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Epidemiology and Prevention of Viral Hepatitis B and C

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1. Introduction

Viral hepatitis is a family of viral infections that affect the liver caused by at least five distinct viruses: hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV). Hepatitis A and E appear as acute self-limiting diseases and do not become chronic; occasionally, a fulminant form of hepatitis develops (acute liver failure), which can lead to death. In contrast, HBV and HCV infections can evolve as serious chronic diseases that often remain clinically silent for decades. Fulminant hepatitis B develops in 0.1–0.6% of acute cases; rarely, it also have been reported among perinatally infected infants. People with chronic hepatitis B and C are infectious to others [1, 2, 3]. HDV is a "defective virus" that requires co-infection with HBV for its own replication. Infection with HDV is associated with the most severe forms of acute and chronic hepatitis in many HBsAg-positive patients [4].

Subjects affected by chronic HBV and/or HCV infection are at increased risk for liver cirrhosis and hepatocellular carcinoma (HCC) later in life. About 5% of all acute HBV infections progress to chronic active infection (persistence of HBsAg for more than 6 months). The risk of developing a chronic hepatitis B decreases with age of infection [5], dropping from 90% in infants <1 years old to 30%-50% in children 1-5 years old and to 5%-10% in adults [1, 6, 7]. Chronic active hepatitis B develops in more than 25% of carriers and often results in cirrhosis; approximately the same proportion of cases dies prematurely from cirrhosis or liver cancer [5]. About 75%-85% of subjects affected by HCV develop a chronic infection, 5%-20% develop cirrhosis and 1%-5% die for cirrhosis or liver cancer [8].

2. Burden of HBV infection

Diseases caused by hepatitis B virus have a worldwide distribution. About one third of the world's population has been exposed to HBV with more than 2 billion people infected

worldwide. Approximately 350 million subjects develop a chronic form and about 600,000 die every year for acute or chronic consequences of hepatitis B [6, 9, 10].

The prevalence of HBV infection varies all around the world. In Western countries, it is relatively rare and acquired primarily in adulthood with a prevalence of HBsAg positive <2% (low endemicity areas). In Asia and most of Africa, HBV infection is common and usually acquired perinatally or in childhood with a prevalence of HBsAg positive 2%-7% in intermediate endemicity areas and $\geq 8\%$ in high endemicity areas [9, 11].

A general decrease of new cases of acute disease was observed in North America in the last decades. Between 1987 and 2004 in the United States, the incidence declined 80%, falling from 10.7 per 100,000 (25,916 cases reported) to 2.1 per 100,000 (6,212 cases reported) in all age groups, and the largest proportional decrease among 0-15 years (-95%) and 15-24 years (-87%) [12]. In 2009, 3,371 new cases were reported to Centre for Diseases Control and Prevention (CDC). Prevalence of HBsAg-positive individuals – chronic infection was generally low (0.33% in 1976-1980, 0.42% in 1988-1994 and 0.30% in 2005-2006). Between 2004 and 2009, 800,000 to 1.4 million persons developed a chronic Hepatitis B, with about 3,000 deaths / year [12,13].

In the European Union, 7,000-8,000 newly diagnosed cases of hepatitis B occur each year. The incidence per 100,000 population has declined over the past ten years from 6.7 cases per 100,000 in 1995 to 1.5 cases per 100,000 in 2007. The prevalence of HBsAg-positives in the general population of European countries reported from ECDC – European Centre for Disease Prevention and Control range from 0.1% to 7%. The higher rates are registered in the southern Europe, being Romania the country with the highest prevalence (>4%), followed by medium prevalence countries (> 1-2%) as Spain, Italy, and Greece. Belgium, Czech Republic, Finland, Germany, Ireland, Netherlands, Slovakia and Sweden reported the lowest prevalence (<1%) [2,14].

Among developing areas, the highest prevalence are described in sub-Saharan regions of Africa ($\geq 10\%$) [15]. In 2005, North Africa and the Middle Eastern region showed lower intermediate HBsAg endemicity across all age groups [16]. China and other countries of East Asia are at high/intermediate endemicity for Hepatitis B. Most people in those regions become infected during childhood and up-to 8–10% of the adult population is chronically infected. There, liver cancer caused by chronic hepatitis B is among the first three causes of death from cancer in men and a major cause of cancer in women [6]. Central Asia and the Caucasus are at intermediate HBsAg endemicity too, with 2–5% of the general population chronically infected by HBV. High HBV prevalence is reported also in the Amazon area (South America), in the north regions of Canada and in Greenland [17].

3. Burden of HCV infection

Every year, 3-4 million people in the world are newly infected with the hepatitis C virus [8]. WHO estimates that approximately 3% (170 million persons) of the world's population has been infected with HCV [18] and about 150 million are chronically infected and at risk of developing liver cirrhosis and/or liver cancer. More than 350,000 people die from related liver diseases every year [8].

The prevalence of HCV infection is higher (up to 15%) in some countries in Africa and Asia. Countries with higher rates of chronic infection are Egypt (15%), Pakistan (4.8%) and China (3.2%).

For most developed countries, the prevalence of HCV infection is <3%.

In the United States, the more recent estimates amount to 17,000 new Hepatitis C virus infections and 2.7-3.9 million chronic infections (prevalence: 1.3%-1.9%) [13, 19]. With an HCV antibody prevalence of 3.25%, persons born during 1945–1965 account for approximately three fourths of all chronic HCV infections among adults [20].

In the European Union, hepatitis C showed a significant increase over the past ten years. The number of newly reported cases incidence raised from 4.3 per 100,000 population in 1995 to 6.9 cases per 100,000 in 2007 (27,000-29,000 newly diagnoses /year). This trend may reflect changes in testing practices and reporting rather than a real increase [14]. The highest prevalence rates (more than 2%) are reported in the southern Europe countries, including Italy, Romania and Spain. Medium prevalence was observed in Bulgaria, France, Greece, and Poland. Countries with low prevalence (less than 1%) include Belgium, Germany, the Netherlands, Sweden, and the United Kingdom [14].

4. Cirrhosis and hepatocellular carcinoma attributable to HBV or HCV

With more than 5% of all cancers worldwide, hepatocellular carcinoma is one of the most common malignant tumors. More than 500,000 cases are estimated every year [21], with a mean annual incidence of around 3-4% [22]. In 2008, WHO estimated that cirrhosis and primary liver cancer caused 849,000 and 695,000 deaths, respectively. These conditions, together, account for approximately one of every forty deaths (2.7%) worldwide [23].

HBV and HCV chronic infection represents the main cause of cirrhosis and is the major contributor to HCC in many parts of the world. Alcohol abuse is a critical risk factor for these diseases, with some evidence for a synergistic effect in the presence of viral infection [24, 25].

The annual risk of HBV-related HCC is 0.5% for asymptomatic HBsAg carriers and 0.8% for chronic hepatitis B cases [26]. Patients with related-HBV cirrhosis present a risk of developing HCC 1,000 times higher than HBsAg-negative controls [27]. The HBV replication status may play an important role in the development of HCC [28-30]. The relative risk of HCC among HBsAg positive subjects could be about ten times higher than those without HBsAg, with approximately a sixty-fold increase in the risk when they are positive for both HBsAg and HBeAg [29].

Whereas liver cancer represents a rare occurrence during the first 10–15 years after HCV-infection [31-35], the risk of HCC increases with the establishment of cirrhosis (yearly incidence between 3–8%) [36-41]. The risk of cirrhosis is <10% in women infected at a young age and >30% in men infected after the age of 40 over a 20 year period [42,43]. Genotype 1b, the most prevalent in Europe and in Japan, could be associated with a higher incidence of HCC than

other genotypes [44,45]. Co-infection of both HBV and HCV has been found in more severe liver diseases than either infection alone [46].

The incidence of HCC reflects the global distribution of HBV and HCV infections with approximately 80% of HCC cases occurring in developing countries. Eastern Asia, Middle Africa and some Western African countries show age-adjusted incidence rates (AAIR) of 27.6–36.6 per 100,000 (in men), 20.8–31.1 per 100,000 and 30–48 per 100,000, respectively. Northern Europe, Australia, New Zealand and the Caucasian populations of North and Latin America (AAIR 1.5–3.0) represent the areas at lowest risk. The AAIR raises to about 10 per 100,000 in men in Southern Europe [47].

In a study published in 2006, Perz et al. estimated that, globally, 57% of cirrhosis cases were attributable to either HBV (30%, ranging from 5% in North America to 57% in WHO Western Pacific Region B) or HCV (27%, ranging from 16% in WHO Africa Regions D/E to 62% in Western Pacific Region A). About three-quarters (78%) of HCC were attributable to HBV (53%) or HCV (25%). The attributable fractions of HCC due to HBV or HCV ranged from 16% in North America to 65% in Western Pacific Region B (China, Cambodia, etc.), and from 13% in Eastern Mediterranean Region (Bahrain, Cyprus, Iran, Jordan, etc.) to 66% in Western Pacific Region A, respectively. The two viruses taken together accounted for >50% of HCC in all of the regions and for >50% of cirrhosis in 8 of 11 regions [48].

5. Risk factors for hepatitis B and C

HBV is transmitted by percutaneous or mucous membrane contact with infected blood or other body fluids of an infected person.

In developing countries the transmission routes are perinatal, early childhood exposure, unsafe injections or needle stick in health care settings, unsafe blood transfusions, unprotected sexual contact [6].

In developed countries infections are mainly transmitted during young adulthood by sexual activity and injecting drug use. Historically, male homosexual contacts have been associated with an high risk for HBV infection [6]. More recently, heterosexual transmission is recognised as the most common cause of acute HBV infection in adults [12]. The risk of sexual transmission is mostly related with multiple sex partners and history of a sexually transmitted infections [7]. In some countries, transmission via household contacts (persons who have prolonged but non sexual interpersonal contacts with someone), has also been demonstrated [1, 6]. Sharing items such as razors or toothbrushes with an infected person also give rises to HBV transmission [10].

HBV is a common cause of occupational disease transmitted from patients to health care workers and also to health care workers' families. The risk of transmission depends on the viral load and exposure frequency but the most important factors in the exposure are health care workers skill levels and expertise and the specific hospital departments environment (e.g., dentists, dental hygienists, emergency medical technicians, first responders, laboratory technologists/technicians, nurses, nurse practitioners, phlebotomists, physicians, physician

assistants, and students entering these professions). In contrast, transmission from health care workers to patients is rare [49]. Dentists and dental staff are the category at the highest risk of infection and transmission of HBV to their patients [50].

Several studies showed that tattooing, acupuncture and beauty treatments are associated with hepatitis B transmission when sterilization or disinfection procedures are unavailable [51-53].

In many contexts, the risk of HBV transmission via transfusion of blood and plasma-derived products has been eliminated through donor screening but in some developing countries it can continue to occur in health care settings by non-adherence to guidelines [12].

Travellers to developing countries with high rates of hepatitis B are considered at high risk, especially subjects who engage in unprotected sex with local commercial sex workers [6, 54].

HCV is a blood borne pathogen, most commonly transmitted through exposure to infectious blood [8].

In the past, blood transfusion represented one of the most serious risk factor for HCV infection. In the late 1980s and early 1990s, specific donor screening for HCV was implemented and the risk of HCV infection from a unit of transfused blood was drastically reduced. As of 2001, the risk is less than one per million transfused blood units [55]. Currently, in Europe, the estimated residual risk for acquiring HCV via blood products ranges from 1 to 40 per 10 million transfusions [7].

Nosocomial transmission of HCV via contaminated substances or multiple dose vials as well as via haemodialysis, is still a concern [7]. Especially in developing countries, the incidence of hepatitis C virus infection among patients on hemodialysis was significantly higher [56].

Although in many developing countries unsafe medical injections and transfusions are still predominant sources of infection, at global level HCV transmission is increasingly driven by injected drugs use [57]. In 2010, about 10.0 million injection drug users (IDUs, range 6.0–15.2 million) could have been anti-HCV positive with a midpoint prevalence of 67.0% among all IDUs globally [58]. Individuals who injected drugs, even if they did so on occasionally in the past, are at highest risk for HCV infection that is rapidly acquired following the initiation of injection drug use and occurs from the sharing of needles, syringes, or other equipment associated with drug use [55]. Increasing age, increasing duration of injecting drug use and imprisonment were identified as risk factors [2, 59, 60].

Less commonly, hepatitis C may be transmitted through sex with an infected person. In 2001, sexual exposures accounted for about 15% of cases of hepatitis C in USA [55]. High-risk sexual behaviour among men who have sex with men (predominantly HIV-positive) may predispose to HCV infection probably via per mucosal route and mucosal damage rather than by sexual contact [7].

Together with HBV, HCV is considered a common cause of occupational hazard for health care workers, significantly correlated with factors such as the type of procedure (replacing a hollow-bore needle in a patient's vein or artery, needle recapping, the use of sharp, etc), the severity of percutaneous injury, the gender of the personnel, expertise levels and hospital wards [49].

Other parenteral exposures such as body piercing and tattooing in potentially nonsterile settings [61], or being born to a hepatitis C infected mother [8] have to be considered important risk factors for HCV transmission. Nevertheless, in 2001 CDC estimated that in USA about 10% of people with HCV infection have no recognized source for their infection [55].

6. Prevention of hepatitis B and C

The hepatitis B vaccine, the first vaccine against a major human cancer, is the milestone in hepatitis B prevention [6].

A plasma-derived vaccine was licensed in the early 1980s. It derived from HBsAg particles purified from the plasma of chronic patients. The vaccine was safe and effective but not well accepted because of fears of transmission of live HBV and other bloodborne pathogens, such as HIV [5].

Since the mid 1980s, a new recombinant hepatitis B vaccine has gradually replaced the plasma-derived vaccine. HBsAg in the vaccine is produced in yeast or mammalian cells into which the HBsAg gene or HBsAg/pre-HBsAg genes are inserted using plasmids [9].

The vaccine has an outstanding record of safety and results really effective in preventing infection and its chronic consequences [6, 7]. After three intramuscular doses, more than 95% of infants, children, and adolescents (0-19 years) and more than 90% of healthy adults develop adequate antibody responses. By 60 years of age, 75% of immunised subjects develop protective antibody titers.

Hepatitis B vaccine is available as monovalent formulations or in combination with diphtheria–tetanus–pertussis, *Haemophilus influenzae* type b, hepatitis A and inactivated polio vaccines [9].

The recommended doses vary with the different formulations of vaccine and the age of the vaccinees. From 2 to 4 times the normal adult dose or an increased number of doses may be necessary in hemodialysis patients or in other immunocompromised subjects to induce protective antibodies [5]. A recombinant vaccine using alum and lipid A as adjuvants is available for adult patients with renal insufficiency [62].

Conventionally, the primary hepatitis B immunization infancy series consists of 3 doses; 4 doses may be administered for programmatic reasons according to the schedules of national routine immunization programmes. For older children and adults, the primary series of 3 doses with appropriate intervals applies [9]. The use of routine booster doses does not appear necessary to maintain long-term protection in successfully vaccinated immunocompetent children [9, 63, 64].

Although some studies suggest that a universal infant vaccination may be more cost-effective in intermediate- and high-endemicity regions, WHO strongly recommends that all newborn infants receive the hepatitis B vaccine at birth [7, 9, 65-69, 75]. Universal immunization beginning at birth and other successful hepatitis B vaccination strategies have drastically

reduced HBV transmission in many high endemicity countries. In recent years, the significantly reduced price of hepatitis B vaccine in developing countries has facilitated its introduction into many more countries [6, 9]. As of 2011, 179 countries had incorporated hepatitis B vaccine as a part of their national infant immunization schedules, and an estimated 69% of the 2008 birth cohort received 3 doses of hepatitis B vaccine [6]. In 2006, approximately 27% of newborns worldwide received a birth dose of hepatitis B vaccine [70].

In areas where HBV is mainly spread from mother to infant at birth, the first dose of vaccine should be given as soon as possible after birth, preferably within 24 hours. The need for catch-up vaccination in cohorts of children with low coverage should be considered to increase the number of protected children since the risk for chronic infection is highest in younger age groups [9].

In intermediate/low endemicity countries target groups for catch-up vaccination can include adolescents and people with risk factors for acquiring HBV infection, such as subjects frequently requiring blood or blood products, dialysis patients, people with chronic liver disease, recipients of solid organ transplantations, people interned in prisons, injecting drug users, household and sexual contacts of people with chronic HBV infection, people with multiple sexual partners, men who have sexual contact with other men, HIV positives [7, 71, 76]. Health-care workers, staff of facilities for developmentally disabled persons and others subjects exposed to blood and blood products must be vaccinated. Immunization remains the best defence not only for the workers themselves, but also to prevent transmission of infectious agents to the their patients [9, 76]. Also unvaccinated or incompletely vaccinated travellers to high endemicity countries should be offered the vaccine before leaving for endemic areas [6].

Prevaccination serological tests are not recommended routinely. Though routine postvaccination testing for immunity is not necessary, it is recommended 1-2 months after the last dose of the vaccine series for high-risk individuals, such as people at risk of occupationally acquired infection, infants born to HBsAg-positive mothers, chronic haemodialysis patients, HIV positives and other immunocompromised people, sex partners or needle-sharing partners of HBsAg positive subjects [9].

In several European countries and in USA, routine prenatal screening of pregnant women for HBsAg to identify newborns who require postexposure immunoprophylaxis has been introduced or recommended [2, 75] and some developing countries are considering this opportunity in order to prevent perinatal hepatitis B virus infection [72-74]. In some European countries, screening programmes for high-risk groups (inject drug users, men having sex with men, contacts of HBsAg-positive individuals, health care workers) have also been carried out [2].

Temporary immunity (3-6 months) may be obtained by administering hepatitis B immunoglobulin (HBIG) for postexposure prophylaxis [9]. HBIG is prepared from the plasma of donors with high concentrations of anti-HBs. The plasma is screened to eliminate positives for HBsAg, antibodies to HIV and hepatitis C virus, and HCV RNA [75]. HBIG is typically used as an adjunct to hepatitis B vaccine for postexposure immunoprophylaxis or as the primary means of protection after an HBV exposure for non-responders to

hepatitis B vaccination [75]. HBIG prophylaxis in conjunction with HBV vaccination may be of additional benefit for infants born to HBsAg-positive mothers, particularly if they are HBeAg positive, subjects exposed to HBsAg-positive blood or body fluids, people sexually exposed to an HBsAg-positive person, and patients who need protection from recurrent HBV infection following liver transplantation [9].

A vaccine against HCV is not yet available [8, 77], and immunoglobulin does not provide protection [18]. The primary prevention is aimed to reduce the risk for HCV transmission [78] and includes:

- avoiding unnecessary and unsafe injections, unsafe sharps waste collection and disposal;
- screening of blood, plasma, organ, tissue, and semen donors;
- controlling use of illicit drugs and preventing the sharing of injection equipment among drug users;
- promoting protected sex with hepatitis C-infected subjects;
- advising household contacts of HCV infected about the risk related to share of sharp personal items;
- avoiding tattoos, piercings and acupuncture performed with not sterilized equipment [8, 79-81].

Identifying persons at risk but not yet infected with HCV provides opportunity for counseling on how to reduce their risk [78].

Travelers should be advised against the use of medical, surgical, and dental equipments not adequately sterilized or disinfected and they should consider the risks about getting a tattoo or body piercing in areas where adequate sterilization or disinfection procedures might not be available or practiced [18].

Secondary prevention aims to reduce risks for liver chronic diseases in HCV-infected persons by identification, counseling, and testing and by providing appropriate medical management and antiviral therapy [78, 82].

The determination of which risk groups to recommend for routine testing should be based on the knowledge of the epidemiologic link between a risk factor and acquiring HCV infection, prevalence of risk factors or behavior for infection in the population, and prevalence of infection among those with a risk factors or behavior [78].

Risk groups to test routinely should be injected illegal drugs users; subjects who received (i) clotting factor concentrates produced before the late 1980s, (ii) blood from a donor who later tested positive for HCV infection, (iii) transfusion of blood / blood components or an organ transplant before the early 1990s; patients on long-term hemodialysis or with persistently abnormal alanine aminotransferase levels [78, 83].

Based on a recognized exposure, healthcare, emergency medical and public safety workers after needle sticks, sharps, or mucosal exposures to HCV-positive blood and children born to

HCV-positive mothers should be tested routinely. Immunoglobulin and antiviral agents are not recommended for postexposure prophylaxis of hepatitis C.

In USA, CDC strongly recommends that adults of all ages at risk for HCV infection should be tested; particularly, those born during 1945–1965 without prior ascertainment of HCV risk should receive one-time testing for HCV [20].

Counselling directed to HCV positives must include messages on how to protect the liver from further harm by receiving hepatitis A and B vaccination if susceptible, reducing alcohol consumption, avoiding new medicines (including over-the-counter and herbal agents) without first checking with their health-care provider, and obtaining HIV risk testing [20]. Persons overweight/obese must lose weight and follow a healthy diet and a physically active health-style [20, 84].

First of all, HCV positives must not donate blood, tissue, or semen and/or share devices that come into contact with blood, such as toothbrushes, dental appliances, razors, and nail clippers, to minimize the risk of transmission to others [20].

Epidemiological surveillance represents the mainstay in the prevention of viral hepatitis since it provides the information for determining new infections and trends in incidence, changing patterns of transmission and persons at highest risk for infection, and for evaluating effectiveness or missed opportunities for prevention [78].

In USA, each week, state and territorial health departments report cases of acute, symptomatic viral hepatitis to CDC's [1].

Most of European countries have a passive mandatory surveillance system for acute hepatitis having clinicians as the main source of data, using an electronic format at the national level, and collecting a similar set of basic data. Underreporting is common, but the exact extent is unknown [8].

Chronic hepatitis B and C, although accounting for the greatest burden of disease, are not reported by most states.

Serologic surveys carried out periodically can add information on geographical variations in prevalence of infections, populations at high risk, trends, and prevention programs [78].

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