Hepatitis B vaccine: long-term efficacy, booster policy, and impact of HBV mutants on hepatitis B vaccination programmes

VHPB meeting, Seville,

11-12 March 2004

Immunization programmes

- Programmes protect against clinical **HBV infection** (in principle all genotypes) and **chronic carriage**
- They mitigate the clinical effects of subsequent infections
- They are leading to the elimination of hepatitis D
- Hepatitis B vaccine is a proven anticancer vaccine, reducing incidence of HCC
- Immunization delays the age of susceptibility

- the rationale for this meeting

Objectives of the meeting

- To review long-term efficacy of hepatitis B vaccine and long-term effectiveness of immunization programmes
- To review data on immune memory induced by hepatitis B vaccine
- To update current recommendations booster immunizations
- To review of potential impact of HBV mutants on immunization programmes

The instant conclusion

- Vaccine is effective in protecting against clinical disease and carrier status for at least 20 years
- Vaccine programmes are highly effective
- No apparent need for boosters
- HBV mutants have little public health significance
- Continue to monitor regularly- if in time significant disease develops, revise recommendations

Conclusion

- Vaccine is effective in the long-term
- Vaccine programmes are highly effective
- Immune memory involves T and B cells
- No apparent need for boosters
- HBV mutants have little public health significance

- but …

Overview

Sense of déjà vu in topics of discussion

- boosters
- immunization doses and schedules
- maternal screening and HBIG
- humoral and cell-mediated immunity
- definitions – anamnestic response, protection, …
- the contrasting needs of public health, individuals and science

General observations

- Focus of the meeting was on **universal vaccination programmes**; issues such as health-care workers and at-risk groups for further, later discussion
- Wide geographical variations between countries and regions:
  - Status of public health and medicalization of public health matters
  - Responses to hepatitis B (e.g. Italy's pioneering role in Europe; Taiwan's and Gambia's prompt and early action)
  - Policies on immunizations and schedules (e.g. Canada's patchwork quilt)
  - Policy-making mechanisms (democracy or decree)
- There is much we still do not know

Long-term efficacy and programme effectiveness

- Many studies in different and varied settings, reflecting public health and scientific interest (helping to assure funding), show long-term efficacy of vaccine
- Taiwan/Singapore: success – greatly reduced rates of HBsAg, HCC, fulminant hepatitis
- Gambia: success – circumstances not typical but efficacy proven
- No change in Taiwan or Gambia in immunization programme – no booster
- Alaska, Catalonia, Italy, Saudi Arabia, Italy - again successful stories

Long-term efficacy and programme effectiveness

- Almost all adequately vaccinated individuals have shown evidence of immunity in the form of persisting anti-HBs and/or in vitro B-cell stimulation or an anamnestic response to a vaccine challenge
- No data to support the need for booster doses in immunocompetent individuals who have responded to a primary course

Long-term vaccine efficacy and programme effectiveness – issues

- Issues to emerge:
  - There may be different recommendations for countries with different levels of HBV endemicity
  - Long-term perspective needed with chronic infection and consequences (40 years for HCC)
- Value of universal immunization stressed

Long-term vaccine efficacy and programme effectiveness – research topics

- Consequences of using HBIG and vaccine together need to be further determined:
  - added value of HBIG in preventing perinatal transmission
  - does it impact (or possibly decrease) long-term immune memory?
  - (possible role in emergence of mutants)
  - does it decrease fulminant hepatitis B in infants?
- What are the baseline data on incidence of fulminant disease?

- All areas for further research

Long-term vaccine efficacy and programme effectiveness – issues

- Common themes that emerged as needing more consideration:
  - Need for longitudinal data; difficulties with collecting and analysing data
  - High drop out rate, and difficulties in tracing, in follow-up studies
  - Result of primary immunization not always known, later questions about responders and non-responders
  - Much consideration needed before decision taken to give a booster vaccination to a cohort – irreparable damage to the study group

Long-term protection – problems in interpretation

- Needs long-term follow up looking for breakthrough infections and study of humoral and cell-mediated immune basis of memory
- Need to distinguish between subclinical and breakthrough infection
- Proposals for definitions of breakthrough and anamnestic response made – acceptable?
- More follow up studies of more than 15 years needed and are in the pipeline
- Number of vaccinees available for follow up shrinking; data become less significant
- Need for standardization of confirmation of laboratory tests

Immune memory

- Research will be of value for other viral vaccines
- HBsAg-specific humoral and cell-mediated immunity well established in vaccinated individuals
- Strong B cell antigens in chronic infection lead to virus neutralization and protective immunity; weak helper T cell and CTL antigens in chronic infection
- Primary immune response a good predictor of the quality of immune memory
- In low endemicity countries, risk of hepatitis B is declining, partially as a consequence of successful vaccination programmes; clinically significant breakthrough infections (sign of waning immunity) will be rare

Immune memory and responses - issues

- Definitions needed:
  - booster (e.g. is third or fourth dose in HB vaccine schedule a booster?); what is the end-point?,
  - natural boosting (may be missed with long sampling intervals) – sceptics and believers in its importance in protecting populations
  - anamnestic response (B- and T-cell responses, clonal selection – role of ethnicity), need to standardize; what is a "delayed anamnestic response"?
  - timing of blood sampling
  - what is the meaning of titres of 1-9 IU/l?

Immune memory and responses - issues

- Reliable, sensitive and easy-to-perform cellular tests needed for immune memory, rather than anamnestic response to revaccination
- Has immunization changed the pattern of immune responses?
- Need to assess status in adolescents exposed to risk and despite loss of HBsAg
- Is antigen sequestered? – could explain weak CTL response
- Immune responses in infants (2 m) better than newborns, and adolescents have better responses than infants (Italian study)

Vaccinations and boosters - issues

- Many studies indicate no need for booster, but further information needed:
  - clinical data on disease burden before any recommendation or decision to boost can be made
  - non-responders – masking early infections?
  - protection/protective levels of antibody – meaning, definition, timing of measurement
  - data on acute cases as measure of protection given by vaccine (but very low rates of acute disease seen)
  - anti-HBsAg rates: different rates of decay; are sustained rates influenced by natural boosting?; are peak GMTs important? (measure level of disease instead?)

Booster response

- Can we use an anamnestic response as a proxy for the presence of immune memory?
- What is the meaning of non-response to a challenge in terms of protection? – does a lack of response mean no protection?

Booster vaccination recommendations

- "To date there are no data to support the need for booster doses of hepatitis B vaccine in immunocompetent individuals who have responded to a primary course."

  Lancet, 2000; 355:561-565
- Booster doses are not (currently) recommended (CDC, VHPB, WHO …) – still valid
- The group reviewed data at 20 years since the licensing of the vaccine and included that no booster dosis are needed

Mutants

- Not a major public health problem currently
- Many mutants seen – some conservative, others (vaccine escape, in MHR) cause drastic changes and lack of neutralization
- Some transient, some stable
- Coexist with wild-type; part of viral quasispecies
- HBsAg and anti-HBs co-exist
- Resistance to antivirals common
- High rates seen in Asian studies, but numbers small (compared with possible figures in failures of initial vaccination)

Mutants – future action/issues

- Questions about selection pressure; will mutants come to dominate and when? – further research
- Is there a need to prepare strategies for eventualities?
- Is there a need to improve antigenicity of current vaccines and assays?
- Study of transmissibility, infectivity and any burden of disease
- Establish independent global network for appropriate monitoring of escape mutants (vaccine, treatment, diagnosis)

General recommendations

- Set up a working group to formulate definitions of terms identified
- Further studies to seek and evaluate clinical data needed for decisions on boosters – more and continued follow-up
- Identify and standardize cellular correlates of protection and correlate results with anamnesis