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Questions:

1. Is 1 $\mu\text{g/ml}$ the “protective” Ab concentration after a 1^o series of Hib conjugate vaccine?
2. Is “priming” protective?
3. Will we see an increase in invasive Hib disease if vaccines with lower immunogenicity are widely used?
4. If so, do we need to take this risk now?

Question: Is 1 $\mu\text{g}/\text{ml}$ the Protective Antibody Concentration for Hib?

Answer:

1. Yes, after PRP polysaccharide vaccine:

- 1 $\mu\text{g}/\text{ml}$ provides long-term protection

Evidence: concentration achieved by $\sim 90\%$ of PRP recipients and in $\sim 20\%$ of controls

2. No, after PRP conjugate vaccine:

- less than 1 $\mu\text{g}/\text{ml}$ provides long-term protection

Evidence: 5 to 30% of infants do not achieve $\text{Ab} \geq 1 \mu\text{g}/\text{ml}$ after the 1^o series. Almost all of them are “primed” for an Ab response to PRP and are protected

Question: Does Immunologic “Priming” Protect Against Hib Disease?

Definition: “Priming” is the rapid rise in antibody to a “protective” concentration in response to Hib exposure (presumably a PRP exposure in the nasopharynx)

- Note:**
- For proteins an anamnestic response results in an Ab rise by 7 days
 - For polysaccharides, Ab rises (if they occur) always occur by 7 days
 - e.g.,
 - older children given 1st dose of PRP
 - toddlers given 1st dose of Hib conjugate
 - toddlers given PRP after 1^o series of conjugate

Therefore, magnitude (not kinetics) of Ab response defines “priming” to Ps antigens.

Question: Is Priming Protective?

Answer 1: Yes, Priming Usually Protects

Evidence: A substantial number of children have declines of anti PRP Ab to $< 0.15 \mu\text{g/ml}$ after Hib conjugate immunization. Almost all of them are protected.

Question: Is Priming Protective?

Answer 2: Priming Doesn't Always Protect

Hypothesis:

- Interval between exposure to organism and invasion may be too short for an Ab response to occur (≤ 4 days)
- Rapid invasion may depend on organism (Mening>Hib>Pneumo), type of exposure and host susceptibility

Evidence:

1. Breakthrough cases of Hib disease do occur in conjugate immunized children who are primed
2. Breakthrough rates increase with age in the UK where only 3 doses of Hib conjugate are used at 2, 3 and 4 mos.

Vaccine Failures after Primary Immunization in the UK

R. Booy, et al Lancet. 1997.349:1197.

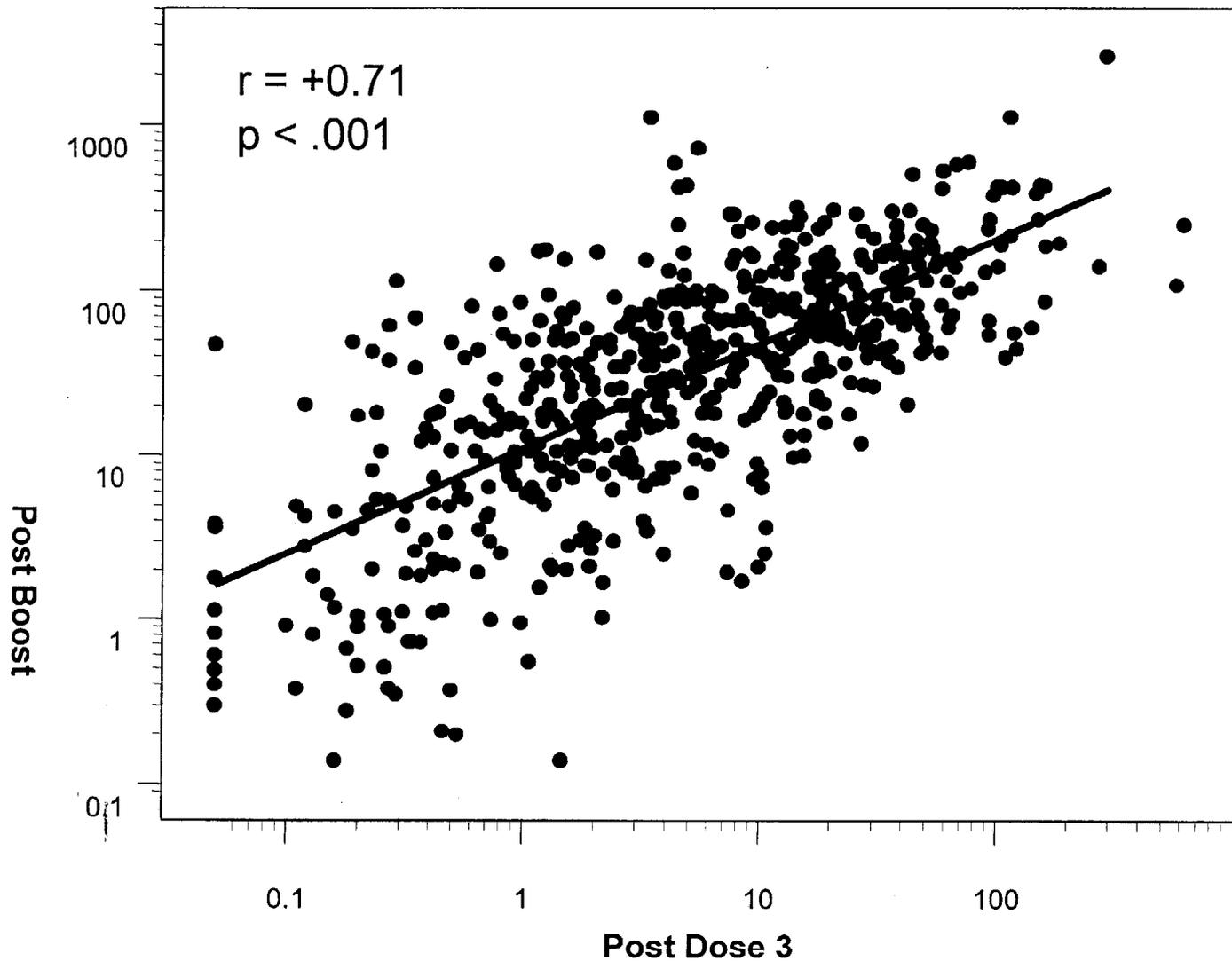
Question: Is Priming Protective?

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Evidence:

1. Breakthrough cases of Hib disease do occur in conjugate immunized children who are primed.
2. Breakthrough rates increase with age in the UK where only 3 doses of Hib conjugate are used at 2, 3 and 4 mos.
3. Older children capable of responding to PRP nevertheless develop meningitis. They respond rapidly to PRP after admission (P. Anderson, et.al).

Response to HbOC 1° Series Predicts the Response to Booster



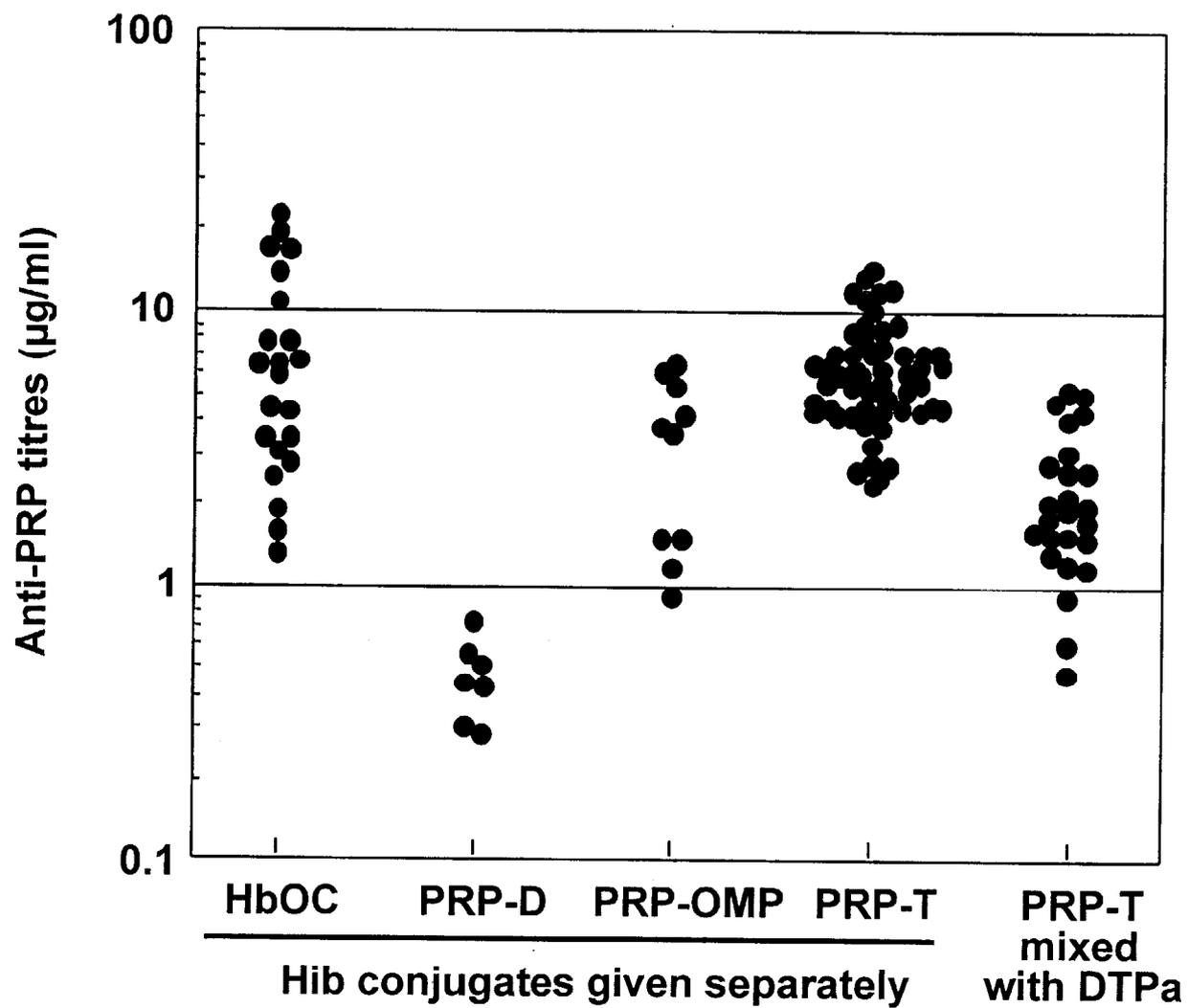
Early Antibody Response in Older Children with Hib meningitis

Question: Will Invasive Hib Disease Increase if Vaccines with Lower Immunogenicity Are Introduced in the US?

Background:

1. Clinical studies of each Hib conjugate show substantial variation in GMC of Ab

GMC one month after a primary series of Hib conjugates



Question: Will Invasive Hib Disease Increase if Vaccines with Lower Immunogenicity Are Introduced in the US?

Background:

1. Clinical studies of each Hib conjugate show substantial variation in GMC of Ab
2. Vaccine responses are more variable in practical use than in clinical studies
 - more variation in timing of doses
 - incomplete immunizations
 - high-risk individuals/groups
3. In some areas or populations, immunization rates are low

Background:

**4. Hib Disease Rates in the United States
Are Now Extremely Low**

CDC. Bisgard et al. Emerging Inf. Dis. 1998. 4:229. Hib rates in US in 1994-95.

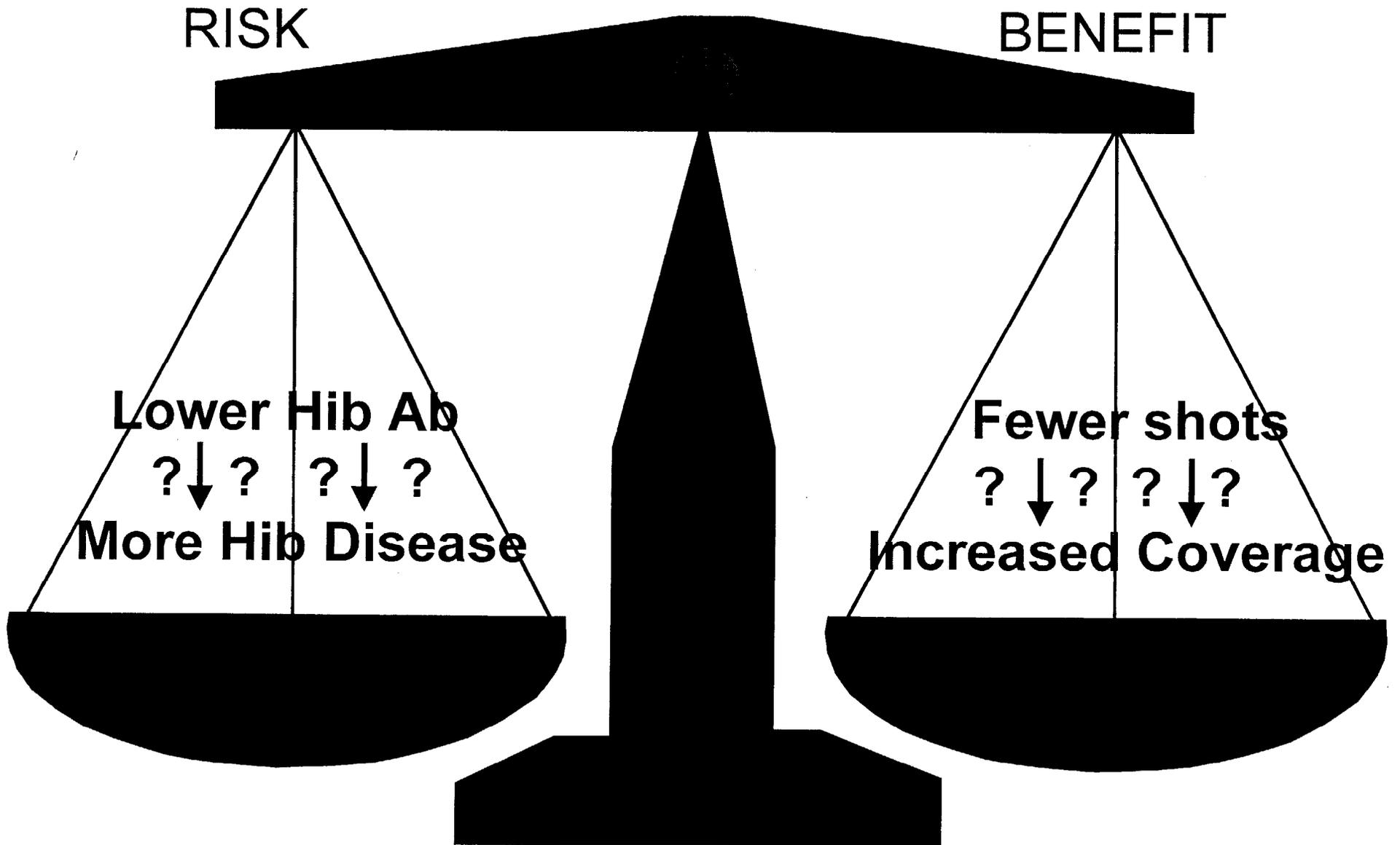
Question: Will Invasive Hib Disease Increase if Vaccines with Lower Immunogenicity Are Introduced in the US?

- Lower vaccine responses will result in lower Hib Ab in infants and older children
- Larger number of children who have to rely on priming alone for protection
- May result in higher Hib colonization rates
 - less herd immunity → increased exposure of unimmunized, partially immunized, immunocompromised etc.

Evidence: - may require 3-7 $\mu\text{g/ml}$ anti PRP to prevent colonization

- Alaskan colonization rates after Hib-OMP were 8%

Question: Do We Need to Make this Decision Now?



Risk vs Benefit

Risk: Question: Will we see more invasive Hib disease?

Answer: Uncertain, but possible

A decline in vaccine effectiveness from 99% to 98% results in 90 cases of Hib disease

Question: What would be the impact of more Hib disease?

Answer: ?Raise questions about vaccine efficacy

Risk vs Benefit

Benefit: Question: Are number of injections significant problem for compliance now?

Answer: Not certain but probably minimal based on current high immunization rates

Question: Can number of injections be reduced without incurring risk?

Answer: Yes:

- DTaP-IPV-HepB Combo available soon
- Combos of Hib with Pneumo and/or Meningococcal Conj. may avoid or reduce suppression

Options

- Introduce DTaP-Hib combinations and perform post-marketing studies of Hib vaccine failures

VS

- Reduce no. of shots with DTaP, IPV and HepB combos
- Assess vaccine failure rates in marketed vaccines with differing immunogenicity (PRP-D, PRP-OMP, HbOC, PRP-T)
- Encourage manufacturers to evaluate other strategies for combining Hib