Background document

"Hepatitis A and E: update on prevention and epidemiology"

Viral Hepatitis Prevention Board Meeting
Antwerp, Belgium, 12-13 March 2009.

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Content

This pre-meeting document is a list of selected abstracts/ references from a Pubmed MEDLINE search on different search terms. The references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author's name.

1. Hepatitis A

Pubmed MEDLINE search on '**Hepatitis A**' or '**HAV**' in all fields and published **from 2008** on**,** was performed. A second search on these results was performed in Endnote with {'**Epidemiology'** or **'Outbreaks'** or '**Prevention'** or '**vaccine**' or '**control**'}. Only the references and the abstracts related to the WHO Regional office for EURO region and USA are shown. . The references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author's name.

Anastassopoulou CG, Kafatos G, Nardone A, Andrews N, Pebody RG, Mossong J, Davidkin I, Gelb D, F DEO, Thierfelder W, Nemecek V, Bruzzone B, Butur D, Barbara C, Sobotova Z, Jones L, Griskevicius A, Hesketh LM, Cohen D, Vranckx R, Tsakris A, Miller E, and Hatzakis A.
The European Sero-Epidemiology Network 2 (ESEN2): standardization of assay results for hepatitis A virus (HAV) to enable comparisons of seroprevalence data across 15 countries.
Epidemiol Infect 137: 485-494, 2009.

SUMMARYThe European Sero-Epidemiology Network 2 (ESEN2) aimed to compare serological results of vaccine-preventable diseases across Europe. To ensure direct inter-country comparability of hepatitis A virus antibody (anti-HAV) measurements, a standardization panel of 150 sera was developed by a designated reference laboratory and tested by participating national laboratories using assays of choice; each country's results were subsequently regressed against those of the reference laboratory. Quantitatively, the assays were generally highly correlated (R2>0.90). Nevertheless, qualitative comparisons indicated that results obtained with different assays may differ despite the usage of well-established international and local standards. To a great extent standardization successfully alleviated such differences. The generated standardization equations will be used to convert national serological results into common units to enable direct international comparisons of HAV seroprevalence data. The results of this study are expected to contribute to the evaluation and potential improvement of the currently employed immunization strategies for hepatitis in Europe.

Garner-Spitzer E, Kundi M, Rendi-Wagner P, Winkler B, Wiedermann G, Holzmann H, Herzog C, Kollaritsch H, and Wiedermann U.
Correlation between humoral and cellular immune responses and the expression of the hepatitis A receptor HAVcr-1 on T cells after hepatitis A re-vaccination in high and low-responder vaccinees.
Vaccine 27: 197-204, 2009.

INTRODUCTION: We recently published a study on the persistence of seroprotection 10 years after primary hepatitis A vaccination in an unselected study population of 1014 vaccinees. The majority of these vaccinees still exhibited sufficient protective antibody levels, while 2% displayed antibody concentrations below detection level. In order to investigate whether the low antibody levels were due to decline after primary vaccination or due to an intrinsic inability to sufficiently respond to hepatitis A antigen, we sought to recruit these low/no responder vaccinees to characterize their immune responses in more detail after booster vaccination in comparison to high responder vaccinees. MATERIALS AND METHODS: Prior to and one week after booster vaccination with a hepatitis A vaccine, antibody levels, cytokine levels (IL-2, IFN-gamma and IL-10) and CD surface marker expression on peripheral blood

mononuclear cells were determined in a study population comprised of 52 individuals. Additionally, the hepatitis A HAV cellular receptor 1 (HAVcr-1) TIM-1, being also expressed on CD4+ T cells and associated with immunomodulatory properties, was measured by RT-PCR before and after hepatitis A booster. RESULTS: Our data indicate that there is indeed a small group of hepatitis A vaccinees that can be classified as low/no responders as their antibody levels remain below the seroprotection level of 20mIU/ml after booster vaccination. We further describe a good correlation between antibody concentrations and cellular responses, showing that low antibody production is associated with low antigen specific cytokine levels (IL-2, IFN-gamma, IL-10) and vice versa. While there was no significant difference in the expression of the most common surface markers on T and B cells before and after booster vaccination in low and high responder vaccinees, the expression of HAVcr-1 on CD4 T cells correlated significantly with the antibody responses and cytokine levels, suggesting this receptor as cellular prediction marker of immune responsiveness to hepatitis A. CONCLUSION: Whether hepatitis A low/non-responders deserve particular attention as a risk group or might display certain resistance to hepatitis A infection due to a lack of the hepatitis A receptor needs further investigations. At this stage we suggest that persons at high exposure risk should be carefully observed.

Greengold B, Nyamathi A, Kominski G, Wiley D, Lewis MA, Hodge F, Singer M, and Spiegel B.
Cost-effectiveness analysis of behavioral interventions to improve vaccination compliance in homeless adults.
Vaccine 27: 718-725, 2009.

AIMS: To estimate the cost-effectiveness of three behavioral interventions provided to enhance hepatitis A virus (HAV) and hepatitis B virus (HBV) joint vaccination (HAV/HBV) compliance among homeless persons living in Los Angeles County. SCOPE: A cost-effectiveness analysis (CEA) based on data from a randomized trial where the costs and compliance data from the trial are incorporated into two Markov models, simulating the natural history of acute and chronic hepatitis infection, following HAV/HBV vaccination. CONCLUSIONS: Reductions in HBV-related disease is cost-effective to society and is associated with substantial improvements in quality of life.

Kyrka A, Tragiannidis A, Cassimos D, Pantelaki K, Tzoufi M, Mavrokosta M, Pedeli X, Athanassiadou F, Hatzimichael A, Konstantopoulos A, Kafetzis D, and Papaevangelou V.
Seroepidemiology of hepatitis A among Greek children indicates that the virus is still prevalent: Implications for universal vaccination.
J Med Virol 81: 582-587, 2009.

A national cross-sectional seroprevalence survey was conducted in order to evaluate the current seroepidemiology of hepatitis A among 1,383 children, aged 0-14 years, residing in Greece. Stratification of the study population was conducted according to age and area of residence. Sera from study participants were tested for the presence of anti-HAV IgG antibodies. Immigrant children, as well as children residing in rural areas, had lower immunization rates. Among unvaccinated children, the seroprevalence rate of anti-HAV was 17.1%. Nationality was shown to have a marginally significant effect since non-immunized immigrant children had a higher seroprevalence rate (22.4% vs. 15.9%, OR = 1.52, P = 0.064). Significant differences between geographic areas for both vaccination coverage and natural immunity were

observed. The study findings indicate that hepatitis A is prevalent in Greece and therefore universal infant hepatitis A immunization should be implemented. J. Med. Virol. 81:582-587, 2009 (c) 2009 Wiley-Liss, Inc.

Nyamathi A, Liu Y, Marfisee M, Shoptaw S, Gregerson P, Saab S, Leake B, Tyler D, and Gelberg L.
Effects of a nurse-managed program on hepatitis A and B vaccine completion among homeless adults.
Nurs Res 58: 13-22, 2009.

BACKGROUND: Hepatitis B virus (HBV) infection constitutes a major health problem for homeless persons. Ability to complete an HBV vaccination series is complicated by the need to prioritize competing needs, such as addiction issues, safe places to sleep, and food, over health concerns. OBJECTIVES: The objectives of this study were to evaluate the effectiveness of a nurse-case-managed intervention compared with that of two standard programs on completion of the combined hepatitis A virus (HAV) and HBV vaccine series among homeless adults and to assess sociodemographic factors and risk behaviors related to the vaccine completion. METHODS: A randomized, three-group, prospective, quasi-experimental design was conducted with 865 homeless adults residing in homeless shelters, drug rehabilitation sites, and outdoor areas in the Skid Row area of Los Angeles. The programs included (a) nurse-case-managed sessions plus targeted hepatitis education, incentives, and tracking (NCMIT); (b) standard targeted hepatitis education plus incentives and tracking (SIT); and (c) standard targeted hepatitis education and incentives only (SI). RESULTS: Sixty-eight percent of the NCMIT participants completed the three-series vaccine at 6 months, compared with 61% of SIT participants and 54% of SI participants. NCMIT participants had almost 2 times greater odds of completing vaccination than those of participants in the SI program. Completers were more likely to be older, to be female, to report fair or poor health, and not to have participated in a self-help drug treatment program. Newly homeless White adults were significantly less likely than were African Americans to complete the vaccine series. DISCUSSION: The use of vaccination programs incorporating nurse case management and tracking is critical in supporting adherence to completion of a 6-month HAV/HBV vaccine. The finding that White homeless persons were the least likely to complete the vaccine series suggests that programs tailored to address their unique cultural issues are needed.

Robesyn E, De Schrijver K, Wollants E, Top G, Verbeeck J, and Van Ranst M.
An outbreak of hepatitis A associated with the consumption of raw beef.
J Clin Virol 2009.

BACKGROUND: In July 2004, a sharp increase of hepatitis A, a notifiable disease in Belgium, was detected. OBJECTIVES: We investigated the outbreak in order to identify the source and take appropriate action. STUDY DESIGN: We conducted an outbreak investigation which included a matched case-control study to analyse the association with a range of food items and food providers. A phylogenetic analysis was used to study the relation between the outbreak cases and the identified source. RESULTS: We registered 269 cases of hepatitis A. Consumption of raw beef (OR 16.0; 95% CI 2.1-120.7) was the most probable way of infection. A food handler working at an epidemiologically linked meat distribution plant had contracted hepatitis A 1 month before the start of the outbreak. HAV strains from the food handler and the patients involved in the outbreak were monophyletically related. CONCLUSIONS: Since serological immunity in Belgium is decreasing over time, foodborne outbreaks

of hepatitis A are a substantial risk. In this outbreak, a single food handler, at the level of the distribution chain, has been identified as the most likely source, through cross-contamination of raw beef. This outbreak investigation suggests the need to consider vaccination against hepatitis A in food handlers.

Suijkerbuijk AW, Lindeboom R, van Steenbergen JE, Sonder GJ, and Doorduyn Y.
Effect of Hepatitis A vaccination programs for migrant children on the incidence of Hepatitis A in the Netherlands.
Eur J Public Health 2009.

BACKGROUND: Since 1998 Municipal Public Health Services (MPHSs) in the Netherlands carried out Hepatitis A (HAV) vaccination programs for Turkish and Moroccan children to reduce import and secondary HAV infections. The aim of this study was to assess the effects of the programs on HAV incidence. METHODS: MPHSs were questioned about HAV vaccination programs for migrant children. Notification data of HAV over the period 1995-2006 were analysed. RESULTS: Since 1998, 19 MPHSs (58%) organized vaccination programs for Turkish and Moroccan children. A large variation in the range of activities in HAV vaccination programs was observed. In the Netherlands, HAV incidence declined, from 6.5 per 100 000 inhabitants in 1995 to 1.3 in 2005. HAV incidence in children of Turkish and Moroccan decent declined from 70.3 per 100 000 in 2000 to 13.5 per 100 000 in 2005. Regions where MPHSs organized vaccination campaigns had the steepest decline in HAV incidence. CONCLUSION: The decline in HAV incidence in the Netherlands coincided with that observed for the rest of Europe. Therefore, also other causes than the enhanced vaccination programs could have contributed to this effect. At present, low priority is placed on continuing these HAV vaccination programs, as in areas without enhanced programs the incidence also declined to very low levels. Because HAV is still endemic in Morocco and Turkey, it remains important that all travellers to these countries are vaccinated against HAV, regardless of their country of origin.

Veldhuijzen IK, van Driel HF, Vos D, de Zwart O, van Doornum GJ, de Man RA, and Richardus JH.
Viral hepatitis in a multi-ethnic neighborhood in the Netherlands: results of a community-based study in a low prevalence country.
Int J Infect Dis 13: e9-e13, 2009.

OBJECTIVES: The prevalence of viral hepatitis varies worldwide. Although the prevalence of hepatitis A virus (HAV) and hepatitis B virus (HBV) infection is generally low in Western countries, pockets of higher prevalence may exist in areas with large immigrant populations. The aim of this study was to obtain further information on the prevalence of viral hepatitis in a multi-ethnic area in the Netherlands. METHODS: We conducted a community-based study in a multi-ethnic neighborhood in the city of Rotterdam, the Netherlands, including both native Dutch and migrant participants, who were tested for serological markers of hepatitis A, hepatitis B, and hepatitis C infection. RESULTS: Markers for hepatitis A infection were present in 68% of participants. The prevalence of hepatitis B core antibodies (anti-HBc), a marker for previous or current infection, was 20% (58/284). Prevalence of hepatitis A and B varied by age group and ethnicity. Two respondents (0.7%) had chronic HBV infection. The prevalence of hepatitis C was 1.1% (3/271). High levels of isolated anti-HBc were found. CONCLUSIONS: We found a high prevalence of (previous) viral hepatitis infections. This confirms previous observations in ethnic

subgroups from a national general population study and illustrates the high burden of viral hepatitis in areas with large immigrant populations.

Ajelli M, Iannelli M, Manfredi P, and degli Atti ML.
Basic mathematical models for the temporal dynamics of HAV in medium-endemicity Italian areas.
Vaccine 26: 1697-1707, 2008.

In some Southern Italy areas Hepatitis A still represents a serious public health issue. In 1996 a big epidemics in Puglia led that region to adopt a mass vaccination programme. In this paper a basic mathematical model for the temporal trends of Hepatitis A Virus (HAV) in Southern Italy is proposed and investigated. The model includes the main distinctive features of HAV in Southern Italy, i.e. multiplicity of exposure factors, and periodic forcing caused by yearly patterns of seafood consumption. The analysis illustrates the role played by the risk factors on equilibria, stability, and the period of HAV oscillations, both natural and in presence of vaccination. The model also fits well temporal trends of HAV in Southern Italy, suggesting that it is a good starting point for more structured modelling.

Al-Aziz AM, and Awad MA.
Seroprevalence of hepatitis A virus antibodies among a sample of Egyptian children.
East Mediterr Health J 14: 1028-1035, 2008.

We determined the seroprevalence of hepatitis A virus antibodies (HAV Ab) among 296 Egyptian children aged 2.5-18 years of different social classes to ascertain whether to give HAV vaccine early in life or to leave children to acquire natural immunity. Overall 61.4% were seropositive for HAV Ab. There was a significant increase in the seroprevalence of HAV Ab with higher age and lower social class; in children aged < 6 years, 72.7% of high and 19.0% of low social class were seronegative for HAV Ab. A national vaccination programme for HAV is not a priority. We recommend vaccination against hepatitis A for high social class children at the preschool period without testing for HAV. Vaccination for middle social class children can be done, but only after testing for HAV.

Amado LA, Villar LM, de Paula VS, and Gaspar AM.
Comparison between serum and saliva for the detection of hepatitis A virus RNA.
J Virol Methods 148: 74-80, 2008.

Due to the ease of collection, oral fluid is being investigated as an alternative to serum for diagnostic and epidemiological purposes. However, for prospective studies involving hepatitis A virus (HAV) RNA detection, a standard methodology must be developed. In the present study, nested RT-PCR and real-time PCR were optimized and evaluated for HAV detection and quantification, using oral fluid from healthy volunteers (n=20) and paired serum/oral fluid samples from individuals involved in a hepatitis A outbreak (n=78). Using nested RT-PCR, HAV RNA was detected in 50% of oral fluid and in 42% of serum samples from acute cases, as well as in 12% of all samples from cases without IgM and total anti-HAV. Using real-time PCR, HAV RNA was detected in 61% of oral fluid and in 71% of serum samples from acute cases, as well as in 17 and 12%, respectively, from patients without HAV markers. Mean viral loads were 1.7+/-3.24 x 10(3)copies/ml in oral fluid and 2.8+/-6.46 x 10(3)copies/ml in serum. Although nested RT-PCR and real-time PCR both detected HAV RNA in oral fluid, real-time PCR was more sensitive. Oral fluid sample testing could be used

as a noninvasive method of detecting HAV RNA during HAV outbreaks.

Anastassopoulou CG, Kafatos G, Nardone A, Andrews N, Pebody RG, Mossong J, Davidkin I, Gelb D, F DEO, Thierfelder W, Nemecek V, Bruzzone B, Butur D, Barbara C, Sobotova Z, Jones L, Griskevicius A, Hesketh LM, Cohen D, Vranckx R, Tsakris A, Miller E, and Hatzakis A.
The European Sero-Epidemiology Network 2 (ESEN2): standardization of assay results for hepatitis A virus (HAV) to enable comparisons of seroprevalence data across 15 countries.
Epidemiol Infect 1-10, 2008.

SUMMARYThe European Sero-Epidemiology Network 2 (ESEN2) aimed to compare serological results of vaccine-preventable diseases across Europe. To ensure direct inter-country comparability of hepatitis A virus antibody (anti-HAV) measurements, a standardization panel of 150 sera was developed by a designated reference laboratory and tested by participating national laboratories using assays of choice; each country's results were subsequently regressed against those of the reference laboratory. Quantitatively, the assays were generally highly correlated (R2>0.90). Nevertheless, qualitative comparisons indicated that results obtained with different assays may differ despite the usage of well-established international and local standards. To a great extent standardization successfully alleviated such differences. The generated standardization equations will be used to convert national serological results into common units to enable direct international comparisons of HAV seroprevalence data. The results of this study are expected to contribute to the evaluation and potential improvement of the currently employed immunization strategies for hepatitis in Europe.

Ansaldi F, Bruzzone B, Rota MC, Bella A, Ciofi degli Atti M, Durando P, Gasparini R, and Icardi G.
Hepatitis A incidence and hospital-based seroprevalence in Italy: a nation-wide study.
Eur J Epidemiol 23: 45-53, 2008.

To define the pattern of HAV infection in Italy and to study the differences among geographic areas (northern, central and southern Italy) and age-classes, we performed HAV antibody testing on sera collected in 1996-1997 from a large sample of the Italian population and compared the results with those of other seroprevalence studies and with incidence data for the period 1985-2005, calculated by a surveillance system specific for acute viral hepatitis based on symptomatic cases. A total of 3,561 sera, collected by hospital-based reference laboratories in 18 out of 20 Italian Regions, were tested; 1,138 (32%, 95% CI: 30.5-33.5) were positive. The age-adjusted prevalence was 60.1% and the age-specific rates were among the highest rates reported in Europe in the 1990s. The age-adjusted seroprevalence showed a significant north-south gradient, increasing from 55% in northern Italy to 68% in southern Italy. Age and area of residence were found to be strong predictors of previous HAV infection: the marked increase in prevalence with increasing age represents a strong cohort effect. In northern Italy, a marked increase with age was observed beginning with the 20- to 29-year age-class, whereas in southern Italy, such an increase was observed beginning with the 12- to 19-year age-class, indicating that northern Italy preceded southern Italy by 10-20 years in terms of improvements in hygiene and sanitation. The incidence of HAV infection shows an evident peak in 1997, when an outbreak occurred in southern Italy, mainly affecting 15- to 24-year-old individuals. In the period from 1998 to 2005, the incidence

drastically decreased (average of 3.2/100,000 inhabitants), reaching a minimum of 2/100,000 inhabitants in 2005.

Aoufi S, Pascasio JM, Sousa JM, Sayago M, Ferrer MT, Gomez-Delgado E, De la Cruz MD, Alamo JM, Gomez-Bravo MA, Bernardos A, and Marquez JL.
Prevalence of hepatitis a and B markers and vaccine indication in cirrhotic patients evaluated for liver transplantation in Spain.
Transplant Proc 40: 2946-2948, 2008.

Vaccination against hepatitis A virus (HAV) and hepatitis B virus (HBV) is generally recommended for patients with chronic liver disease and those evaluated for liver transplantation in the absence of immunity. HAV and HBV infections after liver transplantation are frequent and associated with a worse prognosis. The data suggest that the number of patients with chronic liver disease without naturally acquired immunity against HAV and HBV is substantial, and that new vaccination strategies are needed. The aim of this study was to determine the level of immunity from hepatitis A and B infections and the need for HBV and HAV vaccination among cirrhotic patients evaluated for liver transplantation. We studied HBV and HAV serological markers (HbsAg, anti-HBc, anti-HBs, IgG anti-HAV) in 451 cirrhotic patients evaluated for liver transplantation to investigate the association with gender, age, and etiology of cirrhosis. Negative HBV markers were observed in 57% of patients with 43% displaying one positive HBV marker: HBsAg (+), 9.5%; anti-HBc (+)/anti-HBs (-), 11.5%; anti-HBc (-)/anti-HBs(+), 4.2%; anti-HBc(+)/anti-HBs(+), 17.7%. HBV vaccine indication established in 68.5% of patients was greater among women and hepatitis C virus-negative patients. No differences were observed in age or cause of cirrhosis. HAV vaccination indicated in 6.7% of patients (IgG anti-HVA-negative) was greater among patients with negative HBV markers (9.3% vs 3.3%, P = .018) and younger patients (25.3% of patients </=45 years). In conclusion, there are frequent indication, for HBV vaccine among cirrhotic patients evaluated for liver transplantation, as is time for HAV vaccine, especially among patients younger than 45 years of age.

Bovier PA.
Epaxal: a virosomal vaccine to prevent hepatitis A infection.
Expert Rev Vaccines 7: 1141-1150, 2008.

REVIEW Over the last few decades, different types of inactivated hepatitis A virus (HAV) vaccines have been developed: several aluminum-adjuvanted vaccines and an aluminum-free, virosome-formulated vaccine. Both types of vaccines are whole-virus preparations that are produced by growth of HAV strains in human diploid cell cultures and are subsequently inactivated with formaldehyde. This review summarizes all published papers on a virosome-formulated vaccine, Epaxal, based on formalin inactivated HAV (strain RG-SB) adsorbed to the surface of special liposomes (virosomes), that replace aluminum hydroxide as the adjuvant principle. A single injection of virosomal HAV vaccine is well tolerated and highly immunogenic, with 88-97% of seroprotection 2 weeks after a first dose. HAV virosomal vaccine can be administered concomitantly with other vaccines, without inducing antigenic competition. Direct comparison with aluminum-adsorbed vaccine has shown that the immunogenicity was similar, but fewer local reactions were reported with Epaxal. Recent studies in children have demonstrated that Epaxal Junior is also an excellent HAV vaccine for mass vaccination programs.

Bovier PA.
Recent advances with a virosomal hepatitis A vaccine.
Expert Opin Biol Ther 8: 1177-1185, 2008.

BACKGROUND: Epaxal, a virosomal vaccine against hepatitis A virus (HAV) infection, has been in use for nearly 15 years, especially among at-risk adults. Recent studies have shown that it is also a potent vaccine for children. OBJECTIVE: To summarise recent advances of Epaxal Junior (0.25 ml, paediatric formulation). METHODS: Published papers reporting results on the virosomal HAV vaccine were abstracted and reviewed. RESULTS/CONCLUSION: In a comparative randomised trial, the paediatric dose was found to be highly immunogenic and non-inferior to the standard dose with respect to seroprotection rates. The concomitant administration of virosomal HAV vaccine with routine childhood vaccines was investigated in another trial. The virosomal HAV vaccine did not interact with the antibody response of routine childhood vaccines which in turn did not reduce the antibody response to HAV. In countries that recommend immunisation against hepatitis A, this virosomal vaccine is an excellent candidate with few side effects at the site of injection.

Cao J, Meng S, Li C, Ji Y, Meng Q, Zhang Q, Liu F, Li J, Bi S, Li D, and Liang M.
Efficient neutralizing activity of cocktailed recombinant human antibodies against hepatitis A virus infection in vitro and in vivo.
J Med Virol 80: 1171-1180, 2008.

Hepatitis A virus (HAV) is the major pathogen responsible for acute infectious hepatitis A, a disease that is prevalent worldwide. Although HAV immunization effectively prevents infection, primary immunizations must be administered at least 2 weeks prior to HAV exposure. In contrast, passive immunization with pooled human immunoglobulin (Ig) can provide immediate and rapid protection from HAV infection. Because the use of human sera-derived Igs carries the risk of contamination, we sought to develop recombinant HAV-neutralizing human antibodies. We prepared a combinatorial phage display library of recombinant human anti-HAV antibodies from RNA extracted from the blood lymphocytes of a convalescent hepatitis A patient. Two recombinant human IgG antibodies, HAIgG16 and HAIgG78, were screened from the antibody library by their ability to bind with high affinity to purified, inactivated HAV virions. These antibodies recognized different epitopes of the HAV virion capsid, and competed with both patient sera and well-characterized neutralizing mouse monoclonal antibodies. A cocktailed mixture of HAIgG16 and HAIgG78 at a 3:1 ratio was prepared to compare its combined biological activity with that conferred by each antibody individually. The cocktailed antibodies displayed a stronger neutralizing activity in vitro than that observed with either HAIgG16 and HAIgG78 alone. To determine the in vivo neutralizing abilities of these antibodies, rhesus monkeys were inoculated with cocktailed antibodies and challenged with HAV. Whereas control animals developed hepatitis A and seroconverted to the HAV antibody, animals receiving cocktailed antibodies were protected either from viral infection or from developing clinical hepatitis. These results demonstrate that recombinant human antibody preparations could be used to prevent or treat early-stage HAV infection.

Cardell K, Akerlind B, Sallberg M, and Fryden A.
Excellent response rate to a double dose of the combined hepatitis A and B vaccine in previous nonresponders to hepatitis B vaccine.
J Infect Dis 198: 299-304, 2008.

BACKGROUND: Hepatitis B vaccine has been shown to be highly efficient in

preventing hepatitis B. However, 5%-10% of individuals fail to develop protective levels (>or=10 mIU/mL) of antibodies to hepatitis B surface antigen (anti-HBs) and are considered to be nonresponders. METHODS: A total of 48 nonresponders and 20 subjects naive to the HBV vaccine received a double dose of combined hepatitis A and B vaccine (Twinrix) at 0, 1, and 6 months. The levels of anti-HBs and antibodies to hepatitis A virus (anti-HAV) were determined before vaccination and 1 month after each dose. RESULTS: Among 44 nonresponders, protective anti-HBs levels were found in 26 (59%) after the first dose and in 42 (95%) after the third dose. Among the control subjects, the corresponding figures were 10% and 100%, respectively. All subjects seroconverted to anti-HAV. The titers of both anti-HBs and anti-HAV were lower in the previously nonresponsive subjects (P< .01). CONCLUSION: Revaccination of nonresponders to the standard hepatitis B vaccine regimen with a double dose of the combined hepatitis A and B vaccine was highly effective. This is most likely explained by the increased dose, a positive bystander effect conferred by the hepatitis A vaccine, or both.

Ceyhan M, Yildirim I, Kurt N, Uysal G, Dikici B, Ecevit C, Aydogan A, Koc A, Yasa O, Koseoglu M, Onal K, Hacimustafaoglu M, and Celebi S.
Differences in hepatitis A seroprevalence among geographical regions in Turkey: a need for regional vaccination recommendations.
J Viral Hepat 15 Suppl 2: 69-72, 2008.

Hepatitis A is a worldwide vaccine-preventable infection. Recommendation of vaccination depends on the endemicity of the disease. The World Health Organization recommends universal hepatitis A vaccination in intermediate areas; however, there is no need of mass vaccination in high and low endemicity regions. Therefore, most of the countries are using a vaccination policy according to the endemicity characteristic representing the whole of the country. The endemicity of this infection varies due to sanitary and hygiene conditions and socioeconomic differences among the countries and in various regions of the same country. A sample of 1173 persons between the age of 0 and 91 years from nine randomly selected medical centres from five different geographical centres of Turkey were tested for the level of anti-hepatitis A virus (anti-HAV) immunoglobulin-G antibodies using an enzyme-linked immunosorbent assay. The overall prevalence of anti-HAV antibodies was 64.4% (1142/1173). While the rate of sero-positivity was over 80% in the 5-9 age group and more than 90% after 14 years of age in south-eastern and eastern regions, it was lower than 50% at the age of 5-9 years in central and western regions and remains under 80% in those areas. We conclude that the differences observed in HAV sero-positivity among various geographical regions in Turkey support a universal HAV immunization policy for children currently living in regions of intermediate endemicity.

Chatzimichael A, Schoina M, Arvanitidou V, Ramatani A, and Mantadakis E.
Hematologic complications of hepatitis A: another reason for implementation of anti-HAV vaccination.
J Pediatr Hematol Oncol 30: 562, 2008.

Dalton HR, Stableforth W, Hazeldine S, Thurairajah P, Ramnarace R, Warshow U, Ijaz S, Ellis V, and Bendall R.
Autochthonous hepatitis E in Southwest England: a comparison with hepatitis A.
Eur J Clin Microbiol Infect Dis 27: 579-585, 2008.

The incidence of hepatitis A is falling. In contrast, autochthonous hepatitis E is an emerging infection in developed countries. The objective of this study was to compare both laboratory-confirmed cases of hepatitis A and autochthonous hepatitis E over a 2-year period in Cornwall and Devon and anti-hepatitis A virus (HAV) IgG and anti-hepatitis E virus (HEV) IgG seroprevalence in blood donors. The databases of microbiology laboratories in Cornwall and Devon were searched for the number of diagnostic HEV and HAV assays performed during 2005-2006 and the number of confirmed cases of acute hepatitis A and hepatitis E detected. Patients were followed up until recovery or death. Sera from 500 blood donors from the regional centre were tested for HEV and HAV IgG. In total, 28 cases of autochthonous hepatitis E were identified from 838 assays, and 20 cases of hepatitis A were identified from 4503 assays. Compared to hepatitis A cases, patients with hepatitis E were older (mean age 61 vs. 45 years, P = 0.003), less likely to present in winter (P = 0.028) and had more complications (five vs. one). The IgG seroprevalence rates in blood donors were 45% for HAV and 16% for HEV. There was no relationship between HAV and HEV IgG seropositivity. Autochthonous hepatitis E may be more common than hepatitis A, affects older patients, is less likely to occur in winter and may be associated with more complications. Patients with acute hepatitis, whatever their age or travel history, should be tested for HEV.

Diaz-Mitoma F, Law B, Subramanya A, and Hoet B.
Long-term antibody persistence induced by a combined hepatitis A and B vaccine in children and adolescents.
Vaccine 26: 1759-1763, 2008.

Two cohorts, comprising of subjects aged 1-6 years and 6-15 years were vaccinated with Twinrix according to a 0-, 1- and 6-month schedule. The 1-6 years cohort was followed up for 7.5 years and the 6-15 years cohort for 10 years. At the latest follow-up time point, all subjects were seropositive for anti-HAV antibodies, while 86.5% (32/37) and 95.5% (21/22) had anti-HBs >or= 10 mIU/ml in the 1-6 years and in the 6-15 years cohort. The geometric mean concentrations (GMCs; mIU/ml) were 233 and 680 for anti-HAV antibodies, and 147 and 165 for anti-HBs antibodies, in the 1-6 years and 6-15 years cohorts, respectively. The high persistence of circulating anti-HAV and anti-HBs antibodies in children and adolescents demonstrates the long-term protection offered by Twinrix in these age groups.

Diez-Redondo MP, Almaraz A, Jimenez Rodriguez-Vila M, Santamaria A, de Castro J, Torrego JC, and Caro-Paton A.
[Immunity against hepatitis A virus in patients with chronic hepatitis C].
Med Clin (Barc) 131: 526-529, 2008.

BACKGROUND AND OBJECTIVE: Because of high fatality rate associated with acute infection by hepatitis A virus (HAV) in chronic hepatitis C patients, it is of interest to know the prevalence of immunization against HAV in these patients. PATIENTS AND METHOD: Immunoglobulin G (IgG) IgG HAV antibodies (IgG anti-HAV) were determined in 313 hepatitis C virus antibodies (anti-HCV) positive patients and in 313 anti-HCV negative subjects (control group). Several epidemiological factors were recorded (age, sex, rural vs urban precedence, tattoos, parenteral drugs use, alcohol consumption and surgery). RESULTS: The prevalence of IgG anti-HAV was identical in both groups: 81.2%. However, in those younger than 41 years, this prevalence was greater in those anti-HCV positive than in the control group. Parenteral drugs use and tattoos were more frequent in the first group. The

presence of IgG anti-HAV was associated with age and the rural origin in both groups. CONCLUSIONS: The prevalence of IgG anti-HAV increases with age, and is more frequent in individuals with rural origin. It was also greater in young anti-HCV positive patients, when compared with controls of the same age. This finding can be due to the poor standards of hygiene probably associated with some practices more common in this population, such as parenteral drugs use, tattoos and others.

Divizia M, Cencioni B, Palombi L, and Pana A.
Sewage workers: risk of acquiring enteric virus infections including hepatitis A.
New Microbiol 31: 337-341, 2008.

To determine if sewage workers have an increased risk of acquiring viral infections, 66 workers at a small wastewater plant in north-eastern Italy and 72 control subjects recruited from blood donors were enrolled in a seroprevalence study to determine whether sewage workers are at increased risk of acquiring viral infections. In order to evaluate various risk factors, a questionnaire was filled out by each worker whereas seropositivity to Hepatitis A virus, Coxsackievirus B2 - B3 - B4 - B5, and Echovirus types 1 and 9 was determined in the laboratory. Anti-HAV antibodies were present in 37.8% of sewage workers and 36.1% of subjects in the control group. The difference was not statistically significant in the two groups, whereas a significant association was observed regarding age ($P < 0.3$). No association was observed with the occupational age, or with number and duration of contacts per day. The lack of evident occupational risk for hepatitis A among sewage workers may be explained by the adult age of the workers (mean age 41.3 years, range 22-58 years), and thus the antibody titre against different enteroviruses was determined. No statistically significant differences were evident with the raw values, but considering the 90 degrees percentile as a dichotomic value for the antibody levels a strong and significant association was present with Coxsackievirus B3 (O.R. 22.85, C.I. 95% 2.93-178.08) and Coxsackievirus B2 (O.R. 14.25, C.I. 95% 1.78-113.87). Analysis of the data confirms a limited risk of acquiring infection and/or disease but also the evident possibility of silent exposure to the viruses. The shift in HAV epidemiology and increased morbidity and mortality in adult age suggest that active immunization against hepatitis A should be considered.

El-Karaksy H, El-Sayed R, El-Raziky M, El-Koofy N, and Mansour S.
Cost-effectiveness of prescreening versus empirical vaccination for hepatitis A in Egyptian children with chronic liver disease.
East Mediterr Health J 14: 804-809, 2008.

The aim of the study was to determine the prevalence of anti-hepatitis A virus (anti-HAV) antibodies among 172 children with chronic liver disease, and to calculate the cost-effectiveness of prescreening prior to hepatitis A vaccination. Anti-HAV antibodies were positive in 85.1%. However, seroprevalence of anti-HAV antibodies was 62.1% in children < 5 years and 94.4% in children 5+ years. We conclude that while it is cost-effective to do prescreening before hepatitis A vaccination for children with chronic liver disease aged 5+ years, prescreening might not be cost-effective in those aged < 5 years.

Fabianova K, Castkova J, Benes C, Kyncl J, and Kriz B.
Increase in hepatitis A cases in the Czech Republic in 2008--preliminary report.
Euro Surveill 13: 2008.

The public health protection authorities in the Czech Republic report a rise in cases of viral hepatitis A (HAV) since the end of May 2008. In total, as many as 602 HAV cases have been reported in 2008 until the end of calendar week 39 (28 September).

Ferreira CT, Vieira SM, Kieling CO, and Silveira TR.
Hepatitis A acute liver failure: follow-up of paediatric patients in southern Brazil.
J Viral Hepat 15 Suppl 2: 66-68, 2008.

We retrospectively analysed 33 children and adolescents who had been hospitalized in a liver transplant unit within the previous 10 years for acute liver failure (ALF). The patients' age varied between 2 months and 15 years of age (median 6.2 +/- 5.3), and 21 (63%) were male. Thirteen patients (39%) were immunoglobulin-M anti-hepatitis A virus (HAV) sero-positive. Eleven cases (33%) had an undetermined aetiology. The 13 children with HAV ALF were between 17 months and 15.6 years of age (median 5.8 +/- 4.6) and eight were male (61.5%). All were on a list for urgent liver transplant. Of these, five (38%) died while waiting for a liver. Only one patient recovered spontaneously. Seven patients received a liver transplant; three died in the immediate postoperative period and one died 45 days after transplant. Three children are alive 1, 2 and 5 years after transplant. We conclude that HAV was the most frequent cause of ALF, which had high mortality even when a liver transplant was possible. The results support universal HAV vaccination in this area.

Gilca V, Sauvageau C, McNeil S, Gemmill IM, Dionne M, Dobson S, Ouakki M, Lavoie F, and Duval B.
Setting priorities for new vaccination programs by using public health officers and immunization managers opinions.
Vaccine 26: 4204-4209, 2008.

The objective of this work was to assess the opinions of public health professionals (PHPs) about routinely recommended and new vaccines, and to evaluate the feasibility of using a modified Basic Priority Rating System (BPRS) approach to prioritize new immunization programs. One hundred and thirty six PHPs were invited to participate in the survey and 101 responded. Ninty-eight percent of respondents agreed that "recommended vaccines are very useful" (mean score=9.5 out of 10). Between 47% and 100% of respondents agreed with statements about usefulness, safety, effectiveness and acceptability of seven new vaccines (mean scores 5.7-9.7). The highest BPRS scores were observed for MMRV (7.3), DTaP-IPV-HBV-Hib (7.0), and conjugate ACYW-135 (5.4), followed by HPV (4.8), HAV (4.4), rotavirus (1.6) and zoster vaccine (1.5%). The results demonstrate that PHPs perceive presently recommended vaccines as very useful tools in infection prevention. On the other hand, the perceived usefulness, safety, effectiveness, and acceptability of new vaccines are heterogeneous. This heterogeneity is indicative of the complexity of decision-making around implementation of new immunization programs and the need for tools facilitating program prioritization. The modified BPRS approach using survey responses to five statements on program usefulness, vaccine safety, effectiveness, and acceptance by vaccinators and the population is a simple, feasible and inexpensive method of prioritizing new immunization programs. The method we propose is flexible in choosing target groups and allows a large number of professionals to be involved in the decision-making process about new immunization programs.

Gyarmathy VA, Ujhelyi E, and Neaigus A.

HIV and selected blood-borne and sexually transmitted infections in a predominantly Roma (Gypsy) neighbourhood in Budapest, Hungary: a rapid assessment.
Cent Eur J Public Health 16: 124-127, 2008.

We assessed the prevalence of HIV and selected blood-borne and sexually transmitted infections among a convenience sample of 64 residents of Dzsumbuj, a predominantly Roma (Gypsy) neighbourhood in Budapest, Hungary. No cases of HIV were detected, while the prevalence of hepatitis B infection (anti-HBc) was 27% and syphilis prevalence was 2%. Romas (n = 50) were significantly more likely than non-Romas (n = 14) to have HAV antibodies (80% vs. 43%) and less likely to be HBV immunized (anti-HBs only; 6% vs. 29%). Current drug injectors (n = 13) were more likely than non-injectors (n = 51) to have antibodies against HAV (85% vs. 69%) and HCV (85% vs. 8%). While HIV has not been introduced in this population, risk conditions for a potentially explosive HIV epidemic are present. Health care policies should focus on expanding coverage for HAV and HBV immunizations, and access to HIV preventive services needs to be extended to marginalized, mostly minority populations, such as the Roma in Europe.

Hammitt LL, Bulkow L, Hennessy TW, Zanis C, Snowball M, Williams JL, Bell BP, and McMahon BJ.
Persistence of antibody to hepatitis A virus 10 years after vaccination among children and adults.
J Infect Dis 198: 1776-1782, 2008.

BACKGROUND: Hepatitis A vaccination is effective in preventing disease. However, the duration of protection after vaccination is unknown. METHODS: We enrolled persons who responded to a 3-dose primary series of hepatitis A vaccine. For adults, the first dose was 720 ELISA units (EU) of hepatitis A vaccine, readministered at 1 and 12 months after the first vaccination (hereafter, "0-1-12 months"); for children aged 3-6 years, the first dose was 360 EU, readministered according to 1 of 3 vaccination schedules: 1 and 2 months after the first vaccination ("0-1-2 months"), 1 and 6 months after the first vaccination ("0-1-6 months"), or 1 and 12 months after vaccination ("0-1-12 months"). Specimens collected 1 month and 1-10 years after vaccination were tested for antibody to hepatitis A virus (anti-HAV) by ELISA. Long-term antibody persistence was estimated by using the observed rate of decline in geometric mean concentration (GMC). RESULTS: A total of 144 children and 128 adults were enrolled. Children vaccinated at 0-1-2 months had a significantly lower GMC of antibody than children vaccinated at 0-1-12 months, but this difference was statistically significant only through 4 years of follow-up. All 67 children tested at 10 years and 25 (96%) of 26 adults tested at 8-9 years had detectable anti-HAV. The estimated duration of antibody persistence was 21-27 years, depending on the vaccination schedule. CONCLUSIONS: Anti-HAV persists in adults and children for more than 10 years after the primary vaccination series. Additional studies are needed to evaluate the duration of antibody persistence beyond 10 years and to assess the long-term immunogenicity of the currently recommended 2-dose schedule.

Hendrickx G, Van Herck K, Vorsters A, Wiersma S, Shapiro C, Andrus JK, Ropero AM, Shouval D, Ward W, and Van Damme P.
Has the time come to control hepatitis A globally? Matching prevention to the changing epidemiology.
J Viral Hepat 15 Suppl 2: 1-15, 2008.

For the first time a global meeting on hepatitis A virus (HAV) infection as vaccine preventable disease was organized at the end of 2007. More than 200 experts from 46 countries gathered to investigate the changing global HAV epidemiology reflecting the increasing numbers of persons at risk for severe clinical disease and mortality from HAV infection. The benefits of childhood and adult hepatitis A (HepA) vaccination strategies and the data needed by individual countries and international health organizations to assess current HepA prevention strategies were discussed. New approaches in preventing HAV infection including universal HepA vaccination were considered. This introductory paper summarizes the major findings of the meeting and describes the changing epidemiology of HAV infections and the impact of HepA vaccination strategies in various countries. Implementation of HepA vaccination strategies should take into account the level of endemicity, the level of the socio-economic development and sanitation, and the risk of outbreaks. A stepwise strategy for introduction of HepA universal immunisation of children was recommended. This strategy should be based on accurate surveillance of cases and qualitative documentation of outbreaks and their control, secure political support on the basis of high-quality results, and comprehensive cost-effectiveness studies. The recognition of the need for increased global attention towards HepA prevention is an important outcome of this meeting.

Jablonowska E, Kuydowicz J, and Malolepsza E.
[Efficacy of vaccination against hepatitis A in HIV infected adults from Lodz region--preliminary report].
Przegl Epidemiol 62: 605-612, 2008.

OBJECTIVE: To estimate the prevalence of anti-HAV-T in the group of HIV-positive adults and to assess the efficacy of vaccination against viral hepatitis A. MATERIAL AND METHODS: In HIV-infected outpatients anti-HAV-T was determined (electrochemiluminescence method). Patients susceptible to HAV infection were qualified for vaccination. RESULTS: In the group of 175 HIV-infected patients, 70 persons (40%) were anti-HAV-T positive. Prevalence of anti-HAV-T was significantly higher in patients over 35 years of age. Anti-HAV-T were present in all individuals older than 50 years. So far 47 patients have completed vaccination. Good response (detectable anti-HAV-T 1 month after booster dose) was obtained in 73,0% patients. Individuals with actual CD4 count above 200 cells/ul responded better (81,2%) than persons with CD4 count 200 cells/ul or lower (20%). Nadir CD4 count above 50 cells/ul predicted better response than 50 cells/ul or below (78,8% and 25% respectively). One year after vaccination anti-HAV-T were still detectable in 21 patients (56,8%). CONCLUSIONS: 1. Most of studied HIV-positive patients (60%) were susceptible to HAV infection and should be vaccinated. 2. Good response to vaccination was obtained in 73% of patients and it was higher in persons with actual CD4 count above 200 cells/ul and nadir CD4 count above 50 cells/ul.

Jiang WP, Chen JT, Wang X, Wang YL, Liu Y, Chen WY, Xu WG, Qiu YZ, and Yin WD.
Immunogenicity and safety of three consecutive lots of a new preservative-free inactivated hepatitis A vaccine (Healive): a double-blind, randomized and controlled trial.
Vaccine 26: 2297-2301, 2008.

Immunization is considered as the most effective way for the prophylaxis of hepatitis A virus (HAV) infection. This study aimed to evaluate the immunogenicity and safety of three consecutive lots of a new preservative-free inactivated hepatitis A vaccine

(Healive) in healthy children. A double-blind, randomized and controlled clinical trial was conducted in healthy volunteers aged from 1 to 8 years. Total 400 subjects were enrolled and assigned into four groups, receiving one of the three lots of Healive or an established control vaccine. The vaccination was two-dose regimen with 6 months apart. Anti-HAV titers were determined at the 1st, 6th and 7th month. The results showed that Healive was highly immunogenic in children with 100% seroconversion rate (SR) and 3237-3814 mIU/ml geometry mean titer (GMT) 1 month after the second dose. The immunogenicity of Healive was statistically higher than that of the control vaccine with respect to GMT and SR (P=0.037 to P<0.001). Both Healive and control vaccine were well tolerated with 1-5% incidence of overall adverse reactions (P>0.298). Severe adverse reaction was not reported. Both SRs (1, 6 and 7 months) and GMTs (1 and 7 months) in subjects receiving one of the three consecutive lots of Healive had not statistical difference (P=0.114-0.710), suggesting that Healive was well consistent. The immune responses in younger children (1-3 years) and older children (4-8 years) were similar to each other (P=0.187-0.963). The present study indicated that Healive was greatly consistent between production lots, well tolerated and highly immunogenic in children, which made the preservative-free inactivated hepatitis A vaccine well suitable for inclusion in the routine programme of children vaccination.

Keystone JS, and Hershey JH.
The underestimated risk of hepatitis A and hepatitis B: benefits of an accelerated vaccination schedule.
Int J Infect Dis 12: 3-11, 2008.

REVIEW Hepatitis A virus (HAV) and hepatitis B virus (HBV) are vaccine-preventable. Current recommendations advocate vaccination of non-immune adults at risk of exposure, including travelers to HAV or HBV endemic areas, individuals with high risk of contracting a sexually transmitted infection, and some correctional facility inmates. We review the use of an accelerated schedule to administer the combination hepatitis A and hepatitis B vaccine (Twinrix). Administering three doses over three weeks and a fourth at 12 months provides rapid initial protection of most individuals for whom the standard 6-month vaccination schedule would not be suitable, including last-minute travelers and short-term correctional facility inmates. Furthermore, we consider the role of a universal vaccination strategy in preventing the spread of HAV and HBV.

Kim HS, Kim HS, Lee JY, Jang JS, Shin WG, Kim KH, Park JY, Lee JH, Kim HY, and Jang MK.
Initial thrombocytopenia as a simple, valuable predictor for clinical manifestation in acute hepatitis A.
Scand J Gastroenterol 43: 81-88, 2008.

OBJECTIVE: Although acute hepatitis A (AH-A) is usually self-limited, the clinical manifestations can vary from mild to severe liver dysfunction. However, little is known about the simple, valuable predictors for clinical manifestation in AH-A. The objective of this study was to identify the simple clinical predictors for severe liver dysfunction and its clinical course. MATERIAL AND METHODS: A total of 162 IgM anti-hepatitis A virus (HAV) positive patients were enrolled in the study. Severe AH-A was defined as a prothrombin time <40% of control activity. Various liver-unrelated and liver-related parameters at presentation were compared separately between the severe AH-A group and the non-severe group. RESULTS: Mean age (+/-SD) was 27.5 (+/-7.1) years and the proportion of males was 54% (88/162). Fourteen patients (8.7%)

experienced severe AH-A. Of the liver-unrelated parameters, leukopenia (<4000/microl), thrombocytopenia (<150,000/microl), and high serum C-reactive protein levels (>8 mg/l) at presentation were significant predictors for severe AH-A in a univariate analysis (p<0.05). On multivariate analysis, only thrombocytopenia was an independent predictor for severe AH-A (odds ratio (OR) 5.562, 95% confidence interval (CI) 1.153-26.834, p=0.033). Of the liver-related parameters, there were no independent predictors, as shown by multivariate analysis. The thrombocytopenia group (33%, 54/162) not only had a longer recovery time (28 days (range, 14-140) versus 37 days (20-128), p<0.001), but also more frequent complications (OR 4.632, 95% CI 1.886-11.372, p=0.001) than the non-thrombocytopenia group. CONCLUSIONS: Initial thrombocytopenia may be a simple, valuable predictor for severity and clinical course in AH-A.

Launay O, Grabar S, Gordien E, Desaint C, Jegou D, Abad S, Girard PM, Belarbi L, Guerin C, Dimet J, Williams V, Krivine A, Salmon D, Lortholary O, and Rey D. Immunological efficacy of a three-dose schedule of hepatitis A vaccine in HIV-infected adults: HEPAVAC study.
J Acquir Immune Defic Syndr 49: 272-275, 2008.

BACKGROUND: The immunogenicity of vaccines, including vaccine against hepatitis A virus (HAV), is impaired in patients with HIV infection, requiring revised immunization regimens. METHODS: We evaluated the immunological efficacy and safety of a 3-dose schedule of hepatitis A vaccine in HIV-infected adults. HAV-seronegative HIV-infected adults were randomized to receive either 3 doses of 1440 UI of hepatitis A vaccine (HAVRIX; GlaxoSmithKline, Marly le Roi, France) at weeks 0, 4, and 24 (46 patients) or 2 doses 24 weeks apart (49 patients). RESULTS: At week 28, seroconversion, defined as an anti-HAV antibody >or=20 mIU/mL, occurred in 82.6% and 69.4% of patients in the 3-dose and the 2-dose group, respectively (P = 0.13, intent-to-treat analysis, missing data = nonresponder), and in 88.4% and 72.3% of patients in the 3-dose and the 2-dose group, respectively (P = 0.06, observed analysis). Only 37.9% of patients experienced seroconversion after 1 vaccine dose (intent-to-treat analysis). Anti-HAV antibody geometric mean titers were 323 and 132 mIU/mL in the 3-dose group and 138 and 67 mIU/mL in the 2-dose group, respectively, 28 (P = 0.03) and 72 weeks (P = 0.05) after the first vaccine dose. There were no serious adverse events associated with the vaccine. Multivariate analysis showed no treatment group effect but indicated that absence of tobacco smoking (odds ratio = 2.92, 95% confidence interval: 1.07 to 7.97; P = 0.04) was an independent predictor of response to HAV vaccine. CONCLUSIONS: In HIV-infected adults, immunogenicity of hepatitis A vaccine is poor. Three doses of vaccine were safe and increased antibody titers.

Lee JM, Lee HH, Hwang-Bo J, Shon DH, Kim W, and Chung IS.
Expression and immunogenicity of recombinant VP1 of human hepatitis A virus.
Biotechnol Appl Biochem 2008.

We describe secretory expression and immunogenicity of the recombinant Hepatitis A virus (HAV) VP1 from stably transformed Drosophila melanogaster S2 cells. Southern blot analysis indicated that transformed S2 cells contained multiple copies of the HAV VP1 gene in the genome. Recombinant VP1 was secreted into a culture medium with a molecular weight of 42 - 49 kDa. A maximum production level of 6.24 mg/l of recombinant VP1 was obtained in a T-flask culture of Drosophila S2 cells 5 days after induction with 0.5 mM CuSO4. The recombinant HAV VP1 protein elicited the production of specific IgA in the small intestine by oral immunization and

production of specific IgG in the serum by intraperitoneal immunization. Our findings show that secretory recombinant VP1 from transformed Drosophila S2 cells can be used as an effective experimental immunogen for research in vaccine development.

Majori S, Baldo V, Tommasi I, Malizia M, Floreani A, Monteiro G, Ferrari A, Accordini A, Guzzo P, and Baldovin T.
Hepatitis A, B, and C infection in a community of sub-Saharan immigrants living in Verona (Italy).
J Travel Med 15: 323-327, 2008.

BACKGROUND: In Italy, about 5% of the population is represented by immigrants. The epidemiology of hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV) infection in Africa is very different from Europe; the present study aimed to assess the seroprevalence of viral hepatitis infections in sub-Saharan African immigrants living in Verona. METHODS: A total of 182 illegal immigrants were interviewed concerning sociodemographic characteristics and epidemiological information. Their serum was tested for anti-HAV [immunoglobulin (Ig) G and IgM], HBV (HBsAg, anti-HBs, anti-HBc, HBeAg, and anti-HBe), and HCV (anti-HCV) markers. RESULTS: The immigrants (age: 3 mo-60 y) were mostly single and males, with a higher education; only 50% of them declared having a regular job. Anti-IgG HAV+ prevalence was 99.5% (100% HAV positivity in the younger age bracket). As for HBV, 67.6% (123) of the immigrants were naturally infected and 9.3% had chronic infection; 4.4% were anti-HBs+ isolated (vaccinated). For HBV infection (any HBV marker), a significant difference was only found for increasing age ($p < 0.01$) and married people ($p < 0.001$). A statistically significant prevalence of HBsAg was found among the unemployed ($p < 0.001$) and those with a lower education ($p < 0.05$). Five cases (2.7%) resulted in HCV+ with no reported specific risk factors and with no significantly different sociodemographic features; these people tended to report a low level of education and unemployment. CONCLUSIONS: HAV and HBV positivity is higher than in the autochthonous population. While HAV positivity merely represents past infection, the high prevalence of HBsAg in immigrants and the presence of HBsAg/HBeAg in the same group may represent a risk for HBV transmission. The HCV positivity rate resulted similar to the prevalence of the Italian population.

Melero Ferrer JL, Ortuno Cortes J, Nevarez Heredia A, Yago Baenas M, and Berenguer M.
[Acute acalculous cholecystitis associated with acute hepatitis A virus infection].
Gastroenterol Hepatol 31: 433-435, 2008.

REVIEW Although acute cholecystitis in the context of acute hepatitis A virus (HAV) infection is extremely rare, previous cases have been reported. However, this manifestation of HAV infection is little known. In the present article, we briefly review previously documented cases and present a new case. We report the case of a 39-year-old woman with fever, abdominal pain and moderately elevated transaminase levels who developed jaundice and peritoneal irritation. Diagnosis of acute cholecystitis was given by abdominal ultrasound and magnetic resonance imaging. The patient underwent surgery. In the postoperative period, positive IgM antibody titers for HAV were obtained, confirming the diagnosis of HAV infection.

Michos A, Terzidis A, Kalampoki V, Pantelakis K, Spanos T, and Petridou ET.
Seroprevalence and risk factors for hepatitis A, B, and C among Roma and non-Roma children in a deprived area of Athens, Greece.
J Med Virol 80: 791-797, 2008.

The prevalence and risk factors of hepatitis A, B, and C (HAV, HBV, and HCV) markers were compared in non-Roma and Roma children who lived in a deprived suburb of Athens, Greece. The study included 216 children, 118 Roma and 98 non-Roma of 9 years median age (range 5-15 years). Among Roma children 98.3% had detectable antibodies to HAV, compared with 32.7% among non-Romas ($P < 0.0001$). Regarding HBV, 22% Roma children were identified with evidence of past infection (anti-HBc(+)), among whom five (4% of the total) were chronic carriers (HBsAg(+)), whereas no past infection was detected among the non-Romas ($P < 0.0001$). Markers of past HBV vaccination (anti-HBs(+), anti-HBc(-)) were detected in only 14% Roma but 96% non-Roma children (P-value < 0.0001). There was some indication for intrafamilial transmission of HAV and HBV in Roma school children. Unfavorable living conditions, frequent residency change, lack of child insurance and primary healthcare delivery were significantly associated with seroprevalence of HBV infection among Romas. No child in either group was found positive for HCV markers. These findings document high socioeconomic differentials with regards to preventable communicable diseases, such as HAV and HBV and underline the need for enhancing health policy action targeting pockets of minority childhood populations. Whereas, uptake of HBV vaccination is rather optimal in this general population, the high seroprevalence of HAV among Romas, also calls for implementing general vaccination for HAV, early in life.

Moisseeva AV, Marichev IL, Biloschitchkay NA, Pavlenko KI, Novik LV, Kovinko LV, Lyabis OI, Houillon G, and Rasuli AM.
Hepatitis A seroprevalence in children and adults in Kiev City, Ukraine.
J Viral Hepat 15 Suppl 2: 43-46, 2008.

Ukraine is a zone of moderate hepatitis A endemicity. The changing epidemiology of the disease because of improved hygiene has shifted the burden of Hepatitis A to older age groups where the disease is more severe. Outbreaks have also become more common as more of the population has become susceptible to hepatitis A virus (HAV). To help guide decisions regarding use of hepatitis A vaccine in Ukraine, we examined the presence of antibody to HAV (anti-HAV) in 1001 persons aged 1 to 85 years, visiting four municipal healthcare centres in the Ukrainian capital, Kiev. Overall, the anti-HAV prevalence was 31.9%. Anti-HAV seropositivity increased with age from 9.2% among children aged 1-5 years to 81.7% among persons over 50 years, but less than 50% of subjects less than 50 years were HAV seropositive. No children under 2 years were seropositive. HAV seropositivity was twice as high in children aged 5-11 years old in the low socio-economic status group (income less than 150 US$ per family member per month) than in the middle/high group (11.1% compared to 6.3%) but this disparity disappeared by adolescence. The prevalence of anti-HAV antibodies in adults was not different with respect to district of residence within the city. Considering the proportion of HAV seronegative subjects in all age groups under 50 years, routine vaccination against HAV of children aged 1-2 years old would appear to be an effective schedule for hepatitis A prophylaxis in Kiev.

Motte A, Blanc J, Minodier P, and Colson P.
Acute hepatitis A in a pregnant woman at delivery.

Int J Infect Dis 2008.

We report a case of acute hepatitis A in a 30-year-old pregnant woman with hepatitis onset occurring at time of delivery. Both neonate and her mother were isolated from other patients. The hepatitis A virus (HAV) genotype was Ia. Total anti-HAV antibodies and HAV RNA were not detected from the newborn in a serum collected the first day of life; neither clinical symptoms nor increased ALT levels were observed during the six first days of life. The mother quickly and fully recovered. Hepatitis A has been scarcely reported during pregnancy; four cases, to our knowledge, have been previously described close to delivery. HAV vertical transmission seems to be very rare. No severe outcome has been described in mothers and newborns. Nevertheless, HAV infection might represent a concern in pregnant women in industrialized countries in view of its mortality rate among susceptible adults and its potential involvement in nosocomial outbreaks.

Mukomolov SL, Parkov OV, Davidkin I, Sologub TV, Zheleznova NV, Chkhinzheriia IG, Broman M, and Dudina A.
[Molecular-epidemiologic characteristic of hepatitis A outbreak among workers of food stores network].
Zh Mikrobiol Epidemiol Immunobiol 42-45, 2008.

Investigation of hepatitis A (HA) outbreak developed in 2005 among workers of food stores networkwas performed using conventional epidemiologic diagnostics as well as methods of molecular epidemiology. In 14 of 15 ill persons, using polymerase chain reaction, HAV RNA was detected by PCR in serum obtained on 2 - 25 day of illness (mean - 9.3 days). In 10 cases it was possible to determine nucleotide sequence of VP1/VP2 region of HAV genome and perform phylogenetic analysis of obtained isolates. It was determined that all isolates belonged to subgenotype IA, had high degree of homology and grouped in one cluster. These findings demonstrate their descendance from one source of infection, which, with high degree of probability, was the cook who made salads from fresh vegetables. HAV strain, which caused this epidemic outbreak circulates in Saint Petersburg for a long time and was already detected in 2004. Importance of vaccination against HA for persons working in manufacturing and distribution of food and use of molecular epidemiologic methods of surveillance for this infection is underlined.

Ngui SL, Granerod J, Jewes LA, Crowcroft NS, and Teo CG.
Outbreaks of hepatitis A in England and Wales associated with two co-circulating hepatitis A virus strains.
J Med Virol 80: 1181-1188, 2008.

During 2002, an upsurge in frequency of hepatitis A outbreaks among injecting drug users was observed in England and Wales. As lack of risk factor information and the high mobility of the cases made linkage of outbreaks difficult, the relationship of nucleotide sequences in the VP1/2PA junction of the hepatitis A virus (HAV) genome amplified from serum of case-patients was investigated. A total of 204 HAV RNA positive sera obtained from a network of 23 laboratories were studied. Comparison of the sequences identified two principal strains: ES1 (n=95) belonging to type IB, and ES2 (n=72) to type IIIA. Of the remaining samples, 15 were type IA, 11 were type IB and 11 were type IIIA. ES1 predominated in Doncaster and other towns in Trent and northern England, and ES2 in the Midlands and southern England; the difference in geographical distribution between these two strains was significant ($P<0.0001$). In comparison to the sporadic cases, cases infected by either ES1 or ES2 tended to be

younger, injecting drug users, people in contact with injecting drug users, or those with a history of incarceration in prisons or homelessness (P<0.0001). Cases infected by ES1 tended to be younger than those by ES2 (P<0.0001). The association of the outbreaks to two geographically restricted strains implicates two principal transmission pathways associated with injecting behavior. Identifying these routes may be conducive to preventing further outbreaks.

Normann A, Badur S, Onel D, Kilic A, Sidal M, Larouze B, Massari V, Muller J, and Flehmig B.
Acute hepatitis A virus infection in Turkey.
J Med Virol 80: 785-790, 2008.

Anti-HAV IgM positive serum samples from acute phase hepatitis A patients from various areas in Turkey were tested for viral RNA by RT-PCR (reverse transcriptase polymerase chain reaction), using primer pairs from two different regions of the HAV genome. The PCR products amplified from both genomic regions underwent phylogenetic analyses. A comparison of the regions showed the same genotyping results, and the RT-PCR-2 in the 5'NCR demonstrated greater sensitivity compared to RT-PCR-1 in the VP1-P2A region. The majority of the isolates belonged to genotype IB and are related closely to each other; however, two isolates related even more strongly to the HAV HM175 strain. Two (n = 37) RT-PCR positive sera were classified under genotype IA. A surprising finding emerged for the mean levels of serum transaminases AST and ALT: higher levels were found in patients under 10 years of age compared to older patients. Anti-HAV IgM levels were determined quantitatively and, in addition, the HAV-RNA genome equivalents were ascertained by real time RT-PCR. No evidence was found for an association between viral load and the higher transaminase levels in the younger group.

Nothdurft HD.
Hepatitis A vaccines.
Expert Rev Vaccines 7: 535-545, 2008.

REVIEW The global disease burden associated with hepatitis A virus (HAV) is expected to increase in the coming years due to a shift in the epidemiological pattern of the disease. A decrease in the prevalence of natural immunity is leading to an increased number of adolescents and adults susceptible to a disease that is associated with greater morbidity, mortality and treatment costs in older-age groups. Current HAV vaccines have been shown to be safe, highly immunogenic and confer long-lasting protection against HAV disease. Vaccine-induced antibodies persist for more than 12 years in vaccinated adults and mathematical modeling predicts antibody persistence for more than 25 years in over 95% of vaccine recipients. However, the cost of HAV vaccines has been prohibitive for some countries. Recent studies in countries with transitioning HAV endemicity indicate that the cost-benefit ratio of mass vaccination against HAV would be similar to other routine childhood vaccinations.

Nystrom J, Cardell K, Bjornsdottir TB, Fryden A, Hultgren C, and Sallberg M.
Improved cell mediated immune responses after successful re-vaccination of non-responders to the hepatitis B virus surface antigen (HBsAg) vaccine using the combined hepatitis A and B vaccine.
Vaccine 26: 5967-5972, 2008.

We successfully re-vaccinated hepatitis B virus (HBV) vaccine non-responders using a double dose of the combined hepatitis A virus (HAV) and HBV vaccine. The hope was to improve priming of hepatitis B surface antigen (HBsAg)-specific cell mediated immune response (CMI) by an increased antigen dose and a theoretical adjuvant-effect from the local presence of a HAV-specific CMI. A few non-responders had a detectable HBsAg-specific CMI before re-vaccination. An in vitro detectable HBsAg-specific CMI was primed equally effective in non-responders (58%) as in first time vaccine recipients (68%). After the third dose a weak, albeit significant, association was observed between the magnitude of HBsAg-specific proliferation and anti-HBs levels. This regimen improves the priming of HBsAg-specific CMIs and antibodies.

Oltmann A, Kamper S, Staeck O, Schmidt-Chanasit J, Gunther S, Berg T, Frank C, Kruger DH, and Hofmann J.
Fatal outcome of hepatitis A virus (HAV) infection in a traveler with incomplete HAV vaccination and evidence of Rift Valley Fever virus infection.
J Clin Microbiol 46: 3850-3852, 2008.

Hepatitis A virus (HAV) infection is rarely fatal except in patients with chronic liver disease. In the case reported here, an elderly women died of HAV infection 12 years after incomplete HAV vaccination. The possible role of a concordant Rift Valley fever virus infection acquired in Kenya is discussed.

Perrella A, Vitiello L, Atripaldi L, Sbreglia C, Grattacaso S, Bellopede P, Patarino T, Morelli G, Altamura S, Racioppi L, and Perrella O.
Impaired function of CD4+/CD25+ T regulatory lymphocytes characterizes the self-limited hepatitis A virus infection.
J Gastroenterol Hepatol 23: e105-110, 2008.

BACKGROUND AND AIM: Hepatitis A virus (HAV) causes a transient illness leaving permanent protection against reinfection. Few data are available on the regulatory mechanisms involved in the CD4+ T helper activation. We aimed to investigate the frequency and function of CD3+/CD4+/CD25+ T cells with regulatory function (Tregs) during acute HAV infection. METHODS: We enrolled 35 consecutive patients and 15 healthy donors, enumerated Tregs by flow cytometry assay and evaluated, after immunomagnetical sorting with magnetic beads, their ability to inhibit the proliferation of CD4+/CD25- T lymphocytes at different ratios (1:1, 1:10, 1:20). RESULTS: All patients had the usual course of infection. Our immunological analysis showed Tregs frequency in these patients (6.5% [range, 5-8.8%]; 36 [range, 10-87] cells) did not have any statistical difference compared with healthy donors (6% [range, 5-8%]; 48 (range, 23-71) cells), while their ability to suppress CD4+/CD25- was drastically reduced at different ratios (Mann-Whitney U-test; ratio 1:1, 93% vs 72%, $z = -3.34$, $P < 0.0001$; ratio 1:10, 86% vs 51%, $z = -4.04$, $P < 0.001$; ratio 1:20, 56% vs 30%, $z = -3.43$, $P < 0.0001$). After the seroconversion, CD4+/CD25+ frequency and function in HAV-infected patients did not differ from healthy individuals. CONCLUSION: CD4+/CD25+ T cells seem to be impaired in their function during the HAV acute infection. This evidence might help to determine an optimal T helper cell immune network that is a predisposing factor for a self-limiting disease.

Pontrelli G, Boccia D, M DIR, Massari M, Giugliano F, Celentano LP, Taffon S, Genovese D, S DIP, Scalise F, Rapicetta M, Croci L, and Salmaso S.
Epidemiological and virological characterization of a large community-wide outbreak of hepatitis A in southern Italy.

Epidemiol Infect 136: 1027-1034, 2008.

A large outbreak of hepatitis A virus (HAV) infection occurred in 2004 in Campania, a region of southern Italy, with 882 cases reported between 1 January and 1 August. The local public health authorities and the Italian National Institute of Health carried out investigations in order to characterize the agent, identify the source of infection and the route of transmission, and implement appropriate control measures. A web-based reporting system enhanced the flow of information between public health authorities, providing real-time epidemic curves and frequency distributions. The same 1B HAV genotype was found in 90% of sera from a subset of patients with acute disease, suggesting a local common source. A case-control study in the municipality with the highest attack rate showed that raw seafood consumption, in particular if illegally sold in water, was strongly associated with HAV illness. Samples of seafood systematically collected from retailers were found contaminated by HAV.

Prymula R, Chlibek R, Splino M, Kaliskova E, Kohl I, Lommel P, and Schuerman L.
Safety of the 11-valent pneumococcal vaccine conjugated to non-typeable Haemophilus influenzae-derived protein D in the first 2 years of life and immunogenicity of the co-administered hexavalent diphtheria, tetanus, acellular pertussis, hepatitis B, inactivated polio virus, Haemophilus influenzae type b and control hepatitis A vaccines.
Vaccine 26: 4563-4570, 2008.

This randomized (1:1), double-blind, multicenter study, included 4,968 healthy infants to receive either the 11-valent pneumococcal protein D (PD)-conjugate study vaccine or the hepatitis A vaccine (HAV) (control) at 3, 4, 5, and 12-15 months of age. The three-dose primary course of both vaccines was co-administered with combined hexavalent DTPa-HBV-IPV/Hib vaccine. The pneumococcal PD-conjugate study vaccine did not impact the immune response of co-administered hexavalent vaccine and the control HAV vaccine induced seropositivity (antibodies >or=15 mIU/mL) in all infants. The incidence of solicited symptoms was higher with the 11-valent pneumococcal PD-conjugate study vaccine, yet similar to that induced by concomitant DTPa-HBV-IPV/Hib vaccine. Overall, the reactogenicity and safety profile of the 11-valent pneumococcal PD-conjugate vaccine when co-administered with the hexavalent DTPa-HBV-IPV/Hib vaccine, as well as the immunogenicity of the co-administered hexavalent vaccine, were consistent with previous reports for the licensed DTPa-HBV-IPV/Hib and pneumococcal conjugate vaccines.

Quaglio G, Ramadani N, Pattaro C, Cami A, Dentico P, Volpe A, Pellizzer G, Berisha A, Smacchia C, Figliomeni M, Schinaia N, Rezza G, and Putoto G.
Prevalence and risk factors for viral hepatitis in the Kosovarian population: implications for health policy.
J Med Virol 80: 833-840, 2008.

The prevalence of hepatitis infection among the Kosovarian population is largely unknown. The aim of the study was to evaluate the prevalence and risk factors of hepatitis A, B, C, and D (HAV, HBV, HCV, HDV) infection among the general population and in a group of health care workers in the Kosovo region. Overall, 1,287 participants were recruited, 460 males (36%) and 827 females (64%). Health care workers accounted for 253 individuals (20%), 301 were blood donor candidates (23%), 334 were pregnant women (26%), and 399 (31%) were subjects who had been examined in two clinics for routine laboratory testing. The prevalence of total

anti-HAV was 88.6% (95% CI: 86.69-90.25). Prevalence of anti-HAV among children up to 10 years was 40.5% (95% CI: 29.6-53.15), reaching 70% (95% CI: 62.25-77.10) in the 11-20 age group. Age, living in rural areas and unemployment were factors associated with higher risk of HAV infection. HBsAg was detected in 2.4% (95% CI: 1.57-3.38%) of the study sample, with a significant age trend (P-value:0.0110). Positivity for total anti-HBc was detected in 18.4% (95% CI = 16.27-20.59) of the subjects. Ninety-three subjects (7.2%) were positive for anti-HBs alone. An association between age, HSV-2 positivity, working nurses and HBV infection has been observed. One patient was HDV positive. The prevalence for HCV was 0.5% (95% CI: 0.22-1.12%). HAV infection seems to be high-intermediate, while HBV shows an intermediate endemicity. It is necessary to highlight the importance of an immunization strategy against HAV and HBV in reducing the incidence of the infection. The prevalence for HCV was very low.

Rezig D, Ouneissa R, Mhiri L, Mejri S, Haddad-Boubaker S, Ben Alaya N, and Triki H.
[Seroprevalences of hepatitis A and E infections in Tunisia].
Pathol Biol (Paris) 56: 148-153, 2008.

OBJECTIVE: Viral hepatitis A (HAV) and E (HEV) infections are still frequent in many regions of the world, particularly in developing countries where sanitary conditions and socioeconomic level are frequently low. In this work, we have studied seroprevalences of these two infections in Tunisian children, teenagers and young adults. MATERIAL AND METHODS: The studied population included 3357 individuals from different regions of Tunisia and distributed in three groups 1 (n=1145), 2 (n=707) and 3 (n=1505) with a mean of age of 6.94, 12.84 and 20.71 years, respectively. RESULTS: Rates of HAV infection prevalence of 84.0, 90.5 and 91.7% were found within groups 1, 2 and 3, respectively. These rates are lower than those previously found in the country; thus, primary infection with HAV in Tunisia is progressively shifting to older ages, which is probably due to the improvement of sanitary conditions. Lower anti-HAV prevalences were found in costal regions as compared to the rest of the country. This difference may be due to the higher socioeconomic level of the population living in costal regions. Antibodies against HEV were assessed in individuals of group 3. A seroprevalence of 4.3% was found which indicates that, despite the absence of epidemics, the virus is circulating among the Tunisian population as sporadic cases. CONCLUSION: The present work contributes to a better knowledge of HAV and HEV infections in Tunisia and highlights the need of the establishment of a national program for virological surveillance of hepatitis cases and of further studies to monitor changes in the epidemiology of these infections.

Rigaud M, Borkowsky W, Muresan P, Weinberg A, Larussa P, Fenton T, Read JS, Jean-Philippe P, Fergusson E, Zimmer B, Smith D, and Kraimer J.
Impaired immunity to recall antigens and neoantigens in severely immunocompromised children and adolescents during the first year of effective highly active antiretroviral therapy.
J Infect Dis 198: 1123-1130, 2008.

BACKGROUND: We studied whether severely immunocompromised, human immunodeficiency virus (HIV)-infected children who were beginning highly active antiretroviral therapy (HAART) or changing HAART regimens could spontaneously respond to a recall antigen (tetanus toxoid [TT] vaccine) or respond to a recall antigen and neoantigen (hepatitis A virus [HAV] vaccine) after 3 vaccinations.

METHODS: A total of 46 children who had CD4 cell percentages <15% and who demonstrated a >0.75-log reduction in plasma HIV RNA levels within 4 weeks of starting HAART were randomized to receive vaccinations with either TT or HAV vaccines during the first 6 months of HAART. Study subjects then received the alternate vaccine during the next 6 months of HAART. RESULTS: Despite the early decline in viremia and the later increase in the percentage of CD4 T cells, spontaneous recovery of cell-mediated immunity (CMI) was not seen for TT. Serologic responses to TT required 3 vaccinations and were comparable in both groups. Serologic responses to HAV were infrequent and of low titer, although the group that received HAV vaccine after receiving TT vaccine performed somewhat better. CMI to HAV was virtually absent. CONCLUSIONS: Severely immunocompromised children who are receiving HAART develop CMI and antibody to a recall antigen independent of the timing of vaccination, but they require a primary series of vaccinations. Antibodies to a neoantigen, HAV, developed when vaccination was delayed after initiation of HAART. CMI to a neoantigen was difficult to establish. TRIAL REGISTRATION: Clinicaltrials.gov identifier: NCT00004735/PACTG P1006 .

Rodriguez Lay Lde L, Quintana A, Villalba MC, Lemos G, Corredor MB, Moreno AG, Prieto PA, Guzman MG, and Anderson D.
Dual infection with hepatitis A and E viruses in outbreaks and in sporadic clinical cases: Cuba 1998-2003.
J Med Virol 80: 798-802, 2008.

Viral hepatitis ranks as the fifth cause of morbidity for infectious diseases in Cuba. Epidemics are observed frequently in the population, the hepatitis A virus being the main agent responsible for such epidemics. Previous reports also confirmed the circulation of the hepatitis E virus. From 1998 to 2003, 258 serum samples were collected by the Reference Laboratory on Viral Hepatitis during 33 outbreaks of acute viral hepatitis as well as from 39 sporadic clinical cases. Sera were tested for anti-HAV and anti-HEV IgM by EIA. Overall of the 33 outbreaks studied sera from 12 (36.4%) were positive for anti-HAV IgM only, from 7 (21.2%) were positive for anti-HEV IgM only, and from 14 (42.4%) were positive for antibodies to both viruses. Individually of the 258 sera collected, 137 (53.1%) were positives for anti-HAV IgM, 20 (7.8%) were positives for anti-HEV IgM, 33 (12.8%) were positives for both markers and 68 (26.4%) were negative to both. Of the clinical cases, 4 (10.3%) were positives for anti-HAV IgM, 13 (33.3%) were positives for anti-HEV IgM and 5 (12.8%) were positives for both markers. Seventeen (43.6%) sera were negatives for all viral hepatitis markers available (A-E). A high positivity for HEV was found in outbreaks tested with the kit produced by CIGB. In particular HEV seems to infect individuals of all ages. The results demonstrate the co-circulation of and co-infection with two enterically transmitted viruses; however a higher positivity was observed for anti-HAV than to anti-HEV (53.1% vs. 7.8%) in outbreaks.

Shliakhtenko L, Plotnikova V, Levakova I, Rubis L, Solovieva E, and Mukomolov S.
Modern epidemiology of hepatitis A in the north-western region of the Russian Federation.
J Viral Hepat 15 Suppl 2: 38-42, 2008.

The epidemiological features of hepatitis A virus (HAV) infection were studied in eleven territories located in the north-western region of the Russian Federation. The dynamics of HAV infection in Russia and in the region were evaluated during a 17-year period. The age-specific incidence was calculated and 229 305 patients with

acute HAV were identified. The analysed database included HA mixed with other viral hepatitis infections: it included information about 8 809 HAV patients. Special attention has been paid to the sero-epidemiological studies conducted in St Petersburg city. These studies included analysis of age-specific incidence in persons 20 years of age and older during 6 years and testing of blood sera from 1 892 healthy persons for IgG anti-HAV. In general there is a trend to reduction of HAV incidence in Russia, and in the north-western region, high indices were registered in some provinces in different years. It was established three types of age-specific incidence distribution: predominated incidence in 3-14 years of age (first type), 15-29 years of age (second type) and uniform distribution in different age groups (third type). It was shown that decrease of HAV incidence in children and young adults lead to the reduction of sero-positivity level in the groups 20+ years of age. These characteristics should be taken in account to define indications for HAV vaccine prophylaxis. HAV infection in 10-13% of cases mixed with acute or chronic hepatitis B and C in the last 15 years in St Petersburg. In the middle of 1990s, HAV mostly mixed with acute viral hepatitis of different aetiology, but in the modern time predominated type of mixture was presented by HAV and chronic HBV and HCV infections. The obtained results are useful for viral hepatitis surveillance and control.

Siagris D, Kouraklis-Symeonidis A, Konstantinidou I, Christofidou M, Starakis I, Lekkou A, Papadimitriou C, Blikas A, Zoumbos N, and Labropoulou-Karatza C.
Prevalence of anti-HAV antibodies in multitransfused patients with beta-thalassemia.
World J Gastroenterol 14: 1559-1563, 2008.

AIM: To detect the prevalence of anti-HAV IgG antibodies in adult multitransfused beta-thalassemic patients. METHODS: We studied 182 adult beta-thalassemic patients and 209 controls matched for age and sex from the same geographic area, at the same time. Anti-HAV IgG antibodies, viral markers of hepatitis B virus (HBV) and hepatitis C virus (HCV) infection were evaluated. RESULTS: Anti-HAV IgG antibodies were detected more frequently in thalassemic patients (133/182; 73.1%) than in healthy controls (38/209; 18.2%, P < 0.0005). When we retrospectively evaluated the prevalence of anti-HAV IgG antibodies in 176/182 (96.7%) thalassemic patients, whose medical history was available for the previous ten years, it was found that 83 (47.2%) of them were continuously anti-HAV IgG positive, 16 (9.1%) acquired anti-HAV IgG antibody during the previous ten years, 49 (27.8%) presented anti-HAV positivity intermittently and 28 (15.9%) were anti-HAV negative continuously. CONCLUSION: Multitransfused adult beta-thalassemic patients present higher frequency of anti-HAV IgG antibodies than normal population of the same geographic area. This difference is difficult to explain, but it can be attributed to the higher vulnerability of thalassemics to HAV infection and to passive transfer of anti-HAV antibodies by blood transfusions.

Siberry GK, Coller RJ, Henkle E, Kiefner C, Joyner M, Rogers J, Chang J, and Hutton N.
Antibody response to hepatitis A immunization among human immunodeficiency virus-infected children and adolescents.
Pediatr Infect Dis J 27: 465-468, 2008.

Seventy-one of 84 human immunodeficiency virus (HIV)-infected children [84.5% (95% confidence interval: 75-91.5%)] were hepatitis A virus (HAV) seropositive after 2 doses of HAV vaccine. Higher CD4% and HIV suppression were significantly associated with increased HAV seropositivity rate. In multivariate analysis, CD4 >or=25% and young age were independent predictors of HAV seropositivity. Of 7

children given a third HAV vaccine dose because of negative HAV antibody after 2 doses, 2 (29%) became seropositive.

Tabak F, Ozdemir F, Tabak O, Erer B, Tahan V, and Ozaras R.
Autoimmune hepatitis induced by the prolonged hepatitis A virus infection.
Ann Hepatol 7: 177-179, 2008.

Hepatitis A virus (HAV) is the most common cause of acute viral hepatitis in the world. Rarely, acute infection may persist for a long time. Autoimmune hepatitis (AIH) may provide anti-HAV IgM positivity detection for a prolonged time. On the other hand, HAV as an infectious agent may also trigger AIH. Here we presented a case which seemed like a simple acute viral hepatitis A infection at the beginning but turned out to be an AIH according to the International Autoimmune Hepatitis Group's system. A 21-year-old female was diagnosed as symptomatic acute HAV infection with anti-HAV IgM positivity and elevated aminotransferase levels. The other viral serological tests were negative. On the 6th, 12th and 18th months of the follow up, her anti-HAV IgM positivity still continued and transaminase levels were also 3 to 7 times high of the upper limit of normal. In addition, antinuclear antibody was positive. However, on the 19th month anti-HAV IgM could be detected as negative. Liver histology was prominent. The patient had a score of 16 according to the International Autoimmune Hepatitis Group's system. She was given prednisolone (10 mg/day) and azathioprine (100 mg/day). The aminotransferase levels were detected within normal ranges at the end of the first month of therapy. She was in remission during follow up for 6 years. In conclusion, prolonged HAV infection and AIH may not only trigger each other but also deteriorate the liver histology. AIH should be investigated in cases of long-lasting HAV infection in order to begin the treatment earlier. On the other hand, AIH patients should also be vaccinated for both HBV and HAV to avoid more severe diseases.

Vitral CL, Souto FJ, and Gaspar AM.
Changing epidemiology of hepatitis A in Brazil: reassessing immunization policy.
J Viral Hepat 15 Suppl 2: 22-25, 2008.

Recent studies have shown that the prevalence of antibody to hepatitis A virus (HAV) is decreasing in several Latin American countries. Brazil is a very large and heterogeneous country, showing striking regional differences. With regard to sanitary facilities, 81.7% of the districts in the south-eastern region have sewage systems, compared with only 5.8% in the northern region. Results of sero-epidemiological studies and reported hepatitis A outbreaks indicate a change in the epidemiological pattern of hepatitis A in the country. Individuals, especially those under the age of 10, are mostly unprotected from HAV infection, regardless of their socioeconomic status. During 2000-2005, approximately 14 000-21 000 cases of hepatitis A were reported annually in Brazil, a rate of 7.5-11 cases per 100 000 population. Nationwide, hepatitis A mortality rates declined progressively from 1980 to 2002. As fatal cases constitute a small, but predictable, portion of all acute hepatitis A cases, which are in turn part of the total number of HAV infections, these data suggest that there has been a decline in HAV circulation in all Brazilian regions over the last two decades. Taken together these facts point out that the epidemiological pattern of hepatitis A is changing in Brazil. Besides improvements in sanitary conditions in the poorest Brazilian regions, the introduction of hepatitis A vaccination of young children could be a strategy for controlling HAV infection in the country.

Wasley A, Grytdal S, and Gallagher K.
Surveillance for acute viral hepatitis--United States, 2006.
MMWR Surveill Summ 57: 1-24, 2008.

PROBLEM/CONDITION: In the United States, acute viral hepatitis most frequently is caused by infection with three viruses: hepatitis A virus (HAV), hepatitis B virus (HBV), and hepatitis C virus (HCV). These unrelated viruses are transmitted through different routes and have different epidemiologic profiles. Safe and effective vaccines have been available for hepatitis B since 1981 and for hepatitis A since 1995. No vaccine exists against hepatitis C. REPORTING PERIOD COVERED: Cases in 2006, the most recent year for which data are available, are compared with those from previous years. DESCRIPTION OF SYSTEM: Cases of acute viral hepatitis are reported voluntarily to CDC by state and territorial epidemiologists via CDC's National Notifiable Disease Surveillance System (NNDSS). Reports are received electronically via CDC's National Electronic Telecommunications System for Surveillance (NETSS). RESULTS: During 1995-2006, hepatitis A incidence declined 90% to the lowest rate ever recorded (1.2 cases per 100,000 population). Declines were greatest among children and in those states where routine vaccination of children was recommended beginning in 1999. An increasing proportion of cases occurred in adults. During 1990-2006, acute hepatitis B incidence declined 81% to the lowest rate ever recorded (1.6 cases per 100,000 population). Declines occurred among all age groups but were greatest among children aged <15 years. Following a peak in the late 1980s, incidence of acute hepatitis C declined through the 1990s; however, since 2003, rates have plateaued, with a slight increase in reported cases in 2006. In 2006, as in previous years, the majority of these cases occurred among adults, and injection-drug use was the most common risk factor. INTERPRETATION: The results documented in this report suggest that implementation of the 1999 recommendations for routine childhood hepatitis A vaccination in the United States has reduced rates of infection and that universal vaccination of children against hepatitis B has reduced disease incidence substantially among younger age groups. Higher rates of hepatitis B continue among adults, particularly males aged 25-44 years, reflecting the need to vaccinate adults at risk for HBV infection. The decline in hepatitis C incidence that occurred in the 1990s was attributable primarily to a decrease in incidence among injection-drug users. The reasons for this decrease were unknown but likely reflected changes in behavior and practices among injection-drug users. PUBLIC HEALTH ACTIONS: The expansion in 2006 of recommendations for routine hepatitis A vaccination to include all children in the United States aged 12-23 months is expected to reduce hepatitis A rates further. Ongoing hepatitis B vaccination programs ultimately will eliminate domestic HBV transmission, and increased vaccination of adults with risk factors will accelerate progress toward elimination. Prevention of hepatitis C relies on identifying and counseling uninfected persons at risk for hepatitis C (e.g., injection-drug users) regarding ways to protect themselves from infection and on identifying and preventing transmission of HCV in health-care settings.

Worns MA, Teufel A, Kanzler S, Shrestha A, Victor A, Otto G, Lohse AW, Galle PR, and Hohler T.
Incidence of HAV and HBV infections and vaccination rates in patients with autoimmune liver diseases.
Am J Gastroenterol 103: 138-146, 2008.

OBJECTIVES: Hepatitis A virus (HAV) or hepatitis B virus (HBV) superinfection is associated with an increased mortality in patients with chronic liver diseases (CLD). Despite official recommendations, it was reported that the vaccination rate against

HAV is low in patients with chronic hepatitis C infection. To evaluate the situation in patients with autoimmune liver diseases, we conducted a retrospective cohort study. METHODS: Susceptibility to HAV and HBV infections, course of HAV and HBV infections, vaccination rates against HAV and HBV, and efficacy of hepatitis A/B vaccines were evaluated by antibody testing in 225 patients with autoimmune liver diseases during 1,677 person-years. RESULTS: Susceptibility to HAV/HBV infection was 51/86%. Incidence of HAV/HBV infection was 1.3/1.4 per 1,000 person-years. One HAV infection occurred, but the patient recovered spontaneously. Two patients were HBV-infected after receiving an anti-HBc-positive (antibody to hepatitis B core antigen) donor graft during orthotopic liver transplantation, and one of them developed chronic HBV infection. Vaccination rates were 11% (HBV) and 13% (HAV), respectively. Seventy-six percent of the vaccinated patients (HBV vaccine) developed anti-HBs (antibody to hepatitis surface antigen) >or=10 UI/L. Ten out of 13 vaccinated patients, showing a low or nonresponse to hepatitis B vaccine, had concomitant immunosuppressive therapy. Anti-HAV was detectable in all patients after administration of HAV vaccine. CONCLUSIONS: Patients with autoimmune liver diseases have a high susceptibility to HAV and HBV infections. Vaccination rates are low in this patient cohort and efficacy of hepatitis B vaccine is reduced due to immunosuppressive therapy. Improving adherence to vaccine recommendations is essential to prevent HAV and HBV infections in patients with autoimmune liver diseases.

Xu ZY, Wang XY, Liu CQ, Li YT, and Zhuang FC.
Decline in the risk of hepatitis A virus infection in China, a country with booming economy and changing lifestyles.
J Viral Hepat 15 Suppl 2: 33-37, 2008.

The objective of the study was to identify the protective factors for the rapid decline in the risk of hepatitis A virus (HAV) infection in China between 1990 and 2006. Results of serological follow-up and data on annual hepatitis A incidence were analysed and correlated with economic growth and HAV vaccine output during the same period. In conclusion, both HAV vaccination and changing lifestyles associated with the booming economy contributed to the rapid risk decline. Changing lifestyles played a major role in the decline especially in the areas with booming economy.

Zhuang GH, Pan XJ, and Wang XL.
A cost-effectiveness analysis of universal childhood hepatitis A vaccination in China.
Vaccine 26: 4608-4616, 2008.

The socioeconomic improvement has impacted hepatitis A virus (HAV) infection with a shift from high to intermediate endemicity in many parts of China. The first China-developed inactivated hepatitis A vaccine, with significantly low price, was licensed in 2002, prompting us to evaluate whether universal childhood vaccination is advisable now in China. We considered vaccination scheduled at ages 12 and 18 months for all healthy children, and assumed that a single cohort was enrolled in 2005. A Markov model was used to predict hepatitis A outcomes and costs. Vaccination was compared with no vaccination, and the cost-effectiveness of vaccination was evaluated from the health system and the societal perspectives. The analysis was run separately in five regions (covering all the 31 provinces of Mainland China) defined by anti-HAV prevalence (around 50%, 50-69%, 70-79%, 80-89% and 90%-). The study projects that with the Chinese low-cost vaccine, vaccination could gain quality adjusted life years (QALYs) through the whole country and save health system or societal costs in the lowest, lower, intermediate and higher infection

regions. Vaccination should also be cost-effective in the highest infection region because of low additional costs per QALY gained. However, vaccination would increase the probability of death due to hepatitis A in the highest and higher infection regions by 38 and 37 per million enrolled, respectively, and as vaccine protection loss increases the risk would also occur in intermediate and lower infection regions. The trend that the lower infection level the region has, the more cost-effective vaccination would be is obvious. Sensitivity analyses prove that our conclusions are robust. Considering the potential risk of vaccination, as well as unbalanced socioeconomic developments and significant differences in HAV infection through the whole country, the study suggests that universal childhood hepatitis A vaccination should be first administrated in provinces with the lowest infection level. With knowledge accumulation and further evaluations, the zone of immunization would be considered to be expanded gradually from provinces with lower infection level to those with higher.

Hepatitis A vaccines

WHO position paper

The World Health Organization (WHO) through its department of vaccines and biologicals [1] already offers information and recommendations on the vaccines represented in the Expanded Programme on Immunization (EPI). According to its global mandate, the department is now assuming an extended normative role in this field, and is issuing a series of regularly updated position papers on other vaccines and vaccine combinations against diseases that have an international public health impact. These position papers are concerned primarily with the use of vaccines in large-scale immunization programmes; limited vaccination for individual protection, as executed mostly in the private sector, may be a valuable supplement to the national programmes, but is not emphasized in this policy document. The position papers summarize essential background information on the respective diseases and vaccines, and conclude with the current WHO position concerning their use in the global context. The papers have been reviewed by a number of experts inside and outside WHO, and are designed for use mainly by national public health officials and immunization programme managers. However, the position papers may also be of interest to international funding agencies, the vaccine manufacturing industry, the medical community and the scientific media.

Summary and conclusion

Hepatitis A is an acute, usually self-limiting disease of the liver caused by hepatitis A virus (HAV). HAV is transmitted from person to person, primarily by the faecal-oral route. The incidence of hepatitis A is closely related to socioeconomic development, and seroepidemiological studies show that prevalence of anti-HAV antibodies in the general population varies from 15% to close to 100% in different parts of the world. An estimated 1.5 million clinical cases of hepatitis A occur each year. In young children HAV infection is usually asymptomatic whereas symptomatic disease occurs more commonly among adults. Infection with HAV induces lifelong immunity. In areas of low endemicity, hepatitis A usually occurs as single cases among persons in high-risk groups or as outbreaks involving a small number of persons. In highly endemic areas, most persons are asymptomatically infected with HAV during childhood and clinical hepatitis A is uncommon. In countries of low and intermediate endemicity, adult disease is seen more often and hepatitis A may represents a substantial medical and economic burden.

Currently, 4 inactivated vaccines against HAV are internationally available. All 4 vaccines are safe and effective, with long-lasting protection. None of the vaccines are licensed for children aged < 1 year.

Public health aspects

Hepatitis A is an acute, usually self-limiting infection of the liver caused by hepatitis A virus (HAV). The virus has a worldwide distribution and causes about 1.5 million cases of clinical hepatitis each year. Humans are the only reservoir of

[1] Formerly the global programme for vaccines and immunization (GPV).

Vaccins anti-hépatite A

Note d'information de l'OMS

L'Organisation mondiale de la Santé (OMS) propose déjà, à travers son département des vaccins et produits biologiques (VAB),[1] des informations et des recommandations sur les vaccins utilisés dans le cadre du Programme élargi de vaccination (PEV). Conformément à son mandat mondial, le département assume désormais un rôle normatif élargi dans ce domaine, et publie une série de notes d'information régulièrement actualisées sur d'autres vaccins et associations vaccinales contre les maladies qui ont un impact sur la santé publique au niveau international. Ces notes d'information porteront essentiellement sur l'utilisation des vaccins dans le cadre de programmes de vaccination à grande échelle; l'utilisation limitée de la vaccination aux fins de protection individuelle, telle qu'elle se pratique essentiellement dans le secteur privé, peut compléter utilement les programmes nationaux, mais n'est pas visée par ce type de document. Les notes d'information résument les informations générales essentielles sur les maladies et vaccins respectifs et présentent en conclusion la position actuelle de l'OMS concernant leur utilisation dans le cadre mondial. Ces notes ont été soumises à un certain nombre de spécialistes, à l'OMS et à l'extérieur, et sont destinées principalement aux responsables nationaux de la santé publique et aux administrateurs de programmes de vaccination. Mais les notes d'information peuvent également présenter un intérêt pour les organismes internationaux de financement, les fabricants de vaccins, la communauté médicale et les médias scientifiques.

Résumé et conclusions

L'hépatite A est une infection aiguë du foie, qui évolue en général spontanément vers la guérison et qui est provoquée par le virus de l'hépatite A (HAV). La transmission du HAV d'une personne à l'autre est principalement féco-orale. L'incidence de l'hépatite A est en étroite relation avec le développement socio-économique et les études séro-épidémiologiques montrent que la prévalence des anticorps anti-HAV varie de 15% à près de 100% dans les différentes régions du monde. On estime à 1,5 million le nombre de cas cliniques d'hépatite A survenant chaque année. Chez le jeune enfant, l'infection à HAV reste en général asymptomatique mais elle devient couramment symptomatique chez l'adulte. Elle induit une immunité à vie. Dans les régions de faible endémicité, l'hépatite A se manifeste habituellement par des cas isolés dans des groupes à haut risque ou par des flambées impliquant un petit nombre de personnes. Dans les zones de forte endémicité, la plupart des habitants contractent l'infection dans l'enfance et elle reste asymptomatique; il est alors rare d'observer des cas cliniques d'hépatite A. La maladie se retrouve plus fréquemment chez les adultes dans les pays d'endémicité faible ou moyenne et elle peut alors représenter une charge importante du point de vue médical et économique.

On dispose actuellement au niveau international de 4 vaccins anti-HAV inactivés. Sûrs et efficaces, ils confèrent une protection de longue durée, mais aucun n'est homologué pour les enfants de < 1 an.

Considérations de santé publique

L'hépatite A est une infection aiguë du foie, qui évolue en général spontanément vers la guérison et qui est provoquée par un virus, le HAV. Présent dans le monde entier, il est responsable d'environ 1,5 million de cas cliniques d'hépatite chaque année. L'être humain

[1] Auparavant le Programme mondial des vaccins et vaccinations (GPV).

HAV. Transmission occurs primarily through the faecal-oral route, and is closely associated with poor sanitary conditions. The most common modes of transmission include close personal contact with an infected person and ingestion of contaminated food and water. The virus is shed in the faeces of persons with both asymptomatic and symptomatic infection. Under favourable conditions HAV may survive in the environment for months. Bloodborne transmission of HAV occurs, but is much less common.

The average incubation period is 28 days, but may vary from 15-50 days. Approximately 10-12 days after infection the virus can be detected in blood and faeces. In general, a person is most infectious from 14-21 days before the onset of symptoms, through 1 week after the onset of symptoms.

Antibodies against HAV develop in response to infection and seroprevalence can be used as a marker of viral transmission in a community. The lowest seroprevalence is found in the Nordic countries (about 15%). In other parts of Europe and Australia, Japan and in the United States, 40%-70% of the adult population has demonstrable antibodies to HAV. Practically all adults living in developing areas of the world have serological evidence of past infection.

The risk of developing symptomatic illness following HAV infection is directly correlated to age. In children aged < 6 years, HAV infection is usually asymptomatic, with only 10% developing jaundice. Among older children and adults, infection usually causes clinical disease, with jaundice occurring in more than 70% of cases. Therefore, highly HAV-endemic regions are characterized by asymptomatic childhood infection, with only the occasional occurrence of clinical hepatitis A.

For practical purposes, the world can be divided into areas of low, intermediate and high endemicity, although there may be regional differences in endemicity within a country. In areas of low endemicity the disease occurs mainly in adolescents and adults in high-risk groups (e.g. homosexual

The results of appropriate epidemiological and cost-benefit studies should be carefully considered before deciding on national policies concerning immunization against hepatitis A. As part of this decision process, the public health impact of hepatitis A should be weighed against the impact of other vaccine-preventable infections, including diseases caused by hepatitis B, *Haemophilus influenzae* type b, rubella and yellow fever.

In highly endemic countries, almost all persons are asymptomatically infected with HAV in childhood, which effectively prevents clinical hepatitis A in adolescents and adults. In these countries, large-scale vaccination programmes are not recommended.

In countries of intermediate endemicity where a relatively large proportion of the adult population is susceptible to HAV, and where hepatitis A represents a significant public health burden, large-scale childhood vaccination may be considered as a supplement to health education and improved sanitation.

In regions of low endemicity, vaccination against hepatitis A is indicated for individuals with increased risk of contracting the infection, such as travellers to areas of intermediate or high endemicity.

Il convient d'examiner avec attention les résultats des études épidémiologiques, ainsi que les coûts et les avantages, avant de décider d'une politique nationale en matière de vaccination contre l'hépatite A. Au cours de ce processus décisionnel, on comparera les répercussions de l'hépatite A sur la santé publique par rapport à d'autres maladies à prévention vaccinale, dont l'hépatite B, les infections à *Haemophilus influenzae* type b, la rubéole et la fièvre jaune.

Dans les pays de forte endémicité, quasiment tous les habitants contractent dès l'enfance l'infection qui reste alors asymptomatique et représente une prévention efficace de l'hépatite A clinique chez l'adolescent et l'adulte. Les programmes de vaccination à grande échelle ne sont donc pas recommandés dans ces pays.

Dans les pays d'endémicité moyenne, où une proportion relativement grande de la population adulte est sensible au HAV et où l'hépatite A représente un fardeau important pour la santé publique, la vaccination des enfants à grande échelle pourra être envisagée, en complément de l'éducation sanitaire et d'une amélioration des systèmes d'assainissement.

Dans les régions de faible endémicité, la vaccination contre l'hépatite A est indiquée pour les personnes exposées à un risque accru de contracter l'infection, par exemple celles qui se rendent dans les zones de forte ou moyenne endémicité.

est le seul réservoir. La transmission, principalement par voie fécoorale, est en étroite relation avec des conditions sanitaires médiocres. Les modalités les plus courantes de cette transmission comprennent le contact rapproché avec une personne infectée et l'ingestion d'eau ou d'aliments contaminés. Le virus est excrété dans les fèces, que l'infection soit asymptomatique ou non. Dans des conditions favorables, le HAV peut survivre dans l'environnement pendant des mois. Il arrive qu'il soit transmis par le sang, mais c'est beaucoup moins courant.

L'incubation dure en moyenne 28 jours, mais peut aller de 15 à 50 jours. Il est possible de déceler le virus dans le sang et les fèces environ 10-12 jours après la contamination. Les patients sont les plus contagieux pendant les 2-3 semaines précédant l'apparition des symptômes et la semaine qui suit.

L'organisme produit des anticorps anti-HAV en réaction à l'infection et l'on peut utiliser la séroprévalence comme indicateur de la transmission virale dans une communauté. C'est dans les pays nordiques que l'on trouve la séroprévalence la plus basse (environ 15%). Dans les autres régions d'Europe, en Australie, aux Etats-Unis et au Japon, la proportion d'adultes chez lesquels on décèle des anticorps atteint 40%-70%. Pratiquement tous les adultes vivant dans les pays en développement ont une sérologie établissant des antécédents d'infection.

Il y a une corrélation directe entre l'âge et le risque de développer une forme symptomatique de la maladie à la suite de l'infection par le HAV. Chez les enfants de < 6 ans, elle reste en général asymptomatique: seuls 10% d'entre eux développent un ictère. Chez l'enfant plus âgé et l'adulte, l'infection évolue vers la forme clinique et l'ictère survient dans plus de 70% des cas. Les régions de forte endémicité du HAV se caractérisent donc par une prédominance des infections asymptomatiques de l'enfance et l'apparition occasionnelle seulement d'hépatite A clinique.

A des fins pratiques, on divise le monde en zones de faible, moyenne et forte endémicité, bien que l'endémicité puisse varier d'une région à l'autre dans un même pays. Dans les zones de faible endémicité, la maladie survient principalement chez les adolescents et les adultes appartenant à des groupes à haut risque (par ex. les homo-

men, injection-drug users), persons travelling to countries of intermediate and high HAV endemicity, and in certain subpopulations (e.g. closed religious communities). Some of these groups may also experience periodic outbreaks of hepatitis A. In areas of low endemicity, occasional food and waterborne outbreaks of hepatitis A occur.

In areas of intermediate endemicity, transmission occurs primarily from person to person in the general community, often with periodic outbreaks. In these countries many individuals escape early childhood infection, but are exposed later in life when clinical hepatitis occurs more frequently. In these areas, most cases occur in late childhood and early adulthood.

In areas of high endemicity, where the lifetime risk of infection is greater than 90%, most infections occur in early childhood and are asymptomatic. Thus, clinically apparent hepatitis A is rarely seen in these countries.

Countries in transition from developing to developed economies will gradually move from high to intermediate endemicity, and hepatitis A is likely to become a more serious problem in these areas .

Although hepatitis A is mostly self-limiting and rarely fatal, the disease may represent a substantial economic burden, particularly in countries with low and intermediate incidence rates. In the United States, a region of relatively low hepatitis A endemicity, calculations based on surveillance data from 1989 indicated annual medical and work-loss costs of approximately US$ 200 million.

The pathogen and the disease

HAV is a member of the Picornaviridae family that includes both the enteroviruses and rhinoviruses of humans. Being the only species member, it constitutes its own genus named hepatovirus. HAV is a non-enveloped (naked) virus of 27-28 nm diameter without morphological features differentiating it from other picornaviruses. Four structural proteins encapsulate the RNA genome. Neutralization sites for anti-HAV antibodies are mainly contained in 2 of these proteins. Although 6 genotypes of HAV have been identified, there appears to be no variation detectable by serology in these neutralization sites. The virus is relatively stable at low pH and moderate temperatures, but is inactivated by high temperature (almost instantly at 85 °C/185 °F), and by formalin or chlorine.

HAV itself is not cytopathic and the liver-cell damage is caused by the cell-mediated immune response.

The clinical course of acute hepatitis A is indistinguishable from other types of acute viral hepatitis. Symptoms typically include fever, malaise, anorexia, nausea and abdominal discomfort, followed by dark urine and jaundice. The severity of disease and mortality increases in older age groups. The convalescence following hepatitis A may be slow, and is characterized by fatigue, nausea and lack of appetite. Complications of hepatitis A include relapsing hepatitis, cholestatic hepatitis and fulminant hepatitis. Fulminant hepatitis occurs in approximately 0.01% of clinical infections and is characterized by rapid deterioration in

sexuels, les consommateurs de drogues par injection), les personnes se rendant dans des pays d'endémicité moyenne ou forte du HAV, et certains groupes de population (par exemple, des communautés religieuses fermées). Il arrive que certains de ces groupes connaissent des flambées épidémiques périodiques d'hépatite A. Dans les régions de faible endémicité, des flambées occasionnelles surviennent à la suite d'une transmission par l'eau ou les aliments.

Dans les régions d'endémicité moyenne, la transmission se fait surtout d'une personne à l'autre, souvent avec des flambées épidémiques périodiques. Dans ces pays, de nombreuses personnes échappent à l'infection dans la prime enfance et l'exposition au virus a lieu plus tard, quand l'évolution vers la forme clinique est devenue plus fréquente. La plupart des cas s'observent alors à la fin de l'enfance ou au début de l'âge adulte.

Dans les régions de forte endémicité, où le risque de contracter l'infection au cours de la vie dépasse 90%, la plupart des infections surviennent dans la prime enfance, âge auquel elles restent asymptomatiques. On observe donc rarement l'hépatite A clinique dans ces pays.

Les pays en économie de transition passent graduellement d'une forte endémicité à une endémicité moyenne et il est probable que le problème de l'hépatite A clinique prendra de l'importance dans ces régions.

Bien que l'hépatite A évolue spontanément vers la guérison la plupart du temps et qu'elle soit rarement mortelle, elle peut représenter un fardeau économique important, notamment dans les pays où l'incidence est faible ou moyenne. Aux Etats-Unis, pays d'endémicité relativement faible, les calculs faits d'après des données de surveillance en 1989 montrent que les dépenses correspondant aux frais médicaux et aux journées de travail perdues se montaient approximativement à US $200 millions.

L'agent pathogène et la maladie

Le HAV fait partie de la famille des Picornaviridae qui comprend à la fois les entérovirus et les rhinovirus de l'humain. C'est la seule espèce appartenant au genre hépatovirus. Il s'agit d'un virus non enveloppé (nu) de 27-28 nm de diamètre sans caractères morphologiques le distinguant des autres picornavirus. Quatre protéines structurales forment la capside autour de l'ARN génomique. Les sites de neutralisation pour les anticorps anti-HAV se retrouvent surtout sur 2 de ces protéines. Bien qu'on ait identifié 6 génotypes, il ne semble pas y avoir de variation des sites de neutralisation décelable par la sérologie. Relativement stable à des valeurs faibles du pH et à température modérée, le HAV est inactivé par la chaleur (presque instantanément à 85 °C), par le formol ou par le chlore.

Le HAV n'a pas d'effet cytopathogène par lui-même: les lésions de l'hépatocyte sont dues à la réponse immunitaire à médiation cellulaire.

Il est impossible de distinguer l'évolution clinique de l'hépatite A de celle d'autres hépatites virales aiguës. On trouve classiquement dans les symptômes la fièvre, un malaise général, de l'anorexie, des nausées, des troubles abdominaux, puis des urines foncées et l'ictère. La gravité de la maladie et la mortalité s'accroissent avec l'âge. La convalescence à la suite d'une hépatite A peut être longue et se caractérise par de la fatigue, des nausées et une perte d'appétit. On observe dans les complications des rechutes, l'hépatite cholestatique et l'hépatite fulminante. Cette dernière survient dans environ 0,01% des cas cliniques et elle se caractérise par une dégradation rapide de la fonction hépatique et un taux très élevé de mortalité

liver function and a very high fatality rate. Chronic infection with HAV does not occur. No specific antiviral therapy is currently available.

The etiological diagnosis is made by the demonstration of IgM antibodies to HAV (IgM anti-HAV) in serum. Detection of the virus or viral antigens in the stool is of limited value for routine diagnosis.

Protective immune response

Protective antibodies develop in response to infection and persist for life. The protective role of anti-HAV antibodies has been demonstrated by the protection against hepatitis A resulting from passive immunization with serum immune globulin. The effect of mucosal immunity on HAV infection is not known.

Justification for vaccine control

Although usually a self-limiting disease without serious sequelae and with a low case-fatality rate, human suffering may be considerable. In addition, direct and indirect medical costs including the infection control measures involved may impose a considerable economic burden on society. Cost-benefit analyses from the United States suggest that large-scale immunization programmes might result in cost savings in some communities. However, depending on the costs associated with clinical disease and vaccination (vaccine and administration), such cost-benefit figures will vary considerably between different countries.

In the long term, socioeconomic development will reduce transmission of hepatitis A, particularly through improved sanitation and health education. Unfortunately, in some parts of the world socioeconomic development is slow. No drugs against HAV are currently available, and antiviral medication is unlikely to become a realistic alternative to appropriate vaccines. Immune globulin may be used for pre- and post-exposure prophylaxis, for example, shortly before entering an endemic area or just after likely HAV exposure. However, passive immunization with immune globulin gives only short-term protection (3-5 months) and is relatively costly compared to the long-term immunity from vaccination.

Several vaccines against hepatitis A are now available that are highly efficacious and provide long-lasting protection in adults and in children above 1-2 years of age. In countries where clinical hepatitis A is an important health problem, immunization is likely to be a cost-effective public health tool to control the disease.

Hepatitis A vaccines

Techniques for growing HAV in cell culture have made it possible to generate sufficient amounts of virus for vaccine production. Several inactivated or live attenuated vaccines against hepatitis A have been developed, but only 4 inactivated hepatitis A vaccines are currently available internationally. All 4 vaccines are similar in terms of efficacy and side-effect profile. The vaccines are given parenterally, as a 2-dose series, 6-18 months apart. The dose of vaccine, vaccination schedule, ages for which the vaccine is licensed, and whether there is a paediatric and adult formulation varies from manufacturer to manufacturer. No vaccine is licensed for children aged < 1 year.

clinique. Le HAV ne donne pas d'infection chronique et on ne dispose actuellement d'aucun traitement antiviral spécifique.

Le diagnostic étiologique est posé par la mise en évidence d'anticorps sériques, les IgM anti-HAV. Le dépistage des antigènes viraux dans les selles n'a qu'une valeur limitée pour le diagnostic en routine.

Réponse immunitaire protectrice

Produits en réaction à l'infection, les anticorps persistent ensuite tout le reste de la vie. L'immunisation passive par des immunoglobulines sériques a permis de démontrer leur rôle protecteur. On ne connaît pas l'effet de l'immunité des muqueuses sur l'infection à HAV.

Raison d'être de la vaccination

Bien que normalement cette maladie évolue spontanément vers la guérison sans laisser de séquelles graves et que le taux de mortalité clinique soit faible, les souffrances qu'elle entraîne peuvent être importantes. En outre, les frais médicaux directs et indirects, comprenant les mesures de lutte contre l'infection, peuvent représenter un fardeau économique considérable pour la société. Les analyses faites aux Etats-Unis sur les coûts et les avantages donnent à penser que les programmes de vaccination à grande échelle pourraient permettre à certaines communautés de réaliser des économies. Néanmoins, en fonction des dépenses liées à la maladie clinique et à la vaccination (vaccins et administration), les résultats peuvent varier dans une grande proportion d'un pays à l'autre.

A long terme, le développement socio-économique diminuera la transmission de l'hépatite A, notamment avec l'amélioration des systèmes d'assainissement et de l'éducation sanitaire. Malheureusement ce développement est lent dans certaines régions du monde. On ne dispose actuellement d'aucun médicament contre le HAV et il est improbable que l'on puisse un jour remplacer la vaccination par des traitements antiviraux. Il est possible d'administrer les immunoglobulines à titre de prophylaxie avant ou après l'exposition, par exemple peu avant d'entrer dans une zone d'endémie ou peu après une exposition probable au HAV. Cette immunisation passive ne donne toutefois qu'une protection de courte durée (3-5 mois) et elle est relativement onéreuse, si on la compare à l'immunité à long terme conférée par la vaccination.

On dispose désormais de plusieurs vaccins anti-hépatite A qui sont très efficaces et assurent une protection à long terme chez l'adulte et l'enfant à partir de l'âge de 1-2 ans. Dans les pays où l'hépatite A représente un problème de santé publique important, il est probable que la vaccination serait un moyen rentable de lutter contre cette affection.

Vaccins anti-hépatite A

Les techniques de culture du HAV sur cellule ont permis d'obtenir des quantités suffisantes de virus pour produire les vaccins. Plusieurs vaccins, inactivés ou vivants atténués, ont été développés, mais seuls 4 d'entre eux sont disponibles actuellement au niveau international. Semblables du point de vue de l'efficacité et des effets secondaires, on les administre par voie parentérale en séries de 2 doses séparées par un intervalle de 6-18 mois. La concentration du vaccin, le calendrier de vaccination, l'âge pour lequel le produit est homologué, l'existence d'une forme pédiatrique et d'une forme adulte sont les éléments qui varient d'un fabricant à l'autre. Aucun vaccin n'est homologué pour les enfants de < 1 an.

Three vaccines are manufactured from cell culture adapted HAV propagated in human fibroblasts. Following purification from cell lysates, the HAV preparation is formalin-inactivated and adsorbed to an aluminium hydroxide adjuvant. One vaccine is formulated without preservative; the other 2 are prepared with 2-phenoxyethanol as a preservative.

The fourth vaccine is manufactured from HAV purified from infected human diploid cell cultures and inactivated with formalin. This preparation is adsorbed to biodegradable, 150 nm phospholipid vesicles spiked with influenza haemagglutinin and neuramidase. These virosomes are thought to directly target influenza-primed antibody-presenting cells as well as macrophages, thus stimulating a rapid vaccine-induced B and T cell proliferation in the majority of vaccinees.

A combination vaccine containing inactivated hepatitis A and recombinant hepatitis B vaccines has been licensed since 1996 for use in children aged 1 year or older in several countries. The combination vaccine is given as a 3-dose series, using a 0, 1, 6 month schedule.

Hepatitis A vaccines are all highly immunogenic. Nearly 100% of adults will develop protective levels of antibody within 1 month after a single dose of vaccine. Similar results are obtained with children and adolescents in both developing and developed countries. The protective efficacy of the vaccine against clinical disease was determined in 2 large trials. Among almost 40 000 Thai children aged 1-16 years the protective efficacy was 94% (95% confidence intervals: 82%-99%) following 2 doses of vaccine given 1 month apart. Among approximately 1 000 children aged 2-16 years, living in a highly endemic community in the United States, the efficacy of 1 dose of vaccine was 100% (95% confidence intervals: 87%-100%).

Although 1 dose of vaccine provides at least short-term protection, the manufacturers currently recommend 2 doses to ensure long-term protection. In studies evaluating the duration of protection of 2 or more doses of hepatitis A vaccine, 99%-100% of vaccinated individuals had levels of antibody indicative of protection 5-8 years after vaccination. Kinetic models of antibody decay indicate that the duration of protection is likely to be at least 20 years, and possibly lifelong.

Post-marketing surveillance studies are needed to monitor vaccine-induced long-term protection, and to determine the need for booster doses of vaccine. This is especially true in areas of low endemicity where natural boosting does not occur.

Millions of persons have now been vaccinated against HAV. The current vaccines are well tolerated and no serious adverse events have been statistically linked to their use. Contraindications to hepatitis A vaccination include a known allergy to any of the vaccine components. Hepatitis A vaccine may be administered with all other vaccines included in the Expanded Programme on Immunization and with vaccines commonly given for travel. Concurrent administration of immune serum globulin does not appear to influence significantly the formation of protective antibodies.

General WHO position on new vaccines

Vaccines for large-scale public health use should:

Trois des vaccins sont fabriqués à partir de HAV obtenus par propagation sur culture de fibroblastes humains. Après lyse des cellules et purification, la préparation virale est inactivée par le formol puis adsorbée sur de l'hydroxyde d'alumine. L'un de ces vaccins n'a pas de conservateur et l'on a eu recours au 2-phénoxyéthanol pour les 2 autres.

Le quatrième est fabriqué à partir de HAV purifié, extrait de culture de cellules diploïdes humaines infectées, et inactivé par le formol. Cette préparation est ensuite adsorbée sur des vésicules phospholipidiques de 150 nm de diamètre chargées d'hémagglutinines grippales et de neuramidase. On pense que ces virosomes ciblent directement les cellules se présentant avec des anticorps antigrippaux, ainsi que les macrophages, et qu'ils stimulent alors une prolifération rapide des lymphocytes B et T chez la majorité des sujets vaccinés.

Un vaccin associant le virus inactivé de l'hépatite A et un vaccin recombinant contre l'hépatite B a été homologué depuis 1996 dans plusieurs pays pour la vaccination des enfants de 1 an et plus. On administre 3 doses, la deuxième un mois après la première et la troisième 6 mois plus tard.

Les vaccins anti-hépatite A ont tous une grande immunogénicité. Pratiquement 100% des adultes développent un titre protecteur d'anticorps dans le mois qui suit l'administration d'une seule dose de vaccin. On obtient des résultats similaires pour les enfants et les adolescents tant dans les pays développés que ceux en développement. On a déterminé l'efficacité protectrice du vaccin au moyen de 2 essais de grande ampleur. Dans un groupe de 40 000 enfants thaïlandais de 1-16 ans, elle était de 94% (intervalle de confiance à 95%: 82%-99%) après l'administration de 2 doses à 1 mois d'intervalle. Chez environ 1 000 enfants de 2-16 ans dans une communauté de forte endémicité aux Etats-Unis, l'efficacité d'une seule dose vaccinale a été de 100% (intervalle de confiance à 95%: 87%-100%).

Bien qu'une seule dose vaccinale confère au moins une protection à court terme, les fabricants recommandent actuellement d'administrer 2 doses afin de garantir la protection à long terme. Dans les études pour évaluer la durée de la protection conférée par 2 doses ou plus de vaccin anti-hépatite A, 99%-100% des sujets vaccinés ont donné des titres d'anticorps indiquant l'existence d'une protection 5-8 ans après la vaccination. Les modèles cinétiques de la décroissance du titre des anticorps donnent à penser que la protection dure probablement 20 ans au moins et peut-être la vie entière.

Des études post-commercialisation sont nécessaires pour surveiller la protection à long terme induite par le vaccin et pour déterminer le besoin d'administrer des rappels. Cela est particulièrement vrai dans le cas des régions de faible endémicité où le système immunitaire n'est pas stimulé naturellement.

Des millions de personnes sont désormais vaccinées contre le HAV. Les vaccins actuels sont bien tolérés et la statistique n'a pas mis en évidence de relation entre leur utilisation et d'éventuels effets secondaires. Une allergie connue à l'un quelconque des composants constitue une contre-indication à la vaccination. On peut administrer ce vaccin avec tous ceux qui font partie du Programme élargi de vaccination et ceux que l'on prescrit couramment pour les voyages. L'administration concomitante d'immunoglobulines sériques ne semble pas avoir d'effet significatif sur la production des anticorps.

Position générale de l'OMS concernant les nouveaux vaccins

Les vaccins destinés à être employés à grande échelle en santé publique doivent :

- meet the quality requirements as defined in the current WHO policy statement on vaccine quality;[2]
- be safe and have a significant impact on the actual disease in all target populations;
- if intended for infants or young children, be easily adapted to schedules and timing of the national childhood immunization programmes;
- not interfere significantly with the immune response to other vaccines given simultaneously;
- be formulated to meet common technical limitations, e.g. in terms of refrigeration and storage capacity;
- be appropriately priced for different markets.

WHO position on hepatitis A vaccines

The currently available vaccines against hepatitis A are all of known good quality and in line with the above WHO recommendations. However, they are not licensed for use in children aged < 1 year. The efficacy in children aged < 1 year is variable owing to interference by passively-acquired maternal antibodies. Although the current vaccines result in long-term protection when given as 2 injections 6-18 months apart, high levels of immunity are obtained after 1 dose. Studies addressing the duration of protection following a single dose of vaccine are encouraged.

Planning for large-scale immunization programmes against hepatitis A should involve careful analyses of the cost-benefit and sustainability of different appropriate hepatitis A prevention strategies, as well as an assessment of the possible long-term epidemiological implications of vaccination at different levels of coverage.

In countries where hepatitis A is highly endemic, exposure to HAV is almost universal before the age of 10 years. In such countries clinical hepatitis A is usually a minor public health problem, and large-scale immunization efforts against this disease should not be undertaken.

In developed countries with low endemicity of hepatitis A and with high rates of disease in specific high-risk populations, vaccination of these populations against hepatitis A may be recommended. The high-risk groups include injection-drug users, homosexual men, persons travelling to high-risk areas, and certain ethnic or religious groups. However, it should be noted that vaccination programmes targeting specific high-risk groups may have little impact on the overall national incidence of disease.

In areas of intermediate endemicity, where transmission occurs primarily from person to person in the general community (often with periodic outbreaks), control of hepatitis A may be achieved through widespread vaccination programmes.

Recommendations for hepatitis A vaccination in outbreak situations depend on the epidemiology of hepatitis A in the community, and the feasibility of rapidly implementing a widespread vaccination programme. The use of hepatitis A vaccine to control community-wide outbreaks has been most successful in small, self-contained communities, when vaccination is started early in the course of the outbreak, and when high coverage of multiple-age cohorts is achieved. Vaccination efforts should be supplemented by health education and improved sanitation.

[2] Document WHO/VSQ/GEN/96.02 available from the VAB documentation centre, World Health Organization, 1211 Geneva 27, Switzerland.

- satisfaire aux normes de qualité définies dans le document d'information de l'OMS sur la qualité des vaccins; [2]
- être sans danger et agir efficacement contre la maladie en question dans toutes les populations cibles;
- s'ils sont destinés aux nourrissons ou aux jeunes enfants, être facilement adaptables aux calendriers et à la chronologie des programmes nationaux de vaccination infantile;
- ne pas interférer avec la réponse immunitaire à d'autres vaccins administrés simultanément;
- être formulés de façon à tenir compte des problèmes techniques habituellement rencontrés, par exemple concernant la réfrigération et le mode de conservation;
- être vendus à des prix adaptés aux différents marchés.

Position de l'OMS sur les vaccins anti-hépatite A

Les vaccins anti-hépatite A actuellement disponibles sont tous de bonne qualité et conformes aux recommandations de l'OMS énoncées ci-dessus. Leur administration à des enfants de < 1 an n'est toutefois pas homologuée car, dans ce cas, leur efficacité est variable en raison des anticorps maternels présents dans l'organisme de ces nourrissons. Bien que les vaccins actuels confèrent une protection de longue durée après l'administration de 2 doses injectées à un intervalle de 6-18 mois, une seule dose permet également d'obtenir une immunité élevée. La durée de la protection conférée par l'administration d'une dose unique est donc un point qu'il est recommandé d'étudier.

La planification de programmes de vaccination à grande échelle contre l'hépatite A doit comprendre une analyse soignée des coûts, des avantages, de la viabilité des diverses stratégies de prévention pouvant s'appliquer, ainsi qu'une évaluation des conséquences épidémiologiques éventuelles à long terme avec différents niveaux de couverture.

Dans les pays de forte endémicité, l'exposition au HAV est pratiquement universelle avant l'âge de 10 ans. L'hépatite A sous sa forme clinique est alors en général un problème mineur de santé publique qui ne justifie pas d'entreprendre la vaccination à grande échelle.

Dans les pays développés, où l'endémicité est faible, l'incidence peut rester élevée dans certains groupes à risque pour lesquels la vaccination contre l'hépatite A pourra alors être recommandée. Font partie de ces groupes: les consommateurs de drogues par injection, les homosexuels, les personnes se rendant dans des zones à haut risque et certains groupes ethniques ou religieux. Il faut noter cependant que les programmes de vaccination ciblés sur des groupes spécifiques à haut risque peuvent n'avoir qu'un impact réduit sur l'incidence nationale de la maladie.

Dans les régions d'endémicité moyenne, où la transmission se fait d'une personne à l'autre dans l'ensemble de la population, avec souvent des flambées épidémiques périodiques, on pourra lutter contre l'hépatite A à l'aide de programmes étendus de vaccination.

En situation de flambée épidémique, les recommandations pour la vaccination dépendent de l'épidémiologie de l'hépatite A dans la communauté et de la possibilité de mettre en œuvre rapidement une programme étendu de vaccination. On a observé que les chances de succès étaient les meilleures quand la flambée touchait des communautés de taille réduite, vivant en vase clos, quand la vaccination pouvait démarrer à un stade précoce de la flambée et quand on obtenait une couverture élevée pour des cohortes d'âge divers. L'éducation sanitaire et l'amélioration des systèmes d'assainissement doivent accompagner les efforts de vaccination.

[2] Document WHO/VSQ/GEN/96.02 disponible auprès du Centre de documentation VAB, Organisation mondiale de la Santé, 1211 Genève 27, Suisse.

Although the burden of disease associated with hepatitis A is considerable in many countries, the decision to include hepatitis A vaccine in the routine childhood immunization programmes should be made in the context of the full range of immunization interventions available. This includes hepatitis B, *Haemophilus influenzae* type b, rubella and yellow fever, and in the near future pneumococcal vaccines, all of which are likely to have a more profound public health impact. ■

Bien que le fardeau de morbidité imputable à l'hépatite A soit énorme dans de nombreux pays, la décision d'inclure le vaccin dans les programmes de vaccination systématique des enfants doit se prendre en tenant compte de toutes les vaccinations possibles, contre l'hépatite B, *Haemophilus influenzae* type b, la rubéole et la fièvre jaune, ainsi que la vaccination antipneumococcique dans un proche avenir, car toutes auront probablement de grandes répercussions sur la santé publique. ■

Influenza

Austria (12 January 2000).[1] Influenza activity progressed from the last week of December up to the first week of January, with outbreaks of influenza A(H3N2) in all parts of the country.

Germany (18 January 2000).[1] Influenza activity was still widespread during the second week of January, although consultations for influenza-like illness have started to decline in some regions. Children were most affected, but the highest excess morbidity was in the age group 35 years and above. To date, virus isolates have been mostly influenza A of subtype A(H3N2), some identified as A/Moscow/10/99 (H3N2)-like strain.

Poland (15 January 2000).[1] In January, there was a significant increase in influenza and influenza-like illness amounting to 136 702 cases (353 per 100 000 population) compared to 986 cases in the last 2 weeks of December. The highest number of cases was registered in the south-western part of the country. There were 3 reported deaths due to influenza in patients aged over 70 years; 24% of cases were in children.

Spain (24 January 2000).[1] The influenza epidemic entered its 5th-6th week of evolution during the third week of January. Rates of influenza-like illness had increased to 800 per 100 000 population during the second week. Influenza viruses isolated were similar to the most recent strains – A/Moscow/10/99 (H3N2) and A/Panama/2007/99 (H3N2).

The Former Yugoslav Republic of Macedonia (19 January 2000). During the first 2 weeks of January, 10 600 cases of influenza-like illness were reported from primary health level units with 61 cases hospitalized. Three influenza A cases were diagnosed by antigen detection. ■

[1] See No. 3, 2000, pp. 25-28

Grippe

Autriche (12 janvier 2000).[1] L'activité grippale a progressé entre la dernière semaine de décembre et la première semaine de janvier, avec des flambées de grippe A(H3N2) dans tout le pays.

Allemagne (18 janvier 2000).[1] L'activité grippale est restée générale pendant la deuxième semaine de janvier, bien qu'il y ait eu moins de consultations pour syndromes grippaux dans certaines régions. Les enfants ont été les plus touchés, mains la morbidité excessive la plus élevée a été constatée parmi le groupe d'âge de 35 ans et au-dessus. A ce jour, les isolements de virus ont été surtout de grippe A, soustype A(H3N2), certains ayant été identifiés comme étant de souche analogue à A/Moscou/10/99 (H3N2).

Pologne (15 janvier 2000).[1] En janvier, il y a eu une augmentation marquée de grippe et de syndromes grippaux, atteignant 136 702 cas (353 pour 100 000 habitants), comparé à 986 cas pendant les 2 dernières semaines de décembre. Le nombre le plus élevé de cas a été enregistré dans le sud-ouest du pays. On a signalé 3 décès dus à la grippe chez des malades âgés de plus de 70 ans; 24% des cas étaient chez des enfants.

Espagne (24 janvier 2000).[1] L'épidémie de grippe est entrée dans la 5è à 6è semaine de son évolution pendant la troisième semaine de janvier. Les taux de syndromes grippaux avaient atteint 800 pour 100 000 habitants pendant la deuxième semaine. Les virus grippaux isolés étaient semblables aux souches les plus récentes – A/Moscou/10/99 (H3N2) et A/Panama/2007/99 (H3N2).

Ex-République yougoslave de Macédoine (19 janvier 2000). Pendant les 2 premières semaines de janvier, 10 600 cas de syndromes grippaux ont été signalés par les unités de santé primaire, et 61 cas ont été hospitalisés. Trois cas de grippe A ont été décelés par analyse antigénique. ■

[1] Voir N° 3, 2000, pp. 25-28.

INTERNATIONAL HEALTH REGULATIONS / RÈGLEMENT SANITAIRE INTERNATIONAL

Notifications of diseases received from 28 January to 3 February 2000 / Notifications de maladies reçues du 28 janvier au 3 février 2000

Cholera / Choléra

	Cases / Deaths Cas / Décès	
Africa / Afrique		
Madagascar[1]	8-XII-11.I	
	3 176	121
Americas / Amériques		
Guatemala[1]	10.XII-20.I	
	60	0

Yellow fever / Fièvre jaune

	Cases / Deaths Cas / Décès	
Americas / Amériques		
Brazil / Brésil	23-31.I	
Goiás State		
Alta Paraíso Municipio	2	0
Cavalcante Municipio	1	0
Corumbaíba Municipio	1	1
Doverlândia Municipio	1	1
Niquelândia Municipio	1	0
Mato Grosso State		
Barra do Garça Municipio	1	0
Tocantins State		
Arraias Municipio	1	0

[1] See note on page 37. / Voir note à la page 37.

Newly infected areas / Zones nouvellement infectées

Cholera / Choléra

Africa / Afrique
Madagascar
Toliary Province
Morondava District

Yellow fever / Fièvre jaune
Americas / Amériques
Brazil / Brésil
Goiás State
Cavalcante Municipio
Corumbaía Municipio
Mato Grosso State
Barra do Garça Municipio
Tocantins State
Arraias Municipio

2. Bibliography Speakers Hepatitis A part

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Hepatitis E

Pubmed MEDLINE search on '**Hepatitis E**' or '**HEV**' in all fields and published **from 2008** on, was performed. A second search on these results was performed in Endnote with {'**Epidemiology'** or **'transmission'** or '**Prevention'** or '**vaccine**' or '**control**'}. Only the references and the abstracts related to the WHO Regional office for EURO region and USA are shown. The references are ranged by publication year (most recent first) and for each year in alphabetical order of the first author's name.

Arankalle VA, Lole KS, Deshmukh TM, Srivastava S, and Shaligram US.
Challenge studies in Rhesus monkeys immunized with candidate hepatitis E vaccines: DNA, DNA-prime-protein-boost and DNA-protein encapsulated in liposomes.
Vaccine 27: 1032-1039, 2009.

Complete ORF2 gene (1983bp) of hepatitis E virus (HEV) and the 450bp region within ORF2 containing neutralizing epitope (NE) cloned in pVAX1 and corresponding proteins expressed in baculovirus and prokaryotic systems respectively were evaluated as vaccine candidates. Two doses of liposome encapsulated DNA plus corresponding protein with both ORF2 and NE regions (Lipo-ORF2-DP and Lipo-NE-DP) showed 100% seroconversion and comparable anti-HEV titres in Swiss albino mice. These vaccine candidates were further evaluated as DNA, DNA-prime-protein-boost (DPPB) and liposome formulations in Rhesus monkeys. Monkeys receiving ORF2/NE DNA seroconverted after fourth dose while those immunized employing ORF2-DPPB format seroconverted at 7 weeks post third dose. In view of the delayed weak antibody response, these monkeys were not challenged. Though Lipo-ORF2-DP was immunogenic, 2 of the 4 monkeys developed HEV infection following homologous virus challenge of 100 Monkey Infectious Dose(50). Both monkeys immunized with Lipo-NE-DP and 1 of the 2 monkeys immunized with NE-DPPB showed complete protection, the second monkey being protected from hepatitis with limited viral replication. Irrespective of the type of immunogen, all challenged monkeys were protected from hepatitis. The results document Lipo-NE-DP to be a promising vaccine candidate needing further evaluation.

Bihl F, and Negro F.
Chronic hepatitis E in the immunosuppressed: A new source of trouble?
J Hepatol 50: 435-437, 2009.

REVIEW Chronic hepatitis E virus infection in liver transplant recipients. Haagsma EB, van den Berg AP, Porte RJ, Benne CA, Vennema H, Reimerink JH, Koopmans MP. Hepatitis E virus (HEV) infection is known to run a self-limiting course. Sporadic cases of acute hepatitis due to infection with HEV genotype 3, present in pig populations, are increasingly recognized. Zoonotic transmission seems infrequent. The entity of unexplained chronic hepatitis after liver transplantation has been recognized. Detection of HEV in 2 liver transplant recipients triggered a review of these cases. Freeze-stored sera were available for retrospective analysis. HEV antibodies were determined. For virus detection and identification, a fragment of the gene encoding the major capsid protein (open reading frame 2) was amplified by reverse-transcription polymerase chain reaction and sequenced to identify the genotype. Two months after liver transplantation, case A developed unexplained chronic hepatitis, which developed into cirrhosis. Retransplantation followed 7 years

later, after which chronic hepatitis recurred. In retrospect, HEV RNA was present in serum 3 weeks after the first transplantation and remained present afterwards. HEV RNA was also present in retransplant liver tissue. HEV antibodies appeared late after retransplantation. Case B developed unexplained chronic hepatitis 7 years after transplantation. Retransplantation was needed 5 years later, after which no signs of hepatitis recurred. In retrospect, the period of chronic hepatitis up to the retransplantation coincided with HEV RNA in serum. In case B, antibodies developed, the viral load was much lower than in case A, and the virus seemed to be cleared after retransplantation. Genotyping in both cases revealed 2 unique strains of genotype 3. In conclusion, chronic HEV infection may develop in immunosuppressed patients, who may then serve as long-term carriers of the virus. We hypothesize that HEV may be the cause of chronic hepatitis in liver transplant recipients. (c) 2008 AASLD. [Abstract reproduced by permission of Liver Transpl 2008;14:547-553]. Hepatitis E virus and chronic hepatitis in organ-transplant recipients. Kamar N, Selves J, Mansuy JM, Ouezzani L, Peron JM, Guitard J, Cointault O, Esposito L, Abravanel F, Danjoux M, Durand D, Vinel JP, Izopet J, Rostaing L. Hepatitis E virus (HEV) is considered an agent responsible for acute hepatitis that does not progress to chronic hepatitis. We identified 14 cases of acute HEV infection in three patients receiving liver transplants, nine receiving kidney transplants, and two receiving kidney and pancreas transplants. All patients were positive for serum HEV RNA. Chronic hepatitis developed in eight patients, as confirmed by persistently elevated aminotransferase levels, serum HEV RNA, and histologic features of chronic hepatitis. The time from transplantation to diagnosis was significantly shorter and the total counts of lymphocytes and of CD2, CD3, and CD4 T cells were significantly lower in patients in whom chronic disease developed. [Abstract reproduced by permission of N Engl J Med 2008;358:811-817].

Bouwknegt M, Rutjes SA, Reusken CB, Stockhofe-Zurwieden N, Frankena K, de Jong MC, de Roda Husman AM, and van der Poel WH.
The course of hepatitis E virus infection in pigs after contact-infection and intravenous inoculation.
BMC Vet Res 5: 7, 2009.

ABSTRACT: BACKGROUND: Worldwide, hepatitis E virus (HEV) genotype 3 is observed in pigs and transmission to humans is implied. To be able to estimate public health risks from e.g. contact with pigs or consumption of pork products, the transmission routes and dynamics of infection should be identified. Hence, the course of HEV-infection in naturally infected pigs should be studied. RESULTS: To resemble natural transmission, 24 HEV-susceptible pigs were infected either by one-to-one exposure to intravenously inoculated pigs (C1-pigs; n = 10), by one-to-one exposure to contact-infected pigs (C2-pigs: n = 7; C3-pigs: n = 5) or due to an unknown non-intravenous infection route (one C2-pig and one C3-pig). The course of HEV-infection for contact-infected pigs was characterized by: faecal HEV RNA excretion that started at day 7 (95% confidence interval: 5-10) postexposure and lasted 23 (19-28) days; viremia that started after 13 (8-17) days of faecal HEV RNA excretion and lasted 11 (8-13) days; antibody development that was detected after 13 (10-16) days of faecal HEV RNA excretion. The time until onset of faecal HEV RNA excretion and onset of viremia was significantly shorter for iv-pigs compared to contact-infected pigs, whereas the duration of faecal HEV RNA excretion was significantly longer. At 28 days postinfection HEV RNA was detected less frequently in organs of contact-infected pigs compared to iv-pigs. For contact-infected pigs, HEV RNA was detected in 20 of 39 muscle samples that were proxies for pork at retail and in 4 of 7 urine samples. CONCLUSION: The course of infection differed between infection routes, suggesting that contact-infection could be a better model

for natural transmission than iv inoculation. Urine and meat were identified as possible HEV-sources for pig-to-pig and pig-to-human HEV transmission.

Huang WJ, Zhang HY, Harrison TJ, Lan HY, Huang GY, and Wang YC.
Immunogenicity and protective efficacy in rhesus monkeys of a recombinant ORF2 protein from hepatitis E virus genotype 4.
Arch Virol 2009.

Several antigens derived from hepatitis E virus (HEV) genotype 1 strains have shown immunogenicity and efficacy against hepatitis E in primates and humans. However, the protective effect of a vaccine derived from HEV genotype 4 has not been studied. This study aimed to evaluate the immunogenicity and protective efficacy of the T1-ORF2 (56 kDa) capsid protein derived from HEV strain T1 (genotype 4) in rhesus monkeys. Two doses (40 mug) of alum-absorbed T1-ORF2 capsid protein were administered 4 weeks apart. Seroconversion occurred in all immunized monkeys 1-2 weeks after the first dose. The peak levels of anti-HEV IgG appeared at 2-3 weeks after the second dose and ranged from 5.7 to 196.0 U/ml. All monkeys showed an anamnestic antibody response to the second dose. Control monkeys immunized with saline remained negative for HEV antibodies throughout the pre-challenge period. The immunized monkeys were challenged intravenously with HEV genotypes 1 and 4. Monkeys immunized with T1-ORF2 were protected from infection and hepatitis after challenge with 5 x 10(4) genome equivalents of HEV, regardless of the genotype. After challenge with 5 x 10(5) genome equivalents of HEV genotype 4, the monkeys immunized with T1-ORF2 had a shorter period of raised alanine aminotransferase levels and a shorter duration of fecal shedding compared to control monkeys immunized with saline. In conclusion, these results suggest that, in rhesus monkeys, the T1-ORF2 capsid protein of HEV genotype 4 has similar cross-protective effects to other candidate vaccines derived from HEV genotype 1.

Khuroo MS, Kamili S, and Khuroo MS.
Clinical course and duration of viremia in vertically transmitted hepatitis E virus (HEV) infection in babies born to HEV-infected mothers.
J Viral Hepat 2009.

Summary. Infection with the hepatitis E virus (HEV) causes a self-limiting acute hepatitis. However, prolonged viremia and chronic hepatitis has been reported in organ transplant recipients. Vertically transmitted HEV infection is known to cause acute hepatitis in newborn babies. The clinical course and duration of viremia in vertically transmitted HEV infection in neonates in not known. We studied 19 babies born to HEV infected mothers. Babies were studied at birth and on a monthly basis to evaluate clinical profile, pattern of antibody response and duration of viremia in those infected with HEV. Fifteen (78.9%) babies had evidence of vertically transmitted HEV infection at birth (IgM anti-HEV positive in 12 and HEV RNA reactive in 10) and three had short-lasting IgG anti-HEV positivity because of trans-placental antibody transmission. Seven HEV-infected babies had icteric hepatitis, five had anicteric hepatitis and three had high serum bilirubin with normal liver enzymes. Seven babies died in first week of birth (prematurity 1, icteric HEV 3, anicteric HEV 2 and hyperbilirubinemia 1). Nine babies survived and were followed up for clinical, biochemical, serological course and duration of viremia. Five of 9 babies who survived were HEV RNA positive. HEV RNA was not detectable by 4 weeks of birth in three babies, by 8 weeks in one and by 32 weeks in one. All surviving babies had self-limiting disease and none had prolonged viremia. Thus HEV infection is commonly transmitted from mother-to-foetus and causes high neonatal mortality.

HEV infection in survivors is self-limiting with short lasting viremia.

Legrand-Abravanel F, Mansuy JM, Dubois M, Kamar N, Peron JM, Rostaing L, and Izopet J.
Hepatitis E virus genotype 3 diversity, France.
Emerg Infect Dis 15: 110-114, 2009.

We characterized 42 hepatitis E virus (HEV) genotype 3 strains from infected patients in France in 3 parts of the genome and sequenced the full-length HEV genotype 3f genome found in Europe. These strains are closely related to swine strains in Europe, which suggests zoonotic transmission of HEV in France.

Li T, and Takeda N.
[Hepatitis E vaccine].
Nippon Shokakibyo Gakkai Zasshi 106: 195-200, 2009.

Mansuy JM, Huynh A, Abravanel F, Recher C, Peron JM, and Izopet J.
Molecular evidence of patient-to-patient transmission of hepatitis E virus in a hematology ward.
Clin Infect Dis 48: 373-374, 2009.

Reuter G, Fodor D, Forgach P, Katai A, and Szucs G.
Characterization and zoonotic potential of endemic hepatitis E virus (HEV) strains in humans and animals in Hungary.
J Clin Virol 2009.

BACKGROUND: Hepatitis E virus (HEV) is a common cause of acute, fecally transmitted hepatitis in developing countries. Identification of HEV in indigenous human infection and in domestic pig raising the possibility that HEV infection is also a zoonosis. OBJECTIVES/STUDY DESIGN: Molecular detection and epidemiology of HEV in humans (South-East Hungary) with acute hepatitis and in domestic (pig, cattle) and wild (boar and roe-deer) animals (countrywide) by ELISA and RT-PCR. RESULTS: Between 2001 and 2006, a total of 116 (9.6%) of 1203 human sera were positive by HEV IgM ELISA and 13 (24.5%) of 53 samples were also confirmed by RT-PCR and sequencing. Forty-two (27.3%) of 154, 11 (34.4%) of 32 and 9 (12.2%) of 74 samples were RT-PCR-positive from swine (feces: 22.7%; liver: 30.8%), roe-deer (liver) and wild boar (liver), respectively. Except for an imported infection caused by genotype 1, 19 sequences (human: 12, swine: 4, roe-deer: 1, wild boar: 2) belong to genotype 3 HEV. Genetically identical strains were detected in human and roe-deer and in 2 other human clusters. CONCLUSIONS: HEV is an endemic agent in Hungary. Consumption of raw or undercooked meat-products is one of the possible sources of the indigenous HEV infections. Cross-species infection with genotype 3 HEV potentially involves a food-borne transmission route in Hungary.

Rutjes SA, Lodder WJ, Lodder-Verschoor F, van den Berg HH, Vennema H, Duizer E, Koopmans M, and de Roda Husman AM.
Sources of hepatitis e virus genotype 3 in the Netherlands.
Emerg Infect Dis 15: 381-387, 2009.

Non-travel-related hepatitis E virus (HEV) genotype 3 infections in persons in the Netherlands may have a zoonotic, foodborne, or water-borne origin. Possible reservoirs for HEV transmission by water, food, and animals were studied. HEV genotype 3/open reading frame 2 sequences were detected in 53% of pig farms, 4% of wild boar feces, and 17% of surface water samples. HEV sequences grouped within 4 genotype 3 clusters, of which 1 is so far unique to the Netherlands. The 2 largest clusters contained 35% and 43% of the animal and environmental sequences and 75% and 6%, respectively, of human HEV sequences obtained from a study on Dutch hepatitis E patients. This finding suggests that infection risk may be also dependent on transmission routes other than the ones currently studied. Besides the route of exposure, virus characteristics may be an important determinant for HEV disease in humans.

Savolainen-Kopra C, Al-Hello H, Paananen A, Blomqvist S, Klemola P, Sobotova Z, and Roivainen M.
Molecular epidemiology and dual serotype specificity detection of echovirus 11 strains in Finland.
Virus Res 139: 32-38, 2009.

Echovirus 11 (E-11) has been one of the most frequently discovered human enterovirus (HEV) in Finland during the past few years. We have studied molecular epidemiological patterns of E-11 from 1993 to 2007 exploiting the 257-nucleotide region in the 5'-part of the VP1 used for genetic typing of HEV. Designated genogroup D strains had a striking prevalence among the Finnish strains, a finding in accordance with the recent data from other geographical regions. The subgroup D4, harboring the oldest strains, had become extinct in the beginning of the millennium and D5 strains had taken over. Similarly, a new subgroup of D5 had started to diverge from the main D5 in 2006. However, in addition to endemic D strains, few single strains clustered also to genogroups A and C suggesting importation from more distant locations. The relatively large amino acid sequence variability between and within the genogroups favored the idea of antigenic differences. Neutralization assays confirmed that antigenic differences existed, although all studied E-11 strains were neutralized with antisera against the prototype strain Gregory. Five of the six studied strains belonging to genogroup D were, unexpectedly, also neutralized with antisera against coxsackievirus A9 Griggs.

Teo CG.
Subduing the hepatitis E Python.
Epidemiol Infect 137: 480-484, 2009.

Yano K, Tamada Y, and Yatsuhashi H.
[Epidemiology and management of hepatitis E in Japan].
Nippon Shokakibyo Gakkai Zasshi 106: 188-194, 2009.

Zhang J, Liu CB, Li RC, Li YM, Zheng YJ, Li YP, Luo D, Pan BB, Nong Y, Ge SX, Xiong JH, Shih JW, Ng MH, and Xia NS.
Randomized-controlled phase II clinical trial of a bacterially expressed recombinant hepatitis E vaccine.

Vaccine 2009.

The candidate recombinant hepatitis E vaccine, HEV 239, protect monkeys against infection by hepatitis E virus (HEV). The safety and immunogenicity of the vaccine for humans was assessed in a randomized controlled phase II clinical trial. The study was conducted in an endemic area of southern China and consisted of a dose scheduling, involving 457 adults and a dose escalation component involving 155 high school students. The results showed that the vaccine is safe and immunogenic for humans and suggest that it could prevent new HEV infection.

Zhao C, Li L, Harrison TJ, Wang Q, Song A, Fan J, Ma H, Zhang C, and Wang Y.
Relationships among viral diagnostic markers and markers of liver function in acute hepatitis E.
J Gastroenterol 44: 139-145, 2009.

BACKGROUND: Diagnosis of acute hepatitis E has been based in many clinics predominantly on detection of anti-HEV (hepatitis E virus) antibody. Now, new assays have been developed to detect other HEV markers. Our aim was to investigate the relationships among HEV diagnostic markers and liver function markers in acute hepatitis E. METHODS: Seventy serum samples were collected from non-A, non-B, non-C acute hepatitis patients and tested for HEV markers (HEV antigen and RNA and anti-HEV IgM) and markers of liver function [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total iron binding capacity (TBA), gamma-glutamyl transferase (GGT), total bilirubin (TBIL), and direct bilirubin (DBIL)]. Partial open reading frame (ORF) 2 sequences from HEV RNA-positive samples were cloned and analyzed. RESULTS: The concordances between HEV antigen and HEV RNA and between HEV antigen and anti-HEV IgM were 77.1% and 72.9%, respectively, with significant correlations, while that between HEV RNA and anti-HEV IgM was 61.4% with no significant correlation. Eleven of 25 samples negative for anti-HEV IgM were positive for HEV antigen. The ALT, AST, ALP, TBA, GGT, TBIL, and DBIL levels did not differ significantly between the anti-HEV IgM-positive and -negative groups. However, the ALT, AST, ALP, TBA, and GGT levels were significantly higher in the HEV antigen-positive group than in the HEV antigennegative group. All of the HEV isolates cloned belonged to genotype 4. CONCLUSIONS: HEV antigen was highly correlated with HEV RNA and elevated ALT, AST, ALP, TBA, and GGT levels. Testing for HEV antigen in combination with anti-HEV IgM is useful for the diagnosis of HEV infection.

[Hepatitis E virus. Position of the Blood Study Circle of the Federal Ministry of Health].
Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz 51: 90-97, 2008.

Statement on hepatitis vaccines for travellers. An Advisory Committee Statement (ACS).
Can Commun Dis Rep 34: 1-24, 2008.

Ahmed AI, Vreede RW, Al-Saudi N, Herremans M, and Brouwer JT.

[A man who contracted hepatitis E in the Netherlands].
Ned Tijdschr Geneeskd 152: 2689-2692, 2008.

A 55-year-old man was admitted to our hospital because of malaise, jaundice en cholestatic liver function impairment, 4 days after his return from vacation in Surinam. Serological tests were positive for IgG and IgM antibodies to hepatitis E virus (HEV) and serum PCR was positive, consistent with HEV infection. The infection was acquired in the Netherlands and not abroad, considering the incubation period. The patient recovered spontaneously. HEV infection is rare in the Netherlands and is associated with travel to tropical or subtropical areas. The virus is transmitted by the faecal-oral route through contaminated water or food. Since 2000 there have been cases reported in the Netherlands, without any association with travelling abroad and in which the infection might be related to zoonotic transmission. The diagnosis is primarily based upon serologic tests for the detection of IgM and IgG antibodies to HEV in serum confirmed by immunoblot. It is important that HEV infection is considered in patients with acute hepatitis in whom no other cause can be found for hepatitis, even without any travel history to endemic areas.

Bazaco MC, Albrecht SA, and Malek AM.
Preventing foodborne infection in pregnant women and infants.
Nurs Womens Health 12: 46-55, 2008.

Bernuau J, Nicand E, and Durand F.
Hepatitis E-associated acute liver failure in pregnancy: an Indian puzzle.
Hepatology 48: 1380-1382, 2008.

Bihl F, and Negro F.
[New aspects of HEV infection].
Rev Med Suisse 4: 1863-1866, 2008.

The hepatitis E virus (HEV), known for being the cause of major outbreaks of waterborne hepatitis in Asia and Africa, is an emerging pathogen in industrialized countries. Virologic analyses of sporadic cases in Europe, Japan and the United States have shown that the origin of the infection was through autochthonous viral strains suggesting that the virus is present locally. In addition, transmission is not only enterically through contaminated water but also through ingestion of undercooked infected meat (swine or wild animals) or through infected blood products. Recently, a persistent HEV infection with chronic hepatitis and cirrhosis has been reported in patients with reduced immune surveillance as induced by chemotherapy or post-transplant immunesuppression.

Borgen K, Herremans T, Duizer E, Vennema H, Rutjes S, Bosman A, de Roda Husman AM, and Koopmans M.
Non-travel related Hepatitis E virus genotype 3 infections in the Netherlands; a case series 2004 - 2006.
BMC Infect Dis 8: 61, 2008.

BACKGROUND: Human hepatitis E virus (HEV) infections are considered an emerging disease in industrialized countries. In the Netherlands, Hepatitis E virus

(HEV) infections have been associated with travel to high-endemic countries. Non-travel related HEV of genotype 3 has been diagnosed occasionally since 2000. A high homology of HEV from humans and pigs suggests zoonotic transmission but direct molecular and epidemiological links have yet to be established. We conducted a descriptive case series to generate hypotheses about possible risk factors for non-travel related HEV infections and to map the genetic diversity of HEV. METHODS: A case was defined as a person with HEV infection laboratory confirmed (positive HEV RT-PCR and/or HEV IgM) after 1 January 2004, without travel to a high-endemic country three months prior to onset of illness. For virus identification 148 bp of ORF2 was sequenced and compared with HEV from humans and pigs. We interviewed cases face to face using a structured questionnaire and collected information on clinical and medical history, food preferences, animal and water contact. RESULTS: We interviewed 19 cases; 17 were male, median age 50 years (25-84 y), 12 lived in the North-East of the Netherlands and 11 had preexisting disease. Most common symptoms were dark urine (n = 16) and icterus (n = 15). Sixteen ate pork >/= once/week and six owned dogs. Two cases had received blood transfusions in the incubation period. Seventeen cases were viremic (genotype 3 HEV), two had identical HEV sequences but no identified relation. For one case, HEV with identical sequence was identified from serum and surface water nearby his home. CONCLUSION: The results show that the modes of transmission of genotype-3 HEV infections in the Netherlands remains to be resolved and that host susceptibility may play an important role in development of disease.

Bouwknegt M, Engel B, Herremans MM, Widdowson MA, Worm HC, Koopmans MP, Frankena K, de Roda Husman AM, De Jong MC, and Van Der Poel WH.
Bayesian estimation of hepatitis E virus seroprevalence for populations with different exposure levels to swine in The Netherlands.
Epidemiol Infect 136: 567-576, 2008.

Hepatitis E virus (HEV) is ubiquitous in pigs worldwide and may be zoonotic. Previous HEV seroprevalence estimates for groups of people working with swine were higher than for control groups. However, discordance among results of anti-HEV assays means that true seroprevalence estimates, i.e. seroprevalence due to previous exposure to HEV, depends on choice of seroassay. We tested blood samples from three subpopulations (49 swine veterinarians, 153 non-swine veterinarians and 644 randomly selected individuals from the general population) with one IgM and two IgG ELISAs, and subsets with IgG and/or IgM Western blots. A Bayesian stochastical model was used to combine results of all assays. The model accounted for imperfection of each assay by estimating sensitivity and specificity, and accounted for dependence between serological assays. As expected, discordance among assay results occurred. Applying the model yielded seroprevalence estimates of approximately 11% for swine veterinarians,approximately 6% for non-swine veterinarians and approximately 2% for the general population. By combining the results of five serological assays in a Bayesian stochastical model we confirmed that exposure to swine or their environment was associated with elevated HEV seroprevalence.

Bouwknegt M, Frankena K, Rutjes SA, Wellenberg GJ, de Roda Husman AM, van der Poel WH, and de Jong MC.
Estimation of hepatitis E virus transmission among pigs due to contact-exposure.
Vet Res 39: 40, 2008.

Locally acquired hepatitis E in humans from industrialized countries has been

repeatedly suggested to originate from pigs. Pigs may serve as a reservoir of hepatitis E virus (HEV) for humans when a typical infected pig causes on average more than one newly infected pig, a property that is expressed by the basic reproduction ratio R(0). In this study, R(0) for HEV transmission among pigs was estimated from chains of one-to-one transmission experiments in two blocks of five chains each. Per chain, susceptible first-generation contact pigs were contact-exposed to intravenously inoculated pigs, subsequently susceptible second-generation contact pigs were contact-exposed to infected first-generation contact pigs, and lastly, susceptible third-generation contact pigs were contact-exposed to infected second-generation contact pigs. Thus, in the second and third link of the chain, HEV-transmission due to contact with a contact-infected pig was observed. Transmission of HEV was monitored by reverse transcriptase polymerase chain reaction (RT-PCR) on individual faecal samples taken every two/three days. For susceptible pigs, the average period between exposure to an infectious pig and HEV excretion was six days (standard deviation: 4). The length of HEV-excretion (i.e. infectious period) was estimated at 49 days (95% confidence interval (CI): 17-141) for block 1 and 13 days (95% CI: 11-17) for block 2. The R0 for contact-exposure was estimated to be 8.8 (95% CI: 4-19), showing the potential of HEV to cause epidemics in populations of pigs.

Buti M, Plans P, Dominguez A, Jardi R, Rodriguez Frias F, Esteban R, Salleras L, and Plasencia A.
Prevalence of hepatitis E virus infection in children in the northeast of Spain.
Clin Vaccine Immunol 15: 732-734, 2008.

The prevalence of immunoglobulin G (IgG) anti-hepatitis E virus (anti-HEV) antibodies was studied with a representative sample of 1,249 healthy children aged between 6 and 15 years. IgG anti-HEV antibodies were detected in 57 (4.6%) of the 1,249 samples analyzed, suggesting that some children are exposed to HEV in early childhood.

Chandra V, Taneja S, Kalia M, and Jameel S.
Molecular biology and pathogenesis of hepatitis E virus.
J Biosci 33: 451-464, 2008.

The hepatitis E virus (HEV) is a small RNA virus and the etiological agent for hepatitis E, a form of acute viral hepatitis. The virus has a feco-oral transmission cycle and is transmitted through environmental contamination, mainly through drinking water. Recent studies on the isolation of HEV-like viruses from animal species also suggest zoonotic transfer of the virus. The absence of small animal models of infection and ef?cient cell culture systems has precluded virological studies on the replication cycle and pathogenesis of HEV. A vaccine against HEV has undergone successful clinical testing and diagnostic tests are available. This review describes HEV epidemiology, clinical presentation, pathogenesis, molecular virology and the host response to HEV infection. The focus is on published literature in the past decade.

Chau TN.
Hepatitis E: A potential vaccine-preventable disease needs global concern.
J Gastroenterol Hepatol 23: 827-828, 2008.

Christensen PB, Engle RE, Hjort C, Homburg KM, Vach W, Georgsen J, and Purcell RH.
Time trend of the prevalence of hepatitis E antibodies among farmers and blood donors: a potential zoonosis in Denmark.
Clin Infect Dis 47: 1026-1031, 2008.

BACKGROUND: Antibody to hepatitis E virus (anti-HEV) is prevalent in Western countries, where clinical hepatitis E is rarely reported. The aim of this study was to determine the prevalence of anti-HEV among Danish blood donors and Danish farmers. In addition, we compared the prevalence among 2 sets of serum samples obtained from blood donors 20 years apart. METHODS: Samples from 291 Danish farmers and 169 blood donors that were collected in 1983 and samples from 461 blood donors that were collected in 2003 were tested for anti-HEV. Relevant information on HEV exposure was collected by self-administered questionnaire. RESULTS: Anti-HEV testing was performed on samples after 20 years of storage at -20 degrees C. The prevalence of anti-HEV was 50.4% among farmers and 32.9% among donors in 1983 and 20.6% among donors in 2003 ($P < .05$). Presence of anti-HEV was significantly correlated with increasing age in all 3 groups ($P < .05$). Among donors who had serum samples obtained in 2003, age, contact with horses, and the presence of antibody to hepatitis A virus were associated with the presence of anti-HEV in multivariate analysis. Among farmers, only age was independently associated with the presence of anti-HEV. CONCLUSION: Anti-HEV was highly prevalent among Danes but has decreased in prevalence over the past 50 years. Our study supports the hypothesis that HEV infection in Denmark may be an asymptomatic zoonotic infection.

Dalton HR, Bendall R, Ijaz S, and Banks M.
Hepatitis E: an emerging infection in developed countries.
Lancet Infect Dis 8: 698-709, 2008.

REVIEW Hepatitis E is endemic in many developing countries where it causes substantial morbidity. In industrialised countries, it is considered rare, and largely confined to travellers returning from endemic areas. However, there is now a growing body of evidence that challenges this notion. Autochthonous hepatitis E in developed countries is far more common than previously recognised, and might be more common than hepatitis A. Hepatitis E has a predilection for older men in whom it causes substantial morbidity and mortality. The disease has a poor prognosis in the context of pre-existing chronic liver disease, and is frequently misdiagnosed as drug-induced liver injury. The source and route of infection remain uncertain, but it might be a porcine zoonosis. Patients with unexplained hepatitis should be tested for hepatitis E, whatever their age or travel history.

Dalton HR, Stableforth W, Hazeldine S, Thurairajah P, Ramnarace R, Warshow U, Ijaz S, Ellis V, and Bendall R.
Autochthonous hepatitis E in Southwest England: a comparison with hepatitis A.
Eur J Clin Microbiol Infect Dis 27: 579-585, 2008.

The incidence of hepatitis A is falling. In contrast, autochthonous hepatitis E is an emerging infection in developed countries. The objective of this study was to compare both laboratory-confirmed cases of hepatitis A and autochthonous hepatitis E over a 2-year period in Cornwall and Devon and anti-hepatitis A virus (HAV) IgG and anti-hepatitis E virus (HEV) IgG seroprevalence in blood donors. The databases

of microbiology laboratories in Cornwall and Devon were searched for the number of diagnostic HEV and HAV assays performed during 2005-2006 and the number of confirmed cases of acute hepatitis A and hepatitis E detected. Patients were followed up until recovery or death. Sera from 500 blood donors from the regional centre were tested for HEV and HAV IgG. In total, 28 cases of autochthonous hepatitis E were identified from 838 assays, and 20 cases of hepatitis A were identified from 4503 assays. Compared to hepatitis A cases, patients with hepatitis E were older (mean age 61 vs. 45 years, P = 0.003), less likely to present in winter (P = 0.028) and had more complications (five vs. one). The IgG seroprevalence rates in blood donors were 45% for HAV and 16% for HEV. There was no relationship between HAV and HEV IgG seropositivity. Autochthonous hepatitis E may be more common than hepatitis A, affects older patients, is less likely to occur in winter and may be associated with more complications. Patients with acute hepatitis, whatever their age or travel history, should be tested for HEV.

Dalton HR, Stableforth W, Thurairajah P, Hazeldine S, Remnarace R, Usama W, Farrington L, Hamad N, Sieberhagen C, Ellis V, Mitchell J, Hussaini SH, Banks M, Ijaz S, and Bendall RP.
Autochthonous hepatitis E in Southwest England: natural history, complications and seasonal variation, and hepatitis E virus IgG seroprevalence in blood donors, the elderly and patients with chronic liver disease.
Eur J Gastroenterol Hepatol 20: 784-790, 2008.

AIMS: To report the natural history of autochthonous hepatitis E and hepatitis E virus (HEV) IgG seroprevalence in Southwest England. METHODS: Patients with unexplained hepatitis were tested for hepatitis E and cases followed until recovery or death. Five hundred blood donors, 336 individuals over the age of 60 years and 126 patients with chronic liver disease were tested for HEV IgG. RESULTS: Forty cases of autochthonous hepatitis E (genotype 3) were identified. Hepatitis E was anicteric in 25% of cases and usually caused a self-limiting hepatitis predominantly in elderly Caucasian males. Six of 40 had a significant complication and three patients died, two of who had previously undiagnosed cirrhosis. Hepatitis E shows a seasonal variation with peaks in the spring and summer and no cases in November and December. HEV IgG prevalence increases with age, is more common in men and is 16% in blood donors, 13% in patients with chronic liver disease and 25% in individuals over 60 years. CONCLUSION: Autochthonous hepatitis E is more common than previously recognized, and should be considered in the differential diagnosis in patients with hepatitis, whatever their age or travel history. It carries a significant morbidity and when seen in the context of chronic liver disease carries an adverse prognosis.

de Deus N, Casas M, Peralta B, Nofrarias M, Pina S, Martin M, and Segales J.
Hepatitis E virus infection dynamics and organic distribution in naturally infected pigs in a farrow-to-finish farm.
Vet Microbiol 132: 19-28, 2008.

The objective of the present study was to determine the pattern of Hepatitis E virus (HEV) infection in a naturally infected, farrow-to-finish herd. For that purpose, a prospective study was conducted in randomly selected 19 sows and 45 piglets. Blood samples were collected from sows at 1 week post-farrowing and from piglets at 1, 3, 6, 9, 12, 15, 18 and 22 weeks of age. Furthermore 3 or 5 animals were necropsied at each bleeding day (but at 1 week of age), and serum, bile, liver, mesenteric lymph nodes and faeces taken. HEV IgG, IgM and IgA antibodies were determined in serum

and viral RNA was analysed in all collected samples by semi-nested RT-PCR. Histopathological examination of mesenteric lymph nodes and liver was also conducted. From 13 analysed sows, 10 (76.9%) were positive to IgG, one to IgA (7.7%) and two to IgM (15.4%) antibodies specific to HEV. In piglets, IgG and IgA maternal antibodies lasted until 9 and 3 weeks of age, respectively. IgG seroconversion occurred by 15 weeks of age while IgM and IgA at 12. On individual basis, IgG was detectable until the end of the study while IgM and IgA antibody duration was of 4-7 weeks. HEV RNA was detected in serum at all analysed ages with the highest prevalence at 15 weeks of age. HEV was detected in faeces and lymph nodes for the first time at 9 weeks of age and peaked at 12 and 15 weeks of age. This peak coincided with the occurrence of hepatitis as well as with HEV detection in bile, liver, mesenteric lymph nodes and faeces, and also with highest IgG and IgM OD values at 15 weeks. Finally, different HEV sequences from this farm were obtained, which they clustered within 3 different groups, together with other Spanish sequences, all of them of genotype 3. Moreover, the present study also indicates that the same pig can be infected with at least two different strains of HEV during its productive life. This is the first study characterizing HEV infection in naturally infected pigs with chronological virus detection and its relationship with tissue lesions throughout the productive life of the animals.

De Silva AN, Muddu AK, Iredale JP, Sheron N, Khakoo SI, and Pelosi E.
Unexpectedly high incidence of indigenous acute hepatitis E within South Hampshire: time for routine testing?
J Med Virol 80: 283-288, 2008.

Hepatitis E indigenous to developed countries (hepatitis EIDC) is a form of hepatitis E in persons with no travel history to highly endemic areas. It has been recognized recently as an emerging clinical entity in a significant number of economically developed countries including UK. However, it is still perceived as a rare disease and routine laboratory testing for hepatitis E is not performed. A series of 13 cases of hepatitis EIDC, diagnosed in a 13-month period from June 2005 within a single center in South Hampshire, UK, is presented. These patients were identified after implementing a novel-screening algorithm that introduced routine hepatitis E serological investigations. Patients were middle aged or elderly and males were affected more commonly. Four patients (31%) required hospital admission. All reverse transcriptase-polymerase chain reaction (RT-PCR) confirmed cases carried hepatitis E virus (HEV) genotype-3, which bore close sequence homology to HEV circulating in UK pigs. None of these patients recalled eating undercooked pork products or close contact with pigs during the 2 months preceding the onset of acute hepatitis. In comparison, during the same period, only two cases of hepatitis A and five cases of acute hepatitis B were diagnosed. These data illustrate the importance of introducing routine hepatitis E testing in all patients with unexplained acute liver disease and absence of relevant travel history. Routine testing can clarify hepatitis E epidemiology whilst improving the clinical management of patients with acute liver disease.

Degertekin B, and Lok AS.
Update on viral hepatitis: 2007.
Curr Opin Gastroenterol 24: 306-311, 2008.

PURPOSE OF REVIEW: This is a concise review of recent developments in the field of viral hepatitis, based on publications between December 2006 and November 2007. RECENT FINDINGS: Hepatitis A vaccine has similar efficacy to immune

globulin as postexposure prophylaxis. Entecavir is a potent antiviral agent with a low rate of drug resistance in nucleoside-naive chronic hepatitis B patients but it is not as effective in lamivudine-refractory patients. A combination of adefovir and lamivudine is preferred to adefovir monotherapy for lamivudine-refractory hepatitis B patients. Two orally administered hepatitis C protease inhibitors, telaprevir and boceprevir, were shown to have antiviral activity in hepatitis C genotype 1 patients. A 16-week course of pegylated interferon and ribavirin resulted in a lower rate of sustained virologic response compared with the standard 24-week course. Patients with hepatitis C-related cirrhosis who achieved sustained virologic response to antiviral therapy remain at risk for hepatocellular carcinoma. A novel recombinant hepatitis E vaccine was shown to be safe and effective in preventing infection. SUMMARY: Advances have been made in the prevention of hepatitis A and hepatitis E. It is likely that specifically targeted antiviral therapies for hepatitis C will be available in the next few years.

Di Bartolo I, Martelli F, Inglese N, Pourshaban M, Caprioli A, Ostanello F, and Ruggeri FM.
Widespread diffusion of genotype 3 hepatitis E virus among farming swine in Northern Italy.
Vet Microbiol 132: 47-55, 2008.

Hepatitis E virus (HEV) causes acute hepatitis in humans, and infects several animal species, mostly asymptomatically. Swine and human HEV strains are genetically related suggesting both a zoonotic and a possible foodborne transmission. The prevalence of swine HEV was investigated in 274 randomly selected pigs from six different swine farms of Northern Italy, testing viral RNA in stools by nested reverse-transcription-polymerase chain reaction. HEV genome was detected in 115 stools (42%). All farms resulted positive for HEV, with a prevalence ranging between 12.8% and 72.5%. HEV-positive pigs were detected in all age groups and production stages tested, although infection was more prevalent in weaners than in the older fatteners (42.2% vs. 27.0%). Genetic characterization of swine strains identified was performed by sequencing and database alignment. Phylogenetic analysis on the nucleotide sequences from 16 positive PCR products indicated that all strains belonged to genotype 3. In particular, one group of seven Italian strains clustered close (91.6-96.2% identity) to human and swine European HEV strains.

Feagins AR, Opriessnig T, Guenette DK, Halbur PG, and Meng XJ.
Inactivation of infectious hepatitis E virus present in commercial pig livers sold in local grocery stores in the United States.
Int J Food Microbiol 123: 32-37, 2008.

Hepatitis E virus (HEV) is a zoonotic pathogen and pigs are a known reservoir. Recently we showed that approximately 11% of commercial pig livers sold in local U.S. grocery stores for food consumptions are contaminated by infectious HEV. In this study, a swine bioassay was used to determine if the infectious HEV in contaminated commercial pig livers could be inactivated by traditional cooking methods. Group 1 pigs (n=5) were each inoculated intravenously (i.v.) with a HEV-negative liver homogenate as negative controls, group 2 pigs (n=5) were each inoculated i.v. with a pool of two HEV-positive pig liver homogenates as positive controls, groups 3, 4 and 5 pigs (n=5, each group) were each inoculated i.v. with a pool of homogenates of two HEV-positive livers incubated at 56 degrees C for 1 h, stir-fried at 191 degrees C (internal temperature of 71 degrees C) for 5 min or boiled in water for 5 min, respectively. As expected, the group 2 positive control pigs all

became infected whereas the group 1 negative control pigs remained negative. Four of the five pigs inoculated with HEV-positive liver homogenates incubated at 56 degrees C for 1 h also became infected. However, pigs in groups 4 and 5 did not become infected. The results indicated that HEV in contaminated commercial pig livers can be effectively inactivated if cooked properly, although incubation at 56 degrees C for 1 h cannot inactivate the virus. Thus, to reduce the risk of food-borne HEV transmission, pig livers must be thoroughly cooked.

Feagins AR, Opriessnig T, Huang YW, Halbur PG, and Meng XJ.
Cross-species infection of specific-pathogen-free pigs by a genotype 4 strain of human hepatitis E virus.
J Med Virol 80: 1379-1386, 2008.

Hepatitis E virus (HEV) is an important pathogen. The animal strain of HEV, swine HEV, is related to human HEV. The genotype 3 swine HEV can infect humans and genotype 3 human HEV can infect pigs. The genotype 4 swine and human HEV strains are genetically related, but it is unknown whether genotype 4 human HEV can infect pigs. A swine bioassay was utilized in this study to determine whether genotype 4 human HEV can infect pigs. Fifteen, 4-week-old, specific-pathogen-free pigs were divided into three groups of five each. Group 1 pigs were each inoculated intravenously with PBS buffer as negative controls, group 2 pigs similarly with genotype 3 human HEV (strain US-2), and group 3 pigs similarly with genotype 4 human HEV (strain TW6196E). Serum and fecal samples were collected at 0, 7, 14, 21, 28, 35, 42, 49, and 56 days postinoculation (dpi) and tested for evidence of HEV infection. All pigs were necropsied at 56 dpi. As expected, the negative control pigs remained negative. The positive control pigs inoculated with genotype 3 human HEV all became infected as evidenced by detection of HEV antibodies, viremia and fecal virus shedding. All five pigs in group 3 inoculated with genotype 4 human HEV also became infected: fecal virus shedding and viremia were detected variably from 7 to 56 dpi, and seroconversion occurred by 28 dpi. The data indicated that genotype 4 human HEV has an expanded host range, and the results have important implications for understanding the natural history and zoonosis of HEV.

Gerolami R, Moal V, and Colson P.
Chronic hepatitis E with cirrhosis in a kidney-transplant recipient.
N Engl J Med 358: 859-860, 2008.

Guo H, Zhou EM, Sun ZF, and Meng XJ.
Immunodominant epitopes mapped by synthetic peptides on the capsid protein of avian hepatitis E virus are non-protective.
Viral Immunol 21: 61-67, 2008.

Avian hepatitis E virus (avian HEV) was recently discovered in chickens with hepatitis-splenomegaly syndrome in the United States. The open reading frame 2 (ORF2) protein of avian HEV has been shown to cross-react with human and swine HEV ORF2 proteins, and immunodominant antigenic epitopes on avian HEV ORF2 protein were identified in the predicted antigenic domains by synthetic peptides. However, whether these epitopes are protective against avian HEV infection has not been investigated. In this study, groups of chickens were immunized with keyhole limpet hemocyanin (KLH)-conjugated peptides and recombinant avian HEV ORF2 antigen followed by challenge with avian HEV virus to assess the protective capacity

of these peptides containing the epitopes. While avian HEV ORF2 protein showed complete protection against infection, viremia and fecal virus shedding were found in all peptide-immunized chickens. Using purified IgY from normal, anti-peptide, and anti-avian HEV ORF2 chicken sera, an in-vitro neutralization and in-vivo monitoring assay was performed to further evaluate the neutralizing ability of anti-peptide IgY. Results showed that none of the anti-peptide IgY can neutralize avian HEV in vitro, as viremia, fecal virus shedding, and seroconversion appeared similarly in chickens inoculated with avian HEV mixed with anti-peptide IgY and chickens inoculated with avian HEV mixed with normal IgY. As expected, chickens inoculated with the avian HEV and anti-avian HEV ORF2 IgY mixture did not show detectable avian HEV infection. Taken together, the results of this study demonstrated that immunodominant epitopes on avian HEV ORF2 protein identified by synthetic peptides are non-protective, suggesting protective neutralizing epitope on avian HEV ORF2 may not be linear as is human HEV.

Haagsma EB, van den Berg AP, Porte RJ, Benne CA, Vennema H, Reimerink JH, and Koopmans MP.
Chronic hepatitis E virus infection in liver transplant recipients.
Liver Transpl 14: 547-553, 2008.

Hepatitis E virus (HEV) infection is known to run a self-limiting course. Sporadic cases of acute hepatitis due to infection with HEV genotype 3, present in pig populations, are increasingly recognized. Zoonotic transmission seems infrequent. The entity of unexplained chronic hepatitis after liver transplantation has been recognized. Detection of HEV in 2 liver transplant recipients triggered a review of these cases. Freeze-stored sera were available for retrospective analysis. HEV antibodies were determined. For virus detection and identification, a fragment of the gene encoding the major capsid protein (open reading frame 2) was amplified by reverse-transcription polymerase chain reaction and sequenced to identify the genotype. Two months after liver transplantation, case A developed unexplained chronic hepatitis, which developed into cirrhosis. Retransplantation followed 7 years later, after which chronic hepatitis recurred. In retrospect, HEV RNA was present in serum 3 weeks after the first transplantation and remained present afterwards. HEV RNA was also present in retransplant liver tissue. HEV antibodies appeared late after retransplantation. Case B developed unexplained chronic hepatitis 7 years after transplantation. Retransplantation was needed 5 years later, after which no signs of hepatitis recurred. In retrospect, the period of chronic hepatitis up to the retransplantation coincided with HEV RNA in serum. In case B, antibodies developed, the viral load was much lower than in case A, and the virus seemed to be cleared after retransplantation. Genotyping in both cases revealed 2 unique strains of genotype 3. In conclusion, chronic HEV infection may develop in immunosuppressed patients, who may then serve as long-term carriers of the virus. We hypothesize that HEV may be the cause of chronic hepatitis in liver transplant recipients.

He S, Miao J, Zheng Z, Wu T, Xie M, Tang M, Zhang J, Ng MH, and Xia N.
Putative receptor-binding sites of hepatitis E virus.
J Gen Virol 89: 245-249, 2008.

A truncated structural protein of hepatitis E virus (HEV), p239, occurs as 23 nm particles consisting of partial homodimers. As the latter resemble the HEV capsomere structurally and antigenically, it was postulated that the recombinant protein may serve as a probe for the HEV receptor. This hypothesis was supported by findings that purified p239 bound and penetrated different cell lines that are

susceptible to HEV, and inhibited HEV infection of these cells. The binding was blocked by four of six monoclonal antibodies (mAbs) reactive against the dimeric domain of p239, and by two of three mAbs reactive against its monomeric domain, suggesting that binding may involve a portion of each domain. Mutation affecting the monomeric domain had no effect on binding or capacity to block HEV infection, whereas that affecting the dimeric domain diminished binding of the mutant peptide markedly and abrogated its capacity to block HEV infection. These results suggest that HEV infection might involve distinct receptor-binding sites.

Hu WP, Lu Y, Precioso NA, Chen HY, Howard T, Anderson D, and Guan M.
Double-antigen enzyme-linked immunosorbent assay for detection of hepatitis E virus-specific antibodies in human or swine sera.
Clin Vaccine Immunol 15: 1151-1157, 2008.

A new double-antigen sandwich-based enzyme-linked immunosorbent assay (ELISA) for the detection of total antibodies (immunoglobulin G [IgG] and IgM) specific for hepatitis E virus (HEV) was developed by utilizing well-characterized recombinant protein ET2.1 and its peroxidase-labeled counterpart. Our study showed that the ELISA detected all the positive patient samples (n = 265) regardless of whether they contained IgM or IgG antibodies, or both, while it maintained an excellent specificity of 98.8% with samples from various patient or healthy control groups (total number of samples, 424). The test had a detection limit for anti-HEV IgG antibodies that was equivalent to 62 mIU/ml of the international reference. Compared with the serological status of the specimens determined on the basis of tests performed at the individual collection sites, the testing outcome generated by the new ELISA had a good agreement of 99.3%, with a kappa value of 0.985. The positive predictive value and the negative predictive value for the new test reached 98.1% and 100%, respectively. This ELISA had a positive delta value of 4.836 and a negative delta value of 3.314 (where delta is a measure of the number of standard deviations by which the cutoff is separated from the mean of the sample groups) (N. Crofts, W. Maskill, and I. D. Gust, J. Virol. Methods 22:51-59, 1988), indicating that it had an excellent ability to differentiate the infected and noninfected cohorts. Furthermore, the new design enables the detection of antibodies not only in human samples but also in pig samples. Our preliminary data showed that the ELISA could detect seroconversion in samples from pigs at as early as 14 days postinoculation. The potential utility of detecting specific antibodies in pigs will be an added advantage for managing the disease, with suggested zoonotic implications.

Huang W, Zhang H, Harrison TJ, Lang S, Huang G, and Wang Y.
Cross-protection of hepatitis E virus genotypes 1 and 4 in rhesus macaques.
J Med Virol 80: 824-832, 2008.

The purpose of this study was to determine cross-protection between HEV genotypes 1 and 4, which are prevalent in China. Fecal suspensions of genotypes 1 and 4 from patients, as well as genotype 4 from swine, were inoculated intravenously into rhesus macaques. Each inoculum contained 5 x 10(4) genome equivalents of HEV. After infection, serum and fecal samples were collected serially and the levels of alanine aminotransferase (ALT) and anti-HEV IgG and IgM in sera, and HEV RNA in fecal samples, were measured. Liver biopsies were carried out. All the infected monkeys (12/12) developed anti-HEV IgG and exhibited fecal shedding of virus. IgM was detected in 11 of 12, and ALT elevation occurred about 2-6 weeks post-inoculation in 10 of 12, infected monkeys. Hepatic histopathology was consistent with acute viral hepatitis and the ORF2 antigen of HEV was detected in the granular

cytoplasm of hepatocytes by immunohistochemistry. After recovery from their initial HEV infection, the monkeys were challenged with a heterologous genotype or heterologous source of HEV and monitored for hepatitis and fecal shedding. Previous infection with HEV completely or partially protected against subsequent challenge with a heterologous virus, because 7 of 11 monkeys did not develop HEV infection or shed virus in the feces, and none of them developed hepatitis or exhibited ALT elevation or liver biopsy findings of hepatitis. In conclusion, previous HEV infection may give rise to cross-genotype and cross-host-species protection.

Izopet J, and Kamar N.
[Hepatitis E: from zoonotic transmission to chronic infection in immunosuppressed patients].
Med Sci (Paris) 24: 1023-1025, 2008.

Kamar N, Selves J, Mansuy JM, Ouezzani L, Peron JM, Guitard J, Cointault O, Esposito L, Abravanel F, Danjoux M, Durand D, Vinel JP, Izopet J, and Rostaing L.
Hepatitis E virus and chronic hepatitis in organ-transplant recipients.
N Engl J Med 358: 811-817, 2008.

Hepatitis E virus (HEV) is considered an agent responsible for acute hepatitis that does not progress to chronic hepatitis. We identified 14 cases of acute HEV infection in three patients receiving liver transplants, nine receiving kidney transplants, and two receiving kidney and pancreas transplants. All patients were positive for serum HEV RNA. Chronic hepatitis developed in eight patients, as confirmed by persistently elevated aminotransferase levels, serum HEV RNA, and histologic features of chronic hepatitis. The time from transplantation to diagnosis was significantly shorter and the total counts of lymphocytes and of CD2, CD3, and CD4 T cells were significantly lower in patients in whom chronic disease developed.

Kamihira T, Yano K, Tamada Y, Matsumoto T, Miyazato M, Nagaoka S, Ohata K, Abiru S, Komori A, Daikoku M, Yatsuhashi H, and Ishibashi H.
[Case of domestically infected hepatitis E with marked thrombocytopenia].
Nippon Shokakibyo Gakkai Zasshi 105: 841-846, 2008.

REVIEW A 52-year-old man was admitted to our hospital for fever, jaundice, and general malaise. Laboratory data revealed elevated serum liver enzyme levels (AST 2377IU/L, ALT 2756IU/L) and bilirubin (T-Bil 3.7 mg/dl). Blood count showed a marked decrease of platelets (2.0 x 10(4)/microl). Serological and virological analysis showed positive results for HEV IgM and HEV RNA, indicating a diagnosis of acute hepatitis E. The serum ferritin level was also markedly elevated (23200 ng/ml). A diagnosis of virus associated hemophagocytic syndrome (VAHS) was strongly suggested. This is the first report of hepatitis E most likely accompanied by VAHS

Kaya AD, Ozturk CE, Yavuz T, Ozaydin C, and Bahcebasi T.
Changing patterns of hepatitis A and E sero-prevalences in children after the 1999 earthquakes in Duzce, Turkey.
J Paediatr Child Health 44: 205-207, 2008.

AIM: Hepatitis A and E are enteric viral diseases that are characteristically found in developing countries. Sero-epidemiological data about both infections showed higher prevalence rates soon after the 1999 earthquakes in Duzce, Turkey. The aim of the

present study was to evaluate the data 4 years after the earthquakes. METHODS: The study group included 589 children (72.3% boys) who were between the ages of 6 months and 17 years (mean age 11.5 years). The children were separated into three groups: Group 1 (ages 6 months to 5.9 years), Group 2 (ages 6.0-12.9 years) and Group 3 (ages 13.0-17.0 years). Serum anti-hepatitis A virus IgG and anti-hepatitis E virus IgG were determined using commercial enzyme-linked immunosorbent assay kits. The data were tested for statistical significance with the chi(2)-test. RESULTS: The sero-prevalence rates of hepatitis A and E were 63.8% and 0.3%, respectively. The sero-prevalence rates of both hepatitis A and E increased with age, and there was no significant difference between the genders. Hepatitis A infection was associated with socio-economic condition, crowded living environment, and education level of the family ($P < 0.01$). CONCLUSIONS: Hepatitis A infection is still common, whereas hepatitis E infection appears to be relatively rare in paediatric age groups in Duzce, Turkey.

Khuroo MS, and Khuroo MS.
Hepatitis E virus.
Curr Opin Infect Dis 21: 539-543, 2008.

REVIEW PURPOSE OF REVIEW: Hepatitis E is an emerging infectious disease. This review will focus on recent advances in the zoonotic transmission, global distribution and control of hepatitis E. RECENT FINDINGS: Hepatitis E virus infection is known to cause waterborne epidemics and sporadic infections in developing countries. Recently, there have been several reports on zoonotic foodborne autochthonous infections of hepatitis E in developed countries. Hepatitis E typically causes self-limited acute infection. Recent reports have documented hepatitis E virus causing chronic hepatitis and cirrhosis in patients after solid organ transplantation. High incidence and severity of hepatitis E in pregnant women have been re-confirmed. The reason for high mortality in pregnant women remains ill understood. A recombinant hepatitis E vaccine has been evaluated in a phase 2, randomized, placebo-controlled trial in Nepal and was found to be well tolerated and efficacious. SUMMARY: There has been considerable advance in understanding the epidemiology of hepatitis E virus infections in western countries. The occurrence of chronic hepatitis in organ transplant recipients opens a new chapter in hepatitis E epidemiology. The report on an efficacious and well tolerated recombinant vaccine gives hope for control of the disease in the near future.

Kuniholm MH, and Nelson KE.
Of organ meats and hepatitis E virus: one part of a larger puzzle is solved.
J Infect Dis 198: 1727-1728, 2008.

Lewis HC, Boisson S, Ijaz S, Hewitt K, Ngui SL, Boxall E, Teo CG, and Morgan D.
Hepatitis E in England and Wales.
Emerg Infect Dis 14: 165-167, 2008.

In 2005, 329 cases of hepatitis E virus infection were confirmed in England and Wales; 33 were confirmed indigenous infections, and a further 67 were estimated to be indigenous infections. Hepatitis E should be considered in the investigation of patients with hepatitis even if they have no history of travel.

Lockwood GL, Fernandez-Barredo S, Bendall R, Banks M, Ijaz S, and Dalton HR.
Hepatitis E autochthonous infection in chronic liver disease.
Eur J Gastroenterol Hepatol 20: 800-803, 2008.

Hepatitis E virus is endemic in many parts of the developing world and causes a self-limiting hepatitis in young adults, except in pregnant women and patients with chronic liver disease, where the mortality is high. Locally acquired hepatitis E is increasingly recognized in the developed world. It is caused by hepatitis E virus genotype 3, affects the middle-aged and the elderly, and may be a zoonotic infection from pigs. We present a case of locally acquired hepatitis E infection in a patient with previously undiagnosed cirrhosis, which resulted in subacute liver failure and death. We describe our attempt to trace this infection to a free-range pig farm adjacent to the patient's place of employment. Hepatitis E infection should be considered in the differential diagnosis in patients with decompensated chronic liver disease whatever their age or travel history. When found, the prognosis may be poor.

Mahtab MA, Rahman S, Khan M, Mamun AA, and Afroz S.
Etiology of fulminant hepatic failure: experience from a tertiary hospital in Bangladesh.
Hepatobiliary Pancreat Dis Int 7: 161-164, 2008.

BACKGROUND: Fulminant hepatic failure (FHF) is not uncommon in our clinical practice in Bangladesh. There was a rise in acute hepatitis E virus (HEV) in Bangladesh after the 2004 floods. At that time, most of the country was under water for more than a month, leading to sewage contamination of the water supply. The aim of this study was to investigate the etiology of FHF in Bangladesh. METHODS: In this retrospective study, 23 patients with FHF who presented with severe impairment of hepatocellular function (i.e. encephalopathy, coagulopathy and jaundice) within 6 months of onset of symptoms were included. There were 17 men and 6 women, aged from 18 to 32 years. Four of the women were pregnant. Patients were tested for markers for common hepatotrophic viruses. A relevant history was taken and the Patient Record Book of the Unit was reviewed. RESULTS: 56.52% patients (13/23) had HEV infection, and all were anti-HEV IgM-positive tested by ELISA. HBV infection was detected in 34.78% patients (8/23), all of whom were tested positive for either HBsAg or anti-HBs IgM by ELISA. 8.7% patients (2/23) had a positive history for intake of alcohol and/or drugs. CONCLUSIONS: Acute HEV infection is the leading cause of FHF in Bangladesh. Sewage contamination of the water supply following floods contributes to a higher incidence of HEV infection. HBV infection is also important.

Mansuy JM, Legrand-Abravanel F, Calot JP, Peron JM, Alric L, Agudo S, Rech H, Destruel F, and Izopet J.
High prevalence of anti-hepatitis E virus antibodies in blood donors from South West France.
J Med Virol 80: 289-293, 2008.

Cases of autochthonous acute hepatitis E occur in most industrialized countries and are frequent in the South West of France. The prevalence of anti-hepatitis E virus (HEV) IgG antibodies in blood donors in this area was determined. A total of 529 samples from rural and urban blood donors were tested. The overall prevalence was 16.6%, 19.1% of rural donors and 14.2% of urban donors had anti-HEV antibodies (P

= 0.13). The antibodies were widely distributed among all age groups and the sex ratio of the anti-HEV positive blood donors was 1.12 (P = 0.57). Hunting was the only pastime or profession associated with a high prevalence of anti-HEV antibodies (P = 0.038). The frequency of anti-HEV antibodies in blood donors could reflect active autochthonous transmission in this area of France. As the risk factors for HEV infection in industrialized countries are still unknown, further studies are needed to clarify the epidemiology of HEV infection in the Midi-Pyrenees region.

Matsubayashi K, Kang JH, Sakata H, Takahashi K, Shindo M, Kato M, Sato S, Kato T, Nishimori H, Tsuji K, Maguchi H, Yoshida J, Maekubo H, Mishiro S, and Ikeda H.
A case of transfusion-transmitted hepatitis E caused by blood from a donor infected with hepatitis E virus via zoonotic food-borne route.
Transfusion 48: 1368-1375, 2008.

BACKGROUND: Five cases of transfusion transmission of hepatitis E virus (HEV) have been reported so far. The infection routes of the causative donors remain unclear, however. Also, the progress of virus markers in the entire course of HEV infection has not been well documented. STUDY DESIGN AND METHODS: Nucleic acid testing was performed by real-time reverse transcription-polymerase chain reaction targeting the open reading frame 2 region of HEV. Full-length nucleotide sequences of HEV RNA were detected by direct sequencing. RESULTS: Lookback study of a HEV-positive donor revealed that the platelets (PLTs) donated from him 2 weeks previously contained HEV RNA and were transfused to a patient. Thirteen relatives including the donor were ascertained to enjoy grilled pork meats together in a barbecue restaurant 23 days before the donation. Thereafter, his father died of fulminant hepatitis E and the other 6 members showed serum markers of HEV infection. In the recipient, HEV was detected in serum on Day 22 and reached the peak of 7.2 log copies per mL on Day 44 followed by the steep increase of alanine aminotransferase. Immunoglobulin G anti-HEV emerged on Day 67; subsequently, hepatitis was resolved. HEV RNA sequences from the donor and recipient were an identical, Japan-indigenous strain of genotype 4. HEV RNA was detectable up to Day 97 in serum, Day 85 in feces, and Day 71 in saliva. CONCLUSION: A transfusion-transmitted hepatitis E case by blood from a donor infected via the zoonotic food-borne route and the progress of HEV markers in the entire course are demonstrated. Further studies are needed to clarify the epidemiology and the transfusion-related risks for HEV even in industrialized countries.

Moucari R, and Asselah T.
[Hepatitis E: vaccine in a near future?].
Rev Med Interne 29: 615-617, 2008.

Mushahwar IK.
Hepatitis E virus: molecular virology, clinical features, diagnosis, transmission, epidemiology, and prevention.
J Med Virol 80: 646-658, 2008.

REVIEW Hepatitis E virus (HEV), the sole member of the genus Hepevirus in the family of Hepeviridae, is the major cause of several outbreaks of waterborne hepatitis in tropical and subtropical countries and of sporadic cases of viral hepatitis in endemic and industrialized countries. Transmission of HEV occurs predominantly by

the fecal-oral route although parenteral and perinatal routes have been implicated. The overall death rate among young adults and pregnant women is 0.5-3% and 15-20%, respectively. HEV is a small non-enveloped particle that consists of a polyadenylated single-strand RNA molecule containing three discontinuous and partially overlapping open reading frames. There are four major genotypes of HEV and a single serotype. At present, there are approximately 1,600 sequences of HEV that are already available at INSDC of both human and animal isolates. Diagnostic and molecular assays have been described for the accurate differentiation of ongoing from remote infection of HEV. Identification and characterization of swine HEV in the United States, Japan, and many other countries and their close relationship to locally characterized human HEV found in the same geographic areas prove that HEV is indeed a zoonotic virus and that domestic swine, wild deer, and boars are reservoirs of HEV in nature. A cell culture system for the propagation of the virus has been described, and a very successful phase 2 vaccine trial has been completed. This review summarizes the current knowledge on the molecular biology, clinical features, transmission, diagnosis, epidemiology, and prevention of HEV.

Myint KS, and Gibbons RV.
Hepatitis E: a neglected threat.
Trans R Soc Trop Med Hyg 102: 211-212, 2008.

REVIEW Hepatitis E, responsible for explosive waterborne outbreaks and sporadic cases of acute hepatitis in developing countries, affects predominantly young adults and has a fatality rate as high as 25% in pregnant women. No effective treatment exists for hepatitis E; however, a vaccine using a baculovirus-expressed recombinant hepatitis E capsid protein was recently studied in Nepal. In this review, the progress made in hepatitis E research and the recently concluded vaccine trial of the recombinant protein vaccine are briefly discussed.

Navaneethan U, Al Mohajer M, and Shata MT.
Hepatitis E and pregnancy: understanding the pathogenesis.
Liver Int 28: 1190-1199, 2008.

REVIEW Hepatitis E virus (HEV) is a single-stranded RNA virus that causes large-scale epidemics of acute viral hepatitis, particularly in developing countries. In men and non-pregnant women, the disease is usually self-limited and has a case-fatality rate of less than <0.1%. However, in pregnant women, particularly from certain geographical areas in India, HEV infection is more severe, often leading to fulminant hepatic failure and death in a significant proportion of patients. In contrast, reports from Egypt, Europe and the USA have shown that the course and severity of viral hepatitis during pregnancy is not different from that in non-pregnant women. The reasons for this geographical difference are not clear. The high mortality rate in pregnancy has been thought to be secondary to the associated hormonal (oestrogen and progesterone) changes during pregnancy and consequent immunological changes. These immunological changes include downregulation of the p65 component of nuclear factor (NF-kappaB) with a predominant T-helper type 2 (Th2) bias in the T-cell response along with host susceptibility factors, mediated by human leucocyte antigen expression. Thus far, researchers were unable to explain the high HEV morbidity in pregnancy, why it is different from other hepatitis viruses such as hepatitis A with similar epidemiological features and the reason behind the difference in HEV morbidity in pregnant women in different geographical regions. The recent developments in understanding the immune response to HEV have encouraged us to review the possible mechanisms for these differences. Further research in the

immunology of HEV and pregnancy is required to conquer this disease in the near future.

Nicand E, Bigaillon C, and Tesse S.
[Hepatitis E: An emerging disease?].
Pathol Biol (Paris) 2008.

Although hepatitis E is one of the most important cause of acute clinical hepatitis in young adults throughout the developing world, hepatitis E is rare in western countries (25 to 60 annually by country). In these countries, clinical hepatitis is more common in older people (over 50 years). The possible transmission zoonotically (principally) from swine reservoir opens unexpected insights as an emerging disease. Direct foodborne and occupational exposure to pigs have been identified as routes of transmission. Other routes of transmission should be defined. Human sequences of hepatitis E virus are closely related to swine hepatitis E virus. Anti-HEV seropositivity rates ranges from 2-3% in blood donors to 20% in people exposed to animal reservoir.

Pavio N, Renou C, Di Liberto G, Boutrouille A, and Eloit M.
Hepatitis E: a curious zoonosis.
Front Biosci 13: 7172-7183, 2008.

REVIEW Hepatitis E virus (HEV) is responsible for large waterborne epidemics of acute hepatitis in endemic regions and for sporadic autochthonous cases in non endemic regions. Although the water vector has been thoroughly documented in endemic regions, very little is known about the modes of contamination occurring in non endemic regions. Unlike the other hepatitis viruses, HEV has an animal reservoir. Several lines of evidence, such as the results of phylogenic analysis and studies on direct contamination via infected food products, have suggested that some cases of animal to human transmission occur. However, all the possible sources of human contamination in non endemic areas have not yet been defined, and this point needs to be investigated. The high genetic variability of HEV, which might be an important factor, involved in zoonotic contamination processes, also needs a surveillance plan.

Purcell RH, and Emerson SU.
Hepatitis E: an emerging awareness of an old disease.
J Hepatol 48: 494-503, 2008.

REVIEW Although hepatitis E was recognized as a new disease in 1980, the virus was first visualized in 1983 and its genome was cloned and characterized in 1991, the disease is probably ancient but not recognized until modern times. Hepatitis E is the most important or the second most important cause of acute clinical hepatitis in adults throughout Asia, the Middle East and Africa. In contrast, hepatitis E is rare in industrialized countries, but antibody (anti-HEV) is found worldwide. HEV is a small round RNA-containing virus that is the only member of the genus Hepevirus in the family Hepeviridae. Although similar to hepatitis A virus in appearance, there are significant differences between the two viruses. Hepatitis E is principally the result of a water-borne infection in developing countries and is thought to be spread zoonotically (principally from swine) in industrialized countries. Because diagnostic tests vary greatly in specificity, sensitivity and availability, hepatitis E is probably underdiagnosed. At present, control depends upon improved hygiene; a highly

efficacious vaccine has been developed and tested, but it is not presently available.

Rehman S, Kapur N, Durgapal H, and Panda SK.
Subcellular localization of hepatitis E virus (HEV) replicase.
Virology 370: 77-92, 2008.

Hepatitis E virus (HEV) is a hepatotropic virus with a single sense-strand RNA genome of approximately 7.2 kb in length. Details of the intracellular site of HEV replication can pave further understanding of HEV biology. In-frame fusion construct of functionally active replicase-enhanced green fluorescent protein (EGFP) gene was made in eukaryotic expression vector. The functionality of replicase-EGFP fusion protein was established by its ability to synthesize negative-strand viral RNA in vivo, by strand-specific anchored RT-PCR and molecular beacon binding. Subcellular co-localization was carried out using organelle specific fluorophores and by immuno-electron microscopy. Fluorescence Resonance Energy Transfer (FRET) demonstrated the interaction of this protein with the 3' end of HEV genome. The results show localization of replicase on the endoplasmic reticulum membranes. The protein regions responsible for membrane localization was predicted and identified by use of deletion mutants. Endoplasmic reticulum was identified as the site of replicase localization and possible site of replication.

Renou C, Moreau X, Pariente A, Cadranel JF, Maringe E, Morin T, Causse X, Payen JL, Izopet J, Nicand E, Bourliere M, Penaranda G, Hardwigsen J, Gerolami R, Peron JM, and Pavio N.
A national survey of acute hepatitis E in France.
Aliment Pharmacol Ther 27: 1086-1093, 2008.

BACKGROUND: Few data are available on the incidence, risk factors and contamination pathways involved in acute indigenous hepatitis E in developed countries. AIMS: To draw up an overall picture of hepatitis E cases, to confirm whether or not the majority of the cases were indigenous and to attempt to identify the risk factors and contamination pathways involved in hepatitis E. METHODS: This study was performed in the framework of a national network (ANGH) including 96 participating centres. The 19 centres with at least one case of acute HEV reported a total number of 53 cases. RESULTS: A decreasing South-to-North geographic gradient was observed. A nonspecific clinical profile was observed in many cases. Acute hepatitis E was of indigenous origin in 90% of the patients. The most relevant and/or frequent possible risk factors among the 47 indigenous metropolitan cases were water consumption from a personal water supply, uncooked shellfish consumption and the recent acquisition of a pet pig. CONCLUSIONS: This national survey confirmed that acute indigenous hepatitis E is an emerging disease in developed countries such as France, and suggests that various risk factors are responsible for acute indigenous hepatitis E contamination in non-endemic countries.

Renoux VM, Fleury MJ, Bousarghin L, Gaitan J, Sizaret PY, Touze A, and Coursaget P.
Induction of antibody response against hepatitis E virus (HEV) with recombinant human papillomavirus pseudoviruses expressing truncated HEV capsid proteins in mice.
Vaccine 2008.

A hepatitis E virus (HEV) vaccine would be valuable to reduce the morbidity and

mortality associated with the infection in endemic areas. HEV pseudocapsids and epidermal delivery of HEV ORF2 DNA vaccine by gene-gun have been shown to confer protection against virus challenge in monkeys. Vectorization of a DNA vaccine by virus-like particles is a new immunization approach. We report here the successful immunization of mice with two ORF2 genes encapsidated into human papillomavirus type 31 virus-like particles. The HEV genes ORF2(112-660) and ORF2(112-608) were optimized for expression in mammalian cells and inserted in a baculovirus-derived vector for expression in insect cells. When expressed in Sf21 insect cells, ORF2(112-660) led to the production of irregular 15nm particles that accumulated in the cytoplasm of the cells, whereas ORF2(112-608) induced the production of 18nm particles that were present in both the cell culture medium and the cell cytoplasm. Anti-HEV immune responses were higher for the 15nm particles (HEV112-660) than that for to the 18nm particles (HEV112-608). Delivery into mice of two HEV ORF2 genes via a papillomavirus VLP was very effective in the induction of anti-HEV antibodies. In addition, an effective immune response to human papillomavirus capsids occurred. These engineered pseudoviruses were thus demonstrated to induce immune responses to both hepatitis E virus and human papillomavirus when they were administered to mice intramuscularly.

Rezig D, Ouneissa R, Mhiri L, Mejri S, Haddad-Boubaker S, Ben Alaya N, and Triki H.
[Seroprevalences of hepatitis A and E infections in Tunisia].
Pathol Biol (Paris) 56: 148-153, 2008.

OBJECTIVE: Viral hepatitis A (HAV) and E (HEV) infections are still frequent in many regions of the world, particularly in developing countries where sanitary conditions and socioeconomic level are frequently low. In this work, we have studied seroprevalences of these two infections in Tunisian children, teenagers and young adults. MATERIAL AND METHODS: The studied population included 3357 individuals from different regions of Tunisia and distributed in three groups 1 (n=1145), 2 (n=707) and 3 (n=1505) with a mean of age of 6.94, 12.84 and 20.71 years, respectively. RESULTS: Rates of HAV infection prevalence of 84.0, 90.5 and 91.7% were found within groups 1, 2 and 3, respectively. These rates are lower than those previously found in the country; thus, primary infection with HAV in Tunisia is progressively shifting to older ages, which is probably due to the improvement of sanitary conditions. Lower anti-HAV prevalences were found in costal regions as compared to the rest of the country. This difference may be due to the higher socioeconomic level of the population living in costal regions. Antibodies against HEV were assessed in individuals of group 3. A seroprevalence of 4.3% was found which indicates that, despite the absence of epidemics, the virus is circulating among the Tunisian population as sporadic cases. CONCLUSION: The present work contributes to a better knowledge of HAV and HEV infections in Tunisia and highlights the need of the establishment of a national program for virological surveillance of hepatitis cases and of further studies to monitor changes in the epidemiology of these infections.

Riquet FB, Blanchard C, Jegouic S, Balanant J, Guillot S, Vibet MA, Rakoto-Andrianarivelo M, and Delpeyroux F.
Impact of exogenous sequences on the characteristics of an epidemic type 2 recombinant vaccine-derived poliovirus.
J Virol 82: 8927-8932, 2008.

Pathogenic circulating vaccine-derived polioviruses (cVDPVs) have become a major

obstacle to the successful completion of the global polio eradication program. Most cVDPVs are recombinant between the oral poliovirus vaccine (OPV) and human enterovirus species C (HEV-C). To study the role of HEV-C sequences in the phenotype of cVDPVs, we generated a series of recombinants between a Madagascar cVDPV isolate and its parental OPV type 2 strain. Results indicated that the HEV-C sequences present in this cVDPV contribute to its characteristics, including pathogenicity, suggesting that interspecific recombination contributes to the phenotypic biodiversity of polioviruses and may favor the emergence of cVDPVs.

Schildgen O, Muller A, and Simon A.
Chronic hepatitis E and organ transplants.
N Engl J Med 358: 2521-2522; author reply 2522, 2008.

Seivert M, Belaiche J, and Delwaide J.
[Hepatitis E: a Third World's hepatitis found in Belgium].
Rev Med Liege 63: 549-553, 2008.

Hepatitis E virus is the second cause of acute viral hepatitis of oral-fecal origin in the world. This virus has a vast distribution throughout the world and manifests itself either in epidemic or endemic-sporadic form in many developing countries. Usually, the cases of HEV infection in industrialized countries are observed after a history of travel in an endemic area. However, an increasing number of cases have been attributed to a HEV zoonotic form transmitted by swine. HEV infection can lead to deadly fulminant hepatic failure in 1-4% in the common population, but the mortality incidence reaches 20% in case of third trimester pregnant women infection. The diagnosis of HEV infection can be made using serological tests but today, RT-PCR is considered as the gold standard test. Unfortunately, this technique is not widely available in Belgium yet. There is no treatment for HEV infection, only prophylactic measures as hygiene and sewage treatment can stop epidemics. Recently, a new vaccine, still in research phase, has showed promising outcomes.

Shata MT, and Navaneethan U.
The mystery of hepatitis E seroprevalence in developed countries: is there subclinical infection due to hepatitis E virus?
Clin Infect Dis 47: 1032-1034, 2008.

Shimoyama R.
[Transfusion-transmitted diseases].
Hokkaido Igaku Zasshi 83: 5-21, 2008.

Transfusion-transmitted infection has long been one of the major adverse reactions in blood transfusion. However, the implementation of effective screening tests makes it minor at present. Especially NAT (nucleic acid amplification test) is highly sensitive in detecting infection with HBV, HCV and HIV-1. Now the residual risk of post-transfusion hepatitis has reduced to as low as 1:100000. Not all of the blood-borne infections are included in the category of transfusion-transmitted infection, since donors are interviewed and examined for their health statuses. As to the organisms screening is not prepared or the window period infection, donor interview would be especially important. Namely, only the organisms that are cryptogenic and induce

little symptoms are included in the category of transfusion-transmitted infection. Virus infections which tend to be asymptomatic are among them, such as HBV, HCV, and HIV, as well as bacteria and protozoan infection of long latency and probably prions. At present bacterial contamination is one of the major risks of blood transfusion. West Nile virus (WNV) and hepatitis E virus (HEV) have emerged as members of transfusion transmitted infection. Other newly developing blood-borne infections will be a menace to the blood safety, and thus we should be ready to prepare for preventing them. Selection of the countermeasures should be based on cost benefit analysis. Inactivation of organisms is under study, but its distant adverse effects are not yet clear. Vaccination and the clearance of organisms from the general population would be a more basic countermeasure.

Srivastava R, Aggarwal R, Bhagat MR, Chowdhury A, and Naik S.
Alterations in natural killer cells and natural killer T cells during acute viral hepatitis E.
J Viral Hepat 15: 910-916, 2008.

The mechanism of liver damage in acute hepatitis E is poorly understood. In this study, we assessed the frequency and activation status of natural killer (NK) and natural killer T (NKT) cells and cytotoxic activity of NK cells in the peripheral blood mononuclear cells (PBMCs) obtained from patients with hepatitis E (n = 41) and healthy controls (n = 61). Flow cytometry was used to assess NK (CD3(-)/CD56(+)) and NKT cell (CD3(+)/CD56(+)) fractions (% of PBMCs) and activation status (CD69(+); % of NK, NKT cells). NK cell cytotoxicity was assessed using major histocompatibilities complex-deficient K562 cells as target cells. In 14 patients, the studies were repeated during the convalescence period. Patients had fewer median (range) NK cells [8.9% (2.4-47.0) vs 11.2% (2.6-35.4)] and NKT cells [8.7% (2.8-34.1) vs 13.6% (2.3-36.9)] than controls ($P < 0.05$ each). Activation markers were present on large proportion of NK cells [43.5% (11.2-58.6) vs 15.5% (3.0-55.8)] and NKT cells [41.5% (17.4-71.1) vs 12.8% (3.3-63.2); $P < 0.05$ each] from patients. NK cell cytotoxicity was similar in patients and controls. During convalescence, all the parameters normalized. In conclusion, reversible alterations in NK and NKT cell number and activation status during acute hepatitis E suggest a role of these cells in the pathogenesis of this disease.

Takahashi M, Hoshino Y, Tanaka T, Takahashi H, Nishizawa T, and Okamoto H.
Production of monoclonal antibodies against hepatitis E virus capsid protein and evaluation of their neutralizing activity in a cell culture system.
Arch Virol 153: 657-666, 2008.

Nine murine monoclonal antibodies (mAbs) generated against a recombinant ORF2 protein (amino acids 111-660) of a genotype 4 hepatitis E virus (HEV) strain recognized four sets of epitopes by pairwise competitive ELISA. One mAb (H6225) was able to capture HEV efficiently regardless of genotype and was tested for its ability to neutralize a genotype 3 HEV strain (JE03-1760F) in a recently developed cell culture system for HEV in a hepatocarcinoma cell line (PLC/PRF/5). When PLC/PRF/5 cells were inoculated with HEV (4.0 x 10(5) or 4.0 x 10(6) copies/ml) incubated with 100 microg/ml of a negative control mAb, HEV RNA in the culture medium continued to be detectable after day 14 or 12 post-inoculation (dpi), respectively. However, when cells were inoculated with the two distinct concentrations of HEV that had been mixed with 100 microg/ml of H6225, the harvested culture supernatants were negative for HEV RNA throughout the 60-day observation period. Upon prior mixing of the virus with 10 microg/ml of H6225, HEV RNA in culture supernatant continued to be undetectable until 46 or 28 dpi,

respectively. In conclusion, one mAb (H6225) against HEV capsid protein that can efficiently neutralize HEV in vitro was obtained in the present study.

Taylor RR, Basnyat B, and Scott RM.
A diplomatic disease.
J Travel Med 15: 200-201, 2008.

A 43-year-old diplomat was diagnosed with probable hepatitis C while vacationing in Europe. However, on return to her post in Nepal, she was actually found to have hepatitis E. The differential diagnosis, importance, and prevention of hepatitis E are highlighted.

Turner J, and Green J.
Hepatitis e: a UK perspective.
Br J Hosp Med (Lond) 69: 517-519, 2008.

REVIEW Hepatitis E is increasingly recognized as a cause of viral hepatitis within the UK and should be considered in any patient presenting with acute hepatitis. Mortality rates of around 4% have been described, but are even higher during pregnancy.

Wang CY, Miyazaki N, Yamashita T, Higashiura A, Nakagawa A, Li TC, Takeda N, Xing L, Hjalmarsson E, Friberg C, Liou DM, Sung YJ, Tsukihara T, Matsuura Y, Miyamura T, and Cheng RH.
Crystallization and preliminary X-ray diffraction analysis of recombinant hepatitis E virus-like particle.
Acta Crystallogr Sect F Struct Biol Cryst Commun 64: 318-322, 2008.

Hepatitis E virus (HEV) accounts for the majority of enterically transmitted hepatitis infections worldwide. Currently, there is no specific treatment for or vaccine against HEV. The major structural protein is derived from open reading frame (ORF) 2 of the viral genome. A potential oral vaccine is provided by the virus-like particles formed by a protein construct of partial ORF3 protein (residue 70-123) fused to the N-terminus of the ORF2 protein (residues 112-608). Single crystals obtained by the hanging-drop vapour-diffusion method at 293 K diffract X-rays to 8.3 A resolution. The crystals belong to space group P2(1)2(1)2(1), with unit-cell parameters a = 337, b = 343, c = 346 A, alpha = beta = gamma = 90 degrees , and contain one particle per asymmetric unit.

Wichmann O, Schimanski S, Koch J, Kohler M, Rothe C, Plentz A, Jilg W, and Stark K.
Phylogenetic and case-control study on hepatitis E virus infection in Germany.
J Infect Dis 198: 1732-1741, 2008.

BACKGROUND: Hepatitis E is a classic water-borne disease in developing countries. In Germany, hepatitis E virus (HEV) infections are notifiable. The number of non-travel-associated infections has increased in recent years, but the route of transmission in most is unknown. Our objective was to determine risk factors for autochthonous HEV infections in Germany. METHODS: Cases of HEV met clinical definitions and were confirmed by laboratory analysis (defined as detection of HEV by polymerase chain reaction [PCR] or immunoglobulin M by serologic testing). PCR products from blood or stool samples were genotyped for phylogenetic analysis. A

case-control study included case subjects with autochthonous HEV infection and matched control subjects who were randomly recruited from a population-based telephone list. RESULTS: From May 2006 through August 2007, 76 of 96 persons for whom HEV infection had been reported to the routine surveillance system were interviewed. Sixty-six persons had disease that fulfilled the inclusion criteria: 45 (68%) had autochthonous infection, and 21 (32%) had travel-associated disease. Genotypes 3 or 4 were present in 15 of 15 persons with autochthonous infection, and genotype 1 was present in 8 of 9 persons with travel-associated infection. In conditional logistic regression involving 45 case subjects and 135 control subjects, consumption of offal (41% vs. 19%; odds ratio [OR], 2.7; 95% confidence interval [CI], 1.2-6.2) and wild-boar meat (20% vs. 7%; OR, 4.3; 95% CI, 1.2-15.9) were independently associated with autochthonous HEV infection. CONCLUSION: Hepatitis E is endemic in Germany and likely exists as a food-borne zoonosis. Implicated meat products should be investigated to provide recommendations for preventive measures.

Wu T, Zhang J, Su ZJ, Liu JJ, Wu XL, Wu XL, Lin CX, Ou SH, Yan Q, Shih JW, and Xia NS.
Specific cellular immune response in hepatitis E patients.
Intervirology 51: 322-327, 2008.

AIMS: To evaluate the specific T cell response together with IgM anti-hepatitis-E-virus (HEV) antibodies in acute hepatitis E (HE) patients. METHODS: Blood samples were collected from 11 HE patients every week and assayed for routine blood investigation after onset of disease until their convalescence. Peripheral blood mononuclear cells were separated from some of the blood samples (1-3 samples per patient) and tested for specific T cell response by enzyme-linked immunosorbent spot assay and IgM anti-hepatitis E virus by enzyme-linked immunosorbent assay. RESULTS: A particulate HEV capsid protein, HEV 239, effectively stimulated the response of T cells from HE patients infected by type 1 or type 4 HEV. In acute HE, a burst of HEV-specific cellular immune response occurred, which decreased along with the decreasing IgM anti-HEV antibody titre and normalization of liver function. CONCLUSIONS: HEV open reading frame 2 amino acids 368-606 can effectively stimulate the HEV-specific T cell response in vitro; the specific T cell response decreases along with convalescence and may play a role in the pathogenesis of acute HE and recovery.

Xiong JH, Guo QS, Ge SX, Gu Y, Chen YX, Miao J, Du HL, Shi WG, Zhang J, and Xia NS.
[The preliminary analysis of the recognition epitopes of anti-HEV monoclonal antibodies on HEV ORF2].
Bing Du Xue Bao 24: 83-87, 2008.

Western blot, capture-PCR, blocking ELISA and synthetic polypeptides were used to systematically study the recognition epitopes on HEV ORF2 of 23 anti-HEV monoclonal antibodies(McAbs) which were previously generated in our laboratory directed against HEV ORF2. Results showed that seven McAbs recognized linear epitopes that located at aa408-458 of HEV ORF2 and 16 conformation-dependent McAbs, most of which recognized the surface epitopes of native HEV, located at aa459-606 of HEV ORF2. The systematical study of the recognition epitopes of anti-HEV McAbs on HEV ORF2 provides important information for the investigation of virus receptor and HEV infection mechanism, as well as its vaccine and diagnostics development.

Zaki Mel S, Salama OS, Mansour FA, and Hossein S.
Hepatitis E virus coinfection with hepatotropic viruses in Egyptian children.
J Microbiol Immunol Infect 41: 254-258, 2008.

BACKGROUND AND PURPOSE: Major hepatotropic viruses continue to be important causes of acute viral hepatitis in developing countries. This work was carried out to detect the seroprevalence of hepatitis E virus (HEV) markers in children with acute viral hepatitis due to hepatotropic viruses (A, B and C) and non-A, non-B, non-C acute hepatitis, and to ascertain the influence of HEV superinfection in individuals infected with hepatitis viruses (A, B and C). METHODS: We studied prospectively 162 children with sporadic acute hepatitis who reported to our hospital. Thirteen healthy controls were also included in the study. Laboratory investigations were performed, including complete liver function tests. Complete serological profiles for hepatitis viruses A, B, C and E were evaluated. RESULTS: HEV immunoglobulin G was detected with highest percentage among patients with hepatitis B (56.7%), followed by patients with hepatitis C virus (52.0%), hepatitis A virus (34.1%) and combined hepatitis B and C viruses (30.0%). The detection rate among patients with non-A, non-B, non-C hepatitis was 7.1%. HEV immunoglobulin M was found in 4.5% of hepatitis A virus patients and in 3.3% of hepatitis B patients. The prevalence of HEV immunoglobulin G and immunoglobulin M correlated with the levels of hepatic aspartate aminotransferase and alanine aminotransferase in patients with dual markers of infection with hepatitis E and other viruses compared to patients with acute hepatitis due to A and C viruses. CONCLUSIONS: HEV serological markers are common among children with acute viral hepatitis, especially from hepatitis C and B viruses. There may be increased sensitivity to HEV coinfection in association with hepatitis B and C infections. Dual infection with HEV and other hepatotropic viruses was associated with greater elevation of aspartate and alanine aminotransferases.

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