

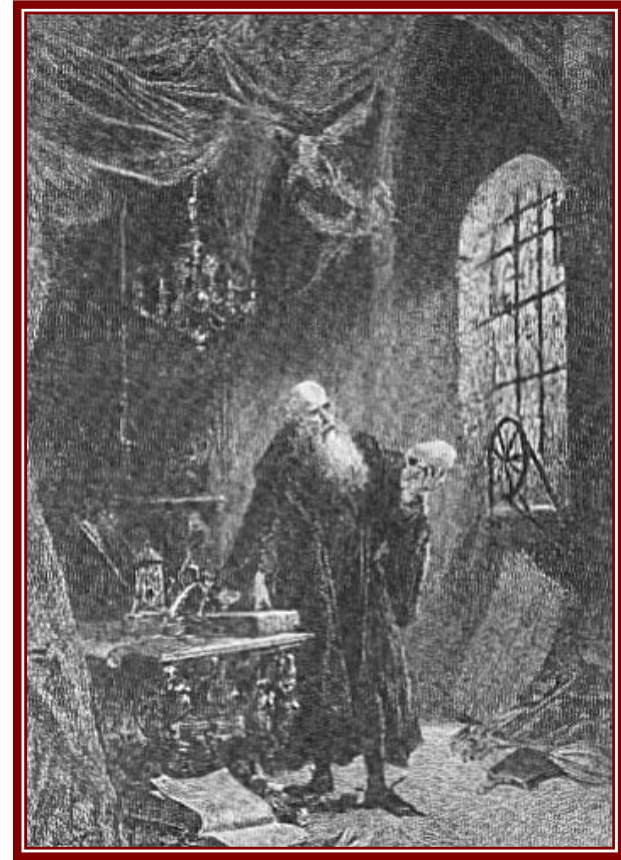
Strategies of the US Advisory Committee on Immunization Practices (ACIP) in developing evidence-based recommendations

Jonathan L. Temte, MD/PhD

Chair – ACIP Evidence-Based Recommendation Work Group

Thanks to Dr. Faruque Ahmed for providing background slides and information

*“Poor fool with all this sweated lore,
I stand no wiser than I was before.
Master and Doctor are my titles;
For ten years now, without repose
I’ve held my erudite recitals
And led my pupils by the nose.
And round we go,
on crooked ways or straight,
And well I know that ignorance
is our fate,
And this I hate.”*



Johann Wolfgang von Goethe
Faust - Part One, 1806

Synopsis

- Charge of ACIP
- Movement to evidence-based vaccine recommendations
- History of efforts to develop the framework for EB vaccine recommendations
- Strategies in developing the framework
- Outcome and approval of a framework

Charge of the
US Advisory Committee
on Immunization Practices

Advisory Committee on Immunization Practices shall provide guidance...

- ...regarding the most appropriate selection of vaccines and related agents for **effective** control of vaccine preventable disease in the civilian population.
- ...on **population groups and/or circumstances** in which a vaccine or related agent is recommended.
- ...on contraindications and precautions for the use of the vaccine and related agents and provide information on **recognized adverse events**.
- ...deliberations on the appropriate use of vaccines to control disease in the U.S, should include **consideration of population based studies such as efficacy, cost benefit, and risk benefit analyses.**

Vaccine Efficacy / Effectiveness

Target Population

Vaccine Safety

Other Considerations



Evidence-based Practice

What is Evidence Based Medicine?

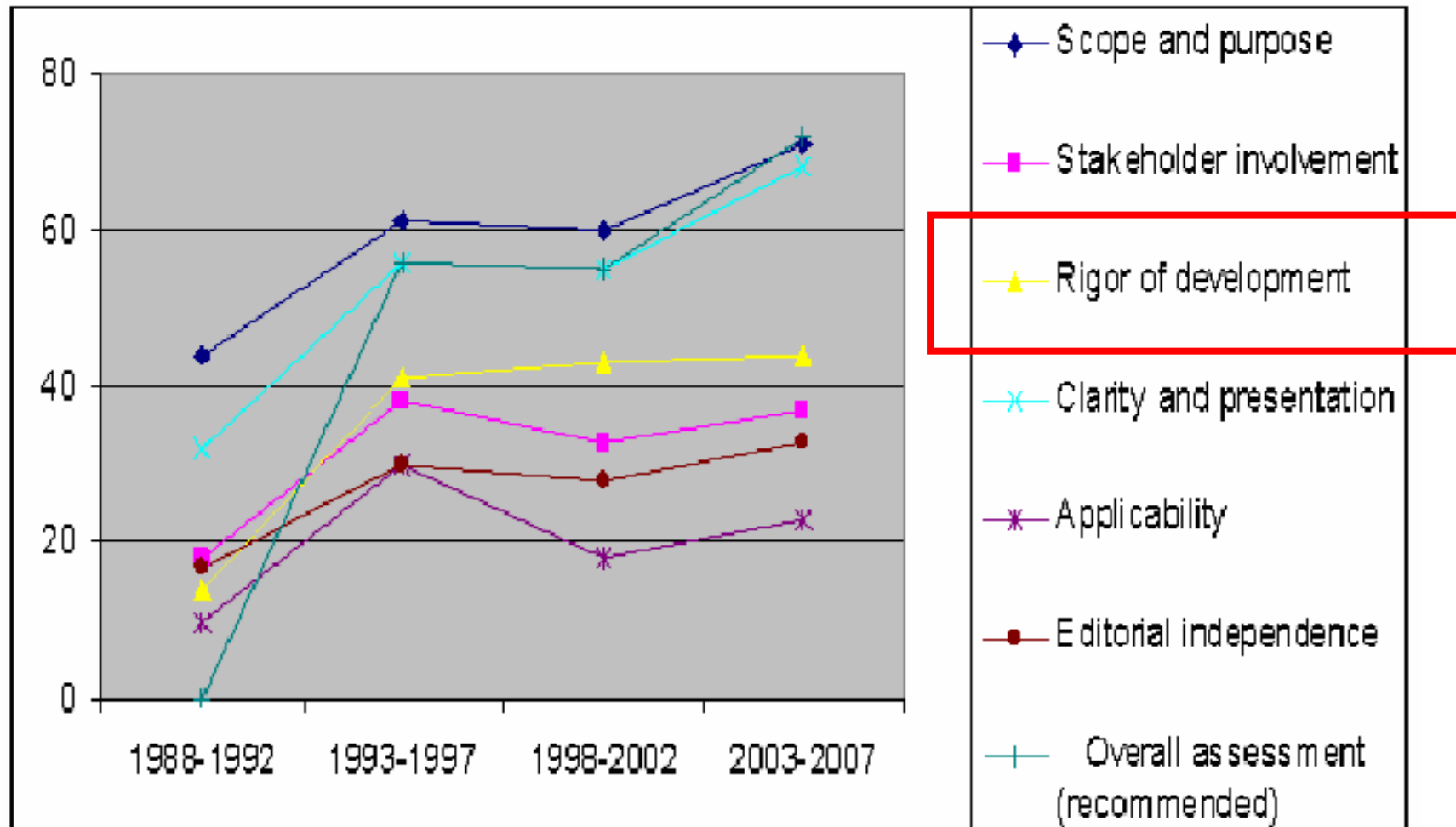
Evidence based medicine (EBM) has been defined as “integrating the best research evidence with clinical expertise and patient values to achieve the best possible patient management” (Sackett, 2000)

Vaccine Stakeholders increasingly require evidence-based recommendation

- American College of Physicians
 - Internal Medicine
- American Academy of Family Physicians
 - Family medicine
- Infectious Disease Society of American
 - Adult and pediatric infectious disease specialists

Quality of 626 Guidelines:

Mean Scores over Time*



*Ref: Alonso-Coello P, et al.



History of efforts to develop the framework for EB vaccine recommendations

ACIP Evidence-based work group

- Initially formed in 2004
 - Charged with developing a framework for assessing the evidence-base in vaccine-related recommendations
- Became inactive due to personnel changes
- Re-initiated in November 2007
 - Monthly teleconferences starting in January 2008
 - Occasional face-to-face meetings during ACIP

ACIP EBRWG

Terms of Reference

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

Initial EBRWG Activities

- Developed guiding principles
- Reviewed several evidence-based systems for developing guidelines

EBRWG Members

- Jonathan Temte – ACIP
- Robert Beck – ACIP*
- Tracy Lieu – ACIP*
- Ned Calonge – USPSTF
- Doug Campos-Outcalt – AAFP
- Jiangcheng Huang – AIM
- Linda Kinsinger – VA
- Joanne Langley – NACI
- Ed Marcuse – AAP
- Virginia Moyer – USPSTF
- Amir Qaseem – ACP
- William Schaffner – NFID
- Holger Schunemann – GRADE
- Vincenza Snow – ACP*
- Litjen (LJ) Tan – AMA
- Jane Gidudu – CDC
- Gail Janes – CDC
- Jean Clare Smith – CDC
- Faruque Ahmed – CDC

EBRWG input and expertise

- Professional Organizations
 - AAFP, AAP and ACP
 - AMA, AIM, NFID, and VA
- Methodological Expertise
 - GRADE
 - USPSTF
- Vaccine Advisory Groups
 - NACI
 - WHO-SAGE discussion group on EBR



Strategies in developing the framework

EBRWG Guiding Principles

- Focus on transparency
- Use of evidence of varying strengths
- Consider individual and community health
- Adopt/adapt an existing system rather than re-create something that may already exist
- Continually strive to improve the process
- First apply proposed process to
 - New recommendations
 - Changes to existing recommendations

Components of Evidence-Based Vaccine Recommendations

- Key Elements for consideration
 - Safety
 - Efficacy
 - Burden of Illness
- Assessment Method for existing Evidence
- Form of Recommendation
- Reporting of Elements and Evidence

Review of EBRWG presentations before ACIP

- February 2010
 - A review of methodological standards for clinical practice guidelines
 - Guidelines for grading the quality of evidence
 - Synthesizing and presenting recommendations

Review of EBRWG presentations before ACIP

- June 2010
 - Organizational perspective and endorsement
 - AAFP
 - AAP
 - ACP
 - Detailed review of GRADE
 - WHO's Strategic Advisory Group of Experts
 - Approach and experience with evidence-based recommendations
 - Presentation of pilot approach to grading evidence
 - Rotavirus
 - MMRV

Issues Raised by ACIP

(June 2010)

- What are the ramifications of the terminology used?
- When would evidence grading be used?
- Why have four evidence levels?
- What if it is not possible to conduct randomized trials in subpopulations?
- Does GRADE take into account biologic information?
- Will cost-effectiveness studies be graded?
- Can GRADE assist in evaluating observational studies assessing risk factors?
- What support will be needed to implement GRADE?
- How will the GRADE approach be translated for the public?

Proposed ACIP Evidence Evaluation System

- Adopt the Grades of Recommendation Assessment, Development and Evaluation (GRADE) framework
- Proposed evidence grades: A, B, C, D
 - Confidence in the estimated effect on health outcomes based on a body of evidence
- Proposed recommendation categories
 - Category I (recommendation for, or against)
 - Category II (recommendation for individual clinical decision making)

Description of Evidence Grades

Grade	Description
A	Further research is unlikely to change the estimated effect on health outcomes
B	Further research may change the estimated effect on health outcomes
C	Further research is likely to change the estimated effect on health outcomes
D	Available data are insufficient to provide a reliable estimate of the effect on health outcomes

Note: Grades reflect the confidence in the estimated effect on health outcomes based on a body of evidence. Further research may not always be possible.

ACIP Recommendation Categories

- Category I
 - Recommendation for, or against
 - Universal (routine) recommendation
 - Certain high-risk groups
- Category II
 - Recommendation for individual clinical decision making
- No recommendation/unresolved issue

Considerations that may Result in a Category II Recommendation

- Smaller net benefit
- Lower evidence grade
- Variability in values attributed to benefits and harms
- Uncertainty about whether the net benefits are worth the costs
 - Cost-effectiveness

Proposed ACIP Wording of Recommendations

- Recommendation for, or against (category I)
 - Use words like
 - “recommend”
 - “recommend against”
 - “should”
 - “should not”
- Recommendation for individual clinical decision making (category II)
 - Use words like “may”

Proposed Format for ACIP Recommendations

- Recommendation
 - ACIP recommends/does not recommend ...
(Recommendation category, evidence level)
- Remarks
 - Explicit consideration of benefits, harms, evidence grade, cost-effectiveness, and values for making a recommendation should be described here
 - For recommendations based on lower evidence grades, the reasoning should be included here

Recommendation Format: Example

Recommendation: ACIP **recommends universal** vaccination of U.S. infants with three doses of rotavirus vaccine administered orally at ages 2, 4, and 6 months (**recommendation category: I, evidence grade: A**).

Remarks: Nearly every child in the U.S. is infected with rotavirus by age 5 years, resulting in approximately 410,000 physician visits, 205,000–272,000 emergency department visits, and 55,000–70,000 hospitalizations each year. Vaccination reduces severe rotavirus diarrhea. Benefits of vaccination are large compared to potential harms.

Format for Evidence Tables

- Benefits
- Safety
- Evidence grade
- Summary of evidence

Benefits: Pentavalent Rotavirus Vaccine*

Outcome	No. of subjects (# studies)	Incidence in controls	Incidence in vaccinated	Vaccine efficacy (95% CI)	Absolute risk per 1000 (95% CI)	Number Needed to Treat (Vaccinate)
Rotavirus diarrhea (RV)	5,627 (2 RCTs)	12.86%	3.47%	73% (66, 78)	-94 (-85, -100)	11
Severe RV diarrhea	5,627 (2 RCTs)	1.99%	0.06%	97% (86, 99)	-19 (-17, -20)	52
Hospitalization for RV diarrhea	57,134 (1 RCT)	0.51%	0.02%	96% (91, 98)	-5 (-5, -5)	205

*Incidence over one full rotavirus season after vaccination.
RCT: Randomized controlled trial.

Safety: Pentavalent Rotavirus Vaccine

Outcome	No. of subjects (# studies)	Incidence in controls	Incidence in vaccinated	Relative Risk (95% CI)	Absolute risk per 1000 (95% CI)	Number Needed to Harm
Intussusception	70,139 (3 RCTs)	1.44 per 10,000	1.73 per 10,000	1.20 (0.37–3.93)	0.03 (-0.1, 0.4)	-
Other serious adverse events*	70,139 (3 RCTs)	2.25%	2.16%	0.96 (0.87–1.06)	-1 (-3, 1)	-
Fever	10,915 (3 RCTs)	38.87%	37.70%	0.97 (0.92–1.01)	-12 (-31,4)	-

*Most frequent were bronchiolitis, gastroenteritis, pneumonia, pyrexia, and urinary tract infection

Evidence Grade:

Pentavalent Rotavirus Vaccine

Outcome	Design (# studies)	Study limitations	Inconsistency	Indirectness	Imprecision	Evidence grade
Rotavirus diarrhea (RV)	RCT (2)	No serious	No serious	No serious	No serious	A
Severe RV diarrhea	RCT (2)	No serious	No serious	No serious	No serious	A
Hospitalization for RV diarrhea	RCT (1)	No serious	No serious	No serious	No serious	A
Intussusception	RCT (3)	No serious	No serious	No serious	No serious	A
Other serious adverse events	RCT (3)	No serious	No serious	No serious	No serious	A
Fever	RCT (3)	No serious	No serious	No serious	No serious	A

RCT: Randomized controlled trial

Summary of Evidence: Pentavalent Rotavirus Vaccine

Comparison	Outcome	Study design (# studies) ^b	Findings	Evidence grade	Overall evidence grade
Rotavirus vaccination vs. No vaccination	Rotavirus diarrhea (RV)	RCT (2)	Decreased risk among vaccinated infants	A	A
	Severe RV diarrhea ^a	RCT (2)	Decreased risk among vaccinated infants	A	
	Hospitalization for RV diarrhea ^a	RCT (1)	Decreased risk among vaccinated infants	A	
	Intussusception ^a	RCT (3)	No difference	A	
	Other serious adverse events ^a	RCT (3)	No difference	A	
	Fever ^a	RCT (3)	No difference	A	

^a Critical outcome (overall grade is based on the lowest grade across the critical outcomes).

^b RCT: Randomized controlled trial.



Outcome and Approval of a Framework

28 October 2010

Final Considerations

- ACIP work groups do not formulate, nor establish policy; rather they review data and present suggested options to the full ACIP
- ACIP's adoption of a recommendation is done so in an advisory capacity to CDC/Department of Health and Human Services
- ACIP approved recommendation relies upon the approval of CDC/DHHS
- Accordingly, an enthusiastic and unanimous outcome helps to move this process along

Final considerations

- On 27 October 2010, significant concerns were expressed by several ACIP members regarding the potential public perception of the levels of evidence
 - (i.e., grades)
- It was strategically essential for ACIP to have a full, unanimous and unambiguous vote for the adoption of an evidence-based framework
- Three options were formulated for the presentation of the evidence level

Option 3: evidence narrative*

- Proposed recommendation categories
 - Category I, Category II
- Replace evidence level with synthesis:
 - Based on evidence from randomized controlled trials with no important limitations, or from well-conducted observational studies with very strong effects
 - Based on evidence from randomized trials with important limitations or from observational studies with special strength
 - Based on evidence from observational studies, or from randomized trials with very serious limitations
 - Based on expert clinical opinion

* As presented before ACIP on 10/28/2010

Approval of the Framework

- ACIP members overwhelmingly preferred a "narrative description" in which an "evidence narrative" is presented based on the GRADE process and synthesis
 - GRADE must go through the evidence synthesis first (from which an evidence narrative can be derived) prior to assigning an evidence grade
 - This keeps within the “spirit” of GRADE

Approval of the Framework

- ACIP unanimously approved of the adoption of an evidence-based framework using an “evidence narrative” statement based directly on the evidence synthesis within GRADE
- Future ACIP recommendations will:
 - indicate the category of recommendation
 - followed by an evidence narrative
 - a remark section will provide explicit synthesis of benefits, harms, evidence assessment, cost-effectiveness, and values for making the recommendation
- CDC and ACIP will begin to implement this process in the coming months



Thank you

Questions ?

