WHO Hepatitis B Booster Policy

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World Health Organization

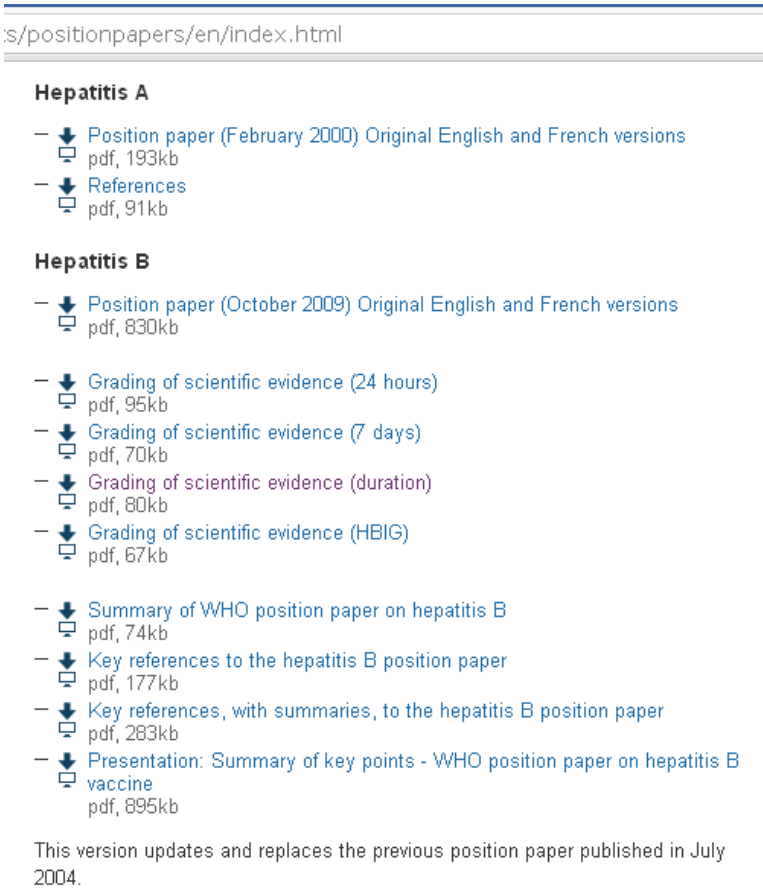
GLOBAL hepatitis PROGRAMME

WHO Vaccine Position Paper

- primarily large-scale immunization programme issues
- individual protection not emphasized
- summarize essential background information
- conclude with WHO position concerning use in global context
- reviewed by experts inside and outside WHO
- designed for use mainly by national public health officials and immunization programme managers
- published in Weekly Epidemiological Record and on website

WHO vaccine position papers

- Process started in 1998
- Each vaccine preventable disease
- Key reference documents
  - Available in all official languages
  - Convergence of all WHO policy for a specific vaccine
- On-line catalogue: www.who.int/immunization/documents/en


s/positionpapers/en/index.html

Hepatitis A

- Position paper (February 2000) Original English and French versions pdf, 193kb
- References pdf, 91kb

Hepatitis B

- Position paper (October 2009) Original English and French versions pdf, 830kb
- Grading of scientific evidence (24 hours) pdf, 95kb
- Grading of scientific evidence (7 days) pdf, 70kb
- Grading of scientific evidence (duration) pdf, 80kb
- Grading of scientific evidence (HBIG) pdf, 67kb
- Summary of WHO position paper on hepatitis B pdf, 74kb
- Key references to the hepatitis B position paper pdf, 177kb
- Key references, with summaries, to the hepatitis B position paper pdf, 283kb
- Presentation: Summary of key points - WHO position paper on hepatitis B vaccine pdf, 895kb

This version updates and replaces the previous position paper published in July 2004.

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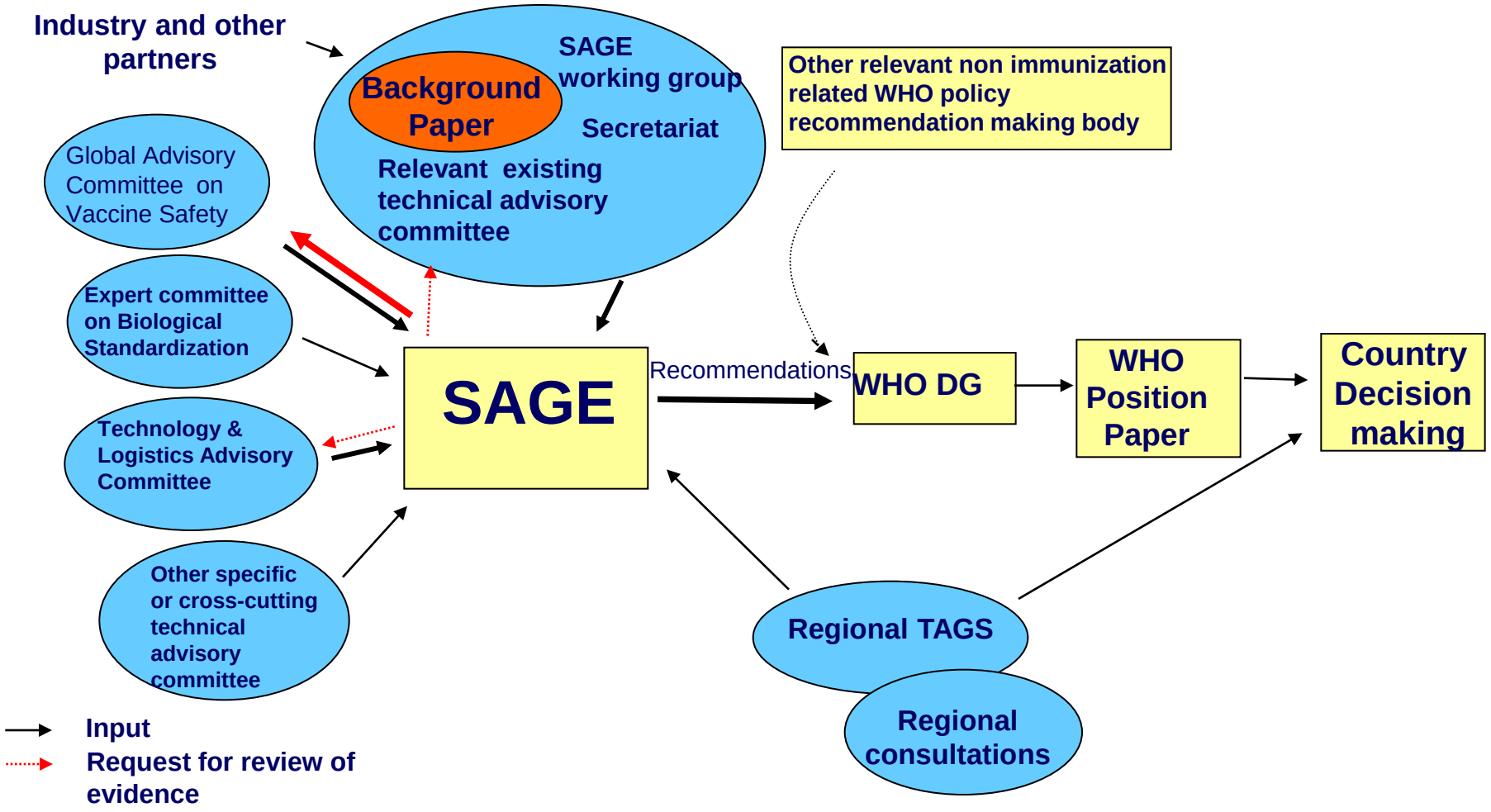
Pathways for WHO Recommendations on Vaccine Use



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PP Development and Updating Process

- Developmental and review process
  - Editorial Board staffed by consultant and IVB staff
  - Literature review, background paper, immunological basis of immunization modules
  - Draft circulated to global experts, regions, interested parties, industry, SAGE working group, SAGE members
  - Revised draft to SAGE members and others on as needed basis
  - Key recommendations agreed by SAGE. Plenary discussion before or after draft paper
- Process compliant with WHO "Guidelines for Guidelines" and WHO Guideline Review Committee

WHO Guidelines for Guidelines

- For principle and/or controversial recommendations:
  - Synthesis of all available evidence
  - Evidence summaries using standard template
  - Formal assessment of quality of evidence
  - Consideration of resource use and costs
  - Linked evidence to recommendations, explaining reasons for judgements
- System for assessing evidence for interventions: GRADE (www.gradeworkinggroup.org)
- Adaptations to GRADE for immunization PP

WHO Position on Hepatitis B Vaccine, WER, 2004

- "Following the primary vaccination schedule, almost all children are protected, probably for life, without the need for booster injections."
- However, "data on the duration of immunity, while substantial, remains incomplete"

RCT: Gambia Hepatitis Intervention Study

- van der Sande et al. Long-term protection against HBV chronic carriage of Gambian adolescents vaccinated in infancy and immune response in HBV booster trial in adolescence. PLoS ONE. 2007 Aug 15;2(1):e753.

- 15 year follow-up
  - Nested RCT: anti-HBs response to HepB boost
  - 492 fully vaccinated as infants, born 1988-1989, identified and matched with original GHIS database

- VE (95% CI) 67.0 (58.2–74.6) against anti-HBc and 96.6 (91.5–100) against HBsAg.

GHIS Analysis (cont.)

- VE against carriage remained high at 15 years of age, similar to previous study at 9 years of age (94% and 97% respectively)
- VE against any infection declined from 82% at 9 years of age to 67% at 15 years of age
- More than 2/3rds of 15 year olds did not have detectable anti-HBs levels, similar to previous observations at 9 years of age

Observational Data

- Review in 2005 by Fitzsimons et al cited 26 studies demonstrating protection 4-15 years following primary vaccination with HepB vaccine
- Eleven additional studies identified evidence of protection as long as 22 years post-vaccination published since 2005-2008 (English literature)
- Total of 37 observational trials using both PDV and RV demonstrated consistent results in regard to long-term protection against infection

Observational Studies

Country/region (group/vaccine)	Years of follow-up	*n*	[Anti-HBs] ≥ 10 mIU/ml (%)	Anti-HBc positive (%)	HBsAg Positive (%)
Micronesia (infants)	15	105	40	7.6	0
Alaska (infants)	15	37	5	0	na
Gambia (infants)	15	1099	13.8[1]	10.1	0.7
Saudi Arabia (infants)	16-18	1355	38	0	0
Taiwan (infants)	20	843	33.6	2.7	1.4
Hong Kong (infants)	22	318	76.5/52.4	?	0

Immunological Basis for Long-term Protection

- Rapid waning anti-HBs following primary immunization
- Half of responders have anti-HBs loss in 5-15 years
- Immune memory persists during long time (despite anti-HBs)
- Immune memory demonstrated among vaccine responders as long as 23 years

Immunological Basis for Long-term Protection (cont.)

- 67% to 76% of vaccine responders demonstrated anamnestic response following booster dose
- Given long incubation of HBV, stimulation of memory cells should trigger sufficient antibody to prevent clinical consequences of HBV infection
- Very few cases of chronic HBV infections in vaccinated cohorts documented
- No clinical HBV disease observed 15-20 years post vaccination

Evidence for Long-term Protection

Quality assessment						Summary of Findings	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Quality	
hepatitis B infection (follow-up mean 15 years; anti-HBc)							
1[1]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness[3]	no serious imprecision	⊕⊕⊕⊕[2] HIGH	CRITICAL
chronic hepatitis B infection (follow-up mean 15 years; HBsAg)							
1[1]	randomized trials	no serious limitations	no serious inconsistency	no serious indirectness[3]	no serious imprecision	⊕⊕⊕⊕[2] HIGH	CRITICAL
hepatitis B infection and chronic infection (various follow-up; anti-HBc and HBsAg)							
34[3]	observational study	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	⊕⊕OO LOW	CRITICAL

Evidence for Long-term Protection

- Should primary hepatitis B series be used for long-term protection against hepatitis B virus infection?

- Evidence for LT protection of HepB by outcome:
  - High quality evidence to support effectiveness of a primary series of HepB to prevent any HBV infection at 15 years post vaccination of infants.
  - High quality evidence to support effectiveness of a primary series of HepB to prevent chronic HBV infection at 15 years post vaccination of infants.
  - Low quality evidence to support effectiveness of a primary series of HepB to prevent HBV infection at up to 22 years post-vaccination of infants.

Cautionary Note

- In several recent observational trials of individuals vaccinated at birth, the response (anti-HBs) to booster HepB at 13-15 years of age, was ~50%
  - Micronesia (Bialek, PIDS 2008) – n=105
  - Alaska (Hammett, Vaccine 2007) – n=37

WHO Position on Hepatitis B Vaccine, WER, 2009

- HBsAg-carrier status or clinical HBV-disease rarely occurs among successfully vaccinated individuals even when the anti-HBs concentrations decline to ≤10 mIU/ml over time.
- Even absent anamnestic response following booster may not signify susceptibility to HBV in such individuals.
- HepB highly efficacious in reducing the HBsAg positivity rate 15–18 yrs after a 4-dose infant HepB (Taiwan), despite 63% vaccinees with no anti-HBs; and anti-HBs undetectable in 29% after booster dose.

WHO Position on Hepatitis B Vaccine, WER, 2009

- RCT (Gambia) showed infant vaccination provided 15 years protection against HBsAg carriage
- Observational studies show effectiveness of HepB in preventing infection up to 22 years post-vaccination of infants
- Although knowledge about duration of protection of HepB incomplete, including knowledge on potential role of natural boosting, no compelling evidence for recommending HepB booster dose in routine immunization programmes.

Thanks

2009 WHO Position Statement I

- All regions/associated counties should develop goals for HBV control appropriate to their epidemiologic situations
- Control goals essential for regions and countries with intermediate/high endemicity of HBV infection or significant subpopulations with these levels of infection
- Serologic surveys of HBsAg serve as primary tool to measure impact of immunization and achievement of the control goals supplemented by acute disease surveillance and mortality data

2009 WHO Position Statement II

- In all regions of the world, all infants should receive the first dose of HepB as soon as possible (<24 hours) after birth. This should be followed by two or three doses to complete the series
- Immunization programmes should work with maternal and child health programmes to promote the administration of HepB birth dose (HepB_BD)
- Timely delivery of HepB birth dose (<24 hours) should be performance measure for all immunization programs