



## Perspective

## Single-dose administration of inactivated hepatitis A vaccination in the context of hepatitis A vaccine recommendations

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## SUMMARY

**Objectives:** Our objective was to identify evidence on the protection achieved by single-dose use of inactivated hepatitis A vaccines in order to evaluate the potential of a flexible booster administration in the form of a second dose.

**Methods:** A search was conducted for evidence on single-dose administration of inactivated hepatitis A vaccine and its potential impacts on long-term seropositivity rates. The main pharmaceutical vaccine manufacturer federations and the corresponding authors of manuscripts were approached for additional epidemiologic data. Correspondence was also sent to the Argentinean Ministry of Health.

**Results:** We identified 15 data sources reporting on protection achieved by a single dose of inactivated hepatitis A vaccine. The consistent finding was that the immune and memory response to the booster dose, or post-booster geometric mean titer, was independent of the time since initial vaccination. The impact of the booster on seroprotection was the same across sexes and age-groups. The longest time interval between initial and booster dose was 10.67 years, indicating that booster doses can be highly immunogenic for up to 10.67 years after primary vaccination.

**Conclusions:** Protective anti-hepatitis A virus antibody levels after a single dose of inactivated hepatitis A vaccine can persist for almost 11 years and increase or reappear after booster vaccination. Further research on the vaccine doses needed to achieve long-term protection against hepatitis A infection is required.

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## 1. Introduction

The hepatitis A virus (HAV) is a fecal–oral transmitted virus with an annual infection incidence that is strongly inversely related to levels of economic development and modern water sanitation. The annual incidence of hepatitis A decreased between 1990 and 2005 as global economic development increased.<sup>1</sup> Paradoxically, because the probability of symptomatic disease resulting from incident infections increases as the age of infection increases, the global burden of hepatitis A disease may have increased over the time period during which incidence declined. HAV infection and disease is preventable by early immunization with inactivated and live-attenuated hepatitis A vaccines. (Live attenuated hepatitis A vaccines are manufactured in China and are used as a single dose, only in children, in some national immunization programs.) Currently, inactivated HAV vaccines

are licensed for administration in a two-dose schedule given at 6–12-month intervals (single dose plus booster dose in the form of a second dose). However, previously published immunogenicity studies and data indicate that inactivated hepatitis A vaccines such as VAQTA (Merck),<sup>2</sup> AVAXIM (Sanofi Pasteur), HAVRIX,<sup>3–5</sup> and EPAXAL (Crucell)<sup>6</sup> are highly protective after a single dose.

Barriers to the introduction of universal hepatitis A immunization of children include high vaccine prices, complex vaccine schedules, and cold chain requirements. The potential off-label use of hepatitis A vaccines by means of single-dose administration are also not well-defined, but might be of relevance for public health decision-making. The traditional Expanded Program on Immunization (EPI) schedule has not targeted children over the age of 1 year, although hepatitis A vaccines are registered for use after 1 year of age. The use of a single-dose schedule would remove barriers to the use of these vaccines for public health purposes, by allowing fewer contacts with children and thereby reducing the costs associated with immunization.

During a meeting of the World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on Immunization in

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November 2011, evidence for hepatitis A vaccine efficacy was noted, especially the strong evidence for the efficacy and safety of both one- and two-dose inactivated hepatitis A vaccines.<sup>7</sup> A request was made for further evidence and review of the long-term protection afforded by single-dose use of inactivated hepatitis A vaccine. Therefore, we aimed to identify existing evidence for protection achieved by single-dose use of inactivated hepatitis A vaccines in order to amend hepatitis A vaccine recommendations. We believe that data evaluating the potential of a flexible dose administration of this vaccine will be helpful for the global public health control of hepatitis A, thereby helping to reduce the tremendous burden associated with this disease.

## 2. Methods

We reviewed the published literature on the long-term protection of hepatitis A vaccines in general by applying systematic search approaches.<sup>8</sup> Using references identified for this previous review, we searched for evidence of single-dose administration of inactivated hepatitis A vaccines and its potential impact on long-term seropositivity rates pre-booster administration. We supplemented this review with a search for previously unidentified gray literature and difficult-to-access data by approaching the main pharmaceutical vaccine manufacturer federations (International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) and Developing Countries Vaccine Manufacturers Network (DCVMN)) and requested additional, more recent epidemiologic data and information providing evidence on single-dose administration and long-term immune protection achieved by inactivated hepatitis A vaccines. Additional requests for evidence were also sent to corresponding authors of manuscripts, as well as to the Argentinean Ministry of Health, since Argentina was the first country to implement a universal single-dose hepatitis A immunization program starting in 2005.<sup>9</sup>

## 3. Results

We identified 15 data sources reporting on protection achieved by a single dose of inactivated hepatitis A vaccine. Data were collected in the following countries: Switzerland ( $n = 3$ ), Nicaragua ( $n = 2$ ), Sweden ( $n = 2$ ), USA ( $n = 2$ ), Thailand ( $n = 1$ ), Israel ( $n = 1$ ), Netherlands/France ( $n = 1$ ), Russia ( $n = 1$ ), and Argentina ( $n = 2$ ). Apart from one study in Russian,<sup>10</sup> all studies were published in English.

Uniformly, the objective of the studies measuring seroprotection rates (SPR) and/or geometric mean titers (GMT) was the assessment of the response to a booster dose by time following the first dose. Table 1 shows the 13 studies and assessments that have reported SPR and/or GMT achieved by single-dose administration of inactivated hepatitis A vaccine with follow-up times  $>12$  months after the initial immunization.<sup>4–6,14–19,21–24</sup> Studies that reported shorter intervals of follow-up were not considered to be relevant, due to current vaccine recommendations and since they do not provide information on longer term protection achieved by single-dose administration (e.g., Bovier et al., 2005<sup>11</sup> or Shouval et al., 1993,<sup>12</sup> 5 months). Out of all studies, nine were conducted among adults, mostly among healthy travelers. Six of the publications reported on children, including two studies that evaluated the population impact (HAV incidence and fulminant hepatic failure) of single-dose administration by means of comparing pre- and post-vaccination period surveillance data. Both of these studies were conducted in Argentina (Table 2).<sup>9,13</sup>

All studies reported observational outcome data (SPR, GMT) on individuals who were HAV-naïve at the time of enrolment in randomized immunogenicity or effectiveness trials. It was consistently found that the immune response to a booster dose,

or post-booster GMT, was independent of the time since initial vaccination. In addition, the impact of the booster on seroprotection was the same across sexes and age-groups. For EPAXAL, no significant difference in post-booster GMT was found between those who received the booster dose at 18–29 months, 30–41 months, or 42–54 months after primary immunization.<sup>14</sup> Hatz et al.<sup>15</sup> also found that a delay in EPAXAL booster of up to 128 months did not influence the memory response to the booster. For VAQTA, immune responses, SPR, and post-booster GMTs were similar independent of the administration of a booster dose at 12 or 18 months after the initial dose, or 6 months after primary immunization.<sup>16</sup> For HAVRIX, delaying the booster for 4–6 years did not influence the immunogenicity of the boost, and all vaccines showed a high anamnestic booster response.<sup>4</sup> Another HAVRIX study confirmed that there was no significant difference between pre-booster GMTs of a delayed booster group (2 years follow-up, with a maximum of 66 months) and the group that followed the recommended schedule.<sup>17</sup> Similar results were observed for AVAXIM, indicating that the post-booster response was similar across the different schedule groups.<sup>18</sup>

The longest time interval between initial and booster dose was 10.67 years and this indicates that a booster dose of inactivated hepatitis A vaccine can be highly immunogenic for up to 10.67 years after primary vaccination. In addition, pre-booster SPRs were similar across groups assigned to different time intervals of booster administration.<sup>15</sup>

## 4. Discussion

We conducted a non-systematic review of the single-dose use of inactivated hepatitis A vaccine. The evidence found on the longest time interval suggests that protective anti-HAV antibody levels after a single dose of inactivated hepatitis A vaccine can persist for almost 11 years and increase or reappear after booster vaccination. In line with the conclusions drawn by all of the studies identified, it appears that there is no need for a booster dose of hepatitis A vaccine within a time-frame of at least 6 years. Other factors, such as anti-HAV endemicity levels, population-specific factors, and the amount of antigen given in the primary vaccine dose, might be further assessed.<sup>3</sup>

The studies considered have certain limitations. In some instances where the study population was divided into subgroups according to different observation times after single-dose vaccine administration, it was not specified which individual had the longest follow-up within the group of delayed booster recipients. For example, Landry et al.<sup>17</sup> stated that the follow-up time was  $\geq 24$  months with a maximum of 66 months between the primary and booster dose administration, but did not indicate if there were differences, e.g., socio-economic, between individuals in the different groups according to length of delay.

Only measurable outcomes such as SPR were considered in the studies, however immunological memory was not assessed directly, as it was assumed to be the explanation for booster responses. Several studies have shown that a booster response does not require the existence of detectable anti-HAV antibodies before the booster dose, since initial vaccination introduced immunological memory (e.g., Iwarson et al.<sup>4</sup>). Although the detection of residual antibody levels by assays is one of the main correlates for immunity against hepatitis A, the detection of antibodies is not the absolute requirement for protective immunity and, depending on the research question, outcome measures such as GMTs may not be appropriate.<sup>25</sup> Nevertheless, lower pre-booster antibody concentrations correlated significantly with lower post-booster values in one study,<sup>15</sup> and most of the studies assessed delays of booster doses of only up to a few years.<sup>19</sup>

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