Viral Hepatitis Prevention Board

Hepatitis B vaccination:

a completed schedule …

enough to control HBV lifelong?

MILAN, ITALY

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Objectives

- To review long-term efficacy of hepatitis B vaccine and field effectiveness of hepatitis B vaccination programmes
- To review recent data on immune memory induced by hepatitis B vaccine and the anamnestic response after a booster dose
- To examine the occurrence and impact of breakthrough infections
- To review data on potential impact of hepatitis B virus mutants
- To evaluate current hepatitis B booster vaccination recommendations
- To evaluate the role of adjuvants in long-term protection
- To discuss current used definitions, standards and terminology

Background/Context

- Italy: first high-income country to introduce universal HBV vaccination of infants 20 years ago (Bulgaria, Israel shortly after); other programmes (including research programmes) now extend up to 25-30 years (Alaska, Taiwan, the Gambia and Thailand)
- Data from high-, intermediate- and low-endemic countries world-wide show:
  - interruption of perinatal transmission
  - dramatic decreases in prevalence of HBsAg carriers
  - No clinical significant cases of hepatitis B detected
  - fall in incidence of HCC
- in successfully vaccinated subjects, no clinical significant hepatitis B cases were detected for up to 30 years (Alaskan data)
- Dramatic declines seen in Italy in HBsAg carriers in pregnant women from 2,4% at the end of the 1980s to a current figure of about 0,86%; similar results in other countries
- Gambia Hepatitis Intervention Study shows that routine HBV vaccination is very successful, giving a strong signal to the rest of Africa
- Success of hepatitis B vaccine as a public health tool – 179/196 countries have added hepatitis B vaccine to their routine immunization program, even low-endemic countries have also done with the exception of Japan and a few northern European countries, who only target at-risk-populations.

Background/context (continued)

- Rapid take up of vaccine since 1999-2000 (thanks to lower vaccine price and, from 2001 onwards, support from the GAVI Alliance), with high coverage rates widely reported and maintained
- Some policy successes
- Modified approach needed for subjects who do not respond fully to vaccination: the immunocompromised, at-risk groups and health-care workers
- Limitations recognized: data, difficulties in follow-up in cohort studies, source of infection often unknown, missing vaccine history;
- Expected decrease in acute cases and chronic carriers in some countries partially offset by rise in acute and chronic cases in immigrants
- Importance of transmission from infected mothers; and of risk factors for new HBV infections - sexual contact with infected individuals, piercing and tattooing ("beauty treatment"), as well as iatrogenic exposure and injecting drug use; most new cases are in unvaccinated subjects (data from Italy)
- Nevertheless, legitimate question: why hold another meeting after the first VHPB hepatitis B booster meeting in 2004 in Seville? Answers relate to
  - question of "immunity" and "need for booster",
  - "protection" with low or no antibody titres
  - the changing dynamics and epidemiology of HBV following successful vaccination campaigns and the consequent changes in natural exposure – meaning for public health focus
  - complex new immunological findings and knowledge of immune memory
  - questions about number of doses needed

Vaccine efficacy: immune response

- The higher the titre of anti-HBs measured 1-3 months after completion of a vaccination course, the longer antibody persistence and the more likely an anamnestic response is detectable
- Titre and long-term persistence of anti-HBs related to age at vaccination, type of vaccine, route of administration, number and timing of doses, sex, body mass index, smoking and possibly genetics
- Titres of anti-HBs after vaccination decline with time to low or undetectable levels - many studies, including meta-analyses, confirm all these observations
- New adjuvants improving immunogenicity of primary vaccination, but effect on reactogenicity and long-term safety and immunity not yet known
- Doubt has been raised regarding overall immunogenicity and efficiency of Hexavac . However, despite the somewhat lower antibody response, the hepatitis B component was sufficiently immunogenic; vaccinees able to mount an anamnestic responses five years after primary vaccination

Immune memory

- Most fully vaccinated subjects have good immune memory and show strong anamnestic responses after booster vaccine offered 10-20 years later, but antibody titres decline rapidly after boosting that occurs 20-30 years after the primary series.
- Immune memory outlasts antibody persistence; data show immune memory persists for at least 20 years after vaccination (so-called "boostability"); boostability more likely to be weak or absent in individuals with low initial titres
- Immune memory is induced by factors including different vaccine types, and different dosage regimens
- Monitoring antibody response is not adequate for determining long-term immunity
- Compared to the Seville VHPB meeting (2004) there is an increasing number of people with no evidence of boostability (failure to respond to a booster with an anamnestic response); this does not automatically signifies susceptibility to clinically significant HBV disease since no cases of acute hepatitis B or chronic carriers have been found in the follow-up studies.

Breakthrough infections

- The definition of breakthrough infection requires further clarification and standardizing, as it could cover several situations:
  - Failure of post-exposure prophylaxis (e.g. in prevention of perinatal infections)
  - HBV infection in a fully vaccinated subject who originally responded serologically to vaccination
  - Unknown vaccination failure (e.g. use of deteriorated vaccine, or inadequate vaccination procedure)
  - HBV infection in a non-responder
  - Evidence of transient presence of HBsAg, HBV DNA, or seroconversion with transient presence of anti-HBc
  - Occult HBV infection in fully vaccinated subjects may occur but appears to be extremely rarely. It is unknown at present if such breakthrough may also lead to clinically significant hepatitis or development of an HBsAg carrier state
- Characteristics of patients in whom these infections occur often not known but genotype or genetic factors may be a factor

Issues and matters for consideration

- How long will immune memory last? For how long does it exceed the duration of anti-HBs antibodies?
- Does decline of anti-HBs mean waning of immunity and increased susceptibility to HBV infection? Should vaccinees be monitored for anti-HBs levels?
- Anamnestic response - size of, what does absence of such a response mean?
- Vaccine escape mutants (S gene) are currently not a public health concern, monitoring should continue
- Antiviral treatment are increasing selection pressure
- Treatment response and resistance - genetic factors
- Poor vaccine coverage need still improvement in a substantial part of the word.
- Immunocompromised people can be seronegative but have HBV infection/disease - need for monitoring?
- New delivery systems (nanoparticles) effective; more powerful adjuvants - experience from new malaria

Terminology and definitions

- Terms needing clarification or definition: immunity and protection, booster, anamnestic response, immune memory, breakthrough infection, “at-risk” groups, case definitions, …
- Protection - meaning, correlates, figure of anti-HBs <10 IU/l, prevention of transmission, protection against infection vs disease (the public health objective), legal implications (protection of HCWs); what does long-term mean?
- Booster – do we mean any vaccine offered at least 5 years after a complete schedule? Or Exposure to natural infection? Dosis?
- Case definitions: countries appear to use different case definitions for acute, chronic infections e.g. in Europe often 3 case definitions are valid EU, WHO Euro and the country.

Future activities

- Further research on the meaning of the presence and maintenance of cellular and humoral immunity in successfully immunized individuals, is needed and how to translate this into public health (need to differentiate academic research interests from public health priorities)
- Evaluation of different vaccination schedules (are 2 injections given at an adequate interval sufficient to provide long-term protection vs 3 doses?)
- Better understanding of the immunological mechanism of long-term protection, of boostability and failure to respond to boosting, and of reasons for inadequate responses to vaccination
- Studies of whether decline in anti-HBs means increased susceptibility to infection, including long-term follow-up of high-risk groups, especially adolescents reaching age of sexual activity
- Analysis of characteristics of people with breakthrough infections
- Monitoring vaccination programmes to control quality and vaccine effectiveness over longer time

Future activities

- Need for studies in migrant populations to determine epidemiology, acute and chronic disease, potential targeting strategies for vaccination, access to care
- Surveillance of clinical significant diseases after hepatitis B infection and breakthrough infections
- Development of strategies to prevent breakthrough infections
- Surveillance and re-assessment of HCWs for immunity and booster vaccination, with prospective studies for optimal schedule for boosting and formulation of policy about what is considered necessary taking into consideration local medical-legal issues
- Assessment of whether sub-clinical, natural infection boosts immunity/protection - clinical long-term significance of transient infection and carriage?

Future activities

- Studies on mutants, influence of genotype and phenotype, including monitoring, global surveillance networks and evaluation of public health relevance
- Studies on timing and selection of antiviral treatment to prevent mutant formation
- Development of vaccination strategies taking into account mutant formation
- In research, standardization of biological reagents, including tests for T and B cells
- Set up a working group to formulate definitions of terms identified

Conclusions

- There is a critical need for a working group to standardize definitions of terms such as sero-protection, breakthrough, anamnestic response, immune memory, etc. Differences in the use of these terms makes comparison of data difficult and confusing.

- Monitoring coverage is not sufficient – serological surveys of markers of HBV infection (as primary end-points) are needed, supplemented by acute disease surveillance and follow up of long-term cohorts of vaccinees

- Protection against clinical disease and the carrier state repeatedly demonstrated among vaccinees after 20-30 years
- Immune memory outlasts antibody persistence; data show immune memory persists for at least 20 years after vaccination

Conclusions

- The hepatitis B community needs to understand whether persons who have lost detectable antibody and no longer develop an anamnestic response are at risk for clinically significant hepatitis B infections (acute disease and the carrier state). Follow-up studies are not documenting disease but surveillance must continue, as well as studies to better understand the mechanism of protection in these individuals if it exists.
- Decision on an offering hepatitis B vaccine booster should be based, not on the amount of anti-HBs still present, but on appearance of disease in the population
- Based on the current scientific evidence, booster should not be considered for public health immunisation programmes