INTRODUCTION TO THE DEVELOPMENT OF EVIDENCE-BASED PUBLIC HEALTH DECISIONS (INCLUDING GRADE)

International Workshop on
Procedures for the Development of Evidence-based Recommendations for Immunization

Robert-Koch-Institut, Berlin, November 22, 2010

Yngve Falck-Ytter, M.D.
Associate Professor of Medicine
Case Western Reserve University, Cleveland, Ohio
Director of Hepatology, VA Medical Center Cleveland, USA

Disclosures

- Member of the GRADE working group which has received funding from various governmental entities in the US and Europe, such as the AHRQ

- GRADE methodologist on WHO panel

- Some of the GRADE work was supported in part by grant # 1 R13 HS016880-01 from the Agency for Healthcare Research and Quality (AHRQ)

Content

- Issues to consider when making public health recommendations
- What makes recommendations evidence-based?
- Illustrate fundamentals of grading systems including GRADE
- What to look for when considering a grading methodology

Developing recommendations

- Developing recommendations for public health decision follows common path:
  - Developers should weigh the desirable consequences vs. the undesirable consequences [for the applicable health care setting] based on the best available evidence and take into account people's values and preferences

Scenario

- A health care worker with documented hepatitis B vaccination (+ surface antibody titers in the past) changes jobs after 10 years

- Her new employer requires adequate surface antibody titers for employment

- Her titers come back low

- What should be done?

Some recommendations

- CDC: "Booster doses of hepatitis B vaccine are not considered necessary" (MMWR 1997)

- RKI: "A single booster shot should be carried out after 10 years" (RKI EB #20, 2010)

- FitzSimons et al 2008: ... Belgium, France, Italy, Luxembourg, the UK, Switzerland showed variation in policies. Booster policies were not well defined and seemed to have different aims and objectives"

- WHO 2009: "...there is no compelling evidence for recommending administering a booster dose of hepatitis B vaccine in routine immunization programmes."

What's the evidence?

- What is the outcome of interest?
  - Often argued on mechanism alone (surface antibody decline, amnestic response to re-challenge)
  - F/u studies: non-endemic countries: 0/2,269 +HBsAG (but exposure + in 24 cases)
  - F/u studies: endemic countries (China, Taiwan, Alaska): 0/1,408 +HBsAG (exposure + 35 cases)
  - Exception: Gambia

Importance of outcomes

Question (PICO)	Intermediate outcomes	Final health outcomes
Should health care worker receive booster vaccination vs. not?	Positive hepatitis B core antibody Amnestic response to re-challenge Loss of protective surface antibody	Mortality Liver cancer Liver cirrhosis Chronic hepatitis B infection Acute sympt. infection

What does evidence-based mean?

Are guidelines evidence-based?

- 1,275 recommendations evaluated from NGC

- Not reliably identifiable rec. in 32%

- Not executable as written

  - Common problem: statement of fact only

- Variability in recommendation strength:

  - Absent 53%, inaccurate 7%

- Why is it so hard?

RCT Citations in Medline
Total: ~300,000 RCTs (out of 20 million citations)

A. Thrombolytic Therapy
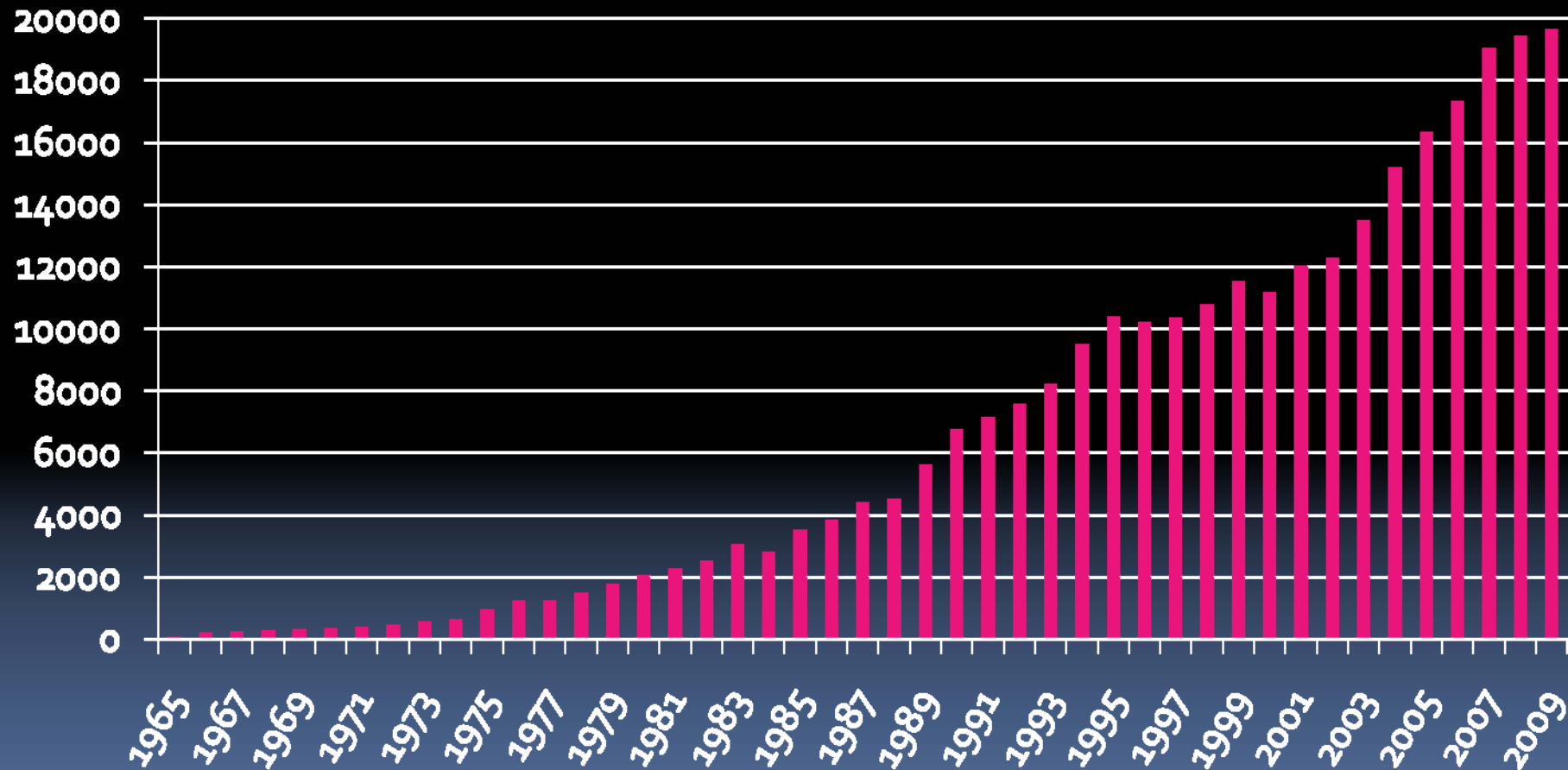
Antman E et. al. JAMA 1992;268:240-48

G. Prophylactic Lidocaine

Odds Ratio (Log Scale)
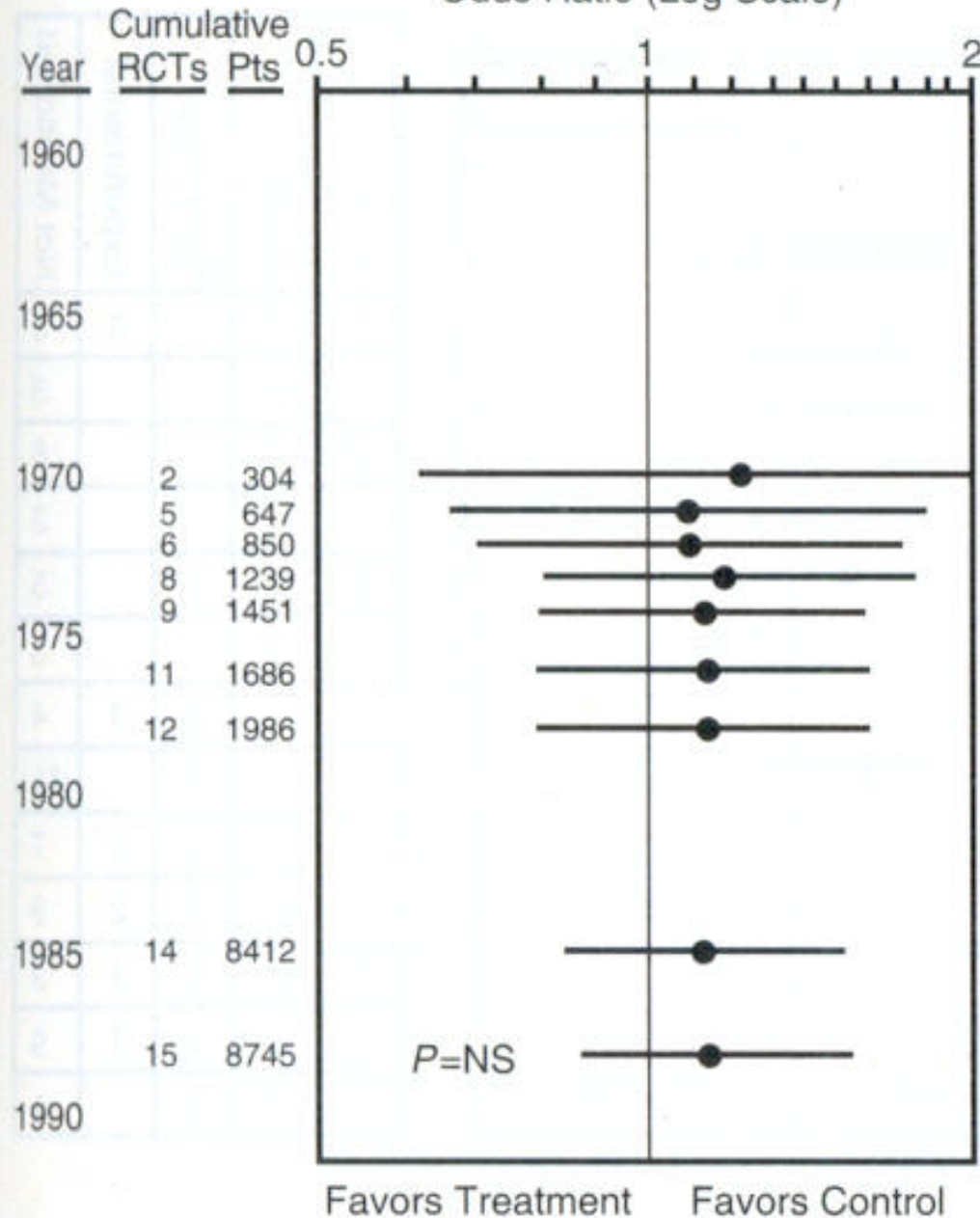
Textbook/Review Recommendations

Antman E et. al. JAMA 1992;268: 240-48

Why evidence-based guidance?
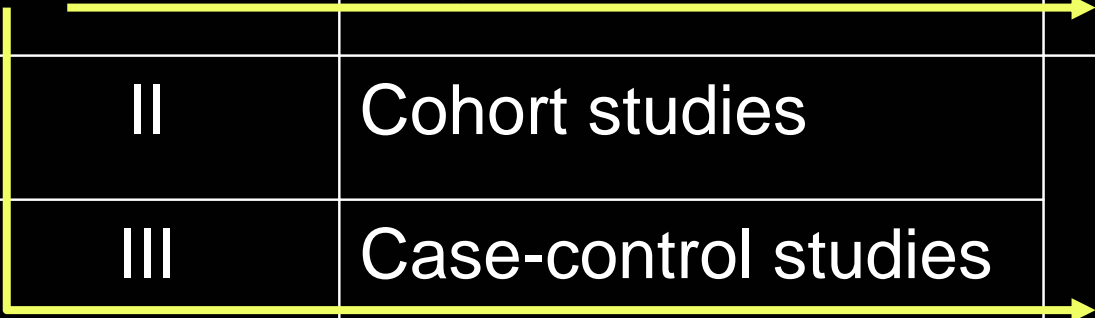
- Standardizing methods across agencies
- Systematic evidence reviews reduces bias
- Increases strength of methodology
- Improves transparency
- Facilitates moving from evidence to recommendations
- Helps formulate actionable recommendations

Evidence grading systems

- 1979: first hierarchy used by the Canadian Task Force on the periodic Health Examination
  - I: ...at least one randomized controlled trial
  - II-1: ...well designed cohort or case-control study...
  - II-2: ... comparisons between times or places or without the intervention. ...dramatic results from uncontrolled experiments....
  - III: Opinions of respected authorities, based on clinical experience, descriptive studies or reports of expert committees.

Simple hierarchies

Level of evidence	Source of evidence	Grades of recomend.
I	SR, RCTs	A
II	Cohort studies	B
III	Case-control studies	
IV	Case series	C
V	Expert opinion	D

German guidelines

From Levels to Grades

Grades equal to levels 45%

Increased grades 1 or 2 steps 48%

Decreased grades 1 or 2 steps - 7%

Increased grades from C to A 27%

Increased grades from B to A or C to B 21%

Science
Level of evidence

Guidelines
Grade of recommendation

1   A
2   B
3
4   C
5   D

Modulated by principles
of need, applicability
or cost-effectiveness

?
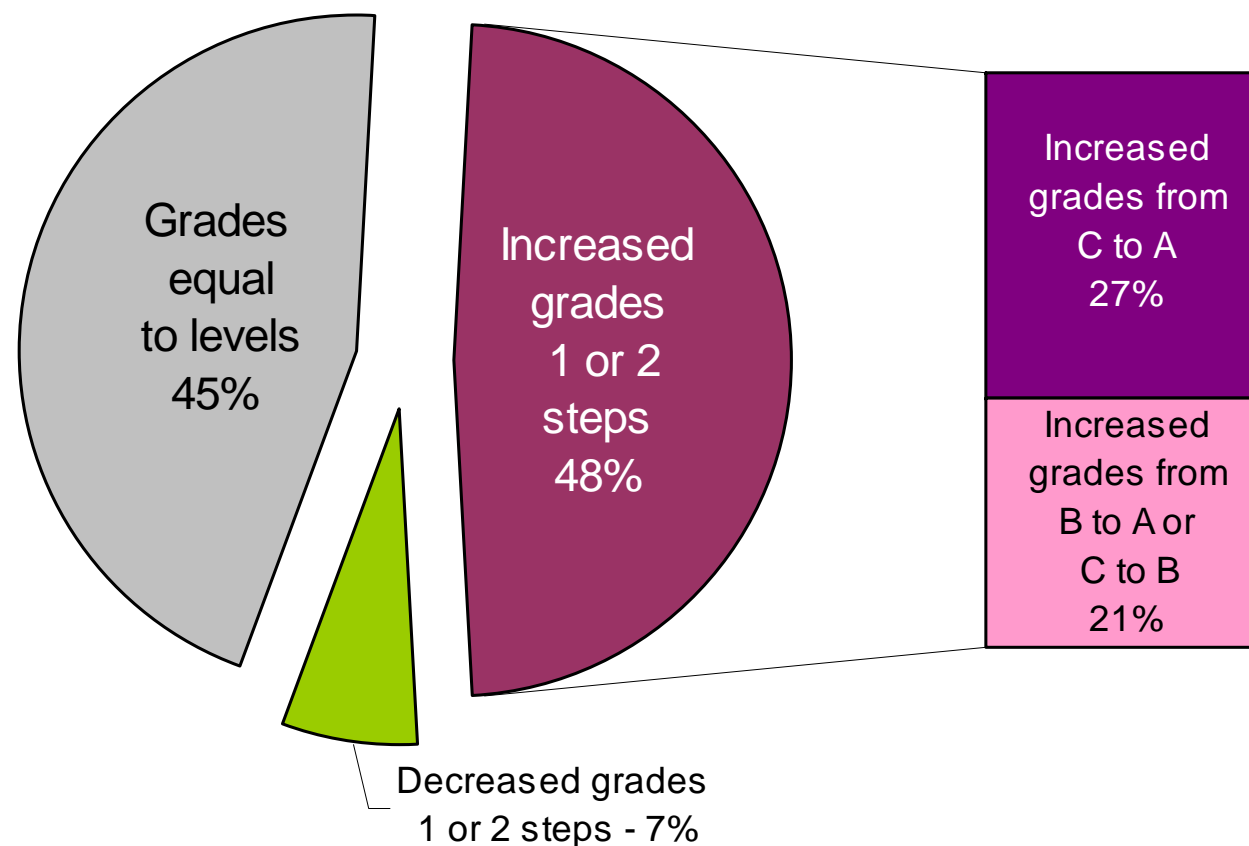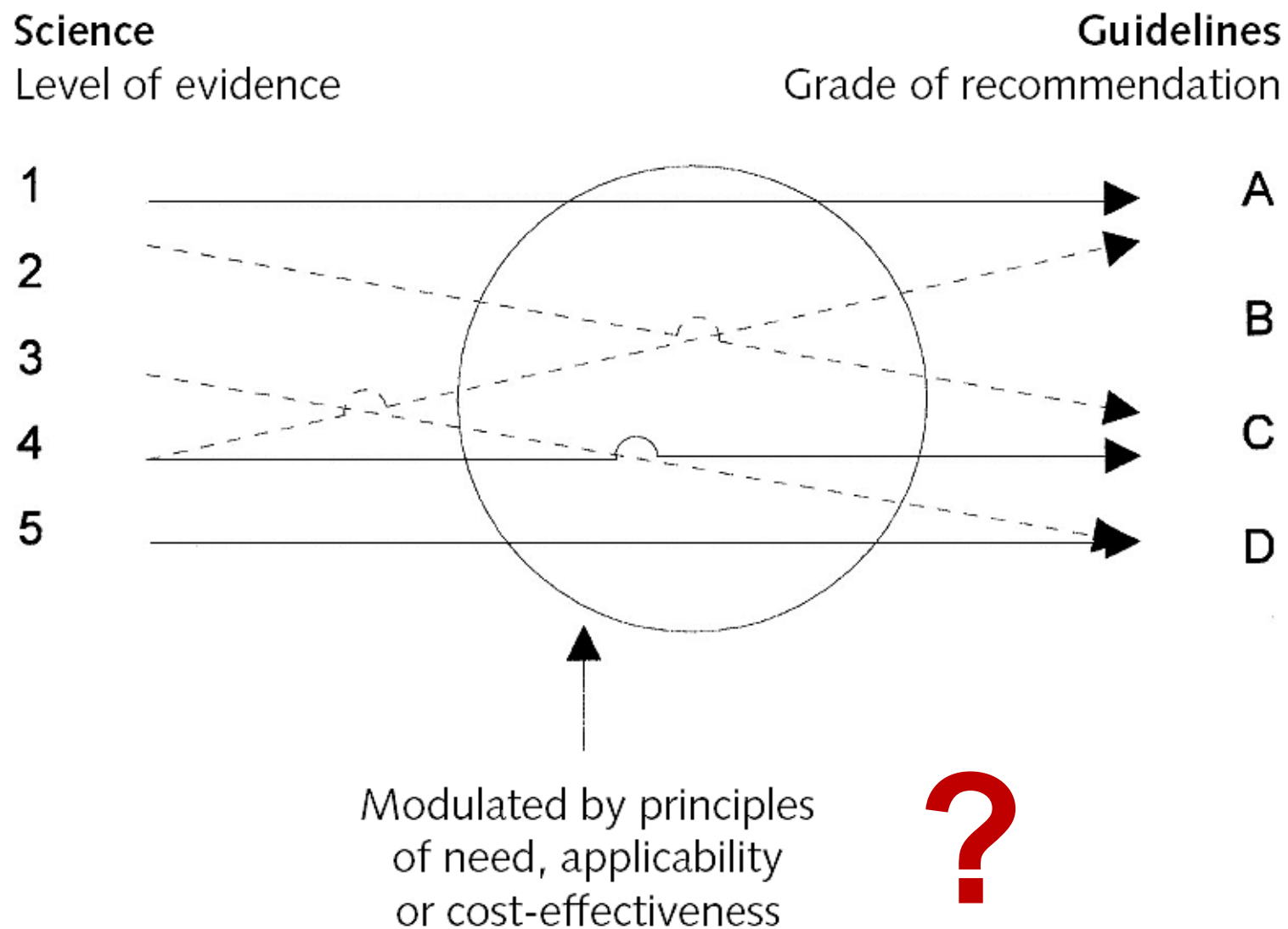
Another example…

P: In patients with acute hepatitis C …
 I : Should anti-viral treatment be used …
C: Compared to no treatment …
O: To achieve viral clearance?

Evidence	Recommendation	Organization
B	Class I	AASLD (2009)
II-1	"Should be initiated…"	VA (2006)
1+	A	SIGN (2006)
-/-	"Most authorities…"	AGA (2006)
-/-	B "It works…"	AWMF(2004)

19

Some other shortcomings

Level of evidence	Source of evidence	Grades of recomend.
Ia Ib	Meta-analysis RCTs	A
II	Cohort studies	B
III	Case-control studies	
IV	Case series	C
V	Expert opinion	D

Systems based on hierarchies

- > 50 system have been using that model for decades
  - Canadian Task Force (now moving to GRADE)
  - Oxford Center of Evidence-based Medicine
  - SIGN (now moving to GRADE)
  - SORT (strength of recommendation taxonomy)
  - American Heart Association
  - …

What makes guidance evidence-based?

- Appraisal of guideline (AGREE collaboration)
    - Scope and purpose (aim, clin. question, population)
    - Stakeholder involvement
    - Rigor of development (systematic review, rating)
    - Clarity and presentation
    - Applicability
    - Editorial independence (e.g., COI)

What to look for in an evidence rating system

1. Defining importance of outcomes
2. **Going from studies to body of evidence**
3. Beyond risk of bias: what other issues define quality of evidence?
4. Overall quality of evidence across outcomes
5. Separation of evidence from strength of recommendation
6. Balancing benefits and downsides
7. Addressing people's values and preferences

Quality of evidence

The quality of evidence reflects the
extent to which our confidence
in the estimate of effect
is adequate to support a particular
recommendation

Grading body of evidence instead of studies

Outcome #1 → Quality: High

Outcome #2 → Quality: Moderate

Outcome #3 → Quality: Low

IIB = < ≡

Old system

Outcome-centric system (e.g., GRADE)

What to look for in an evidence rating system

1. Defining importance of outcomes
2. Going from studies to body of evidence
3. Beyond risk of bias: what other issues define quality of evidence?
4. Overall quality of evidence across outcomes
5. Separation of evidence from strength of recommendation
6. Balancing benefits and downsides
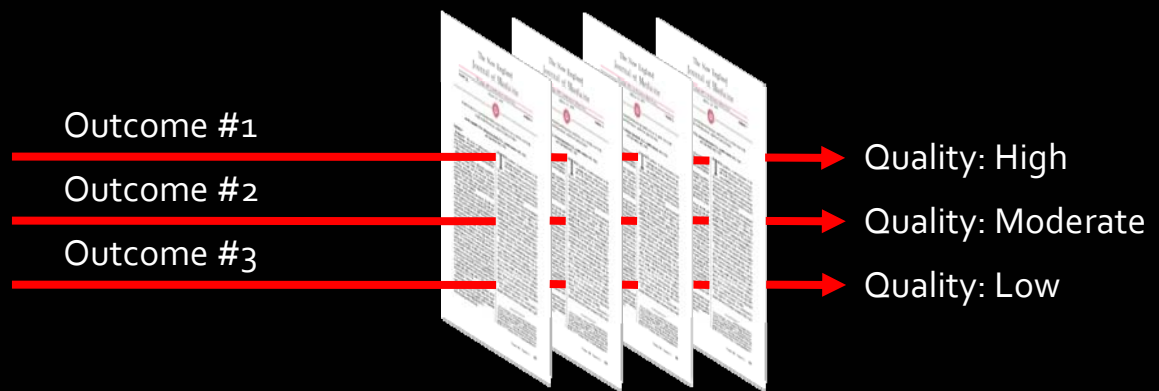7. Addressing people's values and preferences

Misconceptions

- Myth: "…in areas of public health, where there will arguably never be high level evidence…"
    - Numerous high quality RCTs available in the vaccine field (e.g., hepatitis E)
    - ("vaccination"[MeSH Terms] OR "vaccination"[All Fields]) AND Randomized Controlled Trial[ptyp] : 2,817 hits
- Myth: "evidence from observational studies are always categorized as low quality"
    - Upgrading possible for example in GRADE

What changes out confidence in the estimate of effect?

Lower if…

Risk of bias

Inconsistency of effect

Indirect evidence

Imprecise effect estimates

Publication bias

Higher if…

Large effect e.g., in the USA, hepatitis B infection in health care workers (>5 million at risk) decreased from '85-'93 from 8,700 to 1,450

Evidence of dose-response gradient

Conceptualizing quality (GRADE)

High	We are very confident that the true effect lies close to that of the estimate of the effect.	⊕⊕⊕⊕
Moderate	We are moderately confident in the estimate of effect: The true effect is likely to be close to the estimate of effect , but possibility to be substantially different.	⊕⊕⊕○
Low	Our confidence in the effect is limited: The true effect may be substantially different from the estimate of the effect.	⊕⊕○○
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.	⊕○○○

What to look for in an evidence rating system

1. Defining importance of outcomes
2. Going from studies to body of evidence
3. Beyond risk of bias: what other issues define quality of evidence?
4. Overall quality of evidence across outcomes
5. Separation of evidence from strength of recommendation
6. Balancing benefits and downsides
7. Addressing people's values and preferences

Clinical question

Select outcomes

Rate importance

Quality rating outcomes across studies

P I C O	Outcome	Critical
	Outcome	Critical
	Outcome	Important
	Outcome	Important
	Outcome	Less important

Grade down or up

High

Moderate

Low

Very low

Overall quality of evidence

Panel

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

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

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

What to look for in an evidence rating system

1. Defining importance of outcomes
2. Going from studies to body of evidence
3. Beyond risk of bias: what other issues define quality of evidence?
4. Overall quality of evidence across outcomes
5. **Separation of evidence from strength of recommendation**
6. Balancing benefits and downsides
7. Addressing people's values and preferences

Going from evidence to recommendations

- Quality of evidence is often confused with strength of recommendation

- Deliberate separation of quality of evidence from strength of recommendation

- No automatic one-to-one connection as in other grading systems

- Other factors beyond the quality of evidence influence our confidence that adherence to a recommendation causes more benefit than harm

What to look for in an evidence rating system

1. Defining importance of outcomes
2. Going from studies to body of evidence
3. Beyond risk of bias: what other issues define quality of evidence?
4. Overall quality of evidence across outcomes
5. Separation of evidence from strength of recommendation
6. Balancing benefits and downsides
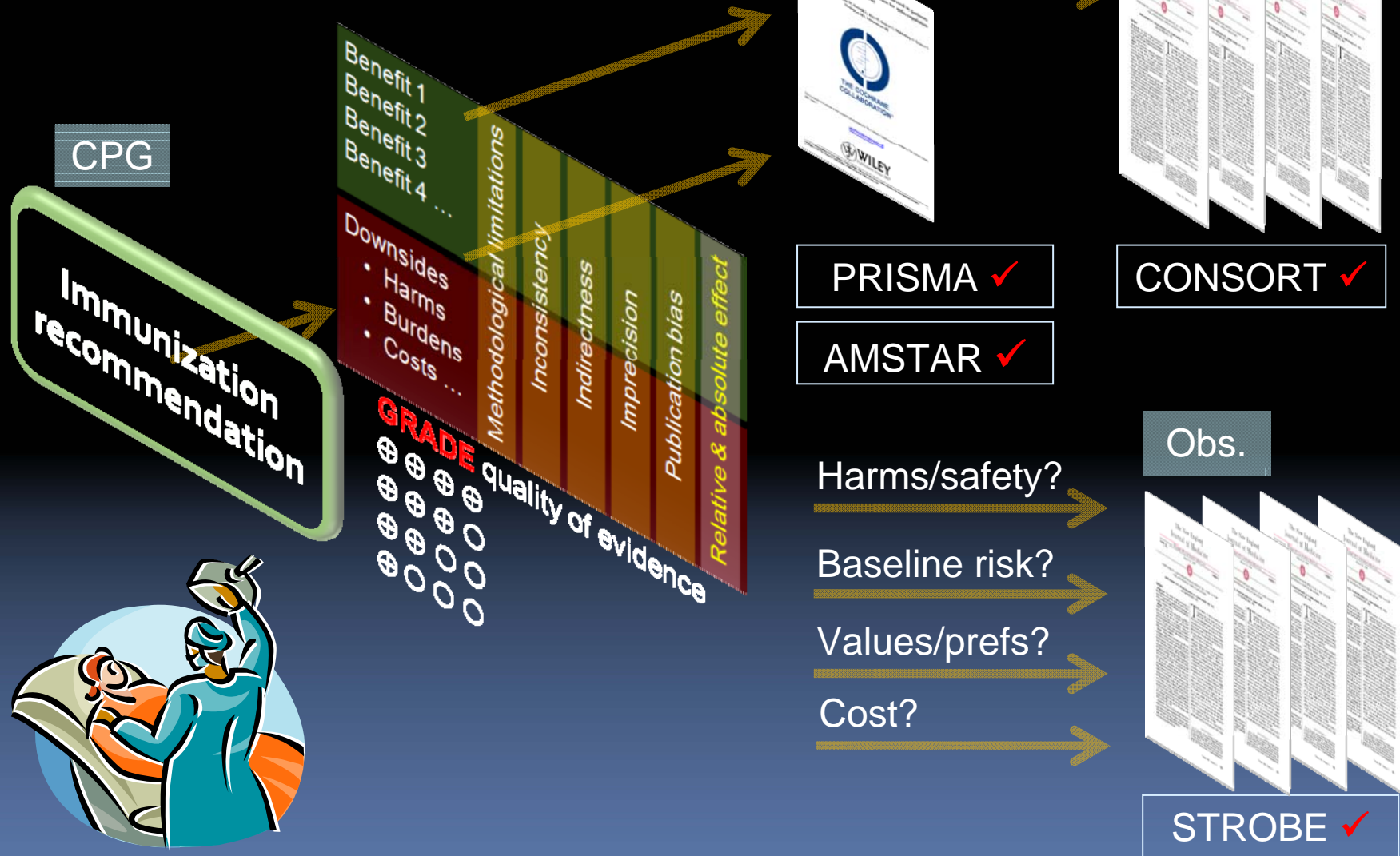7. Addressing people's values and preferences

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."

Moving towards standards

CPG

SR

RCTs

Immunization recommendation

Benefit 1
Benefit 2
Benefit 3
Benefit 4 ...

Downsides
• Harms
• Burdens
• Costs ...

Methodological limitations
Inconsistency
Indirectness
Imprecision
Publication bias
Relative & absolute effect

GRADE quality of evidence

⊕⊕⊕⊕
⊕⊕⊕○
⊕⊕○○
⊕○○○

PRISMA ✓

AMSTAR ✓

CONSORT ✓

Obs.

Harms/safety?

Baseline risk?

Values/prefs?

Cost?

STROBE ✓

Making recommendations actionable

Clarity of recommendation:

- Booster doses of hepatitis B vaccine are not considered necessary

vs.

- We recommend against booster doses of hepatitis B vaccination in HCW who have documented response to initial immunization

What to look for in an evidence rating system

1. Defining importance of outcomes
2. Going from studies to body of evidence
3. Beyond risk of bias: what other issues define quality of evidence?
4. Overall quality of evidence across outcomes
5. Separation of evidence from strength of recommendation
6. Balancing benefits and downsides
7. Addressing people's values and preferences

Values and preferences

- The greater the variability in people's values and preferences,
  or uncertainty in values and preferences,
  the more likely conditional recommendations are warranted

Implications of a *conditional* recommendation

- **Population**: The majority of people in this situation would want the recommended course of action, but many would not

- **Health care workers**: Be prepared to help people to make a decision that is consistent with their own values/decision aids and shared decision making

- **Policy makers**: There is a need for substantial debate and involvement of stakeholders

Implications of a *strong* recommendation

- **Population**: Most people in this situation would want the recommended course of action and only a small proportion would not

- **Health care workers**: Most people should receive the recommended course of action

- **Policy makers**: The recommendation can be adapted as a policy in most situations

Conclusions

1. Most organizations recognize the value of providing graded recommendations by utilizing a methodological rigorous system to rate the quality of the underlying evidence

2. A systematic approach increases transparency and can reduce errors

3. Standardizing on a single, common approach reduces redundancy and fosters collaboration