Vaccination against hepatitis A in children: A review of the evidence

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Abstract: Safe and effective vaccines against hepatitis A have now been available on the market for almost 15 years. This review focuses on the evidence of the effect of such vaccination in children when applied both within routine immunization programs and in groups at high risk of infection, but also as a measure to stop limited or community-wide outbreaks.

Keywords: hepatitis A, vaccination, epidemiology, outbreaks, effectiveness, herd immunity

Epidemiological background

Hepatitis A virus (HAV) is present worldwide and is the agent of one of the most widespread infections transmitted via the fecal-oral route. In countries with poor hygiene and consequent wide presence of feces in the environment, the vast majority of subjects is infected within 5 years of age (usually without any sign or symptom of acute hepatitis), thus acquiring life-long immunity. Outbreaks and epidemics are rare due to the high herd immunity level in the population.

When socio-economic and hygienic conditions improve, the decrease of HAV circulation progressively leads to a decline of herd immunity. Infections usually no longer occur in infancy and early childhood, and susceptibility progressively expands to cohorts of older children, adolescent and adults, when the probability of acute disease (sometimes severe or even fulminant) increases. In these intermediate endemicity countries, HAV infection is transmitted both by direct contact with infected subjects and by ingestion of contaminated food and drinks (WHO 1995). Since HAV circulation is diminished but not eliminated, both large epidemics (like the one registered in 1996–97 in Puglia, Italy) (Malfait et al 1996; Lopalco et al 2005) or more limited outbreaks (frequently starting in schools or day-care centers) can occur.

The incidence of HAV shows a cyclic pattern, with years of peaks and years of troughs. In the USA, for instance, peaks of incidence occurred in 1954, 1961, 1971, and 1989 (Wasley et al 2005).

In countries with very low HAV endemicity, high hygienic standards substantially limit viral spread. Outbreaks are rare, and hepatitis A is typically considered to be a travellers' infection (although this notion has partially been modified in recent times by increasing migration patterns and increasing importation of exotic foods: "hepatitis A is also travelling to us"). In low endemicity countries, subjects infected during travels abroad represent a potential source of infection for others once returned at home.

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Immuonogenicity and efficacy of hepatitis A vaccines

Several inactivated vaccines and one live attenuated vaccine (Mao et al 1997) (widely used in China) are currently available. The development of inactivated hepatitis A vaccines dates back to the end of the 1980s. Both preregistration clinical trials and

large-scale experiences of use showed that such vaccines are strongly and rapidly immunogenic. The minimal level of anti-HAV able to confer protection after vaccination has not been definitely established. Seroconversion is usually defined as the attainment of an antibody titer between 10 and 20 mIU/mL of anti-HAV. Such concentration, normally detected in those who received standard immune globulins two months before, was shown to be able to prevent HAV infection (Bell et al 2004). However, it must be stressed that cellular immunity plays a fundamental role for protection, and that production of anti-HAV following active immunization is certainly directly related to the availability of neutralizing antibodies but, even more importantly, is an indirect means of showing that immune memory has been established.

The majority of subjects are already seroconverts two weeks after a single dose. The percentage reaches 95%–100% 4 weeks after the first vaccine administration (Werzberger et al 1992; Crovari et al 1992; Nalin et al 1993; Van Damme et al 1994).

With regard to immunogenicity of hepatitis A vaccines in children and adolescents, it must be noted that although since the mid-1990s the vaccination schedule specifies administration of two doses only (6 to 18 months apart), data on the first vaccination experiences relate to the formerly used 3-dose schedule (0, 1, 6 month). Two such studies of long-term follow-up consistently showed 100% seroconversion at month 7 (ie, one month after the last dose), when antibody titer also peaked (Geometric Mean Titers or GMTs of anti-HAV of 4133 and 3802 mIU/mL, respectively) (Fan et al 1998; Chan et al 1999). All children in the two studies were still anti-HAV positive at month 60 of follow-up. A study of field efficacy with a different vaccine also showed antibody persistence up to 9 years after immunization (Wiens et al 1996; Werzbereger et al 1998, 2002). Mathematical models of antibody kinetics reported in the same papers predict a persistence of anti-HAV at detectable level for 14–30 years, but immune memory is expected to last much longer, making the need for booster doses later in life unlikely (Van Damme et al 2003).

An interesting study based on the two-dose administration schedule was performed on children in Alaska. The second dose was administered in delay, with a mean interval of 27 months, but seroconversion to anti-HAV occurred all the same, although 17% of subjects were seronegative before the booster dose (Williams et al 2000). This result is further proof that immune memory is already obtained in virtually all subjects after a single dose of vaccine.

An experimental demonstration of the role of immunological memory was provided by studies on chimpanzees, which resulted in protection against a challenge with HAV even in the absence of detectable anti-HAV (Purcell et al 1992).

A specific issue of hepatitis A vaccination at pediatric age is represented by active immunization in the first two years of life, since maternal antibodies might theoretically interfere with response to vaccination.

Although lower seroconversion rates and GMTs of anti-HAV were detected in infants born to seropositive in comparison to those born to seronegative mothers just after the completion of the vaccination course, priming of immune memory occurs (as demonstrated by the similar anamnestic response to a booster dose detected in subjects from both groups) independently from the serological status of the mother (Piazza et al 1999; Dagan et al 2000; Fiore et al 2001).

With regard to efficacy of vaccination, two studies performed using inactivated vaccines (Vaqta and Havrix, respectively), demonstrated the excellent protection afforded by active immunization. In the first study, over 1000 subjects (age range 2–16 years) in a New York City community with high hepatitis A incidence were randomly assigned to vaccine or to placebo. Except for a vaccinated subject who was already incubating the disease (onset of acute hepatitis A 3 weeks after immunization), no other immunized child became ill, compared with 34 cases of hepatitis A that occurred in the placebo recipient group. The protective efficacy was therefore 100% (lower limit of 95% confidence interval [CI]: 87%) (Werzberger et al 1993). The other study involved over 40,000 Thai children living in villages with a high incidence of hepatitis A and aimed at evaluating the effectiveness of two doses of vaccine given one month apart. Effectiveness was 94% (95% CI: 79%–99%) (Innis et al 1994). The observation that in these trials no case of hepatitis A occurred starting from 17 days following the first vaccine administration suggests also the potential for a post-exposure protective efficacy of inactivated hepatitis A vaccines (see following chapter on outbreak control).

Safety of hepatitis A vaccines

Adverse reactions to hepatitis A vaccination are infrequent and generally mild. The most common side-effects are represented by pain, swelling and redness at the injection site, usually of low-grade, and spontaneously resolving in a few hours or days. Such events were reported by less than 25% of vaccinated subjects during a pre-registration clinical trial of an inactivated hepatitis A vaccine (Crovari et al 1992). In other studies, pain at the injection site was reported by up to 56% of vaccinees (CDC 1999). Other adverse events related

to vaccine administration include headache, fatigue, fever, diarrhea, and vomiting. If we exclude headache (reported by about 15% of subjects), the percentage of such systemic reactions is below 5%. Temporal associations between hepatitis A vaccine administration and serious reactions such as anaphylaxis, Guillain-Barré syndrome, brachial plexus neuropathy, transverse myelitis, multiple sclerosis, encephalopathy, and erythema multiforme were reported (Bell et al 2004). However, after >65 million doses were administered worldwide and following a revision of data from different sources collected over 5 years, no serious adverse event was deemed to be causally related to hepatitis A vaccine. Data of the US system of collection of adverse reactions following immunization (Vaccine Adverse Events Reporting System [VAERS]) show that, for those adverse reactions whose background incidence is known, rates reported in vaccinees are not higher than those found in unvaccinated subjects (CDC 1999).

Impact of hepatitis A vaccination: outbreak control and routine immunization

Industrialized countries usually belong to low or very low endemicity regions, but several examples exist of particular areas within these nations characterized by an intermediate endemicity pattern. For example, Puglia in Italy, Catalonia in Spain, the North Bohemian region in the Czech Republic, the south-western states and Alaska in the USA, the whole state of Israel, can be considered as areas where the periodical occurrence of large outbreaks or even epidemics make hepatitis A an important public health issue.

The World Health Organization recommends that hepatitis A vaccination be considered for introduction into routine childhood immunization schedules in countries at intermediate endemicity of infection where hepatitis A represents a significant public health problem. Economic and epidemiological studies should precede decisions on universal vaccination policies (WHO 2000). In other low endemicity countries, hepatitis A vaccine should be administered to subjects belonging to high risk groups like international travelers, military personnel involved in missions abroad, children of immigrant families, intravenous drug users, patients with clotting factor disorders, patients affected with chronic hepatitis, homosexual men, and so on. Some countries also have recommendations for use of hepatitis A vaccination during outbreaks.

Policies of immunization targeted at risk groups, while effective for individual protection, usually fail to control the spread of an infectious agent on a community basis due to the difficulty in identifying those at risk and in effectively implementing their vaccination (as already demonstrated in the past by the experience with hepatitis B vaccine) (Bonanni 1995). Nevertheless, where routine vaccination programs against hepatitis A are not applied due to generally low endemicity but with periodic outbreaks, immunization of those in close contact with cases has proved useful in shortening outbreak duration, provided that a sufficient proportion of subjects is reached by immunization.

In areas at high endemicity for HAV infection, some experiences of control of epidemics using standard immune globulins had demonstrated the inability of such preventive means to get a long-lasting effect (Shaw et al 1986).

The first attempt to stop an outbreak by using a vaccine dates back to 1992, in Alaska, when immunization with a single dose was widely offered to all subjects under 40 years of age, to nonimmune older individuals in the Tok/Glenallen area, to all subjects under 20, and to seronegative subjects in the age range 20–34 in the Kotzebue area. It was possible to demonstrate that the attack rate of HAV infection in the first 60 weeks following vaccination was 12% in unimmunized subjects and 2.1% in vaccinees (most cases occurring few days after active immunization, ie, they were vaccinated during the incubation period). In the Kotzebue area, where only about 50% of eligible individuals were immunized, the epidemic persisted for several weeks, while in the surrounding regions, where coverage reached 80%, the epidemic was virtually eliminated within 8 weeks from the start of vaccination program (Mc Mahon et al 1996).

Other experiences in communities of American Indians showed that routine vaccination of children can interrupt already occurring epidemics, and that keeping up coverage prevents the start of new epidemics (CDC 1999).

In Europe, an intervention conducted in two villages in Slovakia where an epidemic was occurring (121 cases between December 1991 and March 1993, 62 of which in schoolchildren), caused its extinction two months after 2/3 of children were immunized with two doses of vaccine, with only nine further cases before the end of the epidemic in March 1993, 8 of which were in the nonvaccinated group (Prikazsky et al 1994).

Several outbreaks have occurred in Europe originating in day-care centers, and maternal or primary schools (sometimes with spread to the larger community) where vaccination was used in the attempt to shorten the duration of such episodes.

Almost all outbreaks of this kind originate from children of immigrant families born in their adoptive country who periodically travel back (usually in summer)

to their country of origin to visit relatives. The infected children are contagious when school activities start again, and characteristic patterns of HAV transmission to indigenous European children and to the parents (typically about 1 month after the wave in children) are observed (van Gorkom et al 1998).

The 11 cases (5 in children and 6 in household contacts) detected in a nursery school in Central Italy resulted in one of the first attempts to stop imported outbreaks in schools by using hepatitis A vaccination. The program of immunization was accepted by almost all other schoolchildren and school personnel, and by 11/36 cohabitant children and 10/78 cohabitant adults of cases. The last case was detected two months after the start of vaccination, a considerably shorter interval compared to previous similar outbreaks (Bonanni et al 1998).

More recently, two outbreaks (again originating from immigrant children) occurred almost simultaneously on two sides of the city of Florence, Italy, but had very different outcomes. During the first outbreak on the southeastern side of the city, the index case was identified with considerable delay, and the immunization program of case contacts started late as a result of poor communication within the local health unit and the unavailability of a sufficient number of doses. Compliance with the Italian guidelines on hepatitis A vaccine use, which suggest waiting for a second case to occur in secondary schools before starting vaccination of contacts, meant that the infection spread to adolescents and their relatives. Overall, 30 clinically overt cases and 7 asymptomatic infections were detected, and the outbreak lasted for 6 months. On the other hand, a potential outbreak in a maternal school was stopped in the northwestern part of the city because a vaccination program of other schoolchildren and of contacts of the index case was immediately implemented, reaching >80% coverage. Only 3 cases of hepatitis A occurred, one of which may have been connected to other sources of infection. Comparing the two outbreaks enables us to draw some conclusions on the use of hepatitis A vaccine to stop the virus spreading in schools and households. Most important is timely diagnosis of hepatitis A by general practitioners, improved communication channels within the health care setting, the availability of a sufficient number of vaccine doses in every health district for immediate use in case of an outbreak, and the offer of immunization to case contacts irrespective of a presumed 'low-risk' environment, such as secondary schools (Bonanni et al 2005).

To establish individual protection by hepatitis A vaccine in post-exposure prophylaxis, Hepatitis A vaccine was used in HAV susceptible family contacts of acute hepatitis A cases (173 vaccinated and 178 unvaccinated) in a randomized, controlled trial.

Hepatitis A vaccine showed an 82% protective efficacy (95% CI: 20%–96%) in the prevention of secondary cases (79%; 95% CI: 7%–95%, when households were analysed). About 56% of subjects had been immunised within 4 days from the onset of symptoms in primary cases, and 100% within 8 days. Vaccination was required in 18 participants to prevent one secondary infection (Sagliocca et al 1999).

Evidence that clinical disease does not occur at antibody levels lower than those currently accepted as protective, that hepatitis A vaccine has proved effective in controlling outbreaks, and that timely immunization can prevent secondary infections within households, strongly suggests the usefulness of immunization against hepatitis A in traveler children, even for last-minute departures (Connor 2005).

In the last 10 years, the health authorities of some of the countries mentioned above, characterized by generally low endemicity but with areas at intermediate endemicity, introduced universal immunization policies with different target populations. We can now evaluate the epidemiological effects of such decisions.

In the United States in 1999, the Advisory Committee on Immunization Practices (ACIP) issued new recommendations on the public health use of hepatitis A vaccine, amending those of 1996 which focused on vaccinating subjects at risk. The ACIP stated that "… a review of the national epidemiologic data indicates that continued implementation of these recommendations would not result in vaccination of most populations with consistently elevated rates of disease and therefore would have a limited impact on the overall incidence of disease in the United States. To achieve a sustained reduction in HAV rates, a shift is needed to one that achieves widespread routine vaccination of children to prevent infection in these age groups and eventually among older persons."

As a consequence, routine vaccination of children was recommended in states, counties and communities with rates of infection more than double the national average (≥20 cases per 100,000 population) and should also be considered if infection rates were ≥10 cases but <20 cases per 100,000 population (CDC 1999). These recommendations recognized both the role that children play in transmitting HAV to others and the value of population-level action (Poland 2005).

A recently published study aimed at assessing the impact of the current vaccination strategy by evaluating trends in reported cases of hepatitis A since implementation of the recommendations (Wasley et al 2005). Incidence rates in 2003 were compared with those for the prevaccination baseline period (1990–1997) overall and in the 17 states in which children

should routinely be vaccinated, or considered for routine vaccination (vaccinating states). Incidence rates in vaccinating states were also compared with those in the remaining states where there is no recommendation for statewide vaccination of children (non-vaccinating states). Between the baseline period (1990–1997) and 2003, overall hepatitis A rates declined 76% to 2.6 per 100,000, significantly lower than previous lowest points in 1983 (9.2/100,000) and 1992 (9.1/100,000). The rate in vaccinating states declined 88% to 2.5 per 100,000 compared with 53% elsewhere (to 2.7/100,000). Declines were greater among children aged 2 to 18 years (87%) than among persons older than age 18 years (69%); the proportion of cases in children dropped from 35% to 19%. Since 2001, rates in adults have been higher than among children, with the highest rates now among men aged 25 through 39 years.

After implementation of routine hepatitis A vaccination of children, hepatitis A rates have declined to historic lows, accompanied by substantial changes in the epidemiologic profile. Although the precise contribution of vaccination is difficult to assess, given the unavailability of detailed data on vaccination coverage in different states and areas, nevertheless the declines of incidence registered after 1999 have been unprecedented in magnitude and greater in areas in which vaccination of children is occurring.

As a consequence of the documented impact of hepatitis A vaccination on HAV epidemiology, the US health authorities very recently extended the recommendations for hepatitis A routine immunization. Hepatitis A vaccination is now recommended for all children at age 1 year (ie, 12–23 months). The 2 doses in the series should be administered at least 6 months apart. States, counties, and communities with existing hepatitis A vaccination programs for children aged 2–18 years are encouraged to maintain these programs. In these areas, new efforts focused on routine vaccination of children aged 1 year should enhance, not replace, ongoing programs directed at a broader population of children (CDC 2006).

Another proof of the impact of routine vaccination programs against hepatitis A on the epidemiology of this infection comes from the Israeli experience. In Israel, the mean annual incidence of hepatitis A disease was 50.4 per 100,000 during 1993–98. A 2-dose universal hepatitis A immunization program aimed at children aged 18–24 months (without a catch-up campaign) was started in 1999. Incidence of reported hepatitis A disease was monitored in the years 1993–2004. Overall vaccine coverage in Israel in 2001–02 was 90% for the first dose and 85% for the second dose. A decline in disease rates was observed before 1999 among the Jewish but not the non-Jewish population. After initiation of the program, a sharp decrease in disease rates was observed in both populations. The annual incidence of 2.2 to 2.5 per 100,000 during 2002–04 represents a 95% or greater reduction for each year with respect to the mean incidence during 1993–98 ($p < 0.001$).

For children aged 1 through 4 years, a 98.2% reduction in disease was observed in 2002–04, compared with the pre-vaccination period ($p < 0.001$). However, a sharp decline was also observed in all other age groups. In the Jewish population in the Jerusalem district, among whom an active surveillance program was successfully conducted, a more than 90% reduction of disease was demonstrated. Of the 433 cases reported nationwide in 2002–04 in whom vaccination status could be ascertained, 424 (97.9%) received no vaccine and none received 2 doses. This universal toddlers-only immunization program in Israel demonstrated not only high effectiveness of hepatitis A vaccination but also marked herd protection, challenging the need for catch-up hepatitis A vaccination programs (Dagan et al 2005).

Similar results were obtained in Puglia, Italy and in Catatonia, Spain, where routine vaccination of children in the second year of life (Puglia) and/or at adolescent age (Puglia and Catatonia) concomitantly with hepatitis B vaccination were recommended at the end of the 1990s (Lopalco et al 2000). Epidemiologic surveillance shows that peaks of hepatitis A incidence cyclically occurring in the past, were no longer observed in these areas.

Conclusion

Hepatitis A vaccine is one of the most immunogenic vaccines available. Its excellent efficacy in pre-exposure prophylaxis has been documented by several studies. Vaccination has been used (mainly targeting children) in the course of outbreaks and for the prevention of secondary cases.

Active prophylaxis usually shortened the course of outbreaks where coverage reached about 80% of a well-defined target population.

No clinical trial on the effectiveness of HA vaccination during outbreaks (in comparison with human normal immune globulin) is available. Although used in the past for post-exposure prophylaxis, immune globulin preparations have decreased their antibody concentrations, are difficult to get and are not well accepted due to their origin from human blood.

The only clinical trial of vaccine used for post-exposure prophylaxis showed good efficacy (about 80%). However, confidence intervals are wide, and large numbers of subjects for study are very difficult to obtain.

In communities experiencing recurrent epidemics or outbreaks, the use of vaccination seems justified by the high

secondary attack rates and the consequent acceptable cost-effectiveness profile.

However, the implementation of routine vaccination of children and/or adolescents, which has recently proved very effective in its effect on general HAV epidemiology, seems, in the long term, the most reasonable way to get recurrent outbreaks under control in areas where hepatitis A represents a public health problem.

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