Technical workshop: hepatitis B vaccines

Schedules, dosages, interchangeability

Pierre Van Damme, MD, PhD
Viral hepatitis Prevention Board
Centre for the Evaluation of Vaccination
WHO Collaborating Centre
University of Antwerp

Vaccine Preparations

- Available since 1982
- Highly purified preparations of HBsAg (since 1986)
- Aluminium phosphate or hydroxide, as an adjuvant
- In some vaccines thiomersal as preservative,
  - to avoid contamination during development
  - to avoid contamination in multi-dose vaccines
  - Increasing number of vaccines that are thiomersal light or thiomersal free (requested by FDA and strongly encouraged by EMEA)

Thiofree vaccines

Albania		Engerix			
Andorra	hbvaxpro	Engerix			
Armenia					Euvax B
Austria	Hbvaxpro	Engerix			
Azerbaijan		Engerix			
Belarus					
Belgium	Hbvaxpro	Engerix			
Bosnia and Herzegovina		Engerix			
Bulgaria		Engerix			Euvax B
Croatia		Engerix			
Czech Republic		Engerix			
Denmark	Hbvaxpro	Engerix			
Estonia	DNA recombinant***				
Finland	Hbvaxpro	Engerix			
France	Hbvaxpro	Engerix	Genhevac		
Georgia					
Germany	Hbvaxpro	Engerix			
Greece	Hbvaxpro	Engerix			
Hungary	MVD/Recc	Engerix		MVD**	
Iceland					
Ireland	Hbvaxpro	Engerix			
Israel		Engerix			
Italy	Hbvaxpro	Engerix			
Kazakhstan					
Kyrgyzstan					Euvax B
Latvia		Engerix			Euvax B
Lithuania		Engerix			
Luxembourg	Hbvaxpro	Engerix			
Malta		Engerix			
Monaco	Hbvaxpro	Engerix			
Netherlands	Hbvaxpro	Engerix			
Norway	Hbvaxpro	Engerix			
Poland	MVD/Recc	Engerix		MVD**	
Portugal	Hbvaxpro	Engerix			
Republic of Moldova		Engerix			Euvax B
Romania		Engerix			
Russian Federation		Engerix			
San Marino	Hbvaxpro	Engerix			
Slovak		Engerix			
Slovenia		Engerix			
Spain	Hbvaxpro	Engerix			
Sweden	Hbvaxpro	Engerix			
Switzerland	Hbvaxpro	Engerix		HBVaxII**	
Tajikistan					
TFYR Macedonia					
Turkey	MSD	Engerix		MVD**	
Turkmenistan					

Thio+

**simultaneous availability of thio+ and thio-free from same company

Thiomersal

- European Technical Advisory Group of Experts on Immunization (ETAGE, 2004):
  - Endorses the continued use of hepatitis B vaccines in national immunization programmes, including administration of thiomersal containing and thiomersal-free vaccines to newborns for prevention of perinatal transmission.

Hepatitis B: thermo-stability

- Shipped and stored at 2-8 °C
- Freezing should be avoided
  - Dissociation of antigen and alum adjuvant
  - Changes in 3-dimentional structure of Ag
- hepB vaccine tolerates temperatures up to 45°C for 1 week, and up to 37°C for one month without changes of immunogenicity or reactogenicity

Vaccine Preparations

- All vaccines available through UNICEF are quality controlled
- manufacturing plants checked by experts from WHO, UNICEF and academia
- all HBV vaccines are safe, equivalent and very efficacious
- Although the antigen content may differ, hepatitis B vaccines are interchangeable (also between plasma-derived and recombinant)

  (ref. Seto et al. Ped Inf Dis J, 1999)

schedules

- traditional schedules: 0,1,6 or 0,1,2,12 month
  - End result is equal
- CDC recommendations:
  - Minimal 4 weeks between 2 primary injections
  - Dose 3/last dose of primary schedule, at least 2 months after dose 2/previous dose
  - Dose 3/last dose of primary schedule, at least at age of 6 months for infants
  - Schedule: 2,4,6 months
  - Minimal 4 months between dose one and dose3/last dose of primary schedule
  - Examples of shortest schedule: 0,1,4 month – 0,2,4 month

schedules

- Schedule is very flexible
- As many schedules as countries/regions
- even with shorter schedule (than what is recommended by CDC), we are confident that the programme confers protection
    - thus, EPI schedule perfectly acceptable to offer hepB vaccine (6, 10, 14 weeks)
    - fits in existing national programme
- first priority:
  - adapt the hepB schedule to the existing infant immunization programme in the country

Differences in primary schedules illustrates the flexibility of schedules

EU countries (in months)

- 3.4.5.12
- 3.5.12 (2)
- 3.5.11 (2)
- 3.4.5.20
- 2.3.4.15
- 2.3.4.16
- 2.3.4.11 (3)
- 2.4.6.18
- 2.4.6.15 (3)
- 2.4.6
- 2.3.4.

CEE countries (in month)

- 3.4.5.12
- 3.4.5.18
- 3.5.11
- 3.5.12
- 3.4.6.24
- 3.4.5.36
- 3.4.6.18
- 3.41/2.6.18

2.3.4.24
2.3.4.15
2.4.6.15
2.3.5.16
2.4.6.12

table: different schedules in Europe
(source: Eurohepnet project: www.eurohep.net)

Age	**scheme**	**Country**
0-12 hours	0.1.5	Israel
	0,1,6	Bulgaria, Poland, Estonia, Latvia
	0,2,6	Romania
2-3 days	0,1,6	Lithuania
1-2 m	0.2.9	Luxembourg
2m	0,1,6	Germany, Slovakia
3 months	0.2.8	Italy
	0,1,2	Austria
6-7 years	0,1,12	Slovenia
9 years	0,1,6	Malta, Romania
10 years	0,1,6	Germany
11-12 years	0,1,6	Belgium
12 years	0,1,6	Czech republic, Italy, Lithuania, Bulgaria, Estonia
14 years	0,1,6	Hungary, Poland
3 months	0,1,13	Belgium

Flexibility of schedules

- Not necessary to restart the hepB vaccination series, if interval between doses has been extended
- If a child doesn't show up at the immunization visit, the dose should be given at the next visit

hepB vaccine: dosage

- there is no international standard of vaccine potency expressed in mcgr of HBsAg protein
- the relative efficacy of different vaccines cannot be assessed on the basis of differences in HBsAg content
- thus, hepB vaccines are no generic products but the result of different production processes typical for each manufacturer

Prevention of perinatal transmission

- Offer hepB vaccine as soon as possible after birth, within 12-24h
- As a monovalent vaccine
- Efficacy of hepB vaccine offered later than 24h declines over time

  (ref: Marion et al. Am J Epidemiol, 1994)
- If specific hepBIg available, simultaneous administration, at an other injection site
  - Adds 2-3% protective efficacy (97% vs. 95%)
- Birth dose hepB can be combined with birth dose BCG (even increases the hepB antibody response)

  (ref. Ota et al.)

Hepatitis B vaccines

- Can be administered simultaneously with any inactivated or attenuated vaccine (other injection site): DTP, OPV, HepA, Hib, BCG, measles

  (ref: Centres for Disease Control and Prevention. MMWR, 2002.)

  (ref: WHO doc: WHO/V&B/01.31)
- No reason to postpone hepB immunization because of the administration of other vaccines
- FAQ:
  - BCG at birth and hepB at birth: no problem
  - Law: to respect 6 weeks after BCG administration, no real medical evidence for that

Simultaneous administration

- There are no contraindications to simultaneous administration
  - of two inactivated vaccines
  - An inactivated and an attenuated vaccine
- No decreased antibody response nor increased rates of adverse events

Strategies to Prevent Perinatal HBV Transmission

Selective Immunoprophylaxis

- Screen pregnant women for HBsAg
- Give prophylaxis to neonates of HBsAg+ mothers

Pros

- prophylaxis targeted to neonates that need it
- can administer both HBIG/HepB vaccine

Issues

- Requires extensive resources to screen pregnant women/track infants of HBsAg+ mothers
- Programmes not always succesful

Strategies to Prevent Perinatal HBV Transmission

Integrate as Component of Universal Infant Vaccination

- Vaccinate all neonates beginning at birth

Pros

- No need to screen pregnant women
- Very feasible to implement if a high proportion of neonates are born in health care facilities or accessible

Issues

- Need to assure effective HepB vaccine delivery for all neonates

WHO point of view

- Universal vaccination of all infants as an integral part of the national immunization program is the highest priority in all countries

- whenever feasible and according to the local epidemiology, countries should incorporate prevention of perinatal HBV transmission
  - by beginning vaccination of all infants at birth
  - screening pregnant women and provide PEP to exposed infants

WHO point of view

- Prevent perinatal HBV transmission:
  - relative contribution of perinatal transmission to the overall disease burden of HBV (HBeAg prevalence)
  - the feasibility of delivering the first dose of hepatitis B vaccine at birth (<12h.)
    - monovalent HB vaccine must be used at birth
    - HB combination vaccines cannot be used at birth (waste of combination vaccine)
      - Non-hepatitis B components have reduced immunogenicity in children less than 6 weeks of age

Universal HBV vaccine programmes

- 22 out of 43 countries (regions in countries) have a newborn programme
  - because of high or intermediate endemicity
  - because they have no screening programme for pregnant women
  - to save costs of such a screening programme
  - to ensure a higher coverage
  - to start protection at birth

Options for adding hepatitis B vaccine to immunization schedules

Age	*visit*	*HBV1*	*HBV2*	*HBV3*
birth	0		HepB0	HepB0
6 weeks	1	HepB1	HepB1	HepB1
10 weeks	2	HepB2	HepB2	
14 weeks	3	HepB3	HepB3	HepB2

Hepatitis B vaccines

- Perfect safety profile
- Rapid seroconversion & seroprotection
- High level of seroprotection
  - Especially in newborns, infants, children and adolescents (98%)
  - > 95% recipients achieve seroprotection (in healthy adults)

- Very immunogenic in all age groups
- Confers lifelong protection when offered at young age
  - No booster policy for universal hepatitis B vaccination programmes (triggers antibodies and immune memory)

Long-lasting protection: implications

- European consensus group on hepatitis B immunity (October 1998, Florence), Lancet 12 Feb. 2000:
  - no need for booster doses in immunocompetent individuals
  - HB booster vaccination to be considered for mmunocompromised individuals:
    - haemodialysis
    - chronic renal failure/liver disease
    - HIV positive
    - …

Long-lasting protection: benefits

- Maintains immunity in the population
- Reduces morbidity and mortality
- Reduces transmission in the population

- Reduces direct and indirect costs of booster vaccination programs