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CONTENTS

This edition of *Viral Hepatitis* is based on material presented at the Viral Hepatitis Prevention Board meeting on **Hepatitis A and E: Update on Prevention and Epidemiology**, Antwerp, Belgium, March 12-13, 2009.

Editorial

This issue of *Viral Hepatitis* reviews topics covered at the Viral Hepatitis Prevention Board (VHPB)'s spring meeting on *Hepatitis A and E: Update on Prevention and Epidemiology*, held on March 12-13, 2009 in Antwerp, Belgium.

Main topics related to Hepatitis A (HAV) included feedback of the Global HAV meeting held in December 2007 in Miami, and related lessons learned for the WHO European region. Recent information on HAV epidemiology, outbreaks and prevention was also provided and future initiatives were discussed among participants.

With regards to Hepatitis E (HEV), an overview of HEV virology and the disease was given together with its worldwide epidemiology, including data suggesting zoonotic transmission. The emergence of HEV in non-endemic/endemic countries was assessed and future opportunities of an HEV vaccine were discussed.

The state of the art on HAV emphasized the growing public health importance of the disease with related need for control at global level.

Many developing countries are moving from high to intermediate endemicity, with growing cohorts of susceptible young people leading to increased risk of outbreaks. Also, the clinical picture of HAV disease appears to be changing, with seemingly more fulminant HAV cases, especially in Latin America.

Other meeting highlights revealed that HAV burden of disease data is still not well documented and that there is no standardized global approach in terms of HAV control and prevention in spite of the availability of safe and effective HAV vaccines since 16 years. The need for improved surveillance and burden of disease data, together with robust mathematical modeling and economic analyses, particularly in the context of the current financial crisis, was emphasized.

From meeting discussions it appeared that more effective advocacy is needed to place the importance of HAV on the international public health agenda and prioritize HAV on work plans of national and international organizations. Advocacy is also required to maintain the momentum from important international HAV meetings that took place in Miami and Riga, as well as the planned revision of the WHO position paper on HAV.

Meeting discussions concluded that there is a need for "leadership" on HAV to stimulate the production of guidelines, agreement of definitions, strengthening of surveillance, and greater advocacy for HAV prevention and control, and a call for action.

Information shared on HEV showed that, after the declining circulation of HAV, it has now become the most frequently isolated hepatitis virus transmitted through water and food. However, HEV transmission routes are still unclear, (e.g. whether pig reservoirs are responsible for zoonotic transmission), and more research is needed to understand the different clinical presentations of the disease. Also, a clear need was expressed for reliable and standardized diagnostic assays in order to collect accurate burden of disease data.

The opportunity of an HEV vaccine was also discussed among participants. Two candidate vaccines are currently being developed but questions remain in terms of the demand and financing of further development required for commercialization, as well as the urgent need to resolve existing intellectual property issues. In order to advocate and mobilize support for the further development of HEV vaccines there is also a high need for more robust data on the disease burden and impact on society. To this end, partnerships should be established, in particular the potential role of private-public sector partnerships should be investigated.

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on behalf of the Viral Hepatitis Prevention Board

Viral Hepatitis Prevention Board meeting on Hepatitis A and E: Update on Prevention and Epidemiology, Antwerp, Belgium, March 12-13, 2009

Hepatitis A

Has the time come to control hepatitis A globally?

Major findings and conclusions of the Global Hepatitis A Meeting, Miami, December 2007

This meeting to address hepatitis A virus (HAV) infection as a vaccine-preventable disease was the first global initiative, jointly taken by the Centers for Disease Control and Prevention (CDC), the Centre for the Evaluation of Vaccination (CEV)- a World Health Organization (WHO) Collaborating Centre for Prevention and Control of Viral Hepatitis- at the University of Antwerp, the WHO and the Pan American Health Organization (PAHO).

More than 250 delegates from 46 countries uniquely gathered to review surveillance systems, changing HAV epidemiology, diagnostic tools, outbreak control measures, cost effectiveness models of HAV vaccination and HAV immunization programmes, as well as data needed to assess current HAV prevention strategies.

Country presentations on HAV epidemiology included data from Brazil, Mexico, Saudi Arabia, Italy, Turkey, South Africa, China, Korea, Thailand, India, Russia and Ukraine, while country presentations on control and prevention focused on data from Argentina, the Netherlands, Italy (Puglia), Israel, Spain (Catalonia), Australia, Chile, Belarus, Russia and China.

The abstract book from the meeting and presentations are available from the following website: http://www.havmeeting.info/ and a meeting summary, together with twelve country reports, were published in a Supplement of the Journal of Viral Hepatitis [1]. This Supplement also entails an overview table, providing country specific data relating to endemicity (age specific prevalence), outbreaks, as well as HAV vaccination policy, coverage and impact.

The opening presentation was a “state of the art” from Argentina (presented by Angela Gentile), which provided the framework for the two-day meeting, in terms of country-specific example of:

- HAV epidemiology and burden of disease documentation
- decision-making on HAV prevention strategy based on disease burden, cost effectiveness data, vaccine characteristics, programmatic feasibility and social acceptance, and eventual implementation of a national HAV immunization programme.

Several presentations confirmed the global HAV epidemiological shift which started in some countries already in the years 50-70s, as a result from improved sanitation and living conditions.

Main characteristics of this HAV epidemiological shift are:

- a lower prevalence among children with, as a consequence, increased average age of infection and related increased morbidity
- an increased outbreak potential due to HAV virus circulating among cohorts of susceptible older children, adolescents and adults
- high variability in HAV incidence within regions, countries and even cities, with urban/rural, as well as socio-economic differences.

Another common denominator to country specific situations was the general lack of updated epidemiological, burden of disease, incidence and age specific prevalence data in most coun-

tries, with either old data available only and/or mostly regional rather than nation wide country data. The currently limited availability of data was identified as a drawback for taking reasonable immunization policy decisions.
The importance of HAV surveillance was underlined by many countries, in particular the need to collect both age specific prevalence and incidence data. The value of age specific prevalence data collected every 5 or 10 years was recognized to estimate changes in endemicity by assessing population immunity and susceptibility. The importance of incidence data was also stressed to assess burden of disease, identify and control outbreaks, as well as identify infected persons at risk.

From the results presented on a survey performed in 22 European countries in 1990s-2001 through the EUROHEP.NET project (www.eurohep.net), it appeared that surveillance in Europe is characterized by a wide diversity from country to country, with no standardized way of data collection. Also, no standard case definition and outbreak definition is used and, in a number of countries, data are only collected regionally. Overall, this study revealed that there is currently no strong basis to accurately establish HAV burden of disease in Europe.

During the Miami meeting, the increasing use of molecular testing was underlined. This diagnostic tool allows identification of virus transmission sources during outbreaks, the establishment of transmission patterns within populations and the monitoring of vaccine effectiveness. Examples of molecular epidemiological studies, illustrating such applications, were presented, such as the monitoring of circulating HAV strains during outbreaks, proving useful in detecting widely dispersed outbreaks and hidden clusters, or demonstrating links between imported and autochthonous cases. Another application of molecular epidemiology is to detect HAV in urban sewage, allowing the follow up of epidemiological patterns of HAV excretion.

The specific topic of post exposure prophylaxis policy was also presented as immunoglobulins are no longer available in many countries worldwide and HAV vaccine has become increasingly recommended in this context. A study demonstrated high efficacy of HAV vaccine, similar to immunoglobulin, when administered post exposure [2], and led to the update of the Advisory Committee on Immunization Practices (ACIP) recommendation in the USA, summarized as follows: HAV vaccine is preferred to immunoglobulin for healthy persons ≥12 months to 40 years; for persons ≥40 years immunoglobulin is preferred but the vaccine can be used if immunoglobulin cannot be obtained; for children ≤12 months, immunocompromized individuals, persons with chronic liver disease, and persons for whom vaccine is contraindicated, immunoglobulin should be used.

An update was provided on currently available HAV vaccines, which are highly immunogenic and have an excellent safety profile. Their flexibility of administration in combination or co-administration, as well as the long lasting protection was also described. The long term duration of protection with one vaccine dose, ongoing in Argentina, needs further investigation.

An overview of countries or regions with routine childhood vaccination programmes in 2007 was presented, including China (Zheijang Province); Australia (North Queensland); USA; Spain (Catalonia); Italy (Puglia); Israel and Argentina. Related vaccine impact studies performed in Israel and the USA were also discussed, showing a clear indication of indirect herd immunity effect of immunization programmes among non-vaccinated cohorts, thus supporting the need to take such results into account in future cost effectiveness studies.

Overall conclusions of the Global Hepatitis A meeting, Miami, indicated that:

- HAV is a significant cause of morbidity worldwide
- Worldwide HAV mortality is low but cases of fulminant HAV are reported in younger ones
- HAV is increasingly the leading cause for liver transplant due to acute viral hepatitis
- Updated epidemiological country data is missing
- Improved surveillance is needed, with standardized data collection systems and case definition
- Changing HAV epidemiology has led to visualized more severe clinical features of the disease, associated with increased morbidity and mortality
- Improved sanitation should be coupled to HAV routine vaccination programmes in intermediate endemicity countries
- Data on HAV circulating strains should be shared regionally as well as globally to efficiently control outbreaks
- Vaccination of travelers needs to be reinforced in order to reduce HAV importation in low endemicity countries
- Most health economic analyses have shown HAV risk group vaccination strategies to be cost effective
- Health ecomomic analyses of routine HAV vaccination programmes in low endemic countries have been inconclusive but recent data have shown more favourable results, thanks to reduced vaccine prices and the use of dynamic models, taking herd immunity into account
- Consensus was reached over a stepwise HAV prevention strategy at country level:
  - o Invest in accurate surveillance data to document burden of disease, outbreaks, etc
  - o Secure political support
  - o Conduct health economic analyses
- It was recognized that there is an urgent need for global control of HAV by placing the disease in the context of global health priorities
- Future needs include:
  - o Revision of HAV WHO position paper
  - o Need to put HAV on the international agenda
  - o Organization of a 2nd global HAV meeting in 2010 or 2011

Risk factors with an impact on fatality rate in fulminant hepatitis A virus infection

As a follow up from the Miami meeting [1], this presentation focuses on investigations made into reported increasing rates of severe and, in some instances, fulminant HAV cases, particularly in Latin America.

HAV infection has traditionally been considered a self-limited disease, usually asymptomatic in young children, thus deserving little public health attention and allocation of resources. From cumulative

experience, it is known that acute HAV infection resolves spontaneously in >99% of individuals and that fulminant hepatitis is rare, with variable estimated rates, up to 1:10,000 or more in healthy individuals. Mortality in fulminant hepatitis is also rare and mostly associated with older age (>50 years). Reported case fatality rates range between 0-0.1% in infants and children, 0.4% at age 15-39 and 1.1-1.8% in patients >50y of age [3,4]. There are scarce reports on HAV transmission from pregnant women to their offspring (reviewed in [5]). Patients with chronic liver disease have been identified as a potential risk group for fulminant hepatitis [6]. Prior to the era of liver transplant, survival rates from fulminant hepatitis caused by HAV were relatively higher than survival rates of fulminant hepatitis caused by paracetamol poisoning. HBV, HCV or halothane, with 66% rates reported in 1988 [7]. In recent years, survival rates have exceeded 89% thanks to improved patient management and intensive care [8,9].

Fulminant HAV case reports in children seem to be rising, as shown in Table below. Figures from Latin America, in particular Argentina, are worrying, as well as cases reported from Brazil for which a very low success of liver transplantation was reached. However, these reports might not be representative of national data since they are retrospective and released by individual centres, see Table below [10-13].

Fulminant Hepatitis A in children

Number of reports is rising?		
Turkey	4 cases	Jun 2004 - Nov 2006
UK	9 cases	1991 - 2000
Argentina	128 cases	May 1982 - Sep 2002
Argentina	41 cases	Sep 2003 - Jan 2006
Brazil	13 cases	1998 - 2007
Reports are retrospective and released bij individual centres		

Comparable rising incidence of fulminant HAV cases was reported from a Korean institute [14], with a 4-fold increase from 3.4% in 2004 to 13.0% in 2008, irrespective of age, with, however, good survival rates observed (85.7%), thanks to improvement in treatment, intensive care and liver transplantation.

Reports from the US Liver Failure Study Group published in 2008 [8] indicate that 3% of acute liver failure cases in adults are caused by HAV, and 4% in children, indicating that fulminant HAV is also present in countries of the Western world. However, reports from two US registries: United Network of Organ Sharing (UNOS) and Acute Liver Failure Study Group (ALFSG) databases, have shown a significant decline in the number of liver transplants due to fulminant HAV from 1988 until 2005 in the UNOS, and 1998-1999 until 2005 for ALFSG [9].

Factors with an impact on the fatality rate in fulminant HAV relate to the host, viral factors, and treatment for liver failure which has steadily improved over the years, leading to increased survival rates.

Little information is available from the literature on main risk factors associated with fulminant HAV and liver failure, including:

- age of infection
- chronic liver disease and HCV or HBV co-infection
- paracetamol intake
- potential viral factors
- questionable worse prognosis during pregnancy

In terms of impact related to host factors, increased severity of HAV infection has been reported in the elderly, individuals co-infected with HCV, HBV and HIV, and pregnant women [15-18]. Chronic HCV and HBV carriers have also been reported to be at higher risk for developing fulminant HAV, with HBsAg carriers even reported to be at 9-fold increased risk [19,20].

In general, there is enough evidence to suggest that a cellular immune reaction leads to a cytopathic effect during HAV infection. However, there is practically no information available on the role of the immune system in fulminant HAV infection.

Investigations into viral factors have indicated some genetic diversity with HAV sequence variations at the VP1/2A junction, and (sub)genotypes, despite a unique HAV serotype. However, so far, no confirmed correlation could be established between defined HAV sequences and increased risk of developing fulminant HAV. Also, results from studies conducted in Germany, Japan, Argentina and Israel are conflicting and inconclusive as to whether minor genetic substitutions of viral sequences may have an impact on viral replication and cytopathic effect [21-26].

In conclusion, age, underlying liver disease, hepatitis co-infections and paracetamol intake are confirmed as major risk factors associated with increased risk of fulminant HAV, whereas viral factors are not confirmed. On the other hand, improved intensive care and liver transplantation have significantly reduced fatality rates from fulminant HAV over time.

The incidence of fulminant HAV is low and more data is needed, in particular from countries that might be mostly affected worldwide, in order to better assess and understand the apparent reported increase of fulminant HAV cases in children.

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Update on Hepatitis A epidemiology, prevention and control

HAV outbreaks and control measures

HAV outbreak molecular investigations

EVENT is a European network to improve the detection of food borne viruses and related outbreaks, focusing on HAV, HEV and Norovirus.

Six HAV genotypes have been identified of which genotypes I and III are the most common types infecting humans. Genotype IA is spreading worldwide whereas IB is dominating in the Middle East. Genotype IIIA is mainly found in Asia. Genotypes IV, V and VI are infecting monkeys (who, in turn, can infect humans).

The region most commonly used for typing the HAV genome has been the C-terminal VP1/2A region, whereas arguments exist for using the N-terminal VP3-VP1 fragment. Based on structural characteristics of the HAV virus, VP1 in the N-terminal would be the preferred choice, since it is a protein protruding on the exterior of the virus and easily accessible for antibodies. In order to study which region should be used to type HAV genome, the EVENT network compared sequences of available isolates in the two regions.

A total of 102 European isolates were used for comparison, originating from Hungary (24), Spain (4), the Netherlands (8), Sweden (48) and GenBank (18), a database of publicly available nucleotide sequences maintained by the US National Center for Biology Information. These 102 isolates, were most commonly genotype IA and IB. Many of the IB strains were from isolates from the Netherlands and Sweden, imported by immigrant children traveling to their home country in the Middle East. Similarly, the majority of genotype IIIA strains were identified in Dutch and Swedish isolates and resulted from import by individuals traveling to Asia.

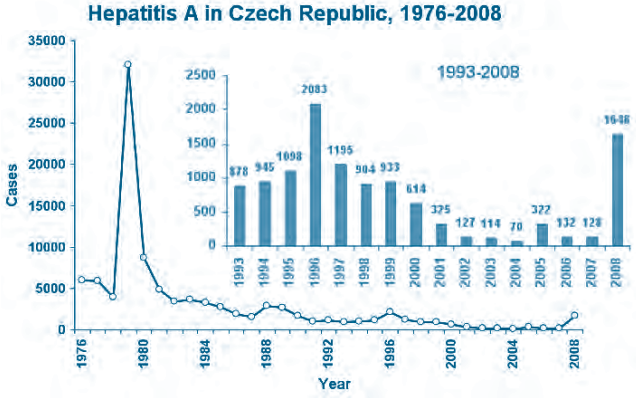
Comparisons of the VP3/VP1 and VP1/P2A regions in the 102 HAV isolates showed that there were more unique strains in the N-terminal end compared to the C-terminal end, indicating the N-terminal end would be the best choice for typing. However, since many countries have been using the C-terminal region for sequencing for many years, it was decided to continue with this region. If an identical sequence is found in another country, the laboratory will be alerted and the N-terminal region will also be sequenced for these strains. If identical strains are encountered, epidemiologists from

these countries will be informed to search for a possible common source of infection. Information in the EVENT database allows to monitor and control infection in risk groups and outbreaks. For instance, genotype IA strains isolated from infected men who have sex with men (MSM) in The Netherlands and France were shown to also spread in the food chain in Spain (Barcelona) and in Sweden.

A database for HAV sequences from the EVENT network is being developed and kept at the National Institute for Public Health and the Environment (RIVM) in the Netherlands. This database will be easily accessible to EVENT network members and sequences obtained can be blasted to easily identifiable identical sequences. Once the database is established, more countries will be invited to participate in the network. The practical difficulties of making the EVENT database public were underlined during the meeting.
Since there is no agreement between the USA and Europe on the standard HAV genomic region to be sequenced, it was proposed at the meeting that a standardization should be adopted. CDC was previously using a shorter region within VP1/P2A and is now sequencing the whole HAV genomes from sporadic cases. During outbreak situations, CDC could adopt to the longer fragment used by the EVENT network in order to make comparisons of outbreak sequences possible.

HAV outbreak in Czech Republic, 2008

In the Czech Republic, HAV incidence had been steadily declining since the 90's to very low incidences as of 2000. The incidence was lowest in 2004 with only 70 cases reported.
When analyzing HAV reports over the period 1993-2007 a clear seasonality effect was observed, with increase starting in summer and maxima in autumn. Social factors such as transmission among susceptible school and preschool children probably play a role in this seasonality pattern.
In 2008, a more than 10-fold increase in reported cases was seen compared to the period 2003-2007 (see Figure below), leading to an incidence of 16/100,000 population [1]. The increase in HAV incidence started end May 2008 and was maximal in September, with almost 500 HAV cases reported. The morbidity due to HAV in 2008 was substantially higher than what could be expected, based on observations from the previous years. When considering HAV morbidity by region, increases in 2008 were seen in all regions with highest incidences in the urban area of Prague (73.6/100,000) and in central Bohemia (17.8/100,000). During the 2008 outbreak, 58% of HAV cases were male and 42% female.

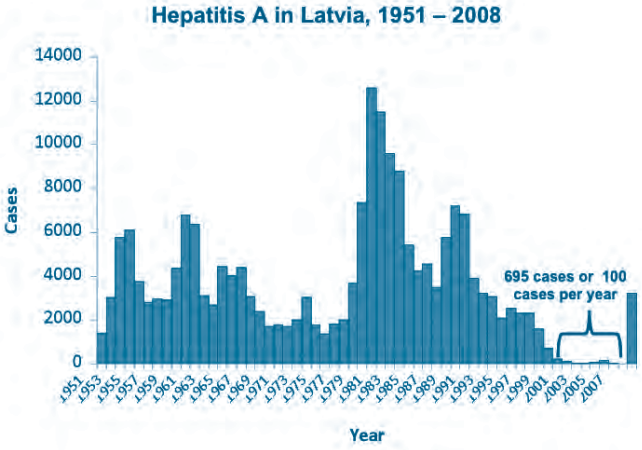


An explanation for the large 2008 outbreak can be found in the very low incidence reported over the preceding years, leading to an increased population of susceptibles. The age distribution shifted over the years: past HAV infections in late 80's and 90's mostly occurred in children and adolescents while the 2008 outbreak mainly affected young and older adults. In the 25-34 years age group, HAV infection was associated with injection drug users (IDU) while many infected older adults were homeless. Overall, the distribution of risk populations among HAV cases reported in 2008 was similar to the one seen among cases in the late 90's; for a large majority no risk factor could be identified. Importation of HAV infection through person-to-person contact was mentioned as an important contributing factor in the 2008 outbreak, while water or food born spread was excluded. Molecular typing results of the 2008 outbreak cases will become available in the near future, including information relating to index cases.

Control measures taken in the Czech Republic during the outbreak were coordinated by the Ministry of Health and included contact tracing and pre- and post exposure HAV vaccination. A total of 10,353 individuals received at least one vaccine dose. Among these, 104 individuals became ill; the time to onset of the disease relative to vaccination in these cases is currently under investigation.

HAV outbreak in Latvia, 2008

In Latvia, regular epidemic cycles of HAV have been observed over the last decades. The latest community-wide outbreak occurred in the period 1988-1990, with almost 20,000 cases reported. Since then, HAV incidence has steadily declined to very low rates of ~100 cases/year during the period 2001-2007 (see Figure below).



An unexpectedly high number of 3,236 HAV cases was reported between November 2007 and December 2008 [2], mainly in the urban region around the capital Riga. Incidence peaked in October 2008, which is in line with the usual seasonal distribution of HAV epidemics. Initially, more cases were reported in males but the gender difference was gradually leveling off towards the end of 2008. In parallel with the 2008 outbreak in Czech Republic, the highest incidences were seen in young adults whereas during previous HAV epidemics in Latvia, children were mostly affected. In 2008, the proportion of children involved in the HAV outbreak was 10-20%. A total of 17 deaths due to HAV were reported during the outbreak in patients with underlying disease.

Also similarly to the outbreak in Czech Republic, HAV spread in Latvia occurred primarily among drug users (i.e. up to 35% of cases during the first months, mainly in Riga), and was followed by a community-wide spread within the general population and to other regions of the country.

The low incidence in 2000 – 2007 and the longer periods between epidemic cycles in Latvia can be explained by an overall improvement in hygiene and rapid decrease in birth rate in the 90's. The considerable proportion of persons with low socioeconomic status living in household clusters may also have influenced the HAV spread. Furthermore, food borne spread was suggested since a substantial number of cases (at least 47) was associated with a restaurant.

Most recent data for Latvia in January-February 2009 show that approximately 80 new cases continue to be notified each week and it is expected that the HAV epidemic will continue for another two years.

Outbreak control measures taken in Latvia included recommendation of HAV vaccination, although not refunded within the public health system. HAV vaccine was administered throughout the entire epidemic, with highest numbers of individuals vaccinated during later months of the epidemic, i.e. between 1,600 and 2,000/month in October-December 2008. However, due to lack of public health funding, mainly due to current financial crisis, no change of policy was implemented in Latvia other than providing more information on vaccination.

Additional control measures included systematic epidemiological investigation of all notified HAV cases in the form of:

- patient or relatives interview,
- visiting places of work or study of the patients, and
- collection of epidemiological information.

Information on preventive measures against HAV was regularly disseminated via the mass media and recommendations for inhabitants, food handlers, and staff of educational establishments were distributed and made available from the Latvian Public Health Agency website (http://www.sva.gov.lv). Information and recommendations on prevention of HAV were disseminated via communications to school boards, health inspectorate, food and veterinary service, schools and other establishments. Seminars on HAV prevention for healthcare workers, including medical staff of educational establishments, were also organized. In the future, prevention of HAV in Latvia will be further strengthened through communication with the public in order to increase knowledge about vaccination. Surveillance and control measures will be continued and information will be exchanged at international level.

Technical meeting on Hepatitis A outbreak response, organized by ECDC in Riga, November 2008

Following the 2008 HAV outbreaks in Latvia, Czech Republic and Slovakia, the European Centre for Disease Prevention and Control (ECDC) in collaboration with the Public Health Agency of Latvia, organized a technical meeting on HAV outbreak response, held in Riga in November 2008 [3].

In view of the changing HAV epidemiology, there is a need for accessible technical guidelines and control options for outbreak situations, particularly in terms of vaccination strategies. Therefore the ECDC brought together public health representatives from these recently affected countries with experts in outbreak investigation, laboratory diagnosis and outbreak response to share country experiences. This initiative was also supported by the WHO Regional Office for Europe.

Outcomes of the ECDC Riga technical meeting, November 2008:
One important conclusion from the meeting was that guidance on when to consider a universal accelerated vaccination strategy versus targeted vaccination coverage of at-risk populations to significantly impact on the outbreak would be helpful.

At the Riga meeting, some short-term steps were proposed including exchange of information between affected Member States in terms of information sheets for the public, epidemiological study protocols developed, and molecular laboratory methods for HAV. Future steps identified included developing technical guidelines on HAV outbreak response, such as vaccination strategies, definition of 'contacts' in HAV contact tracing, guidance on environmental sampling for HAV, and surveillance data to be collected.

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Vaccines and immune response

Long-term immunity induced by HAV vaccines

HAV vaccines from various manufacturers are widely available, including combined vaccines against HAV/HBV and HAV/Typhoid fever.

Observed anti-HAV antibody persistence shows that up to 15 years after completion of vaccination schedule, most vaccinees still have anti-HAV antibodies i.e. 91%-100% of children and 96% of young healthy adults [1]. Most recent data of ongoing follow-up studies in over 200 adult vaccinees show that only few lost antibodies at 15 years post-vaccination [Van Herck, unpublished data].

A long-term immunity study conducted in Austria, in an adult unselected study population with mean age 54.7 years, showed that 98.3% of 1,016 vaccinees still had protective antibody levels 10 years after primary vaccination [2]. The vaccine-induced antibody titers after 10 years showed an age-related trend with higher titers in younger adults. Among those younger than 50 years, females had significantly higher titers than male vaccinees. Lower titers were seen in subjects with a higher body mass index. This study confirms that antibodies persist for more than 10 years following primary HAV vaccination [2]. Based on these findings, the national recommendation in Austria for HAV booster vaccination of travelers, was changed from every 10 years to every 20 years. With regards to the 20 year booster recommendation for travelers in Aus-

tria, the comment was made that the Ministry of Health would not make decisions based on mathematical modeling of antibody levels but more on figures relating to protection against disease. However, the 20 year booster recommendation can be considered as a conservative approach from a safety perspective. Long term immunity can be expected since the HAV vaccine is highly immunogenic.
Mathematical models using log-linear extrapolation have predicted anti-HAV antibodies to persist for at least 14-25 years in children, and 20-25 years in adults [3-5]. Because the antibody levels tended to stabilise after 6 years, more complex modeling (linear mixed model), was performed with inclusion of antibody level before second vaccine dose and body mass index. This resulted in predictions that better correlated with observed values.
Validation of the latter model in 2004 resulted in an excellent model fit for the estimation period up to year 10. Moreover, the initial prediction that overall it would take 25 years before 5% of vaccinees would become anti-HAV seronegative, was confirmed and this was also consistent with reports from other vaccines [4, 6].
Direct evidence of long-lasting protection beyond persistence of antibodies was found in experimental infection of vaccinated chimpanzees and also by demonstrating in humans the presence of memory B- and T-cells by means of in vitro cell-mediated immunity (CMI) tests. Indirect evidence was obtained by showing an anamnestic immune response with rapidly increasing anti-HAV titers elicited by a vaccine booster dose given at 12 years after primary vaccination [7]. Further research of cellular immune response to booster dose administered long after primary vaccination is being performed.

Several investigations relating to long-term immunity elicited by HAV vaccines are ongoing. Observed anti-HAV persistence data beyond 15 years are being collected. Model-based predictions will be re-validated using the year 11-15 observed data. In addition, a different approach of modeling, as it has been used for analyzing response to a Human Papilloma Virus vaccine and which estimates the number of memory cells induced by vaccination, will also be applied to the HAV vaccine data in order to provide more insight on long-term immune memory [8].
Further long-term follow-up after vaccinating children, including modeling predictions, is still ongoing. Also, the effect of maternal antibodies on antibody persistence when vaccinating very young children remains to be investigated.
To date there are insufficient data about the immune response elicited when a single primary dose is given. In cases where a second dose is given up to 5-8 years after the single primary dose, good indication exists that an excellent anamnestic response to the delayed second dose develops. This is even the case if detectable antibodies were lost at the time of the second dose (see Table below) [9-12].

Anti-HAV antibody response to delayed second dose of HAV vaccine

Number of vaccinees	Time of delay between 1st and 2nd dose (months)	GMT before 2nd dose (IU/L)	GMT after 2nd dose (IU/L)	Reference
124	24–66	116	3342	Landry 2000 [12]
25	48–72*	32	2993	Iwarson 2002 [9]
156	20-31	66	1544	Williams 2003 [11]
97	18-54**	39-50	2385	Beck 2003 [10]

* up to 8 years ** 8-11 years

However, the longer term duration of protection with one dose needs further investigation, especially when vaccinating young children and/or in conditions of low endemicity where no natural boosters occur. Data to come from Argentina, where the single-dose schedule is being implemented nation-wide, are expected to bring additional information.

Correlation between humoral and cellular immune responses
The HAV vaccine non-responsiveness rate (antibody titer below 10 mIU/ml) in the long-term immunity study conducted in Austria [2], was rare (2%). In this study, low/non-responsiveness had only been defined on the basis of antibody levels and the mechanisms of non-responsiveness are largely unknown. Non-responsiveness could be due to a decline of antibodies or due to an intrinsic inability to respond to HAV antigen, while risk factors such as older age and higher body mass index can also be associated with low antibody response. The correlation between humoral and cellular immune responses after booster vaccination of low and non-responders compared to intermediate and high responders was investigated in another study [13].
A good correlation between antibody titers and cellular responses after booster vaccination was observed and low antibody production was associated with low antigen specific cytokine levels. The expression of one particular CD4 T cell receptor (HAVcr-1) correlated significantly with the antibody responses and cytokine levels, suggesting this receptor as cellular prediction marker of immune responsiveness to HAV vaccine, but this requires further investigation. The small, but significant, percentage of real HAV non-responders does not justify routine evaluation of immune response. It was commented that one case of primary vaccine failure was observed in Italy 2 years ago, but experience in Thailand in licensing studies showed that the rate of non-responders is negligible (1-2%). Risk populations such as travelers and health care professionals may need more careful observation. Also, the question was raised regarding non responsiveness within the context of single-dose vaccination schedule, such as is currently the case in Argentina.

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Prevention and Control Strategies

Global overview on the effectiveness of HAV vaccination programmes

HAV control and prevention strategies vary, depending on the country. In some countries, vaccination is focused on population groups who are at increased risk, such as international travelers or IDUs. Other countries have implemented universal vaccination as part of routine infant and childhood vaccination programmes or to control outbreaks.

Routine infant and childhood vaccination has the advantage of protecting children, i.e. the age group with the highest disease and infection rates, and provides herd immunity with benefits outside of vaccinated cohorts. This eventually results in protection extending to the entire population.

A list of selected countries and regions that implemented routine childhood HAV vaccination in 2007 is presented in the Table right above.

In most countries implementing routine HAV vaccination, high coverage rates of at least 85% were reported, except for the Puglia region in Italy where coverage was <20% in toddlers and 65% in adolescents. Routine HAV vaccination resulted in substantial decreases in HAV incidence in all countries listed in the Table above [1-6], often with declines not only seen in the vaccinated age cohort but also in non-vaccinated age groups, suggesting herd immunity. Temporal trends in declining HAV incidence make it difficult to measure the contribution of the HAV vaccine to the declining incidence. For

Selected Countries with Routine Childhood Hepatitis A Vaccination Programs, 2007

Country	Target Ages	Year Begun	Comments
Zhejiang Province, China	1-15 years	1992	Single dose live attenuated vaccine
North Queensland, Australia	18 months; catch-up to age 6 years	1999	Indigenous population
United States	2-18 years (regional)	1999	2006 - national (12 months)
Puglia Region, Italy	15 months 12 years	1997	HAV/HBV vaccine for adolescents
Israel	18 months	1999	Two dose
Argentina	12 months	2005	Single dose
Minsk, Belarus	6 years	2003	Single dose

CDC

instance in Belarus, a decline in HAV incidence was noted already before the routine vaccination programme was launched. Nevertheless, a significant difference in HAV incidence between vaccinated children aged 1-17 years age versus their non-vaccinated peers (0.31/10,000 versus 6.2/100,000) was noted in this country.

In the USA, incremental ACIP recommendations led to a nationwide HAV vaccination programme.

By 1996, HAV incidence rates appeared to vary according to race and ethnicity, with highest rates in Hispanics and American Indian/Alaskan natives, leading to initial focus in 1996 of HAV vaccination strategy on these high risk communities.

In 1999, based on data of effective community-based HAV vaccination programmes, ACIP recommended vaccination of children of 11 Western states with baseline (1987-1997) rates twice the national rate (i.e. >20/100,000 population) and to consider HAV vaccination for 6 states with rates 10-20/100,000. This strategy led to coverage rates of 57% (range 13-71%) among 24-35 month old children in the 11 high incidence states and 43% (range 2-57%) in the 6 intermediate incidence states. Among adults, the overall coverage was 12.1% and about 15-25% among those at risk.

This approach led to a very low overall incidence of 1.2/100,000 in 2006, without geographical variation, which is the lowest incidence rate since the introduction of HAV surveillance. When comparing the 2004 situation with the prevaccination 1996-1997 period, significant declines were seen in hospitalizations due to HAV (decline by 69%) and ambulatory visits (decline by 42%) [7]. The total estimated direct medical expenditures for HAV related hospitalizations and ambulatory visits declined by 68.1%. By 2004, a 32% reduction in HAV related mortality since introduction of the vaccine was noted [8].

After HAV vaccine was licensed in the USA for use in children 12-23 months old, routine nationwide HAV vaccination was implemented in 2006 by integrating the vaccine into the routine childhood vaccination programme.

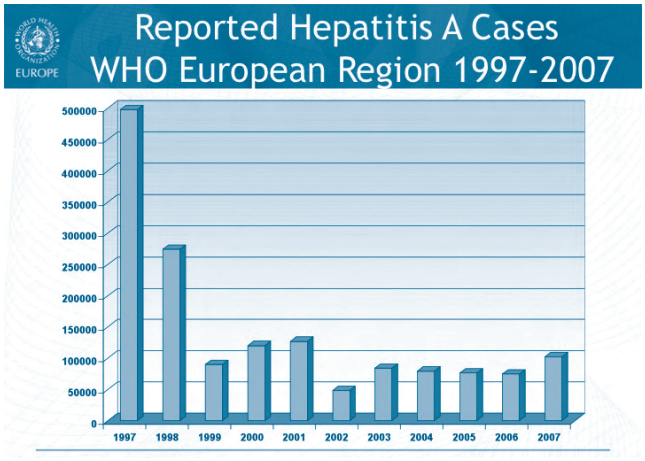
Currently, ACIP recommends HAV vaccination for:

- Children at the age of one year (i.e. 12-23 months)
- Persons at high risk of infection:
  - Traveling to or working in countries with high or intermediate endemicity
  - MSM
  - Persons who use injection and/or non-injection drugs
  - Persons who have occupational risk for infection
  - Persons with clotting-factor disorder
  - Persons with chronic liver disease
  - Non traveling contacts of international adoptees

To conclude, routine HAV vaccination programmes had a considerable impact on public health. HAV vaccination was effective in protecting vaccinated individuals and was able to reduce HAV incidence despite modest vaccination coverage. A growing body of evidence of considerable herd immunity among unvaccinated children and adults exists.
In order to improve HAV control internationally, the international cooperation should develop recommendations for countries considering implementing HAV vaccination programmes. Better surveillance and data on HAV disease burden are needed to identify the increased number of susceptibles due to epidemiological shift. When considering vaccination strategies, the level of endemicity, socio-economic development and sanitation, as well as the risk of outbreaks need to be taken into account, while vaccine costs and cost-effectiveness analyses also play an important role.

Update on HAV epidemiology and prevention in WHO European Region

The HAV incidence in the WHO European region has known an important decline particularly in the late 90's, which is mainly due to the decreasing number of reported HAV cases in former Soviet Union countries (see Figure below).



However, in 2007, for the first time in 5 years, an overall 40% increase in HAV incidence was reported in the region, resulting in a total of 102,747 cases, largely due to an increased number of HAV reports in Eastern European countries (see Table below). Incidence varied largely between countries, with very high rates (69-224/100,000) noted in Central Asian countries Kyrgyzstan, Tajikistan, Uzbekistan and Kazakhstan, which is about 100-fold higher than incidences in Western European countries. HAV thus remains a problem in the WHO European region, although mainly limited to a core set of countries.

Hepatitis A Incidence rate in WHO European region countries per 100,000 (2007)

Country	HAV Incidence (per 100,000)	Country	HAV Incidence (per 100,000)
Kyrgyzstan	224.21	Italy	1.97
Tajikistan	160.36	France	1.64
Uzbekistan	117.86	Switzerland	1.51
Kazakhstan	69.86	Austria	1.4
Georgia	42.54	Czech Republic	1.26
Bulgaria	36.65	Germany	1.1
Serbia	29.01	Sweden	0.8
Armenia	28.64	Ireland	0.7
Romania	23.24	Norway	0.6
Azerbaijan	19.63	U.K.	0.6
Greece	2.7	Denmark	0.5
Spain	2.25	Finland	0.3
Belgium	2.08	Portugal	0.2

In 2008, outbreaks of variable size occurred in several countries, including the Czech Republic (1,616 cases), Latvia (2,235 cases), Slovakia (569 cases), and some smaller outbreaks in Spain, Ukraine and Russia. Also HAV outbreaks in Tajikistan and Kazakhstan were recently reported but the number of cases is currently unknown.

Source of transmission and risk groups also vary, depending on the country. In Eastern European countries, suspected cause was mainly contaminated water. In Western European countries, HAV epidemics were related to behavioural risk factors such as IDU and MSM. Contaminated seafood (Spain) or infected food handlers (Latvia) were also identified as outbreak causes.

Measures taken to control HAV outbreaks varied from country to country and included:

- Patient isolation
- Quarantine
- Surveillance of contacts
- Disinfection, removal of environmental infection source
- Targeted vaccination
- Post exposure prophylaxis (PEP) by vaccinating the contacts
- Preventive vaccination of high risk groups (regardless of contact status)
- Risk communication

Examples of the different vaccination strategies used in different countries to control HAV are detailed in the Table below:

HAV Control Strategies

Country	Vaccine	Target group
Belarus	HepA	6 years; Part of country
Cyprus	HepA	Risk Groups
Finland	HepA	IDU
Greece	HepA	> 12, +6 months
Israel	HepA / HepAHepB	18, 24 months; and risk groups
Italy	HepA	Travelers, outbreak control*
Kazakhstan	HepA	Risk groups
Malta	HepA / HepAHepB	Travelers
Monaco	HepA	5 months; 1 year;
Romania	HepA	Outbreak contacts, during flooding
San Marino	HepA / HepAHepB	On request
Slovenia	HepA	In case epidemiological indications

* Italy: routine childhood vaccination in Puglia region

The HAV surveillance at the WHO Regional Office for Europe is very fractionated and would gain of consolidation. Currently it is organized at three different levels:

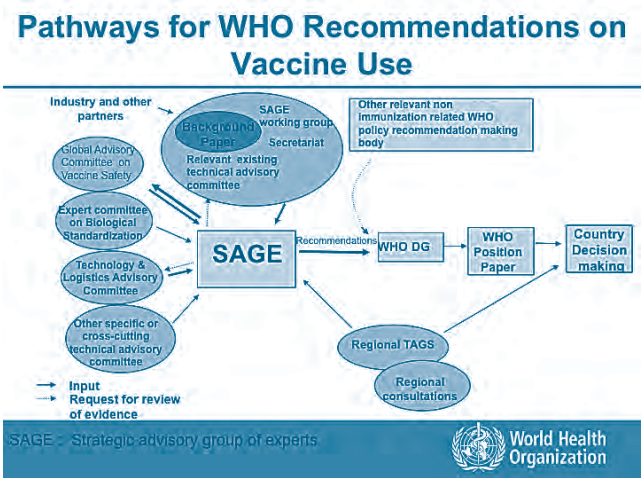
- An Annual Joint Reporting Form is issued

- A publicly available Computerized Information System for Infectious Diseases (CISID) at http://data.euro.who.int/CISID is maintained by the Surveillance and Monitoring team within the Communicable Diseases Unit (CDS)
- Event monitoring and outbreak notification go through the Alert and Response Team at CDS.

In case of an outbreak it is even more confusing as the local public heath representatives are legally obliged to report to both the ECDC and WHO Regional Office for Europe. Hence, there are no WHO regional surveillance guidelines for HAV and standard definition of contacts and a list of identified risk groups are lacking.
Responsibilities regarding control of viral hepatitis are also organized in a complex way within the WHO Regional Office for Europe, and are divided between the HIV/AIDS team, the TB team, and CDS. In terms of HAV outbreak control there is currently no consolidated set of response guidelines. The ECDC Riga meeting held in November 2008 after the outbreaks in the Czech Republic, Latvia and Slovakia and the Global HAV meeting held in November-December 2007 in Miami both concluded that guidelines on outbreaks are needed, especially due to the current increasing number of HAV outbreaks. Although the need for development of guidance on outbreak response at global level was agreed, it was defined as a long term action plan, without any specific timeline identified.

Review of the WHO Hepatitis A Vaccine Position Paper: need for an update?

WHO position papers are issued for each vaccine preventable disease in official languages and are designed for use mainly by national public health officials and immunization programme managers, thereby influencing country decision making. These position papers are key reference documents that summarize essential background information, concluding with current WHO recommendations concerning vaccine use in global context, rather than for individual protection. The development of WHO position papers is outlined in figure below.



WHO position papers are published in Weekly Epidemiological Record and on the WHO website (http://www.who.int/immunization/documents/positionpapers/en/).

The current WHO position paper on hepatitis A vaccine (HepA) dates from 2000 [9] and its revision is tentatively scheduled for late 2010.

The current position paper (2000) includes specific positions for countries, depending on their HAV endemicity:

- 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 travelers to areas of intermediate or high endemicity.

In the current HepA position paper, several topics requiring update were identified, such as changing HAV epidemiology and global burden data, as well as currently available vaccines and most recent long-term protection data. The status of vaccination programmes will be reviewed globally, including the use of HepA vaccine for outbreaks, which is not included in the current position paper. Also, a stronger recommendation for universal introduction of HepA vaccine in areas of low and intermediate endemicity will be considered.

In addition, a list of issues not currently addressed need to be included in the updated position paper:

- Provide guidance to countries to detect changing epidemiology, especially for historically high prevalence countries
- Use of HepA vaccine for contacts of cases of acute hepatitis A
- In line with the new WHO approach of assessing evidence of interventions, a review and “grading” of evidence [10] should be performed e.g.
  - Is HepA vaccine effective to prevent disease/death?
  - Are booster doses of HepA vaccine needed?
  - Is HepA vaccine effective for outbreak control?
  - Is HepA vaccine effective for post-exposure prophylaxis (PEP)?
  - Is immunoglobulin effective for PEP?
  - Should contacts of HAV cases be given PEP?

For the first time, viral hepatitis prevention and control was on the agenda of the World Health Assembly in May 2009 to draw attention on the burden of viral hepatitis, including HAV infections, globally. Implementation of HAV control measures including vaccination would be considered in order to prevent the emergence of HAV in developing countries. [This agenda item was shifted to the 2010 due to a shortened World Health Assembly meeting necessitated by the H1N1 global pandemic.]

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Hepatitis E

Virology, epidemiology, natural history and pathogenesis of HEV

HEV discovery and characterization

In the winter of 1955–1956 a severe outbreak of waterborne hepatitis in New Delhi, India occurred following a monsoon storm flooding the sewage system and contaminating the city's water supply. The outbreak was assumed to be caused by HAV until 1980, after the development of a diagnostic test in the late seventies, Dr. Purcell and his colleagues showed that the New Delhi outbreak victims were not infected with HAV, suggesting it was a new virus. In 1990, the virus genome was cloned, sequenced, and eventually renamed HEV. In the most recent classification, HEV has been placed in its own taxonomic group of the Hepeviridae, genus Hepevirus. HEV may be confused with HAV due to similarities in the clinical picture of both diseases. A comparison of HEV and HAV characteristics is presented in the Table below. HEV has a wider host range (including man, non-human primates, pigs, rats, chickens, and possibly cattle and sheep) than HAV (man and non-human primates only).

Comparison of enterically transmitted hepatitis viruses HAV and HEV

	HAV	HEV
Virus family	Picornaviridae	Hepeviridae
Nucleic acid	Plus strand RNA	Plus strand RNA
Size	28 nm	32-34 nm
Genomic size	7.5 kb	7.2 kb
Virus stability	Very stable	Less stable
Transmission	Feces/(blood)	Feces/(blood)
Infectious titre in feces	10^6-10^9	10^4-10^7
Host range	Primates	Primates, pigs, rats, chickens, cattle, sheep, etc.
Naturally attenuated strains	No (?)	Yes (?)
Dose-response infection	No	Yes
Incubation	2-5 weeks	3–7 weeks
Chronicity	Not reported, but persistent hepatitis A of up to 15 months duration has been described	Not common (kidney transplant patients)
Mortality	1-2%	<1%, but 15-25 % in pregnant females
Severity of disease	Increases with age	Increases with age
Vaccine available	Yes	Yes, under development

The most common genome regions for typing are in the ORF1 or ORF2 (capsid protein) region. The highly conservative ORF2 structural capsid protein has been used as the basis for vaccine development.

HEV sequence analysis revealed at least 5 genotypes. Genotypes 1 and 2 were found in human cases, types 3 and 4 were isolated mainly from human and swine, but also from wild boar, deer, mongoose (genotype 3), and cat (genotype 4). Genotype 5 was found only in avian isolates and is not transmittable to primates; it is also more diverse and could still be classified as another type. Genotypes 1 to 4 form one serotype, which is important for vaccine development. HEV genotypes have been subdivided into subgenotypes, 24 in total, unfortunately mostly based on limited sequencing. There is an urgent need to re-evaluate some of these subtypes.

Further analysis of a dendogram containing 119 complete HEV genomes demonstrates that there are two major clades within genotype 3: Group 3-I mainly from Asia and USA and group 3-II mainly isolated from European samples. Genotypes 3 and 4 are considered to be less virulent compared to genotypes 1 and 2. Since this differ-

ence cannot be explained by differences in sequences, the host immune response may also play a role, but current data are too limited to allow meaningful interpretation.

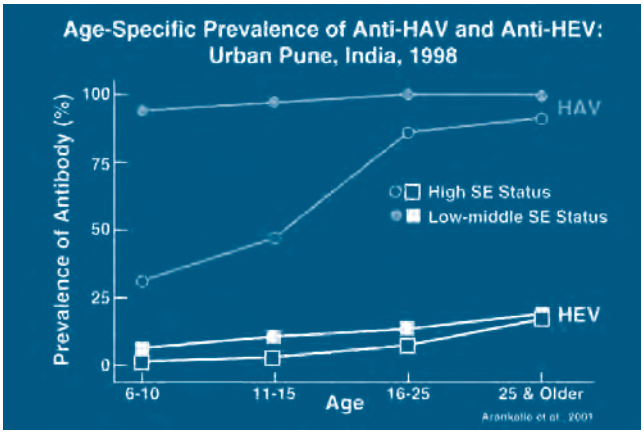
HEV thermostability has been examined in three studies; two studies of HEV in faeces, analyzed in vitro [1, 2], and one study of HEV in pork liver, analyzed in vivo [3]. The results were surprisingly consistent: HEV was resistant to heating at 56°C (i.e. the temperature of medium rare meat) for 30 minutes to one hour (all three studies) and residual live HEV was still present after heating at 60°C (temperature of medium-cooked meat) for one hour (one study). However, it was completely inactivated after heating for one hour at 66°C (temperature of medium well-cooked meat) (one study) and at 70-71°C (temperature of well done meat) for 10 minutes to one hour (all three studies).

Epidemiology, including molecular investigations

Sero-epidemiological studies show that HEV is highly endemic in tropical and subtropical regions. In these regions HEV is the first or second most important cause of acute clinical hepatitis in adults, with large epidemics usually associated with fecal contamination of drinking water in Central and South-East Asia, the Middle East, and Africa. Industrialized countries in North-America and Europe have been considered as non-endemic regions with only sporadic cases reported even in patients who were never linked to areas of HEV endemicity. This geographical pattern suggests a strong socioeconomic component to the epidemiology of enteric HEV. It should be noted that HEV has not been looked for in many countries and is substantially underreported.

In contrast to the geographic distribution of the disease incidence, HEV antibodies are present worldwide, but in endemic countries such as India, the prevalence of HEV generally does not follow the typical pattern for an enterically transmitted virus like HAV. HEV infection is rare in young children and does not reach peak prevalence (33%-40%) until early adulthood [4]. However, age specific prevalence of HEV in Egypt was found to be more similar to the one of HAV [5].

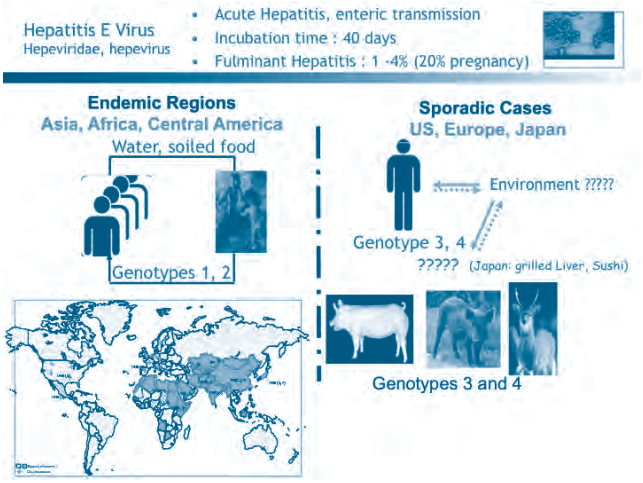
In endemic countries such as India and Egypt, a change in HAV seroprevalence towards older age was noted among high socioeconomic (SE) status populations, while no change was seen among low socioeconomic status population. A comparable trend was noted for HEV, but this occurred to a much lesser extend (see Figure below) [6].



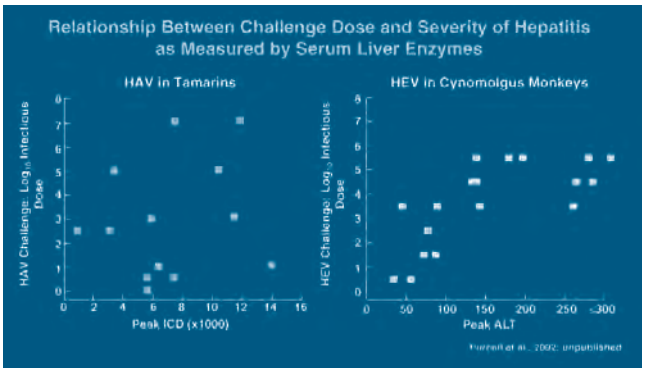
SE: Socioeconomic

In non-endemic regions, anti-HEV seroprevalence is low, ranging from 1% to 5%. Age specific prevalence of HEV antibodies in the USA is higher than what could be expected from the low incidence of HEV cases [7]. Reports of autochthonous cases in non-endemic areas without history of traveling to endemic areas raised the suspicion of an animal reservoir for HEV in industrialized countries. Both genotypes 3 and 4 were recovered from swine, mainly in the same regions as they were recovered from humans. In industrialized countries, where HEV incidence is low, the high anti-HEV prevalence may result from subclinical infections with attenuated less virulent genotypes 3 and 4, which are possibly of swine or other animal origin (see Section on zoonotic transmission).

The Delhi epidemic in 1955 mainly affected older children and young adults, which is a typical age-specific pattern for waterborne HEV epidemics, and is believed to be caused by genotype 1. Sporadic HEV cases due to genotypes 1 and 2 in developing countries also occur mostly in older children and younger adults. In contrast, sporadic HEV cases in industrialized countries caused by less virulent genotypes 3 and 4 (see Figure below) occur on average at a much older age, often in elderly or immunologically compromised individuals.



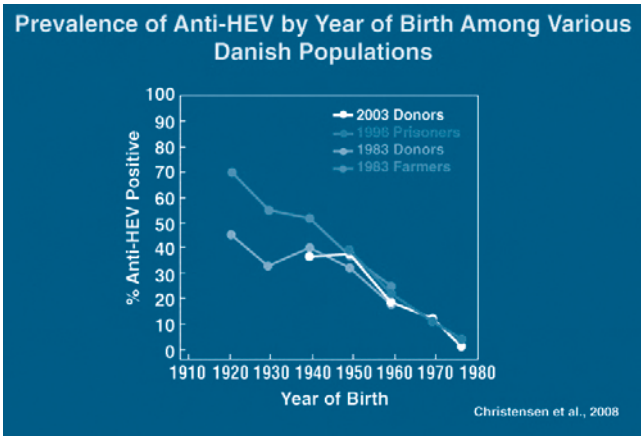
Experimental infection of cynomolgus macaque monkeys with various HEV doses shows, unlike HAV infection, a dose-response with lower dose inoculation (see Figure below), resulting in absence of alanine aminotransferase (ALT) elevation or disease symptoms but with virus replication and shedding.



Thus, viral load of inoculum may be a factor responsible for clinical presentation of the infection and disease. To date, it has not

been demonstrated that the apparent relationship between severity of HEV infection and the infectivity titer of inoculum in primate models also applies to infected humans. Severe HEV outbreaks in Pakistan and India linked to heavy water contamination also suggest that there is a correlation between HEV disease severity and dose-response. Such correlation may explain why risk of death linked to HEV infection is so variable from community to community. However, it should be noted that virulence of the viral strain or isolate and the host immune response are other determinants playing a role in the clinical presentation of HEV.

HEV appears to be an emerging disease although historical records suggest that HEV disease may be more ancient than initially thought. HEV may have been recognized as an emerging disease because the disease was previously under-diagnosed due to the lack of a reliable, standardized commercial serological assay. Like HAV, the number of HEV infections is diminishing over time in industrialized countries, such as in Denmark [8], as shown in the figure below, where half of anti-HEV positives were infected in the early 20th century.

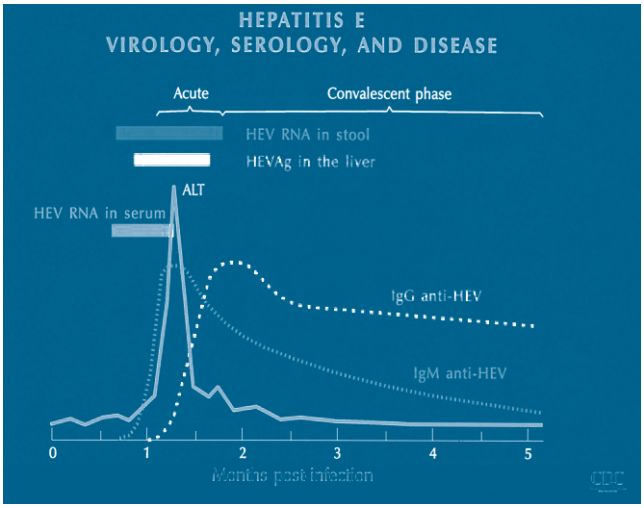


Natural history and pathogenesis of HEV

Clinical manifestations of HEV were investigated after experimental oral inoculation of volunteers with pooled stool extracts from presumed cases of non-A, non-B hepatitis [9, 10]. Shedding of virus was detected in serum and in stool, first by means of immune electron microscopy and later by polymerase chain reaction (PCR). The steep increase in viral load in stools and serum to high concentrations suggests that several cell types are involved in a massive virus production. ALT elevations were seen followed by clinical signs of liver pathology, together with HEV specific antibody development (see next Figure). Clinical symptoms include prodromic syndromes with enlargement of the liver followed by jaundice and dark urine.

Inoculated primates can only develop acute hepatitis although HEV infection can also be subclinical in these animals. Chronic liver disease in primates was never observed. Also no mortality was observed in infected pregnant rhesus monkeys.

Few data are available on cellular immune responses in HEV infection. In vitro studies suggest a role of innate immunity in terms of natural killer (NK) and NK T-cells in the pathogenesis of HEV disease [11]. T-cell immune responses have been observed during acute infection [12] and the CMI response was found to correlate with anti-HEV antibody response [13, 14]. CMI data also suggest



that immune reactivity mainly occurs in the intra hepatic compartment, which is the major disease site, and less in peripheral blood cells [15]. Natural history of HEV in human subjects and in experimentally infected primates strongly suggests that the host immune response rather than direct HEV cytotoxicity mediates liver pathology but this hypothesis still needs to be confirmed by ongoing studies. The host immune response results in characteristic liver pathology, leading to various clinical presentations ranging from icteric, symptomatic hepatitis or even fulminant hepatic failure (in pregnant women) to anicteric hepatitis with ALT elevation but without jaundice; and to asymptomatic infection without ALT elevation but with virus shedding and immune response. The mechanism of hepatocytic necrosis in acute hepatitis E may involve apoptosis, as was suggested by concordant elevations in an apoptosis marker and ALT in chimpanzees.

HEV in pregnant women

Mortality due to HEV is generally low (approximately 0.5 – 4.0% of patient population), except for pregnant women in the third trimester, where mortality rates can reach up to 20% [16]. A higher mortality due to HEV in pregnant women, particularly from certain geographical areas in India, is described in literature but not explained. Controversial information is available in literature [17-19]. The reason for fulminant hepatic failure in HEV-infected pregnant women is unknown. Several hypotheses exist (hormonal, immunological factors, …) but all require further investigation.

Chronic HEV

It was believed for many years that HEV is responsible for acute hepatitis that does not become chronic. However, a much worse prognosis has been observed in HEV cases with underlying chronic liver disease and recent cases show that in immunocompromised individuals HEV can progress to chronicity [20-22], often with development of cirrhosis.

For instance, during the period 2004-2006, liver and kidney transplant patients in the South-West of France (Toulouse University Hospital, Rangueil), with acute elevation of liver-enzyme levels, were screened for HEV infection using molecular tools after all other causes of hepatitis had been ruled out. HEV RNA was found in 14 (6.45%) patients, all were of genotype 3. The average age of these 14 patients was 49 years (range 28-67), the majority were male (11/14), the median time since transplantation was 57 months (range 6-168) and 7 (50%) patients were asymptomatic.

In six patients (43%) HEV resolved spontaneously but in the remaining 8 patients (57%), HEV infection evolved to chronic infection, confirmed by the presence of persisting elevated liver enzyme levels and positive HEV RNA at 15 months after the acute phase. Follow-up biopsies among chronically infected patients showed a worsening of cirrhosis and fibrosis within 18 months after diagnosis. In patients who were able to clear the virus, the time since last transplantation was longer and those evolving to chronic HEV were more immunosuppressed. Since 2004, the University Hospital of Toulouse identified a total of 16 (59.3%) HEV cases to be chronic, of which 4 cases were able to clear the virus after reducing the dose of immunosuppressants. Kidney transplant cases with chronic HEV were also reported in the South-East of France (region of Marseille) with HEV RNA present two years after transplantation but in the absence of increased liver enzymes and with rapid evolution to liver fibrosis and cirrhosis [23-25]. The occurrence of chronic HEV in organ transplant patients was also confirmed in The Netherlands, where two cases of chronically infected liver transplant patients rapidly evolved to cirrhosis and decompensating cirrhosis [21].

In general, HEV infection in organ transplant patients is asymptomatic, with less important elevation of liver enzymes, delayed or absent seroconversion, but often with persistent serum HEV RNA. In nearly 60% of cases, HEV evolves to chronic infection, with high risk of cirrhosis. Currently, there is no treatment available for chronic HEV infection. Therapeutical use of neutralizing monoclonal antibodies against HEV, human or chimpanzee derived, could be considered as a future option for this setting of chronically infected organ transplant patients.

The mechanism of HEV chronicity in the setting of organ transplant patients remains unclear and a longer follow-up of these patients is required to assess the natural history of chronic HEV infection. The pathogenic effect of HEV on the liver is immune mediated, while on the other hand, those who are immunocompromised due to immunosuppression therapy are not able to clear the virus. This indicates that the immune system is needed for clearing the virus and that a balance between both aspects needs to be reached. Apparently, reducing immunosuppression therapy enables the patient to clear the virus and even restore liver function but currently it is not understood through which mechanism this occurs. In this context, the role of HEV-specific T-cells in the HEV pathogenicity is being investigated. In non-immunocompromised patients, no HEV related liver cirrhosis was reported.

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Zoonotic transmission of HEV

HEV in animals

HEV spread from human to human does not seem to be an efficient transmission route; it is therefore likely that in industrialized, non-endemic countries, sporadic infections with genotypes 3 (or 4) are caused through an animal reservoir. The widespread presence of HEV genotype 3 in pigs, wild boars and other mammals indeed suggests that human infections may have a zoonotic origin, which is also supported by cross-species HEV transmission shown in several experimental models, see Figure below.

Cross-Species Transmission of HEV

Genotype	Natural Host	Other susceptible Hosts
1	Human	Nonhuman primates (swine, rat, horse??)
2	Human	Nonhuman primates
3	Swine (domestic, wild)	Human, nonhuman primates, Sika deer, Mongoose
4	Swine	Human, nonhuman primates
5	Chicken	Other avian species?

There are also many reports on the detection of HEV antibodies in serum samples from different animals but these results are often obtained using tests that are developed and evaluated for detecting HEV antibodies in human samples during the acute phase of the disease. The reliability of these results is therefore questionable [1].

Possible animal reservoirs

Animal	Country	Ab Prevalence
Swine	Worldwide	30-80%
Rat	India, Brazil	50-80%
Cat	Japan	33%
Dog	Brazil	7%
Sheep	India, China, Brazil	
Goat	India, China, Brazil	
Wild boar	Japan, France, Germany, Italy, Spain, Hungary	5-42%
Deer	Japan, Hungary	2.6%
Chicken	USA, Brazil, Australia	20-30%
Bovine	Brazil	1.42%
Horse	Egypt	13%
Mongoose	Japan	8.3%

High anti-HEV prevalences were noted in some domestic animals such as rats, cows, sheep and goat, but no virus has been isolated or characterized from these species.

Cross species transmission was studied in experimental models, as shown in the Figure below. It was not possible to infect swine with genotypes 1 and 2 isolated from humans, whereas genotype 3 was fully permissive between humans and swine.

Crossing the Species Barrier

Genotype	Natural Host	Exp Models	Infection
1 & 2	Human	Macaque	+
		Swine	-
		Rat	+
3	Human	Macaque	+
		Swine	+
	Swine	Macaque	+
		Swine	+
		Chicken	nd
		Rat	nd
		Lamb	+
Avian	Chicken	Macaque	-
		Swine	-
		Chicken	+
		Rat	nd
		Turkey	+

nd: not determined

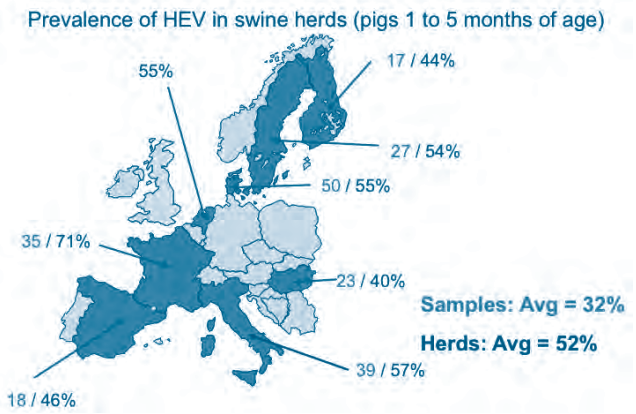
The pig is one of the most important animal reservoirs for HEV (genotype 3 and 4). Sequencing of the HEV genotype 3 genomes in the ORF 1 and ORF2 regions from human, swine and wild boar samples collected in different countries shows that there are geographical clades of HEV strains regardless of host.

HEV is highly contagious among swine. Natural infection in swine is asymptomatic and generally occurs around 10 weeks of age, after weaning when maternal antibodies are lost, and is followed by viral excretion between the age of 12 and 15 weeks. Seroconversion generally takes place at 16-20 weeks of age. Experimental infection had no effect in pregnant gilts [2]. Few liver lesions are seen in experimentally infected swine, with no increase of liver transaminases (AST and ALT). Extra-hepatic sites of multiplication include the small intestine, colon, and lymph nodes and high excretion occurs in bile and spleen. HEV RNA could be detected in most organs and excreta of experimentally infected swine, as well as in several muscle samples up to 11% of the liver sample were positive, which is important in view of meat consumption [3].

It is estimated that up to more than 90% of swine herds in the USA, Europe and Asia are infected with HEV genotype 3 (USA, Europe) or 4 (Asia).

The HEV working group of EVENT within the Foodborne Virus in Europe network (FBVE) determined the prevalence and type of HEV in swine herds.

The average HEV prevalence in swine herds in Europe at sample level is 32% and 52% at herd level (see Figure below).



In this European collaborative study, the highest HEV prevalence was found in France, where more than 70% of swine herds are affected.

The intra-herd prevalence in France is variable with an average of 25%, ranging from 2.5 to 80%). Strains isolated from swine are of subtypes 3c, 3e and 3f and are very closely related to those found in humans, supporting the hypothesis of zoonotic transmission. In contradiction, a national survey of acute hepatitis cases performed in the framework of the French national Association Nationale des Hépato-Gastroentérologues des Hôpitaux Généraux (ANGH) network does not favour the hypothesis of zoonotic transmission since a decreasing South-to-North geographic gradient, with 15% of HEV cases reported in the Northern part and 85% HEV cases occurring in the Southern part of France, particularly South-West was noted [4], while this distribution is opposite to the geographical distribution of swine herds in France, with highest concentrations in the North-West. More clusters were found on regional level than on host species levels. Possible risk factors identified from this study were water consumption from a personal water supply and one case of recent acquisition of a pet pig.

In Italy, HEV genotype 3 is widespread among farm pigs and wild boars and HEV strains isolated from Italian swine are circulating all over Europe. HEV RNA could be detected in 42% of pigs tested in Northern Italy and in 25% of wild boars [5, 6]. In the same region, anti-HEV prevalence in farm swine was 50% of the tested pigs with 97% of farms found anti-HEV positive [7]. Similarly to the situation in France, the high concentration of swine farms and wild boars in the North of Italy contrasts with the higher seroprevalence in the population from the South of the country and therefore does not support the zoonotic transmission hypothesis. However, many swine farms and wild boars are also found in Sardinia.

In Sweden, recent testing showed that 60% of pig farms had HEV RNA positive piglets, with 20% of piglets being positive in faeces. Among wild boar serum samples collected in different regions of Sweden, 18% of piglets and 4% of young pigs were positive for anti-HEV antibodies, and in 3.4% of the tested piglets/young pigs RNA could be isolated.

In Spain, a recent survey found up to 97% of pig farms positive for anti-HEV IgG antibodies [8] while the FBVE study found 46% of Spanish herds positive. Differences in pig age, the sensitivity of the ELISA assays used, as well as the characteristics of the farms studied, may be significant factors influencing the numbers of HEV seropositive farms described. In the Netherlands, PCR-based prevalence of HEV is approximately 50% in swine herds and 4% in wild boars [9].

With an overall 52% of swine herds in Europe positive for anti-HEV, swine represent a huge reservoir for HEV genotype 3 in Europe. The high degree of homology between human and swine HEV strains suggests possible zoonotic transmission from domestic swine to humans. Even though in some cases human/swine strains isolated were 100% identical, there is no direct proof of swine to human transmission. Foodborne transmission via inappropriately processed pork might occur and several findings support the hypothesis of zoonotic HEV transmission through direct contact with infected pork meat. Studies conducted in the USA as well as in Europe suggests that personnel exposed to swine or swine meat (in veterinaries, butchers, slaughterhouse) had higher anti-HEV prevalence (11% to 51.1%) than matched, non-exposed individuals [10, 11], however, the same studies also show that it differs per state (USA) and that in the Netherlands no effect was found if the validated diagnostic algorithm is used. Studies from Japan also suggest a zoonotic source of HEV infection through consumption of raw or undercooked meat (deer, wild boar, pork) [12-14]. Evidence of association between HEV infection sources and meat consumption was also found in Indonesia where prevalence in pregnant women with Muslim religion is lower than in those with Hindu religion (2% versus 21%) [15].

Commercial pork livers can be positive for HEV RNA, e.g. 11% of livers tested in USA [16] and 6.5 % of livers in the Netherlands [17]. The main conclusion of several studies was that heating to 56°C was insufficient to obtain complete inactivation of HEV viruses, however, heating to 70°C resulted in complete inactivation of HEV in infected pork liver within minutes [16], underlining the importance of cooking meat thoroughly. Consumption of offal or wild boar meat was also associated with HEV infection [18]. Other possible sources of HEV exposure include shellfish consumption and blood transfusion (Japan).

HEV in the environment

Several studies conducted in Europe and the USA were able to detect HEV in environmental samples, such as waste and surface water [9, 19].

For instance, in Spain, urban sewage samples collected in Barcelona were frequently HEV positive, as detected by PCR between 1994 and 2002 (43.5%) [19], and remained present in 2006-2008 (28.1%), while during the same time interval, HAV presence in sewage water substantially declined from 57.4% to 3.1%. Similarly, in the region of Valencia, 31.7% of sewage samples collected in 2007-2008 were HEV positive, whereas HAV was isolated in only 2.4% of them. It should be noted that the HAV vaccine has been distributed in a pilot program in Catalonia for pre-adolescents since 1999. In Valencia, a region immediately south of Catalonia, HAV vaccines are distributed only among groups at risk as a result of handling food. River water samples collected in Spain and analyzed for HEV PCR were negative. The majority of HEV strains isolated from selected representative samples from sewage treatment plants or sludge generated in a pig slaughterhouse belonged to genotype 3 and sporadically genotype 1 was present.

The results strongly suggest that HEV has replaced HAV as the most frequently detected hepatitis virus potentially transmitted through local faecal contaminated water or food in South-Western Europe. The substantial reduction in the number of HAV positive sewage samples could be attributed to considerable improvements in sanitation. However, these improvements have not had an equivalent effect on the circulation of HEV genotype 3 in the area. Improved sanitation seems insufficient to eliminate HEV from the

environment since the continued circulation of this virus is maintained, possibly due to other animal hosts, such as swine. Contamination of food and water through their contact with sewage not being properly treated and biosolids presenting HEV may represent a significant HEV risk for human populations, even in industrialized areas. While HEV has been shown to be present in farm animals for a long time, knowledge regarding spread via crops is limited. It is difficult to detect with a good level of sensitivity virus presence in artificially contaminated food products. Further investigations are needed to clarify whether frequent subclinical, undetected infections from food products could occur.

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Based on presentations by
R. Purcell, National Institutes of Health, Maryland, USA;
N. Pavio, Veterinary National School, Maisons-Alfort, France;
R. Girones, University of Barcelona, Barcelona, Spain;
E. Duizer, National Institute for Public Health and Environment (RIVM), Bilthoven, The Netherlands;
H. Norder, Swedish Institute for Infectious Disease Control (SMI), Stockholm, Sweden
and A. Zanetti, University of Milan, Milan, Italy.

Hepatitis E and its emergence in (non-)endemic areas in Europe, USA and Asia

The FBVE/EVENT collaboration also studied the prevalence and type of HEV among acute non-A, non-B, non-C hepatitis patients in Europe. An overall HEV prevalence of 7.1% was found (Denmark 4.8%, Finland 7.2%, France 6.9%, Hungary 8.4%, Spain 8.5%, Sweden 6.1% and The Netherlands 5.6%).

Sweden and Denmark

Among clinical hepatitis cases reported between 1993 and 2008 at the Swedish Institute for Infectious Disease Control (SMI), the proportion of patients with HEV RNA in serum was 71% for those who were anti-HEV IgM positive and 19% for those who were anti-HEV IgG positive. Serotyping of the HEV RNA positive samples showed that the majority was due to genotype 1 and travel related (86%) but 11 cases (14%) were genotype 3 positive. Among these 11 genotype 3 cases, the majority (9/11) was male, mean age was 54 years, and none had a travel history outside Europe. The gender and age pattern is very comparable to other European data.

Based on a presentation by
H. Norder, Swedish Institute for Infectious Disease Control, Stockholm, Sweden.

Southwest England, UK

HEV epidemiology was studied in Cornwall, in Southwest England, a location with a stable population and few immigrants. Since 2001, a total of 51 acute HEV cases were identified in the region with median age 64 years and male to female ration of 3:1. Three quarters of them presented with jaundice and symptoms ranged from asymptomatic through mild hepatitis to acute liver failure. Most patients recovered in 4 to 6 weeks, except for three patients who died, including 2 cases due to liver failure.

Anti-HEV IgG seroprevalence in Southwest England increases with age and is more common in men. Rates were 16% in blood donors and 13% in patients with chronic liver disease (CLD) [1]. A possible explanation for such high seroprevalence might be that HEV infection is often unrecognized. For instance, diagnosis of HEV infection is frequently missed, e.g. in patients with drug-induced liver injury, in patients with decompensated alcoholic liver disease, or when neurological syndromes occur with HEV infection. The HEV seroprevalence data presented from Southwest England were based on anti-HEV IgG (Wantai China). There are divergent seroprevalence results across developed countries and this may be a reflection of the differing assays used as they have differing sensitivities and specificities. In this context, the lack of up-to-date, reliable, standardized and validated HEV diagnostic tools was considered as a critical issue. Also, based on the high seroprevalence data, it was assumed that HEV probably is a more common cause of acute viral hepatitis than initially thought, with significant morbidity and mortality, as well as poor prognosis in CLD, with a mortality of up to 70%. Multiple regression analyses of data collected between 1990 and 2000 in several countries identified alcohol and pork meat consumption, and HBV co-infection as independent predictors of mortality in CLD. This observation could have a number of explanations, but might be explained by unrecognised HEV infection in patients with pre-existing CLD.

Based on several assumptions regarding CLD prevalence, HEV related mortality in CLD patients, and HEV seroconversion rate, it was hypothesized that up to 13,000-26,000 deaths occur annually in developed countries. However, the validity of this provocative hypothesis needs to be confirmed and additional studies are ongoing.

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Based on a presentation by
H. Dalton, Royal Cornwall Hospital Trust, Truro, UK.

The Netherlands

HEV was first reported in the Netherlands in 1993 when 1.1% of blood donors were found anti-HEV positive. Endemic, non travel related HEV cases were reported in 2003 in the Northern part of the country [1] and a first fatal HEV infection in a patient with presumed hepatocellular carcinoma occurred in 2004 [2]. In Dutch cases of unexplained acute hepatitis (non-A, B, C hepatitis), an anti-HEV IgG seroprevalence of 6% was found [3].

Being male, older than 50 years and having an underlying disease were identified as important factors for the development of disease after infection with HEV genotype 3 [4]. A few cases had a history of blood transfusion, which might be the source of their infection as transmission of HEV via blood has previously been described. Person-to-person spread did not seem to be an efficient transmission route for HEV genotype although HEV efficiently spreads from pig to pig [5]. Contact with pigs did not seem to be a risk factor but other potential risk factors which are being investigated in the Netherlands include blood transfusion, pork meat (in particular organs) consumption and contact with other animals such as horses, cows, dogs and rodents.

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Based on a presentation by
E. Duizer, National Institute for Public Health and Environment (RIVM), Bilthoven, The Netherlands.

France

The French national reference centre for HEV (www.cnr.vha-vhe.aphp.fr/cadrecnr.htm) records over 150 human indigenous HEV cases per year, including 1-2 yearly fulminant cases and several chronic cases in transplant patients.

In the area around Paris, a rate of 3.2% anti-HEV prevalence has been reported among blood donors [1], which is similar to that of other industrialized countries. However, in the Southwest region of the country (Midi-Pyrénées), a higher seroprevalence among donors of 16.6% was found [2]. Hunting was the only factor significantly associated with this high prevalence. Despite the relatively high proportion of HEV seroprevalence among blood donors, limited evidence of HEV transmission through blood transfusion exists in France; only one case of a child with a hematological problem was reported in Marseille. The incidence of HEV was stable in Southwest France from 2003 to 2007 with 10-16 cases/year and no seasonal or gender variations were observed [3]. The majority of patients (96.8%) had not traveled abroad and were mainly infected with genotype 3 (predominantly subtype 3f). Clinical manifestations ranged from asymptomatic infection to severe hepatitis with an apparent, but non-significant age-related increase in disease. In 2008, in the Southwest region of France a total of 17 acute hepatitis cases were diagnosed HEV RNA positive, all with genotype 3 strain.

In addition to animal to human transmission, molecular evidence

suggests that human to human HEV transmission may also occur, as was observed in a French hematology ward [4].

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Based on a presentation by
JM Mansuy, Institut Fédératif de Biologie,
Toulouse, France.

Germany

HEV infections became notifiable in Germany in 2000. Since then, HEV incidence in Germany increased from 31 reports in 2001 to 101 cases in 2008.

The proportion of non travel related HEV cases also increased in recent years from 33% in 2003 to 61% in 2007, and in most cases the route of transmission is unknown. The first proven case of autochthonous HEV infection in the country dates from 2004 and was identified with a genotype 3 strain. A chronic HEV infection was first reported in a renal transplant patient who was able to clear the virus after his immunosuppression therapy was changed.

Risk factors for HEV studied on 66 patients in Germany in 2006-2007 included consumption of offal or wild boar meat [1], suggesting that HEV exists as a food borne zoonosis. HEV RNA analysis of archived serum samples from wild boars collected in 1995-1996 showed that 5.3% was positive, and isolates were closely related with genotype 3 isolates of pigs from the Netherlands [2]. Recent seroprevalence studies found high anti-HEV seroprevalence rates of 14% among blood donors and 19% among forestry workers. HEV transmission through blood transfusion is not studied in Germany, but systematically testing for HEV of transplant patients has just started. Currently, anti-HEV testing is ongoing among about 9000 participants of the German Health Interview and Examination Survey for Adults (DEGS), which is a nationwide study conducted from 2008 till 2011 by the Robert Koch Institute.

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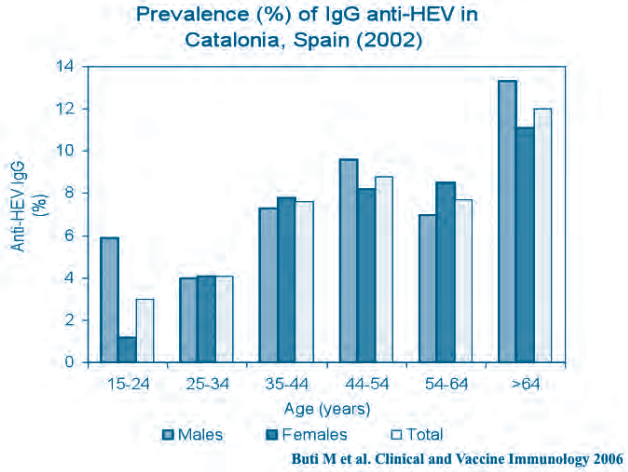
Based on a presentation by
W. Jilg, University of Regensburg, Regensburg, Germany.

Catalonia, Spain

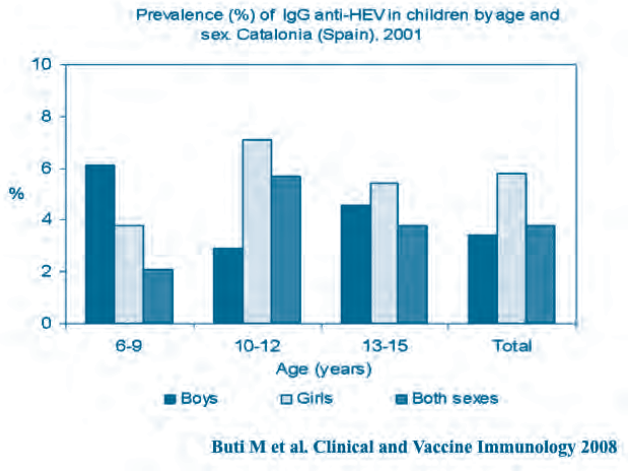
The overall anti-HEV IgG prevalence in the Spanish population was reported to be 5.5% in 1995 [1].

More recently, a community-based seroepidemiological survey conducted in 2002 in Catalonia, Spain, detected anti-HEV IgG antibodies in 7.3% of the 1,280 healthy adult subjects and prevalence increased with age (see Figure below) [2].



Among the socio-demographic and clinical variables investigated, previous surgery was the only factor statistically associated with the presence of anti-HEV antibodies.

Unlike most other countries, Spain reported data of HEV in children. In order to have a complete picture of the HEV epidemiology, it is important that data of HEV in children is generated, particularly with regards to symptomatic versus asymptomatic character, severity of disease, and antibody persistence. Results of a seroepidemiological survey conducted in 2001 in 1,249 children aged 5 to 15 years living in Catalonia show that HEV seroprevalence among children was 4.6%, suggesting that some children are exposed to HEV in early childhood [3]. The prevalence slightly decreased with age and tended to be higher in girls (5.8%) than in boys (3.4%), although the difference was not statistically significant (see Figure below). No significant correlation with any of the socio-demographic or medical variables studied was identified.



IgM anti-HEV antibodies, suggesting recent HEV infection, were detected in two (3.5%) children with IgG anti-HEV antibodies. Both were aged 12 years, were asymptomatic, had no past history of acute viral hepatitis, were born in Spain, and also had IgG anti-HAV and anti-HBV antibodies.

It was hypothesized that more severe forms of HEV disease in adults might be a case of re-exposure after subclinical infection in childhood and subsequent loss of antibodies.

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Based on a presentation by
M. Buti, General University Hospital Vall d'Hebron, Barcelona, Spain.

Italy

Acute HEV is quite uncommon in Italy, accounting for approximately 1.2% of all acute hepatitis cases yearly reported to the surveillance system (~30 cases/year).

The HEV case definition applied to study acute hepatitis patients from January 1994 to December 2008 was as follows:

- HEV RNA detected in sera or stools by nested reverse transcriptase (RT)-PCR, or,
- IgM anti-HEV positive, or,
- seroconversion to anti-HEV IgG.

As such, HEV was diagnosed in 20.3% of the non-A, non-B and non-C hepatitis patients. Most acute HEV cases are travel related. Sporadic cases of non travel related diseases are usually caused by genotype 3.

Several seroprevalence studies performed in the general population indicate that anti-HEV prevalence rates range from 1-3% in the Northern region of the country to 3-6% in the South, including the Italian islands. Higher rates were noted among IDU-especially those infected with HIV-, MSM, and patients with chronic HCV.

Risk factors were studied on a population of acute non-A, non-B, non-C hepatitis patients reported between 1994 and 2008. HEV positive patients were mostly male (83%), with a mean age of 31.5 years and elevated ALT. The vast majority (90%) was travel-related, for 7% of cases the source of infection was unknown, and 3% had previous contact with an infected patient.

Clinical features of HEV cases reported in Italy indicate that infections are usually self-limited with normalization of ALT levels within 3-6 weeks. The mean duration of HEV RNA presence in serum and stools is 8 days and 11 days, respectively, whereas anti-HEV IgG can be detected up to 25 months post infection.

The discrepancy between high anti-HEV prevalence versus low autochthonous HEV incidence may be due to asymptomatic infections caused by native, attenuated HEV strains that rarely cause clinical disease. The preference of genotype 3-related disease for elderly and immunologically compromised individuals, adds weight to this hypothesis.

Based on a presentation by
A. Zanetti, University of Milan, Milan, Italy.

USA

Autochthonous HEV cases have been reported in the USA since 1997. In 1997, seroprevalence among blood donors was found to be 14-31%, 16% among MSM, and 23% among IDU [1]. These prevalence values were confirmed by later studies reported in 2002 [2-4]. Despite the fact that different HEV serologic assays were used, seroprevalence rates reported by the different studies were quite similar. For selected populations like IDU and MSM, correlations were found between HAV or HBV positivity and some risk factors studied (such as IDU duration and HIV seropositivity), but no such association could be found for HEV, with exception of an age trend.

In the context of the large National Health and Nutrition Sample Survey (NHANES III) conducted in the USA between 1988 and 1994, epidemiology of HEV was studied to examine associations between HEV seropositivity and putative risk factors [5]. To this end, a nationally representative sample of the US population was studied for anti-HEV IgG antibodies, using a highly sensitive and specific enzyme immunoassay, developed at the NIH, which detects antibody to genotypes 1 and 3 equally reliably. The sensitive assay may detect remote infections (as opposed to acute infections) better than commercial tests designed to diagnose HEV.

Serum samples from 18,695 study participants aged ≥ 6 years, including children and elderly and with oversampling of hard to reach population groups were included in the study. One important limitation of the study was that foreign travel history of participants was not recorded. HEV seroprevalence results of this national survey are presented in the Table below.

Prevalence of anti-HEV IgG in the USA (1988-1994)

Variable	N	% anti-HEV IgG positive (95% CI)
All subjects	18695	21 (19, 23)
Gender		
Female	10124	20 (18, 23)
Male	8571	22 (19, 24)
Race/Ethnicity		
White (reference)	7052	22 (20, 24)
Black	5312	15 (13, 16)*
Mexican-American	5527	20 (18, 22)
Other	804	20 (17, 24)
Country of birth		
US (reference)	15051	20 (18, 22)
Mexico	2357	31 (29, 33)*
Other	1233	26 (23, 30)*
Region of residence		
South (reference)	8168	15 (12, 17)
Northeast	2372	21 (17, 25)*
Midwest	3655	27 (22, 31)*
West	4500	25 (21, 29)*

** $p < 0.05$ compared to reference group*

Kuniholm et al, 2009 [5]

The overall HEV seroprevalence in the US population was 21.0%. Prevalence was rare in children and increased with age. Age-adjusted prevalence was higher in men than in women.

A lower prevalence rate was noticed for Black participants compared to White or Mexican-American participants and these differences could currently not be explained. Significantly higher HEV rates were found among those born in a foreign country and this difference was noted as of the age of 20 years. Marked geographical differences were seen with higher prevalence in the Midwest and West, correlating with high density of swine farms in the Midwest, and lowest prevalence in the Southern part of the country, across all racial groups.

HEV prevalence was significantly higher in metropolitan areas versus non-metropolitan areas while no association with socio-economic markers could be identified.

Having multiple sex partners or consumption of non-commercial water (well or spring water) did not appear to increase risk for HEV infection, while a higher HEV prevalence was noted among those with a history of military service (most probably travel related).

The presence of pets at home, in particular dogs, was significantly associated with increased risk of HEV positivity. Although anti-HEV is commonly found in many animals, HEV RNA is rarely detected in animals other than swine, suggesting that pets may be accidental rather than primary hosts.

In line with previous studies, frequent consumption of organ meat was identified as a risk factor, while this was not true for pork/ham consumption. Extensive geographic and racial/ethnic heterogeneity suggest other mechanisms of exposure than pets, organ meat or contact with developing countries.

Another significant risk factor for HEV was being anti-HCV positive. The association of anti-HEV with anti-HCV is consistent with the hypothesis of transfusion-transmitted HEV infection, but blood transfusion history was not collected in the survey. The presence of anti-HAV antibodies was only correlated with HEV in older participants.

In general, the HEV prevalence in this study is similar to estimates observed in previous studies of US blood donors [1, 4], and is also similar to estimates for European countries, using the same assay. A substantial proportion of HEV seroprevalence in the NHANES III study likely results from travel related exposure in developing countries. Although exposure to HEV appears to be common in the US population, clinical HEV disease of autochthonous origin is rarely reported. This discrepancy may be due to exposure to less virulent genotype 3 virus or, if indeed clinical symptoms develop in a dose dependent manner. It is also possible that autochthonous HEV is underreported in the US, in part because it is not routinely tested as there is no FDA-licensed diagnostic test for anti-HEV. Only non-standardized reagent tests are commercially available while the use of WHO standard to validate the test is highly recommended. There is also a need for standardization of seroepidemiology in terms of establishing a case definition and guidelines for the validation of diagnostic tests.

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Based on a presentation by
K. Nelson, John Hopkins School of Medicine, Baltimore, USA.

Bangladesh

As an example of the severity of HEV disease in an endemic region, Bangladesh data have been presented.

Bangladesh is a country with high population density and 70% of population living in poverty. An ongoing outbreak of fatal jaundice among women was reported in August 2008 in East Arichpur, an urban area near Dhaka. Subsequently, households were surveyed for jaundice and serological tests for HAV and HEV were performed. Between August 2008 and January 2009 a total of 2,460 individuals (5.4% of the total population residing in East Arichpur) reported new onset of jaundice. The mean age of patients was 25 years (range 0-98) with 56% aged between 15 and 34 years. A total of 18 deaths (0.7%) were reported in this period, including 10 women of reproductive age, 4 men, 2 neonates and 2 still births. The risk of death was 7/1,000 in East Arichpur and 1/1,000 in West Arichpur. The outbreak was characterized by a higher case fatality in pregnant women. Among the adult deaths and their contact neighbors (N=78), 91% presented with fever, 99% had yellow eyes and 81% yellow skin. Among living patients (N=44) with current or a history of jaundice, 84% were anti-HEV IgM positive and 14% were anti-HAV IgM positive. Risk factor investigation showed that the outbreak was associated with water contamination at the level of household water taps due to inadequately designed and maintained water distribution system.

This outbreak is highly unlikely an isolated event, as jaundice was also reported at a high rate (2.8%) in an adjacent community. Moreover, among cases identified between November 2008 and January 2009 in Dhaka, 20% were associated with community clusters. Urbanization and migration of workers from rural parts of the country to urban slums may play an important role in HEV epidemiology in Bangladesh. There is a clear need for infrastructure improvement, but better municipal water sanitation alone will not solve the problem as exposure outside the home is also reported as potential risk factor.

Another survey of neonatal deaths in urban communities found 12% of neonatal deaths associated with maternal jaundice during pregnancy. Although no laboratory confirmation is available for these individuals, these figures do suggest that more investigation is needed in the causes of neonatal death associated with maternal jaundice, which might be due to HEV. It is therefore recommended that such data be collected and modeled in order to obtain evidence-based figures. WHO is currently working on the evaluation of global HEV burden of disease, hence all results from studies should be provided to WHO.

Based on a presentation by
E.S. Gurley, International Centre for Diarrhoeal Disease Research, Infectious Disease and Vaccine Sciences Programme, Dhaka, Bangladesh.

HEV vaccine and its future

Two candidate recombinant HEV (rHEV) vaccines are being developed.

A recombinant HEV vaccine, under development at GlaxoSmith-Kline Biologicals (GSKBio), contains a truncated genotype 1 capsid protein expressed in insect cells (20 µg protein adsorbed to 0.5 mg alum/0.5 mL dose) [1]. Preliminary results of the first administration in men conducted in the USA at Walter Reed Army Institute of Research indicated the vaccine to be safe and immunogenic [2] and have led to further evaluation of the vaccine in an endemic setting.
The safety and efficacy of the vaccine was evaluated in a phase II trial [3] including healthy adults from army units in Kathmandu, Nepal, a country with documented HEV disease epidemiology. Before the trial was conducted, a cohort study in military personnel from the same region in Kathmandu documented an annual HEV disease attack rate of ~2%, indicating that HEV is as a major health problem for the proposed study population. A total of 1,794 screened participants, susceptible to HEV infection, received three vaccine doses or placebo and were followed for a median of 804 days. Any suspected clinical acute hepatitis cases were evaluated with clinical laboratory tests (ALT, bilirubin) and serum and stool specimens were collected for confirmation by means of RT-PCR and IgG/IgM. Most clinically suspected acute cases of viral hepatitis were HEV positive; co-infection with other agents was uncommon.
Three doses of the rHEV vaccine offered 95% protection against HEV and the vaccine elicited an immune response in all subjects. Although antibody seropositivity declined to ~50% after 800 days, vaccinees continued to be protected, suggesting that protective immune memory had been established. The vaccine was well-tolerated with a similar proportion of subjects reporting adverse events in the study vaccine and placebo groups, except for injection site pain which was increased in the vaccine group.

Another candidate recombinant HEV vaccine (p239), expressed in E. Coli bacteria (30µg protein absorbed to 0.8mg of aluminum hydroxide/0.5 ml dose), is currently under development at the Chinese National Institute of Diagnostics and Vaccine Development in Infectious Diseases (NIDVD), Xiamen University, China, with the support of a government grant. Subsequent vaccine production and commercialization is planned with a Chinese vaccine manufacturer [4].

The safety and immunogenicity of this candidate HEV vaccine was initially assessed in a phase II dosage-escalation clinical trial conducted in a rural area of southern China [5]. Seroepidemiological investigation performed in the preceding two years showed that the study area is endemic for HEV. The overall HEV prevalence estimate for the region was 43% (range 25%-66%) while seroprevalence increased to higher rates for males than for females after the age of 30 years [6]. Safety assessments in this phase II study showed that both local and systemic reactions to the vaccine were noted but only a few were of grade 3 intensity. Overall, the vaccine was well tolerated and no serious adverse events were reported. Three doses of the candidate vaccine elicited a good immune response with 100% seroconversion. Although vaccine induced antibody levels were lower than in control pooled serum samples of acute HEV infection, titers were still higher than in control samples from asymptomatic infection or from a seropositive general population. Limited efficacy results of this phase II study suggest that two doses of the vaccine could prevent new HEV infection, although the results were less solid due to difficulties in reliable detection of HEV infection.

A large phase III study to evaluate the safety and efficacy of the candidate HEV vaccine was recently conducted in the Dongtai County situated north of Shanghai. An active surveillance system, involving village clinics and local hospitals, was set up in the region to identify patients who reported fatigue or loss of appetite for more than 3 days. Serological testing of these cases to confirm HEV infection included ALT, anti-HEV (IgM and IgG) and serum RT-PCR. The estimated HEV incident rate resulting from this surveillance in the 12 month period between October 2006 to October 2007 was 5.0/10,000. The proportion of HEV infections among male and female individuals was similar and highest among adults aged 25-65 years. Isolates obtained during the surveillance study were mostly genotype 4 and a few were of genotype 1. The HEV prevalence in the Dongtai County was 48.5% with 8.3% new infections per year.

The phase III clinical study included two study groups, the candidate HEV vaccine group (dosage: 30µg protein) and a control group receiving commercial HBV vaccine, and it was conducted in two stages. Phase IIIa (~1,000 subjects/group) was to confirm immunogenicity and safety in the general population and phase IIIb (~50,000 subjects/group) was to demonstrate efficacy over 12 months after completing vaccination course and to re-confirm vaccine safety. The phase III trial completion was due May 2009.

GSK Bio's HEV vaccine development has been put on hold on the grounds that the demand from payers in the developed as well as the developing world is not established; neither the existence of a robust private market or the willingness of governments to pay for the vaccine. The phase II proof of concept study with a pilot lot was successful, but an additional 4 to 5 years of clinical investigations with up-scaled development lots of vaccine would be needed to establish a commercial scale process and manufacturing consistency, while pediatric and adult female studies remain to be done. The establishment and validation of a manufacturing facility would constitute a major investment for any would-be producer.
Since the use of a vaccine against a disease that is endemic in Asia or Africa, but rare in industrialized economies like Europe and in the USA, is uncommon, the discussion was turned to what is the commercial opportunity for a manufacturer of an HEV vaccine. The question was raised whether the VHPB or another international organization could play an advocacy role. While a return on investment potentially amounting to several hundred million dollars for commercial companies to develop and market the vaccine is dubious, a case should be built to involve institutions like GAVI or the Bill and Melinda Gates Foundation. To make the investment case for these institutions, accurate burden of disease and vaccine effectiveness data are needed, as well as insight into the costs of HEV disease without a prevention program. Additionally,

intellectual property issues linked to the development of the vaccines may need to be resolved.

In answer to the reiterated need to start gathering and catalyzing HEV data, a concrete initiative was mentioned to organize a meeting in order to initiate a product development partnership for an HEV vaccine. With regards to current options for the future availability of a commercialized HEV vaccine, a Good Manufacturing Practice (GMP)-compliant production facility by a Chinese manufacturer is expected to be ready in July 2009. Also, several Asian vaccine companies were mentioned to be interested in producing combined HAV/HEV vaccines but intellectual property issues for patented virus sequences need to be resolved first. A recommendation was made to commercial companies for the development of a combined vaccine to be administered to children. HEV was also put on the agenda for discussion at the World Health Assembly.

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and related meeting discussions.

Conclusions

Hepatitis A

Lessons learnt from the first global meeting on control of hepatitis A: Has the time come to control hepatitis A globally?

- The meeting on HAV (Miami, Florida, USA, 30 November-1 December 2007) was a unique opportunity for experts from all parts of the world to present and discuss:
  - o the global HAV epidemiological shift towards lower endemicity;
  - o country-specific data on HAV epidemiology, surveillance, control measures and prevention strategies, including current immunization programmes;
  - o immunogenicity, safety and long tem protection afforded by currently available HAV vaccines;
  - o examples of molecular epidemiology used as diagnostic tools.
- Consensus was reached at the meeting on a stepwise approach recommended to countries considering implementation of childhood immunization programmes: collecting accurate surveillance data, securing political support, and conducting health economic analyses.
- Future needs identified during the meeting were mainly related to the lack of accurate country data and robust mathematical models needed to estimate the global burden of disease.
- HAV needs a higher priority on the international agenda.
- Further research was recommended on risk factors with an impact on the fatality rate of fulminant HAV. As a preliminary result, age of infection, underlying disease, pregnancy and possibly viral factors could play a role, whereas improved intensive care and transplantation were seen to reduce mortality. However, more country data are needed to confirm a global trend towards rising fulminant HAV cases, currently reported from Latin America.

Update on hepatitis A epidemiology, prevention and control

Changing epidemiology and outbreaks

- Networking and partnership are growing, present and future, which contribute to improved HAV surveillance through virus detection and typing.

- There is good evidence for significant declines in HAV incidence since the early 1990s with improvement of hygiene and sanitation, and changes in socioeconomic conditions (such as rapid decline in birth rates), including dramatic and rapid decrease to historic low incidence values in the USA.
- In the WHO European region, an approximate 5-fold decrease in HAV incidence has been observed over the period 1997-2007. However, a 40% increase was noted in 2007, mainly affecting Eastern European countries. In 2007, 100,000 cases were still reported in the region, with a 0.5% fatality rate, mainly from Central Asian countries.
- While the HAV epidemiological picture is changing and may ultimately affect the transmission patterns, basic routes of transmission have remained unchanged to date: person-to-person, contaminated food and water, and risk groups, still consisting of travelers, MSM, IDUs, carers of children, and immigrant children returning to countries of origin with high endemicity levels.
- Several outbreaks were also reported in the WHO European region in 2008, with variable transmission sources and risk groups, and for which control measures varied according to the country.
- A 2008 Czech Republic HAV outbreak was characterized by higher morbidity than previously reported, and highest incidence shift from childhood towards adult age. The outbreak is mainly attributed to very low incidence reported in the previous years and related high number of susceptibles, with high transmission rates among IDUs and homeless. Control measures included contact tracing and pre- and post-exposure vaccination.
- A 2008 Latvia HAV outbreak with highest incidence among young adults, initially started among IDUs, then spread within the general population. Several outbreak causes were identified, mainly steadily decreasing incidence and high number of susceptibles, as well as low socioeconomic conditions. Control measures included vaccine recommendation, epidemiological investigation of cases, and a range of information campaigns and initiatives on HAV prevention.
- A November 2008 Riga meeting was organized by ECDC and the Public Health Agency of Latvia (with support of WHO Regional Office for Europe) as a first initiative towards international HAV outbreak response and guidelines, focusing on outbreak alert and adequate control measures, in particular vaccination strategies.

Immune response to hepatitis A vaccines

- HAV antibodies persist for at least 15 years after primary vaccination (with higher titers observed in young adults and females); data beyond 15 years are being collected.
- Models, using up to 10 year antibody persistence data, predict 95% of vaccinees to remain anti-HAV positive 25-30 years post primary vaccination.
- Long term protection beyond antibody persistence is being investigated by studying cellular mediated immune response and post booster anamnestic response.
- Exceptional low antibody responsiveness to booster vaccination correlates with low CMI response, as shown in a study in Austria.
- Results of a one dose schedule from Argentina will complement data showing protection after a delayed second dose.
- Very low rates of HAV non-responders have been reported to date in different countries. However, monitoring of risk populations (i.e. travelers and healthcare professionals) is recommended.

Prevention and control strategies

- Two main HAV vaccination strategies are adopted by countries, either targeted at risk groups or introduced in routine childhood vaccination programmes.
- Routine HAV vaccination of children has led to decreased incidence rates in most countries that have adopted such programmes, even with modest coverage rates, and including non-vaccinated cohorts (indicated herd immunity). This is illustrated by the example of the USA where the ACIP recommendations started with a risk group approach in 1999 until the implementation of a nation-wide vaccination programme in 2006, which led to 90% declines in incidence.
- In the 2000 HAV WHO position paper, HAV routine vaccination is not recommended in high endemicity countries but may be considered in intermediate endemicity countries; in low endemicity countries, only risk group vaccination is recommended.
- It is anticipated that the revision of the WHO position paper on HAV in 2010 will include a stronger recommendation for HAV vaccination in intermediate endemicity countries. It will also cover the epidemiological shift and a standardized assessment of interventions.

Challenges, needs and future steps

- Newer and more robust HAV surveillance data -with agreed guidelines and standardizations- are needed to support policy decisions, including more information on age distribution, case-fatality rates, etc. at regional and national levels.
- Different parts of the HAV genome are used for phylogenetic analyses, e.g. in Europe and the USA, hampering global assessment and comparison of strains responsible for outbreaks in different regions.
- Public availability of EVENT HAV sequences database in Europe would contribute to improved outbreak investigations.
- Clusters of increased HAV morbidity/mortality are often explained by co-infection, e.g. in Eastern Europe and in Latin America. If indeed the number of fulminant HAV cases is rising, the role of co-infections, including HAV/HBV, HAV/HCV, HAV/HDV, HAV/HIV needs to be better established and understood. Rethinking and proactivity regarding co-infection rate is needed, e.g. sending

questionnaires to country and collection of sera in order to have a better global/national view per country.
- Long term immunity in children, in particular very young children where maternal antibodies still play a role, as well as protection after one dose schedule, need further investigation.
- More insight on long term immunity is expected from modeling data based on more recent observed data from 11 to 15 years, as well as using a newer modeling approach, taking cellular immune memory into account.
- HAV outbreaks are known to alternate with years when the population is immune. It is therefore recommended not to wait until the population becomes susceptible again to implement prevention measures.
- The current absence of a standardized HAV prevention strategy and lack of pressure on countries and institutions to take measures resulting in reprioritization of HAV was underlined during meeting discussions. The VHPB, together with other international organizations, considers guidelines on HAV case definition, surveillance guidance, vaccine use, and especially outbreak response, as important future steps in the prevention and control of HAV.
- Improved standardization of the current flow of mandatory reporting from Member States to the WHO Regional Office for Europe and to ECDC was recommended in order to enhance outbreak control, surveillance and prevention of HAV, especially by filling the policy vacuum existing at local level.
- In spite of the growing awareness of the public health importance of HAV, the burden of disease is not yet properly recognized and a global action by WHO is encouraged, all the more so with the availability of safe and effective vaccines. The need for advocacy was underlined during the meeting as well as the related role to be played by groups like VHPB in this area.

Hepatitis E

Virology, epidemiology, natural history and pathogenesis of HEV

- HEV and HAV viruses belong to distinct families but both diseases have numerous similarities, including the clinical picture.
- HEV virus was cloned and sequenced in 1990, with at least 5 genotypes identified, among which genotypes 1-4 are involved in human cases and belong to a single serotype, an important element for vaccine development.
- The epidemiological pattern of HEV is strongly associated with socioeconomic factors. High endemicity is found in tropical and subtropical regions versus low endemicity in industrialized regions of North America and Europe, where only sporadic cases are reported, with a decreasing number over time.
- The virus is mainly transmitted by contaminated water and food supply.
- Reporting of HEV is not consistent across countries, it is notifiable in e.g. Germany, the UK and the USA but not in Australia, Canada, Hong Kong and most European countries.
- Sporadic cases reported with no history of travel to endemic countries suggest an animal reservoir in industrialized, non endemic regions. This hypothesis is supported by the widespread presence of genotype 3 among pigs, wild boars and other mammals.
- HEV is prevalent worldwide, with highest prevalence in endemic regions and a seroprevalence shift towards older age, similarly to HAV.
- Natural history of HEV suggests that liver pathology is mediated by the host immune response, with clinical manifestations ranging from symptomatic or even fulminant hepatic failure to asymptomatic infection, but with virus shedding.
- Correlation between HEV disease severity and dose-response has been experimentally observed in monkeys, as well as suggested by HEV outbreaks, but host immune response and virulence of strain are also key determinants of clinical presentations of a disease.
- In most cases the infection is self-limited with normalization of ALT levels within 3-6 weeks.
- The severity of the disease increases with the age of the infected person.
- Higher mortality due to HEV in pregnant women is described but not explained, warranting further investigation.
- Chronic HEV infection has been reported in organ transplant patients in France and the Netherlands but the mechanism remains unclear.

Zoonotic transmission of HEV in Europe

- HEV human-to-human transmission seems to be limited but the virus is highly contagious among pigs. Experimental cross-species transmission also suggests the possibility of zoonotic transmission of HEV.
- Several animal species represent potential reservoirs, with highest anti-HEV seroprevalence among pigs and wild boars worldwide, mainly in Japan and Europe (52% HEV seropositivity among swine herds in Europe).
- Several studies conducted in different parts of the world support the assumption that HEV infection may occur from consumption of raw or undercooked meat, mainly pork, wild boar and deer, and possibly shell fish.
- HEV has been found in environmental samples in the USA and Europe, in particular genotype 3 in studies conducted in Spain. Further investigations are needed to detect the presence of HEV in non animal food products (crop) and establish potential risk of contamination.

Hepatitis E and its emergence in (non-)endemic areas in Europe, US and Asia

- Overall, 7.1% HEV prevalence has been reported among acute non-A, B, C hepatitis patients in Europe.
- Non-travel related HEV cases found in Sweden, the Netherlands, Southwest England, Southwest France, Germany and Italy were reported as genotype 3, mainly in >50-year-old males.
- Main identified risk factors/potential transmission routes in relation to reported HEV cases in Europe included travel to endemic countries, age >50 years, HBV or HCV co-infection, previous surgery, blood transfusion, consumption of pork offal or wild boar meat, and contact with other potential reservoir species (cows, dogs, non-rat rodents), hunting, alcohol consumption, IDU, and MSM.
- Underlying disease (in particular CLD patients), organ transplantation, and pregnancy were identified as factors for a worse prognosis of HEV disease.
- Anti-HEV seroprevalence reported among blood donors in Europe ranges from 1.1% (the Netherlands) to 3.2% (Paris, France), 14% (Germany) and 16.6% (Midi-Pyrénées, France) while 14-31% range was reported in the USA. Despite the relatively high proportion of anti- HEV seroprevalence among blood donors, limited evidence of HEV transmission through blood transfusion exists.
- Anti-HEV seroprevalence among children has uniquely been reported in Spain (Catalonia), with 4.6% rate and (non-significant) trends towards decreasing seroprevalence with age and higher seroprevalence among girls. But no specific risk factors for infections with HEV have been indentified in this cohort.
- Overall, anti-HEV seroprevalence reported in the USA is 21%, with higher rates in the Midwest and West, correlating with pig farms concentrations, versus lower prevalence in the South.
- In comparison with European data, potential risk factors identified in the USA similarly included travel/contact with HEV endemic regions, HCV-positivity, consumption of organ meat and contact with pets (in particular dogs), while pork meat consumption was not significantly associated with HEV seroprevalence.
- Discrepancy between high anti-HEV seroprevalence and rare autochthonous cases reported in the USA might be explained by the main presence of genotype 3 being a less virulent strain, or it might be due to major underreporting.
- In Dakha, Bengladesh, a jaundice outbreak has been ongoing since August 2008. Cases are associated with HEV contaminated water consumption and characterized by higher fatality rate in pregnant women and neonates (12%).

HEV vaccine and its future

- A recombinant HEV (rHEV) vaccine has been developed at GSK Biologicals. Results from the safety and efficacy Phase II trial in Nepal showed that this rHEV vaccine was well tolerated, inducing 95% protection after 3 doses.
- Another recombinant HEV vaccine has been developed at Xiamen University, China, with completed Phase II trial which showed that the vaccine is well tolerated. Limited efficacy results from the trial indicate that the vaccine could prevent infection. Results of a Phase III trial with planned completion in April 2009 should confirm both vaccine safety and efficacy.
- While the return of investment is currently unclear, GSK-Bio's HEV vaccine development is currently on hold. Several Asian manufacturers have expressed interest in producing an HEV vaccine, but patent issues need to be resolved first.
- A way to make HEV vaccines more attractive in terms of economic return and larger markets could be the production of HAV/HEV combined vaccines.

Challenges, needs and future steps

- An accurate HEV epidemiological evaluation is currently not possible because of lacking data, major underreporting, and the absence of standardized diagnostic assays, validated using WHO standard.
- Epidemiological studies need to be established to estimate the burden of disease, to investigate outbreaks, and to develop prevention strategies.
- Anti-HEV seroprevalence data should be collected in children in order to generate a complete picture of HEV epidemiology, particularly in terms of asymptomatic/symptomatic character, severity of disease, and antibody persistence. Also, further investigation of the hypothesis that genotype 3 and 4 are less virulent types could help to understand the clinical picture and the burden of disease.
- Reliable and validated HEV standard diagnostic assays (PCR and serology), as well as testing protocols need to be developed.
- The association of HEV with liver disease based on anti-HEV IgG data should be confirmed by additional anti-HEV IgM testing.
- Given the high seroprevalence rate in blood donors, HEV thermostability needs further investigation.
- HEV burden of disease data in pregnant women and neonates should be collected and modeled in order to obtain evidence-based figures to secure prioritization of this issue on the agenda of international organizations.
- Solid seroepidemiological data and vaccine effectiveness data should be collected. This information can be the basis for vaccine manufacturers to be able to decide whether to continue with the development of the HEV vaccine, to involve vaccine development partnership and/or investigate in HAV/HEV combination vaccines.

Based on a presentation by D. FitzSimons, WHO.

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Breaking News

WHO issued a review of the position paper on Hepatitis B vaccines.

The October 2 issue of the WHO periodical "Weekly Epidemiological Record" covered the latest WHO position paper on hepatitis B vaccines. To access it, go to: http://www.who.int/wer/2009/wer8440.pdf

All WHO position papers on vaccines are available in alphabetical order at http://www.who.int/immunization/documents/positionpapers.

www.vhpb.org

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