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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.

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.[1] 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),[2] AVAXIM (Sanofi Pasteur), HAVRIX,[3–5] and EPAXAL (Crucell)[6] 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.[7] 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.[8] 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.[9]

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,[10] 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.[4–6,14–19,21–24] 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[11] or Shouval et al., 1993,[12] 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).[9,13]

All studies reported observational outcome data (SPR, GMT) on individuals who were HAV-naive 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.[14] Hatz et al.[15] 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.[16] 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.[4] 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.[17] Similar results were observed for AVAXIM, indicating that the post-booster response was similar across the different schedule groups.[18]

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.[15]

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.[3]

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.[17] stated that the follow-up time was ≥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.[4]). 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.[25] Nevertheless, lower pre-booster antibody concentrations correlated significantly with lower post-booster values in one study,[15] and most of the studies assessed delays of booster doses of only up to a few years.[19]

Table 1
Seroprotection rates (SPRs) and geometric mean titers (GMTs) following single-dose administration of inactivated hepatitis A vaccines, by length of follow-up

Author	Study type	Intervention	Population	Outcome single dose vaccination	Other results and comments
Beck et al., 2003[14]	Open-label, non-comparative study	EPAXAL, 0.5 ml	115 healthy adults aged 20–70 years, Switzerland	SPR (anti-HAV AB ≥20 mIU/ml): 18–29 months, 67%; 30–41 months, 77%; 42–54 months, 70% SPR (anti-HAV AB ≥10 mIU/ml): 18–29 months, 89%; 30–41 months, 91%; 42–54 months, 85%	No significant difference found for GMT in dependence of booster administration interval
Hatz et al., 2011[15]	Observational data	EPAXAL, 0.5 ml	130 adults aged 20.5–73 years, Switzerland 1999 study: 9–54 months booster interval, 104 adults 2006 study: 98–128 months booster interval, 26 adults	SPR all (anti-HAV AB ≥20 mIU/ml), 9–128 months: 46.2% SPR all (anti-HAV AB ≥10 mIU/ml), 9–128 months: 59.2% GMT all, 9–128 months: 17 (95% CI 13–22) SPR subgroup (n = 26) (anti-HAV AB ≥20 mIU/ml), 98–128 months: 50% SPR subgroup (n = 26) (anti-HAV AB ≥10 mIU/ml), 98–128 months: 53.8% GMT subgroup, 98–128 months: 24 (95% CI 14–41)	Sex-specific analysis: SPR males (anti-HAV AB ≥20 mIU/ml), 9–128 months: 27.6% SPR males (anti-HAV AB ≥10 mIU/ml), 9–128 months: 41.4% SPR females (anti-HAV AB ≥20 mIU/ml), 9–128 months: 61.1% SPR females (anti-HAV AB ≥10 mIU/ml), 9–128 months: 73.6%
Herzog 2010[21]	Observational seroepidemiology study	EPAXAL, 0.5 ml	130 children aged 2–17 years, initially enrolled 2005, Nicaragua	SPR of 101 vaccinated children (anti-HAV AB ≥10 mIU/ml), 5.5 years: 95.1% (5 individuals dropped below threshold) GMC, 5.5 years: 74.4 (95% CI 60–92)	Loss to follow-up until 2010: two infected children and four of the 105 protected children
Hornick et al., 2001[16]	Observational data based on randomized vaccine trial	VAQTA, 50 U	360 adults aged 18–71 years, randomized to three groups by booster dose timing, USA	SPR group 3 (n = 118) (anti-HAV AB ≥10 mIU/ml), 1.5 years: 96.6% (95% CI 90.4–99.3%) (85/88) GMT group 3, 1.5 years: 121.3 (95% CI 90.9–161.8)	Comparable responses regardless of booster dose administration at 6, 12, or 18 months
Iwarson et al., 2002[4]	Observational data based on vaccination 1994–96	HAVRIX 1440	25 health travelers aged 36–50 years, Sweden	SPR (anti-HAV AB ≥10 mIU/ml), 4–6 years: 72% (18) GMC, 4–6 years: 32	
Iwarson et al., 2004[5]	Observational data based on vaccination 1994–98	HAVRIX 1440	54 healthy travelers aged 31–50 years, Sweden	SPR (anti-HAV AB ≥10 mIU/ml), 4–8 years: 64.8% (35) GMC, 4–8 years: 21	Extension of Iwarson et al., 2002 study Five individuals followed-up for 8 years; one of them had detectable antibodies after 8 years (GMT 69)
Landry et al., 2001[17]	Observational study	HAVRIX 1440	249 travelers aged ≥18 years, 124 received delayed booster (max. 66 months) and 125 received two doses (6–12-month interval), Switzerland	SPR (anti-HAV AB ≥33 mIU/ml), ≥2 years: 68% GMT, ≥2 years: 116 (95% CI 78–175)	No statistically significant difference between pre-booster GMT of delayed booster group and group with two doses (89% SPR after 6–12 months)
Lolekha et al., 2003[18]	Data based on open, randomized, clinical trial	AVAXIM 80 U Three groups varying by schedule of booster (month 6 (group A), 12 (group B), 18 (group C))	215 healthy children enrolled/ 202 followed up, aged 5–10 years, Thailand	SPR group C (n = 66) (anti-HAV AB ≥20 mIU/ml), 1.5 years: >98% GMT group C, 1.5 years: 124 (95% CI 102–151)	Strong booster response, similar across groups

Table 1 (*Continued*)

Author	Study type	Intervention	Population	Outcome single dose vaccination	Other results and comments
Mayorga Pérez et al., 2003[6]	Data based on placebo-controlled trial	EPAXAL, 0.5 ml	274 children aged 1.5–6 years (122 in vaccine group), Nicaragua	GMC, 15 months: 236.8 mIU/ml (95% CI 173.4–323.5)	
Nalin 1995[22]	Data based on randomized controlled trial	VAQTA, 25 U	Children aged 2–17 years; 1037 enrolled in 1991; 519 received vaccine, USA	SPR (anti-HAV AB ≥10 mIU/ml), 1.5 years: 89% (69/78) GMT, 1.5 years: 39	Follow-up data of Werzberger et al., 1992 Antibody levels 6–18 months after booster persisted independent of pre-booster antibody level (<99%)
Orr et al., 2006[19]	Data based on open-label, randomized prospective study/ immunogenicity trial	VAQTA (226 individuals) AVAXIM, 160 U (225 individuals)	451 healthy adults, aged 18–21 years, 95.4% males, recruits and short-term military service personnel (temporarily in endemic regions), Israel	SPR (anti-HAV AB ≥10 mIU/ml), 2 years: 93% GMC 2 years: AVAXIM (n = 69): 56.8 (95% CI 44.4–72.7) VAQTA (n = 61): 36.9 (95% CI 27.9–48.7) Mixed (n = 46): 50.3 (95% CI 37–567.5) Total (n = 176): 47.4 (95% CI 40.5–55.4)	No significant differences between VAQTA and AVAXIM in terms of SPR at month 24 Strong booster response, including those who were seronegative before booster dose
Overbosch et al., 2005[23]	Data based on open, randomized, controlled study/immunogenicity trial conducted 1998–2002	Group A: Viatim (comb. AVAXIM and Typhim Vi) Group B: HA/Vi vaccine	360 healthy adult volunteers enrolled/356 completed initial study, aged 16–65 years; group A: 177, group B: 179, Netherlands, France	SPR (anti-HAV AB ≥20 mIU/ml), 3 years: group A, n = 112: 99.1%; group B, n = 104: 99% GMT, 3 years, group A (n = 112) 425 (95% CI 345–524); group B (n = 103) 258 (95% CI 202–329)	Significant increase in antibody levels after booster dose
Sabanin et al., 2010[10] (Russian) and Akimkin et al., 2007[24] (abstract)	Data based on immunogenicity trial	AVAXIM, 160 U HAVRIX 1440 Hep-A-in-Vac (HepA vaccine + IG), used sequentially	15 000 adults (Russian military personnel) vaccinated with one dose (1996 and 2008) 300 AVAXIM-vaccinated individuals assessed in 5 years after vaccination	SPR (anti-HAV AB ≥20 mIU/ml), (AVAXIM) 5 years: 90% Hepatitis A incidence/acute cases: No case of hepatitis A among 2002–2006 AVAXIM recipients Decrease in incidence up to 2000 among military personnel in general (4.0/1000 in 2000)	Only single-dose AVAXIM results reported

anti-HAV AB, anti hepatitis A virus antibodies; 95% CI, 95% confidence interval.

Table 2
Hepatitis A virus (HAV) incidence and fulminant hepatic failure (FHF) following single-dose administration of inactivated hepatitis A vaccines

Author	Study type	Intervention	Population	Outcome single dose vaccination	Other results and comments
Cervio et al., 2011[13]	Retrospective review of fulminant hepatic failure cases, based on effectiveness trial	AVAXIM 80 U; one-dose HepA universal immunization program, implemented in Argentina in 2005	Children aged 3 months to 18 years, admitted to selected health centers (1993–2008)	Cases of HAV-associated FHF: Pre-immunization program (1993–2005): 54% (165/304) of FHF cases caused by HAV infection Post-immunization program (2005–2008, i.e., up to 3 years after program started): 27.7% (18/65) of FHF cases caused by HAV infection	Population is a mixture of single- and two-dose vaccine recipients, since private sector uses two doses and public sector uses one dose; the private sector accounts for 12%
Vacchino 2008[9]	Surveillance data	AVAXIM 80 U; one-dose HepA universal immunization program, implemented in Argentina in 2005	Children aged 12 months	Hepatitis A incidence: Pre-immunization program (1995–2004): incidence range 70.5–173.8/100 000 Pre-immunization program and pre-outbreak (1998–2002): mean incidence 85.5/100 000 (95% CI 66.7–104.3) Post-immunization program (2007, i.e., up to 2 years after program started): incidence decreased by 88% to 10.3/100 000 compared to mean incidence 1998–2004 Age-group- and vaccinating-region-specific decreases were all significant	Data source was public health surveillance Decreases could be partially associated with natural immunity from an outbreak in 2003–2004 Issue with 12% of children receiving two doses in Argentina

95% CI, 95% confidence interval.

The representativeness of the study populations in the studies may also be questioned, since they were very specific in terms of age or other criteria (e.g., soldiers[19]).

Additional research is needed on long-term cohorts vaccinated with a single dose of hepatitis A vaccine, as well as evaluations of populations where this policy is in place (e.g., Argentina). Such studies will guide future decisions on the need for and timing of booster doses. In addition, more studies are required to assess the cost savings and coverage of single-dose hepatitis A vaccination policies. Predictions under various scenarios suggest that, compared to no vaccination, the one-dose schedule vaccination in Argentina could save over US$ 15 million, while a two-dose schedule at months 12 and 18 would save US$ 13.8 million. However, the cost-effectiveness of hepatitis A vaccination is highly dependent on country-specific endemicity levels and within-country variations and the comparison used.[20] Taking into consideration the endemicity level of hepatitis A, it is important to study if the response to a natural exposure among single-dose vaccine-protected individuals is comparable to a booster response, which would be of significant relevance for one-dose use in highly endemic settings.

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References

1. Jacobsen KH, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. *Vaccine* 2010;**28**:6653–7.
2. Werzberger A, Mensch B, Kuter B, Brown L, Lewis J, Sitrin R, et al. A controlled trial of a formalin-inactivated hepatitis A vaccine in healthy children. *N Engl J Med* 1992;**327**:453–7.
3. Iwarson S. Are we giving too many doses of hepatitis A and B vaccines? *Vaccine* 2002;**20**:2017–8.
4. Iwarson S, Lindh M, Widerström L. Excellent booster response 4–6 y after a single primary dose of an inactivated hepatitis A vaccine. *Scand J Infect Dis* 2002;**34**:110–1.
5. Iwarson S, Lindh M, Widerström L. Excellent booster response 4 to 8 years after a single primary dose of an inactivated hepatitis A vaccine. *J Travel Med* 2004;**11**:120–1.
6. Mayorga Pérez O, Herzog C, Zellmeyer M, Loaisiga A, Frösner G, Egger M. Efficacy of virosome hepatitis A vaccine in young children in Nicaragua: randomized placebo-controlled trial. *J Infect Dis* 2003;**188**:671–7.
7. World Health Organization. Meeting of the Strategic Advisory Group of Experts on Immunization, November 2011—conclusions and recommendations. *Wkly Epidemiol Rec* 2012;**1**:15–6.
8. Ott JJ, Irving G, Wiersma ST. Long-term protective effects of hepatitis A vaccines: a systematic review. *Vaccine* 2012;**31**:3–11.
9. Vacchino MN. Incidence of hepatitis A in Argentina after vaccination. *J Viral Hepat* 2008;**15**(Suppl 2):47–50.
10. Sabanin IV, Rikhter VV, Kuzin SN. [Assessment of effectiveness and immunogenicity of hepatitis A vaccination in servicemen of Internal Forces of Ministry of Internal Affairs of Russia] (in Russian). *Zh Mikrobiol Epidemiol Immunobiol* 2010;**1**:35–9.
11. Bovier PA, Farinelli T, Loutan L. Interchangeability and tolerability of a virosomal and an aluminium-adsorbed hepatitis A vaccine. *Vaccine* 2005;**23**:2422–7.
12. Shouval D, Ashur Y, Adler R, Lewis JA, Armstrong ME, Davide JP, McGuire B, et al. Single and booster dose responses to an inactivated hepatitis A virus vaccine: comparison with immune serum globulin prophylaxis. *Vaccine* 1993;**11**(Suppl 1):S9–14.
13. Cervio G, Trentadue J, D'Agostino D, Luque C, Giorgi M, Amoni J, Debbag R. Decline in HAV-associated fulminant hepatic failure and liver transplant in children in Argentina after the introduction of a universal hepatitis A vaccination program. *Hepat Med* 2011;**3**:99–106.
14. Beck BR, Hatz C, Brönnimann R, Herzog C. Successful booster antibody response up to 54 months after single primary vaccination with virosome-formulated, aluminum-free hepatitis A vaccine. *Clin Infect Dis* 2003;**37**:126–8.
15. Hatz C, van der Ploeg R, Beck BR, Frösner G, Hunt M, Herzog C. Successful memory response following a booster dose with a virosome-formulated hepatitis A vaccine delayed up to 11 years. *Clin Vaccine Immunol* 2011;**18**:885–7.
16. Hornick R, Tucker R, Kaplan KM, Eves KA, Banerjee D, Jensen E, Kuter B. A randomized study of a flexible booster dosing regimen of VAQTA® in adults: safety, tolerability, and immunogenicity. *Vaccine* 2001;**19**:4727–31.
17. Landry P, Tremblay S, Darioli R, Genton B. Inactivated hepatitis A vaccine booster given ≥24 months after the primary dose. *Vaccine* 2001;**19**:399–402.
18. Lolekha S, Pratuangtham S, Punpanich W, Bowonkiratikachorn P, Chimabutra K, Weber F. Immunogenicity and safety of two doses of a paediatric hepatitis A vaccine in Thai children: comparison of three vaccine schedules. *J Trop Pediatr* 2003;**49**:333–9.
19. Orr N, Klement E, Gillis D, Sela T, Kayouf R, Derazne E, et al. Long-term immunity in young adults after a single dose of inactivated hepatitis A vaccines. *Vaccine* 2006;**24**:4328–32.
20. Ellis A, Rüttimann RW, Jacobs RJ, Meyerhoff AS, Innis BL. Cost-effectiveness of childhood hepatitis A vaccination in Argentina: a second dose is warranted. *Rev Panam Salud Publica* 2007;**21**:345–56.
21. Herzog C. EPAXAL®-Aluminium free. Presentation and personal communication at the SAGE Hepatitis A Working Group Meeting, Buenos Aires, Argentina, 2010.
22. Nalin DR. VAQTA hepatitis A vaccine, purified inactivated.In: Drugs Fut. 20. Barcelona, Spain: Prous Science Publishers; 1995. p. 24–9.

23. Overbosch D, Peyron F, Picot N, Varichon JP, Dumas R, Chambonneau L, Weber F. Combined typhoid fever and hepatitis A vaccine: comparison of immunogenicity and safety to concomitant monovalent vaccine over 3 years. *J Travel Med* 2005;**12**:319–26.
24. Akimkin VG, Hepatitis A universal vaccination of military personnel: the Russian experience. Global Hepatitis A Meeting, Miami, USA, 2007. Available at: http://www.docstoc.com/docs/47968689/EFFECTIVENESS-OF-UNIVERSAL-HEPATITIS-A-IMMUNIZATION-OF-YOUNG-CHILDREN.(accessed February 3, 2012).
25. Van Damme P, Banatvala J, Fay O, Iwarson S, McMahon B, Van Herck K, et al. Hepatitis A booster vaccination: is there a need? *Lancet* 2003;**362**:1065–71.