GRADE for the development of evidence-based recommendations for immunization

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Disclosure

- Co-chair GRADE Working Group
- Work with various guideline groups using GRADE
- No direct personal for profit payments for work related to the topic area
- *American College of Physicians (ACP)* Clinical Practice Guidelines Committee
- WHO: Expert Advisory Panel on Clinical Practice Guidelines and Clinical Research Methods and Ethics & chair of various guideline panels

Content

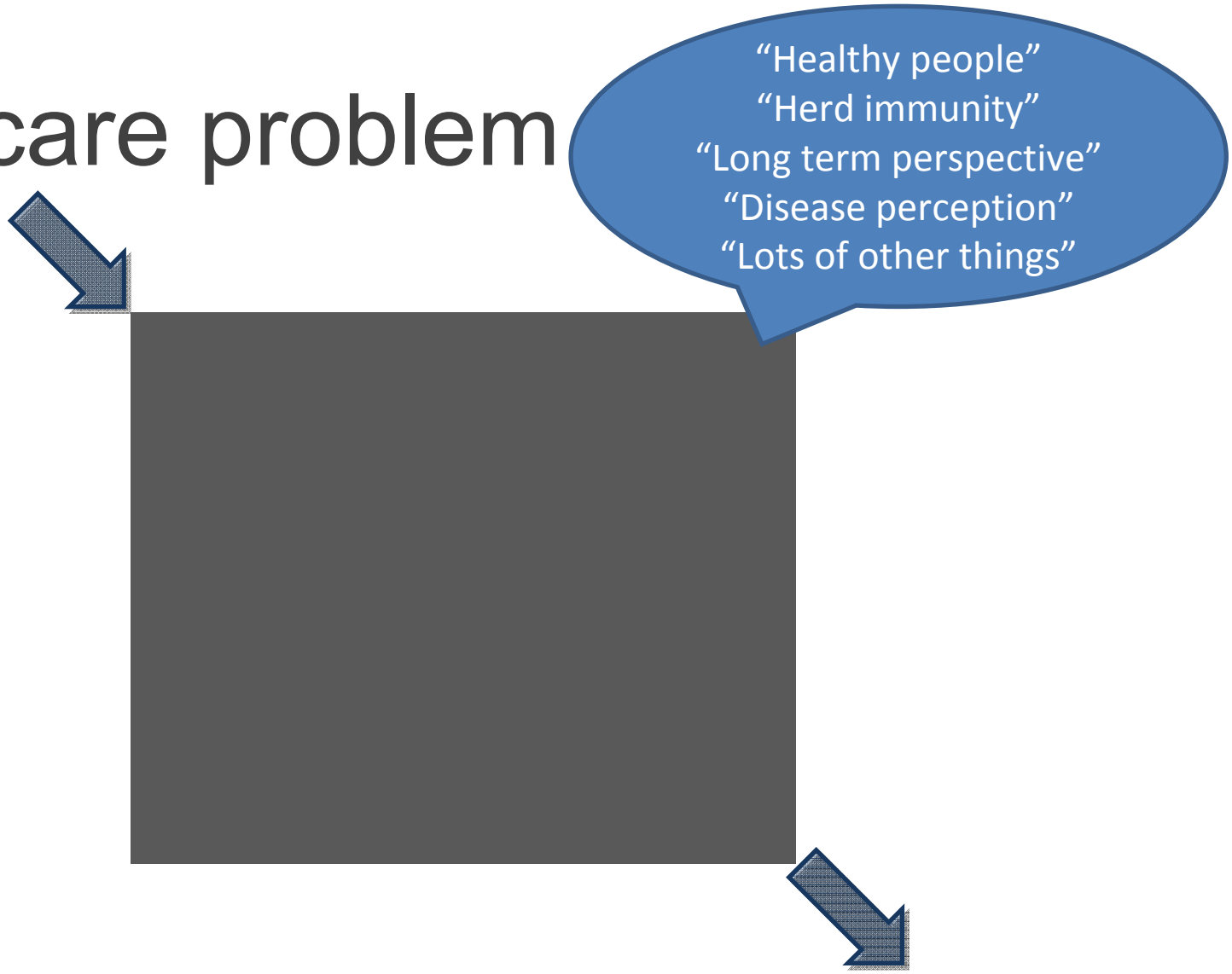
GRADE and immunizations

- Quality of evidence
- Going from evidence to recommendations

GRADE Uptake

- World Health Organization
- Allergic Rhinitis in Asthma Guidelines (ARIA)
- American Thoracic Society
- American College of Physicians (ACP)
- Canadian Task Force for the Preventive Services
- European Respiratory Society
- European Society of Thoracic Surgeons
- British Medical Journal
- Infectious Disease Society of America
- UpToDate®
- National Institutes of Health and Clinical Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- Cochrane Collaboration
- Clinical Evidence
- Agency for Health Care Research and Quality (AHRQ)
- Partner of GIN
- Over 40 major organizations

Healthcare problem



recommendation

Guideline development Process (for WHO)

Health Research P

Review

Improving the use of resea introduction

Andrew D Oxman*[1], Atle Fretl

Review

Improving the use of resea 1. Guidelines for guidelines

Holger J Schünemann*[1], Atle I

Published: 21 November 2006

Health Research Policy and Systems 2006, **4**:13 doi:10.1186/

This article is available from: http://www.health-policy-syster

Key issues

Guidelines for guidelines
Priority setting
Group composition and consultation process
Managing conflicts of interest
Group processes
Determining which outcomes are important
Deciding what evidence to include
Synthesis and presentation of evidence
Grading evidence and recommendations
Integrating values and preferences in guidelines
Incorporating considerations of cost-effectiveness, affordability implications
Incorporating considerations of equity
Adaptation, applicability and transferability
Reporting guidelines
Disseminating and implementing guidelines
Evaluation

GRADE

Evidence based healthcare decisions

State and circumstances

Population/societal values and preferences

Haynes et al. 2002

Case scenario

A 13 year old girl who lives in rural Indonesia presented with flu symptoms and developed severe respiratory distress over the course of the last 2 days. She required intubation. The history reveals that she shares her living quarters with her parents and her three siblings. At night the family's chicken stock shares this room too and several chicken had died unexpectedly a few days before the girl fell sick.

Potential interventions: antivirals, such as neuraminidase inhibitors oseltamivir and zanamivir

Framing a foreground question

Population: Avian Flu/influenza A (H5N1) patients

Intervention: Oseltamivir

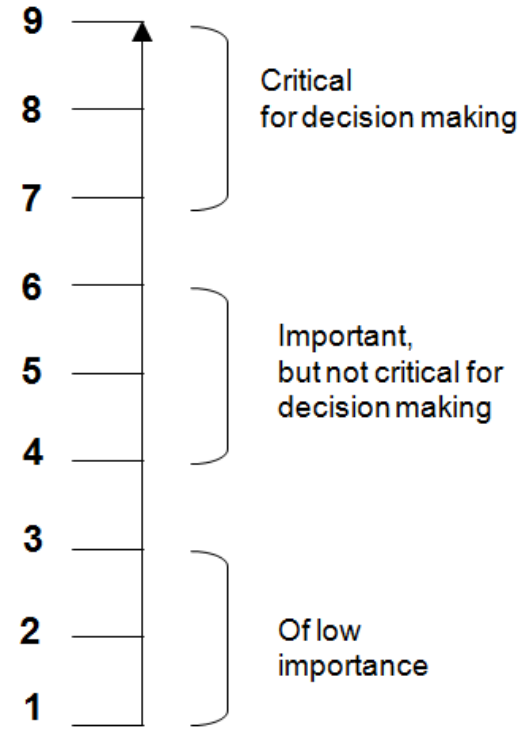
Comparison: No pharmacological intervention

Outcomes: Mortality, hospitalizations, resource use, adverse outcomes, antimicrobial resistance

Schunemann, et al., The Lancet ID, 2007

Choosing outcomes

- Desirable outcomes
  - lower mortality
  - reduced hospital stay
  - herd immunity (new cases)
  - reduced resource expenditure
- Undesirable outcomes
  - adverse reactions
  - the development of resistance
  - costs of treatment



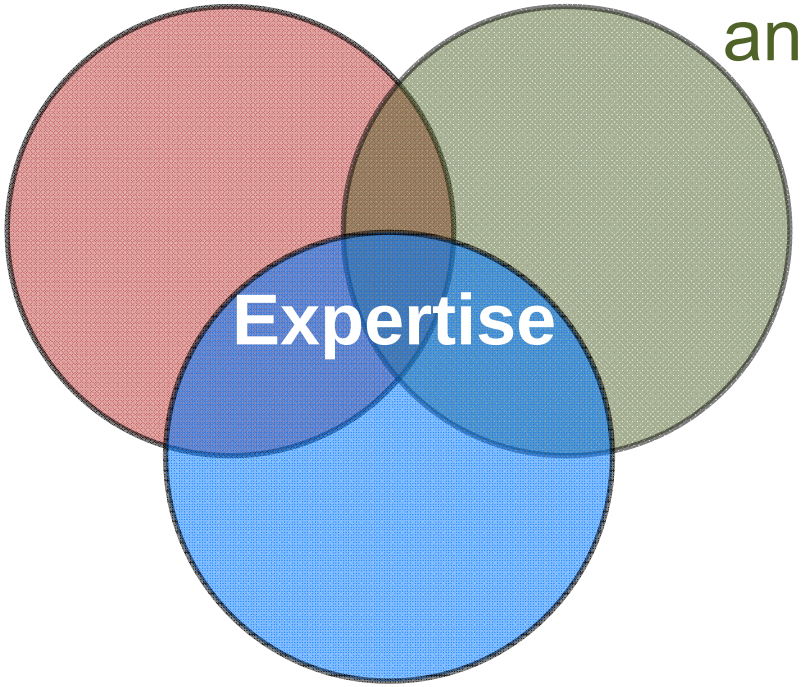
- Every decision comes with desirable and undesirable consequences

  →Developing recommendations must consider of desirable and undesirable outcomes

Evidence based healthcare decisions

State and circumstances

Population/societal values and preferences



Evidence about effects

Haynes et al. 2002

GRADE: recommendations & quality of (a body of)evidence

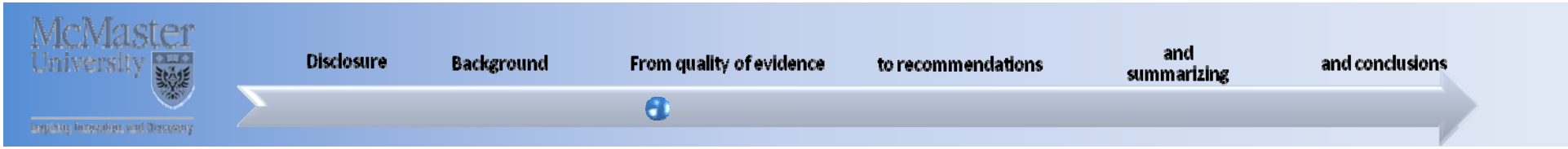
Clear separation, but *judgments* required:

1) Recommendation: 2 grades – conditional (aka weak) or strong (for or against an action)?
   - Balance of benefits and downsides, values and preferences, resource use and quality of evidence

2) 4 categories of quality of evidence:

   ⊕⊕⊕⊕ (High), ⊕⊕⊕◯(Moderate), ⊕⊕◯◯(Low), ⊕◯◯◯(Very low)?
   - methodological quality of evidence
   - likelihood of bias related to recommendation
   - by outcome and across outcomes

*www.GradeWorking-Group.org



GRADE Quality of Evidence

In the context of making recommendations:

- The quality of evidence reflects the extent of our confidence that the estimates of an effect are adequate to support a particular decision or recommendation.

Figure 1. *Belief and confidence: a two-dimensional weather report. (Reprinted by permission from the Wall Street Journal).*

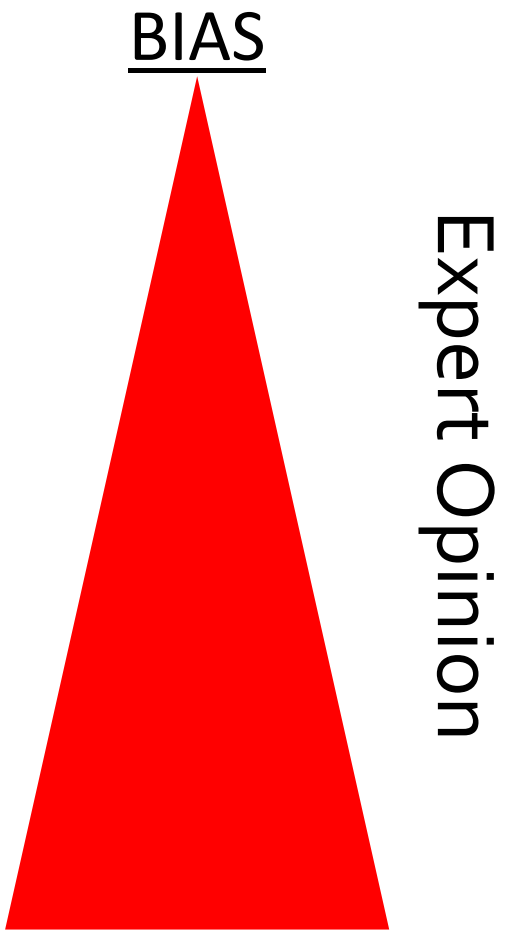
Likelihood of and confidence in an outcome

Simple hierarchies are (too) simplistic

STUDY DESIGN

- Randomized Controlled Trials
- Cohort Studies and Case Control Studies
- Case Reports and Case Series, Non-systematic observations

Expert Opinion



Schünemann & Bone, 2003

Determinants of quality

- RCTs ⊕⊕⊕⊕
- observational studies ⊕⊕◯◯
- 5 factors that can lower quality
  1. limitations in detailed design and execution *(risk of bias criteria)*
  2. Inconsistency *(or heterogeneity)*
  3. Indirectness *(PICO and applicability)*
  4. Imprecision *(number of events and confidence intervals)*
  5. Publication bias
- 3 factors can increase quality
  1. large magnitude of effect
  2. plausible residual bias or confounding
  3. dose-response gradient

1. Design and Execution / Risk of Bias

Examples:

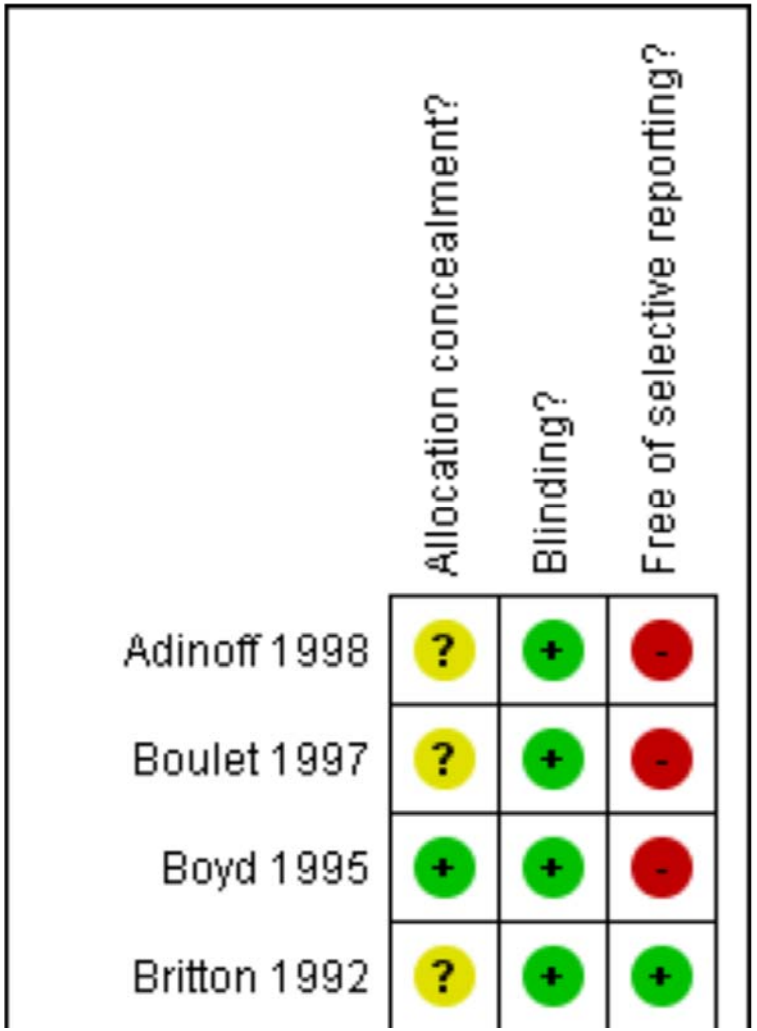
- Inappropriate selection of exposed and unexposed groups
- Failure to adequately measure/control for confounding
- Selective outcome reporting
- Failure to blind (e.g. outcome assessors)
- High loss to follow-up
- Lack of concealment in RCTs
- Intention to treat principle violated

Design and Execution / RoB

Regular treatment with salmeterol for chronic asthma: serious adverse events (Review)

Cates CJ, Cates MJ

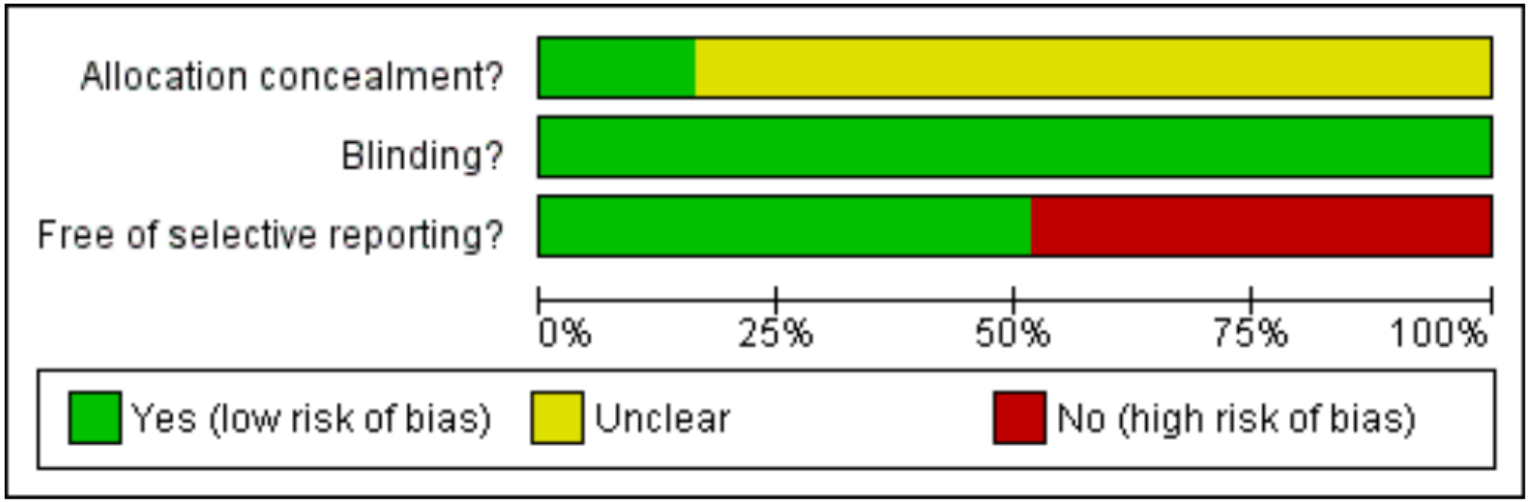
Figure 4. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.



From Cates , CDSR 2008

Design and Execution / RoB

Figure 3. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies.



Overall judgment required

2. Publication Bias

- Should always be suspected
  - Only small “positive” studies
  - For profit interest
  - Various methods to evaluate – none perfect, but clearly a problem

3. Inconsistency of results (heterogeneity)

- if inconsistency, look for explanation
  - patients, intervention, comparator, outcome
- if unexplained inconsistency lower quality

Reminders for immunization uptake

Analysis 2.1. Comparison 2 letter reminders vs. control, Outcome 1 Immunized.

Study or subgroup	Letter reminders n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Odds Ratio M-H,Random,95% CI
2 Preschool-child				
Campbell1994T87	54/87	59/105		1.28 [0.71, 2.28]
Lieu1997T69	82/153	47/136		2.19 [1.36, 3.52]
Lieu1998T82	72/162	78/219		1.45 [0.95, 2.19]
Oeffinger1992T27	33/116	31/122		1.17 [0.66, 2.07]
Young1980T63	51/106	34/105		1.94 [1.11, 3.39]
Subtotal (95% CI)	**624**	**687**		**1.58 [1.26, 1.99]**

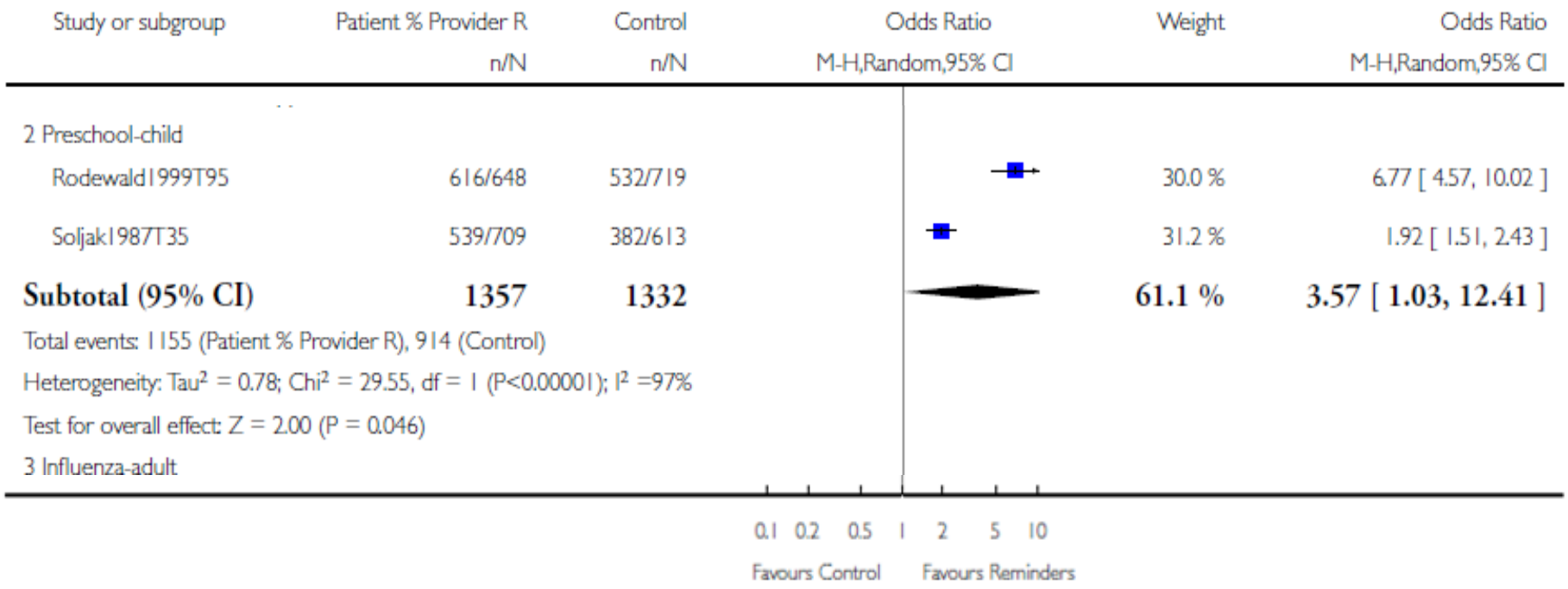
Total events: 292 (Letter reminders), 249 (Control)

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.08$, df = 4 (P = 0.40); $I^2 = 2\%$

Test for overall effect: Z = 3.92 (P = 0.000088)

Jacobson et al., CDRS 2005

Analysis 6.1. Comparison 6 patient & provider reminder vs. control, Outcome 1 Immunized.



Jacobson et al., CDRS 2005

4. Imprecision

- Small sample size
  - small number of events
- Wide confidence intervals
  - uncertainty about magnitude of effect

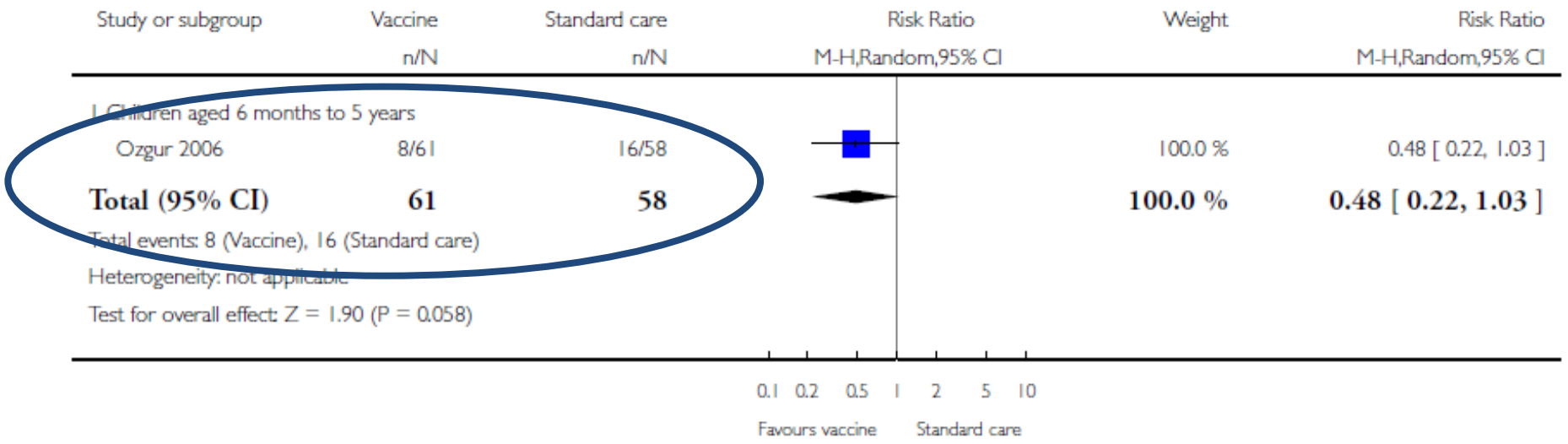
Example: Immunization in children

Analysis 4.3. Comparison 4 Inactivated vaccines - (cohort studies by age group), Outcome 3 Otitis media.

Review: Vaccines for preventing influenza in healthy children

Comparison: 4 Inactivated vaccines - (cohort studies by age group)

Outcome: 3 Otitis media



Jefferson et al., CDRS 2008

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)					

0.001 0.01 0.1 1 10 100 1000

Favours treatment Favours control

5. Directness of Evidence generalizability, transferability, applicability

- differences in
  - populations/patients (children – neonates, women in general – pregnant women)
  - interventions (all vaccines, new - old)
  - comparator appropriate (new policy – old or no policy)
  - outcomes (important – surrogate: cases prevented – seroconversion/immunogenicity)
- indirect comparisons
  - interested in A versus B
  - have A versus C and B versus C
  - Vaccine A versus Placebo versus Vaccine B

What can raise quality?

1. large magnitude can upgrade
   (RRR 50%/RR 2; RRR 80%/RR 5)
   - criteria
     - everyone used to do badly
     - almost everyone does well
   - parachutes to prevent death when jumping from airplanes

Reminders for immunization uptake

Review: Patient reminder and recall systems to improve immunization rates

Comparison: 7 Patient Reminders (summary) vs. control

Outcome: 1 Immunized

Study or subgroup	Patient Reminder Sum n/N	Control n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
4 Other-adult					
Hogg1998T101	21/866	4/458			2.82 [0.96, 8.27]
Sansom2003T514	242/279	197/245			1.59 [1.00, 2.55]
Siebers1985T36	20/72	3/39			4.62 [1.28, 16.70]
Subtotal (95% CI)	**1217**	**742**			**2.19 [1.21, 3.99]**
Total events: 283 (Patient Reminder Sum), 204 (Control)					
Heterogeneity: $Tau^2 = 0.10$; $Chi^2 = 2.93$, df = 2 (P = 0.23); $I^2 = 32\%$					
Test for overall effect: Z = 2.57 (P = 0.010)					

Citation: Jacobson Vann JC, Szilagyi P. Patient reminder and recall systems to improve immunization rates. *Cochrane Database of Systematic Reviews* 2005, Issue 3. Art. No.: CD003941. DOI: 10.1002/14651858.CD003941.pub2.

What can raise quality?

2. dose response relation
   - childhood lymphoblastic leukemia
     - risk for CNS malignancies 15 years after cranial irradiation
     - no radiation: 1% (95% CI 0% to 2.1%)
     - 12 Gy: 1.6% (95% CI 0% to 3.4%)
     - 18 Gy: 3.3% (95% CI 0.9% to 5.6%)

3. all plausible residual confounding may be working to reduce the demonstrated effect or increase the effect if no effect was observed

All plausible residual confounding would overestimate effect

- Hypoglycaemic drug phenformin causes lactic acidosis
- The **related** agent metformin is under suspicion for the same toxicity.
- Large observational studies have failed to demonstrate an association
  - Clinicians would be more alert to lactic acidosis in the presence of the agent
- Vaccine – adverse effects

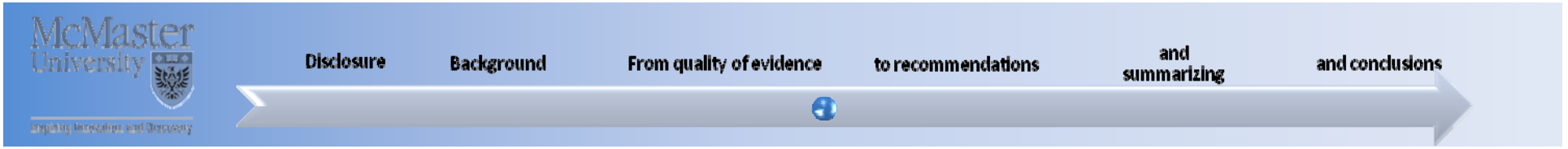


Table 1 Bradford Hill criteria of causality and their relation to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) criteria for upgrading and downgrading

Bradford Hill criteria	Consideration in GRADE
Strength	Strength of association and imprecision in effect estimate
Consistency	Consistency across studies, ie, across different situations (different researchers)
Temporality	Study design, specific study limitations; RCTs fulfil this criterion better than observational studies, properly designed and conducted observational studies
Biological gradient	Dose–response gradient
Specificity	Indirectness
Biological plausibility	Indirectness
Coherence	Indirectness
Experiment	Study design, randomisation, properly designed and conducted observational studies
Analogy	Existing association for critical outcomes will lead to not downgrading the quality, indirectness

Schünemann et al. JECH 2010

GRADE and immunizations

- Can herd immunity following immunisation and indirect effects on the co-circulation of other pathogens typically be ascertained only through the use of observational epidemiological methods?
  - Frequently yes, but innovative randomized controlled trials (RCTs) using cluster-randomization increasingly can be (are) done
- A 94% protective effect of a live, monovalent vaccine against measles is classified as “moderate level of scientific evidence.”
  - GRADE’s strength of association criteria maybe applied to increase the grade by 2 levels – from “low” to “high” - possible in this situation

GRADE and immunizations

- GRADE ratings do not give credit to "*gradient* of effects with scale of population level impact compatible with degree of coverage."
  - GRADE's dose-response criterion would apply to such gradients
- May anti-vaccination lobby groups abuse the ratings
  - Abuse of any system is possible: equally likely that increased transparency provided by the GRADE framework can strengthen, rather than undermine, the trust in vaccines and other interventions

Quality assessment criteria

Study design	Initial quality of a body of evidence	Lower if	Higher if	Quality of a body of evidence
Randomised trials	**High**	**Risk of Bias** **Inconsistency**	**Large effect** **Dose response** **All plausible residual**	**A/High** (four plus: ⊕⊕⊕⊕)
		Indirectness **Imprecision**	**confounding & bias** -Would reduce a demonstrated effect -Would suggest a spurious effect if no effect was observed	**B/Moderate** (three plus: ⊕⊕⊕◯)
Observational studies	**Low**	**Publication bias**		**C/Low** (two plus: ⊕⊕◯◯)
				D/Very low (one plus: ⊕◯◯◯)

Pentavalent Rotavirus Vaccine: Evidence Profiles

Outcome	Design (# studies)	Study limitations	Inconsis-tency	Indirect-ness	Impreci-sion	Other considera-tions	Incidence in controls	Incidence in vaccinated	Vaccine efficacy (95% CI)	Absolute risk per 1000 (95% CI)	Number Needed to Treat (Vaccinate)	Evidence grade
Rotavirus diarrhea (RV)	RCT (2)	No serious	No serious	No serious	No serious	None	12.9%	3.5%	73% (66, 78)	-94 (-85, -100)	11	A
Severe RV diarrhea	RCT (2)	No serious	No serious	No serious	No serious	None	2.0%	0.1%	97% (86, 99)	-19 (-17, -20)	52	A
Hospitalization for RV diarrhea	RCT (1)	No serious	No serious	No serious	No serious	None	0.5%	0.02%	96% (91, 98)	-5 (-5, -5)	205	A
Intussusception	RCT (3)	No serious	No serious	No serious	No serious	None	1.4 per 10,000	1.7 per 10,000	1.20 (0.37–3.93)	0.03 (-0.1, 0.4)	-	A
Other serious adverse events	RCT (3)	No serious	No serious	No serious	No serious	None	2.3%	2.2%	0.96 (0.87–1.06)	-1 (-3, 1)	-	A
Fever	RCT (3)	No serious	No serious	No serious	No serious	None	38.9%	37.7%	0.97 (0.92–1.01)	-12 (-31,4)	-	A

Quality of evidence

Outcome	Design (# studies)	Study limitations	Inconsis-tency	Indirect-ness	Impreci-sion	Other considera-tions	Evidence grade
Rotavirus diarrhea (RV)	RCT (2)	No serious	No serious	No serious	No serious	None	A
Severe RV diarrhea	RCT (2)	No serious	No serious	No serious	No serious	None	A
Hospitalization for RV diarrhea	RCT (1)	No serious	No serious	No serious	No serious	None	A
Intussusception	RCT (3)	No serious	No serious	No serious	No serious	None	A
Other serious adverse events	RCT (3)	No serious	No serious	No serious	No serious	None	A
Fever	RCT (3)	No serious	No serious	No serious	No serious	None	A

Benefits: 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
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)	-
Fever	10,915 (3 RCTs)	38.9%	37.7%	0.97 (0.92–1.01)	-12 (-31,4)	-

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
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)	-
Fever	10,915 (3 RCTs)	38.9%	37.7%	0.97 (0.92–1.01)	-12 (-31,4)	-

Content

- Quality of evidence
- **Going from evidence to recommendations**

Healthcare problem

recommendation

Strength of recommendation

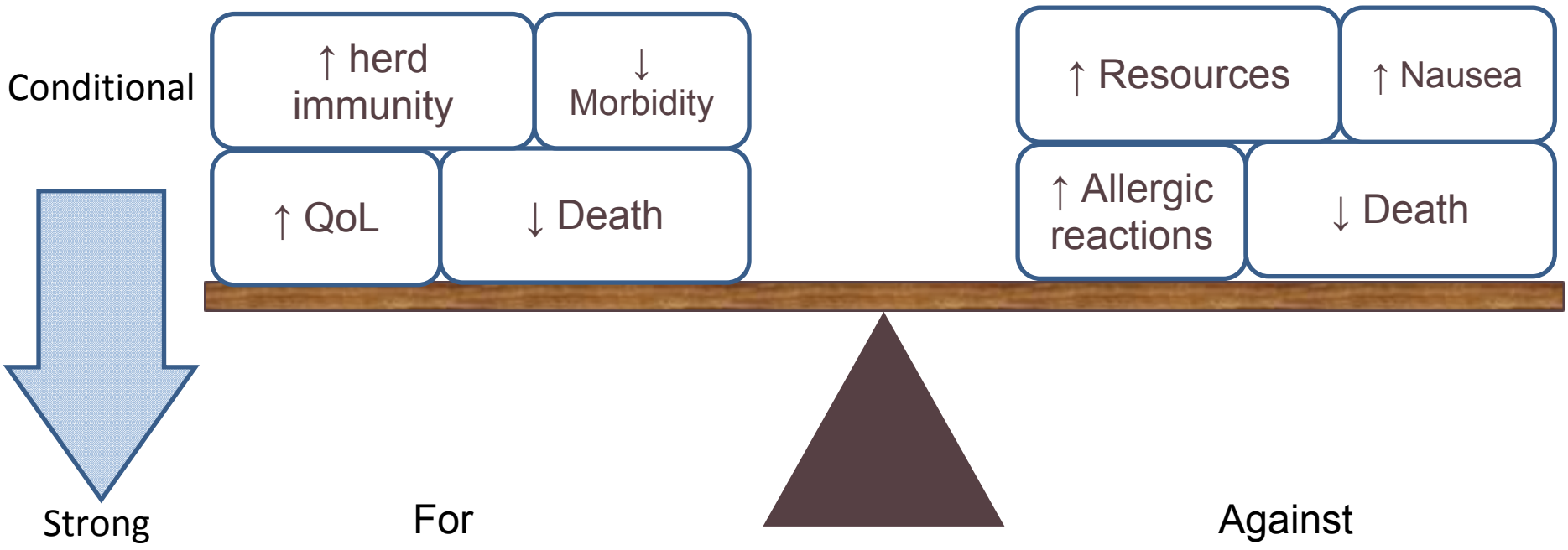
"The strength of a recommendation reflects the extent to which we can, across the range of patients for whom the recommendations are intended, be confident that desirable effects of a management strategy outweigh undesirable effects."

- Strong or conditional

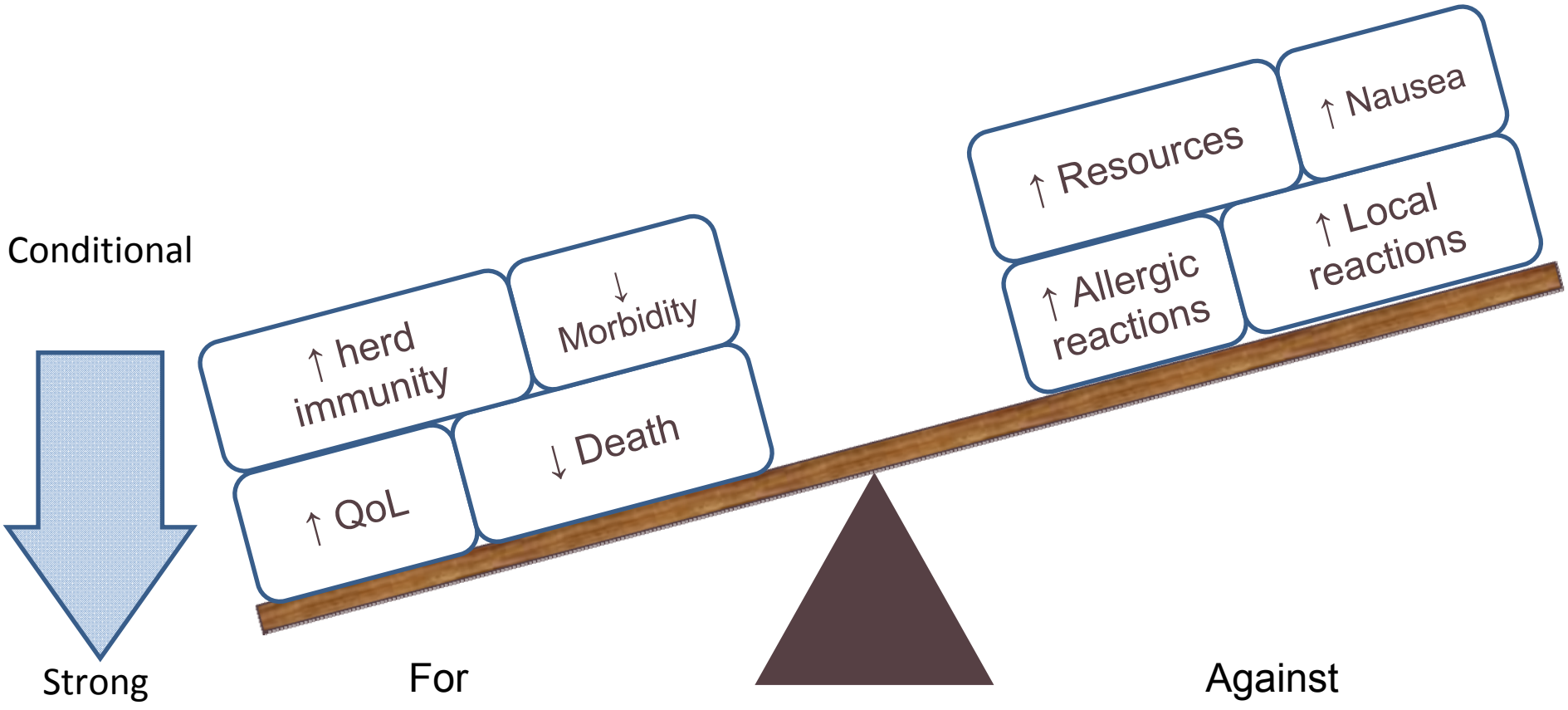
Determinants of the strength of recommendation

Factors that can strengthen a recommendation	Comment
Quality of the evidence	The higher the quality of evidence, the more likely is a strong recommendation.
Balance between desirable and undesirable effects	The larger the difference between the desirable and undesirable consequences, the more likely a strong recommendation warranted. The smaller the net benefit and the lower certainty for that benefit, the more likely weak recommendation warranted.
Values and preferences	The greater the variability in values and preferences, or uncertainty in values and preferences, the more likely weak recommendation warranted.
Costs (resource allocation)	The higher the costs of an intervention – that is, the more resources consumed – the less likely is a strong recommendation warranted

Balancing benefits and downsides



Balancing benefits and downsides



Implications of a *strong* recommendation

- Policy makers: The recommendation can be adapted as a policy in most situations
- Patients: Most people in this situation would want the recommended course of action and only a small proportion would not
- Clinicians: Most patients should receive the recommended course of action

Implications of a *conditional* recommendation

- Policy makers: There is a need for substantial debate and involvement of stakeholders
- Patients: The majority of people in this situation would want the recommended course of action, but many would not
- Clinicians: Be more prepared to help patients to make a decision that is consistent with their own values/decision aids and shared decision making

Case scenario

A 13 year old girl who lives in rural Indonesia presented with flu symptoms and developed severe respiratory distress over the course of the last 2 days. She required intubation. The history reveals that she shares her living quarters with her parents and her three siblings. At night the family's chicken stock shares this room too and several chicken had died unexpectedly a few days before the girl fell sick.

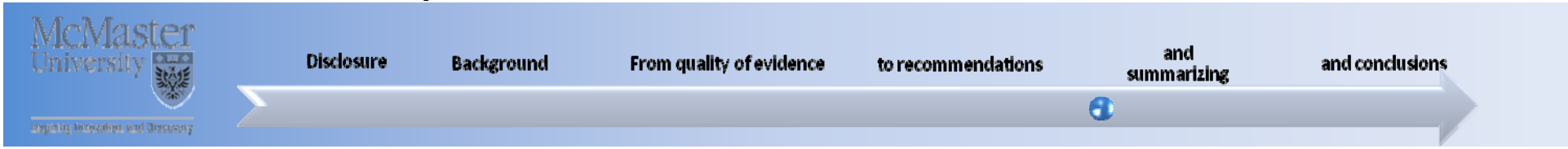
Methods – WHO Rapid Advice Guidelines for Avian Flu

- Applied findings of a recent systematic evaluation of guideline development for WHO/ACHR
- Group composition (including panel of 13 voting members):
  - clinicians who treated influenza A(H5N1) patients
  - infectious disease experts
  - basic scientists
  - public health officers
  - methodologists
- Independent scientific reviewers:
  - Identified systematic reviews, recent RCTs, case series, animal studies related to H5N1 infection

Oseltamivir for Avian Flu

Summary of findings:

- No clinical trial of oseltamivir for treatment of H5N1 patients.
- 4 systematic reviews and health technology assessments (HTA) reporting on 5 studies of oseltamivir in seasonal influenza.
  - Hospitalization: OR 0.22 (0.02 – 2.16)
  - Pneumonia: OR 0.15 (0.03 - 0.69)
- 3 published case series.
- Many in vitro and animal studies.
- No alternative that was more promising at present.
- Cost: 40$ per treatment course



From evidence to recommendation

Factors that can strengthen a recommendation	Comment
Quality of the evidence	Very low quality evidence
Balance between desirable and undesirable effects	Uncertain, but small reduction in relative risk still leads to large absolute effect
Values and preferences	Little variability and clear
Costs (resource allocation)	Low cost under non-pandemic conditions

Recommendation: In patients with HIV and drug resistant TB requiring second line drugs, the expert panel recommends/suggests to (not) administer ART (? recommendation, ? quality evidence).			
Population: HIV positive individuals with drug resistant TB requiring second line drugs			
Intervention: ART use during TB treatment vs ART non-use			
Factor	**Decision**	**Explanation**	
High or moderate quality evidence *(is there high quality evidence?)* The higher the quality of evidence, the more likely is a strong recommendation.	☐ Yes ☐ No	⊕⊕◯◯	There is limited evidence from published studies to evaluate ART use in HIV-TB coinfected patients receiving second line drugs for XDR-TB and MDR-TB. However, using IPD from longitudinal cohort studies, we found moderate quality evidence from observational studies that there
Certainty about the balance of benefits versus harms and burdens *(is there certainty?)* The larger the difference between the desirable and undesirable consequences and the certainty around that difference, the more likely a strong recommendation. The smaller the net benefit and the lower the certainty for that benefit, the more likely is a conditional/weak recommendation.	☐ Yes ☐ No	Although there is some uncertainty about cure, there is a significant decrease in hazards ratio for death even after controlling for initial CD4 count	▪ Cure and survival appear to be more likely in drug resistant TB requiring second line drugs if ART is used during TB treatment. o HR of 3.17 (1.46, 6.9) for cure and HR of 0.41 (0.26, 0.63) for death in ART vs. non ART group. o No significant change in HR for cure [HR 2.93(0.98, 8.69)], and decreased HR for death [HR 0.23 (0.12, 0.46)] if controlling for initial CD4 count (HR 0.23)
Certainty or similarity in values *(is there certainty?)* The smaller the variability or uncertainty around values and preferences, the more likely is a conditional or weak recommendation.	☐ Yes ☐ No		▪ Little uncertainly regarding the outcomes of cure and survival. Significant uncertainly regarding effects of ART on other outcomes, including adverse events, default, time to smear and culture conversion and timing of ART initiation.
Resource implications (are the resources consumed worth the expected benefit) The higher the costs of an intervention compared to the alternative that is considered and other cost related to the decision – that is, the more resources consumed – the more likely is a conditional/weak recommendation.	☐ Yes ☐ No	More resources required for concomitant ART use	▪ Need for more skilled providers trained in HIV and drug resistant TB care and drug-drug interactions.
Overall strength of recommendation	Strong or conditional		

Complex data & decisions: yes/no?

Example: Oseltamivir for Avian Flu

Recommendation: In patients with confirmed or strongly suspected infection with avian influenza A (H5N1) virus, clinicians should administer oseltamivir treatment as soon as possible (strong recommendation, very low quality evidence).

Remarks: This recommendation places a high value on the prevention of death in an illness with a high case fatality. It places relatively low values on adverse reactions, the development of resistance and costs of treatment.

Schunemann et al. The Lancet ID, 2007

Issues in guideline development for immunization

- Causation versus effects of intervention
  - Causation not equivalent to efficacy of interventions
  - Bradford Hill
    - Nearly half a century old – tablet from the mountain?
- Harms caused by interventions
  - Assumption is that removal of vaccine (or no exposure) leads to NO adverse effects
- How confident can one be that removal of the exposure is effective in preventing disease?
  - Whether immunization or environmental factors: will depend on the intervention to remove exposure

Formulate question

Select outcomes

Rate importance

Outcomes across studies

Create evidence profile with GRADEpro

Rate quality of evidence for each outcome

P
I
C
O

Outcome Critical

Outcome Critical

Outcome Important

Outcome Not important

Summary of findings & estimate of effect for each outcome

High
Moderate
Low
Very low

Randomization increases initial quality

Grade down

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Confounders

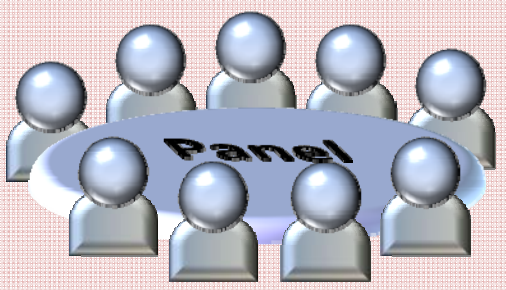
Systematic review

Guideline development

Formulate recommendations:
•For or against (direction)
•Strong or weak/conditional (strength)

By considering:
❑Quality of evidence
❑Balance benefits/harms
❑Values and preferences

Revise if necessary by considering:
❑Resource use (cost)



Grade
overall quality of evidence
across outcomes based on
lowest quality
of ***critical*** outcomes

- "We recommend using…"
- "We suggest using…"
- "We recommend against using…"
- "We suggest against using…"

Conclusions

- Practice guidelines should be based on the **best available** evidence to be evidence based
- GRADE combines what is known in health research methodology and provides a structured approach to improve communication
- Criteria for evidence assessment across questions and outcomes
- Criteria for moving from evidence to recommendations
- Systematic
  - four categories of quality of evidence
  - two grades for strength of recommendations
- Transparency in decision making and judgments is key

Confidence in evidence

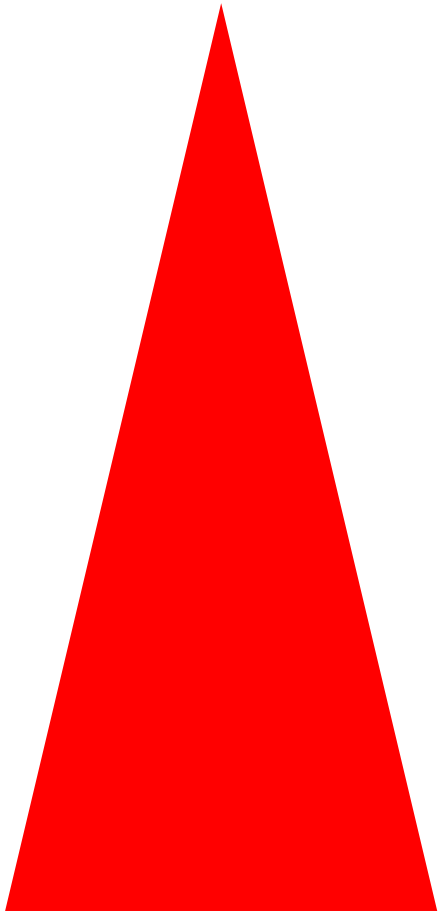
- There always is evidence
  - "When there is a question there is evidence"
- Better research $\Rightarrow$ greater confidence in the evidence and decisions

Hierarchy of evidence
based on quality

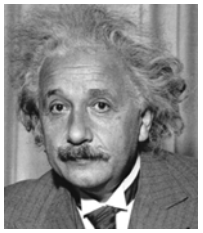
STUDY DESIGN

- Randomized Controlled Trials
- Cohort Studies and Case Control Studies
- Case Reports and Case Series, Non-systematic observations
- Expert Opinion

BIAS



“Everything should be made as simple as possible but not simpler.”



Explain the following?

- Confounding, effect modification & ext. validity
- Impact of loss to follow-up
- Concealment of randomization
- Blinding (who is blinded in a double blinded trial?)
- Intention to treat analysis and its correct application

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

HULTON/GETTY

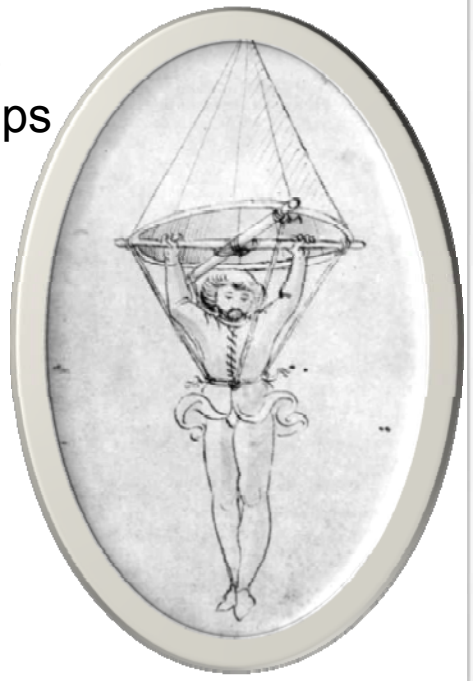
Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials

BMJ, 2003

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gordon C S Smith, Jill P Pell

Relative risk reduction:
….> 99.9 % (1/100,000)
U.S. Parachute Association reported 821 injuries and 18 deaths out of 2.2 million jumps in 2007



Interpretation of grades of evidence

- ⨁⨁⨁⨁/A/High: Further research is very unlikely to change confidence in the estimate of effect.
- ⨁⨁⨁◯/B/Moderate**:** Further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate.
- ⨁⨁◯◯/C/Low: Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate.
- ⨁◯◯◯/D/Very low: We have very little confidence in the effect estimate: Any estimate of effect is very uncertain.