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ABSTRACT

In March 2009 the Viral Hepatitis Prevention Board (VHPB) organized a meeting in Antwerp, in order to review the status of epidemiology and prevention of both hepatitis A and E. International hepatitis experts from the public health and academic sector provided the state of the art on HAV and emphasized the growing public health importance of the disease, in particular in intermediate endemicity regions, and the need for control at global level. The information shared on HEV showed clearly that it is emerging, but still a lot of efforts are needed to clarify among others the transmission routes, the clinical presentations and the burden of disease. First data on hepatitis E vaccines were discussed, showing a promising safety and efficacy profile. The meeting was concluded with lessons learnt, challenges, needs and proposed step forwards for both diseases.

Hepatitis A and E: Update on prevention and epidemiology

1. Introduction

In March 2009, the Viral Hepatitis Prevention Board (VHPB) organized a meeting to review the epidemiology of both hepatitis A and hepatitis E and to determine the status of prevention of these two diseases. For hepatitis A, the specific objectives were to provide feedback from the global meeting held in Miami, Florida, in December 2007, which posed the question "Has the time come to control hepatitis A globally?"; to give an update on epidemiology and prevention; to draw lessons for western Europe and the WHO European Region; and to identify future initiatives and related topics. For hepatitis E, the objectives were to provide an overview of the virology, to review the disease and its epidemiology globally, including zoonotic transmission of hepatitis E virus, to assess its emergence in non-endemic/endemic countries, and to examine the prospects for a hepatitis E vaccine.

2. Hepatitis A

2.1. Epidemiology

As the broad epidemiological picture of hepatitis A changes, the public health importance of the disease is increasingly being recognized. It is a significant cause of morbidity globally, even if the mortality rate due to hepatitis A is low (improved intensive care and transplantation have contributed to the reduction in deaths). Although the basic routes of transmission are well understood – from person-to-person, and through contaminated food and water – and effective and safe vaccines exist, the epidemiology is changing, in particular in countries with intermediate endemicity of hepatitis A. Improved sanitation and living standards mean that fewer countries remain highly endemic but in countries where the endemicity of hepatitis A is low or intermediate more people lack immunity to hepatitis A virus (HAV) infection and the risk of outbreaks grows. In such circumstances, these outbreaks can prove to be long and difficult to control. Furthermore, the burden of symptomatic disease is shifting towards adolescents. People at-risk include travellers to endemic countries, men who have sex with men, injecting drug users, and carers of children, and the general population can also be at risk through subsequent person-to-person spread from localized outbreaks, as a consequence of decreasing general population immunity. The clinical picture is well known, but surprisingly high rates of fulminant hepatitis are being seen in pregnant women and children.

The Miami meeting set the international stage for contemplating global control of hepatitis A. Other recent conferences, such as the technical meeting on responses to hepatitis A outbreaks organized by the European Centre for Disease Prevention and Control (Riga, Latvia, November 2008) [1], have underlined the importance of vaccination and informing the general public about good hygienic measures (e.g. washing of hands) for prevention. Models show that vaccination of people at-risk is a cost-effective strategy. It also became apparent that recent data are lacking for many countries and surveillance needs to be improved with standardized data collection and use of case definition, and molecular biological data on hepatitis A viruses needs to be shared globally and within regions.

In Europe, the World Health Organization (WHO), through its Regional Office for Europe, and the European Centre for Disease Prevention and Control are mandated to prevent and control hepatitides, and the two organizations work well together. Networking and partnership are flourishing, as exemplified by the European Concerted Action on Viral Hepatitis (EUROHEP) and the network for harmonizing hepatitis A virus typing and alerting on hepatitis A outbreaks (EVENT). More generally, communication is improving, with greater use of the Internet as a means of providing and exchanging information.

Nevertheless, public advocacy and political will to act to prevent and control hepatitis A are lacking. The discussion of viral hepatitis by the WHO's Executive Board in January 2010 should help to rectify that situation. Furthermore, WHO is in the process of updating its previous position paper on hepatitis A vaccines issued in the year 2000 [2].

Increasing numbers of developing countries are moving from high endemicity of hepatitis A, in which conditions clinical cases

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in adults are uncommon as most children are exposed to HAV, to intermediate rates. In many industrialized countries incidence rates have declined steadily since the mid-1990s to low levels. The low endemicity in most of Europe means increasing susceptibility of young people in whom the disease can appear symptomatically. Seasonal outbreaks reflect import through holiday travel during the summer in addition to the expected variation seen in domestic cases throughout the year.

Europe has experienced numerous outbreaks in the past ten years caused by contaminated water and food. Annually about 100 000 cases are now being reported in the WHO European Region, with about 500 deaths, but poor data mean that the burden of disease is not fully known. There are few national or regional data, although the statistics that do exist show wide variations in incidence rates—up to 1000-fold between the low rates in western Europe and the highly endemic countries of central Asia. Little information is available on the age distribution of cases or the case-fatality rate. In many countries, old data are still being used as the basis for policy decisions. Despite those weaknesses the evidence is clear that the incidence rates have been declining significantly over the past 15 years where hygiene, sanitation and socioeconomic conditions (and associated rapid declines in birth rates) have improved. In the USA the decrease in incidence following the introduction of universal vaccination programmes has been dramatic and rapid, with the rate now at a historically low figure.

The price of the decline in incidence rates is the growing size of susceptible populations and therefore the greater likelihood of outbreaks in countries with low or intermediate endemicity. That consequence has been amply borne out by the number of outbreaks being seen in parts of central and eastern Europe as well as a rise in incidence rates. These outbreaks have been linked to transmission among injecting drug users, poor living conditions (shared facilities), food handling by contaminated kitchen staff, the return of children of immigrants from visits to their countries of origin with higher endemicity, and carers of children. Evidence is accumulating that some outbreaks of hepatitis A are unrecognized or misdiagnosed (e.g. as leptospirosis) and thus their full extent is unknown.

Two outbreaks were described in detail—one in the Czech Republic in the second half of 2008 (the first major outbreak there for 12 years) and the other in Latvia. The first, with more than 1600 cases, was mainly concentrated in Prague and particularly effected people aged 20–45 (predominantly men; in most cases no risk behaviour was identified, but for those with risk behaviours it was drug use) and 50–60 years. In Latvia, after eight years with less than 100 cases reported a year, a community-wide outbreak began at the end of 2007. By the end of 2008 more than 3200 cases had been reported, with a peak in the autumn, and the outbreak continued into 2009. Cases were mostly in adults and the proportion in drug users declined from 35% during the first few months to low values. A considerable proportion of the cases were in people with low socioeconomic status, often the unemployed (42%), with clusters in households living in housing estates. One large cluster was associated with a restaurant. Vaccination against hepatitis A, which is recommended but not reimbursed in the public health system, began to be taken up in the last four months of 2008. The public health authorities promulgated information about preventive measures regularly in the mass media and issued recommendations for food handlers, staff of educational establishments, food and veterinary services, as well as the general public. Further steps included seminars on prevention for health-care workers.

2.2. Fulminant disease

On rare occasions infection with HAV results in fulminant disease, and patients with chronic liver disease are at an increased risk for developing severe or fulminant hepatitis. Major factors include age, underlying liver disease, co-infection with other hepatotropic viruses and intake of paracetamol. Mortality due to fulminant hepatitis is rare and linked to hepatitis A in patients older than 50 years. The number of cases of fulminant hepatitis A in children appears to be rising and several cases have been recently reported from Argentina in particular. Improved intensive care and liver transplantation have markedly reduced the fatality rates of fulminant hepatitis A. Conflicting and as yet unconfirmed data have been reported on minor genetic substitutions of viral sequences with a putative impact on viral replication and cytopathic effect. A further question mark is set against the possible role of HAV infection in fulminant disease in pregnant women.

2.3. Virology

Viral genotyping is being extensively used as a means of identifying sources of viral transmission in outbreaks, tracking transmission patterns within populations and in epidemics, detecting widely dispersed outbreaks and hidden clusters, and for monitoring vaccine effectiveness. Molecular epidemiology has shown that genotype IA of HAV is the most common type (and that it has been circulating for many years in men who have sex with men), type IB dominates in the Middle East (and was found to be the cause of the largest ever described outbreak among tourists and travellers, in this case returning from Egypt to Europe) and that at least four other genotypes have been identified in human cases of hepatitis A throughout the world.

In order to improve the detection and surveillance of food- and water-borne viruses (and rare and emerging diseases attributable to enteric viruses) and outbreaks caused by them, the European Commission launched the EVENT project to develop laboratory tools and database infrastructure. It brings together several teams across Europe for harmonizing typing of HAV and raising alerts about outbreaks of hepatitis A. Viral sequences provided through this network are being uploaded and shared in a database that is being maintained at the National Institute for Public Health and the Environment in the Netherlands. The database will be easy to access for the network members and sequences obtained can be analysed easily. Since most groups have sequenced the C-terminus of the virus, by consensus this region will be used and compared.

2.4. Vaccines and vaccination

Safe and effective vaccines have been licensed since 1992, but are significantly underused. The vaccines are highly immunogenic, with antibodies to HAV persisting for at least 15 years and there are good indications that these confer long-term protection. Based on current scientific evidence, protection is considered to be lifelong after a complete hepatitis A vaccination schedule (two doses). Long-term protection after a single dose needs to be further surveyed. The vaccines can be delivered alone or as a combination vaccine, administered with flexible schedules. 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 successful, with good coverage rates and declines in incidence of 90%. Countries or regions having implemented universal immunization (e.g. Israel, Italy (Puglia), Spain (Catalonia) and the USA) have demonstrated a successful impact on the incidence of hepatitis A; the data for the USA are particularly striking, with evidence of a two-thirds decrease in admissions to hospital and markedly lower medical expenditures between 1996 and 2004. Targeted policies, especially for travellers have also shown to be effective and are being adopted by different countries on the basis of others' experiences. Vaccination is included as post-exposure prophylaxis of contacts.

In highly endemic countries large-scale vaccination programmes against hepatitis A 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, WHO recommends that large-scale childhood vaccination may be considered as a supplement to health education and improved sanitation. In regions of low endemicity, vaccination is indicated for individuals with increased risk of infection, such as travellers to areas of high or intermediate endemicity. In determining national policies, the results of appropriate epidemiological and cost-benefit studies need to be carefully considered and the public health impact weighed against the impact of other vaccine-preventable diseases. WHO is in the process of revising its position paper on hepatitis A, issued in 2000, with a view to: updating and evaluating the data on disease burden and epidemiology, vaccine products and availability, and immunization protection data; reviewing the use of vaccine in outbreaks and for contacts of cases; and issuing guidance to countries where the prevalence rates are declining from high levels.

2.5. Challenges

Little progress has been made in control of hepatitis A despite the availability of vaccines for more than 16 years. Indeed, with more countries shifting from high to intermediate, outbreaks are likely to be more frequent and to last for a couple of years (as exemplified by the current outbreak in Latvia). Public health authorities need guidance on how best to control outbreaks (e.g. through vaccination, improvements in sanitation and hygiene, or treatment with immunoglobulin – although its availability is limited).

Public health authorities need answers to the following questions:

- How to raise the importance of hepatitis A on the international public health agenda and to maintain that concern?
- How to convince countries not to wait until the population becomes completely non-immune before introducing vaccination?
- How to introduce hepatitis A as a public health priority into organizations' inflexible work plans and budgeting process (e.g. annual and biennial cycles)?
- 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 as health-care shifts into the State sector 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)?

2.6. Needs and proposed steps forward

Through the presentations and discussions, the participants of the meeting identified the following needs:

- better data on the burden of disease (and risk of fulminant hepatitis) to support policy decisions, with robust mathematical models and improved methods for estimating the global burden of disease as well as improved surveillance, with agreed guidelines and standardization (e.g. of case definition, terms such as "contact" and "risk group", contact tracing and management, and epidemiological evaluation of risk factors);
- consideration of reassessing priorities, given that the estimated morbidity and mortality due to hepatitis A exceeds those due to some other vaccine-preventable diseases currently being given priority in Europe; the size of the outbreaks of hepatitis A such as those in Latvia and Czech Republic (thousands of cases) underlines the public health relevance of the disease;
- agreed, streamlined and formalized coordination between WHO and the European Centre for Disease Prevention and Control on reporting (e.g. on resolving potential confusion between International Health Regulations (2005) and the European Union's reporting requirements) and between those bodies and public health bodies; further, guidance from, and coordination among, international agencies to fill the policy vacuum in which each country implements different strategies;
- health economic analyses of hepatitis A vaccine interventions and policies;
- recommendations on vaccine policies and measures for countries to respond to large outbreaks, as guidance currently being given to countries is sub-optimal. The identified urgent need for outbreak guidelines and recommendations confirms the conclusions of the European Centre for Disease Prevention and Control's technical meeting on hepatitis A outbreak response (Riga, November 2008);
- more attention paid to outbreak control and responding to imported hepatitis A in travellers;
- further information on immune memory, efficacy of single-dose vaccination, and duration of protection after vaccination in order to inform policy-making;
- greater and effective advocacy, to maintain momentum from recent international meetings and feed into processes such as the World Health Assembly discussions.

A clear message was the need for progress towards the production of guidelines, agreement of definitions, strengthening of surveillance and greater advocacy of hepatitis A prevention and control, including a call for action.

Broad input was invited into the revision of WHO's position paper on hepatitis A, scheduled for 2010.

3. Hepatitis E

3.1. Epidemiology

Water-borne epidemics of hepatitis have been known in Africa and Asia for a long time, but hepatitis E was only recognized as a distinct human disease in 1980 through the application of serological tests that ruled out hepatitis. Reporting of hepatitis E is not consistent between countries; it is not notifiable in for example the UK and USA, but is in, for instance, Australia, Canada, Germany and Hong Kong.

Hepatitis E virus (HEV) is now established as a major cause of sporadic cases as well as epidemics of hepatitis, and, in countries with low or intermediate rates of hepatitis A, HEV has become the most frequently isolated hepatitis virus transmitted through water and food. The virus is mostly transmitted by contaminated water. Indeed, one of the worst outbreaks of waterborne hepatitis, in New Delhi, India, in 1955–1956, which was thought to be due to hepatitis A virus for more than 20 years, was later confirmed to be due to contamination of the drinking-water supply with HEV from sewage during monsoon floods. Food-borne transmission and person-to-person spread are much less common. Epidemiological studies of the different genotypes revealed that zoonotic spread of HEV can be the principal mode of transmission in certain regions.

Overall, HEV is recognized as an important pathogen in tropical and subtropical regions, being one of the two leading causes of acute hepatitis in adults in North Africa, Asia and the Middle East.

Hepatitis E is the most common acute viral hepatitis in adults in Nepal, occurring in rainy season outbreaks and presenting a major health problem for soldiers. It is widely prevalent in Bangladesh; investigation of a recent outbreak of nearly 3000 cases in a densely overcrowded settlement near Dhaka found cases predominantly in adults, with a higher case-fatality rate in pregnant women, and an association with contaminated water (but not the drinking water). Evidence from India and Pakistan further points to the role of environmental factors in the epidemiology; for instance, the freezing of smaller rivers in winter can favour concentration of viral contamination into unfrozen watercourses, resulting in heavy viral inocula. In Indonesia 10-fold higher seroprevalence rates of antibodies to HEV have been detected in Hindus than in Muslims, a finding that has been taken to indicate the potential role of eating pork.

Until recently, cases of hepatitis E outside Asia were generally rare and mainly related to travel, but non-travel risks are now known to include older age, consumption of raw pig meat or pork products more than once a week, underlying disease, and receipt of a transfusion of blood from a person in the incubation period for hepatitis E. Despite the relatively high HEV seroprevalence rates found in blood donors, limited evidence exists of transmission of HEV through blood transfusion. It may indeed be a zoonotic infection, with reservoirs possibly in pigs, wild boars, cows, sheep, goats and deer. Cases of hepatitis E are mostly self-limited and infection generally does not become chronic. The severity of the disease increases with age. Hepatitis E causes a higher mortality in pregnant women where the disease condition is accentuated with the development of fulminant liver disease - mortality rates may reach 20%. Based on recent limited data HEV seems to emerge as a cause of chronic liver disease in immunosuppressed individuals such as organ-transplant recipients.

HEV shares many similarities with HAV. Both are non-enveloped, spherical, single-stranded RNA viruses, with similar routes of transmission; both cause jaundice. Five genotypes of HEV have been identified (genotypes 1–4 causing human infections and genotypes 3 and 4 also causing infections in swine). Limited sequencing results indicate that there may be at least 24 subgenotypes, but further studies are needed. Different patterns of infection are seen with genotypes 1–4. Genotype 1 is endemic in North Africa and Asia, causes sporadic cases and can lead to outbreaks, and is the source of infections in travellers. Sporadic cases due to genotypes 1 and 2 have been identified in developing countries, mainly in young adults. Genotype 3 is common in western Europe and is found in humans and swine also in the USA and Japan, with a probable reservoir in pigs and other animals (e.g. wild boars) and can cause local outbreaks. Genotype 4 is mainly restricted to east Asia. The average age of cases of infection with genotypes 3 and 4 is more than 50 years.

3.1.1. Risk factors

A series of reports were presented at the meeting for six European countries or regions therein. Sporadic endemic infections due to genotype 3 do occur and risk factors include eating pork more than once a week, older age, male sex, and underlying conditions (including HIV infection). Seroprevalence rates vary widely, within and between countries: from 2 to 3% in northern France to 15–16% in south-western France and south-west England. It is possible, of course, that there are reporting biases for different countries and regions, and that increasing numbers of cases may reflect more active searching for infections.

3.1.2. Food-borne transmission

Transmission has been demonstrated through contaminated food (deer sushi, wild boar, undercooked/grilled pig's liver, Japanese clams, and possibly offal). Active viral RNA has been isolated from pork products in shops. Other routes of transmission, however, remain unclear. The experimental contamination of fruit, plants and vegetables with HEV was unsuccessful in causing onward transmission (in line with the results of experiments with other pathogens).

3.1.3. Zoonotic transmission

Occasional human infections in industrialized countries may explain the finding of antibodies in blood donors and people with animal contacts (and a higher seroprevalence rate of anti-HEV antibodies has been detected in swine handlers in the USA and in older farmers in Denmark). The virus has been detected in surface waters (17% in the 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). HEV is highly contagious among pigs. Extrahepatic sites of viral replication, including edible parts of pig (ham), have been detected. Infection is asymptomatic in pigs (with no pathology observed in pregnant gilts); although genotyping shows clustering of human and porcine strains by country, identical sequences have not been identified in pairs of viruses from human and pigs in all regions. Contact with pigs has, however, not been definitively confirmed as a risk factor (see below).

3.1.4. Country reports

In France some 150 indigenous cases are reported a year, including a few fulminant cases and chronic cases from transplantation. The causative agent is HEV genotype 3. The north (low seroprevalence rate)–south (high rate) gradient is puzzling, because most swine herds are found in north and west of the country, and the presumed animal reservoirs are heavily infected with same genotypes as found in humans.

In the Netherlands a prevalence rate of about 6% was reported in acute hepatitis patients, and in people in contact with pigs the rate (11–55% or more) was higher than in general population, but the rate in blood donors was less than 0.5%. Nevertheless, and paradoxically, in the Netherlands contact with pigs does not seem to be a risk factor for hepatitis E, but other potential risk factors such as blood transfusion, consumption of pork meat, and contact with other animals like cows, dogs, horses were identified. Person-to-person transmission is not an efficient route.

In Germany about 50–100 cases are being recorded a year, with more than half being the result of autochthonous infections. HEV genotype 3 RNA was detected in sera from wild boars, and the sequences clustered with that from a pig in the Netherlands. The number of reported cases in humans has been on the increase over the past eight years, and with a seroprevalence rate of more than 10%, the suggestion was made that there are some 100,000 infections a year. Testing for anti-HEV antibodies is being included in a prospective nation-wide seroprevalence study to collect data on health status, health-related behaviour, health care and living conditions of some 9000 people in 180 cities all over Germany due to end in late 2011.

In Spain improved sanitation and introduction of vaccination against hepatitis A led 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 HEV RNA. Seroprevalence studies showed rates of anti-HEV antibodies of 7.3% in adults and 4.6% in children. No risk factor for infection with HEV has been identified.

In Italy only about 30 cases of acute hepatitis E are reported each year, and most of those are related to travel to the Indian subcontinent. Sporadic cases, usually caused by genotype 3, do occur and may be zoonotically linked to wild boars and other mammals; HEV RNA was commonly detected in pigs and wild boar in northern Italy. Inapparent infections possibly due to attenuated virus in circulation (as suggested by disease in immunocompromised sub-

jects and elderly) may explain the discrepancy between the scarcity of cases of hepatitis E and the anti-HEV prevalence rate (between 1–3% in the north and 3–6% in the south).

In the USA, the National Health and Nutrition Examination Survey (NHANES), the largest study of HEV to date, showed rates of 15–30% positivity for IgG antibodies to HEV in general population (21% overall for nearly 19,000 subjects), with marked geographical variation (higher in areas with swine herds) and racial and ethnic heterogeneity while no association with socioeconomic markers was identified. The study did not, however, look into a history of travel abroad. Risk factors included birth in Mexico, a history of military service, pet ownership (dog), and piped water (rather than well water); eating pork products was not associated with seropositivity, whereas liver consumption was. An association was found with anti-HCV and anti-HBc positivity (consistent with HEV being a transfusion-transmitted infection). Exposure to genotypes 1 and 3 was detected. It was postulated that the genotype 3 virus is less virulent than other genotypes and exposure is to only low doses of virus, although clinical symptoms develop in a dose-dependent manner.

3.1.5. Morbidity and mortality

The accumulating evidence is tending to overturn received wisdom. No longer is hepatitis E rare in industrialized counties but it may be the most common cause of acute viral hepatitis, with significant morbidity and mortality, with potentially a poor prognosis in chronic liver disease. Estimates indicate possibly 13,000–26,000 deaths a year in chronic liver disease patients in industrialized countries. The question was raised as to whether subclinical cases constitute a human reservoir?

3.2. Clinical pathology

Unlike HAV, a dose-response effect has been observed for HEV (and confirmed for genotype 1 in animal models). The pathology seen depends on the virulence of strain of HEV and on the host's immune response. The potential for chronic hepatitis E has been observed in transplant patients and those with cirrhosis. High mortality rates in pregnant women (15–20%) are being reported, but the data are still very mixed. Deaths are also reported in patients with chronic liver disease. In south-west England 20% of patients diagnosed as having drug-induced liver injury were found to be seropositive for anti-HEV antibodies (to the extent that the original diagnosis is not considered to be secure without testing for HEV infection). Other possible consequences of unrecognized infection include inflammatory polyradiculopathy.

Pathological signs coincide with viraemia in stool and serum. Pathogenesis does not appear to be a direct cytopathic effect of the virus itself; the mechanism is hypothesized to be due to apoptosis.

3.3. Vaccines

Work on developing a vaccine has focused on a highly conserved region of the structural capsid protein in the open-reading frame 2 of HEV. The viral protein is highly immunogenic, producing long-lasting neutralizing antibodies.

Two candidate vaccines are in the pipeline. A recombinant truncated capsid protein vaccine (three doses) gave 95% protection in a phase II trial in young healthy adults (soldiers) in Nepal, and was well tolerated and safe (but the study involved the testing of only a pilot lot) [3]. It was stated that the vaccine needs 4–5 years' more work and further investment of at least US$ 50 million for research and development to the licensing stage. A large phase III trial of a recombinant structural protein (p239) vaccine (three doses) has been initiated in adults in China; the company involved is reported to be setting up a manufacturing plant. Early results show that it is safe and effective against infections due to genotypes 1 and 4 [4]. The crucial questions to be answered are what is the demand for a hepatitis E vaccine (in other words, how great a burden of disease is needed before public health authorities implement a widespread vaccination programme) and who will pay for further vaccine development and production, especially in the current financial climate? Also, should it be formulated for children and can it be combined with other vaccines? Experience with other vaccines for diseases common in developing countries shows that intellectual property issues have to be resolved.

3.4. Needs and future steps

Altogether better data are needed, including time trends (not looked at in the NHANES study in the USA) and behavioural factors (as in the nation-wide study in Germany). HEV infection seems to be widely under-reported, and data are lacking for whole regions (e.g. Middle East, where there is considerable burden of hepatitis), and unrecognized. Epidemiological studies need to establish the burden of disease (including the high mortality in fulminant disease in pregnancy), as well as to investigate outbreaks, epidemiology and prevention in south Asia. WHO is one of the agencies working on hepatitis E data in order to understand better the burden of disease.

Also, studies need to determine the implications for blood safety (given the high seroprevalence rate in blood donors in some European countries) and to focus on infection in childhood. HEV needs to be actively sought, and cases of drug-induced liver injury need to be tested for HEV infection. The role of HEV in hepatitis in organ-transplant recipients needs to be further defined, with research into treatment options (such as decreasing immunosuppressive therapy). It is also not clear whether subclinical infection predisposes to severe disease on reinfection.

Consensus needs to be reached on reliable and validated diagnostic tools (PCR and serology) and testing protocols. For instance, no anti-HEV antibody assay has been licensed by the US Food and Drug Administration. WHO standardized reagents exist. Although non-standardized reagents are commercially available, it is strongly recommended that standardized reagents should be used. Genotyping of a consensus region of HEV RNA is needed in order to elucidate the molecular biology and molecular epidemiology of hepatitis E.

Although two candidate vaccines are in development and being tested in clinical trials, there is still a long way to go. More epidemiological information is needed on groups at potential risk in industrialized countries in order to provide the basis for vaccine manufacturers to decide whether to continue their research and development and for public health authorities to make decisions about potential vaccination programmes and strategies. The effectiveness of a two-dose (instead of the current studied three dose schedule) vaccine regimen and duration of immunity are not known yet. Consideration needs to be given to combination vaccines containing HEV antigen and to immunization policies that target children and adolescents in endemic regions (cf. policies on rubella for schoolgirls).

A further issue is the question of how to advocate for a vaccine against a disease that affects some of the most impoverished people and countries? Advocacy is needed together with the mobilization of support, a potential role for international bodies such as the World Health Assembly, whose Executive Board will consider the matter of viral hepatitis in January 2010. The potential exists for mobilizing funding through focus on maternal and infant mortality (in the context of the health-related Millennium Development Goals). No project development partnership exists (as it does for other disease and vaccines) to coordinate gathering of data and approaches to donor agencies. (In 2008, the GAVI Alliance decided

to remove hepatitis E from its list of vaccines under consideration for its vaccine investment strategy [5].) There may well be a potential role for private-public sector partnerships, but issues such as those relating to intellectual property would have to be resolved.

In the light of the seroprevalence data and the uncertainty about the introduction of candidate vaccines, it is too early to formulate a statement on prevention, except for encouraging good hygienic practices (proper cooking of pork and hand-washing), especially as there is no specific therapy for altering the course of HEV infection.

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