Assessing the cost-effectiveness of a single-dose hepatitis B revaccination among infants not responding to the initial vaccine series and born to hepatitis B-infected mothers.

Eric Hall, MPH
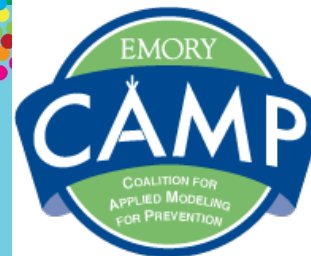**Rollins School of Public Health**
Emory University

Eli Rosenberg, PhD
Rollins School of Public Health
Emory University

Conflicts of interest statements

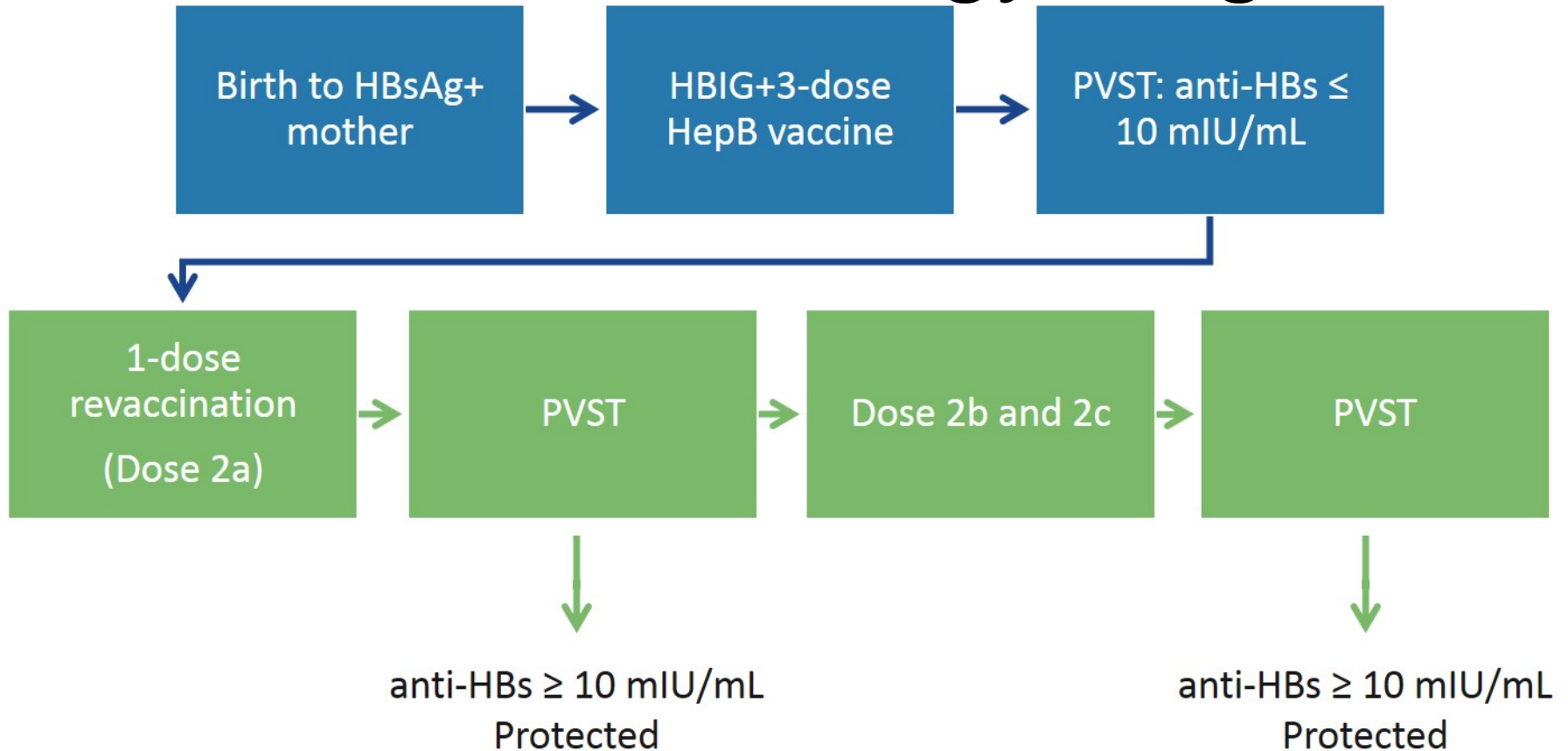- None of the authors have conflicts of interest

Methods: Study question

- Is a 1-dose hepatitis B revaccination strategy among infants born to hepatitis B-infected mothers who do not respond to the initial hepatitis B vaccination series cost-effective compared to the current 3-dose strategy?

- Societal perspective
  - Direct and indirect costs

Methods: Intervention(s)

- The intervention strategy considered is a 1-dose revaccination strategy among infants born to hepatitis B-infected mothers who do not respond to the initial vaccine series.

- Time frame and analytic horizon
  - Intervention time frame: 1 year
  - Analytic horizon: 1 year

- Discounting
  - Discounting is not included due to the 1 year horizon. Any costs that differ between the two strategies occur during the revaccination process.

Intervention strategy diagram

```
┌─────────────────┐      ┌─────────────────┐      ┌─────────────────┐
│  Birth to HBsAg+ │ ──▶  │  HBIG+3-dose    │ ──▶  │  PVST: anti-HBs ≤│
│     mother       │      │  HepB vaccine   │      │   10 mIU/mL     │
└─────────────────┘      └─────────────────┘      └─────────────────┘

┌─────────────────┐      ┌─────────────┐      ┌─────────────────┐      ┌─────────────┐
│  1-dose         │ ──▶  │             │ ──▶  │                 │ ──▶  │             │
│  revaccination  │      │    PVST     │      │  Dose 2b and 2c │      │    PVST     │
│  (Dose 2a)      │      │             │      │                 │      │             │
└─────────────────┘      └─────────────┘      └─────────────────┘      └─────────────┘
```

anti-HBs ≥ 10 mIU/mL   anti-HBs ≥ 10 mIU/mL
Protected   Protected

Individuals who are not protected after dose 2a go on to receive doses 2b & 2c, which mirrors the current 3-dose strategy. Therefore, the cumulative risk of hepatitis B infection is the same in both strategies.

Abbreviations: HBsAg+, hepatitis B surface antigen positive; HBIG, hepatitis B immune globulin; PVST, post-vaccination serologic testing; anti-HBs, antibody to hepatitis B surface antigen.

Methods: Economic model

- Decision tree model utilized to assess the cost-minimization of 1-dose vs 3-dose revaccination strategies.
  - Compared costs per person in each strategy
    - Cost per person = sum of direct and indirect costs associated with receiving each vaccine dose and PVST.
- Conduct analysis under three epidemiologic scenarios.
  - Scenario A, B and C

Methods: Health outcomes

- Model estimates the number of protected and unprotected individuals under each epidemiological scenario.

  – The number of protected individuals and cumulative risk of infection are assumed to be the same for each strategy.

  – There is not a difference in health outcomes between the two strategies.
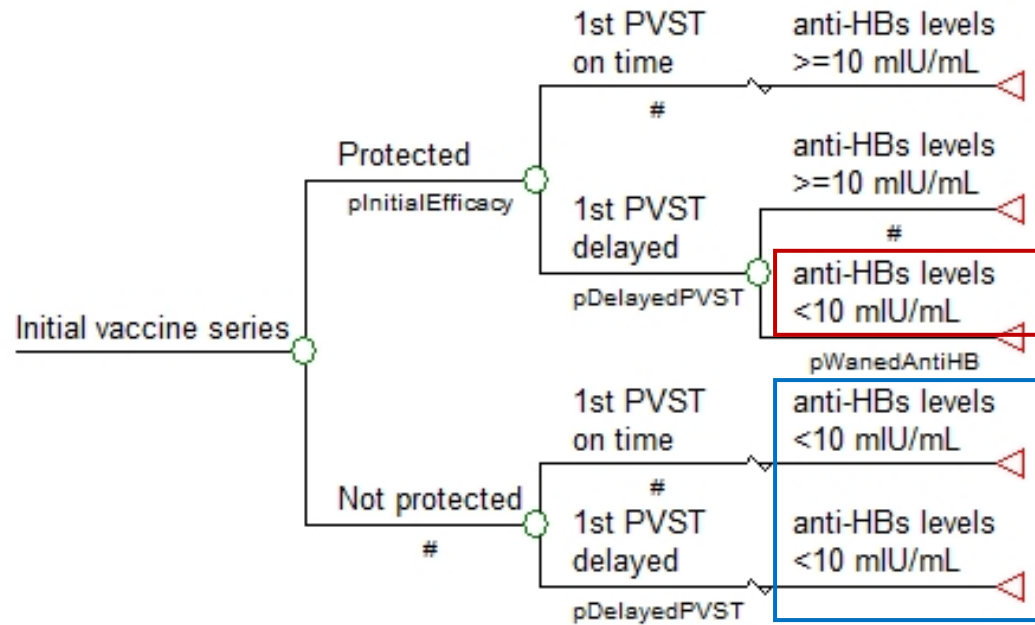
  – *Cost-minimization*

Methods: Epidemiological model
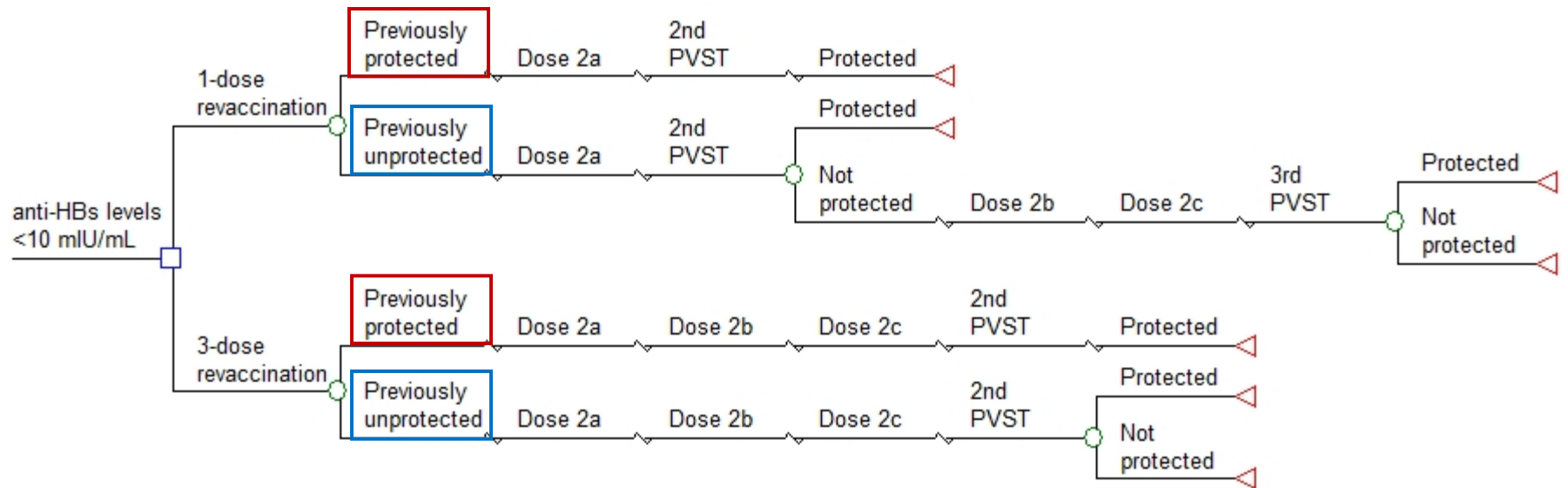
Proportion that are "previously protected" and "previously unprotected" are determined by the different epidemiologic scenarios.

Methods: Scenarios

Scenario	P protected after initial series	Timing of PVST	P of anti-HBs <10 among seroprotected	1st PVST: P <10mlU/mL	N indicated for revaccination	P of indicated w/protection
A	0.980	All PVSTs on time	0.000	0.020	496	0.000
B	0.973	20.4% >6 months	0.107[d]	0.048	1,190	0.438
C	0.668	21.3% >6 months	0.121[d]	0.349	8,650	0.049

Methods: Inputs – Probabilities

Parameter	Base case	Lower	Upper	Definition/assumptions	Source
Population and risk					
N infants born to HBsAg+ mother	24,784				[1]
P of infants protected after initial vaccination series	0.973	0.668	0.980	Base case is weighted average based on birth weight[2,5]. Upper efficacy limit[4]. Lower value is weighted average from previous analysis[3].	[1,2,3,4]
P of 1st PVSTs >6 months after final dose	0.204	0	0.213	Upper value is the 95% confidence interval upper limit	[2,5]
P of anti-HBs <10 among seroprotected with a PVST >6months	0.107	0	0.121	Weighted average of 7-8 months, 9-10 months, 11-12 months, 13-14 months and 15-16 months after final vaccine dose. Upper value is the 95% confidence interval upper limit	Calculated[2,5]
Decision tree analysis					
P of infants indicated for revaccination who are previously protected	0.438	0	0.500	Scenarios calculated from population and risk parameters.	Calculated
P protected from single revaccination dose (dose 2a)	0.778	0.000	0.900	Base case is calculated from two studies with a 4-dose schedule of 0, 1, 2, 12 months.	Calculated[4,6,7]
P protected from 2nd full series	0.948	0.918	0.978	Among infants in PBHPP	[2]

Methods: Inputs – Costs

Costs	Base case	Lower	Upper	Definition/assumptions	Source
P of vaccines purchased publicly	0.530	0.000	1.000	n/a	8
Cost of 1 vaccine dose, private	$22.40			Engerix B, private sector cost	9
Cost of 1 vaccine dose, public	$11.60			Engerix B, private sector cost	9
Cost of 1 vaccine dose, average	$16.68	$11.60	$22.40	Base case is weighted average	Calculated
P of vaccines administered publicly	0.200	0.000	1.000	n/a	8,10
Cost of vaccine administration, private	$29.63			Converted to 2016 USD with medical care CPI	8,11
Cost of vaccine administration, public	$8.31			Converted to 2016 USD with medical care CPI	8,11
Cost of administering 1 vaccine dose, weighted average	$25.37	$8.31	$29.63	Base case is a weighted average	Calculated
Cost of HBsAg testing to identify infection	$14.07	$11.26	$16.88	Hepatitis B surface antigen eia (CPT code 87340). National limitation amount with range of ±20%	12
Cost of HBsAG confirmatory test	$14.07	$11.26	$16.88	Hepatitis B surface antigen eia (CPT code 87341), only used if test 87340 is positive. National limitation amount with range of ±20%.	12
Cost of anti-HBs to identify immunity	$20.42	$16.34	$24.50	Hepatitis B surface antibody (CPT code 86317). National limitation amount with range of ±20%	12
Cost of blood draw	$3.00	$2.40	$3.60	Routine venipuncture (CPT code 36415). National limitation amount with range of ±20%	12
Cost of outpatient consultation for testing and results interpretation	$70.74	$56.59	$84.89	Included in all PVSTs. Converted to 2016 USD with medical care CPI and calculated range of ±20%	1,11
Cost of caregiver missing work (2 hours for each PVST/vaccine visit)	$17.40	$7.25	$44.29	Per hour. Base case is median national average from May 2015.	13
Cost of travel to receive vaccine	$24.04	$5.00	$35.00	Converted to 2016 USD with overall CPI	8,11

Methods: Sensitivity analyses

- Univariate threshold analysis of proportion protected by a single dose revaccination
  - Range: 0.0-0.9

- Tornado diagram
  - Considered all probability and cost parameters

- Two-way sensitivity analysis
  - Proportion protected by a single dose (range: 0.0-0.9)
  - Proportion of infants who were previously protected (range: 0.0-0.5)

Results: Costs

Scenario	Strategy	N	Cost per individual	Difference per individual	Total cost	Dose 2a efficacy threshold
A	1-dose revaccination	496	$349.93	$119.81	$173,453	0.45
	3-dose revaccination	496	$469.74	Reference	$232,841	n/a
B	1-dose revaccination	1,190	$314.02	$155.72	$373,568	0.03
	3-dose revaccination	1,190	$469.74	Reference	$558,818	n/a
C	1-dose revaccination	8,650	$345.91	123.83	$2,991,989	0.42
	3-dose revaccination	8,650	$469.74	Reference	$4,063,071	n/a

Scenario	P protected after initial series	Timing of PVST	P of anti-HBs <10 among protected	1st PVST: P <10mIU/mL	N indicated for revaccination	P of indicated w/protection
A	0.980	All PVSTs on time	0.000	0.020	496	0.000
B	0.973	20.4% >6 months	0.107	0.048	1,190	0.438
C	0.668	21.3% >6 months	0.121	0.349	8,650	0.049

Results: Costs

Scenario	Strategy	N	1 dose during a well-child visit			2 doses during a well-child visit			3 doses during a well-child visit		
			Cost per individual	Total cost	Dose 2a efficacy threshold	Cost per individual	Total cost	Dose 2a efficacy threshold	Cost per individual	Total cost	Dose 2a efficacy threshold
A	1-dose revaccination	496	$336.85	$166,970	0.54	323.77	$160,486	0.67	264.93	$131,321	0.67
	3-dose revaccination	496	$410.90	$203,675	n/a	352.06	$174,509	n/a	293.22	$145,343	n/a
B	1-dose revaccination	1,190	$306.68	$364,836	0.18	299.33	$356,093	0.40	240.49	$286,095	0.40
	3-dose revaccination	1,190	$410.90	$488,820	n/a	352.06	$418,822	n/a	293.22	$348,824	n/a
C	1-dose revaccination	8,650	$333.47	$2,884,387	0.52	321.04	$2,776,873	0.65	262.20	$2,267,929	0.65
	3-dose revaccination	8,650	$410.90	$3,554,127	n/a	352.06	$3,045,184	n/a	293.22	$2,536,240	n/a

| Scenario	P protected after initial series	Timing of PVST	P of anti-HBs <10 among protected	1st PVST: P <10mlU/mL	N indicated for revaccination	P of indicated w/protection
A	0.980	All PVSTs on time	0.000	0.020	496	0.000
B	0.973	20.4% >6 months	0.107	0.048	1,190	0.438
C	0.668	21.3% >6 months	0.121	0.349	8,650	0.049

14

Results: Sensitivity analyses

Sensitivity Analysis:
Efficacy of Dose 2a and Proportion with Previous Protection

15
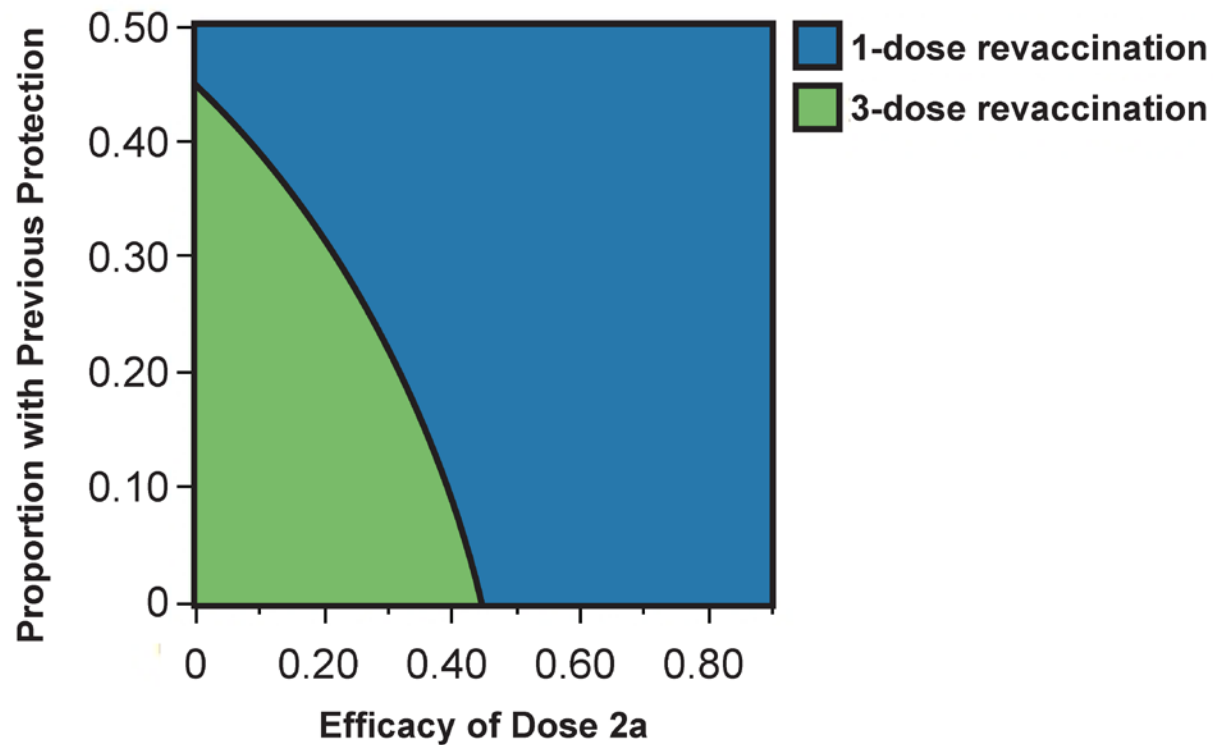
Results: Influential variables

- Tornado diagram of difference in cost (per person) of the 3-dose vs 1-dose strategy
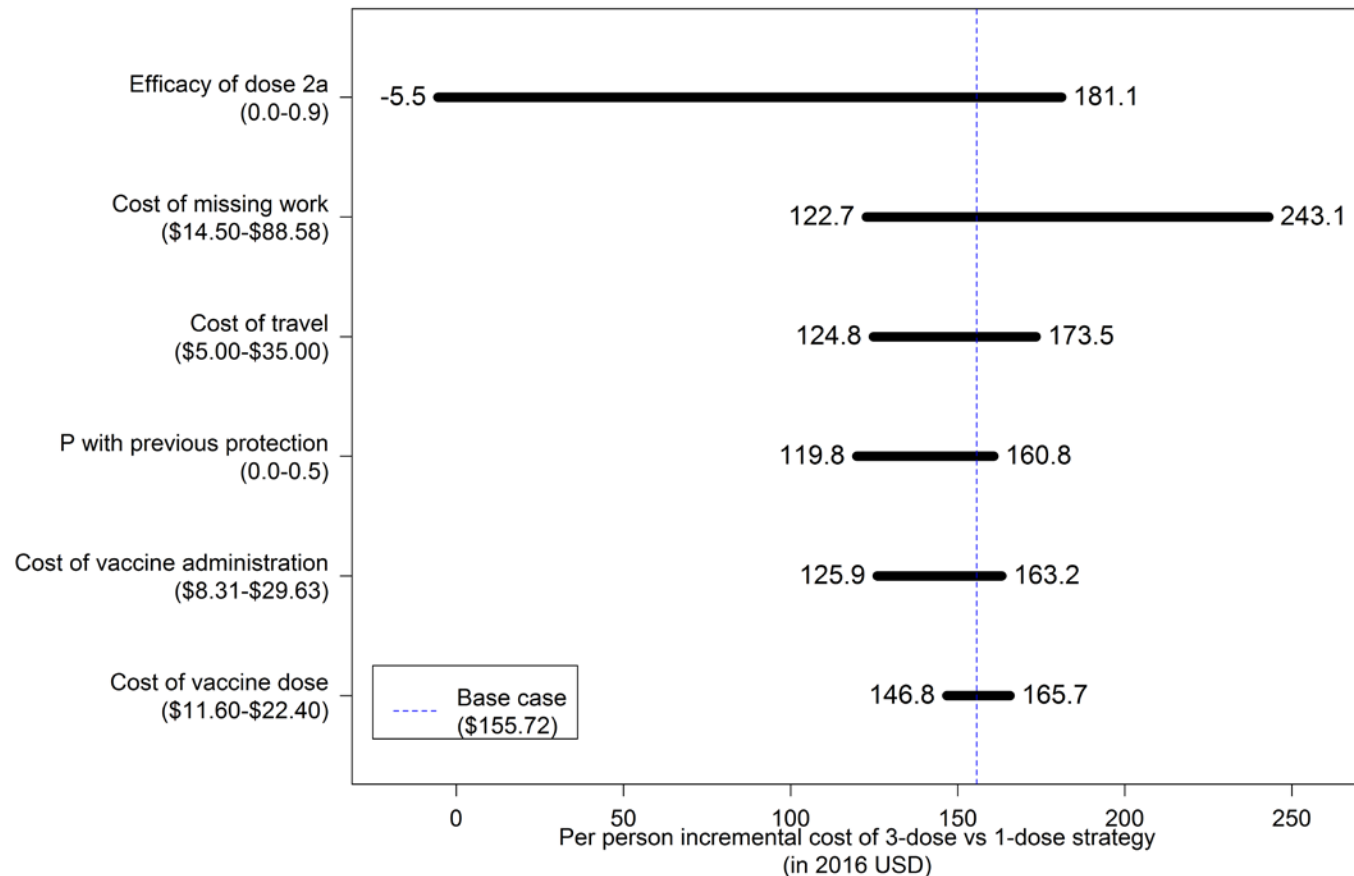
Summary of findings

- A 1-dose revaccination strategy reduces costs compared to the current 3-dose strategy across a wide array of scenarios.

- A 1-dose revaccination strategy is a lower cost option under the assumption that 1, 2 or 3 of the vaccinations occur during a previously scheduled well child visit.

Limitations

- Assume risk of infection is the same in 1-dose and 3-dose revaccination strategies
  - This assumption is dependent on the structure of the 1-dose revaccination strategy, in which individuals who are not protected after dose 2a go on to receive dose 2b and 2c, thus having the same experience as everybody in the current 3-dose revaccination strategy.

- Assume that dropout is the same for both strategies.

- Assume that infants born to mothers infected with hepatitis B are correctly identified and that they receive the initial vaccine series and PVST

Relation to other studies

- A recent study assessed the cost-effectiveness of the National Perinatal Hepatitis B Prevention Program (PHBPP) and concluded the program is a cost-effective use of resources.[1]
  - Authors advocate for an expansion of the program to ensure that it reaches all children born to hepatitis-B infected mothers.

- In 2015, it was recommended that initial PVSTs occur 1-2 months after completion of the initial vaccine series (9-12 months of age) for infants born to hepatitis B-infected mothers to ensure PVST test results are representative of protection.[5]
  - Implementing this 1-dose revaccination strategy will also help correctly identify protected individuals without them having to undergo a full 3-dose revaccination series.

Peer review comments

- This presentation was reviewed in accordance with ACIP Guidance for Health Economics Studies.[14]

- "Why weren't revaccination using 2-doses and no-revaccination considered as strategies?"

  - After giving two additional doses, it is more practical to continue with a third dose rather than include another PVST after dose 2b and possible continued non-response.

    - Single-dose revaccination is most consistent with other recommendations (e.g., for health-care personnel).

  - A nonintervention (no revaccination) strategy was not included because it would be unethical to leave infants who do not respond to the initial vaccine series unprotected.

References

- 1. Barbosa, C., Smith, E. A., Hoerger, T. J., Fenlon, N., Schillie, S. F., Bradley, C., & Murphy, T. V. (2014). Cost-effectiveness analysis of the national Perinatal Hepatitis B Prevention Program. *Pediatrics, 133*(2), 243-253. doi:10.1542/peds.2013-0718

- 2. Ko, S. C., Schillie, S. F., Walker, T., Veselsky, S. L., Nelson, N. P., Lazaroff, J., . . . Murphy, T. V. (2014). Hepatitis B vaccine response among infants born to hepatitis B surface antigen-positive women. *Vaccine, 32*(18), 2127-2133. doi:10.1016/j.vaccine.2014.01.099

- 3. Schillie, S. F., & Murphy, T. V. (2013). Seroprotection after recombinant hepatitis B vaccination among newborn infants: a review. *Vaccine, 31*(21), 2506-2516. doi:10.1016/j.vaccine.2012.12.012

- 4. Schillie, S., Walker, T., Veselsky, S., Crowley, S., Dusek, C., Lazaroff, J., . . . Murphy, T. V. (2015). Outcomes of infants born to women infected with hepatitis B. *Pediatrics, 135*(5), e1141-1147. doi:10.1542/peds.2014-3213

- 5. Schillie, S., Murphy, T. V., Fenlon, N., Ko, S., & Ward, J. W. (2015). Update: Shortened Interval for Postvaccination Serologic Testing of Infants Born to Hepatitis B-Infected Mothers. *MMWR Morb Mortal Wkly Rep, 64*(39), 1118-1120. doi:10.15585/mmwr.mm6439a6

- 6. Assateerawatt, A., Tanphaichitr, V. S., Suvatte, V., & Yodthong, S. (1993). Immunogenicity and efficacy of a recombinant DNA hepatitis B vaccine, GenHevac B Pasteur in high risk neonates, school children and healthy adults. *Asian Pac J Allergy Immunol, 11*(1), 85-91.

- 7. Lolekha, S., Warachit, B., Hirunyachote, A., Bowonkiratikachorn, P., West, D. J., & Poerschke, G. (2002). Protective efficacy of hepatitis B vaccine without HBIG in infants of HBeAg-positive carrier mothers in Thailand. *Vaccine, 20*(31-32), 3739-3743.

References

- 8. Zhou, F., Shefer, A., Wenger, J., Messonnier, M., Wang, L. Y., Lopez, A., . . . Rodewald, L. (2014). Economic evaluation of the routine childhood immunization program in the United States, 2009. *Pediatrics, 133*(4), 577-585. doi:10.1542/peds.2013-0698
- 9. Centers for Disease Control and Prevention (CDC). (2016). CDC vaccine price list.   Retrieved from www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/
- 10.   Groom, H., Kolasa, M., Wooten, K., Ching, P., & Shefer, A. (2007). Childhood immunization coverage by provider type. *J Public Health Manag Pract, 13*(6), 584-589. doi:10.1097/01.PHH.0000296134.70014.b0
- 11.   Bureau of Labor Statistics (BLS). (2016). Consumer Price Index (CPI) Detailed Report June 2016. Retrieved from http://www.bls.gov/cpi/cpid1606.pdf
- 12.   Center for Medicare & Medicaid Services (CMS). (2016). Clinical diagnostic laboratory fee (CLAB). Retrieved from https://www.cms.gov/Medicare/Medicare-Fee-for-Service-Payment/ClinicalLabFeeSched/
- 13.   Bureau of Labor Statistics (BLS). (2016). May 2015 National Occupational Employment and Wage Estimates United States.   Retrieved from http://www.bls.gov/oes/current/oes_nat.htm
- 14.   Centers for Disease Control and Prevention (CDC). (2017). Advisory Committee on Immunization Practices: Guidance for Health Economics Studies.   Retrieved from www.cdc.gov/vaccines/acip/committee/guidance/economic-studies.html