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

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ABSTRACT

Purpose: In April 2007, Panama introduced Hepatitis A universal vaccination using a two-dose schedule (*Havrix® 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.
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.
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.
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.

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

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CI, confidence interval; HAV, hepatitis A vaccine; HDN, Hospital Del Niño; HEP, Hospital De Especialidades Pediátricas; HepA, hepatitis A; HISMA, Hospital Integrado San Miguel Arcángel; ICD, international classification of diseases; IgM, immunoglobulin M; MEIA, microparticle enzyme immunoassay; MoH, Ministry of Health; NBR, negative binomial regression; SAGE, Strategic Advisory Group of Experts; SAS, Statistical Analysis System; UMV, universal mass vaccination; WHO, World Health Organisation.

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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 *Vaqta*® (Merck) are licensed in Europe and the United States, *Epaxal*® (Crucell) in Switzerland and Argentina and *Healive* 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: <15years).

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 incidences 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 Pediatricas [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,