New Framework for Developing Evidence-Based Recommendations by the ACIP

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Outline

- Overview of new evidence framework of the U.S. Advisory Committee on Immunization Practices (ACIP)
- Methodology for evaluating evidence
- Format for presenting evidence
- Key factors for formulating recommendations
- Format for presenting recommendations

New ACIP Evidence Framework

- **ACIP unanimously voted to adopt the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach in October 2010**
  - Quality of evidence for benefits and harms
  - Going from evidence to recommendations
- **Quality of evidence for benefits and harms is only one factor in developing a recommendation**
  - Other key factors include balance of benefits and harms, values, and health economic data

GRADE Uptake

- Agency for Health Care Research and Quality (AHRQ)
- American College of Chest Physicians
- American College of Physicians
- American Thoracic Society
- Allergic Rhinitis in Asthma Guidelines
- Infectious Diseases Society of America
- UpToDate
- British Medical Journal
- Canadian Cardiovascular Society
- Clinical Evidence
- Cochrane Collaboration
- European Society of Thoracic Surgeons
- National Institute Clinical Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

Overview of New ACIP Evidence Framework

- **Recommendation categories**
  - A: Applies to all persons in an age- or risk-based group
  - B: Recommendation for individual clinical decision making
- **Evidence type or quality**
  1. Randomized controlled trials (RCTs), or overwhelming evidence from observational studies
  2. RCTs with important limitations, or exceptionally strong evidence from observational studies
  3. RCTs with notable limitations, or observational studies
  4. RCTs with several major limitations, observational studies with important limitations, or clinical experience and observations

Evidence Type

- **The four evidence types represent a general hierarchy reflecting confidence in the estimated effect of vaccination on health outcomes (benefits, harms)**
  - Randomization minimizes potential bias and confounding, and randomized controlled trials (RCTs) are considered the gold standard for assessing vaccine efficacy
  - However, observational studies may provide more relevant information for rare or long-term outcomes
  - Observational studies provide useful information of the effect of vaccination under the conditions of everyday practice and when RCTs are not ethical or feasible

Steps

- Formulate specific questions to be answered by a recommendation
- Identify important outcomes for every question (benefits, harms)
- Summarize evidence for important outcomes
- Categorize type of evidence for each outcome
- Assess underlying values related to outcomes
- Judge the balance of benefits and harms
- Assess health economic data
- Formulate a recommendation

Methodology for Categorizing Evidence

Study design	Initial evidence type	Criteria for moving down	Criteria for moving up	Final evidence type
Randomized Controlled Trial (RCT)	1	Risk of bias Inconsistency Indirectness Imprecision Publication bias	Strength of association Dose-Response Direction of all plausible residual confounding or bias	1 2
Observational study	3			3 4

http://www.gradeworkinggroup.org/

RCTs are initially classified as evidence type 1, and observational studies as evidence type 3. Five GRADE criteria are used for moving down the evidence type. Three GRADE criteria are primarily used to move up the evidence type. These criteria determine the final classification of the evidence type.

Risk of Bias

Examples:

- Inappropriate selection of vaccinated and unvaccinated groups
- Failure to adequately measure/control for confounding
- Selective outcome reporting
- Lack of blinding
- High loss to follow-up
- Lack of allocation concealment in RCTs
- Intention to treat principle violated

Inconsistency

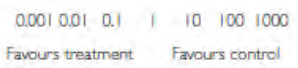
Analysis 6.1. Comparison 6 Inactivated vaccine versus placebo (RCTs), Outcome 1 Influenza.

Review: Vaccines for preventing influenza in healthy children

Comparison: 6 Inactivated vaccine versus placebo (RCTs)

Outcome: 1 Influenza

Study or subgroup	Vaccine n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 Inactivated vaccines (one dose)					
Beutner 1979a	28/300	82/275		41.8 %	0.31 [0.21, 0.47]
Clover 1991	9/54	36/82		16.6 %	0.38 [0.20, 0.72]
Gruber 1990	10/54	37/77		18.7 %	0.39 [0.21, 0.71]
Hoberman 2003a	15/273	22/138		17.7 %	0.34 [0.18, 0.64]
Hoberman 2003b	9/252	4/123		5.2 %	1.10 [0.35, 3.50]
Subtotal (95% CI)	**933**	**695**		**100.0 %**	**0.36 [0.28, 0.48]**
Total events: 71 (Vaccine), 181 (Control)					
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.13$, $df = 4$ ($P = 0.39$); $I^2 = 3\%$					
Test for overall effect: $Z = 7.42$ ($P < 0.00001$)					
2 Inactivated vaccines (two doses)					



Jefferson T, Rivetti A, Harnden A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in healthy children. *Cochrane Database of Systematic Reviews* 2008, Issue 2. Art. No.: CD004879. DOI: 10.1002/14651858.CD004879.pub3.

Inconsistency refers to the heterogeneity of results across studies. This slide shows the results of five studies assessing the efficacy of influenza vaccine in preventing influenza in healthy children. Overlapping 95% confidence intervals of the risk ratios, non-significant P value for heterogeneity (P=0.39), and a low I-square (I-sqaure=3%) indicate that the results are consistent.

Inconsistency

- **If inconsistency, look for explanation**
  - Population
  - Intervention
  - Comparator
  - Outcome
- **If unexplained inconsistency, move down evidence type**

Indirectness

- **Question addressed is different from the available evidence regarding the population, intervention, comparator, or outcome**
  - General population vs. subpopulations
  - Old vaccine vs. new formulation of the vaccine
  - Precancerous lesions vs. cancers

Indirectness

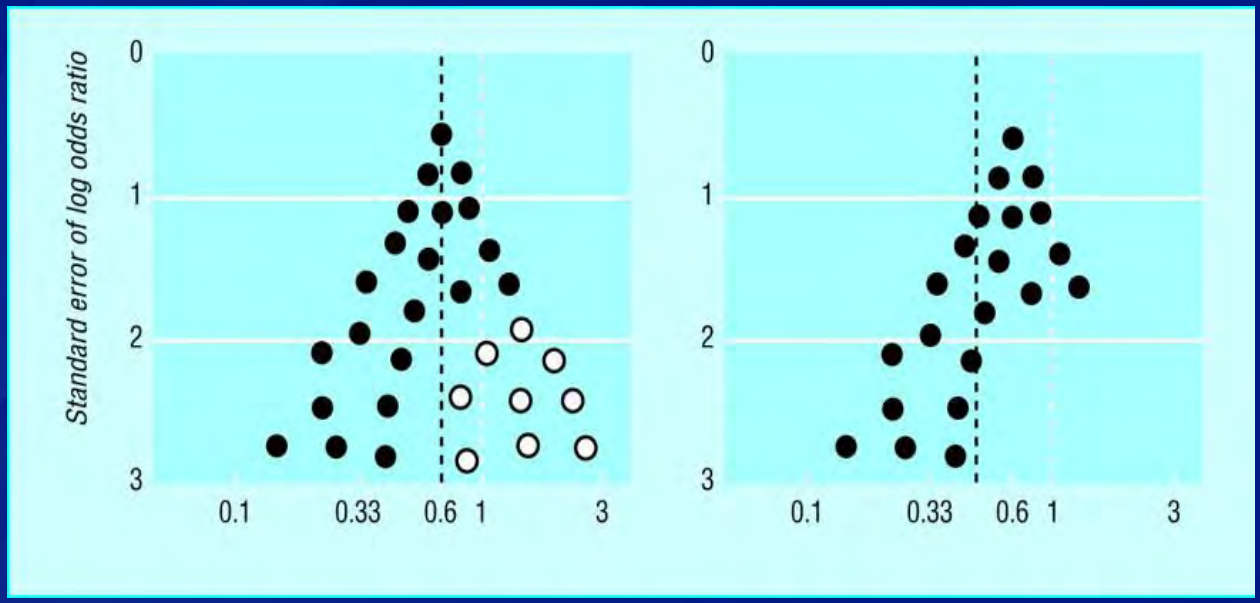
- **Indirect comparisons**
  - Interested in vaccine A versus vaccine B
  - Have A versus placebo and B versus placebo

Imprecision

- **Primarily assessed using the 95% confidence interval around the pooled *risk difference***
- **Move down for imprecision if the recommendation would differ if the upper or lower range of the confidence interval represented the risk difference**

Publication Bias

- **Funnel plots can help detect publication bias**
  - Graph the size of the study vs. the outcome
  - Plots may reveal a lack of smaller statistically insignificant studies



Slide courtesy of Dr. Craig Umscheid

In the graph on the left, the results of 30 studies are plotted, with odds ratio on the x-axis and standard error on the y-axis. A graph with symmetric distribution suggests no publication bias. An asymmetric distribution, as shown in the graph on the right, suggests publication bias.

General Approach when Moving Down the Evidence Type for an Outcome

- **Study level**
  - Identification of "flaw"
  - Is it important for the outcome of interest?
  - If important, is the severity of the problem likely to change the estimated effect of vaccination?
- **Body of evidence level**
  - How many studies are affected?
  - Are other GRADE criteria met for moving down?
  - Does the sum of limitations warrant moving down?

Strength of Association

- **The stronger the association, the less likely it is that all of the apparent benefit or harm can be explained by residual confounding or bias**
- **Move up by one level if strong association**
  - Relative Risk > 2 (or < 0.5)*
- **Move up by two levels if very strong association**
  - Relative Risk > 5 (or < 0.2)

*At least 2 studies

Dose Response

- Increasing vaccine efficacy with increasing number of doses
- Declining disease incidence with increasing population vaccination rates

Direction of Residual Confounding or Bias

(Hypothetical Example)

- Vaccine X suspected of being associated with adverse event Y
- Publicity may result in an increased spontaneous reporting of adverse event Y in vaccinated persons compared to that in unvaccinated persons
- Epidemiological studies find no association
- Initial evidence type of 3 can be moved up to 2 because no association found despite the bias associated with differential reporting due to publicity

What If It Is Not Possible to Conduct Randomized Trials in Subpopulations?

- **The indirectness criterion can be used to assign evidence type for subpopulations not included in trials**
- **Experts judge applicability of the evidence for the general population to subpopulations**
- **Example: Rotavirus vaccine**
  - Evidence type for vaccine efficacy in healthy infants: 1
  - Efficacy data not available for infants with chronic gastrointestinal tract diseases
    - Based on experts' judgment of the applicability of the evidence, evidence type may be assigned as 2 or 3 using the indirectness criterion

Does the Evidence Framework Take Biologic Information into Account?

- **Biologic information may be taken into account when assessing applicability of indirect evidence**
- **Examples**
  - Applicability of evidence for the general population to subpopulations
  - Applicability of evidence for an old vaccine to a new formulation of the vaccine
  - Applicability of evidence for shorter-term outcomes to long-term outcomes (e.g., hepatitis B infection vs. liver cancer)

Expert Judgment

- Categorizing evidence involves judgments that are inherent to any evidence evaluation system
- One strength of the GRADE approach is that it requires explicit judgment that is made transparent to users so that disagreements can be resolved

Format for Presenting Evidence

- **Evidence Tables**
  - Benefits and Harms
  - Evidence type

Benefits and Harms

Outcome	No. of subjects (# studies)	Incidence in controls	Incidence in vaccinated	Vaccine efficacy (Relative risk)	Absolute risk	Number Needed to Treat (Harm)
Outcome 1						
Outcome 2						
Outcome 3						

Evidence tables showing the magnitude of benefits and harms should include the number of subjects, number of studies, incidence in controls, incidence in vaccinated, vaccine efficacy or relative risk, absolute risk difference, and number need to treat for each outcome. Both the relative and absolute effects of vaccination are shown.

Type of Evidence

Outcome	Design (# studies)	Risk of bias	Inconsis-tency	Indirect-ness	Impreci-sion	Other consider-ations*	Evidence type
Outcome 1							
Outcome 2							
Outcome 3							

*Strength of association, dose-response, plausible residual confounding, publication bias.

Evidence tables showing the type of evidence should include the study design, the number of studies, the five GRADE criteria for moving down the evidence type, the three GRADE criteria for moving up the evidence type, and the final evidence type.

Examples of Presenting Evidence Type for Post-licensure Vaccine Safety Studies

- Combination Measles, Mumps, Rubella, and Varicella vaccine (MMRV)
- Rhesus-based tetravalent rotavirus vaccine (Rotashield)

MMRV Vaccination: Febrile Seizure after Dose 1*

Finding	Design (# studies)	Risk of bias	Inconsis-tency	Indirect-ness	Impreci-sion	Other consider-ations	Evidence type
Increased risk 5-12 days after vac	Observ-ational (2)	No serious	No serious	No serious	No serious	**Yes**[†]	2
Decreased risk 13-30 days after vac	Observ-ational (2)	No serious	No serious	No serious	**Serious**[‡]	None	4

*MMRV compared to MMR+V vaccination for children ages 12-23 months.

[†]Moved up initial evidence type of 3 by one level because relative risk ~2 based on consistent evidence from two studies (*strength of association*).

[‡]Moved down initial evidence type by one level because of *imprecision*.

One study indicated a decrease but not significant, one study found no association.

This slide shows the evidence type for the combination MMRV vaccine compared to separate injections of MMR and varicella vaccine. Febrile seizure after the first dose is assessed at two points in time in the two studies: 5 to 12 days after vaccination, and 13 to 30 days after vaccination. Because the study design is observational for both studies, the initial evidence type is 3. For the finding of increased risk of febrile seizure 5 to 12 days after vaccination, the initial evidence type of 3 has been moved up by one level to 2 using the strength of association criterion of relative risk of about 2. For the finding of decreased risk of febrile seizure 13 to 30 days after vaccination, the initial evidence type of 3 has been moved down by one level to 4 because of imprecision.

Rotashield Vaccination: Risk of Intussusception

Finding	Design* (# studies)	Risk of bias	Inconsis-tency	Indirect-ness	Impreci-sion	Other consider-ations	Evidence type
Increased risk 3-14 days after vac	Observa-tional (2)	No serious	No serious	No serious	No serious	**Yes**†	1

*Included cohort and case-control studies available at the time the ACIP withdrew its recommendation; Excluded ecological studies.

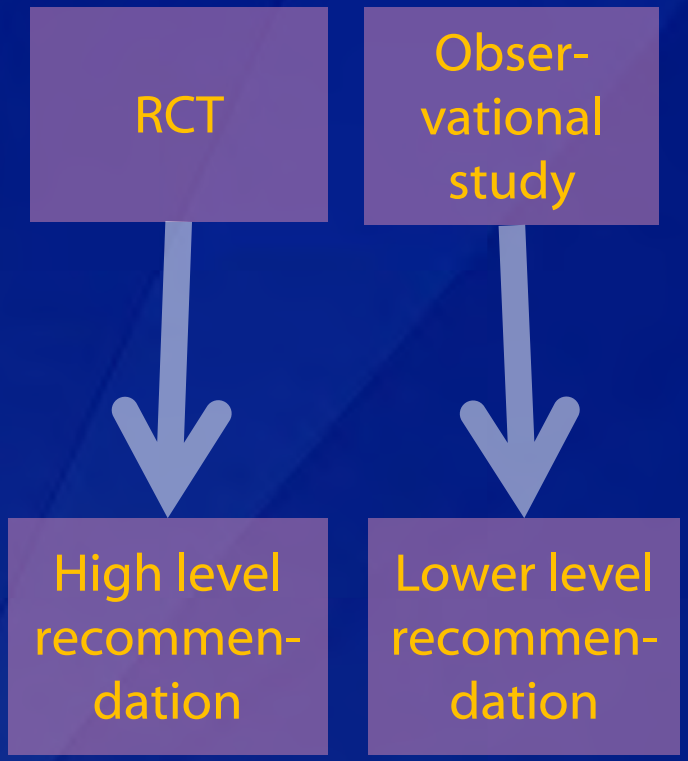
†Moved up initial evidence type of 3 by two levels because relative risk of intussusception for vaccinated compared to unvaccinated infants is greater than 5 (*strength of association*).

This slide shows the evidence type for the risk of intussusception after Rotashield vaccination. Rotashield vaccine was withdrawn from the U.S. market in 1999 because of a reported association with intussusception. The initial evidence type of 3 has been moved up by 2 levels because the relative risk is greater than 5.

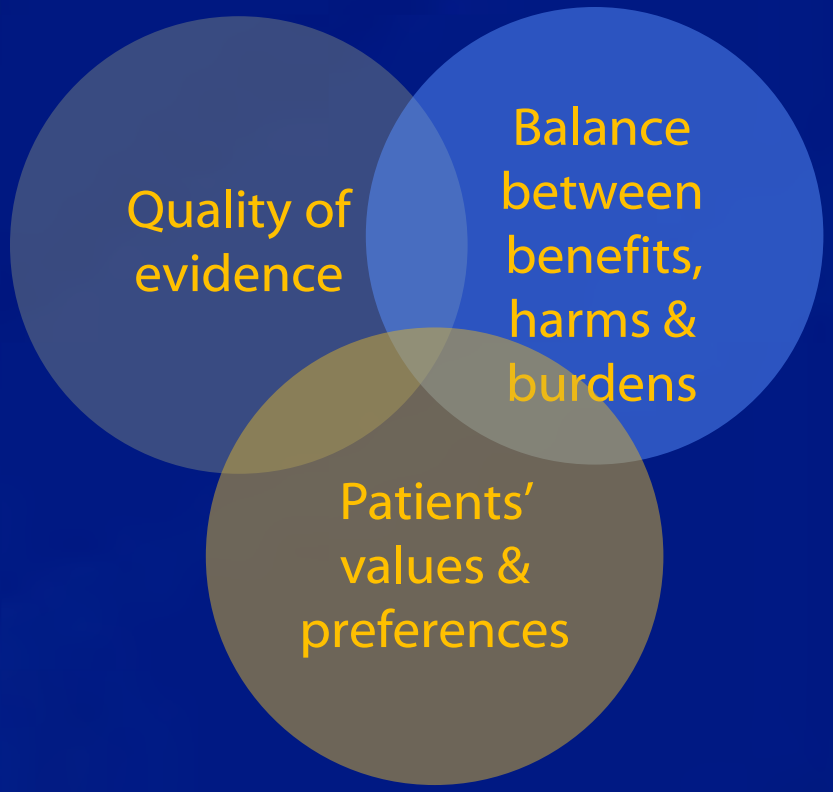
Going from Evidence to Recommendations

- Deliberate separation of type or quality of evidence from recommendation category
- No automatic one-to-one connection as in other grading systems
- Other factors beyond the type of evidence influence the recommendation category

From Evidence to Recommendations



Old system



GRADE

Slide courtesy of Dr. Yngve Falck-Ytter

In the old system, data from RCTs resulted in high level recommendations, and data from observational studies resulted in lower level recommendations. In the GRADE system, the recommendation category depends not only on the quality of evidence but also on the balance between benefits and harms and on values and preferences.

ACIP Recommendation Categories

- **Category A: Applies to all persons in an age or risk group**
  - Desirable effects outweigh undesirable effects (recommendation for)
  - Undesirable effects outweigh desirable effects (recommendation against)
- **Category B: Individual clinical decision-making**
- **No recommendation/unresolved issue**

Desirable: benefits, savings. *Undesirable:* harms, costs.

Considerations for Formulating Recommendations

Key Factors	Explanation
Evidence type for benefits and harms	The higher the confidence in the estimated effect of vaccination on health outcomes, the more likely is a category A recommendation.
Balance between benefits and harms	The larger the difference between the benefits and harms, the more likely is a category A recommendation. The smaller the net benefit and the lower certainty for that benefit, the more likely is a category B recommendation.
Values	The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely is a category B recommendation.
Health economic data (e.g., cost-effectiveness)	The lower the cost-effectiveness, the more likely is a category B recommendation.

Balance Between Benefits and Harms

- **Smaller net benefit**
  - Low burden of disease (baseline risk)
  - Small absolute effect of vaccination
  - Small relative effect of vaccination

Values

- Relative importance of outcomes related to benefits, harms, and costs
- Values should reflect those of the people affected

Health Economic Analyses

- Health economic analyses based on modeling often presented to the ACIP
- The above methodology for categorizing the type or quality of evidence is not intended to be applied to economic modeling studies

ACIP Wording of Recommendations

- **Category A**
  - Use words like "recommend," "recommend against," "should," "should not"
- **Category B**
  - Use words like "may," "suggest against"

Format for Presenting ACIP Recommendations

- **Recommendation**
  - ACIP recommends/does not recommend … (Recommendation category, Evidence type)
- **Remarks**
  - The key considerations behind the recommendation should be described here

Example of Applying Framework to New Vaccine

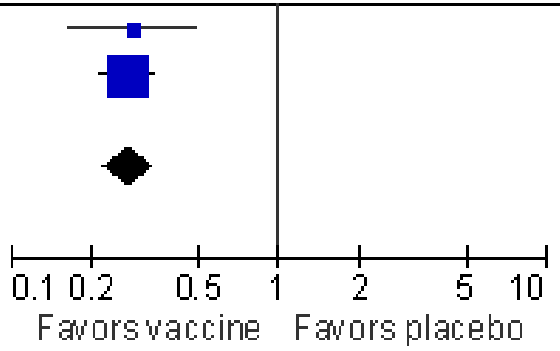
- **Human-bovine reassortant pentavalent rotavirus vaccine (RotaTeq)**
- **Used studies available at the time of the 2006 ACIP recommendation**
  - Included phase 3 studies of the pentavalent vaccine (excluded phase 1 and 2 studies that used a different vaccine formulation)
  - Excluded studies of rotavirus vaccines using other rotavirus strains (e.g., human-rhesus, human, lamb, bovine)

Pentavalent Rotavirus Vaccine Outcome: Rotavirus Diarrhea

Study or Subgroup	Vaccine Events	Vaccine Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Block 2007	15	551	54	564	14.8%	0.28 [0.16, 0.50]
Vesikari 2006	82	2207	315	2305	85.2%	0.27 [0.21, 0.34]
Total (95% CI)		**2758**		**2869**	**100.0%**	**0.27 [0.22, 0.34]**
Total events	97		369			

Heterogeneity: $Chi^2 = 0.02$, df = 1 (P = 0.89); $I^2 = 0\%$

Test for overall effect: Z = 11.68 (P < 0.00001)



- Pooled risk ratio = 0.27 (95% CI: 0.22, 0.34)
- Pooled vaccine efficacy = 73% (95% CI: 66, 78)*
- Pooled incidence in controls (weighted) = 12.9%
- Pooled incidence in vaccinated = 3.5%**

*Pooled vaccine efficacy = (1 – pooled risk ratio) x 100

**Incidence in vaccinated = incidence in controls x pooled risk ratio

This slide shows results from two studies of the efficacy of pentavalent rotavirus vaccine in reducing rotavirus diarrhea. The pooled risk ratio using meta-analysis is 0.27 with confidence interval of 0.22 to 0.34. The pooled vaccine efficacy is 73%, the pooled incidence in controls is 12.9%, and the pooled incidence in vaccinated is 3.5%. The formulae for calculating pooled vaccine efficacy and pooled incidence in vaccinated are shown at the bottom.

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)	12.9%	3.5%	73% (66, 78)	-94 (-85, -100)	11
Severe RV diarrhea	5,627 (2 RCTs)	2.0%	0.1%	97% (86, 99)	-19 (-17, -20)	52
Hospitaliza-tion for RV diarrhea	57,134 (1 RCT)	0.5%	0.02%	96% (91, 98)	-5 (-5, -5)	205

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

Data from the previous slide for the outcome rotavirus diarrhea are shown here in the format of an evidence table. The absolute risk difference is the incidence in vaccinated minus the incidence in controls, expressed per 1000 instead of percent or per 100. The number needed to treat is one divided by the absolute risk difference. Data are also shown for the outcomes severe rotavirus diarrhea and hospitalization for rotavirus diarrhea.

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 Treat
Intussus-ception	70,139 (3 RCTs)	1.4 per 10,000	1.7 per 10,000	1.20 (0.37–3.93)	0.03 (-0.1, 0.4)	-
Other serious adverse events	70,139 (3 RCTs)	2.3%	2.2%	0.96 (0.87–1.06)	-1 (-3, 1)	-

This slide shows the evidence table for safety for the outcomes intussusception and other serious adverse events. The absolute risk difference for intussusception is 0.03 per 1000, or 3 per 100,000. However, it is not statistically significant. The absolute risk difference is also not statistically significant for other serious adverse events. The number needed to treat is not meaningful when the absolute risk difference is not statistically significant.

Evidence Type: Pentavalent Rotavirus Vaccine

Outcome	Design (# studies)	Risk of bias	Inconsis-tency	Indirect-ness	Impreci-sion	Other consider-ations	Evidence type
Rotavirus diarrhea (RV)	RCT (2)	No serious	No serious	No serious	No serious	None	1
Severe RV diarrhea	RCT (2)	No serious	No serious	No serious	No serious	None	1
Hospitaliza-tion for RV diarrhea	RCT (1)	No serious	No serious	No serious	No serious	None	1
Intussus-ception	RCT (3)	No serious	No serious	No serious	No serious	None	1
Other serious adverse events	RCT (3)	No serious	No serious	No serious	No serious	None	1

RCT: Randomized controlled trial

The first row shows the evidence type for the outcome rotavirus diarrhea. The initial evidence type is 1 because the study design for the two studies is RCT. No serious limitations were detected for any of the five GRADE criteria for moving down the evidence type, and so the final evidence type is also 1. Similarly, the final evidence type for the other outcomes shown here is also 1.

Summary of Evidence

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

*Critical outcome (overall evidence type is based on the critical outcomes).
RCT: Randomized controlled trial.

The overall evidence type is based on the evidence type for the critical outcomes. In this example, severe rotavirus diarrhea, hospitalization for rotavirus diarrhea, intussusception, and other serious adverse events are considered critical for making a recommendation. Members of a guideline or recommendation panel decide which outcomes are critical.

Considerations for Formulating Recommendations:
Pentavalent Rotavirus Vaccine (RotaTeq)

Key factors	Comments
Balance between benefits and harms	Benefits are large compared to potential harms
Evidence type for benefits and harms	1
Values	Parents likely to place high value on preventing severe rotavirus diarrhea
Cost-effectiveness	Vaccine price not known. Vaccine is likely to be cost-saving from the societal perspective at a cost of $42 per dose

[The vaccine price was not known when the ACIP recommended routine use of rotavirus vaccine in 2006].

Recommendation for Use of Rotavirus Vaccine (RotaTeq)

- **Recommendation**:
  ACIP recommends vaccination of U.S. infants with three doses of rotavirus vaccine administered orally at ages 2, 4, and 6 months (recommendation category: A, evidence type: 1).

  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. Benefits of vaccination are large compared to potential harms.

Example of Risk-based Recommendation

- **Recommendation**:
  Pneumococcal polysaccharide vaccine should be administered to children aged 2 years or older with certain underlying medical conditions, including a cochlear implant (recommendation category: A, evidence type: …).

  Remarks: …

Example of Recommendation Against

- **Recommendation**:
  ACIP recommends that the 2010-11 Afluria vaccine should not be administered to children aged 6 months through 8 years (recommendation category: A. evidence type: …).

  Remarks: …

Example of Recommendation for Individual Clinical Decision Making

- **Recommendation**:
  The 2010-11 Afluria vaccine may be used for a child aged 5 to 8 years with a medical condition that increases the child's risk for influenza complications if no other age-appropriate influenza vaccine is available (recommendation category: B, evidence type: …).

  Remarks: ...

Summary of New ACIP Evidence Framework

- **Recommendation categories**
  - A: Applies to all persons in an age- or risk-based group
  - B: Recommendation for individual clinical decision making
- **Evidence type**
  1. Randomized controlled trials (RCTs), or overwhelming evidence from observational studies
  2. RCTs with important limitations, or exceptionally strong evidence from observational studies
  3. RCTs with notable limitations, or observational studies
  4. RCTs with several major limitations, observational studies with important limitations, or clinical experience and observations

For more information please contact Centers for Disease Control and Prevention

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

National Center for Immunization & Respiratory Diseases
Immunization Services Division

Additional Slides

Institute of Medicine

- **Eight standards for developing rigorous, trustworthy clinical practice guidelines**
  1. Establishing transparency
  2. Management of conflict of interest
  3. Guideline development group composition
  4. Evidence based on systematic reviews
  5. Method for rating strength of recommendations
  6. Articulation of recommendations in a standardized form
  7. External review
  8. Updating

Ref: IOM. Clinical Practice Guidelines We Can Trust. March 23, 2011