Immunogenicity and safety of a novel yeast *Hansenula polymorpha*-derived recombinant Hepatitis B candidate vaccine in healthy adolescents and adults aged 10–45 years

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**ABSTRACT**

The aim was to determine whether the immunogenicity of an investigational hepatitis B vaccine (spHB) is at least as high as that of a licensed control vaccine, Engerix B\(^®\), and to evaluate its safety before inclusion in new pediatric combination vaccines. Two randomized, controlled, blind-observer, Phase 3 trials were performed: one in Argentina (344 participants aged 10–15 years, 10 \(\mu\)g HBsAg/dose) and one in Uruguay (344 participants aged 16–45 years, 20 \(\mu\)g HBsAg/dose). Both vaccines were given in a 0, 1, 6 month schedule to all participants with a baseline anti-Hep B antibody titer <0.6 mIU/mL. Antibody titers were measured pre-dose 1, 1 month after dose 2, pre-dose 3, and 1 month after dose 3. Statistical non-inferiority analyses were performed on seroprotection rates (SP) post-dose 3 (% with anti-Hep B titers \(\geq 10\) mIU/mL; delta non-inferiority limit of \(-10\)%). In both studies, SP for the spHB vaccine was 100% and the spHB vaccine was non-inferior in terms of SP to the licensed control vaccine. GMTs post-dose 3 were approximately 1.8- and 4.1-fold higher for spHB in the 10–15 year and 16–45 year age groups, respectively. Reactogenicity was low for each vaccine, after each dose. This highly immunogenic hepatitis B candidate vaccine was selected for further investigation as a component of new pediatric combination vaccines.

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1. Introduction

Despite prophylactic Hepatitis B (Hep B) vaccination being in place for more than two decades, Hep B infection remains a major public health problem. According to World Health Organization (WHO) data, approximately 350 million people live with chronic infection, and approximately 75% of these live in areas of hyperendemicity where hepatitis B surface antigen (HBsAg) rates of seropositivity may reach 35%. Worldwide, more than 2 billion people have been infected with the Hep B virus, and approximately 1 million deaths are attributable each year to Hep B-associated cirrhosis and hepatocellular carcinoma [1].

In 1992 the WHO recommended all countries to integrate Hep B vaccination into their national vaccination calendar, and endorsed the universal vaccination of infants against Hep B [2]. By December 2007, 171 countries had included Hep B vaccination in their national program [3]. In highly endemic regions, Hep B infection most commonly occurs in the perinatal period (>20% of all infections) or in early childhood (>60% of all infections), increasing the risk of chronic disease and its sequelae, with infants who become infected having a 70–90% chance of becoming chronic Hep B carriers [4].

South America is considered as an area of intermediate Hep B endemicity, although there is a wide variation in the incidence of Hep B infection, generally with low prevalence rates occurring in southern parts of South America (e.g. about 0.6% in Chile) and high prevalence rates occurring in northern parts, with about 70% of the population in the Amazon Basin showing serological evidence of past or current Hep B infection [5]. In Latin America the highest seroprevalence is found in the Dominican Republic (21.4%), followed by Brazil (7.9%), Venezuela (3.2%), Argentina (2.1%), Mexico (1.4%) and Chile (0.6%); in all of these countries, an increase in seroprevalence is found among those aged \(\geq\) 16 years, suggesting that sexual transmission is the major route of infection [6,7].

Currently, most Hep B vaccines are based on recombinant Hepatitis B surface antigen (HBsAg) produced from recombinant yeast (e.g. *Saccharomices cerevisiae*, *Pichia pastoris*) or recombinant mam-
malian cells (e.g. Chinese Hamster Ovary [CHO]). Such Hep B vaccines are highly immunogenic, inducing protective anti-Hep B antibody titres (≥10 mIU/mL) in approximately 95% of vaccinees [3,8].

Previous data have shown that CHO-derived recombinant Hep B vaccines, which contain the S-protein component of the Hep B surface protein, together with the pre-S1 and pre-S2 domains, are more immunogenic than S. cerevisiae-derived recombinant Hep B vaccines made using the adw2 Hep B virus subtype [9–11]. More recently, a new, easily scalable yeast expression system based on Hansenula polymorpha, with high expression of recombinant HBsAg and downstream purification, has been performed and the resulting antigen particles have been shown to be very similar to CHO-derived particles, with limited differences in peptide composition [12,13].

Although HBsAg vaccines with local strain specificity have been produced, the quality of the protection of H. polymorpha-derived HBsAg/adw2 vaccines to infections with heterologous virus strains remains poorly documented, even though some studies have shown differences in antigen-antibody recognition patterns using H. polymorpha-derived HBsAg in three different antigenic forms (adw2, ayw3 and adr) [14]. Several such vaccines have been developed, evaluated in clinical trials and licensed [15–18].

Within the scope of pediatric combination product development, sanofi pasteur (formerly Aventis Pasteur) has taken on the development of a novel yeast H. polymorpha-derived recombinant Hep B vaccine candidate using 2-phenoxy-ethanol/formaldehyde as preservative, with high expression of recombinant HBsAg and downstream purification, has been performed and the resulting antigen particles have been shown to be very similar to CHO-derived particles, with limited differences in peptide composition [12,13].

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The investigational vaccine (batch number PFAGL003-04 for the study in Argentina, and batch numbers PFAGL003-06-A (first and second doses) and PFAGL003-06-B (third dose) for the study in Uruguay), which includes using 2-phenoxy-ethanol/formaldehyde as preservative, was produced and supplied by sanofi pasteur (formerly Aventis Pasteur), Argentina. For the study in Argentina (participants aged 10–15 years), each 0.5 mL dose contained 10 µg of purified recombinant HBsAg adsorbed onto 0.3 mg of aluminum hydroxide; for the study in Uruguay (participants aged 16–45 years), each 1 mL dose contained 20 µg purified recombinant HBsAg adsorbed onto 0.6 mg of aluminum hydroxide. For both studies, the investigational vaccine was supplied as a liquid in a vial. The physicochemical properties of the investigational vaccine are described by Diminsky et al. [13], and full details including the sequence are provided in the Universal Protein Resource (UniProt) as number P03141 [19].

For each group, the vaccine was administered by IM injection into the deltoid muscle.

2.2. Vaccines and vaccine administration

The investigational vaccine (batch number PFAGL003-04 for the study in Argentina, and batch numbers PFAGL003-06-A (first and second doses) and PFAGL003-06-B (third dose) for the study in Uruguay), which includes using 2-phenoxy-ethanol/formaldehyde as preservative, was produced and supplied by sanofi pasteur (formerly Aventis Pasteur), Argentina. For the study in Argentina (participants aged 10–15 years), each 0.5 mL dose contained 10 µg of purified recombinant HBsAg adsorbed onto 0.25 mg of aluminum hydroxide; for the study in Uruguay (participants aged 16–45 years), each 1 mL dose contained 20 µg purified recombinant HBsAg adsorbed onto 0.5 mg of aluminum hydroxide. For both studies, the comparator vaccine was supplied as a liquid in a pre-filled syringe.

2.3. Serologic testing

Blood samples for determination of HBsAg antibodies were collected from each participant just before the first dose, at 1 month post-dose 2, and just before and at 1 month post-dose 3. Serologic analyses for HBsAg antibodies were done in a blinded manner with respect to group but not with respect to visit at the sanofi pasteur central clinical immunology laboratory (Swiftwater, Pennsylvania, USA) using a commercially available radioimmunoassay kit (AUSAB®, Abbott Laboratories, North Chicago, Illinois, USA). The kit contained polystyrene beads coated with HBsAg (human origin), which were incubated with test samples, reference standards, or quality controls. Specific antibodies present in the samples bound to the solid phase HBsAg on the beads. The beads were washed...
and radiolabeled $^{125}$I-HBsAg was added. The radiolabeled antigen bound to antibodies on the beads and created a radioactive antigen-antibody-antigen complex. Radioactivity levels were then measured in counts per minute (CPM) with a gamma counter. The CPM was proportional to the level of HBsAg antibodies present in the sample and was converted to mIU/mL using the formula developed by Hollinger [20].

2.4. Reactogenicity and safety

All participants were included in the evaluation of reactogenicity and safety. After each vaccination, each participant was observed for 30 min to monitor any immediate reactions. By convention, any event occurring within the 30 min following a vaccination was considered to be related to the vaccination and was termed a 'reaction'. For the next 7 days, each participant recorded the onset, duration and intensity of pre-defined (solicited) injection site reactions (erythema/redness, edema, induration, pain) and solicited systemic reactions (pyrexia/fever, asthenia, headache, malaise, myalgia, nausea, vomiting, diarrhea), and also of any non-solicited injection site or systemic event, daily on diary cards (by convention, solicited events were considered to be related to the vaccination, and hence termed 'reactions'). Non-solicited injection site and systemic events that occurred between 8 days after each vaccination and the next visit were collected by the participant, and were assessed by the Investigator for their relationship to the vaccination. From 1 month to 6 months post-dose 3 only serious adverse events (SAEs) were collected by the participant; these SAE data were collected by the Investigator by telephone at 6 months after the third vaccination.

Mild, moderate and severe pain was defined as ‘spontaneous pain and well tolerated’, ‘pain restricting movement’, and ‘pain preventing normal daily activity’, respectively. For erythema/redness and edema, a diameter of 0.5 to <2 cm was graded as mild, a diameter of 2 to <5 cm was graded as moderate, and a diameter of ≥5 cm was graded as severe. For induration and for all systemic events except for pyrexia/fever, assessments of mild, moderate and severe were defined as ‘easily tolerated’, ‘sufficiently discomfiting to interfere with normal activity’ and ‘prevent normal activity’, respectively. For fever, mild, moderate and severe were defined as axillary temperature 37.1–38 °C (inclusive), 38.1–39 °C (inclusive), and ≥39.1 °C, respectively.

2.5. Statistical analyses

For the two studies, the statistical hypothesis for the primary objective was that the anti-Hep B seroprotection rate (defined as the percentage of participants with an anti-Hep B antibody titre ≥10 mIU/mL at 1 month post-dose 3) achieved in the investigational vaccine group was non-inferior to that achieved in participants receiving the comparator vaccine. For the non-inferiority test, the 95% confidence interval [CI] of the difference between the investigational (test) minus comparator (reference) vaccines was calculated based on the Wilson score method with-

spHB = sanofi pasteur *Hansenula polymorpha*-derived recombinant Hep B candidate

a 10 μg purified recombinant HBsAg

b 20 μg purified recombinant HBsAg

FAS = Full Analysis Set; PP = Per Protocol Analysis Set; SAS = Safety Analysis Set

Fig. 1. Summary of participant disposition.
Table 1
Seroprotection rates (anti-Hep B ≥ 10 mIU/mL) 1 month post-dose 3 (full analysis set population).

<table>
<thead>
<tr>
<th>Timepoint</th>
<th>Age group (country)</th>
<th>spHB</th>
<th>Engerix B®</th>
<th>Difference (spHB minus Engerix B®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-dose 1</td>
<td>10–15 years (Argentina)/N=164</td>
<td>0 (0;2.2)</td>
<td>0 (0;2.2)</td>
<td>NP</td>
</tr>
<tr>
<td></td>
<td>16–45 years (Uruguay)</td>
<td>0</td>
<td>0</td>
<td>NP</td>
</tr>
<tr>
<td>2 months (post-dose 2)</td>
<td>10–15 years (Argentina)/N=164</td>
<td>92.7 (87.6;96.2)</td>
<td>73.9 (66.5;80.5)</td>
<td>NP</td>
</tr>
<tr>
<td></td>
<td>16–45 years (Uruguay)</td>
<td>91 (85;95)</td>
<td>55 (47;63)</td>
<td>NP</td>
</tr>
<tr>
<td>6 months (pre-dose 3)</td>
<td>10–15 years (Argentina)/N=164</td>
<td>99.4 (96.6;100)</td>
<td>95.2 (90.7;97.9)</td>
<td>NP</td>
</tr>
<tr>
<td></td>
<td>16–45 years (Uruguay)</td>
<td>96 (91;98)</td>
<td>70 (62;77)</td>
<td>NP</td>
</tr>
<tr>
<td>7 months (post-dose 3)</td>
<td>10–15 years (Argentina)/N=164</td>
<td>100 (97.8;100)</td>
<td>99.4 (96.6;100)</td>
<td>0.6 (-1.7;3.4)</td>
</tr>
<tr>
<td></td>
<td>16–45 years (Uruguay)/N=151 [spHB] and N=147 [Engerix B]</td>
<td>100 (97.6;100)</td>
<td>95.9 (91.3;98.5)</td>
<td>4.1 (0.77;8.62)</td>
</tr>
</tbody>
</table>

Data are seroprotection rate (% participants with anti-Hep B ≥ 10 mIU/mL) (95% CI). spHB = sanofi pasteur *Hansenula polymorpha*-derived recombinant Hep B candidate. NP = not performed.

a 10 µg purified recombinant HBsAg in Argentina and 20 µg purified recombinant HBsAg in Uruguay.
b Engerix B® Pediatrico in Argentina and Engerix B® in Uruguay.
c Data from per protocol analysis set.

out continuity correction, and the hypothesis of non-inferiority was to be rejected if the lower bound of the two-sided 95% CI for the difference of the seroprotection rates was below −10%.

Descriptive statistics were calculated for continuous data (anti-HBs: log10 mean titre and standard deviation, geometric mean titre [GMT], 95% CI of the GMT [calculated using the normal approximate method]) and for categorical data (seroprotection: number, percentage of participants, 95% CI of the percentage [calculated using the exact binomial method]). The GMT was calculated assuming that the log10 transformation of the titer data follows a normal distribution. First, the mean was calculated on the log10 titer data using the usual calculation for normal distribution; anti-log transformations were than applied to these results to provide GM Ts. The geometric mean is defined as follows:

\[
GM = \left( \prod_{i=1}^{n} y_i \right)^{1/n} = 10^{\left(\frac{1}{n} \sum_{i=1}^{n} \log_{10}(y_i)\right)}
\]

where \((y_1, y_2, \ldots, y_n)\) are the observed titers or individual ratios for each subject.

A sample size of 344 participants in each study (to obtain 258 evaluable participants assuming about 25% non-evaluability) was calculated using the Farrington and Manning formula to obtain an overall power of 90% for the non-inferiority testing [21].

![Fig. 2](image-url) Anti-Hep B geometric mean titres following spHB or Engerix B® Pediatrico/Engerix B® in Argentina (10–15 years) (a) and Uruguay (16–45 years) (b).
Solicited injection site and systemic reactions within 7 days after each dose in Argentinean participants aged 10–15 years (safety analysis set population).

Table 2

<table>
<thead>
<tr>
<th>Injection site reactions</th>
<th>10–15 years (Argentina)</th>
<th>30 days post-dose 3 (%)</th>
<th>Systemic reactions</th>
<th>30 days post-dose 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At least one injection site reaction</td>
<td>spHB</td>
<td>N = 172</td>
<td>Dose 1</td>
<td>Dose 2</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Severe</td>
<td>61</td>
<td>35.5</td>
<td>43</td>
<td>25.0</td>
</tr>
<tr>
<td>Erythema/Redness</td>
<td>7</td>
<td>4.1</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>0.6</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Edema</td>
<td>3</td>
<td>1.7</td>
<td>4</td>
<td>2.3</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Induration</td>
<td>5</td>
<td>2.9</td>
<td>3</td>
<td>1.7</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Pain</td>
<td>1</td>
<td>0.6</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Systemic reactions</td>
<td>71</td>
<td>41.3</td>
<td>27</td>
<td>15.7</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Pyrexia/Fever</td>
<td>4</td>
<td>2.3</td>
<td>6</td>
<td>3.5</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.0</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>28</td>
<td>16.3</td>
<td>10</td>
<td>5.8</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Headache</td>
<td>41</td>
<td>23.8</td>
<td>14</td>
<td>8.1</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Malaise</td>
<td>10</td>
<td>5.8</td>
<td>6</td>
<td>3.5</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>10</td>
<td>5.8</td>
<td>6</td>
<td>3.5</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>0.6</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1</td>
<td>0.6</td>
<td>1</td>
<td>0.6</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>2.3</td>
<td>4</td>
<td>2.3</td>
</tr>
<tr>
<td>Severe</td>
<td>0</td>
<td>0.0</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

spHB = sanofi pasteur *Hansenula polymorpha*-derived recombinant Hep B candidate. Data are number and percentage of participants with at least one reaction.

* 10 μg purified recombinant HBsAg.

3. Results

3.1. Participant characteristics

In each country a total of 344 participants (172 participants in each vaccine group) were enrolled as planned (aged 10–15 years in Argentina and 16–45 years in Uruguay). The number of participants in the Full Analysis Set (FAS; participants who received at least one injection, analyzed by randomized group), and the Per Protocol Analysis Set (PPAS; participants who had no major protocol deviation) and the Safety Analysis Set (SAS; participants who received at least one injection, analyzed by vaccine received) are presented in Fig. 1.

The PPAS, which included only participants who were seronegative to HBsAg prior to the first dose, was used for the primary immunogenicity analysis of non-inferiority and for the descriptive immunogenicity data at 30 days post-dose 3. The SAS was used for all safety analyses.

In each study, the participants receiving each vaccine were of similar age (approximately 13 and 30 years in Argentina and Uruguay, respectively) and body mass index (approximately 19 and 25 kg/m² in Argentina and Uruguay, respectively). In Argentina, more females that males were included in each group (female: male ratio 1.2–1.3), whereas in Uruguay more males than females were included (female: male ratio 0.41–0.55); this difference was not considered to be clinically relevant and was not considered to have any impact on the interpretation of the immunogenicity or safety data.

3.2. Immunogenicity

The proportion of seroprotected participants (anti-Hep B ≥10 mIU/mL) at each timepoint and the non-inferiority analysis 1 month post-dose 3 for each study (PPAS) is presented in Table 1.

For each age group, the anti-Hep B seroprotection rate was similar for the investigational vaccine and the comparator. For both age groups, statistical analysis confirmed non-inferiority of the investigational vaccine, with the lower bound of the two-sided 95% CI for the difference being greater than the clinical limit set for non-inferiority (-10%) in each age group.

The GMT data at each timepoint are shown in Fig. 2a (Argentina, 10–15 years of age) and Fig. 2b (Uruguay, 16–45 years of age). In both age groups, in terms of descriptive assessment of the GMT (95% CI) data, the response to the investigational spHB at 1 month post-dose 3 (PPAS) was 1.8-fold higher than the response to Engerix B® Pediatrico (Argentina; 10–15 years) (8799 [7413;10444] versus 4854 [3844;6129] mIU/mL) and 4.1-fold higher than the response to Engerix B® (Uruguay; 16–45 years) (5782 [4419;7565] versus 1409 [943;2104] mIU/mL), with no overlap of 95% CIs. Similarly, at 1 month post-dose 1 and prior to dose 3, the GMTs for the spHB groups were markedly higher than for the comparator, with no overlap of 95% CIs.

3.3. Safety and reactogenicity

The incidence of immediate reactions was low in both vaccine groups for each age range, and was slightly higher for the spHB vacci-
In both age groups, and for both the investigational and comparator products, the incidence of solicited adverse reactions was comparable and generally decreased with successive vaccinations. Few adverse reactions were rated as severe.

In all groups the most commonly reported solicited injection site reaction was pain, the incidence of which decreased in each age and vaccine group with successive vaccinations. Slightly more pain was reported for the investigational vaccine group than for the comparator. This incidence of the other solicited injection site reactions was low, and was similar in each age and vaccine group.

All groups except following spHB in participants aged 16–45 years (Uruguay) reported an SAE (the majority being due to an outbreak of Q Fever). No SAE was considered to be related to the investigational or comparator vaccine.

### 4. Discussion

These two studies evaluated the immunogenicity and safety of an investigational recombinant Hep B *Hansenula polymorpha*-derived vaccine (spHB) administered at Day 0 and at 1 month and 6 months post-dose 1 (0, 1, 6 month schedule) in comparison to Engerix B® Pediatric (participants aged 10–15 years in Argentina) or Engerix B® (participants aged 16–45 years in Uruguay). Participants were randomized at Day 0 to receive either the investigational or comparator vaccine.

The immunogenicity of each vaccine was strong with >95% of participants in each age and vaccine group being seroprotected (using the correlate marker for seroprotection of anti-HBs ≥10 mIU/mL) at 1 month post-dose 3. Following the investigational vaccine the seroprotection rate was statistically non-inferior to that following the commercially available comparator. These results suggest that the majority of participants in both vaccine and age groups would be expected to be protected against Hep B infection.
In terms of GMT, the immune response to the comparator vaccine in participants aged 10–15 years (4854 mIU/mL) and 16–45 years (1409 mIU/mL) was similar to that reported in previous studies using 10 μg Engerix B® in adolescents [22,23,24] and 20 μg Engerix B® in adults [25,26,27] at 1 month after a standard 0, 1, 6 month dosing schedule. In comparison, in our study, the GMT response to the investigational vaccine was approximately 1.8- and 4.1-fold higher than the response to the comparator in participants aged 10–15 years and 16–45 years, respectively. Higher peak anti-Hep B antibody titres have been shown to be associated with longer antibody persistence [28] and it has been shown that high titres following primary series vaccination correlate with the retention of seroprotection up to 15 years later [29].

The investigational vaccine was well tolerated in both age groups, and the overall safety profile was comparable to that observed for the comparator vaccine and to that described in the literature for yeast-derived Hep B vaccines [30]. There were few immediate adverse reactions in any group and most adverse events were of mild or moderate intensity. No serious adverse events occurred in either age or vaccine group.

The investigational candidate spHB vaccine, based on its high immunogenicity and good safety, qualified for further clinical development as a component in future pediatric combination vaccines. Combination vaccines that contain HBsAg have facilitated the integration of Hep B vaccination into existing infant immunization programs and have contributed to improved compliance [8]. It is planned that such integration of the candidate Hep B vaccine will help to increase vaccine coverage in the pediatric population.

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