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CONTROL OF VIRAL HEPATITIS IN EUROPE

Report on a WHO Working Group

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ABSTRACT

Reported cases of acute viral hepatitis total over 2 million annually in the European Region, and many more infections are asymptomatic or go unreported. A WHO Working Group met to review the control of viral hepatitis in Europe, and recommended that notification and reporting of cases should be compulsory, and that all countries should have national programmes to control viral hepatitis. The report summarizes the epidemiology and strategies for control of the various types of viral hepatitis, which vary from type to type. Better diagnostic tests still need to be developed for hepatitis C and E, the main causes (parenterally and enterically, respectively) of hepatitis non-A, non-B. Vaccine development is at an early stage. Improved hygiene is limiting the prevalence of hepatitis A, but its incidence is shifting to the adult population. The vaccine against hepatitis A needs to be refined before it can become commercially available. A vaccine against hepatitis B is already available and should be integrated into childhood immunization schedules in all countries, and all high-risk groups, particularly health care workers, should be vaccinated as well. This will also help control hepatitis Δ, which only infects people in conjunction with hepatitis B.

Keywords

COMMUNICABLE DISEASE CONTROL
HEPATITIS, VIRAL, HUMAN
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CONTENTS

Introduction

From 22 to 25 April 1991, a Working Group on the Control of Viral Hepatitis in Europe was convened by the Regional Office in Munich, Germany. The participants of the Group expressed their gratitude to Professor F. Deinhardt and his staff for the excellent facilities and organization of the meeting, and to Pasteur Mérieux Sérums & Vaccins, SmithKline Beecham Biologicals and Merck Sharp & Dohme Research Laboratories for financial support.

The meeting was chaired by the late Professor F. Deinhardt and Professor G. Papaevangelou. The Rapporteur was Dr W. Jilg and Dr B. Bytchenko acted as Secretary. A list of participants is attached as Annex 3.

The scope and purpose of the meeting were:

- to review the epidemiological situation with regard to viral hepatitis types A, B, C, Δ, and E in the European Region and in the world, with special attention to the surveillance and control of viral hepatitis B,
- to reach a consensus on a common policy on immunization against hepatitis B,
- to formulate recommendations for a harmonized calendar of immunization in the European Region including hepatitis B vaccination.

This report summarizes the epidemiology and strategies for the control of hepatitis A, B, C, Δ, and E, and some important biological characteristics of their etiological agents.

In addition, it summarizes the recommendations, prepared by four working groups, for the surveillance and prevention of viral hepatitis, and for further research and development. The detailed report of the working group on hepatitis B appears as Annex 1. The reports of the other three working groups (on diagnosis, surveillance and studies of seroprevalence; the prevention of viral hepatitis A, C and E; and research and development) are available from the Communicable Diseases unit of the Regional Office.

Viral hepatitis in Europe – current situation

Viral hepatitis continues to be a serious public health problem in the European Region. The reported incidence for all types of acute viral hepatitis varies from 10–50 per 100 000 inhabitants in northern/western Europe up to 400 per 100 000 and more in the southern/eastern part of the Region. An estimate of the total annual number of reported cases of acute viral hepatitis is over 2 million for the whole Region, which has a population of nearly 900 million people.

Although viral hepatitis is a notifiable disease in most countries, the actual incidence of the various types is difficult to quantify for two main reasons: first, infections are often asymptomatic and, second, acute cases are severely under-reported. This trend will probably increase further when more acute cases are treated at home instead of being admitted to hospital. In addition, in some countries of Europe, the quality of surveillance has been inadequate in the past owing to the lack of specific and sensitive diagnostic reagents. Furthermore, the assays available at present for hepatitis C virus (HCV) are still unsatisfactory, and test systems are not generally available for the diagnosis of infection caused by hepatitis E virus (HEV). These facts have to be considered in evaluating the following data.

Hepatitis A

Epidemiology

Man is the only epidemiologically important host and reservoir of hepatitis A virus (HAV). Although protracted courses of HAV infection occur, its evolution to chronic hepatitis has never been observed.

The improvement in socioeconomic, hygienic, and living conditions has led to a substantial decline of HAV infection in the Region, particularly in the northern part of Europe. Nevertheless, HAV infection still continues to be endemic in certain areas of the southern and eastern parts of Europe, mainly due to HAV transmission through unsafe water and food.

As a consequence of the decrease in HAV infection, its incidence has shifted to the adult population, with an increase in the relative frequency of symptomatic infections. Epidemics are uncommon: most infections are transmitted from person to person, and intrafamilial spread is frequent. Nevertheless, travelling to endemic countries remains the main cause of HAV infection in northern/western Europe. An important source of foodborne infection in some areas is raw shellfish. The recent shift of the peak age of infection in certain countries to young adults, the increase in travel to endemic areas, and the remaining foci of infection in some countries sustain the risk of epidemics that could become extensive in certain population groups, such as people living in immigrant or refugees camps, gypsies, or those affected by disasters.

Vaccination against hepatitis A

The propagation of HAV in cell culture has allowed the development of both live and killed hepatitis A vaccines. Clinical trials with both attenuated and inactivated vaccines has shown that they are safe and well tolerated by adults. Recently, a highly purified formalin-inactivated vaccine developed by several laboratories has been subjected to extensive clinical testing. Adverse reactions were generally mild and self-limited. The conversion rates after one dose ranged from 91% to 100%, and reached 100% after three doses. Mean antibody levels after one dose were about 10 times higher than the levels achieved when immune serum globulin was administered, and increased significantly after the second and third dose. Although results are not yet available from human protection studies, chimpanzee challenge studies have demonstrated the protective efficacy of the vaccine.

Analysis of the genetic relatedness of different wild type virus strains has demonstrated the remarkable genetic conservation of the HAV genome. In a few instances, human strains were identified that varied from most human isolates by as much as 16–24% of nucleotide base positions. Nevertheless, even the genetically most divergent HAV strains were antigenically closely related, as shown by radioimmuno-competition assays, serum neutralization tests, or cross

challenge experiments in monkeys. These findings imply that a vaccine containing only one viral strain will probably protect against all strains.

The use of such a vaccine to immunize people living in foci of high endemicity or travelling to endemic areas would reduce the remaining incidence of the disease. Only the inclusion of the vaccine into the programme of childhood immunization, however, will guarantee the eventual disappearance of hepatitis A.

Hepatitis B

Epidemiology

Western European countries belong to the regions of low endemicity for hepatitis B virus (HBV) infection, with the prevalence of hepatitis B surface antigen (HBsAg) carriers in the general population below 1%. Much higher prevalence is found in this region in the typical high-risk groups such as medical and dental personnel, recipients of blood and blood products, dialysis patients, residents of institutions for the mentally retarded, homosexuals, prostitutes and intravenous drug abusers. These typical risk groups account for only a relatively small percentage of all hepatitis B cases, however. Most infections occur in individuals who do not belong to one of these groups, and the main mode of transmission is probably heterosexual contact.

Basically, a similar epidemiological situation is found in Mediterranean countries such as Greece, Italy and Spain. For unknown reasons, however, the carrier rate in this area is higher, with an average rate of about 3%.

The most serious situation exists in some countries of eastern and central Europe. In many areas, carrier rates in the adult population vary from 5% to 10%, making this region one of intermediate endemicity. In many of the countries of this area, such as Bulgaria, Romania or the former USSR, nosocomial infections with HBV may also play an important role. The reuse of unsterile medical equipment and the inappropriate use of blood and blood products is widespread, and substantial HBV transmission may occur in this manner.

Vaccination against hepatitis B

Besides hygienic measures, vaccination is the most important method of controlling hepatitis B. In many European countries, strategies for the selective immunization of individuals belonging to high-risk groups have been recommended, with the main target group usually being medical personnel. Such strategies have led in some areas (such as Germany) to a significant decrease in HBV infections in health care workers, but have had little influence on the general population.

Even in low endemicity countries, only the universal immunization of all infants will help to control hepatitis B on a population basis. Nevertheless, little effect on disease incidence will be seen for 15–25 years using this strategy. Disease incidence will decrease earlier (after 5–10 years) if immunization of all adolescents is instituted. This is a population that is more difficult to reach, however.

The best strategy for the control of hepatitis B would be to immunize both infants and adolescents, as well as continuing the immunization of adults in defined high-risk groups.

A vaccine trial performed in Italy in the area of Afragola (an area with a population of about 60 000 people with a very high incidence of hepatitis B) from 1983 until the present has demonstrated the feasibility and efficacy of such a mass vaccination strategy. General immunization of all infants in the first year of life and of older children has decreased the incidence of hepatitis B from 91 to 10 cases per 100 000 per year, and reduced the percentage of chronic carriers from 9.2% to 1.0% in 1–10-year-old children.

This study was used in Italy to support the introduction of immunization of all newborn babies and all children at 12 years of age, a programme that has been approved by the Italian Government. Other low endemicity countries such as New Zealand and the United States have also recommended the immunization of all newborn babies with hepatitis B vaccine. A pilot project to immunize all children at 12 years of age is planned for Catalonia in Spain.

Mass vaccinations against hepatitis B can be simplified considerably if hepatitis B vaccine is given simultaneously with other childhood vaccines (BCG, diphtheria, pertussis, tetanus and poliomyelitis). As long as two or three closely spaced immunizations are

given along with a booster dose after 6–15 months, hepatitis B vaccination is flexible enough to fit into virtually all national childhood immunization schedules.

Studies carried out to test whether hepatitis B vaccine could be given simultaneously with BCG, DPT (diphtheria, pertussis, tetanus), and oral and inactivated poliovirus vaccines show that it may be used with the other vaccines without losing its immunogenicity, without reducing the immune response to the other tested antigens, and without increasing adverse reactions.

Hepatitis B infections leading to HBs-antigenemia despite protective levels of circulating antibodies have been observed in 32 infants born to HBsAg carrier mothers in southern Italy who were immunized with hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine. In one infant, who developed a chronic carrier state after an acute serious clinical hepatitis B infection, HBV was detected carrying a stable mutation in the common antigenic determinant *a*. The antigenicity of the *a* determinant in this mutant had partly been lost.

It is unclear at present whether the other infected infants also carry this mutant; however, identical mutants have been reported in a patient after liver transplantation who was given monoclonal anti-HBs to prevent reinfection of the homograft, and in a child (immunized with HBIG and hepatitis B vaccine) born to a carrier mother of Chinese origin in Singapore. Nothing is known at present about the frequency of this mutant in the population; long-term follow-up studies and surveillance are clearly needed to determine whether the emergence of such a mutation has to be considered in designing future hepatitis B vaccines.

Hepatitis Δ

Hepatitis Δ is caused by the hepatitis Δ virus (HΔV), a defective RNA pathogen whose infectivity depends on helper functions provided by HBV. Current estimates indicate that not less than 5% of carriers of HBsAg are also infected by the hepatitis Δ virus worldwide; since there are at least 300 million antigen carriers globally, the number of

such people infected by HΔV is likely to be at least 15 million. The distribution of HΔV in the world falls into three epidemiological patterns of infection:

- high endemicity (accompanied by high HBV endemicity),
- intermediate endemicity (accompanied by intermediate or high HBV endemicity),
- low endemicity (accompanied by low, intermediate or high HBV endemicity).

In northern Europe, the endemicity of HΔV is low in a context of low HBV endemicity; in southern Europe and the Balkans the endemicity is intermediate, in a context of intermediate or high HBV endemicity. An exceptionally high prevalence of HΔV has been found in Romania and some of the Asian republics of the former USSR.

HΔV causes infection when coinfecting with HBV, or superinfecting persons already infected by HBV. The outcome, however, is different: coinfection usually runs a self-limited course followed by clearance of HBV and HΔV, while superinfection often results in chronic HΔV infection superimposed on the chronic HBV infection. Several studies have shown that HBsAg carriers with serological evidence of exposure to HΔV have liver disease that is usually more severe and progressive than uncomplicated hepatitis B. Although some reports exist of clinically silent chronic HΔV infections, superinfection of chronic carriers of HBV often leads to clinically overt chronic hepatitis that is usually more severe than ordinary hepatitis B.

As HΔV needs the help of HBV to infect people and replicate, successful vaccination against hepatitis B also protects against HΔV infection. At present, however, no method is available to protect chronic HBsAg carriers against HΔV superinfection. The development of a vaccine against HΔV is hampered because neutralizing epitopes of the HΔV are not known. Although in one study some sort of protection was achieved in woodchucks by immunization with complete Δ antigen, other studies have shown that anti-Δ antibodies have no neutralizing effect.

Hepatitis C

Etiological agent

Hepatitis C virus (HCV) has been cloned and completely sequenced, although much of the epidemiology, pathophysiology, and immunology of this disease is not yet understood. This virus is the major cause of parenterally transmitted hepatitis non-A, non-B worldwide. The prevalence of antibodies to HCV ranges between 0.2% and 1.7% and suggests that HCV is a readily transmitted virus with a relatively low frequency of clinically apparent disease. It is, however, associated with a high frequency of chronic infections and eventual morbidity in a significant number of infected individuals. HCV has been implicated as one of the major causative agents of primary hepatocellular carcinoma in Japan, and has also been shown to be strongly associated with cases of cryptogenic cirrhosis.

HCV is an enveloped pestivirus/flavivirus-like virus with a diameter of less than 50 nm. Based on the general similarities to portions of both Flavivirus and Pestivirus genomes, HCV should be included within the family Flaviviridae as a separate genus.

Diagnosis of HCV infection

For diagnostic purposes, several proteins of HCV have been expressed in *Escherichia coli* and yeast. The first generation test systems detected antibodies against a non-structural component of HCV by using a recombinant protein (C100-3) derived from the NS4 region of the HCV genome. These antibodies (anti C100-3) were detected in most patients with post-transfusion hepatitis all over the world, as well as in a considerable percentage of individuals with sporadic non-A, non-B hepatitis.

A high prevalence of anti C100-3 was found in such risk groups as haemophiliacs (70–90%), intravenous drug abusers (50–90%), and haemodialysis patients (1–30%). In the normal population (as reflected by volunteer blood donors) in Europe, the prevalence of anti-HCV ranges from 0.1% to 3%. Antibodies to C100-3 appear about 3–4 months (10 weeks to 12 months) after infection. These

antibodies show a long-term persistence in chronic carriers of HCV; evaluation of anti-HCV, therefore, is a good test for detecting chronic HCV infection but is not suitable for the diagnosis of acute cases.

Second generation test kits now available contain, in addition to C100-3, fragments of two other viral proteins, the presumptive core protein (C22) and another non-structural component (C33). Antibodies to these proteins appear early during infection in most patients; the new assay also seems to have a somewhat higher specificity.

Vaccine development

Possible target proteins for neutralizing antibodies are the presumptive structural proteins C, E1 and E2. Recombinant vaccinia virus constructs that express these proteins were used to immunize chimpanzees; the first results of this trial indicate that this procedure gives some degree of protection against challenge with infectious virus. Possible impediments to the development of a recombinant or tissue culture derived HCV vaccine are the existence of a highly variable region within the amino-terminus of E2, as well as the recent discovery of different serotypes of HCV.

Hepatitis E

Hepatitis E virus (HEV) is the major etiological agent of enterically transmitted hepatitis non-A, non-B. It has been shown to be distributed worldwide, particularly in areas where poor sanitation facilitates the transmission of waterborne pathogens.

HEV is an approximately 32 nm diameter non-enveloped spherical particle that shows many physicochemical properties common to members of the Caliciviridae. The genomes of two HEV isolates have now been cloned and completely sequenced. Cynomolgus macaques have been shown to be the most suitable primate model for studies of HEV infection.

HEV is transmitted via the faecal/oral route. Epidemics and outbreaks are usually associated with the consumption of sewage-polluted water. The spread of infection from infected persons (in households, communities or hospitals) is very limited. The highest attack rates are

observed in young and middle-aged adults with an unusually high mortality rate in infected pregnant women. HEV is widely distributed in tropical and subtropical countries. It is not considered to be a major public health problem in western European countries, but it is a major problem in the Asian republics of the former USSR. There is some evidence, however, that sporadic cases may occur in western Europe (in Italy and Spain).

HEV infections were diagnosed initially by immune electron microscopy in stools; now, a fluorescence antibody-blocking test and a western blot test have been developed that can be used to detect antibodies in patients' serum.

The expression of immunoreactive recombinant proteins of HEV, especially major structural proteins, may provide the basis for the development of a candidate vaccine against this virus.

Conclusions

Effective control of viral hepatitis in Europe requires an improvement in the surveillance system, the improvement of hygienic conditions, vaccination against hepatitis B and, in the near future, the appropriate use of the hepatitis A vaccine.

Measures to control the various types of viral hepatitis are costly, and the economic impact of the disease is of great concern. As large national programmes for the control of hepatitis, especially hepatitis B, are being considered, more complete cost–benefit and cost–effectiveness analyses are needed of various options for control strategies. Such analyses would be useful for the selection of an optimal strategy for a given community.

In addition to the optimal use of all the available possibilities to control viral hepatitis, further research is necessary.

Recommendations

Diagnosis, surveillance, notification

1. The notification and reporting of viral hepatitis must be improved. This requires the development of a standard case definition. All countries

of the Region should report cases of viral hepatitis promptly to the Regional Office. Reporting outbreaks of viral hepatitis to national health authorities and to the Regional Office should be compulsory.

2. Active surveillance, either on the basis of disease-oriented investigation of all cases or as sentinel surveillance, should be promoted. The efficacy of surveillance systems should be evaluated periodically, with feedback to the primary sources of notification (general practitioners, hospitals, etc.).

3. Data obtained by surveillance systems should be complemented by new prevalence studies in groups such as recruits (military and civil service) and pregnant women.

4. Each country should establish laboratory facilities for the etiological diagnosis of viral hepatitis. The Regional Office should further develop the regional network of reference laboratories, promote the exchange of expertise and reference materials between laboratories, and produce a manual on laboratory and epidemiological methods for the surveillance of viral hepatitis.

Hepatitis A

5. Surveys of the prevalence of HAV and the containment and monitoring of outbreaks should continue, with special attention to the shift of incidence in age groups.

6. Hygienic conditions should be improved wherever necessary as an important measure for the control of hepatitis A.

7. Immunoglobulin preparations used for pre- or post-exposure prophylaxis should have specific anti-HAV expressed in IU per litre.

8. When effective vaccines against HAV are commercially available, they should be considered for use in immunization programmes to meet the specific needs of each country. Vaccines should be tested for their efficacy in post-exposure situations and for inducing long-term immunity.

Hepatitis B

9. The Regional Office should establish a regional programme for the control of viral hepatitis B to assist national programmes in their efforts to control HBV infection.

10. The routine immunization of infants and adolescents should receive the highest priority. Hepatitis B vaccination should be integrated into the routine infant immunization programme in all countries. Adolescent immunization should be added where economically feasible.

11. High-risk groups should be vaccinated. These include health care workers, clients and staff of institutions for the mentally retarded, household and regular sexual contacts of HBV carriers, patients with repeated exposure to blood and blood products (such as haemodialysis patients and patients with haemophilia and thallassaemia), intravenous drug abusers, people at risk of HBV infection through sexual exposure (such as prostitutes, homosexually active males, patients undergoing treatment or investigation for sexually transmitted diseases, travellers to endemic areas who are likely to have sexual contact), and people residing in or frequently travelling to areas highly endemic for HBV infection or who are likely to require medical treatment while abroad.

12. Special consideration must be given to hepatitis B control in immigrants, refugees, and population groups of high HBV endemicity; children adopted from areas of high endemicity should be screened for HBsAg and, if positive, household contacts should be vaccinated.

13. If maternal HBsAg screening is feasible, infants of HBsAg-positive mothers should be treated with HBIG and hepatitis B vaccine at birth. Post-exposure prophylaxis with HBIG and/or hepatitis B vaccine may be considered for people exposed to HBV in the health care setting, or through sexual contact with an infectious individual.

14. Control of HBV and other bloodborne infections in the health care setting depends not only on the immunization of health care workers but also on effective infection control measures. Infection control programmes should therefore be established and include universal precautions, appropriate disinfection and sterilization of medical equipment, disposal of contaminated waste, and availability of safe blood and blood products.

Hepatitis C

15. All blood and tissue donations should be screened for antibodies to HCV with the available tests; all antibody-positive donors should be excluded from donation.

16. Serological surveys should be encouraged to define the prevalence of HCV in Europe.

17. Research should focus on the development of better test systems (especially tests that can detect acute and chronic infection) and on the characterization of immuno-dominant proteins as the basis for the development of an HCV vaccine.

Hepatitis E

18. In non-endemic areas, the main risk group for HEV infection may be travellers to countries with high HEV endemicity; special attention should be given to jaundiced patients with a history of recent travel to such areas. Physicians should be alerted to the problem of fulminant cases of HEV infection, particularly among pregnant women.

19. The Regional Office should be informed of cases of suspected HEV infection and specimens should be sent to WHO collaborating centres on viral hepatitis at the Institute of Poliomyelitis and Viral Encephalitis in Moscow, the Russian Federation, or to the Centers for Disease Control, the United States.

20. Research priorities should be the development of laboratory tests suitable for rapid differentiation between hepatitis E and other forms of viral hepatitis, and the elucidation of the mechanisms responsible for the perpetuation of HEV in various environments.

Research and development

21. Research activities should concentrate on:

- the development of specific, sensitive, readily available, and inexpensive test systems for the diagnosis of hepatitis C and E;

- the use and development of vaccines, specifically for hepatitis A and B, and the use of recombinant DNA technology to develop and produce vaccines against hepatitis C and E; and
- further studies to discover and define new human hepatitis viruses.

Annex 1

REPORT OF THE WORKING GROUP ON HEPATITIS B

Several factors must be considered by WHO, national public health authorities, and health care personnel in designing programmes for the control of hepatitis B.

These include:

(a) an understanding of the epidemiology and economic impact of hepatitis B (Surveillance and epidemiological studies of the incidence, prevalence and impact of hepatitis B on morbidity and mortality form the basis of a rational national policy for the control of hepatitis B.);

(b) the appropriate use of hepatitis B vaccine and HBIG for pre- and post-exposure prophylaxis;

(c) the prevention of HBV transmission in the health care setting (This includes the prevention of transmission in blood transfusion and from patient to patient, from patient to health care worker and from health care worker to patient.);

(d) the prevention of transmission in the community, including perinatal and horizontal transmission within families, institutions, and the school setting;

(e) the prevention of HBV infection as an STD (HBV must be recognized as a major STD, and HBV control must be integrated into existing STD control programmes at all levels.);

(f) the prevention of HBV in immigrants, refugees and other population groups from areas of high endemicity and the prevention of spread to the general population;

(g) the appropriate use of hepatitis B reagents for screening and diagnosis;

(h) education and training;

(i) monitoring and evaluation.

Recommendations

Regional Office programme for the control of viral hepatitis

1. The Regional Office should establish a programme for the control of viral hepatitis. This programme should assist national control programmes in the areas of policy development, strategies for control, epidemiological evaluation and monitoring, training, the provision of educational materials, and the acquisition of vaccine and reagents through procurement, bulk purchase, or local production as appropriate.

National programmes for the control of viral hepatitis

2. National programmes for the control of viral hepatitis should be established and/or strengthened. These programmes should evaluate the epidemiological situation and the economic impact of viral hepatitis, and should establish national priorities and recommendations. These national programmes should also coordinate activities with national programmes on the control of HIV infection, STD control, blood transfusion, occupational health and other areas of common interest.

The appropriate pre-exposure use of hepatitis B vaccine through the routine immunization of infants and adolescents

3. This strategy should receive the highest priority because it will lead to the long-term control of hepatitis B in the population.

Hepatitis B vaccine should be integrated into the routine infant immunization programme in all countries. If no maternal HBsAg screening is done, the first dose of hepatitis B vaccine should be given at birth.

Adolescent immunization should be added to the infant immunization programme where economically feasible and where an appropriate infrastructure for delivery exists. Ideally, a combined programme

of infant and adolescent immunization will provide optimal and timely long-term control of HBV infection in the population.

The appropriate pre-exposure use of hepatitis B vaccine through the immunization of high-risk groups

4. A number of high-risk groups should be vaccinated. Among the first are health care workers. Because HBV infection is their main infectious occupational hazard, immunization of this group should receive high priority. All health care workers with exposure to blood should be informed of the risk of HBV infection and of the availability of a safe and effective vaccine, and be actively offered hepatitis B vaccine free of charge by their employers. Ideally hepatitis B vaccination should be given during training.

Other high-risk groups requiring vaccination are:

(a) clients and staff of institutions for the mentally retarded and other institutions such as orphanages, prisons, and drug treatment programmes, depending on the local epidemiological situation;

(b) household and regular sexual contacts of HBV carriers as a matter of high priority;

(c) patients with repeated exposure to blood and blood products such as haemodialysis patients, patients with chronic kidney disease who are likely to need dialysis, and patients with haemophilia and thallassaemia;

(d) intravenous drug abusers;

(e) people at risk of HBV infection through sexual exposure, such as:

- prostitutes,
- homosexually active males,
- patients undergoing treatment or investigation for STD,
- travellers to endemic areas who are likely to have sexual contact;

(f) people residing in, or frequently travelling to, areas highly endemic for HBV infection, or who are likely to require medical treatment while abroad; and

(g) household contacts of children adopted from areas of high endemicity, if screening of the children for HBsAg is positive.

Special consideration must be given to hepatitis B control in immigrants, refugees, and population groups with high HBV endemicity.

The appropriate post-exposure use of hepatitis B vaccine through maternal screening and the treatment of infants of carrier mothers

5. Many countries have a policy of screening all or high-risk pregnant women for HBsAg and treating infants of HBsAg-positive mothers with HBIG and hepatitis B vaccine at birth. Such programmes should be considered, based on the relative importance of perinatal transmission in the context of overall HBV transmission.

Appropriate post-exposure prophylaxis with HBIG and/or hepatitis B vaccine

6. This may be considered for people at risk of HBV infection through accidental exposure in the health care setting, sexual exposure to an infected individual, or accidental exposure to contaminated medical equipment.

Pre-/post-immunization testing

7. Screening for HBV markers before immunization is not recommended for routine infant or adolescent immunization, but may be cost–effective in certain high-risk groups depending on the cost of testing, the cost of vaccine, and the prevalence of HBV markers in the group.

Post-immunization testing is also not recommended for routine infant or adolescent immunization, but may be considered, as above, for certain high-risk groups.

Other control measures

8. Control of HBV and other bloodborne infections (such as HCV, HIV, etc.) in the health care setting depends not only on the

immunization of health care workers but also on effective infection control measures.

Therefore,

- infection control programmes at the national and institutional level should be established;
- universal precautions should be taken as an integral part of infection control measures;
- the appropriate disinfection and sterilization of medical equipment and the disposal of contaminated waste are essential;
- safe blood and blood products must be made available by testing each unit for HBsAg.

Reagents and vaccines

9. The appropriate availability, use and quality control of reagents and vaccines should be assured.

Education and training

10. The education and training of health care workers, policy-makers and the public about the risks, consequences, modes of transmission and modalities of prevention of HBV infection should be of the highest priority.

Monitoring and evaluation

11. Monitoring and evaluation should be an integral part of national HBV control programmes. Well designed cost–effectiveness and cost–benefit studies should be performed in countries beginning routine infant and/or adolescent immunization to evaluate this strategy and to serve as a model for other countries in the Region.

Annex 2

WORKING PAPERS AND BACKGROUND DOCUMENTATION[a]

Working papers

ICP/OCD 016/6	Association of HB vaccine with other vaccines, Dr P. Coursaget
ICP/OCD 016/7	HCV and HEV: etiology, laboratory diagnosis, and perspectives for vaccine development, Dr D.W. Bradley
ICP/OCD 016/8	Viral hepatitis as an occupational disease, Dr M. Kingma
ICP/OCD 016/9	Heterosexual transmission of hepatitis B virus, Dr P. Piot, Dr M. Vandenbruaene, Dr E. Kegels & Dr C. Goilav
ICP/OCD 016/10	Hepatitis D: prevalence in Europe. Diagnosis and approaches to control, Dr M. Rizzetto & Dr A. Ponzetto
ICP/OCD 016/11	Regional impact of hepatitis A, Professor G.J. Papaevangelou
ICP/OCD 016/12	Variability of hepatitis A virus isolated in different regions, Professor G. Siegl
ICP/OCD 016/13	Epidemiology of HEV infection in the European Region, Professor M.S. Balayan
ICP/OCD 016/14	Cost–effectiveness and cost–benefit aspects of various strategies for control of viral hepatitis, Professor B. Cvjetanovic
ICP/OCD 016/15	Catalonian programme to control hepatitis B, Dr M. Bruguera, Dr J.M. Sanchez Tapias & Dr Ll. Salleras
ICP/OCD 016/16	An escape mutant of hepatitis B in immunized subjects, Dr A.R. Zanetti & Dr A.J. Zuckerman

[a] Available from the Communicable Diseases unit, WHO Regional Office for Europe, Scherfigsvej 8, DK-2100 Copenhagen Ø, Denmark.

ICP/OCD 016/17	Integration of hepatitis B vaccine into the EPI, Dr M. Kane, Dr C.J. Clements & Dr D.J. Hu
ICP/OCD 016/18	Current status of HAV vaccine development, Dr F. André & Dr A. Hepburn
ICP/OCD 016/19	Hepatitis B in 1990 – where are we and where are we going? Dr M. Kane, Dr Y. Ghendon & Dr P.-H. Lambert
ICP/OCD 016/20	HAV vaccine, Dr M.R. Hilleman
ICP/OCD 016/21	Regional situation regarding viral hepatitis, Dr B. Bytchenko
ICP/OCD 016/22	Approaches to control of viral hepatitis in Italy, Professor G. da Villa
ICP/OCD 016/23	Hepatitis in Romania, Dr A. Combiescu & Dr D. Butur
ICP/OCD 016/24	Epidemiology of hepatitis in Bulgaria, Dr S. Popova
ICP/OCD 016/25	Epidemiology and prevention of hepatitis B in France, Dr A. Goudeau
ICP/OCD 016/26	Viral hepatitis in the USSR, Professor S.M. Klimenko
ICP/OCD 016/27	Immunization strategies for control of hepatitis B in Germany, Dr W. Jilg
ICP/OCD 016/28	Diagnostis tests and studies on HCV seroprevalence in Europe, Dr M. Roggendorf

Background documentation

ICP/CDS 003/m01	Viral hepatitis in Europe – further trends and targets: Report on a meeting, Munich 11–13 June 1985
WHO/MIM/HEP/87/WP28	Third meeting of the Technical Advisory Group on Viral Hepatitis, Geneva, 2–5 November 1987: viral hepatitis in Europe – current situation, Dr B. Bytchenko

Annex 3

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