analysis is usually done to confirm HepA cases as per local algorithm. However, unconfirmed cases were reported as unspecified hepatitis which corresponds to an acute liver inflammation, mostly caused by HepA virus infection characterized by destruction of liver cells and presence of inflammatory cells in liver tissue. These outcomes were extracted using the International Classification of Diseases (ICD) codes; ICD 10 code B15.9 and ICD 9 code 070.1 was used to denote ‘hepatitis A without hepatic coma’ and ICD 10 code B19.9 and ICD 9 code 070.9 was assigned to ‘unspecified hepatitis without hepatic coma’, as reference [19,20].

For incidence estimations, we collected data on population by age group, year and region from the Directorate of Statistics and Census of the National Controller Office (Contraloría General de la República) [21]. Data were grouped by region (West, Central, Panama and North-East) and age (<1 year, 1–4 years, 5–9 years, 10–14 years, 15–19 years, 20–24 years, 25–49 years and ≥50 years) and year of the study. No exclusion criteria were applied for the time-trend analysis.

Vaccine dose information was provided by the Expanded Programme on Immunization for years from 2007 to 2010 and vaccine coverage was calculated at six months interval. Partial vaccine coverage population included subjects who had received at least one vaccine dose and the complete vaccine coverage population included those who had received both vaccine doses. Denominator data for vaccine coverage per study year were derived from children who aged less than one year in the previous year.

The outcome of the time-trend analysis was the occurrence of hepatitis-related outcomes in the post-vaccine introduction period (2008–2010) as compared with the baseline period (2000–2006) and the incidence of hepatitis-related outcomes by year, age and region. The annual incidence of hepatitis-related outcomes was calculated per 100,000 subjects with 95% confidence intervals (CI). Year-wise comparisons were made between the mean and median for number of cases and incidenes for baseline and the post-vaccine introduction period.

Negative binomial regression (NBR) model was used to compare trends in the number and incidence of hepatitis-related outcomes under study to assess vaccination impact [22,23]. To account for the actual vaccination impact, the already existing trend of reduced HepA cases was compared with the expected trends derived from the NBR model. The covariates included for this mathematical model were year, age group, region and vaccination period (baseline period = 0, transition period = 1 and post-vaccination period = 2). p Values were calculated for the regression coefficients (or rate of change) in the hepatitis-related outcomes and values less than 0.05 were considered significant. The same model was also used to predict number of cases and incidence of hepatitis-related outcomes in a hypothetical situation, where the HAV was not included in UMV.

2.2. Hospital-based surveillance

The hospital-based active surveillance was conducted between July 2009 and October 2011 at two hospitals located in Panama City (Hospital Del Niño [HDN] and Hospital de Especialidades Pediatrías [HEP]) and one hospital (Hospital Integrado San Miguel Arcangel [HISMA]) located in the neighbourhood of San Miguelito found on the outskirts of Panama City. These hospitals had a total catchment population of over one million, derived from Panama City neighbourhoods where the majority of HepA cases were reported. This surveillance aimed to validate the reported outcomes from the passive reporting system.

Children with clinical diagnosis of possible acute HepA (children between >1 month and <15 years of age who attended one of the designated hospitals for an acute disease characterized by discrete onset of symptoms [dark urine, anorexia, malaise, extreme fatigue and abdominal pain] and jaundice) were eligible for study inclusion. Potential participants with confirmed diagnosis of non-viral hepatitis were excluded.

Blood samples were collected from all enrolled subjects and serum was tested for transaminase levels. Serological diagnosis was done at the hospital laboratory where each participant was enrolled.

A probable case of HepA was defined as a possible HepA case with a serum aspartate aminotransferase [AST] and alanine aminotransferase [ALT] level 2.5-times higher than the maximum limit of normal range for the laboratory of each hospital (HDN: ALT = 11–66 units/litre [U/L], AST = 15–46 U/L; HEP: ALT = 7–56 U/L,
AST = 5–40 U/L and HISMA: ALT = 21–72 [boys], 9–52 U/L [girls], AST = 17–59 U/L [boys], 14–36 U/L [girls].

A confirmed acute HepA case was defined as a probable case of acute HepA presenting a positive result for immunoglobulin M (IgM) for HepA virus. All probable HepA cases were assessed for acute HepA infection using microparticle enzyme immunoassay (MEIA) to detect the presence of anti-HepA virus IgM antibodies. MEIA was performed in a private central laboratory. An index value >1.20 indicated a positive test result; an index value <0.80 indicated a negative test and values between 0.80 and 1.20 indicated an indeterminate result. A new serum sample was tested when the first sample resulted in an indeterminate result.

The occurrence of confirmed acute HepA cases and percentage of IgM anti-HepA virus positive cases were analysed by year, age group and vaccination status for the hospital-based surveillance population.

All statistical analyses for both methodologies were performed using Statistical Analysis System (SAS) Version 9.2.

2.3. Ethical aspects

The studies were conducted in accordance with the International Conference on Harmonisation guideline for Good Clinical Practice, the Declaration of Helsinki and local rules and regulations. The studies also complied with the International Guidelines for ethical review of epidemiological studies. For the subjects included in the hospital-based surveillance, written informed consent was obtained from a parent/guardian before the study started. The protocol and other documents associated with both the methodologies were reviewed and approved by the Institutional Review Board and Independent Ethics Committee of Panama.

3. Results

3.1. Epidemiologic surveillance system databases and time trend analyses

Between 2000 and 2010, a total of 12,665 viral hepatitis cases (HepA = 2587; unspecified hepatitis = 10,078) were recorded. In 2000, there were 2769 cases (969 per 100,000 subjects) which reduced to 941 cases (28.7 per 100,000 subjects) by 2006. An additional reduction in cases was also observed during 2008 (446 cases [13.1 per 100,000 subjects]), 2009 (271 cases [7.9 per 100,000 subjects]) and 2010 (130 cases [3.7 per 100,000 subjects]) in comparison to the baseline mean incidence of 51.1 per 100,000 subjects.

Mean number (±Standard Deviation [SD]) of viral hepatitis cases during the baseline period (2000–2006) and post-vaccination period (2008–2010) were 1565 (±588) and 282.3 (±158), respectively. Compared to the baseline mean, there was an overall mean reduction of 82% and among all 4 regions, highest reduction (85%) was observed in Panama. The occurrence of HepA cases and unspecified hepatitis cases also gradually reduced (Fig. 1).

Reduction in the incidence of hepatitis-related outcomes was also observed among all age groups during the post-vaccination period (Fig. 2, Supplementary Table 1). In Panama the incidence of viral hepatitis also reduced during the post-vaccination period: 2008 (11.0 per 100,000 subjects), 2009 (11.1 per 100,000 subjects) and 2010 (3.1 per 100,000 subjects).

A 90% reduction in hepatitis A incidence in the vaccinated population was noted, and 87% in the general population.

The observed viral hepatitis-related outcome (38.1% in 2008; 56.5% in 2009; 75.8% in 2010) was lower than expected during post-vaccination period (Fig. 3). Using this model, an additional impact of vaccination after 2007 was also confirmed when the overall viral hepatitis incidence was observed to be 3.7 per 100,000 in 2010 instead of the expected incidence of 14.6 per 100,000 (Fig. 4). A significant reduction (58%; p < 0.0001) in the incidence of overall hepatitis-related outcome was also observed (after adjusting for year, age and region effect) during 2008–2010 as compared with baseline period (2000–2006). A decline in incidence of HepA cases by 52% (p = 0.0054) and unspecified hepatitis cases by 62% (p < 0.0001) was observed in post-vaccination period compared to baseline period (Table 1). During 2000–2010, a significant decline (p < 0.01) in the occurrence of overall viral hepatitis-related outcome was observed in subjects aged <1 year and ≥20 years as compared to the subjects aged 1–4 years (targeted vaccine age group).

Between 2007 and 2010, 241,288 first and 129,720 second doses of HAV were administered in Panama via the Expanded Program on Immunisation. Vaccine coverage among subjects who received partial vaccination was minimum in 2010 (70.7%) and maximum (99.8%) in 2008. The vaccine coverage of 66.4% was observed in subjects who received complete vaccination in 2009 (Fig. 1).

3.2. Hospital-based surveillance

During the hospital-based surveillance, 42 subjects (15 subjects in 2009, 17 subjects in 2010 and 10 subjects in 2011) with possible HepA were enrolled. Mean age of the enrolled subjects was 5.81 years (SD ± 4.49 years). The study population included equal number of boys and girls. All subjects reported AST and ALT levels above the maximum reference range corresponding to probable cases. Most subjects (95.2%; 40/42) visited two hospitals located in Panama City (HDN and HEP).

Nine subjects (21.4%) were subsequently confirmed as having acute HepA: eight occurred in 15 probable cases in 2009 (33.3%) and one occurred in 17 probable cases in 2010 (5.9%). Of 10 probable acute HepA cases, no confirmed acute HepA cases occurred in 2011. Of the nine confirmed cases, eight were not vaccinated with HAV and one had unknown vaccination status.

The highest number of confirmed acute HepA cases was reported in subjects aged 5–9 years (40% [95% CI: 12.2–73.8] in 2009); followed by subjects aged 10–14 years (27.3% [95% CI: 6.6–61.0] in 2009). There were two confirmed cases in subjects aged 1–4 years (1 each in 2009 and 2010) who were not vaccinated with HAV.

4. Discussion

HepA virus infection and the prevalence of anti-HepA virus antibodies are strongly influenced by the economic and sanitary condition of the region [5,7,24]. Improved sanitation and accessible safe drinking water decreases child morbidity and mortality rates, increases the mean age of infection [4,5,24], thereby increasing the risk of getting infected later in life [24]. This has been evidenced by the endemicity shift of HepA as per recent reports in Latin American countries [9,24,25]. Hence, the strategy to introduce HepA vaccination into the UMV in Panama was warranted.

WHO recommends a two-dose inactivated HAV that should be given at age ≥1 year [26]. Some countries may consider a single dose schedule as it is believed to show high immune response [14]. However, two-dose HAV is still preferred for immunocompromised individuals and those at substantial risk of contracting HepA [26] as evidenced in Israel [16]. Both long-term [27,28] and model-based studies [29,30] suggested a two-dose HAV induced antibody persistence for at least 15 and 40 years after primary vaccination, respectively. There are also reports of long-term persistence of 17 years with a three-dose vaccination schedule showing protective HAV antibody levels [31]. Additionally, WHO recommends that the Strategic Advisory Group of Experts (SAGE) Hepatitis A Working
Fig. 1. Reduction of viral hepatitis (hepatitis A and unspecified hepatitis combined) cases and vaccine coverage among subjects who received two vaccine doses. West region included: Bocas del Toro, Chiriquí, Ngöbe Buglé; Central region included—Coclé, Herrera, Los Santos, Veraguas; Panama region included—Panamá Este, Panamá Oeste, Panamá Metro, San Miguelito; Northeast region included—Colón, Darién, Kuna Yala; Baseline = mean of pre-vaccination period from 2000 to 2006; 2007 was the ‘transition year’ of vaccine introduction; Post-vaccination period = mean of post-vaccination period from 2008–2010; The arrows indicate the difference in reduction of the number of cases in the post-vaccination period compared to the baseline period; Full vaccination: for the subjects who received full vaccination (both the doses of Hepatitis A vaccine); Partial vaccination: for the subjects who received partial vaccination (at least one dose of Hepatitis A vaccine).

Group should continue monitoring the long-term protection and HAV impact either used in single or two-dose schedules [32]. The impact of two-dose schedule of HAV was evaluated for the first time in Panama after three years of vaccine introduction which was in line with the WHO recommendation. Our results showed a decline in the number of hepatitis-related outcomes in Panama over time (2000–2010). Though a decreasing trend was observed, supporting the major sanitary improvements in early 2000’s reported by the Ministry of Health, Panama [33], a greater decline in the incidence of HepA cases after 2007 was noted.

**Table 1**

Summary of negative binomial regression model for incidence of viral hepatitis-related outcome.

<table>
<thead>
<tr>
<th>Outcome type</th>
<th>Independent variables</th>
<th>$e^{(β)}$</th>
<th>$p$ value</th>
<th>Rate of change</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>LL</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Year</td>
<td>0.97</td>
<td>0.4180</td>
<td>−3.07</td>
<td>0.90</td>
</tr>
<tr>
<td></td>
<td>Post-vaccination vs pre-vaccination</td>
<td>0.48</td>
<td>0.0054</td>
<td>−52.48</td>
<td>0.28</td>
</tr>
<tr>
<td>Unspecified</td>
<td>Year</td>
<td>0.86</td>
<td>&lt;0.0001</td>
<td>−14.36</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Post-vaccination vs pre-vaccination</td>
<td>0.38</td>
<td>&lt;0.0001</td>
<td>−62.20</td>
<td>0.27</td>
</tr>
<tr>
<td>Overall</td>
<td>Year</td>
<td>0.87</td>
<td>&lt;0.0001</td>
<td>−12.77</td>
<td>0.84</td>
</tr>
<tr>
<td></td>
<td>Post-vaccination vs pre-vaccination</td>
<td>0.42</td>
<td>&lt;0.0001</td>
<td>−58.01</td>
<td>0.31</td>
</tr>
</tbody>
</table>

$e^{(β)}$: Exponentiated regression coefficients (i.e., $\exp(β)$). $p$-Value: Probability value at alpha = 0.05 level. Negative binomial regression model: \( \log(\text{No. of Hepatitis related outcomes}) = \text{Intercept} + (\text{coefficient} \times \text{year}) + (\text{coefficient} \times \text{age group}) + (\text{coefficient} \times \text{regions}) + (\text{coefficient} \times \text{vaccination}). \) Note: vaccination is dummy variable where pre-vaccination (2000–2006) = 0, Transition (2007) = 1 and Post vaccination (2008–2010) = 2. The result related to age group and region is not provided in this table.

* Rate of change is calculated by \((e^{(β)} − 1) \times 100\% \).

95% CI of $e^{(β)}$: Lower and upper limit for the two sided 95% confidence interval of $\exp(β)$. 

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**Fig. 3.** Trend over time for the occurrence of hepatitis-related outcome by observed versus expected number of cases. (A) Trend over time for overall occurrence of viral hepatitis (hepatitis A and unspecified hepatitis) related outcome by observed versus expected number of cases; (B) Trend over time for occurrence of hepatitis A outcome by observed versus expected number of cases (C) trend over time for occurrence of unspecified viral hepatitis outcome by observed versus expected number of cases. 2000–2010: study period; 2000–2006: baseline period; 2007: transition year; 2008–2010: post-vaccination period. Negative binomial regression model: $\log(\text{no. of hepatitis related outcomes}) = \text{Intercept} + (\text{coefficient} \times \text{year})$. Negative binomial model was used to predict the cases from year 2000–2010 using the baseline period. Arrow mark indicates the year of vaccine introduction.
Therefore, we believe reduction during the post-vaccination period was due to the vaccine’s effect. NBR model showed that the observed viral hepatitis cases were substantially lower than the expected cases, thereby demonstrating vaccination impact. During outbreaks, most cases (~90%) were laboratory-confirmed HepA cases compared to cases (~10%) during post-vaccination period. Differences between number of HepA and unspecified hepatitis cases might be attributed to differences in surveillance procedures during outbreaks. Both surveillance procedures suggest a direct vaccine impact on the incidence of HepA cases in the targeted vaccine group. After vaccine introduction, similar reductions in the rate of acute HepA cases have been observed in the United States (1.0 to 0.4 cases per 100,000 subjects) during 2007–2011 [34], Argentina (single-dose HAV) (85.5 per 100,000 subjects in 1998–2002 to 10.2 per 100,000 subjects in 2007) [35] and Israel (50.4 per 100,000 subjects in 1993–1998 to 2.5 per 100,000 in 2004) [15,16].

Although in 2010, the vaccine coverage for the first dose was 71% and only 40% for complete vaccination due to vaccine supply issues in Panama. However, our surveillance reports indicated a 91.7% reduction in hepatitis-related outcomes in all age groups (including adolescents and elderly) compared to the baseline mean suggesting a possible high degree of vaccine-induced herd protection. Following HepA immunization of toddlers in the United States, a reduced number of outbreaks was observed [36]. After the implementation of routine HepA vaccination across 17 states in the United States, despite low vaccine coverage (25% to 50%), a large decrease in the incidence of HepA cases was observed [37–39]. Israel experienced a remarkable decrease in the number of HepA cases during 2001–2005 by employing routine HepA vaccination among toddlers [12,16]. Although a lesser proportion of Israeli children received the complete HepA vaccination course (77% vaccine coverage), marked herd protection among children up to 3 years of age was observed [12].

Additionally, there was a smaller difference in first and second dose vaccine coverage during the first year than the second year. Thus, confirming a substantial reduction in HepA transmission rates even with low coverage, supporting the fact that HAV offers protection against infection and viral excretion, also seen in animal models [38].

Our studies had some limitations. For the trend analysis, data used from passive surveillance system for the retrospective time-trend analysis might be an underestimation of disease burden. The underestimation could be due to lack of specificity in laboratory tests used for confirmed HepA cases. Regarding hospital-based surveillance; conducted in only three sentinel reference hospitals might not completely represent the diversity of socio-economic
conditions in Panama. To overcome these limitations, future studies might be necessary including primary care facilities around the sentinel hospitals.

Strengths include the combination of retrospective time-trend analyses and active hospital-based surveillance to document the vaccination impact which made our results robust. Furthermore, active surveillance was performed at sentinel hospitals post-vaccine introduction that was reconciled with passive surveillance to detect any potential under-reporting in the surveillance system. As a result, no under-reporting was noted.

Our study suggested that the introduction of a two-dose HAV has contributed to the reduction in the overall incidence of hepatitis-related outcomes in Panama. Impact of HAV in all age groups in both the settings suggested herd protection in the early phases of the vaccine implementation. Additional monitoring is required to document a sustained long-term effect of the vaccine.

Source of funding

The study was funded by one or more of companies within the GlaxoSmithKline group of companies. The sponsor was involved in all stages of the study, conduct and analysis. GlaxoSmithKline Biologicals SA also paid all costs associated with the development and the publication of the present manuscript.

Trademark

_Havrix junior_ is a trademark of the GSK group of companies.

_Vaqta_ is a trademark of Merck & Co. Inc.

_Epaxal_ is a trademark of Crucell Switzerland AG.

_Healive_ is a trademark of Simonov Biotech Co. Ltd.

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All the authors had full access to the data and the corresponding author took the final responsibility for submitting the manuscript.

Conflict of interest statement

MMC, EOB and RD are employees of the GSK group of companies and own restricted shares in the GSK group of companies. SF is an employee of GSK group of companies. DE and OT (or their institutions) received funding from GSK group of companies to conduct the study. DE is a member of the National Research System of Panama SENACYT. RC reports no competing interests. The study was funded by one or more of companies within the GlaxoSmithKline group of companies. The sponsor was involved in all stages of the study, conduct and analysis. GlaxoSmithKline Biologicals SA also paid all costs associated with the development and the publication of the present manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.04.100

References


