Cost-Effectiveness Updates and Hepatitis B Vaccine Long-Term Protection Studies

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Overview

- Updates to cost-effectiveness analyses
  - Identifying vaccine non-responders (healthcare personnel [HCP] with primary vaccine failure)
- Long-term protection studies
  - Continuing hepatitis B (HepB) vaccine-induced protection

Identifying Vaccine Non-Responders Background

- Increasing proportion of HCP vaccinated in infancy and adolescence
- Post-vaccination testing for protection
  - Not recommended after routine vaccination
  - Recommended for HCP who are at ongoing risk for percutaneous injury[1]

[1]MMWR 1997

Seroprotection as Surrogate of Hepatitis B Protection

- HepB vaccine-induced antibody to hepatitis B surface antigen [anti-HBsAg] ≥10 mIU/mL correlates with priming for immune memory when measured soon* after completion of vaccination series
- Anti-HBs <10 mIU/mL identifies poor response and non-response

*Usually 1-2 months after series
West DJ. Vaccine 1996;14:1019-27

Limitation of Post-Vaccination Testing for Identifying HepB Vaccine Response

- Anti-HBs wanes over months, years
- Anti-HBs <10 mIU/mL at time distant from vaccination does not distinguish[1,2]
  - Responders (protected) >90%,
  - Non-responders (susceptible) <10%
- Substantial proportion of new HCP with anti-HBs <10 mIU/mL expected

[1]MMWR 2005
[2]Or have chronic HBV infection

Approaches for Identifying HepB Vaccine Response among Vaccinated HCP[1]

- Pre-exposure evaluation for protection
- Post-exposure management with evaluation for continuing protection

[1]Applies to both trainees and non-trainees

Pre-Exposure Evaluation

- Anti-HBs ≥10 mIU/mL: No post-exposure prophylaxis for hepatitis B
- Anti-HBs <10 mIU/mL: 1 dose HepB vaccine (challenge dose), re-measure anti-HBs
  - Anti-HBs <10 mIU/mL: 2 more HepB doses to complete revaccination, re-measure anti-HBs
  - Anti-HBs <10 mIU/mL: Susceptible HCP counseled to seek post-exposure management for exposures*

*Unless previously hepatitis B virus infected

Post-Exposure Management and Evaluation for Continuing Protection

- No management prior to blood and body fluid exposure
- Post-exposure management
  - Simultaneous testing of HCP for anti-HBs, and source patient for hepatitis B surface antigen (HBsAg)
  - HCP with anti-HBs <10 mIU/mL revaccinated (± HBIG)

HBIG = Hepatitis B Immune Globulin

Cost-Effectiveness Analyses

- Model and inputs previously described (ACIP, June 2012)
- Results listed separately for trainees and non-trainees

Definition of Healthcare Trainees

- Persons entering school and/or obtaining new job skills that involve contact with patients or with blood or other body fluids (BBF) from patients in a healthcare, laboratory, or public-safety setting[1]

[1]Provisional Work Group definition adapted from MMWR. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. June 29, 2001/50(RR11);1-67.

Difference in Trainees Relative to Non-Trainees

- Younger by 10 years
  - Higher total medical costs, QALY losses
- Higher probability of blood, body fluid exposure
- More likely HepB vaccinated at age <1 year
  - More rapid waning of post-vaccination antibody
  - Smaller proportion* responds to challenge dose of HepB vaccine
  - Open to different interpretations of protection

* HCP with anti-HBs <10mIU/mL at time distant from vaccination

Cost-Effectiveness Analyses Original Model

- Assumed protection when antibody to hepatitis B surface antigen (anti-HBs) ≥10 mIU/mL in persons with documented HepB vaccine series
  - At any time of measurement; initially, after a challenge dose, or revaccination
- HCP assumed unprotected until seroprotection established with anti-HBs ≥10 mIU/mL

Cost-Effectiveness: Original Model
Protection if Anti-HBs ≥10mIU/mL†

	Pre-exposure		Post-exposure	
ICER*	1st year	10 years	1st year	10 years
Trainees	$247,754	$42,275	$128,565	$57,756
Non-trainees	$692,833	$169,334	$360,416	$252,970
HBV infections (per 100,000)**				
Trainees	4	--	47	--
Non-trainees	0	--	7	--

†At any time after a hepatitis B series, including after a challenge dose
*ICER=incremental cost-effectiveness ratio
**Estimated rate of infections with strategy

Recombinant HepB Vaccine ≥3-Dose Primary Series

- Proportions seroprotected by age at vaccination*
  - ~95% of healthy term infants (vaccination starting at birth)[1]
  - >90% HCP <40 years[2]
  - ~85% HCP ≥40 years[2]

*Anti-HBs testing ~1-2 months after completion of HepB vaccination

[1]MMWR 2005 [2]Averhoff F et al. Am J Prev Med 1998

Cost-Effectiveness Analyses Revised Model-95% Protection

- Request (June 2012) for revised assumption of protection based on proportion of infants seroprotected in clinical vaccine trials
- Anti-HBs test results not required for determining protection
- Model retains costs of testing, revaccination

[1]Anti-HBs = Antibody to hepatitis B surface antigen HBsAg= hepatitis B surface antigen; marker of current infection

Cost-Effectiveness: Revised Model
(95% Protection Regardless of Anti-HBs Level)

	Pre-exposure		Post-exposure	
ICER	1st year	10 years	1st year	10 years
Trainees	$4,542,467	$893,619	$2,270,801	$917,859
Non-trainees	$3,149,183	$796,140	$1,610,998	$1,114,364
HBV infections (per 100,000)*				
Trainees	0.7	--	3.0	--
Non-trainees	0.4	--	1.7	--

ICER=incremental cost-effectiveness ratios
*Estimated infections with strategy

Summary
Cost-Effectiveness Analyses

- ICERs sensitive to assumptions of vaccine-induced protection
- First year ICERs* substantially higher than 10 year ICERs regardless of assumption of protection
  - Pre-exposure approach more cost-effective in the long-term
  - Post-exposure approach is more cost-effective in the short term

*ICERS = incremental cost-effectiveness ratios

Long-Term HepB Vaccine Protection

- Ensuring hepatitis B protection for remotely vaccinated HCP relies on continuing vaccine-induced protection during the healthcare career
- 18-20+ years approximate age of matriculation for many HCP trainees, new HCP hires
- Evidence for long-term protection after infant vaccination approximately 20 years
  - Populations with increased prevalence chronic hepatitis B virus infection

Infant HepB Vaccination (Starting at Birth)

- Prevent perinatal and early childhood hepatitis B infection
  - Chronic hepatitis B virus infection (~90% infants, ~30% children <5 years versus ~ 6% adults)
  - Premature death ~25% (cirrhosis, liver failure, hepatocellular carcinoma)
- Reductions in chronic hepatitis B infections
- ≥70% reduction in hepatocellular carcinoma before age 20 years

McMahon BJ. Hepatology 2011;54:801-7; Chang M-H et al. JNCI 2009;101:1348-55; Wichajarn K et al. Asian Pacific J Cancer Prev 2008;9:507-10; Sun Z et al. Cancer Detect Prev 1991;15:313-8; Zun Z et al. Vaccine 2011;29:7835-41.

Long-Term Outcomes of Persons HepB Vaccinated during Infancy References

[1]McMahon BJ et al. Ann Intern Med 2005;142:333-41

[2]McMahon BJ et al. J Infect Dis 2009;200:1390-6

[3]Poovorawan Y et al. J Viral Hepat 2011;18:369-375

[4]Zhu C-L, et al. Vaccine 2011;29:7835-41

[5]Ni Y-H et al. J Hepatology 2012;57:730-5

[6]Lai M-W et al. Gastroenterology 2012:on-line

[7]Su F-H, et al. Vaccine 2007:25:8085

Populations and Vaccines

Population	Chronic Hepatitis B Endemicity*	Dates of Vaccination	Vaccine type - Number of Doses
Alaska Native[1,2]	Intermediate	1981-1982	Plasma-3
Thailand [3]	High	1986 -1988	Recombinant-4
Qidong, China[4]	High	~1980	Plasma-3
Taipei, Taiwan[5]	High	1984 -1992	Plasma-4
Taoyuan, Taiwan[6]	High	1984 -1986	Plasma-4
Northern Taiwan[7]	High	~1986 or later	Plasma-4

* Substantial declines during the follow-up period

Design, Subjects, Age at Vaccination

Population	Design	Initial Number of Subjects	Age at Vaccination
Alaska Native[1,2]	**Cohort**- persons in 15 villages	1578 (246 ages <5 yrs)	**>6 months - 50+ years**
Thailand [3]	**Cohort**-vaccine trial	222	Birth
Qidong, China[4]	**Cohort**-vaccine trial	806	Birth
Taipei, Taiwan[5]	**Seroprevalence**- convenience sample	>1000 per survey ~10-400 per age group	Birth
Taoyuan, Taiwan[6]			
Northern Taiwan[7]	**Seroprevalence**- college enrollees	843	Birth

Follow-up Schedules

Population	Schedule of Follow-up Serologic Testing
Alaska Native[1,2]	Annually, years 1-11; then year 15, 22
Thailand [3]	Annually, years 1-20 (excluding year 11 and 16)
Qidong, China[4]	Years 1, 5, 10, 20, 24
Taipei, Taiwan[5]	1 x convenience sample
Taoyuan, Taiwan[6]	1 x convenience sample
Northern Taiwan[7]	1 x college entrance

Age, Number of Subjects at Last Follow-up, Record of Vaccine History

Population	Period (years)	Age (years)	No. of Vaccine Recipients in Final Report	Record of Vaccination
Alaska Native[1,2]	22	22->70	**493** (31% of cohort)	Medical
Thailand [3]	20	mean 19.6	**109** (49% of cohort)	Study
Qidong, China[4]	24	24	**219** (24% of cohort) uninfected at age 5 years	Study
Taipei, Taiwan[5]	25	20-24	**583**	Personal; national database
Taoyuan, Taiwan[6]	>18	18-21	**35**	Not stated
Northern Taiwan[7]	20	18-21	**843**	Personal

Exclusions

Population	Received Booster Dose HepB Vaccine	Known Infected, e.g., Perinatal	Vaccine *Non*-Responder
Alaska Native[1,2]	Excluded	Excluded	Excluded
Thailand [3]	63% (69/109) received booster at age 5 years	Excluded	Excluded
Qidong, China[4]	Excluded	Excluded (28 infants, 105 children infected before age 5 years)	Excluded
Taipei, Taiwan[5]	Not stated	Unknown	Not reported
Taoyuan, Taiwan[6]	Not stated	Unknown	Not reported
Northern Taiwan[7]	Excluded	Unknown	Not reported

Results
Natural Boosting*

Population	End Point	% (N/N) with Natural Boost in Anti-HBs
Alaska Native[1,2]	Year 15	**7.9%** (62/783) RR 1.94 ages <19 years vs. older age groups
Thailand [3]	First 10 years Second 10 years	**10.0%** **10.7%**
Qidong, China[4]	Years 10 – 20	**23%** (116/503)
Taipei, Taiwan[5]	---	---
Taoyuan, Taiwan[6]	---	---
Northern Taiwan[7]	---	---

*Increase in antibody to hepatitis B surface antigen [anti-HBs] without anti-HBc or other marker of hepatitis B infection

Acute Hepatitis B Infection

Population	Investigated, Monitored	Source of Information	Cases of Acute Hepatitis
Alaska Native[1,2]	Yes	History, medical record	None identified
Thailand [3]	Yes	History, liver enzyme elevation	None identified
Qidong, China[4]	No	---	---
Taipei, Taiwan[5]	No	---	---
Taoyuan, Taiwan[6]	No	---	---
Northern Taiwan[7]	No	---	---

Subclinical and Chronic Hepatitis B Virus Infections†

Population	Subclinical Infection, % (N/N)	Chronic infection* % (N/N)
Alaska Native[1,2]	**1.0%** (5/493) (plus 3/493 transient anti-HBc positive)	**None**
Thailand [3]	**22.0%** (24/109)	**None** (2/24 transient HBsAg or HBV DNA)
Qidong, China[4]	**6.8%** (12/219 subjects uninfected at age 5 years)	**2.2%** (4/219)
Taipei, Taiwan[5]	**6.7%** (39/583)	**2.0%** (12/583)**
Taoyuan, Taiwan[6]	**2.9%** (1/35)	**5.7%** (2/35) (1 mutant)
Northern Taiwan[7]	**2.7%** (23/843)	**1.4%** (12/843)**

†Persistently positive anti-HBc
*HBsAg-positive, or HBV DNA-positive among anti-HBc positive
*"Most" attributed to failure to prevent perinatal transmission

Hepatitis B Vaccine "Weak" or Non-Response

Population	Time since Vaccination at Determination of Response	"Weak" or Non-Response % (N/N)	Chronic infection (HBsAg+)
Alaska Native[1,2] (Vaccinated ages >6 months)	<6 months post-vaccination	**6%** (85/1436)	**15 year follow-up** Non-responders **4.22** Responders **0.61***
Qidong, China[4] (Vaccinated at birth)	"Post-vaccination"	**4.7%** (41/875)	Excluded
	Age 5 years	31.9% (257/807)	**20 year follow-up** **1.1%** (3/257)

* Rate per 1000 person years, $P = 0.01$ †(31.9%)

Summary of Long-Term Protection Studies -- 2012

- Hepatitis B vaccination started in infancy or at birth protects responders from acute and chronic hepatitis B infection for at least 20 years
- Subclinical hepatitis B infection uncommon
- Vaccine non-responders remain susceptible to acute and chronic hepatitis B infection
- Mutant hepatitis B virus infection rare, and can be associated with chronic infection; monitoring may be needed

Long-term Protection Studies Limitations

- Small number of studies; declining number of participants
- Primarily plasma derived vaccine
- Varying follow-up schedules, exclusion criteria, definitions
- Limited HBV DNA testing for mutant hepatitis B virus infection

Studies to Inform Future Decisions

- Correlates of protection in the absence of antibody to hepatitis B surface antigen (anti-HBs)
- Active monitoring for hepatitis B protection among vaccine recipients
- Comprehensive evaluation of vaccinated HCP (responders, non-responders) and unvaccinated HCP exposed to blood and body fluid from hepatitis B surface antigen (HBsAg) positive patients

Studies to Inform Future Decisions Cont'd

- Additional long-term studies of protection (e.g., infants vaccinated with recombinant vaccine)
- Trials to examine higher dosage, or more immunogenic vaccines to induce protection among 3-dose vaccine non-responders
- Evaluation of antiviral therapy for post-exposure prophylaxis

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