

Viral Hepatitis Prevention Board

HEPATITIS A AND E

Update on prevention and epidemiology

**ANTWERP, BELGIUM
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Objectives

- **Hepatitis A**
 - Provide feedback from the Miami meeting (December 2007): “Has the time come to control hepatitis A globally?”
 - Draw lessons for western Europe and the WHO European Region
 - Provide an update on epidemiology and prevention
 - Identify future initiatives and related topics
- **Hepatitis E**
 - Give an overview of the virology
 - Review hepatitis E disease and its global epidemiology
 - Explain the zoonotic transmission of hepatitis E virus
 - Assess emergence in non-endemic/endemic countries
 - Examine the prospects for a hepatitis E vaccine

Hepatitis A: general observations

- Growing recognition of the public health importance of hepatitis A
- Miami meeting (December 2007) set the international stage for contemplating global control of hepatitis A; other recent conferences have underlined the key role of vaccination
- Broad epidemiological picture is changing; basic routes of transmission remain the same: person-to-person, contaminated food and water, with risk groups including travellers to endemic countries, men who have sex with men, injecting drug users, carers of children
- Clinical picture well known, although there is a possibly increasing incidence of fulminant hepatitis especially in Latin America
- Improved intensive care and transplantation reduce mortality
- Virology of hepatitis A is well understood
- Importance of prevention (from hand-washing to vaccination)
- Effective and safe hepatitis A vaccines exist

Hepatitis A: general observations

- In Europe, WHO and ECDC mandated to prevent and control hepatitis, with reportedly good communication between the two organizations
- Growing networking and partnership, present and future, including EVENT, supranational organizations, and the EC's EUROHEP.NET
- Increasing use of the Internet as a means of communication and provision of information
- Public advocacy is lacking
- Global policy: World Health Assembly will discuss viral hepatitis in May 2009 and WHO preparing to revise its position paper

Hepatitis A: epidemiology

- Many developing countries are moving from high to intermediate endemicity, with large cohorts of susceptible young people
- Burden of disease not fully known, but still 100 000 cases reported in WHO European Region
- Case-fatality rate of about 0.5% means about 500 deaths per year
- Limitations to current data – old (but still used for policy decisions), few national or regional data, little information on age distribution, case-fatality rate, etc
- Nevertheless good evidence for very significant declines in incidence since early 1990s where hygiene, sanitation and socioeconomic conditions have improved (including rapid decrease in birth rates), including dramatic and rapid decrease in incidence in the USA to a historically low value
- Bangladesh study showed that hepatitis A clinical disease is seen in high-endemicity countries

Hepatitis A: epidemiology

- Still wide ranges (100–1000-fold) in incidence across WHO European Region, with high endemicity still in Central Asia and Kazakhstan and low endemicity in the west
- A consequence of declining incidence is the growing size of susceptible populations and therefore a greater likelihood of outbreaks in countries with intermediate endemicity
- Outbreaks and rising incidence rates are being seen in central and eastern Europe, linked also to initial transmission among injecting drug users, poor living conditions (shared facilities) and food handling
- Role of children of immigrants returning to countries of origin with higher endemicity and of carers
- Some outbreaks are unrecognized or misdiagnosed (e.g. leptospirosis) and their extent is unknown
- Viral factors have a potential role (as yet, unproven) on fatality rate in fulminant hepatitis A
- Coinfection and underlying liver disease may contribute to fulminant disease

Hepatitis A: virology

- Viral genotyping is being extensively used, and provides a useful tool for tracking epidemics (e.g. long circulation of type IA in men who have sex with men)
- Genetic data is uploaded and shared in databases
- Increased networking and mechanisms using molecular epidemiological information for alerting public health authorities and epidemiologists

Hepatitis A: Vaccines and vaccination

- Safe and effective vaccines have been licensed since 1992, but are significantly underused
- The vaccines are immunogenic, can be administered as a single vaccine or as a combination vaccine, administered by flexible vaccination schedules, and provide long-lasting antibody persistence, observed during 15 years, and protection
- Modelling predicts good and even longer-term protection
- Phenomenon of low responders (low antibody titres) reported in 2-10% of vaccines in one study (non-responders are rare), possibly due to reduced expression of HAV receptor, an observation that should be confirmed; other reported risk factors include age and obesity
- Protection after a single dose needs to be surveyed

Hepatitis A: vaccination

- Vaccination policies are many and varied, ranging from being part of national universal immunization programmes for children to targeting at-risk groups
- National immunization programmes have been very successful, with good coverage rates and resulting in declines in incidence of 90% (very good US data)
- Countries or regions having implemented universal immunization (e.g. Israel, Italy (Puglia) and USA) have demonstrated a successful impact on the incidence of hepatitis A
- Targeted policies have also shown to be effective (at least for travellers), and are being adopted by different countries on the basis of others' experiences
- Vaccination is included as post-exposure prophylaxis of contacts and in complex emergencies

Hepatitis A: challenges

- Little progress has been made in control despite the availability of vaccines for 16 years
- With more countries shifting from high to intermediate and from intermediate to low endemicity, outbreaks are likely to be more frequent and to last for a couple of years (e.g. current outbreak in Latvia)
- How best to provide guidance to countries on control of outbreaks (e.g. vaccine, immunoglobulin treatment, or improved sanitation/hygiene)
- How to place and/or maintain hepatitis A higher on the international public health agenda? How to convince countries not to wait until the population becomes completely non-immune before introducing vaccination?
- How to introduce hepatitis A priorities into inflexible organization workplans and budgeting process (e.g. annual and biennial cycles)?

Hepatitis A: challenges

- How will the current economic crisis affect funding (e.g. health ministry budgets for vaccines and vaccine programmes and human resources, how will the State respond to the increased burden and expectations health care shifts from the private sector)?
- How can vaccination be encouraged when the cost is not refunded by the State?
- How to manage sensitive issues around data sharing (e.g. political interference or concerns, commercial interests, public health priorities)? WHO has experience of problems with influenza virus data

Hepatitis A: needs and proposed steps forward

- Need for better data on burden of disease and risk of fulminant hepatitis to support policy decisions
- The estimated number of deaths exceeds deaths due to some other vaccine-preventable diseases currently being given priority in the European Region, implying the need for a reassessment of priorities
- Surveillance needs to be improved, with agreed guidelines
- Standardization is part of strengthening of surveillance (e.g. standardization of case definition, terms such as "contact" and "risk group", criteria, contact tracing and management, and epidemiological evaluation of risk factors)
- Robust mathematical models are needed with improved methods for estimating the global burden of disease

Hepatitis A: needs and proposed steps forward

- Careful consideration needs to be given to recommendations on booster doses
- Recommendations should be prepared on vaccine policies and measures for countries to respond to outbreaks and complex emergencies
- Need for health economic analyses of vaccine interventions and policies
- Further information is needed on immune memory, efficacy of single-dose vaccination, and duration of protection after vaccination in order to inform policy-making
- Need to focus on outbreak control and to address the issue of imported hepatitis A in travellers
- Size of outbreaks such as that in Latvia and Czech Republic (thousands of cases) underline public health relevance

Hepatitis A: needs and proposed steps forward

- Need for agreed, streamlined and formalized coordination between WHO and ECDC on reporting (e.g. on resolving potential confusion between International Health Regulations (2005) and EU reporting regulations) and between those bodies and public health bodies
- Guidance currently being given to countries is sub-optimal
- Need for guidance from, and coordination among, international agencies to fill the policy vacuum in which each country implements different strategies
- Greater and effective advocacy, to maintain momentum from Miami and Riga meetings and build on the outcome of the forthcoming World Health Assembly discussions
- Broad input invited into revision of WHO position paper
- VHPB might consider whether to lead moves towards the production of guidelines, agreement of definitions, strengthening of surveillance and greater advocacy for hepatitis A prevention and control, and a call for action

Hepatitis E: epidemiology

- Seemingly an old disease
- Hepatitis E virus shares many similarities with HAV; five genotypes identified, one not involved in human infection; 24 subgenotypes
- Hepatitis E virus has become the most frequently isolated hepatitis virus transmitted through water and food because of decline in hepatitis A
- Hepatitis E is not notifiable everywhere (it is in Germany)
- Until recently, hepatitis E outside Asia was related to travel (genotype 1); non-travel risks include older age, underlying disease, consumption of raw pig meat or pork products more than once a week, and receipt of a blood transfusion in the incubation period

Hepatitis E: epidemiology

- Different patterns seen for infection with genotypes 1 and 3
 - genotype 1 is probably endemic in Asia, causes sporadic cases and can lead to outbreaks, and is the source of infections in travellers
 - environmental factors (freezing of smaller rivers) can favour concentration of contamination into unfrozen watercourses leading to heavy viral inocula of virus (evidence from India and Pakistan)
 - hepatitis E is the most common acute viral hepatitis in adults in Nepal and prevalent in Bangladesh, causes fulminant hepatitis in pregnant women
 - 10-fold higher seroprevalence rates of antibodies detected in Hindus than Muslims in Indonesia

Hepatitis E: epidemiology

- Genotype 3 is common in western Europe, with a probable reservoir in pigs and other animals (e.g. wild boars) and can cause local outbreaks; occasional human infections explain seroprevalence rate in blood donors and people with animal contacts and lead to the clinical picture in chronic liver disease and alcohol-related liver disease
- The virus is found in surface waters (17% in Netherlands) and in pigs (in particular genotype 3) - data show extensive infection among swine herds (figures of up to 90% of herds in USA, Europe and Asia were quoted)
- Infection is asymptomatic in pigs (with no pathogenesis in pregnant gilts); genotyping shows clustering of human and porcine strains by country, however, identical sequences have not been identified in pairs of viruses from human and pigs in all regions
- Transmission by contact and through contaminated food (deer sushi, wild boar, undercooked/grilled pig's liver, Japanese clams, possibly offal); active viral RNA obtained from pork products in shops. But other routes of transmission unclear - experimental contamination of hepatitis E virus on fruit, plants and vegetables unsuccessful (in line with experiments with other pathogens)
- Seroprevalence rates show a wide range, from 2-3% (northern France) to 16% (southern France and Cornwall), and about 6% in acute hepatitis patients; prevalence in people in contact with pigs (11-55% (Netherlands) or more) higher than in general population

Hepatitis E: epidemiology

- France: 150 cases/year, including a few fulminant cases and chronic cases from transplantation; genotype 3, north (low) - south (high) gradient although most swine herds in north and west; indigenous cases, 3-16% seroprevalence rates, presumed animal reservoir heavily infected with same genotypes
- Spain: Improved sanitation and introduction of vaccination against hepatitis A lead to rapid reduction in detection of hepatitis A viral RNA in environmental samples in Barcelona and Valencia in a short period but little reduction in hepatitis E RNA
- Italy: acute hepatitis E uncommon; sporadic cases due to genotype 3 and zoonotically linked (pigs); inapparent infections possibly due to attenuated virus in circulation (as suggested by disease in immunocompromised subjects and elderly)
- Reporting bias from countries
- **Prevalence of hepatitis E positivity in non-ABC hepatitis patients about 7% (cause of rest unknown)**
- Do subclinical cases constitute a human reservoir?

Hepatitis E: epidemiology

- Estimates of indicated possibly 13 000 – 26 000 deaths a year in chronic liver disease patients in western Europe
- US (NHANES) study: the largest to date, showed rates of 20-30% IgG positivity, with marked geographical variation (higher in areas with swine herds); risk factors included birth in Mexico, a history of military service, pet ownership (dog), and piped water (rather than well water); eating pork products not associated, liver consumption was; association with anti-HCV and anti-HBc positivity (consistent with transfusion-transmitted infection)

Hepatitis E: clinical pathology

- Unlike HAV, a dose-response effect has been observed (and confirmed for genotype 1 in animal model), and depends of virulence of strain and on host immune response
- Hepatitis E virus is highly contagious in pigs
- Pathological signs coincide with viraemia in stool and serum
- Extrahepatic sites of viral replication, including edible parts of pig (ham) have been detected
- Pathogenesis: not a direct cytopathic effect of HEV – its mechanism is hypothesized to be due to apoptosis
- High mortality rate in pregnant women (15-20%), but very mixed data
- Mortality also seen in chronic liver disease; potential for chronic E disease (in transplant patients) and cirrhosis

Hepatitis E: vaccines

- Two candidate vaccines in the pipeline
- Viral protein vaccines tested successfully
- Recombinant truncated capsid protein vaccine (3 doses) gave 95% protection in a phase II trial in Nepal, was well tolerated and safe (but study involved testing only of a pilot lot); vaccine needs 4-5 years more work and at least US\$ 50 million investment
- Large phase III trial initiated in adults in China of a recombinant structural protein (p239) vaccine (3 doses); company involved setting up a manufacturing plant
- Crucial question about what is the demand for a hepatitis E vaccine and who will pay for further vaccine development and production?
- Intellectual property issues need to be resolved

Hepatitis E: needs and future steps

- Diagnostic tools: need for consensus on reliable and validated tools (PCR, serology) and testing protocols
- WHO standardized reagents exist; non-standardized reagents are commercially available, but strongly recommended to use standardized reagents
- Need to pay attention to infection in childhood (key to the epidemiology); does subclinical infection predispose to severe disease on reinfection?
- Better data needed, including time trends (not in US study) and behavioural factors (e.g. nation-wide study in Germany); infection seems to be widely under-reported; data absent for whole regions (e.g. Middle East where there is considerable disease)
- Much more information needed about disease burden (deaths - high mortality in pregnancy), outbreaks, epidemiology and prevention in south Asia; WHO working on hepatitis E data

Hepatitis E: needs and future steps

- Investigate blood safety implications (high seroprevalence rate in blood donors in some European countries)
- Further study in organ-transplant recipients, including treatment options (decrease immunosuppressive therapy)
- Hepatitis E virus needs to be looked for (e.g. in transplant recipients)
- Unrecognized infections; need to test cases of drug-induced liver injury for hepatitis E virus
- Genotyping needed for molecular biology and molecular epidemiology
- Effectiveness of 2-dose vaccine regimen and duration of immunity are not known
- In the light of the seroprevalence data, too early to formulate statement of prevention, except for encouraging good hygienic practices (proper cooking of pork and hand-washing)

Hepatitis E: needs and future steps

- How to advocate for a vaccine against a disease that affects some of the most impoverished people and countries? Need to advocate and mobilize support – role of World Health Assembly. Potential for mobilizing funding through focus on maternal and infant mortality (in the context of the Millennium Development Goals)
- More epidemiological information needed from developed countries on groups at potential risk in order to persuade manufacturers
- No project development partnership (as exists for other disease and vaccines) to coordinate gathering of data and approaches to donor agencies
- Consideration of potential role of private-public sector partnerships, but would need to resolve intellectual property issues
- Consideration needs to be given to combination vaccines containing hepatitis E antigen
- Consideration needs to be given to immunization policies that target schoolgirls in endemic regions (cf. rubella)