

# **Early GRADEs – Cost Effectiveness Analysis (CEA), values and evidence in establishing immunization recommendations**

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David R. Curry, MS  
Executive Director  
Center for Vaccine Ethics and Policy  
Associate, NYU Division of Medical Ethics

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# Center for Vaccine Ethics and Policy

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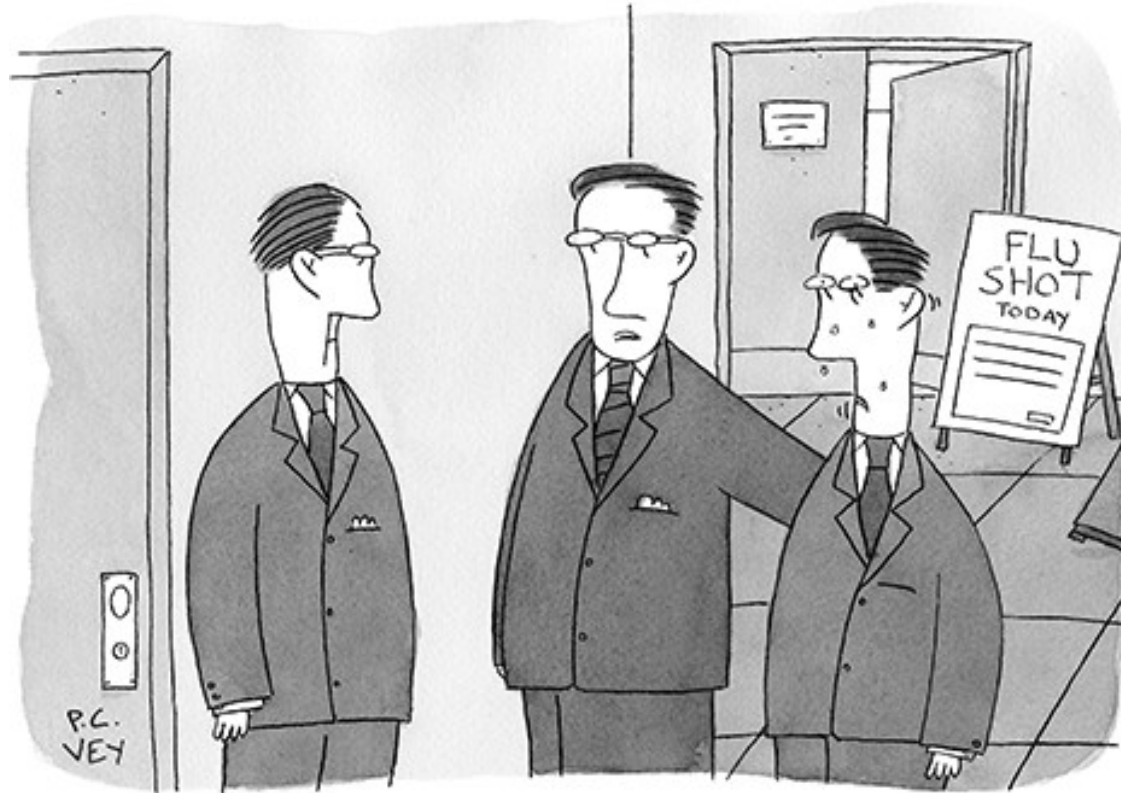
The Vaccine Education Center at  
The Children's Hospital of Philadelphia

## Mission:

**Contribute significantly to global public health as the leading independent, academically-based center focused on immunization and vaccine ethics and policy**

**Decision Ecology**  
**GRADE**  
**Values**  
**Health Economics/CEA**

# Vaccines, “Hesitancy” and Popular Understanding



***“Howard takes all the flu shots that other employees refuse to take.”***

# What is the short-list of strengths we should want for ACIP vaccine recommendations:

- **Expert**
- **Evidence-based**
- **Explicit**
- **Effective**
- **Independent**
- **Transparent**
- **Comprehensive**
- **Adaptive**

# Decision Ecology

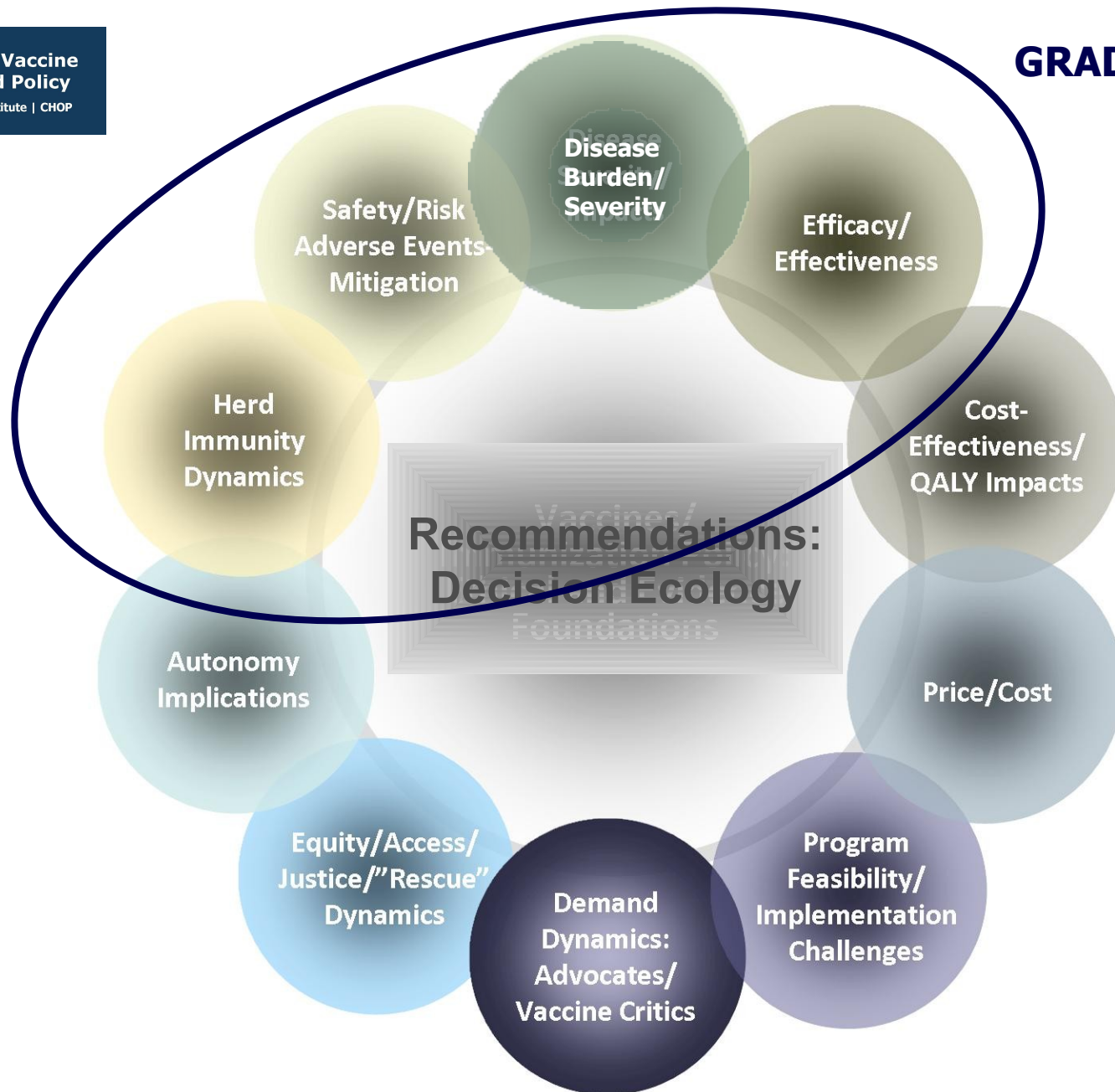
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# **GRADE – Grading of Recommendations Assessment Development and Evaluation**





# Development of ACIP/CDC vaccine recommendations using GRADE

Jon Temte, MD/PhD

Advisory Committee on Immunization Practices

Atlanta, GA

June 20, 2012



# ACIP EBRWG Terms of Reference

Charge: To develop a uniform approach to making explicit the evidence base for ACIP recommendations



- Evidence Imperfect...  
Tools Blunt
- But must be Explicit/  
Transparent...
- Provide visibility to the  
sausage-making...

## Perceived GRADE Deficits - Structural -

- Grading of Evidence may not address key factors
  - Burden of Disease
  - Indirect Benefit
- Limitations with Safety Assessments
  - Observational in nature
  - Rare events
- Limitation in Categories of Recommendations
  - Types
  - Alignment with strength of evidence

## Perceived GRADE Deficits - Procedural -

- Arbitrariness
  - incorporating values
  - Thresholds for upgrading / downgrading
  - Expert guidance
- Over-reliance on RCTs
  - Inherent lower quality of observational studies
- Reliance on External Methodology Experts
  - From outside of CDC

## Areas for Clarification

- Guidance
  - Ranking importance of outcomes
  - Determining values and preferences
  - Assignment of recommendation category
  - Drafting language
  - Upgrading / Downgrading evidence
    - “bias” in industry-sponsored studies
    - blinding
    - statistical approaches
    - levels of limitation (serious vs. minor vs. no)

## Areas for Clarification

- Additional categories
  - “no recommendation for or against due to insufficient evidence ”
  - Time limited
- Adjustment of Evidence Tables
- Issues with use of Safety Evidence
  - Post-licensure

# GRADE is

- Much more than a rating system
- An approach to
  - framing questions
  - choosing outcomes of interest
  - rating the importance of the outcomes
  - evaluating the evidence
  - incorporating evidence with considerations of values and preferences to
  - arrive at recommendations
- A guide to using those recommendations

Slide courtesy of Dr. Signe Flottorp



## GRADE is NOT...

- "the final truth"
- Without subjective judgments
- A mechanistic solution to assess our confidence in the evidence or the recommendations
- Limited to assessing quality of scientific evidence only
- A guide to the whole process of conducting systematic reviews or developing guideline recommendations

### Update on GRADE

Faruque Ahmed, PhD  
NCIRD  
Centers for Disease Control and Prevention

Advisory Committee on Immunization Practices  
Atlanta, GA  
June 20, 2012



Slide courtesy of Dr. Signe Flottorp



*“I was just guessing  
at numbers and figures  
pulling the puzzles apart*

*Questions of science  
science and progress  
do not speak as loud as my heart”*

Development of  
ACIP/CDC  
vaccine recommendations  
using GRADE

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Advisory Committee on Immunization Practices  
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**Coldplay – “The Scientist”**  
**A Rush of Blood to the Head - 2002**



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# Values





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## Vaccine

journal homepage: [www.elsevier.com/locate/vaccine](http://www.elsevier.com/locate/vaccine)



### Review

# Methods for developing evidence-based recommendations by the Advisory Committee on Immunization Practices (ACIP) of the U.S. Centers for Disease Control and Prevention (CDC)

Faruque Ahmed<sup>a,\*</sup>, Jonathan L. Temte<sup>b</sup>, Doug Campos-Outcalt<sup>c</sup>,  
Holger J. Schünemann<sup>d</sup>, for the ACIP Evidence Based Recommendations Work Group (EBRWG)<sup>1</sup>

<sup>a</sup> Immunization Services Division, Centers for Disease Control and Prevention, 1600 Clifton Rd. NE, Mailstop A-19, Atlanta, GA 30333, USA

<sup>b</sup> Department of Family Medicine, University of Wisconsin School of Medicine and Public Health, 777 South Mills Street, Madison, WI 53715, USA

<sup>c</sup> Department of Family & Community Medicine, University of Arizona College of Medicine, 550 E. Van Buren Street, Phoenix, AZ 85004, USA

<sup>d</sup> Department of Clinical Epidemiology and Biostatistics, McMaster University Health Sciences Centre, Room 2C10B, 1200 Main Street West, Hamilton, ON L8N 3Z5, Canada

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### ABSTRACT

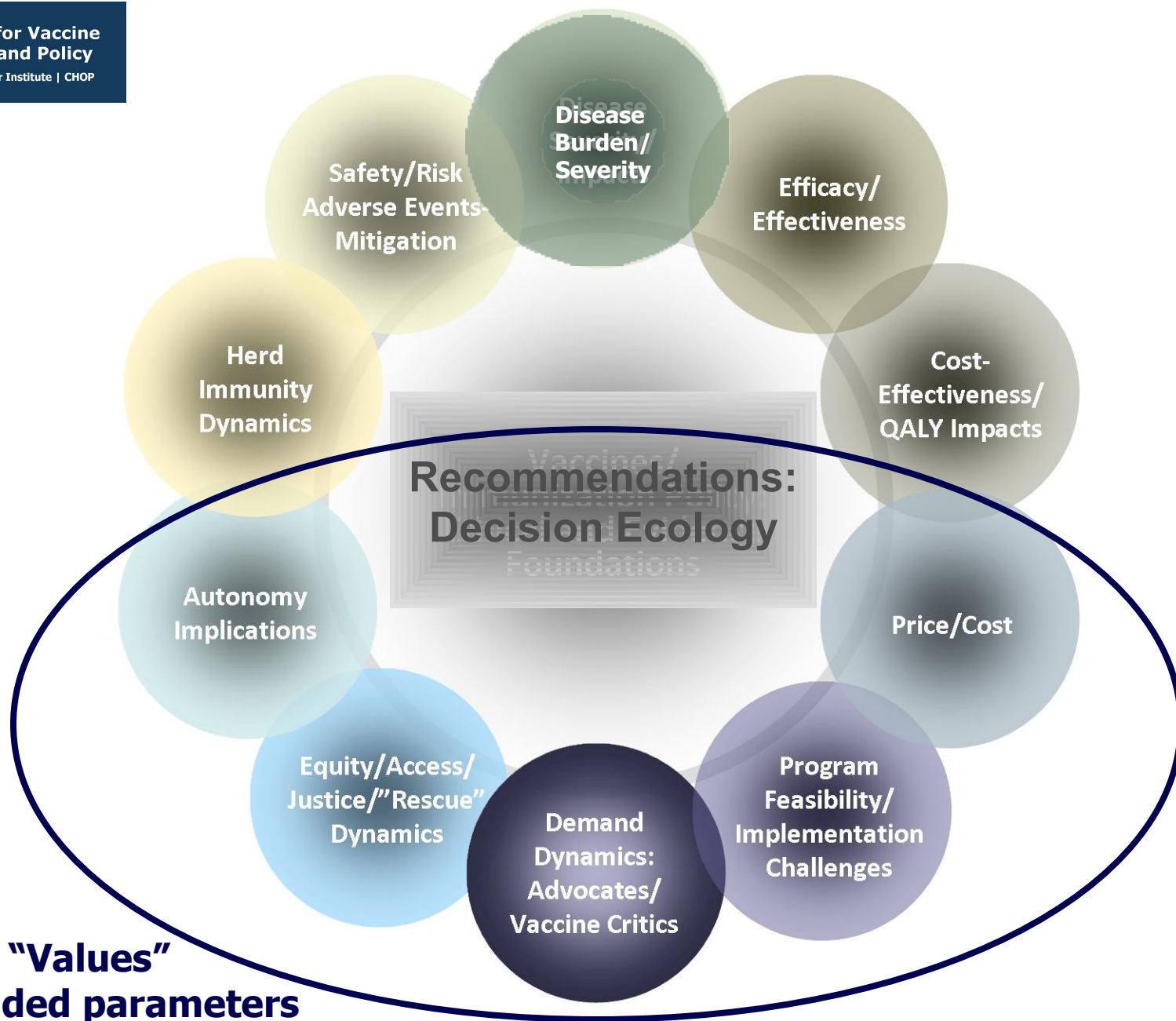
The Advisory Committee on Immunization Practices (ACIP) provides expert external advice and guidance to the Director of the Centers for Disease Control and Prevention and the Secretary of the U.S. Department of Health and Human Services on use of vaccines and related agents for control of vaccine-preventable

### **3.8. Values and preferences**

Values can be described as the relative importance of outcomes related to benefits, harms, and costs.

Values, as well as ethical considerations, play a key role in developing recommendations. The values should reflect those of the people affected, including the general population, patients, clinicians, and policymakers...

...When values are particularly important for the interpretation of recommendations, the key values that are considered in making a recommendation should be described.



**"Values"  
grounded parameters**

**How should we make  
values and preferences,  
ethics, and implementation  
evidence explicit in  
recommendation processes**

**???**

**Table 8. Considerations for Formulating Recommendations: 23-valent Pneumococcal Polysaccharide Vaccine in immunocompromised adults**

Key factors	Comments
Evidence type for benefits and harms	Inconsistent evidence for all-cause pneumonia; limited data from RCT not generalizable to the US HIV+ population
Balance between benefits and harms	Some uncertainty about benefits. Vaccine appears to be safe in this population
Value	ACIP pneumococcal work group consensus regarding the importance of preventing critical pneumococcal outcomes
Cost-effectiveness	Cost-effectiveness in the general adult population demonstrated; uncertainty around the assumptions utilized in cost-effectiveness analysis

Summary: Benefits are likely greater than harms. High values were placed on prevention of the morbidity and mortality of pneumococcal infection among immunocompromised adults. (recommendation category B; evidence type 3/4)

**Table 8. Considerations for Formulating Recommendations: Quadrivalent HPV Vaccine for Males**

Key factors	Comments
Balance between benefits and harms	Benefits are greater than potential harms
Evidence type for benefits and harms	Evidence Type 2 Benefit Evidence Type 2 Harm RCT Evidence Type 4 Harm O
Value	High value placed by ACIP HPV Work Group on prevention of cancer in males
Cost-effectiveness	HPV4 is most cost-effective if all HPV associated outcomes prevented, vaccine cost lower than current price, female coverage low (such as 30% 3-dose coverage at age 12 years)
RCT= randomized controlled trial O= observational study  <b>Summary for Benefits and Harms: Benefits are greater than potential harms and overall evidence type is 2. There is high value placed on prevention of cancer in males. Quadrivalent HPV vaccine is most cost-effective if all HPV associated outcomes are prevented, vaccine cost is lower than current price, or female coverage is low. Recommendation for routine vaccination of males aged 11 or 12 years with HPV4 administered as a 3-dose series (recommendation category A; evidence type 2)</b>	

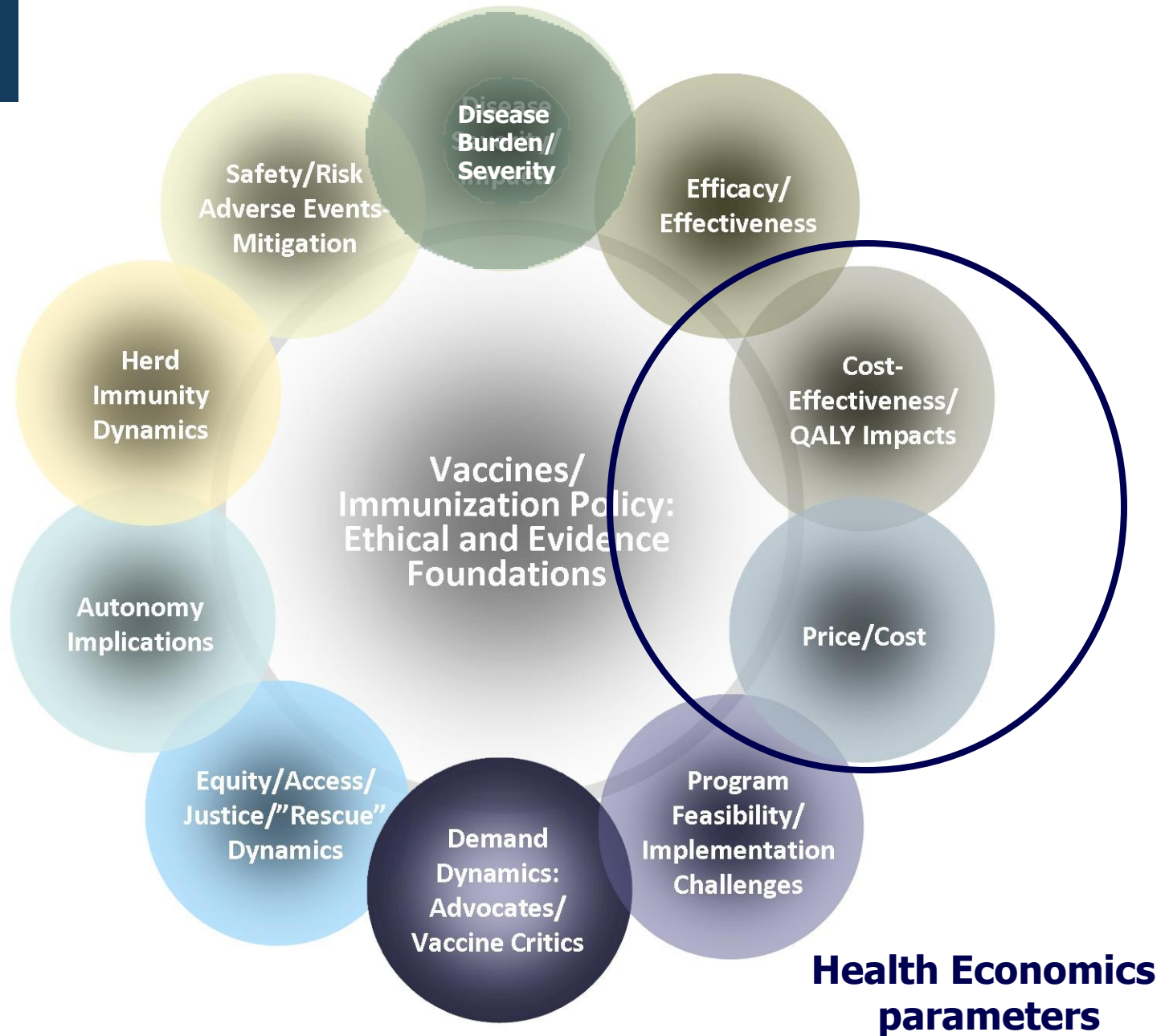
**Table 4. Considerations for Formulating Recommendations: Hepatitis B Vaccine for Adults with Diabetes**

Key factors	Comments
Balance between benefits and harms	Benefits are greater than potential harms
Evidence type for benefits and harms	Benefits: Evidence type 2 Harms: Approximately 30 year hepatitis B vaccine history indicates serious adverse events and anaphylaxis extremely rare
Values	High values on preventable outcomes <sup>a</sup> for persons <60 years and moderate to high values for persons >60 years assigned by ACIP Hepatitis Work Group
Cost-effectiveness	Vaccination is most cost effective for adults with diabetes for ages <60 years
<sup>a</sup> Preventable outcomes consist of acute hepatitis, fulminant hepatitis, chronic hepatitis, cirrhosis, hepatocellular carcinoma, liver transplantation, death	

# **Health Economics/ CEA – Cost Effectiveness Analysis**

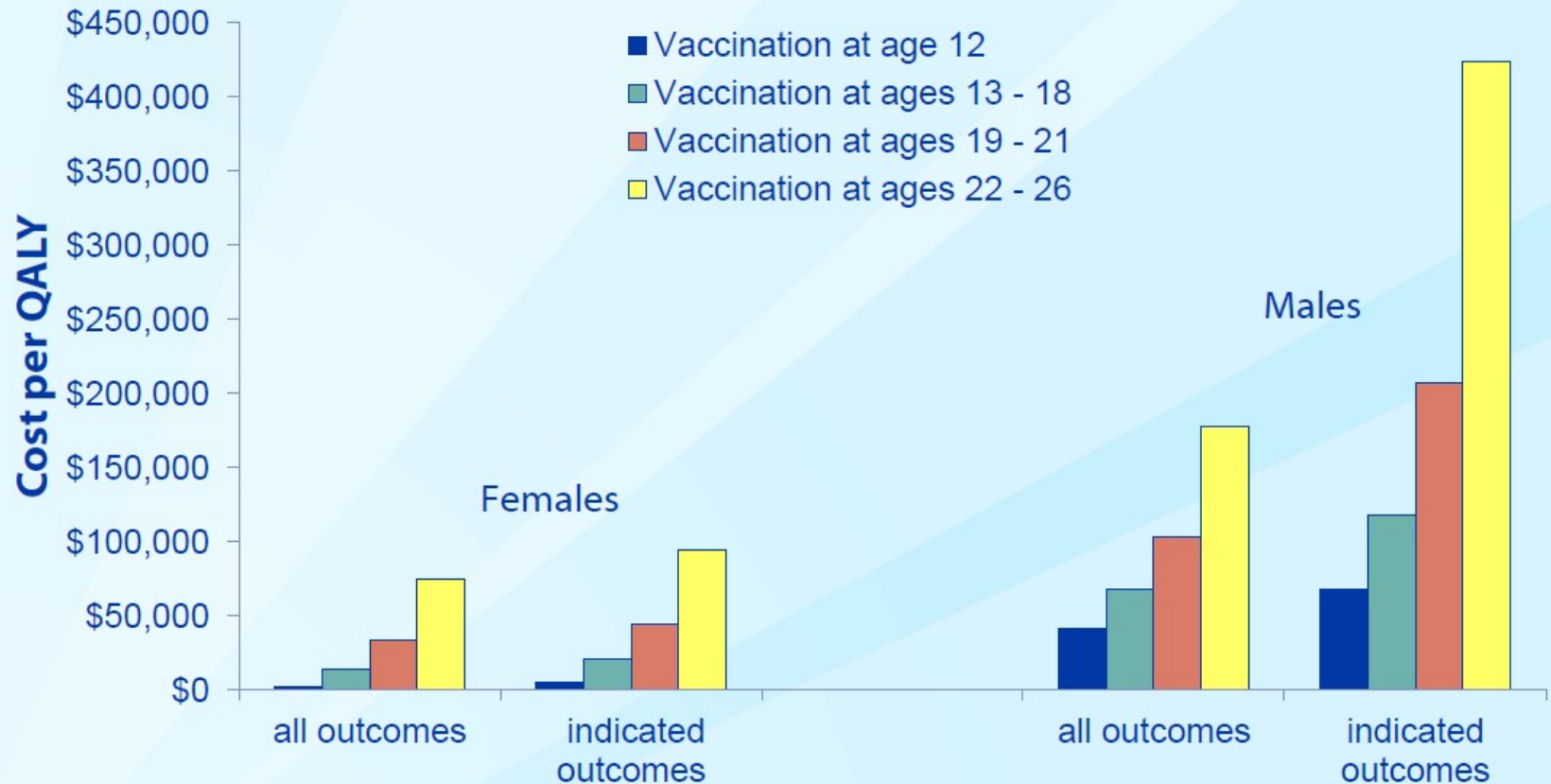
### **3.9. Health economic data**

Economic analysis is an important factor that informs judgments in formulating recommendations (e.g., cost-benefit, cost-utility, cost-effectiveness). Use of a fixed cut-off threshold such as \$50,000 or \$100,000 per quality adjusted life year (QALY) for determining cost-effectiveness, however, ignores other determinants of value [30].





# Cost per QALY gained by age at vaccination\*



\*Lower coverage scenario: 3-dose coverage 30% at age 12, 50% by age 26 (after ~ 20 yrs)

Vaccination of older age groups is incremental to vaccination of younger age groups. Results for male vaccination show the incremental cost-effectiveness of expanding male vaccination to include additional age groups, in the context of an existing vaccine program for females aged 12-26 years. Coverage assumptions apply to males and females. "Indicated" outcomes include cervical outcomes, vaginal, vulvar, and anal cancers, and genital warts. All outcomes include indicated outcomes plus oropharyngeal cancer, penile cancer, and recurrent respiratory papillomatosis. QALY: quality-adjusted life year.

**How should we make  
health economics and cost-  
effectiveness evidence  
explicit in recommendation  
processes**

**???**

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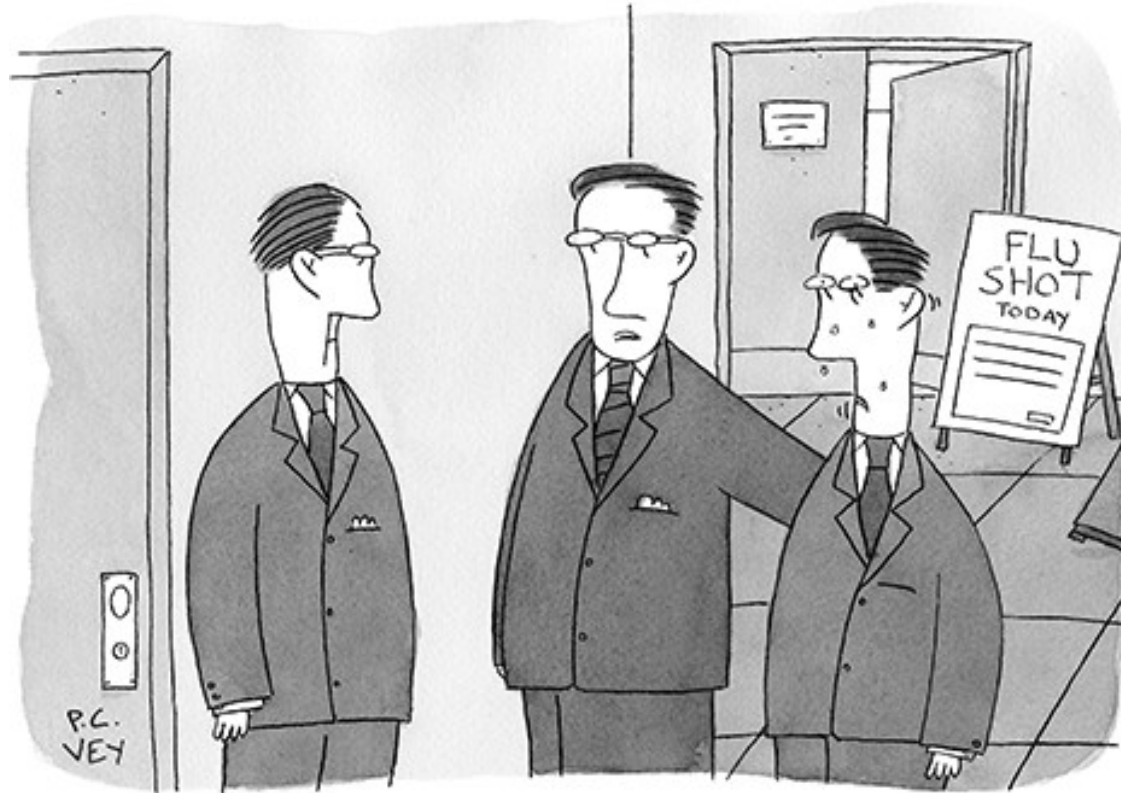
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**B** ▪ Expert

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**B** ▪ Explicit

**A** ▪ Effective

**A** ▪ Independent

**B** ▪ Transparent

**B** ▪ Comprehensive

**A** ▪ Adaptive



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