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Prevention of viral hepatitis (B and C) reassessed

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As hepatitis B and C share modes of transmission, their combined occurrence is not uncommon, particularly in areas where both viruses are endemic and in individuals at high-risk of parenteral infection. Both viral hepatitis infections form an important global public health problem, responsible for over half a billion chronic infections worldwide. Their distinctive characteristics impact upon their epidemiology, transmission, and the success of the different prevention strategies. Since several decades a safe and effective vaccine has been available to prevent hepatitis B virus (HBV) infection. Universal vaccination is the cornerstone of global HBV control. Despite major success, vaccine uptake is hampered, and increasing efforts are required to eliminate acute and chronic hepatitis B. Unlike hepatitis C and HIV, HBV has not captured sufficient attention from policymakers, advocacy groups, or the general public: a major challenge for the future. Although progress has been made in the development of an hepatitis C vaccine, short-term successes are not expected. Even without a vaccine, successes can be reported in the field of hepatitis C due to e.g. implementation of universal precautionary measures in health-care settings, screening of

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blood and blood products, and identification and counselling of infected people. Despite important efforts, transmission in injecting drug users is increasing.

Key words: hepatitis B; hepatitis C; prevention; vaccination; risk groups.

HEPATITIS B

Virus and transmission

The hepatitis B virus (HBV) is a double-stranded, enveloped virus of the family Hepadnaviridae. HBV is currently classified into eight genotypes (A–H), associated with particular geographic distributions. HBV is carried in blood and in other body fluids, including saliva, semen and vaginal secretions, which are capable of transmitting HBV. The highest concentrations of the virus can be found in blood and serous exudates (up to 10^9 virions/mL). HBV remains viable for 7 days or longer on environmental surfaces at room temperature.[1]

Its primary routes of transmission are due to exposure in the perinatal period (often called vertical transmission) or during early childhood (non-sexual person-to-person transmission), sexual transmission, and percutaneous exposure to blood or infectious body fluids.

Most *perinatal infections* occur among neonates of pregnant women with chronic HBV infection. The likelihood of a neonate developing chronic HBV infection is 70–90% for those born to HBeAg-positive mothers (~high titres of HBV DNA) and <15% for those born to HBeAg-negative mothers.

Most *early childhood infections* occur in households of people with chronic HBV infection. The most probable mechanism involves unapparent percutaneous or permucosal contact (e.g. bites, breaks in the skin, dermatologic lesions, skin ulcers) with infectious body fluids.

Sexual transmission has been estimated to account for 50% of new infections among adults in industrialised countries.

Finally, other *parenteral or percutaneous exposure* forms another major source of HBV transmission (e.g. needle-stick injury and mucous membrane splash in the health-care setting, unsafe injections, tattooing, piercing, sharing razors or toothbrushes) in many countries. Worldwide unsafe injection practises are thought to account for over 21 million HBV infections each year.[2] While transfusion-related infections have currently become very rare in industrialised countries thanks to the improved serology and advances in molecular blood screening, surgery and dental care may still be a source of HBV infection.

Clinical spectrum

Acute hepatitis B has a long incubation period (90 days on average) during which the individual is infectious. Individual responses to the infection vary greatly, ranging from subclinical infection with a mild 'flu-like' illness without jaundice to the complete clinical picture of hepatitis.

Although the acute infection is more clinically expressed in adults, infections in infants and pre-school-age children are at greatest risk of becoming chronic, thereby increasing the risk of cirrhosis and primary hepatocellular carcinoma (HCC) later in

life, probably due to the effect of age on the immune system's ability to clear and eliminate the infection. About 90% of adults recover completely, although this may require 6 months or more. About 1% of adults develop fulminant hepatitis, an exceptionally severe form of the disease which is almost always fatal unless liver transplantation is performed.[3] About 1–10% of acutely infected adults and 30–90% of infected babies will become chronically infected and remain infectious.

Persistence of HBV infection is diagnosed by the detection of HBsAg in the blood for at least 6 months or through detection of HBV DNA even in the absence of detectable HBsAg in patients with occult HBV infection. The natural history of chronic HBV infection can vary dramatically between individuals, from a chronic carrier state (i.e. being infectious without showing any symptoms or any abnormalities on laboratory testing) over clinically insignificant or minimal liver disease without ever developing complications, to clinically apparent chronic hepatitis. Chronic HBV infection can be either 'replicative' (with positive HBeAg and high viral load) or 'non-replicative'. In the latter case, reactivation can occur either spontaneously or by immune suppression. Patients with chronic HBV and replicative infection have a generally worse prognosis and a greater chance of developing cirrhosis and/or HCC than those without HBeAg.[4]

Epidemiology

Globally, hepatitis B is one of the most common infectious diseases. Estimates indicate that at least 2 billion people have been infected with HBV, with over 378 million people being chronic carriers (6% of the world population). Some 4.5 million new HBV infections occur worldwide each year, and 15–40% of those infected will develop cirrhosis, liver failure or hepatocellular carcinoma.[5–7]

A model was recently developed to estimate HBV-related morbidity and mortality at country, regional and global levels. This model calculates the age-specific risk of acquiring HBV infection, acute HBV, and progression to chronic HBV infection. HBV-related deaths among chronically infected people were determined from HBV-related cirrhosis and HCC mortality curves, adjusted for background mortality. For the year 2000, the model estimated 620,000 people died worldwide from HBV-related causes: 94% from chronic and 6% from acute HBV. Without vaccination, infections acquired during the perinatal period, in early childhood ($<$5 years old), and $\geq$5 years of age accounted for 21%, 48%, and 31% of HBV-related deaths, respectively.[8]

On the basis of sero-epidemiological surveys, the World Health Organization (WHO) (http://www.who.int/ith/maps/hepatitisB2007.jpg) has classified countries into three levels of endemicity according to the prevalence of chronic HBsAg carriage: high ($\geq$8%), intermediate (2–8%) and low ($<$2%).[9,10] Approximately 75% of the world's chronic hepatitis B carriers live in Asian countries.[11] Importantly, chronic carriers of HBV are not only at risk of developing the long-term progression of the infection but also represent a significant source of infection to others.

In areas of high endemicity the life-time risk of HBV infection is $>$60%, and most transmission occurs from mother-to-child during the perinatal period (e.g. in Asian and central European countries), or horizontally during early childhood, particularly between siblings (e.g. in African countries). In areas of intermediate endemicity, the life-time risk of HBV infection varies between 20 and 60%, and infections occur in all age groups through the four modes of transmission, but primarily in infants and children. In areas of low endemicity, infection occurs primarily in adult life by sexual or parenteral transmission (e.g. injection drug use).

Vaccines against hepatitis B

Available vaccines

Safe and effective HBV vaccines have been available since the 1980s, and immunisation with HBV vaccine remains the most effective means of preventing HBV disease and its consequences worldwide. Vaccination is 95% effective in preventing chronic infections from developing; HBV vaccine is therefore the first vaccine against a major human cancer.

After the first-developed plasma-derived vaccines – which continue to be used, mostly in the low and middle-income countries – different manufacturers have successfully developed recombinant DNA vaccines against HBV (commercialised since 1986).[9,12,13] These exist either as monovalent vaccines or in a broad range of combination vaccines that include an HBV component, especially for vaccination during infancy and early childhood. Such combination vaccines contain tetanus, diphtheria, pertussis (whole-cell or acellular), polio, and/or *Haemophilus influenzae b* components, or combine hepatitis A and B antigens.

More recently, so-called third-generation hepatitis B vaccines – based on the S, pre-S1, and pre-S2 antigens, or using new adjuvants – have been and are being developed. These vaccines specifically aim to enhance the immune response in immunocompromised patients and non-responders.[14,15] Additional doses of hepatitis B vaccine (e.g. simultaneous administration of two doses at different injection sites) can elicit a seroprotective response in about half of the non-responders.[15]

Vaccination schedule

Immunisation against hepatitis B requires the (intramuscular) administration of three doses of vaccine given at 0, 1, and 6 months. More rapid protection can be achieved through the adoption of either an accelerated schedule (0, 1, 2 months) or a super-accelerated schedule (0, 7, 21–28 days), each including three doses of vaccine administered within a much shorter interval, but followed by a fourth dose of HBV vaccine given at 12 months.[15,16]

Vaccine safety

The extensive use over several decades of both plasma-derived and recombinant HBV vaccines has confirmed their safety and excellent tolerability.[17] Side-effects are generally mild, transient, and confined to the site of injection (erythema, swelling, induration). Systemic reactions (fatigue, slight fever, headache, nausea, abdominal pain) are uncommon. However, in recent years the safety of different vaccines, including hepatitis B vaccine, has been questioned, particularly in some countries. Subsequent epidemiological studies, reviewed by the Global Advisory Committee on Vaccine Safety (http://www.who.int/vaccine_safety/en/) concluded that no causal relation has been established and that the allegations were unfounded. Vaccination is therefore not contraindicated in people with a history of multiple sclerosis, Guillain–Barré syndrome, autoimmune disease (e.g. systemic lupus erythematosis or rheumatoid arthritis), or other chronic diseases.[1,18]

Hepatitis B vaccination is contraindicated for people with a history of anaphylactic allergy to yeast or any vaccine component. People with a history of serious adverse events (e.g. anaphylaxis) after receipt of hepatitis B vaccine should not receive additional doses.[1]

Immunogenicity and long-term protection

Seroprotection against HBV infection is defined as having an anti-HBs level $\geq$10 IU/L, measured 1–3 months after a complete immunisation schedule.[9,12,13] Reviews on the use of HBV vaccine in neonates and infants report seroprotective levels of anti-HBs antibodies at 1 month after the last vaccine dose for all schedules in 93–100% of vaccines.[19–22]

A huge interpersonal variability has been demonstrated in the immune response in healthy subjects. As such, fast/high, intermediate, slow/poor, and even non-responders can be discriminated on the basis of the magnitude and the kinetics of the immune response to HBV vaccination.[23,24] The antibody response to hepatitis B vaccine has been shown to depend on the type, dosage, and schedule of vaccination used, as well as on age, gender, genetic factors, comorbidity, and the status of the immune system of the vaccinee.[25,26] Immunodeficient patients require higher doses of vaccine and more injections (at months 0, 1, 2, and 6) to achieve an adequate and sustained immune response.

Follow-up studies in countries of both high and low endemicity have shown that vaccine-induced antibody persists over periods of at least 10–20 years, and that duration of anti-HBs is related to the antibody peak level achieved after primary vaccination.[27,28] Even if antibody concentrations decline over time, clinically significant breakthrough infections are rare. Those who lose their anti-HBs after a successful vaccination usually show a rapid anamnestic response when given an additional dose of vaccine several years after the primary course of vaccination or when exposed to HBV, showing that the immunological memory for HBsAg can outlast antibody persistence and provides long-term protection against acute disease and the development of the HBsAg carrier state.[29,30] Hence, for immunocompetent children and adults, the routine administration of booster doses of vaccine is not required to sustain long-term protection.[31]

Prevention of HBV infection

Primary prevention of new infections

All major health authorities agree that the most effective approach to reducing the burden of HBV is primary prevention of infection through universal vaccination and control of disease transmission in risk groups (listed in Table 1). This requires knowledge of the mode of disease transmission and modification of behaviour through individual education to practise safe sex and good personal hygiene. Screening of all donated blood and maintenance of strict aseptic technique with invasive health interventions has reduced the likelihood of contracting HBV in the health-care setting.[32] Though immunising risk groups is certainly desirable, strategies for HBV control based on risk group vaccination and the screening of pregnant women have failed to adequately control HBV infection in the community. Universal vaccination of subsequent age cohorts will ultimately also interrupt transmission in risk groups.

Universal immunisation. In 1991, the WHO called for all countries in the world to include hepatitis B vaccine in their national infant and/or adolescent immunisation programs. Substantial progress has been made in implementing this WHO recommendation: by the end of 2006, 168 countries had implemented or were planning to implement a universal HBV immunisation program for newborns, infants and/or adolescents. Of these, 119 countries (62%) – mainly situated in Europe, North and South America, Northern

Table 1. Hepatitis B risk groups (for whom vaccination is recommended).

At risk of perinatal transmission:
- Neonates born to HBsAg-positive mothers (either with persistent HBV infection or who had acute hepatitis B during their pregnancy)

At risk of parenteral exposure:
- Injection drug users
- Patients with specific medical conditions, putting them at increased risk of attracting HBV or of more severe consequences in case of an HBV infection
  - Haemophiliacs
  - Those frequently receiving blood or blood products
  - Haemodialysis patients and candidates for hemodialysis
  - Transplant patients and candidates for transplant
  - Chronic non-hepatitis B liver disease patients
- Groups with occupational risk, i.e. Workers whose occupation potentially involves exposure to blood and other body material, such as health-care workers and public safety workers, their trainees and those in related professions

At risk of sexual exposure:
- Heterosexuals with multiple sex partners
- Men who have sex with men
- People attending sexually transmitted infections clinics
- Sex workers

Settings with close person-to-person contact:
- Developmentally disabled people and staff in long-term care facilities
- Inmates and staff of correctional facilities and prisons

Groups without a single specific mode of transmission:
- Contacts (i.e. household contacts, other social contacts, and sex partners) of people with acute or chronic HBV infection
- Families adopting children originating from regions of intermediate or high hepatitis B endemicity
- Travellers to HBV-endemic regions
- Immigrants or refugees from countries of intermediate or high hepatitis B endemicity

Africa and Australia – reported HBV infant vaccination coverage over 80% after the third dose.[33]

High coverage with the primary vaccine series among infants has the greatest overall impact on the prevalence of chronic HBV infection in children.[10] According to model-based predictions, universal HBV infant immunisation would prevent up to 75% of global deaths from HBV-related causes, depending on the vaccination coverage for the complete series. Adding a birth dose to prevent perinatal transmission would increase that proportion to 84%.[8]

In countries with high or intermediate disease endemicity, the most effective strategy is to start immunisation at birth (<24 h) or, in case of routine maternal HBV screening, immunise at-risk neonates and incorporate the vaccine into the routine infant immunisation schedule. Countries with low endemicity may consider immunisation of children or adolescents as an addition or alternative to infant immunisation.[10,33]

Indeed, the remarkable effectiveness of hepatitis B newborn and infant immunisation programs has already been demonstrated in a variety of countries and settings.[34–36] The results of implemented universal hepatitis B programs have become apparent in terms of reduction not only in the incidence of acute hepatitis B infections but also in the carrier rate in immunised cohorts and in hepatitis-B-related mortality – two different ways to assess the impact of a hepatitis B vaccination program.[37]

Risk group vaccination programs. Table 1 lists groups of people at increased risk of acquiring hepatitis B, or at risk of more severe consequences in case of HBV infection, for whom vaccination is recommended.

HBV infection is a well-recognised occupational risk for health-care workers (HCWs). The risk of HBV infection is primarily related to the degree of contact with blood in the work place and also to the hepatitis B e antigen (HBeAg) status of the source person. Indeed, in the case of an injury from needles contaminated with blood containing HBV, additional HBeAg positivity increases the risk of getting infected (as demonstrated by serological evidence) from 23–37% to 37–62%, and the risk of developing clinical hepatitis from 1–6% to 22–31%.[1,38]

Percutaneous injuries are among the most efficient modes of HBV transmission; nevertheless, most HBV-infected HCWs could not recall an overt percutaneous injury. Because HBV has been demonstrated to survive in dried blood at room temperature on environmental surfaces for at least 1 week, HBV infections may also result from (in)direct exposure to blood or body fluid that inoculate HBV into cutaneous scratches, abrasions, burns, other lesions, or on mucosal surfaces. The potential for HBV transmission through contact with environmental surfaces has been demonstrated in investigations of HBV outbreaks among patients and staff of haemodialysis units.[1,39]

Serological studies during the 1970s, demonstrating a prevalence of HBV infection in health-care professionals approximately 10 times higher than in the general population, have led to recommendations for routine pre-exposure vaccination against hepatitis B and the use of standard precautions to prevent exposure to blood and other potentially infectious body fluids since the early 1980s. The implementation of these recommendations resulted in a sharp decline in the incidence of HBV infection among HCWs.[1] Nevertheless, infections still occur, from patient to health-care worker and vice versa, as well as iatrogenic transmission between patients.[2] Indeed, a recent study in the Netherlands demonstrated substantial variation in the way different medical practitioners dealt with blood exposure incidence, in spite of existing guidelines.[40] Moreover, the 75% vaccine uptake measured recently in the United States leaves substantial room for improvement.[41]

HBV-infected health-care workers should be screened for HBeAg and monitored for viral load. The European Consensus Group[1] drew up guidelines recommending that HCWs with HBV DNA levels of 10^4 genome equivalents/mL should be restricted from performing exposure-prone procedures, a cut-off level that attempted to balance the risk of infection against the withdrawal of essential specialist staff.[2,42]

An adequate referral strategy for counselling and treatment of the injection drug users (IDUs) and for preventive services for household contacts and sex partners should be established, preferably integrating multiple viral hepatitis prevention services with HIV and sexually transmitted infections services, drug rehabilitation programs, needle-exchange programs and other drug-related services.[43]

Despite the availability of HBV vaccines and the existence of clear recommendations to vaccinate IDUs – ideally as soon as possible after the start of their drug use – the vaccine uptake in this risk group consistently remains below 30%.[16,44] Alongside personal risk behaviours, the association between social network characteristics of IDUs and drug injection risk behaviours has also been shown.[45]

Pre-vaccination testing for serological markers of HBV infection is recommended in IDUs. Since the immunogenicity of HBV vaccines may be somewhat lower in IDUs, specially in those known to be infected with HIV, follow-up testing for anti-HBs after completion of their vaccination, and subsequent counselling if required, should be performed.[43,44]

Hepatitis B screening and prevention is recommended for all adolescents and adults who engage in unsafe sexual behaviour. These groups include: (a) heterosexuals having sexual contact with HBV-infected people or with multiple partners; (b) men who have sex with men; (c) people attending sexually transmitted infection clinics; and (d) sex workers (i.e. all people who provide sex for money or other forms of remuneration).

Special attention should be given to:

- vaccination programs adapted to the needs of these groups; follow-up testing for anti-HBs after completion of their vaccination series, and counselling if they do not respond to the vaccination, should be established;
- health education messages addressed to sex workers and their clients;
- confidentiality and appropriate counselling;
- respecting anonymity, e.g. by assigning a unique code number to the sex worker;
- promotion of outreach programs and accelerated vaccination schedules to guarantee higher vaccination coverage.

The risk of HBV transmission in utero is relatively rare and is estimated to account for $<2\%$ of mother-to-child transmission. The risk of transmission is highest in mothers with chronic replicative infection, or in mothers who suffer an acute HBV infection during the third trimester of pregnancy. Even if HBV can be detected in breast milk, there is no evidence supporting HBV transmission by breastfeeding.[46]

Perinatal transmission is prevented by either starting universal immunisation at birth, or by screening all pregnant women and immunising at risk newborns.

Pregnancy or breastfeeding is not a contraindication to vaccination against hepatitis B. Limited data suggest that a developing foetus is not at risk for adverse events when hepatitis B vaccine is administered to a pregnant woman. Available vaccines contain non-infectious HBsAg and should cause no risk for infection to the foetus.[1] For the vaccination of the at-risk newborn see below.

Vaccination of all household contacts of people identified as acute hepatitis B patients or chronic HBsAg carriers is recommended. However, people who have casual contact with acute hepatitis B patients or chronic HBsAg carriers at schools and offices are at low risk of catching HBV infection. Hepatitis B vaccination is therefore not recommended for these people unless in special circumstances or medical conditions that might facilitate transmission.[43]

The recommendation to vaccinate developmentally disabled people in long-term care facilities and their staff has clearly shown an effect on the risk for HBV transmission in such facilities. Similarly, vaccination of inmates and staff of correctional facilities and prisons is recommended. In addition, some countries recommend vaccination of day-care children and staff where they have contact with high-risk children.[43]

Post-exposure prophylaxis (PEP)

Both passive–active PEP with hepatitis B immune globulin (HBIG) combined with hepatitis B vaccine and active PEP with hepatitis B vaccine alone have been demonstrated to be highly effective in preventing transmission after exposure to HBV from mother to newborn. Its effectiveness is determined mainly by the timely administration of the initial dose of vaccine (and/or HBIG), and diminishes the longer after exposure it is initiated.

Although the post-exposure efficacy of the combination of HBIG and the hepatitis B vaccine series has not been evaluated for occupational or sexual exposures, it can be

presumed that the increased efficacy of this regimen observed in the perinatal setting compared with HBIG alone would apply to these exposures.[39,47] Antiviral PEP is not available for HBV.

Various international bodies consistently recommend PEP with hepatitis B vaccine and, if available and feasible, combined with HBIG for infants born to HBsAg-positive mothers (within 24 h), unvaccinated infants whose mothers or primary care-givers have acute hepatitis B, sexual contacts of people with acute hepatitis B, and people occupationally exposed to HBsAg-positive blood, depending on their vaccination and vaccine response status.[47] Household and sexual contacts of people with chronic HBV infection do not need prophylaxis with HBIG, but should be vaccinated. In the case of exposure to a source with unknown HBV infection status, hepatitis B vaccine without HBIG is recommended for unvaccinated people.[1,39,46] In general, PEP for HBV will be warranted for previously unvaccinated people if wounds, non-intact skin, or intact mucous membranes might have been exposed to blood or body fluids from one or more other people. A person for whom the vaccination status cannot adequately be assessed shortly after exposure should be considered unvaccinated.[39,46]

Secondary prevention of HBV transmission

Patients with known HBV infection should be advised to avoid unprotected sexual intercourse, including oro-anal and oro-genital contact, until they have become non-infectious or their partners have been successfully vaccinated. Referral to specialised health-care services for counselling and treatment, and referral of the clients' household contacts and sex partners to preventive services, is recommended.

Infected or exposed people should refrain from donating blood, plasma, organs, tissue, or semen until follow-up testing by the health-care provider has excluded seroconversion.[39]

Tertiary prevention of the pathological consequences of chronic HBV

Long-term antiviral treatment by (pegylated) interferon or nucleos(t)ide analogues has been shown to reduce the risk for disease progression and HCC by about 50% in patients with chronic hepatitis B and advanced fibrosis or cirrhosis.[46] Treatment options and management plans are reviewed elsewhere in this issue.

HEPATITIS C

Virus and transmission

Hepatitis C is caused by the hepatitis C virus (HCV), an RNA virus classified within the Flaviviridae family.[48] HCV is a blood-borne agent that is efficiently transmitted parenterally through blood and blood products.[49] Before the discovery of HCV in 1989, blood transfusion and the use of plasma-derived products was a frequent cause of hepatitis C transmission. In high-income countries the rapid improvement of health-care conditions, virus inactivation in blood products, and the implementation of anti-HCV screening of blood donations have led to a sharp decrease in the risk of post-transfusion hepatitis C.[50–52] However, infection continues to occur via other modes of apparent and inapparent parenteral transmission. HCV is parenterally ten times less transmissible than HBV but more easily transmitted than HIV. Currently, unsafe injecting drug use is the main mode of transmission in most parts of the Western world

(accounting for nearly 90% of new HCV infections in that part of the world), whereas unscreened contaminated blood transfusion, unsafe therapeutic injections, and folk-medicine practises still represent an important source of infection in low and middle-income countries.[50,53] There is also solid evidence of nosocomial transmission of HCV during invasive procedures. Major gynaecological and cardiovascular surgery carry a high-risk; however, microsurgery, in particular ophthalmic, as well as the use of multi-dose vials have also been implicated.

Other reported sources of infection are needle-stick exposure in health-care workers,[54] sharing a razor or toothbrush with an infected individual,[55] and unsafe body piercing and tattooing.[56]

Even if transmission of HCV between monogamous partners is thought to be rare, sexual transmission of HCV has been shown to increase significantly with multiple sexual partners.[57] The large reservoir of HCV carriers and the fact that sexual intercourse is common means that even a low rate of sexual transmission can account for a substantial number of new infections.[58] However, in many cases, no apparent transmission factor or route is reported.[59] Amongst blood donors in the United States, 50% of those with HCV infection did not admit to having risk factors.[60]

HCV infection is uncommon in children because perinatal transmission, which is responsible for most cases of paediatric infection in the Western world, has been documented to occur in only about 3–10% of cases in different populations. Transmission is believed to occur in utero as a consequence of a high viral load in the mother (in particular, from mothers who are HIV-co-infected).[61–65]

Clinical spectrum

The incubation period for hepatitis C before the onset of clinical symptoms is on average 6–7 weeks. In acute infections, the most common symptoms are fatigue and jaundice; however, the majority of cases (60–70%) even those that develop chronic infection (50–85% of those infected), are asymptomatic for years. Fulminant hepatitis C disease is rarely observed. Chronic disease is difficult to recognise because symptoms are mild and infection passes silently and insidiously from the acute to the chronic phase. In fact, the vast majority of those affected are symptom-free for at least 20 years. Serological diagnosis of acute HCV infection is based upon the detection of HCV RNA. Persistence of HCV infection is diagnosed by the presence of HCV RNA in the blood for at least 6 months.

Epidemiology

Acute HCV infection often occurs asymptomatically (>60% of cases) and therefore remains clinically unrecognised. Consequently, and because many new infections are not diagnosed or reported, defining the precise incidence of hepatitis C infection is difficult. An additional problem in HCV surveillance data is the fact that even the reported cases are not by definition related to the incidence of infection. A significant proportion of so-called newly identified infections are in fact old chronic infections. The presence of IgM antibodies, the usual serological marker of acute infection, is not reliable in the case of HCV infection. Two alternative approaches exist: window period testing (an RNA-positive and anti-HCV-negative sample indicates acute infection) and IgG avidity. Determining the IgG avidity (antigen binding force) can distinguish recent (low avidity) from chronic (high avidity) infection.[66] Currently there is no

standard agreed methodology for these assays, and they are not used in routine practise, making it very difficult to distinguish acute from chronic infections.[67]

Even though increasing knowledge on HCV transmission and exposure, and the subsequent preventive programs, have resulted in the incidence of new cases declining in most high-income countries, the prevalence of chronically infected individuals is still high, with at least 130–170 million carriers of HCV worldwide.[68,69]

Prevalence in the general population

The WHO (http://www.who.int/ith/maps/hepatitisc2007.jpg) estimates that the worldwide prevalence of chronic HCV infection is at least 3%, ranging from 1% in high-income countries to around 5% in low- and middle-income countries.[70]

The prevalence of chronic HCV carriers varies greatly depending on geographical location, the primary mode of transmission, and the characteristics of the population analysed.[59]

The number of infected individuals is particularly high in Egypt. In the Nile delta seroprevalence ranges from 19% in the 10–19-year-old age group to approximately 60% in the 30-year-old age group, and has been reported to be associated with parenteral anti-schistosomiasis therapy carried out with inadequately sterilised injection material.[71,72] In the general population there is evidence for an age-related distribution of HCV infection, with prevalences that are minimal in childhood and progressively higher with increasing age.

Prevalence in risk groups

Certain risk groups have been shown to have above-average HCV prevalences (listed in Table 2).

In Europe, up to 60–70% of injecting drug users living in urban areas are seropositive for HCV antibodies. The rate of infection depends on age, duration, and frequency of injection drug use, with 25% of infections occurring during the first year of addiction, 50% after 5 years, and up to 90% for more than 5 years of injection drug use.[73]

Table 2. Groups at risk of hepatitis C virus (HCV) infection in industrialised countries.

Group at risk	Estimated prevalence range (%)
Injection drug users	35–90
Haemophiliacs treated before 1990	50–90
Thalassemics	42–83
Haemodialysis patients	10–45
People who received a blood transfusion before 1991	5–10
Children born from HCV-positive mothers	3–10
Incarcerated people (strong link to injecting drug use)	30–80
Migrants coming from endemic regions	Related to country of origin
Health-care workers (although at increased risk, prevalence in Europe comparable to the prevalence in the general population)	Related to country of origin
HIV-infected people	25–35
Patients with unexplained persistently elevated ALT	15

ALT, alanine aminotransferase.

Prevention of hepatitis C infection

There is no vaccine against HCV. Research is in progress, but the high mutability of the HCV genome complicates vaccine development. Although 20% of patients with acute HCV infection clear the virus spontaneously, lack of knowledge of any protective immune response following HCV infection is impeding vaccine research. Although some studies have shown the presence of virus-neutralising antibodies, it is not clear whether or how the immune system is able to eliminate the virus. Thus, from a global perspective, the greatest impact on HCV disease burden will likely be achieved by focussing efforts on reducing the risk of HCV transmission from nosocomial exposures (e.g. screening of blood, rigorous implementation of infection control, reduction of unsafe injection practises) and high-risk behaviours (e.g. injection drug use).

Scrupulous adherence to fundamental infection control principles – including the use of disposable injection materials, safe injection practises, appropriate aseptic techniques, and adequate disinfection techniques for non-disposable equipment – is essential to prevent iatrogenic transmission of blood-borne viruses.[74–77]

Communication of information about hepatitis C is an important element in the implementation of any hepatitis C prevention strategy, and should include:

- health education and awareness campaigns targeted to the general public to increase the awareness of risk factors for HCV infection, methods to prevent HCV infection, the importance of determining the HCV infection status for people with risk factors for infection, and the importance of a medical evaluation of HCV-infected people;
- professional medical education programs to improve the awareness of HCV infection and chronic hepatitis C and its implications, the importance of identifying risk factors for infection and diagnostic testing in all patient populations, recent advances in treatment options for chronic hepatitis C, and counselling messages for infected people;
- collaboration with patient support groups to improve health education, prevention efforts, and treatment compliance.

Hepatitis C prevention activities (e.g. harm- and risk-reduction counselling, testing, medical management, or referral) should be included in existing clinical practise and prevention programs for people with similar risk factors for infection, including:

- programs to treat and prevent sexually transmitted infections;
- programs for the prevention and treatment of illicit use of injection drugs;
- HIV/AIDS voluntary counselling and testing programs;
- Correctional facilities health programs.[68]

Primary prevention of new infections

Vaccine development. Attempts to develop a vaccine against HCV encountered several major hurdles. As a consequence, this development has not yet resulted in success, despite major research efforts over many years.

The RNA polymerase that orchestrates HCV replication is prone to errors. As such, mutations in the viral genome occur, and a quasi-species is formed in the infected host. By this mechanism, HCV has the ability to escape immune control by cytotoxic T

lymphocytes (CTLs) and by antibodies against various regions of the viral envelope proteins gpE1 and gpE2, and to persist in HCV-infected people.[78–82]

Propagating HCV in cell culture has been impossible for many years; more recently, human hepatoma cell lines have successfully been infected with the 2a strain of HCV.[83–86] This has led to the in-vitro generation of hybrid viruses from other HCV genotypes, which has been extremely important in vaccine development and in research on the immune response to HCV infection.[87,88]

Although several studies in chimpanzees and in humans have demonstrated that recovery from a previous HCV infection results in significant immunity to avoid persistence of a subsequent HCV infection, even with other HCV genotypes, this protective immunity is not completely effective.[89,90]

Strategies to develop an HCV vaccine aim at inducing both a strong humoural (neutralising antibodies) immune response and a cellular (T-helper 1 as well as CTL) immune response. Further knowledge on correlates of protection (including vaccine-induced immune memory) and on cross-protection against the various HCV genotypes will certainly guide vaccine development.

Several vaccines combining viral proteins and adjuvants are being investigated, some of which have entered the earliest phases of clinical development. Viral proteins used in the vaccines include the envelope glycoproteins gpE1 and gpE2, and several $CD4^+$ and $CD8^+$ epitopes, derived from various virion and non-structural proteins, that are highly conserved among the different HCV genotypes (e.g. the nucleocapsid C protein). These viral proteins are formulated in combination with different adjuvants, with bacterial pore-forming toxoids, with heat shock proteins, and with influenza-based virosomes.[91]

One of the advantages of DNA vaccines is their ability to generate cytotoxic lymphocyte responses. Therefore this strategy is also appealing to HCV vaccine development. Again, several genes coding for viral proteins are tested preclinically, often in a strategy where DNA vaccine is used for priming, followed by a protein-based vaccine to boost T-helper 1 and humoural immune responses.[91]

Another strategy to improve the immune response is the use of a defective or attenuated viral or bacterial vector expressing HCV-specific antigens, which then can benefit from the additional immune response elicited by the vector. Some of these vaccines are also in the preclinical phase of development.[91]

Finally, the ability to propagate HCV in cell culture also offers the possibility of exploring the development of killed or attenuated HCV vaccines.[91]

One of the lessons learnt from the experience with hepatitis B vaccine is that, even with an effective HCV vaccine, the prevention of chronic persistence of HCV infection and its consequences remains very important. Mathematic modelling demonstrated that in Greece, unless there is a dramatic decline of over 80% of new infections, the incidence of cirrhosis, HCC and liver-related death will continue to rise for at least the next 30 years.[92]

Routine screening of donors and viral inactivation of blood products. After the 1970s and 1980s, transmission via blood and blood products in high-income countries was substantially reduced due to effective virus-inactivation procedures, exclusion of paid blood donors, questioning donors for high-risk behaviours, testing for HIV, and using surrogate markers associated with non-A–non-B hepatitis. The implementation of routine HCV testing of blood donors further reduced the risk of transmission of HCV via blood transfusion. Currently many countries have introduced nucleic acid testing, shortening the window period, and in combination with the above measures, virtually eliminating the risk of transmission. Safety of blood supply remains a major source of public concern in low- and middle-income countries.

Prevention of nosocomial and iatrogenic transmission. Investigations looking at nosocomial infections clearly show the relationship between unsafe injection procedures and high chronic HCV infection rates. In some countries unsafe injection techniques are now the predominant transmission route of HCV infection. Therapeutic injections are reported to account for 2 million new HCV infections each year. Many of these injections are performed in less-than-ideal conditions, often with reuse of needles or multi-dose vials, and mainly, but not exclusively, in low- and middle-income countries.

Up to the early 1990s dialysis units were a good example of hyperendemic health-care settings; prevalence ranged between 4 and 60% in different European countries.[52]

Standard precautions for infection control exist and must be applied: there must be supervision and observation of compliance with existing guidelines and recommendations, and periodic review of both practise and guidance.[2]

Increased injection safety may also be enhanced by reducing the number of injections, sometimes requiring behavioural changes in both patients and health-care workers. Single-dose vials should be used wherever possible. If multi-dose vials must be used, the septum should always be pierced with a sterile needle, and this needle needs to be removed immediately after taking one dose.

Prevention of transmission in injecting drug users. Because of the major role of direct percutaneous exposure in the transmission of HCV, educational programs are of paramount importance. Where possible, addiction treatment should be offered. Injecting drug users should have access to sterile needles, syringes, swabs, filters, spoons, water, and any other equipment required to inject drugs. Collaborating with patient support groups can enhance the impact of prevention programs.[68]

In Europe, harm-reduction interventions (e.g. needle-exchange programs, methadone substitution programs) showed a limited impact on HCV incidence and prevalence among IDUs during the 1990s.[52,93] Due to the high infectivity of HCV, many IDUs are already infected before they enter these programs. In Eastern Europe in particular transmission in IDUs remains uncontrolled, with a risk of IDUs spreading HCV into the general population.[52]

Prevention of sexual transmission. Because of the low risk of HCV transmission, monogamous couples do not need to use barrier protection (condoms), although they should be advised that condoms may reduce the risk of transmission. On the other hand, HCV-infected individuals with multiple sexual partners or engaging in high-risk sexual practises should be advised to use barrier protection.

Perinatal transmission and breastfeeding. There is at present no known way of reducing the risk of perinatal transmission. Women diagnosed with HCV infection should be informed of the potential risk of transmission in pregnancy.

The risk of perinatal transmission is approximately 3–10% for neonates of anti-HCV-positive mothers. High HCV-RNA levels at delivery, and HIV coinfection, significantly increase this risk.[64] Elective cesarean section has not been shown to reduce the risk. Invasive foetal monitoring and prolonged labour after rupture of membranes should be avoided.

HCV does not appear to be transmitted by breastfeeding.[77]

Identification and testing of people at increased risk. It is clear that testing for HCV should be undertaken only if counselling can be given and if possible appropriate treatment is available.

Screening of the general population is not recommended. However, the following groups with an increased risk of infection were identified to receive HCV testing, counselling concerning risk and harm-reduction, and if applicable substance use treatment:[68]

- those who have (or might have) received blood products prior to introduction (1991) of second-generation enzyme-linked immunosorbent assay tests;
- haemophiliacs;
- hemodialysed patients;
- children born to mothers who have hepatitis C;
- current or previous users of injection drugs;
- donors for organ or tissue transplantation;
- individuals with persistently unexplained elevated serum alanine aminotransferase (ALT) levels; of all patients with persistently elevated serum ALT levels, 15% prove to be chronically infected with HCV.

Health-care, emergency medical, and public safety workers should be tested for HCV infection only after percutaneous or mucosal exposure to HCV-positive blood.[69]

Routine HCV screening is not recommended in pregnant women unless they belong to a risk group for HCV infection.

Screening of sexual partners of infected people, taking into account the low risk of transmission in monogamous partners, is of limited use, but the result can offer reassurance.

Some countries also screen immigrants from countries with high prevalence of HCV infection.

Post-exposure prophylaxis

There is currently no recommended post-exposure prophylaxis to prevent HCV infection, either by immunoglobulins or by antivirals.[94] The risk of HCV transmission after either sexual or percutaneous exposure is relatively low (1.8% for percutaneous exposure). Existing guidelines therefore recommend immediate testing of the source, and immediate and follow-up testing (e.g. after 4–6 months) for the exposed person. In the case of acute infection there is a proven benefit in early treatment.

There are different views on the treatment options: pegylated interferon alone or in combination of ribavirin. As for treatment of chronic HCV, genotypes seem to play an important role here too. Highest sustained virological response (SVR) for people infected by genotype 1 is obtained if treatment is started as soon as possible after the diagnosis of acute HCV infection. For genotypes 2 and 3, treatment could be delayed at least 12 weeks after diagnosis, allowing patients to achieve spontaneous clearance, without reducing the overall SVR. Patients infected with genotype 1 having a detectable HCV RNA level at week 4 showed an increased SVR if treatment was prolonged to 24 weeks.[95]

Secondary prevention of HCV transmission

Infected people should be counselled so that they can prevent transmission to other people. Patients diagnosed with HCV infection should not donate blood or organs. Injecting drug users who continue to inject drugs should not share needles, syringes and other equipment. Possible sexual transmission should be discussed. It seems likely that

if condoms are used consistently then sexual transmission will be reduced. Given the very low rate of transmission – outside the HIV co-infection situation (see above) – monogamous partners may choose not to use them.

There is currently no consensus on the management of HCV-infected health-care workers and students. Although there is a lower risk of transmission than with HBV, if transmission occurs there is a greater risk of an ensuing chronic infection in the patient. Based on current published data, however, screening HCWs for HCV and restricting HCV-infected HCWs is not justified. HCWs whose work includes exposure-prone procedures (EPPs) should know their HCV status in order to make informed career choices and to enable them to receive counselling and treatment.[42]

Tertiary prevention of the pathological consequences of chronic HCV

All HCV-infected people should be evaluated to determine their stage and degree of liver disease. The possibility and benefits of antiviral treatment should be established. Counselling to prevent further liver injury from disease cofactors, alcohol abuse or infection with other hepatitis viruses or HIV is required. Patients with chronic HCV should be encouraged to undergo testing for HBV and HIV markers, particularly when specific risk factors are identified. HBV vaccination should be recommended to HCV carriers who are negative for all HBV markers. Hepatitis A virus vaccination is also recommended for non-immune individuals.

The primary goals for treatment of HCV are to reduce morbidity and mortality, ideally through cure by complete elimination of HCV and normalisation of ALTs, or else through stopping disease progression and improving quality of life. Adequate treatment can reduce the reservoir of chronic carriers and thereby diminishes transmission.

Treatment options and management plans are reviewed in Chapters 7 and 8.

SUMMARY

As hepatitis B and C viruses share modes of transmission, their combined occurrence is not uncommon, particularly in areas where both viruses are endemic and in individuals at high-risk of parenteral infection. Both viral hepatitis infections form an important global public health problem, responsible for over half a billion chronic infections worldwide.

Their distinctive characteristics impact upon their epidemiology and transmission, and the success of the different prevention strategies.

For several decades safe and effective vaccines have been available to prevent HBV infection. Universal vaccination is the cornerstone of global HBV control. Despite major success, vaccine uptake is hampered, and increasing efforts are required to eliminate acute and chronic hepatitis B. Unlike hepatitis C and HIV, HBV has not captured sufficient attention from policymakers, advocacy groups or the general public: a major challenge for the future.

Although progress has been made in the development of an HCV vaccine, short-term successes are not expected. Even without a vaccine, successes can be reported in the field of hepatitis C due to e.g. implementation of universal precaution measures in health-care settings, screening of blood and blood products, and identification and counselling of infected people. Despite significant efforts, HCV transmission in injecting drug users is increasing.

Practice points

- despite the availability and widespread use of effective hepatitis B vaccines, efforts are required to optimise uptake of the vaccine in universal and risk group immunisation programs
- because the development of a hepatitis C vaccine has not yet been successful, prevention and control measures are the major challenge to all those involved in public health
- screening for HBV and/or HCV should be followed by adequate management of positive patients, including counselling, referral, and possible treatment if available
- nosocomial transmission of viral hepatitis can and should be prevented by reinforcing and maintaining blood donor selection and screening procedures, strict adherence to universal safety measures in health-care settings, and thorough evaluation and communication of nosocomial infections
- immigrants should be socially fully integrated, including access to health services, to control the epidemic spread of imported infections
- the HBV and HCV epidemic among IDUs needs to be controlled by continuous educational programs for the general public and health professionals, accessible substance abuse treatment and rehabilitation programs (including outreach to homeless and socially excluded users), implementation/reinforcement of harm-reduction programs, HBV testing and vaccination of non-immune IDUs, and HCV testing and treatment in correctional facilities
- the possibility and benefits of HCV treatment should be established; adequate treatment can reduce the reservoir of chronic carriers, thereby diminishing transmission

Research agenda

- to make sure that HBV vaccination does not lose its place on the agenda of governments, agencies, and international organizations, as a consequence of its success so far and the interest in other vaccine-preventable diseases
- to further investigate the long-term protection after HBV vaccination and the role of cell-mediated immunity
- to assess the impact of HBIG in perinatal transmission and its possible effect on the immune response later in life
- to measure the impact of globalisation and international migration on the incidence of new hepatitis B cases
- to better understand the role of HBV genotypes in transmission, natural history and treatment
- to continue research on the treatment of (acute) HBV cases
- to improve/optimise HBV surveillance and to quantify the impact of HBV mutants.
- good surveillance data for HCV are absent in many regions of the world, and consequently there are gaps in our understanding of incidence, risk factors, transmission, and disease progression

- improvements in assays and/or testing algorithms for hepatitis C are required to optimise surveillance data
- development of hepatitis C vaccines is needed
- more insight into HCV immunology and cross-protection is required
- there is a need to measure the impact of globalisation and international migration on the incidence of new hepatitis B and C cases

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