



Viral Hepatitis Prevention Board

**The impact of viral hepatitis treatment, vaccination
non-responders, and occult hepatitis on public health**

**VILNIUS, LITHUANIA
25 and 26 March 2019**

Objectives

- Hepatitis C – obstacles to treatment: non-responders, reinfection and relapse
 - Definition of treatment failure
 - Public health impact of treatment failure
- Hepatitis B vaccine non-responders
 - Definition
 - Potential public health impact
 - Review guidelines
- Occult hepatitis B
 - Definition and incidence
 - Importance for vaccination programme effectiveness
 - Potential public health impact and review guidelines
- Overall: agree on guidance on how to deal with non-response to vaccination and treatment in the context of elimination of hepatitis B and C viruses as global health threats

Terminology: need for clarification and definitions

- control/elimination/eradication – elimination versus eradication
- reinfection, relapse, recurrence
- failure to treat/treatment failure
- failure to vaccinate/vaccine failure
- definition of protection after HBV vaccination (≥ 10 or ≥ 100 IU/L?)
- waning anti-HBs titres after vaccination/loss of immune memory
- non-adherence
- recent/former injection of drugs
- occult infection/latent infection

Context

- WHO has set elimination targets for HCV infections to be achieved by 2030, including 90% reduction in incidence and 65% reduction in mortality; goals for hepatitis B include similar targets for testing, treatment and mortality, 90% reduction in prevention of mother-to-child transmission, and complete blood and injection safety
- Hepatitis B and C meet the criteria for disease elimination, with benefits that outweigh costs, but HBV and HCV infections remain underdiagnosed and undertreated
- Elimination programmes are under way in many different countries
- Great progress has been made globally in introducing HBV vaccine and reducing prevalence, complications and mortality rates among vaccinated cohorts; the main remaining challenge is to increase the coverage of the birth dose of HBV vaccine
- Introduction of direct-acting antivirals has made hepatitis C curable regardless of HCV genotype; their availability is increasing and prices are falling; also, the price of diagnostics is now close to that of therapeutic agents in many countries
- Research progress includes steps towards development of a vaccine against HCV infection and advances towards candidate anti-cccHBV DNA agents, as well as review of older candidate HBV vaccines, research on which has been abandoned.

HCV treatment - issues and needs

- Success factors for the introduction of HCV treatment programmes have been demonstrated in several countries: these factors include high-level political support (as, e.g., in Egypt, Georgia and Scotland), sustained funding, and rapid administration of treatment after diagnosis (Egypt)
- As a large proportion of chronically infected people is not aware of their infection, screening and treatment of HCV need to be scaled up to population levels (with targeting of different subpopulations and groups), but barriers to screening and scale up remain: financial, practical and logistical
- Political support and commitment need to be generated, and then political will and funding need to be sustained
- Technical hubs, sources of support and information need to be created to facilitate the elimination of viral hepatitis (e.g. the Coalition for Global Hepatitis Elimination)
- Action is needed to redress the lack of national registries and of quality control of data in many countries
- Recurrence of HCV infection is rare but happens, owing to either relapse (viraemia with same genotype/strain) or reinfection (viraemia with new genotype/strain)
- Risk factors for infection with HCV are well established and understood, but reinfection remains a major challenge in some at-risk populations

HCV treatment- issues and needs (continued)

- Progress has been made with introduction of pangenotypic direct-acting antiviral agents; but changing characteristics are being noted of infected people being treated with DAAs
- Need to improve adherence to HCV treatment regimens
- Need to review policies that do not allow retreatment of HCV-reinfected subjects
- Need to recognize and manage drug-drug interactions, including treatments for other co-morbidities (e.g. especially tuberculosis) and alternative medications (phytotherapies)
- Better political and financial support needed relative to and for linkage with other public health programmes such as HIV/AIDS, malaria and tuberculosis

Research needs

- Evaluate harm reduction, including mental health counselling and opioid substitution therapy
- Improve treatment of coinfections – HIV, HCV, HBV, tuberculosis
- Development of HCV vaccine

Hepatitis C treatment relapses and non-responders – discussion group outcome

Impact on public health and progress towards achievement of elimination goals for HBV and HCV

- Effect of treatment relapses and non-responders is seen at different levels - individual, community, policy-making – but low or very low impact of relapse or non-response to treatment on public health in most countries, although much inter- and intra-country variation (depending for instance on epidemiology, genotype distribution, and health infrastructure)
- Case finding, access to care and primary prevention are priorities, with need to identify re-infections, especially in drivers of the epidemic such as PWIDs in countries where they constitute a large population
- Parallel epidemics in different subgroups need parallel strategies and actions
- In some low- and middle-income countries nosocomial HCV infections constitute a serious problem and are a major route of HCV transmission
- Greater progress towards elimination goals will follow improvements in other areas, such as national planning, financing and implementation of health information systems to follow up the cascade of care

Hepatitis C treatment relapses and non-responders –
discussion group outcome:

Is there a need to adapt or create need guidelines or recommendations?

- Several WHO and international guidelines exist (from preparing national plans to HCV treatment); the problem is more one of their implementation at country level than creating new guidance
- Support could come in the form of resource mobilization, coordination, creation of knowledge hubs and networks, and generation and maintenance of the will to make national plans work
- Guidance may be needed for specific target groups (e.g. for screening every six months people on HIV pre-exposure prophylaxis, and screening high-risk patients to detect reinfection after sustained viral response) and in the form of country-specific guidelines that reflect the local context
- Areas such as education about harm reduction need further assessment

Hepatitis C treatment relapses and non-responders – discussion group outcome

What role can VHPB play in this process?

- VHPB is already contributing to national planning in countries in the European region through its annual country meetings; VHPB could consider further supporting countries in cooperation with partners such as WHO and patient groups
- VHPB could provide further support to patient associations for increasing awareness and conducting advocacy
- VHPB could foster local coalitions of stakeholders for social mobilization
- Specifically VHPB could identify for WHO gaps in knowledge and local expertise by collecting real-life data from different countries, and it can identify and facilitate ways to work towards the agreed elimination goals
- VHPB could draft a position paper on non-responses and reinfection, with agreed definitions and identification of gaps in knowledge, for publication in a major journal

Hepatitis B vaccine - low or non-responders: findings and issues

- Current licensed second-generation vaccines serve excellently for routine immunization purposes; eleven monovalent vaccines are prequalified by WHO
- Low or non-response to hepatitis B vaccination, however, occurs in about 5-10% of vaccinees (with higher rates in older people) and asymptomatic infections are reported
- Undetected HBV in donated blood in regions with inadequate screening of blood products is a significant concern for transfusion medicine
- Several risk factors for non-responsiveness have been identified including viral and host factors – i.e. age, sex, smoking, viral envelope mutations and co-morbidities (especially renal failure, diabetes mellitus, obesity, and vitamin D deficiency)
- Breakthrough infections may occur in newborns to mothers with high viral load despite administration of HBIG and vaccine
- What is the definition of protection after HBV vaccination? – still no clear answer

Hepatitis B vaccine - low or non-responders: needs and future research

- No “new” vaccines for low or non-responders have been developed, but some previous candidates rejected on financial grounds are being reviewed; inclusion of pre-S₁/pre-S₂/S antigen elements improves immunogenicity and protection but most such candidate vaccines are not licensed in the western hemisphere; their greater costs and restricted licensure render them likely to be used in only specific circumstances (less “a luxury” than a niche market for specific non-responders)
- Revaccination of non- and low responders with Fendrix® (licensed in Europe for patients in renal failure but not registered for non-responders) or HBVaxPro-40® gave better seroconversion rates and higher titres, but with greater reactogenicity, than standard alum-adjuvanted vaccines
- Alternative vaccination strategies to improve immune response in low or non-responders include: alternative routes of administration (intradermal routes), different adjuvants, addition of pre-S₁/pre-S₂ antigens or higher doses of S antigen
- Available data suggest that pre-S₁/pre-S₂/S vaccines may be used to bypass non-responsiveness to conventional yeast-derived vaccines - (currently there is only one such vaccine available in a few countries)

Hepatitis B vaccine - low or non-responders: needs and future research (continued)

- Unmet need for protection of several high-risk populations of low or non-responders to conventional hepatitis B vaccines - from HIV-infected subjects to cancer patients including those in oncohaematology units, transplant recipients, patients with coeliac disease, renal disease, chronic non-HBV liver disease as well as obese subjects and people with diabetes
- More research into immunological basis of response to hepatitis B vaccine, such as: examination of meaning of primary antibody titres for low or non-responders and loss of immune memory; better definition of neutralizing anti-HBs antibodies and other humoral mechanisms; variability of individual gene expression and role of granulocytes and secretion of granulin
- Further development of new vaccines: Heplisav[®] (licensure approved by FDA, with a recommendation for post-marketing surveillance; two-dose regimen, with good seroconversion rates) and pre-S₁/pre-S₂/S antigen vaccines (e.g. Sci-B-Vac, licensed in Israel; very encouraging responses with improved immunogenicity)
- Further results of clinical trials in non-responders are expected for new adjuvants, in particular the toll-like receptors (e.g. TLR 9 in Heplisav[®] and the alum-based AS04)

Impact of low or non-responses to hepatitis B vaccines on public health and achievement of elimination goals – outcome of discussion groups

- All three groups agreed that the issue of non-responders does not have a significant impact on public health nor is it a threat to the elimination of HBV provided that vaccination is performed correctly with quality-controlled vaccines (even though rates of non-response are not monitored systematically (for example cancer patients))
- Most persons effectively respond to vaccination, and those at risk for non-response are well delineated and for them treatment guidelines exist; non-response is not a threat to attaining elimination targets
- One issue is persons vaccinated as infants now entering health care occupations; accept their vaccination records as proof of protection or revaccinate? General agreement for vaccination, particularly of those people conducting exposure-prone procedures.
- One group with poor vaccine response is older adults – outbreaks of hepatitis B among persons in residential living facilities - the new Heplisav[®] or other more immunogenic PreS/S vaccines may have a role in this niche market

Impact of low or non-responses to hepatitis B vaccines on public health and achievement of elimination goals – outcome of discussion groups (continued)

Is there a need for an update of guidelines or recommendations?

- Current policies address sufficiently the issues of key populations and management
- Nevertheless, it could be useful to draft recommendations on management of non-responders, covering, for example, monitoring of progress towards elimination goals and seroprevalence studies (including use of dried blood spot testing) seeking inter alia more information on immune memory and protection

What role can VHPB and other stakeholders play in this process?

- VHPB should review whether WHO's recommendations are sufficient, and, if needed, adapt them and work with other stakeholders to promote them
- VHPB could provide educational materials based on policies to help HCWs to manage non-responders (for both testing and vaccination schedules)
- VHPB can also help in disseminating tools developed by others, such as the infographics on patient management developed in Canada (British Columbia Centre for Disease Control) and/or developing new versions
- One group suggested that VHPB convene a one-day technical meeting on measures to bypass non-responsiveness and to evaluate alternative options and new vaccine developments.
- VHPB could stimulate the generation of more data on the risks for non-responders and on outcomes

Occult hepatitis B

- Advances have been made in understanding the molecular and immunological mechanisms of occult HBV infection, including identification of previously unknown exit routes for HBV antigens from hepatocytes
- The recently published Taormina consensus statement on occult HBV infection defines the condition and sets out clinical implications: HBV can be transmitted and infection can be reactivated (in both cases leading to typical hepatitis B) and contribute to progression to cirrhosis and promote HCC development – but results show wide discrepancies, perhaps resulting from use of different diagnostic techniques
- The definition of occult hepatitis agreed at the Taormina meeting is: *The presence of replication competent HBV DNA (i.e. episomal HBV covalently closed circular DNA [cccDNA]) in the liver and/or HBV DNA in blood of persons testing negative for hepatitis B surface antigen (HBsAg) by currently available assays.*
- This definition implies that HBV-infected subjects who did not seroconvert to anti-HBs, became anti-HBc positive but lost detectable HBsAg can still be potential carriers of HBV; moreover, occult HBV may still be present in nuclei of hepatocytes even in anti-HBc+/anti-HBs+ subjects who recover from HBV infection
- Diagnosis: The gold standard is detection of circulating HBV DNA by PCR techniques - probes should cover at least three different genomic regions with primers to detect replication-competent HBV DNA; anti-HBc blood tests can be used as a surrogate marker
- Several challenges need to be overcome, including detection of low HBV DNA levels, variations and reproducibility in HBV DNA concentrations over time, the need for repeated tests, and the lack of reliable surrogates for HBV DNA (resulting in underestimation of prevalence rates); novel or improved tests are being developed (to detect linearized HBsAg and HB core-related antigen)
- Patients at risk for occult HBV infection should require periodic monitoring of alanine aminotransferase activities and HBV DNA concentrations

Occult hepatitis B (continued)

- Despite major advances in securing the safety of blood products, occult HBV infection remains a risk for transfusion-transmitted infections in regions where blood products are only tested for HBsAg (i.e. in donations positive only for anti-HBc; estimated infectious dose is 16-160 HBV virions)
- Protection against occult HBV infection presents an important challenge for blood bankers: the risk of occult HBV depends on several factors, including variable epidemiology, quality and cost of diagnostic tests, design of screening strategies, and the outcome of debates about how to reduce costs of blood testing while ensuring blood safety; it raises also issues about what message to give to blood donors about potential infection

Research required and open questions:

- Development of new antiviral agents which can either eliminate cccHBV-DNA or enhance the immune response to HBV
- Epidemiological and clinical research; better surveillance and detection of HBV mutants
- Immune response to HBV in occult infection, immune control mechanisms and possible pathogenic consequences (fibrosis, cirrhosis and HCC)
- Research on other controls of gene expression than traditional immune responses. i.e. transcriptional and post-translational responses, including autophagy resulting from ER stress and HBV protein X activity, and pathogenetic role of different HBV mutants and defective HBsAg
- Need new methods to distinguish between HBsAg produced by integrated HBV DNA in liver cells and free circulating HBsAg in plasma or serum, and more sensitive, standardized assays for the detection of HBV DNA in hepatocytes

Occult hepatitis B – output of discussion groups

Impact on public health and progress towards achievement of elimination goals for HBV

- The meeting did not identify compelling evidence to support the contention that occult HBV infection will have an effect on **public health and elimination goals**
- The groups agreed that, in view of the risk of HBV reactivation, occult HBV infection deserves greater attention from various disciplines including oncologists, haematologists, internists and infectious disease experts
- One of the hurdles in diagnosing occult HBV or HBV reactivation is poor access to HBV DNA testing and prolonged intervals until blood test results are obtained in many countries
- In many regions epidemiological data on prevalence of HBV have been generated decades ago and impact of vaccination is not always monitored. The groups called for more research on incidence, morbidity and mortality of HBV infection, and on determination of residual risk for blood transfusion
- Diagnostics: the groups called for better methods of detection and promotion of optimal blood transfusion approaches to ensure safety for recipients; and stressed the importance of regulatory aspects of blood transfusion, which vary widely between countries

Occult hepatitis B – output of discussion groups (continued)

Recommendations and guidelines

- Broad endorsement and dissemination of the Taormino statement and guidelines are needed
- Overall, no need for changes to or additional guidelines, but there might be a need to revise current guidelines on blood testing and screening, in relation to local/national prevalence and for a possible revision of guidelines for transfusion
- Vaccination of subjects in advance of transplantation and/or immunosuppressive interventions was recommended
- Better risk assessment is needed, with a modelling study that includes costs
- Further studies are recommended to determine the prevalence of occult HBV infection in the general population (with establishment of denominators), as well as morbidity and mortality rates

Role of VHPB

- A major action for VHPB will be to endorse the Taormina statement and guidelines
- VHPB could produce a report on the issues, including relevance for blood transfusion and stressing the importance for and role of regulatory authorities
- VHPB could advocate and support risk assessment in general population

Extra slide on issues that arose during the groups' discussions on overall potential VHPB and stakeholder contribution:

- Shift focus to supporting countries in developing and/or implementing of their national Hepatitis elimination plans
- Identification for WHO of gaps in knowledge and local expertise by collecting real-life data from different countries, by identifying and facilitating ways to work towards the agreed elimination goals
- Continue working towards ensuring high coverage of the birth dose of hepatitis B vaccine
- Support the monitoring of the performance of programmes towards those agreed elimination goals