

ST02 Why does Hepatitis A Emerge in Low Endemic Countries and Can it be Prevented?**ST02.1 Introduction**

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Hepatitis A is one of the most widespread vaccine-preventable infectious diseases; it causes a significant disease burden in the world, with 1.5 million estimated cases each year. Because a wide variety of surveillance systems are used globally, the real burden of hepatitis A is underestimated.

In the past few decades improved sanitary conditions, and the implementation at national and international levels of vaccination programmes for individuals at increased risk, have contributed to a reduction of the disease burden. Many countries (in particular those with intermediate endemicity) have experienced an epidemiological shift towards lower endemicity. As a consequence, adults and adolescents increasingly remain susceptible and are thus at risk of clinically more severe disease.

The extent to which hepatitis A can spread within at-risk populations has recently been described in several European countries. Transmission may be further 'amplified' by migrant populations, injecting drug users, infected food-handlers; some of these are hard-to-reach communities.

This highlights the need for increased awareness, and well-structured surveillance and outbreak reporting systems. Specific risk group vaccination, particularly targeting travelling populations, is recommended in low endemicity countries, whereas universal vaccination programs of children are recommended in areas of intermediate endemicity.

An increasing number of middle income countries are considering joining those who have already implemented universal hepatitis A vaccination programmes. In Israel and the United States, universal hepatitis A immunization of young children has proven effective in rapidly reducing disease incidence and maintaining very low incidence levels even across other age groups, demonstrating the development of herd immunity. Mass vaccination programmes also proved effective in localized regions of intermediate to high HAV endemicity of industrialized nations with otherwise low endemicity, such as the Puglia region of Italy and the Catalonia region of Spain.

We are at a turning point of hepatitis A control; the changing epidemiology of hepatitis A should go hand in hand with matching hepatitis A immunization programmes.

ST02.2 The European Experience

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During the last 10 years in the European Union (EU), although figures may vary among countries, the overall incidence of hepatitis A has decreased from 15.1 per 100,000 population in 1996 to 3.9 per 100,000 in 2006. This has been stated recently by Eurosurveillance. In most countries a shift in epidemiology of hepatitis A towards higher age groups can be observed. However, the EU is a very heterogeneous region with respect to hepatitis A surveillance and incidence and therefore - according to epidemiologic pattern of the disease in the respective country - different strategies to fight hepatitis A may be appropriate.

Within the EU we can roughly differentiate two types of epidemiologic patterns of hepatitis A: Type I countries are typically rich EU countries with highly developed social systems and a long tradition of immigration. They have very few autochthonous cases of hepatitis A. The type II countries are mostly those who were integrated in EU during the last decade. These countries are characterized by a fast growth of their economy and they tend to have needed migrants only during the last 10-15 years. They have impressive improvements of their hepatitis A incidence, but are considered "endemic" regions.

- To fight hepatitis A in the EU three strategies may be applicable:
- General immunization very early in childhood will offer the best approach for immunizing all children, but this is costly and the hepatitis A vaccine is currently not licensed for use in children below 1 year of age.
- A better targeting of the risk groups would be achieved by immunizing only those, who are attending public nurseries or kindergarten. This approach would therefore be more cost effective.
- From the view of cost effectiveness the best way to use the HAV vaccine would be the selective immunization of high risk groups only. This would include all those with migration background only. On ethical grounds this is an impracticable option and will raise a number of problems.

ST02.3 The North American Experience

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Hepatitis A (HA) is considered a low-incidence, non-endemic disease in the United States (US) and Canada. However, certain subpopulations were found to have relatively high incidence rates that approached those more typical of developing countries where HA is considered an endemic disease. In the early 1990's in the US, high incidence rates were found in predominantly Hispanic communities in the states bordering Mexico. In day-care, schools and other community settings, children with asymptomatic HA infections, acquired from cross-border travel to Mexico, contributed to transmission of HA. High incidence rates were also found among indigenous North American populations (American Indian/Alaska Natives). The HA incidence in the US West dramatically decreased after implementation of a targeted HA immunization program recommended by the CDC Advisory Committee on Immunization Practices (ACIP) in 1999 for children living in the 11 western states with reported average HA rates ≥ 20 cases per 100,000 population. These recommendations were expanded to include routine vaccination of children in all 50 states in 2005.

Other groups in the US identified at higher risk of acute HA infection included international travelers to high-incidence areas, men who have sex with men, injecting- and non-injecting drug users, and correctional facility inmates. Infected food handlers and HA virus-contaminated food originating in HA endemic areas were associated with food-borne outbreaks.

Although the data are incomplete, population groups at high-risk for HA in Canada are similar to those observed in the US. However, instead of cross-border international travel, increased risk of HA infections have been reported among children visiting friends and relatives (VFR) in Asia and among adults visiting Latin America. Canada has had targeted HA immunization programs directed at high risk groups and continues to consider the cost-benefit of universal childhood HA immunization.

As international travel continues to grow, especially involving the VFR category of travelers, and dispersion patterns of returned travelers into the general population become less predictable, universal immunization of children and/or adolescents against HA in low-incidence countries may result in substantial disease rate reductions among the vaccine recipients themselves, as well as among their older susceptible contacts - in whom HA infection is more likely to cause increased morbidity and mortality.

ST02.4 Clinical Features of the Virosomal Hepatitis A Vaccine (Epaxal®)

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Inactivated hepatitis A vaccines have been available since the early 1990s. To be effective they require an adjuvant to improve the immunogenicity and aluminium salt was the first adjuvant used. The only inactivated hepatitis A vaccine that uses virosomes as adjuvant is Epaxal® (CruCell). This vaccine was first introduced in 1994 and is now licensed in over 40 countries worldwide.

Immunopotentiating Reconstituted Influenza Virosomes (IRIVs) are spherical vesicles of ~150 nm in diameter that are made up of phospholipids, lecithin (phosphatidylcholine) and cephalin (phosphatidylethanolamine), with fusion active influenza glycoprotein haemagglutinin and neuraminidase intercalated into the phospholipid bilayer. As such, IRIVs are constituted of biodegradable components and mimic the natural way of presenting and processing antigens to immunocompetent cells. IRIVs have been shown to elicit both cell-mediated and humoral immune responses without inducing a nonspecific inflammatory response. The inactivated hepatitis A virus particles (RG-SB strain) are adsorbed onto virosomes.

In several clinical trials, Epaxal® has shown to be highly immunogenic in all age groups and to confer a rapid and long-lasting protection against hepatitis A. In a placebo-controlled field trial in 1.5-6 year old children in Nicaragua, no cases of anti-HAV IgM seroconversion occurred in 122 children, 6 weeks to 18 months after having received a single dose of Epaxal®.

The vaccine has demonstrated an excellent and consistent safety profile in all clinical trials. Direct comparisons have shown significantly less injection site pain of Epaxal®, as compared to the most widely used aluminium adsorbed vaccine. This has been attributed to the biodegradable nature of virosomal constituents.

In view of its excellent efficacy and tolerability profile, the virosomal based hepatitis A vaccine can be considered an attractive tool in controlling hepatitis A - not only for the traveler but also in universal mass vaccination programs.