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TOPIC HIGHLIGHT

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Hepatitis A: Epidemiology and prevention in developing countries

Elisabetta Franco, Cristina Meleleo, Laura Serino, Debora Sorbara, Laura Zaratti

Elisabetta Franco, Laura Zaratti, Department of Public Health, University Tor Vergata, via Montpellier 1, 00133 Rome, Italy
Cristina Meleleo, Laura Serino, Debora Sorbara, Specialization School for Hygiene and Preventive Medicine, University Tor Vergata, via Montpellier 1, 00133 Rome, Italy
Author contributions: Franco E designed the research; Meleleo C, Serino L, Sorbara D and Zaratti L performed the literature search and evaluation; all authors contributed to writing the paper.
Correspondence to: Elisabetta Franco, MD, Professor of Hygiene, Department of Public Health, University Tor Vergata, via Montpellier 1, 00133 Rome, Italy. franco@med.uniroma2.it
Telephone: +39-06-72596122 Fax: +39-06-2025285
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Abstract

Hepatitis A is the most common form of acute viral hepatitis in the world. Major geographical differences in endemicity of hepatitis A are closely related to hygienic and sanitary conditions and other indicators of the level of socioeconomic development. The anti-hepatitis A virus (HAV) seroprevalence rate is presently decreasing in many parts of the world, but in less developed regions and in several developing countries, HAV infection is still very common in the first years of life and seroprevalence rates approach 100%. In areas of intermediate endemicity, the delay in the exposure to the virus has generated a huge number of susceptible adolescents and adults and significantly increased the average age at infection. As the severity of disease increases with age, this has led to outbreaks of hepatitis A. Several factors contribute to the decline of the infection rate, including rising socioeconomic levels, increased access to clean water and the availability of a hepatitis A vaccine that was developed in the 1990s. For populations with a high proportion of susceptible adults, implementing vaccination programs may be considered. In this report, we review available epidemiological data and implementation of vaccination strategies, particularly focusing on developing countries.

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Key words: Hepatitis A; Developing countries; Endemicity; Seroprevalence; Vaccine

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INTRODUCTION

Hepatitis A is the most common form of acute viral hepatitis worldwide. The first description of hepatitis (epidemic jaundice) is generally attributed to Hippocrates and outbreaks of hepatitis A have been recognized for centuries, affecting both military and civilian populations[1].

The hepatitis A virus (HAV) is a small non-enveloped single-stranded RNA virus. It is thermostable and acid-resistant. For some time after its identification, HAV was thought to be an enterovirus; in 1991, it was sub classified as a member of the Hepatovirus genus of the family Picornaviridae. HAV replicates in hepatocytes and interferes with liver function, sparking an immune response that causes liver inflammation. HAV is acquired by the fecal-oral route. Person-to-person transmission is com-

mon and generally limited to close contacts[2].

A typical symptomatic presentation includes non specific prodromal symptoms with variable combinations of fever, malaise, weakness, anorexia, nausea, vomiting, arthralgias and myalgias. Prodromal symptoms tend to decrease with the onset of jaundice, although anorexia, malaise and weakness may persist or increase transiently. Jaundice lasts for several weeks and is followed by a convalescent period. The peak infectivity occurs during the two weeks before the onset of jaundice or elevation of liver enzyme levels when the concentration of virus in the stool is highest. When jaundice appears, the viral concentration in the stool declines and most patients are noninfectious after one week[2,3].

The expression of clinical symptoms varies greatly with the age of the infected person. Approximately 50% of children with hepatitis A under the age of 6 years are asymptomatic, with most of the remaining having mild symptoms, often not recognized as hepatitis. Less than 5% of children below 4 years of age and less than 10% of children between ages 4 and 6 years with hepatitis A develop jaundice. Starting from 6 years of age to adulthood, more than 75% develop the characteristic illness traits with jaundice and dark urine[3,4]. Although rare, HAV infection can cause acute liver failure and death (in approximately 0.2% of clinical cases) and this risk increases with age and the presence of chronic liver disease[5].

Acute hepatitis A symptoms are similar to those of other viral hepatitis and serological testing for the detection of immunoglobulin M (IgM) antibodies to HAV (anti-HAV) is required to confirm the diagnosis. IgM anti-HAV is usually detectable when symptoms appear and concentrations decline to undetectable levels within 6 mo for most patients. However, cases of patients that test positive for IgM anti-HAV more than 1 year after infection have been reported. Immunoglobulin G (IgG) anti-HAV appears early in the course of the infection and remains detectable throughout the person's lifetime. Total anti-HAV tests are often used in epidemiological investigations or to detect susceptibility to HAV but they do not identify acute infection. Vaccines, available since the early 1990s, are not yet widely used, therefore most individuals with anti-HAV acquired immunity through infection[3].

GLOBAL EPIDEMIOLOGY OF HEPATITIS A

Approximately 1.5 million clinical cases of hepatitis A occur worldwide annually but the rate of infection is probably as much as ten times higher. The incidence rate is strongly related to socioeconomic indicators and access to safe drinking water: as incomes rise and access to clean water increases, the incidence of HAV infection decreases. The association of HAV infection risk with standards of hygiene and sanitation, the age-dependent clinical expression of the disease, and lifelong immunity determine the different patterns of HAV infection observed worldwide.

The HAV endemicity level for a population is defined by the results of age-seroprevalence surveys; a systematic review on the global prevalence of HAV infection was recently published by the World Health Organization (WHO)[6].

Areas of the world can be characterized as having high, intermediate and low endemicity for hepatitis A. In less developed countries with very poor sanitary and hygienic conditions, HAV infection is highly endemic and most persons become infected in early childhood. Because infection occurs at an early age when the disease is often asymptomatic, reported rates of the disease in these areas are relatively low and outbreaks are not common. Areas of high endemicity include most of Africa, Asia and Central and South America. Conditions which contribute to the propagation of the virus among young children in these areas include household crowding, poor levels of sanitation and inadequate water supplies[3,6,7].

In developing countries and some regions of developed countries, which include Eastern Europe, parts of Africa, Asia and America, sanitary and hygienic conditions vary and some children avoid infection during early childhood. Peak rates of infection commonly occur in later childhood or adolescence. Paradoxically, since HAV transmission occurs in these areas in older age groups, reported rates of hepatitis A can be higher than in less developed countries where HAV transmission is more highly endemic. Person-to-person transmission in large community-wide epidemics accounts for a significant amount of the disease in these areas. These outbreaks are very difficult to control with standard measures like hand washing and immune globulin administration to contacts of cases. Outbreaks are also observed in child care centers and schools and occasionally large food borne epidemics occur, such as in Shanghai in 1988 where the outbreak was associated with shellfish consumption[8]. In some areas, conditions are such that disease trends are cyclical; HAV is transmitted in community-wide outbreaks until the population is exhausted of susceptible persons, after which there is a period of several years until a new cohort of susceptible children reaches the age when clinical disease is more frequent[3,6,7].

In most developed countries, such as North America, Western Europe, Australia and Japan, sanitation and hygienic conditions are generally good and infection rates in children are generally low. Peak rates of infection and reported disease tend to be among adolescents and young adults. In these areas, large community-wide outbreaks with extended person-to-person transmission can still contribute significantly to the burden of hepatitis A disease. In addition, occasional outbreaks in child care centers or residential institutions and food borne or waterborne epidemics can occur. In some countries with very low prevalence (e.g. Northern Europe), disease predominates among specific adult risk groups: travelers to countries where hepatitis A is endemic; intravenous drug users; and men with a history of homosexual behavior. The prevalence of anti-HAV increases gradually with age, primarily reflecting declining incidence, changing endemicity and

a resultant lower childhood infection rate over time[2-4,6,9,10].

PREVALENCE OF HEPATITIS A: FOCUS ON DEVELOPING COUNTRIES

Africa

Information on HAV infection in Africa is limited. Available data shows that most of Africa remains a high endemicity region, with the exception of subpopulations in some areas, such as white people in South Africa. In the 1990s, almost all black children in South Africa were anti-HAV-positive by the age of 12 years and almost 100% of black adults had antibodies to HAV before the age of 20 years, while only 30%-40% of white adults were anti-HAV-positive by the age of 20 years, rising to about 60% by the age of 40-49 years[11,12]. North Africa has an intermediate level of anti-HAV seroprevalence. Studies from the 1980s showed nearly universal immunity in many countries; a 100% immunity rate by age 10 years was found in Algeria and nearly 100% of adults were anti-HAV positive in Morocco. More recent data shows that, in general, urban areas have experienced a decline in hepatitis A infection, while rates in rural areas remain high and the prevalence is generally lower in higher social classes[6].

The significant increase in the seroprevalence with older age and lower social class was confirmed in a 2008 study in which 296 Egyptian children aged 2.5-18 years of different social classes were tested to evaluate whether to give HAV vaccine early in life or to leave children to acquire natural immunity. Overall, 61.4% were seropositive; anti-HAV was detected in 27.3% of high and in 81% of low social class children aged < 6 years[13].

In Tunisia, child infection rates remain high with differences between urban and rural settings, depending on the development of the areas considered. In 2002, the overall seroprevalence in an area of central Tunisia was 60% among students aged 5-23 years (44% in children < 10 years old, 58% in those 10-15 years of age and 83% in those > 15 years of age). Regardless of age, seroprevalence rates for HAV were significantly lower in urban areas than in sub-urban and rural areas. At the age of 10, 21.3% of school children living in urban areas and 87.7% of those living in rural areas had antibodies to HAV[14]. In a larger study performed in three different regions of Tunisia in 2007, HAV seroprevalence was 84.0%, 90.5% and 91.7% in three groups with a mean age of 6.94, 12.84 and 20.71 years respectively[15].

In its recent report, WHO presents the information about HAV seroprevalence in North Africa and Middle East together because the trend of the infection is the same in both regions. In Yemen in the 1980s, a near 100% seroprevalence was detected, while in a recent study from Kuwait the prevalence of anti-HAV was 28% in adults. The highest prevalence was among the group with non educated parents, which reflects the relationship of the disease to low social background[6,16].

Sub-Saharan Africa has some of the highest anti-HAV prevalence rates in the world and nearly all older children and adults are naturally immunized. In Liberia in the late 1970s, more than 80% of 4-5 year olds had antibodies to HAV, which suggested an incidence rate of 45% per year between the first and fourth birthdays. In the same period in Senegal, nearly 100% of children had antibodies to HAV by age 5 years and in Nigeria more than 90% of adults had HAV antibodies. In the 1990s in Cameroon, adult prevalence was greater than 90% and in Sierra Leone a study of urban schoolchildren found a 97% prevalence rate. Although recent studies are not available, it is likely that Sub-Saharan Africa continues to have a very high HAV incidence rate and, correspondingly, a very high seroprevalence rate from childhood[6,7].

Asia

HAV seroprevalence rates vary considerably among countries in Asia, with some continuing to have high rates and others making a transition to moderate or low incidence.

Low endemicity areas include Japan and others countries such as Taiwan where the prevalence has decreased markedly in the last years. In fact, while in the 1970s the prevalence of anti-HAV in adults was more than 90%, later studies show that in the Taipei metropolitan area, the prevalence was nearly 0% and in the rural areas only very few adolescents and young adults showed signs of previous infection[17].

In the moderate endemicity countries, such as Korea, Indonesia, Thailand, Sri Lanka and Malaysia, the available data shows that the incidence rate may be decreasing, at least in urban areas, and the age at infection increases from very early to late childhood, which increases the risk of outbreaks. The number of cases of adult hepatitis A has progressively been increasing during the last several decades in Korea. In addition, the pattern of age-specific seroprevalence of anti-HAV has changed with economic growth. The prevalence of anti-HAV in the 10-50 year age range has declined rapidly during the last 3 decades. As a result, this age group has a high risk for HAV infection and clinically overt hepatitis A is increasing in adolescents and adults[6,18,19].

In China and India, the two most populous countries in the world that have shown a very rapid socio-economic development in the last years, many high endemicity areas for HAV infection coexist with others, making a transition to moderate incidence[6,7,20].

Hepatitis A has been a relevant public health problem in China. More than 300 000 cases of clinical hepatitis A were reported during a shellfish-associated outbreak in Shanghai in 1988; however, in the following two decades, the annual national incidence rate of hepatitis A dropped dramatically. In urban China in the early 1990s, although up to one-half of 10 year olds had antibodies to hepatitis A, the seroprevalence in most cities did not reach 100%, even for those aged 60 and above, leaving susceptible population groups and creating the possibility of outbreaks. In 2006, two major hepatitis A incidents occurred in China: one was an outbreak in a school in the

south and the other was an epidemic involving multiple HAV strains in the Autonomous Region of northwestern China[21,22].

In India, heterogeneous pockets of susceptible and exposed individuals may co-exist in different regions. About 15 years ago, the cord blood anti-HAV level in Indian newborns was almost 100%, which in turn reflected the maternal antibody prevalence. In recent studies, this level has come down to 50%-60%. Some studies also show that seroprevalence of HAV antibodies was lowest in the 6 mo to 2 year age group and maximum exposure to HAV occurred from 2 to 5 years of age. These observations may be the first indication of the epidemiological shift of the age of acquisition of the HAV infection in the community, even if the current available data does not confirm a consistent decline in childhood HAV seroprevalence rates and increased susceptibility to HAV in young adults[20,23,24].

Nowadays, in many other Asian countries, HAV infection is still highly endemic. Studies from Pakistan in the 1980s, 1990s and 2000s indicate that more than half of children acquire immunity by their preschool years and nearly all adolescents and adults are immune. Between the 1980s and 1990s in Nepal, nearly all adolescents were immune by age 15. In Bangladesh, more than half of 5 year olds and nearly all adolescents and adults are immune[6].

Central and South America

Latin American countries show many of the characteristics of developing countries, with migration from rural communities to cities leading to urban areas of low income and social deprivation. Improvements in public health programs and sanitary conditions have had an impact on the epidemiological patterns of HAV infection in developing economies and so previous studies showing Latin America to be an area of high endemicity with almost universal infection before the age of 10 years may no longer be valid. It is, nevertheless, difficult to estimate the exact incidence of hepatitis A because of the high proportion of subclinical infection and anicteric disease and the different surveillance programs. It has been estimated that the real incidence is 10 times higher than that reported[25-27].

The endemicity patterns continue to be high in several Latin America countries, such as the Central and the Caribbean areas, where studies performed between 1990 and 1999 showed a very high seroprevalence rate and found that more than half of the children had developed immunity by their second birthday and nearly all adults in both rural and urban areas were immune to HAV[6,7].

Data from recent studies has shown that the prevalence of anti-HAV is decreasing in several South American countries, including Argentina, Bolivia, Brazil, Venezuela, Chile and Uruguay where there has been a shift from high to medium endemicity. This shift was obtained with the improvements in public health programs and sanitary conditions in most parts of these areas[25,26].

A multicenter study carried out between 1996 and 1997 in six countries, including Mexico, the Dominican Republic, Chile, Brazil, Venezuela and Argentina, showed a general decrease in HAV seroprevalence rates compared to previous reports, except for the Dominican Republic where a total prevalence of 89.0% was detected and where the seroprevalence of HAV in children between 1 and 5 years of age was more than 50%. The seroprevalence rates were 81.0% in Mexico, 64.7% in Brazil, 58.1% in Chile, 55.7% in Venezuela and 55.0% in Argentina. In the 5-10 year old age group, seroprevalence rates have also decreased compared with previous reports. This suggests that the epidemiology is shifting from high to intermediate endemicity, with the population susceptible to HAV infection shifting from children to adolescents and adults. Even in Mexico, where anti-HAV prevalence remained high, it was shown that the average age at infection among children hospitalized with hepatitis increased from 6 years in 1991-1993 to 10 years in 2003-2005. Furthermore, data from Brazil, Argentina, Venezuela and Mexico shows that HAV seroprevalence is significantly lower in people living in medium and high socioeconomic conditions[6,7,26].

In the same six countries, a seroepidemiological study was undertaken in 2002-2003 to determine whether this pattern has changed. Analysis of the different age groups showed that at age 6-10 years, 30% of children in Chile and 54%-55% in Brazil, Venezuela and Argentina had been infected, compared with almost 70% in Mexico and 80% in the Dominican Republic. At age 11-15 years, nearly 90% in Mexico and 91% in the Dominican Republic had been infected, compared with 54% in Argentina, 62% in Venezuela, 60% in Brazil and 70% in Chile. By age 31-40 years, over 80% of the populations in all six countries had been exposed to HAV. In all of the countries except Brazil and Venezuela, the seroprevalence of anti-HAV was significantly higher in females than in males. In Mexico, Argentina and Brazil, anti-HAV seroprevalence was significantly higher in the low than in the middle/high socioeconomic groups. Seroprevalence rates in American Indian and Amazonian populations tend to be higher, except for some extremely isolated villages. The results show that there has been a shift from high to medium endemicity of HAV infection in a large part of Latin America, which may result in more clinical cases in adolescents and adults and a greater potential for outbreaks[25,28].

In Bolivia, studies performed in the same rural area in 1987 and ten years later showed a significant decrease in the seroprevalence rates from 86.9% to 28.4% in children less than 5 years of age, although rates in older children and adults remained very high in both study years. Most seroprevalence studies from Mexico and Venezuela performed between the 1990s and 2000s showed that about 50% of 10 year olds were immune but significant differences in seroprevalence were related to socioeconomic status[6].

In Argentina, a sharp reduction in the infection rate was reached by the introduction of a universal HAV vac-

cination program in 2005 and other countries, like Brazil and Chile, are evaluating the possibility of introducing a specific prevention policy[29-31].

PREVENTION OF HEPATITIS A INFECTION

Adequate supplies of safe drinking water and proper disposal of sewage within communities, combined with personal hygiene practices, such as regular hand washing, reduce the spread of HAV[32]. There was a marked reduction in virus transmission in most developed countries several decades ago due to improvements in living standards, better sanitation and environmental conditions. The same trend was observed during the 1990s in several developing countries with increasing economic prosperity. These changes occurred without a specific vaccination strategy, underscoring the critical importance of environmental and personal hygiene and sanitation to prevent fecal-oral transmission of pathogens[17].

Safe and effective inactivated hepatitis A vaccines have been available since 1992 worldwide and are generally used in developed countries to protect risk groups and stop outbreaks. The different vaccines are similar in terms of efficacy and side-effects, highly immunogenic, inducing antibodies to HAV that persist for at least 15 years. Based on current scientific evidence, protection is considered to be life long after a complete hepatitis A vaccination schedule (two doses). Long-term protection after a single dose needs to be further surveyed. The vaccines can be delivered alone or in combination and administered with flexible schedules[33,34].

Vaccination policies range from being part of national universal immunization programs for children to targeting at risk groups.

National immunization programs have been successful, with good coverage rates and declines in incidence up to 90%. Countries or regions that have implemented universal immunization, e.g. Israel, Italy (Puglia), Spain (Catalonia) and the United States, have demonstrated a successful impact on the incidence of hepatitis A; the data for the United States is particularly striking, with evidence of a two-thirds decrease in admissions to hospital and markedly lower medical expenditures between 1996 and 2004. Targeted policies, especially for travelers, have also been shown to be effective and are adopted by different countries and vaccination is included as post-exposure prophylaxis of contacts[35].

In some rapidly developing countries, a new approach to control and prevention of HAV epidemics using a vaccine is being considered. In South America, several trials to evaluate the immunogenicity and safety of inactivated HAV vaccine were performed among Argentinean and Chilean children[36,37], while cost-benefit studies were performed in Brazil, where a hypothetical vaccination strategy was developed to eliminate hepatitis A[28].

In 2005 in Argentina, a universal hepatitis vaccination with a single dose at 12 mo of age was implemented. Argentina's Ministry of Health was established to monitor the impact and follow up the strategy in order to evaluate the need for a second dose. Surveillance data showed an important decline in hepatitis A incidence rates in 2007, when the rate recorded was the lowest in the last 12 years. It is important to consider that these declines since 2005 have been unprecedented in magnitude and have been observed in all age groups and regions, showing a marked herd immunity effect. Brazil and Chile reassessed their immunization policy after cost-effectiveness studies and looking at the successful results of the areas where vaccines were introduced[29].

In China, at the same time when lifestyles began changing and the country's economy boomed, hepatitis A vaccines were introduced. A safe and immunogenic live attenuated HAV vaccine based on the H2 strain has been developed and licensed by the Chinese State Drug Administration. The vaccine meets the requirements of China and WHO for the manufacture of biological substances and is now widely applied in the immunization program to prevent HAV epidemics in China and other countries, such as India[38]. Recent Indian studies with this vaccine have confirmed its high immunogenicity and excellent safety profile[39,40].

Recommendations for the use of the hepatitis A vaccine vary considerably among countries. Guidance from WHO on hepatitis A vaccines emphasizes the need to consider the cost-benefit and sustainability of various prevention strategies in the context of the epidemiological characteristics of the setting where vaccination is being considered. In more developed countries, hepatitis A vaccine is primarily being used to protect persons at increased risk, such as travelers to areas where hepatitis A is endemic, men who have sex with men, or persons with chronic liver disease. Hepatitis A vaccination currently has few indications in the areas of the world where the infection is highly endemic and where most of the population is already immune. In areas of intermediate or high endemicity that are transitioning to a lower level of transmission, shifts in the age-specific patterns of the disease result in an increasing proportion of susceptible adolescents and adults, often in urban areas or higher socioeconomic classes, among whom outbreaks may occur[3,32-40,41].

In these settings, HAV vaccination may be considered on the basis on epidemiological and cost-effectiveness studies.

CONCLUSION

Hepatitis A virus is still a major cause of infection and disease in the world and heterogeneous pockets of susceptible and exposed individuals may co-exist in rapidly developing societies. Thereafter, small localized or large outbreaks of HAV infection will remain a threat in such areas. The situation demands that conclusive guidelines be produced for HAV vaccination in these communities after characterizing them appropriately. WHO is in the process of revising its position paper on hepatitis A, issued in 2000, with a view to: update and evaluate the data

on disease burden, epidemiology, vaccine products and availability and immunization protection; review the use of the vaccine in outbreaks and for contacts of cases; and issue guidance to countries where the prevalence rates are declining from high levels. In determining national policies, the results of appropriate epidemiological and cost-benefit studies need to be carefully considered and the public health impact weighed[18,32].

REFERENCES

1 **Krugman S**. The Gordon Wilson Lecture. The ABC's of viral hepatitis. *Trans Am Clin Climatol Assoc* 1992; **103**: 145-156
2 **Koff RS**. Hepatitis A. *Lancet* 1998; **351**: 1643-1649
3 **Wasley A**, Fiore A, Bell BP. Hepatitis A in the era of vaccination. *Epidemiol Rev* 2006; **28**: 101-111
4 **Shapiro CN**, Margolis HS. Worldwide epidemiology of hepatitis A virus infection. *J Hepatol* 1993; **18** Suppl 2: S11-S14
5 **Keeffe EB**. Hepatitis A and B superimposed on chronic liver disease: vaccine-preventable diseases. *Trans Am Clin Climatol Assoc* 2006; **117**: 227-237; discussion 237-238
6 **WHO.** The Global Prevalence of Hepatitis A Virus Infection and Susceptibility: A Systematic Review. Available from: URL: whqlibdoc.who.int/hq/2010/WHO_IVB_10.01_eng.pdf
7 **Jacobsen KH**, Wiersma ST. Hepatitis A virus seroprevalence by age and world region, 1990 and 2005. *Vaccine* 2010; **28**: 6653-6657
8 **Halliday ML**, Kang LY, Zhou TK, Hu MD, Pan QC, Fu TY, Huang YS, Hu SL. An epidemic of hepatitis A attributable to the ingestion of raw clams in Shanghai, China. *J Infect Dis* 1991; **164**: 852-859
9 **Broman M**, Jokinen S, Kuusi M, Lappalainen M, Roivainen M, Liitsola K, Davidkin I. Epidemiology of hepatitis A in Finland in 1990-2007. *J Med Virol* 2010; **82**: 934-941
10 **Franco E**, Giambi C, Ialacci R, Coppola RC, Zanetti AR. Risk groups for hepatitis A virus infection. *Vaccine* 2003; **21**: 2224-2233
11 **Tufenkeji H**. Hepatitis A shifting epidemiology in the Middle East and Africa. *Vaccine* 2000; **18** Suppl 1: S65-S67
12 **Johnston L**. Hepatitis A and B-A brief overview. *SA Pharmaceutical Journal* 2010; **77**: 40-45
13 **Al-Aziz AM**, Awad MA. Seroprevalence of hepatitis A virus antibodies among a sample of Egyptian children. *East Mediterr Health J* 2008; **14**: 1028-1035
14 **Letaief A**, Kaabia N, Gaha R, Bousaadia A, Lazrag F, Trabelsi H, Ghannem H, Jemni L. Age-specific seroprevalence of hepatitis a among school children in central Tunisia. *Am J Trop Med Hyg* 2005; **73**: 40-43
15 **Rezig D**, Ouneissa R, Mhiri L, Mejri S, Haddad-Boubaker S, Ben Alaya N, Triki H. [Seroprevalences of hepatitis A and E infections in Tunisia]. *Pathol Biol (Paris)* 2008; **56**: 148-153
16 **Alkhalidi J**, Alenezi B, Al-Mufti S, Hussain E, Askar H, Kemmer N, Neff GW. Seroepidemiology of hepatitis A virus in Kuwait. *World J Gastroenterol* 2009; **15**: 102-105
17 **Chen JY**, Chiang JC, Lu SN, Hung SF, Kao JT, Yen YH, Wang JH. Changing prevalence of anti-hepatitis A virus in adolescents in a rural township in Taiwan. *Chang Gung Med J* 2010; **33**: 321-326
18 **Kim YJ**, Lee HS. Increasing incidence of hepatitis A in Korean adults. *Intervirology* 2010; **53**: 10-14
19 **Moon HW**, Cho JH, Hur M, Yun YM, Choe WH, Kwon SY, Lee CH. Laboratory characteristics of recent hepatitis A in Korea: ongoing epidemiological shift. *World J Gastroenterol* 2010; **16**: 1115-1118
20 **Barzaga BN**. Hepatitis A shifting epidemiology in South-East Asia and China. *Vaccine* 2000; **18** Suppl 1: S61-S64
21 **Cao J**, Wang Y, Song H, Meng Q, Sheng L, Bian T, Mahemuti W, Yierhali A, Omata M, Bi S. Hepatitis A outbreaks in China during 2006: application of molecular epidemiology. *Hepatol Int* 2009; **3**: 356-363
22 **Xu ZY**, Wang XY, Liu CQ, Li YT, Zhuang FC. Decline in the risk of hepatitis A virus infection in China, a country with booming economy and changing lifestyles. *J Viral Hepat* 2008; **15** Suppl 2: 33-37
23 **Mathur P**, Arora NK. Epidemiological transition of hepatitis A in India: issues for vaccination in developing countries. *Indian J Med Res* 2008; **128**: 699-704
24 **Chadha MS**, Lole KS, Bora MH, Arankalle VA. Outbreaks of hepatitis A among children in western India. *Trans R Soc Trop Med Hyg* 2009; **103**: 911-916
25 **Tanaka J**. Hepatitis A shifting epidemiology in Latin America. *Vaccine* 2000; **18** Suppl 1: S57-S60
26 **Tapia-Conyer R**, Santos JI, Cavalcanti AM, Urdaneta E, Rivera L, Manterola A, Potin M, Ruttiman R, Tanaka Kido J. Hepatitis A in Latin America: a changing epidemiologic pattern. *Am J Trop Med Hyg* 1999; **61**: 825-829
27 **Gentile A**. The need for an evidence-based decision-making process with regard to control of hepatitis A. *J Viral Hepat* 2008; **15** Suppl 2: 16-21
28 **Zahdi MR**, Maluf I, Maluf EM. Hepatitis A: the costs and benefits of the disease prevention by vaccine, Paraná, Brazil. *Braz J Infect Dis* 2009; **13**: 257-261
29 **Vacchino MN**. Incidence of Hepatitis A in Argentina after vaccination. *J Viral Hepat* 2008; **15** Suppl 2: 47-50
30 **Vitral CL**, Souto FJ, Gaspar AM. Changing epidemiology of hepatitis A in Brazil: reassessing immunization policy. *J Viral Hepat* 2008; **15** Suppl 2: 22-25
31 **Valenzuela MT**. [Vaccines against hepatitis A and B in Chile]. *Rev Med Chil* 2009; **137**: 844-851
32 **WHO**. Hepatitis A, 2008. Available from: http: //www.who.int/mediacentre/factsheets/fs328/en/
33 **Orli T**, Arguedas MR. Hepatitis A Vaccination. *Current Hepatitis Reports* 2006; **5**: 45-48
34 **Center for Disease Control and Prevention**. Prevention of Hepatitis A Through Active or Passive Immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Available from: http: //www.cdc.gov/mmwr/preview/mmwrhtml/rr4812a1.htm
35 **FitzSimons D**, Hendrickx G, Vorsters A, Van Damme P. Hepatitis A and E: update on prevention and epidemiology. *Vaccine* 2010; **28**: 583-588
36 **López EL**, Contrini MM, Mistchenko A, Debbag R. Long-term immunity after two doses of inactivated hepatitis A vaccine, in Argentinean children. *Pediatr Infect Dis J* 2010; **29**: 568-570
37 **Abarca K**, Ibánez I, Perret C, Vial P, Zinsou JA. **Immuno**genicity, safety, and interchangeability of two inactivated hepatitis A vaccines in Chilean children. *Int J Infect Dis* 2008; **12**: 270-277
38 **Zhuang FC**, Qian W, Mao ZA, Gong YP, Jiang Q, Jiang LM, Chen NL, Chai SA, Mao JS. Persistent efficacy of live attenuated hepatitis A vaccine (H2-strain) after a mass vaccination program. *Chin Med J (Engl)* 2005; **118**: 1851-1856
39 **Bhave S**, Bavdekar A, Madan Z, Jha R, Bhure S, Chaudhari J, Pandit A. Evaluation of immunogenicity and tolerability of a live attenuated hepatitis a vaccine in Indian children. *Indian Pediatr* 2006; **43**: 983-987
40 **Faridi MM**, Shah N, Ghosh TK, Sankaranarayanan VS, Arankalle V, Aggarwal A, Sathiyasekaran M, Bhattacharya N, Vasanthi T, Chatterjee S, Choudhury J, Mitra M. Immunogenicity and safety of live attenuated hepatitis A vaccine: a multicentric study. *Indian Pediatr* 2009; **46**: 29-34
41 **Mor Z**, Srur S, Dagan R, Rishpon S. Hepatitis A disease following the implementation of universal vaccination: who is at risk? *J Viral Hepat* 2010; **17**: 293-297

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