Prevention and control of perinatal transmission of hepatitis B and C

VIENNA, AUSTRIA

1-2 June 2017

Objectives

The Viral Hepatitis Prevention Board (VHPB) organized a meeting in Vienna (1-2 June 2017) in order: to provide an overview of the current epidemiology of transmission of hepatitis B and C viruses (HBV and HCV) from mother to child; to discuss the impact of perinatal transmission on the achievement of the goals for elimination of viral hepatitis; to review the scientific evidence for the prevention and control of perinatal HBV transmission through timely birth dose vaccination, the administration of hepatitis B immunoglobulin (HBIg) and treatment, and for improving the prevention and control of perinatal HCV transmission through treatment; to examine the scientific evidence on prevention and control of perinatal HBV and HCV transmission; to identify challenges and objectives for improving prevention of perinatal transmission of HBV and HCV and for securing success in attaining the goals for elimination by 2030; and to present examples of prevention, discuss lessons learned and identify opportunities.

Rationale and context

In May 2016, 194 Member States of the World Health Organization (WHO) made a commitment to eliminate viral hepatitis as a public health threat by 2030 [1], and global and regional strategies and targets have been adopted to achieve that goal [2]. At all levels, prevention of mother-to-child transmission of hepatitis B and C virus is a crucial intervention in those plans to achieve that goal.

Considerable progress has already been made in the prevention and control of viral hepatitis. But, although most countries have introduced universal hepatitis B vaccination in their immunization programmes, as of February 2016 only about 70 have national hepatitis elimination plans in place or in development [2]. Indeed, further work is needed on core measures such as universal HBV vaccination (including a timely birth dose), diagnosis, treatment and harm reduction.

Broad regional and national differences are seen in reported prevalence rates of viral hepatitis, and many cases of infection are not detected or reported. Globally, hepatitis B and C are found predominantly in WHO's African and Western Pacific regions (68% of globally reported cases [3]) - in these two regions more than 6% of the population is positive for hepatitis B surface antigen (HBsAg). China, however, has already reached the Western Pacific regional target of less than 1% prevalence of HBV infection in children under 5 years of age. Low HBsAg prevalence rates are reported in Latin America as well as in North America and Western Europe.

Even though perinatal transmission of HBV is less frequent in Africa than in Asia, it is responsible for two thirds of HBV-related liver disease in Africa, where mother-to-child transmission of HBV is a neglected problem. In the USA, where a perinatal hepatitis B prevention programme was begun in 1990, a recent study showed that 1.1% of infants born to HBsAg-positive mothers were infected [4].

For hepatitis C, prevalence rates of 1.5-2.3% are reported in WHO's Eastern Mediterranean and European regions [3]. Although in the WHO Region of the Americas prevalence rates are generally

low, they vary across and within regions and countries. In the USA (where the Centers for Disease Control and Prevention (CDC) estimates that 3.5 million people live with HCV), after years of declining rates the incidence of acute HCV infection has increased three-fold in recent years, and increasing number of children are being born with HCV. The increase in new infections is considered real and not just due to better ascertainment. Europe is also seeing epidemiological changes due to changing demography, with waves of movement within and immigration into the continent, and many HBV and HCV infections are seen in parents (and their offspring) who immigrated into countries in the European Union from countries with high prevalence rates (not only in Africa and Asia but also eastern Europe) [5].

Globally, many children are still being born to mothers who are positive for hepatitis B surface and/or e antigen, even where vaccination coverage rates are high, since not all women of childbearing age belong to the age cohort that has been vaccinated. Factors associated with transmission include mothers' HBeAg positivity (HBeAg is the only HBV antigen to cross the placenta and is tolerated in utero) and high viral load. Although WHO estimates that globally the proportion of children under 5 years of age with new HBV infections is around 1.3%, mother-to-child transmission accounts for more than 30% of the 257 million people globally living with HBV infection [6]. It occurs even in low prevalence settings in industrialized countries. Some 90% of infants born to HBeAg-positive mothers develop chronic hepatitis B virus infections, as do between 5% and 20% of those born to HBsAg-positive/HBeAg-negative mothers. Not everywhere is hepatitis B immunoglobulin (HBIg) available or affordable, reducing the possibility of preventing additional infections.

For HCV, overall 5% of children born to chronically HCV-infected mothers are infected. Best estimates indicate that about 13 million children aged 1-15 years are infected with HCV worldwide (among the estimated 71 million people with chronic HCV infection), and WHO estimates that some 15-30% of those who are chronically infected face the risk of liver cirrhosis within 20 years. Infected children show no signs of acute illness and mostly have mild liver injury, although some extrahepatic manifestations and non-organ-specific autoantibodies are seen. In infected children spontaneous viral clearance rates of 20-25% are reported.

In many cases when HBV or HCV infection is detected in pregnant women, there is poor linkage with and referral to care systems. Reporting and recording systems are often poor and inadequate, with poor input of data from the private sector.

The licensing and introduction since 2012 of safe and effective directly acting antivirals (DAAs) to cure HCV infections has radically changed thinking about prevention and control of hepatitis C in adults. The high price of these treatments, although negotiable and generally declining, remains an issue, and even at discounted prices significant costs and budgetary impact are likely to persist for some time. Treatment of chronic hepatitis B remains suppressive rather than the curative treatments now available for chronic hepatitis C, and therefore is long term. WHO has issued guidelines on the treatment of both HBV and HCV infections [7, 8]. For children and pregnant women, more data are needed on their safety and effectiveness.

General considerations for strategies to prevent mother-to-child transmission

Policies for prevention and control of chronic hepatitis B virus infections exist but they are not always put into practice, leading to what was described as policy dissonance. In addition, specific policies are needed to guide prevention of perinatal transmission of HCV. Policies should include

actions within a strategic health system approach and will need monitoring and verification for impact and effectiveness.

Chronic hepatitis B

In the USA and Europe infection of infants born to HBsAg-positive mothers was associated with younger maternal age, high viral load, birth of mother in countries or areas of high prevalence of HBV, and the infant not receiving the full schedule of hepatitis B vaccine in the first year of life or not receiving the birth dose in time.

For hepatitis B, recommended actions that already exist comprise:

- universal hepatitis B vaccination to reduce incidence
- timely administration of birth dose vaccination (within hours of birth to babies born to HBsAg-positive/HBeAg-positive mothers and no later than 24 h post-partum to reduce incidence
- antenatal screening of pregnant women with linkage to care and follow-up of infants
- administration of HBIg (if affordable and available), and
- antiviral treatment of HBsAg-positive pregnant women with high viral load (i.e. with tenofovir)[*]

WHO visualizes these elements as a pyramid of actions in an incremental approach to preventing mother-to-child transmission of HBV (Fig.1), starting from the base of three doses of hepatitis B vaccine as part of universal infant immunization programmes, regardless of the HBsAg, HBeAg and HBV DNA status of the pregnant woman. The hierarchy of elements progresses through timely administration of a birth dose of vaccine, screening of pregnant women and treatment, in favour of which evidence is rapidly accumulating and which, with antivirals alone or in combination, is likely to become increasingly relevant for women with high viral load in the near future.

Their use in pregnancy is, of course, predicated on regulatory approval. (In its guidelines issued in 2015, WHO omitted a specific recommendation on prevention of mother-to-child transmission of HBV because available evidence was limited and poor.) Antiviral treatment can be viewed as treatment per se and as prevention of both future possible transmission and disease progression.

[*] Reference to “tenofovir” is taken to be a reference to tenofovir disoproxil fumarate (TDF), which is currently one of the recommended treatment of HCV infection and chronic hepatitis C.

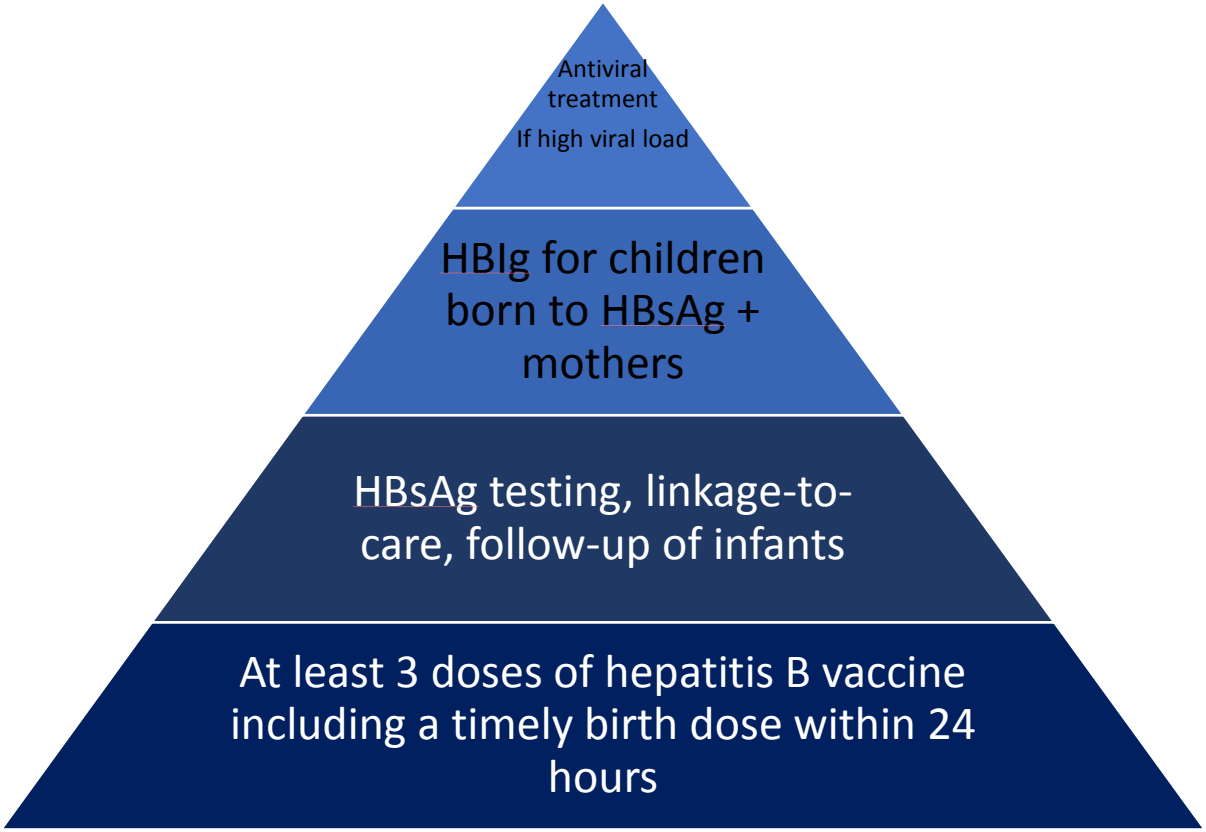


Fig. 1 Incremental approach to prevention of mother-to-child transmission of HBV [*Source: WHO*]

Universal hepatitis B vaccination

It is essential to ensure the completion of at least three scheduled doses as part of routine infant or childhood immunization programmes. By the end of 2015, 185 countries in the world reported having policies in place, but questions exist about the efficiency and reach of some programmes. There are serious concerns about the reliability of data on coverage rates and reports of considerable percentages of people being missed by vaccination, especially among immigrants, in various European countries.

Timely administration of birth dose of a hepatitis B vaccine

Current recommendations indicate administration of the birth dose within 12 or 24 hours of birth, but some countries are adopting more aggressive policies, giving the first dose within 6 hours or even 1 hour of birth.

The coverage of the birth dose of vaccine is reported to be only 39% globally, but with much higher regional rates (more than 70%) in WHO's American and Western Pacific regions[3]. The practice is not well implemented in Africa and not universally observed in Europe. There are issues of feasibility, for instance, GAVI, the Vaccine Alliance does not support the provision of monovalent hepatitis B vaccine. Also, in Africa where only some 50% of births may take place in health facilities; on the other hand, nearly 80% of pregnant women attend an antenatal clinic at least once (thus generating an opportunity to raise awareness). A new community-based intervention (NéoVac) is being launched in three African countries (Burkina Faso, Madagascar and Senegal) to improve

coverage of timely birth dose of hepatitis B vaccine and of neonatal care practices that contribute to child survival [9].

In both health care settings and communities, knowledge about the value of timely birth administration of vaccine is often limited. Within the health care system, timely administration of a birth dose depends on health care workers being well informed and on good communication between health care teams as well as awareness among parents. Both these essential elements should be promoted. At the community level, parents need to have greater awareness of the vital role of the procedure.

The use of hepatitis B vaccine alone to prevent infections in newborns of HBsAg-positive/HBeAg-negative mothers is supported by evidence, which suggests that it may be equally as effective as the combination of vaccine and HBIg [10-12]. In terms of follow-up, neonatal and child health programmes in high-income countries are recommended to conduct post-vaccination serological testing for anti-HBs, and anti-HBc and HBsAg as required, at an appropriate age (for instance, 9-12 months, or 1 or 2 months after final dose if vaccination series is delayed).

Administration of HBIg

Early studies in Taiwan indicated that, in combination with timely hepatitis B vaccination, administration of HBIg is very effective in preventing mother-to-child transmission of HBV. Nevertheless, the contribution of HBIg to the prevention of transmission of HBV from mothers remains complex. (Concerns previously raised about the emergence of envelope protein mutants in HBIg recipients do not seem to have materialized.) Divergent policies and views exist about the recommendation for the additional use of HBIg, and it is no longer used in some countries. This disparity has various sources, including limited availability and supply, cost (rendering its use impractical or unfeasible in Africa), and limited value for newborns born to HBsAg-positive/HBeAg-negative mothers.

Antenatal screening of pregnant women

By preventing viral transmission, the measures recommended by WHO (see above) ineluctably prevent chronic hepatitis B. The question then arises of how to detect and diagnose HBV infection in pregnant women and whether HBV-infected pregnant women should be treated (see below).

Policies for screening for maternal HBV infection vary by country. In the USA, the current strategy is to screen all pregnant women for HBsAg. Infants of HBsAg-positive women receive hepatitis B vaccine and HBIg within 12 hours of birth, and all other infants receive the vaccine before hospital discharge. In a survey of 21 European countries, 18 had a policy to prevent transmission to children of HBsAg-positive mothers consisting of giving vaccine and HBIg whereas three give vaccine only [13]. In Denmark, which does not have a universal hepatitis B vaccination programme, pregnant women have been screened for HBV since 2005.

Studies have shown that screening and preventive measures for HBV are cost-effective, but that judgment tends to depend on costs within each country. Testing for HBsAg and then for HBV DNA is more cost-effective than testing for HBsAg, HBeAg and then HBV DNA, although that conclusion could change if and when HBV DNA testing becomes more widely available and affordable. Modelling in the USA shows that the current strategy for preventing perinatal HBV remains cost-effective compared to the universal hepatitis B vaccination strategy. One preventive strategy was considered to be cost-saving compared to the current strategy: all pregnant women are screened for HBsAg, and HBsAg-positive women have their HBV DNA load measured. Antiviral prophylaxis is

offered for four months, starting in the third trimester to women with DNA load ≥106 copies/mL. Hepatitis B vaccine and HBIg are administered at birth to infants of HBsAg-positive women, and vaccine administered before hospital discharge to infants of HBsAg-negative women. That should be considered for continuing the decrease in the burden of perinatal hepatitis B in the United States [14].

Several references were made to the criteria for screening. (These were extensively discussed at a previous VHPB meeting on screening for chronic hepatitis [15][14].)

Numerous other issues need to be addressed and need more research, including when in pregnancy to test (for instance, whether in the first trimester and subsequently thereafter); diagnosis and diagnostic tests (for example, current PCR test are detecting more low-level infections); availability of rapid and point-of-care tests; and how to improve the collection of data on immigrants, including information about country of origin.

Antiviral treatment

Guidelines have been issued for the clinical management and treatment of people with chronic hepatitis B, but a critical review of literature provides only a qualified affirmative response to the question of whether HBV-positive pregnant women should be treated. High-quality evidence in support of using antiviral treatment for prevention of vertical HBV transmission is scarce and most of the data that exist relate to infections with HBV genotype C.

The European Association for the Study of the Liver (EASL), in its guidelines issued in 2017, [16] recommends screening for HBsAg in the first trimester of pregnancy, and that, for an HBsAg-positive woman of child-bearing age without advanced fibrosis who plans a pregnancy in the near future, it might be prudent to delay therapy until the child is born. Pregnant women with chronic hepatitis B and advanced fibrosis or cirrhosis should be treated with tenofovir disoproxil fumarate (TDF) and those on entecavir or another nucleos(t)ide analogue be switched to tenofovir. In all pregnant women with high HBV DNA levels (greater than 200,000 IU/ml) or HBsAg levels (greater than 4 $\log_{10}$ IU/ml) antiviral prophylaxis with tenofovir should start at week 24–28 of gestation and continue for up to 12 weeks after delivery.

The American Association for the Study of Liver Diseases (AASLD) in its guidelines for the treatment of chronic hepatitis B issued in 2016 recommends the use of antivirals in all HBsAg-positive pregnant women with viral loads >200,000 IU/mL (although the quality of evidence is low) [17]. A critical review of literature, however, provides only qualified support for setting that threshold for viral load as the level at which antiviral treatment should be started.

WHO's guidelines, issued in 2015 [8], concluded that for HBV-monoinfected pregnant women the indications for treatment are the same as for other adults, and tenofovir[1] is recommended. No recommendation was made on the routine use of antiviral therapy to prevent mother-to-child HBV transmission (ref 8, p89). WHO's Guidelines Development Group concluded that the principal

[1] Cited data that mention "tenofovir", a nucleoside analogue antiviral, refer to tenofovir disoproxil fumarate but that medicine affects renal function and lowers bone density. Tenofovir alafenamide fumarate is a prodrug that is less toxic, but it has not yet been tested on HBV-infected women post-partum.

indication to treat mothers throughout pregnancy should be the necessity for treatment of chronic hepatitis B in the mother. For women already on therapy who become pregnant, treatment may not need to be discontinued. The quality of the evidence again was not strong.

High-quality evidence for effectiveness of nucleos(t)ide analogues in prevention of mother-to-child transmission of HBV is limited to two randomized controlled clinical trials conducted in China [18] and Taiwan (unpublished). The former showed that in a cohort of 200 HBeAg-positive mothers with an HBV DNA level of more than 200,000 IU/mL during the third trimester, the rate of mother-to-child transmission of HBV was lower among those who received tenofovir therapy than among those who received usual care without antiviral therapy. The findings elicited much comment on the methodology of the study both in the medical literature and at the meeting, where it was also observed that generally flaws in published articles compromise the preparation of guidelines. Also, most of the evidence relates to HBeAg-positive mothers infected with HBV genotype C.

Outstanding issues include safety, although the safety of treatment with tenofovir has been repeatedly confirmed in HIV-infected pregnant women and their newborns. Supportive arguments are also drawn from the experience of treating HIV infection and disease where antivirals are being administered safely at birth. Questions remain unanswered about whom to treat, when to start, and what are optimal regimens for treatment of children as well as whether to treat HBV-positive pregnant women. The use of antivirals (alone or in combination) is likely to be considered soon for use in women with high viral loads.

Chronic hepatitis C

Transmission of HCV from a mother to her child occurs in 4–8% of births to women with HCV infection, and the rate is more than twice as high in births to women with HIV and HCV co-infection [1, 19]. Maternal HCV viraemia increases the risk of transmission. There are no proven interventions yet to reduce the risk of transmission.

The clinical course of chronic hepatitis C in children differs from that in adults. It is generally mild and children's development is normal but 30-40% progress later in life to chronic active infection, with persistent viraemia and abnormal alanine transferase activities and a wide spectrum of histopathological changes have been seen in the livers of infected children. HIV co-infection accelerates disease progression. Correlates of transmission and disease progression also include ethnicity, obesity, co-morbidities and genetic factors [20].

Antenatal screening of pregnant women

The licensing and availability of new safe and effective direct acting antivirals (DAAs) might represent an additional justification for screening for HCV infection markers. Overall policies for HCV screening vary by country but routine screening of pregnant women for HCV infection is generally rare. For instance, in both Belgium [21] and Switzerland the proportion of doctors who test all pregnant women for HCV varied widely across the country; in the latter, from 19% in the east to more than 60% in the south and south-west [22]. In the USA testing for HCV is recommended for several groups including all adults born between 1945 and 1965 and people who inject or have injected drugs. Although CDC does not recommend it for pregnant women, arguments in favour of such action were advanced at the meeting. HCV infection in women of child-bearing age in the USA (many living in rural areas and a history of injecting drugs is more frequently being reported among them) is increasing; an estimated 29,000 HCV-infected women give birth each year, possibly causing 1700

infections in newborns: the number reported is only 200 a year [23]. In Switzerland about 550 HCV-infected women give birth each year; with a transmission rate of about 6% the authorities would expect to see 27 cases a year, but less than half that number are actually reported. Reported seroprevalence rates of HCV in pregnant women vary widely across the world, from 0.1% in Brazil, 0.3% in London (UK) and the Netherlands and 0.7% in Switzerland to 2.3% in Ukraine, 3.0% in sub-Saharan Africa 4.7% in Pakistan, and 8.5% in Egypt and Yemen. It is likely that more than half of HCV-infected newborns are not diagnosed as the infected mothers are not tested during pregnancy. Screening of pregnant women may open the door to appropriate management of the infection including treatment (of mothers and children) and education about the infection and ways of transmission.

Views are divided between universal screening and risk-based selective screening during pregnancy as the best and most cost-effective approach, with conflicting findings having been published. Some studies show that it is cost-effective (e.g. in London [24]), whereas others do not (in Amsterdam, although it could be for first-generation non-Western migrants, who could be targeted for screening [25]). The calculation of cost-effectiveness will depend on the cost of the DAAs and consideration of indirect costs.

Arguments against universal screening include the absence of a vaccine, no approved treatment in pregnancy, the low transmission rate, the high rate of spontaneous clearance of HCV and persistence of maternal antibodies, and cost. Risk-based screening has problems too: many risk factors are not disclosed or remain unknown, and in the past the use of lists of risk groups and behaviours (as in the early days of the HIV/AIDS epidemic) failed. Nevertheless, selective screening of people in groups with the highest prevalence rates, such as prisoners and people who inject drugs, was likely to detect more cases of infection than screening pregnant women. It was suggested that specific testing algorithms could provide clarity. Such considerations would be important in the debate on where to focus limited resources, which may change when more is known about antiviral agents that reduce mother-to-child transmission or when it is established that these drugs have a better result in children when treatment is initiated early.

Discussions of the issue of criteria for screening, in particular for HCV infections, reflected the outcomes of previous VHPB meetings on screening [15, 26].

Antiviral treatment

Treatment of HCV-infected women before pregnancy would be the best way to prevent both infection of infants and maternal disease progression.

EASL and WHO have published guidelines for clinical management and treatment of chronic hepatitis C (see ref. 6), recommending use of DAAs. EASL advised that treatment should be considered without delay in HCV-infected women of child-bearing age who wish to get pregnant [27]. WHO observed that more data are needed on treatment of pregnant women: none of the DAAs has been so evaluated. AASLD's guidance issued in 2015 made no recommendation for pregnant women [28].

As with treatment of chronic hepatitis B, a critical review of literature showed that high-quality supporting evidence is limited. Questions about the safety of DAAs in pregnant women, when to start treatment of both pregnant women and infected children, and optimum regimens for treatment of children remains unanswered. No treatment with such an indication is licensed yet.

Virology, genotypes and transmission

For mother-to-child transmission of both HBV and HCV, high maternal viral load carries a high risk of infection of the neonate. Also, some evidence was presented for an association of peripheral blood monocytes with perinatal transmission of both HBV and HCV.

Hepatitis C

Other maternal risk factors for HCV transmission include obstetric practices that expose the infant to infected maternal blood during vaginal delivery and prolonged rupture of membranes [29], but neither Caesarian section nor breastfeeding increase risk of transmission [20, 30]. (EASL, however, does not recommend Caesarian sections for HCV-infected mothers.) However, the mechanism of perinatal transmission of HCV is still unclear. Although HCV genotypes are geographically distributed, the identity of the genotype does not seem to be a risk factor for infection with HCV.

Hepatitis B

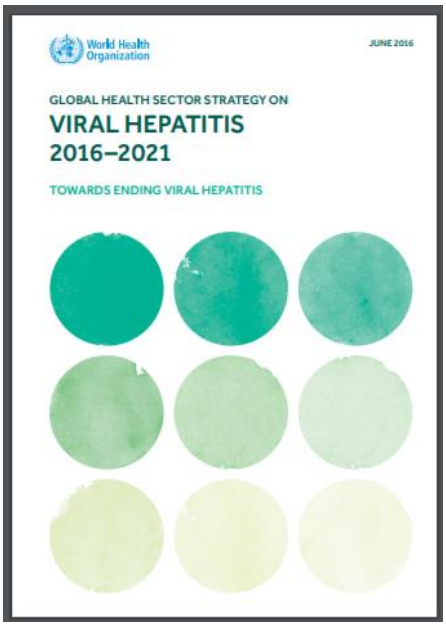
HBV genotypes have a distinct geographical distribution. Analysis of genotypes shows the impact of the slave trade in the 9th to 19th centuries [31], and similar movements of people and viruses are being mirrored in the migrations within and to Europe. Regional differences have been seen in HBeAg-positivity, with higher rates in south-east Asia than in sub-Saharan Africa, probably owing to genetic factors. Furthermore, HBV can develop mutations in the region of the genome coding for HBeAg, a phenomenon that might explain the different natural histories of HBV infections seen and modes of transmission [32].

Current vaccines against HBV may have lower post-exposure efficiency against genotypes E and F and possibly *y* subtypes (higher incidence rates of chronic infection are seen in infants born to mothers with the *ay* subtype compared with the *ad* subtype). Asymptomatic occult HBV infections occur even in newborns who have apparently protective levels of anti-HBs. Suboptimal protection may be due to heterologous HBsAg subtypes but the predominant reason is late administration of the birth dose of current vaccines. Third-generation vaccines promise greater efficacy, but they are more expensive to manufacture. Their introduction could be considered in depending on health economics and health care priorities [33].

Although some infants born to mothers with high viral load become infected, the reason why not all such infants do so is not yet known. Other pathological and virological issues that are neither resolved include the causality of intrauterine or perinatal infection with HBV, the relationship between high levels of HBV viraemia and transmission of HBV to embryos (what is the threshold for transmission?), the role of precore or core promoter region mutations and of HBeAg, and the effect of microhaematological leaks on transmission.

Policy development

WHO developing an incremental approach for prevention of mother-to-child transmission, building on progress and experience with developing and implementing regional frameworks, including those for the triple elimination of hepatitis B, HIV and syphilis. In its global health sector strategy on viral hepatitis it has set global and regional targets for service coverage, including vaccination and prevention of mother-to-child transmission of HBV, aiming to prevent 50% of the latter by 2020 and 90% by 2030. Mechanisms for measuring impact and verification will be needed. The Organization has revised its position paper on hepatitis B vaccines [34], and is reviewing data on safety and effectiveness of, and access to, antivirals (alone or in combination) in preventing mother-to-child transmission of HBV.



http://www.who.int/hepatitis/strategy2016-2021/ghss-hep/en/

In the WHO European Region considerable progress is being made in implementing policies, strategies and action plans towards hepatitis B elimination targets. The Regional Office for Europe still encounters gaps and weaknesses in data (including the fact that only eight of the 53 countries in the Region routinely collect data on screening pregnant women for HBsAg). It supports Member States in developing national action plans and strengthening control of hepatitis B, and draws on the advice of the European Technical Advisory Group of Experts on Immunization.

In the ***USA***, hepatitis B vaccine is included in the Vaccines for Children Programme which covers nearly half of young children nationally. The frequency of screening of pregnant women, followed by vaccination and administration of HBIg within 24 hours of birth has increased greatly. Overall the result has been to lower the rate of perinatal infections with HBV to less than 1% of births to HBsAg-positive mothers. The National Academies of Sciences, Engineering and Medicine has issued a national strategy for the elimination of hepatitis B and C, with targets for 2030 [35]. For hepatitis B the strategy comprises screening all pregnant women for HBsAg and testing all positive women for HBV DNA (with prophylaxis within 12 hours of birth for all infants born to infected women), universal vaccination of all infants, as well as routine vaccination of unvaccinated children, adolescents and adults at risk. CDC has numerous ongoing HBV programmes and elimination strategies, and is actively responding to recent increases in hepatitis B in people who inject drugs (PWID), and revising the ACIP statement on hepatitis B vaccine. Through an advisory committee CDC is developing guidance for perinatal testing and prevention of HCV infection. In April 2017 CDC hosted a symposium that endorsed the hepatitis B and C elimination strategy [36].

Activities of the ***European Centre for Disease Prevention and Control*** (ECDC) relating to mother-to-child transmission of HBV and HCV include collection of surveillance data and estimates of prevalence among pregnant women, but it recognizes the incompleteness of the data gathered on chronic viral hepatitis, especially HBV, and reporting biases. It undertook two surveys relating to antenatal screening, and found that only 2 out of 29 responding countries screened pregnant women for HCV infection (in one case only selectively) [37]. Considerable variations were seen in antenatal screening of pregnant women for HBsAg and reporting, and ECDC identified challenges for effective screening and generating standardized advice on preventing mother-to-child transmission as a lack of data, insufficient capacity to reach at-risk populations, and lack of resources – problems not limited to Europe. In 2017 ECDC published scientific advice for implementing and strengthening

antenatal screening programmes (for HIV, syphilis, rubella as well as hepatitis B), focusing not just on the general population but migrant populations, women engaging in high-risk behaviour and women who refuse vaccination. It plans further activities including preparation of a specific prevention programme on prevention of mother-to-child transmission of HBV and of a monitoring system for evaluation of national responses to hepatitis B and C

EASL publishes clinical practice guidelines on prevention of transmission of HBV and HCV, which cover screening of pregnant women and treatment (administration of HBIg and vaccine for hepatitis B and antiviral therapy). The latest revisions appeared respectively in 2017 and 2016, respectively. ***AASLD*** similarly formulates and updates evidence-based guidelines on hepatitis B and C.

A critical review of the literature underlined the importance of credible evidence for decisions about care of patients, immunoprophylaxis (and failures) and antiviral therapy. Guidance should be based on consensus and be flexible. Discussion highlighted the need to take into account medicolegal considerations of guidelines and recommendations, the status of which differs between countries; they should not be legally binding.

Needs and issues

Continued work on strengthening health systems is vital not only in general but also for making progress towards the elimination targets set out in global and regional health sector strategies for viral hepatitis. Countries without national plans should be urged to prepare, adopt and implement them. Issues of monitoring and evaluation were raised, in particular how to incentivize countries to evaluate implementation of existing policies and to adhere to guidelines?

Several more specific themes and needs were identified.

Data

- Better epidemiological and programmatic data, especially prevalence rates, with verification of data (for example, those on coverage rates and timing of vaccine administration) and better analyses of data;
- Better access to and use of data (such as data mining and large-data IT applications) and improved sharing and transfer of data between various sources of information (including diagnostic laboratories, cancer registries, birth registries and other demographic databases);
- An agreed case definition for perinatal infection (it was noted that the US Council of State and Territorial Epidemiologists was due to reach a decision on one such definition imminently), and establishment of criteria for laboratory diagnosis and epidemiological data;
- Epidemiological models of hepatitis B should take account of different viral genotypes.

Screening and diagnosis

- Sound, evidence-based and agreed recommendations on screening of pregnant women for HCV infection, in particular in high prevalence areas and regions, with engagement of high-level decision-makers in elaborating more extensive national guidelines;
- Screening should be accompanied by long-term follow up of both HCV/HBV-infected children (including HBV DNA positive (occult) infections) and mothers for monitoring of the natural history and the consequences of viral infection and treatment if appropriate.
- Development of available and affordable rapid and point-of-care tests for diagnosis and measuring viral load.

Treatment

- Better documentation of the effectiveness of antiviral treatment of HBV infection in pregnant women and young children, with more robust evidence for the treatment of HBsAg-positive mothers - specifically, evaluation and/or confirmation of the effectiveness and safety of the current (tenofovir derivative, tenofovir alafenamide) and future hepatitis therapies;
- In the absence of an approved treatment of hepatitis C in infected pregnant women or children, research and development must continue, including definition of the optimum regimen, including the age of commencement, for treatment with DAAs of children with HCV infection.

Knowledge and information

- Redressing low awareness of and poor knowledge about HCV transmission and infection and its health consequences among both pregnant women and health care providers (including general practitioners who have a major role in diagnosis, referral and prevention of hepatitis B and C but are largely unprepared, and, within clinical settings, obstetricians and gynaecologists);
- Better communication among members of health care teams;
- Greater, more effective and appropriate communication for the general public and populations at risk (such as migrants from countries endemic for viral hepatitis), including materials in appropriate languages and interpreters.

The way forward

One-size-fits-all solutions are not appropriate, and the following proposals represent the consensus of the meeting:

- Tailoring strategies for the prevention of mother-to-child transmission to particular contexts, with, in the case of HBV infection, account being taken of viral genotypes, subgenotypes and even serotypes;
- Continued work to raise and sustain political commitment at national and regional levels (including the European Commission), especially at this time of austerity and limited resources for health;
- Further development and full implementation of national plans under the aegis of WHO's global health sector strategy on viral hepatitis;
- Evaluation of existing programmes and policies for HBV and HCV, for instance through seroepidemiological surveys to determine and confirm reductions in prevalence rates and monitoring the implementation of guidelines (for example, whether pregnant women are screened and whether HBIg and vaccine are administered to children of positive mothers in a timely manner);
- A more holistic and integrated approach by health authorities, for instance by building on experience in three WHO regions of work towards triple elimination of hepatitis B, HIV and syphilis (quadruple in the Americas, where Chagas disease is included) through the integration of screening for HBV infection into existing programmes for screening for HIV and syphilis as part of antenatal care;

- A clear focus on the promotion and incremental introduction of antenatal screening of pregnant women for HBsAg, timely administration of a birth dose of hepatitis B vaccine, and other measures such as administration of HBIg and antivirals;
- Given the likely favourable benefit/ratio of universal screening of pregnant women for HCV infection, fulfilment of several conditions (in particular, cost-effectiveness, availability and affordability of DAAs and sufficient human resources) in many countries before introduction of that screening;
- Consideration by national authorities of policies on who can prescribe antiviral agents for HBV and HCV; existing policies vary widely across different jurisdictions;
- Pressure on pharmaceutical companies and research institutes for agreement on appropriate data for gaining approval of treatments for HCV infection in pregnancy;
- Continued efforts by stakeholders to educate, inform and engage health care professionals, especially obstetricians, gynaecologists and family physicians, in work towards preventing and control hepatitis B and C, including involvement of involving patients in awareness campaigns and families in counselling.

A clear message to emerge is that the **timely administration of the birth dose of hepatitis B vaccine does prevent mother-to-child transmission of hepatitis B virus** and VHPB expects WHO to issue clear guidance on the importance of timeliness and how to achieve it.

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