Do scientific data all have the same value? A proposal from the National Committee on Immunization

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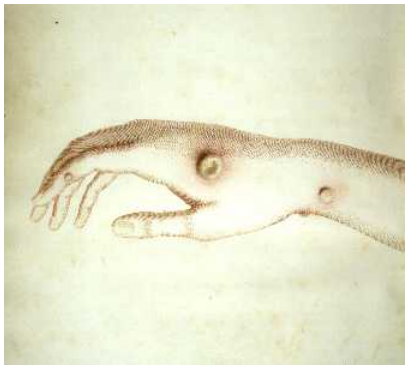
JASP 27 oct 2006

Objectives:

- To recognize that scientific data used for the evaluation of vaccine efficacy and effectiveness can vary in quality
- To review practices that can help obtain the highest quality research
- To review a proposal for evidence review being considered by NACI

Cette présentation a été effectuée le 27 octobre 2006, au cours du Symposium "Mettre la science au service des programmes d'immunisation, le rôle des comités d'experts" dans le cadre des Journées annuelles de santé publique (JASP) 2006. L'ensemble des présentations est disponible sur le site Web des JASP, à l'adresse http://www.inspq.qc.ca/jasp.

How sound was the first evidence of immunization efficacy ?



Countway Library of Medicine, Harvard University
<www.countway.library.edu>

- England, 1700's: common practice to inoculate with smallpox
- Jenner observes that some people do not get smallpox, investigation reveals they had cowpox
- 14 May 1796 pus from Sarah Nelmes inoculated into 8 year old James Phipps, he develops pustular exanthem, recovers
- 1 July JP inoculated again, no disease
- Later prepares a publication describing 23 patients

Back to basics - critical appraisal of articles: What is the purpose of the study ?

Diagnosis	**Prognosis**	**Causation**	**Therapy/ Prevention**
•Blind comparison with gold standard? •Adequate spectrum of disease among patients?	•Inception cohort assembled? •Baseline features measured reproducibly?	•Was the study design strong? •Assessment of exposure and outcome unbiased?	Assignment of patients randomized? Clinically important outcomes assessed objectively?

Criteria for critical appraisal of an article on therapy/prevention

- Assignment of patients randomized?
- Was there at least 80% followup?
- Were both statistical and clinical significance considered?
- If the study was negative, was power assessed?
- Clinically important outcomes assessed objectively? (benefits and harms)

Users guides to the medical literature, JAMA

James Gillray (1757-1815)
The Cow-Pock, or, the Wonderful Effects of the New Inoculation!

Evidence-based recommendations

- Evidence exists in a hierarchical fashion; some studies are more subject to bias than others
- A standardized approach decreases variation, is reproducible, makes decision making transparent
- History:
  - Canadian Task Force on Preventive Health Care (CTFPHC) formed in 1976 (CMAJ 1979;121:1193-1254)
  - 1980s methodology accepted by US Preventive Services Task Force(Woolf 1990 J Clin Epidemiol)

Design Hierarchy : levels

- **1**
  - Individual randomized controlled clinical trial
  - systematic review with or without meta-analysis
  - Non-randomized trial
  - Prospective cohort study
- **2**
  - retrospective cohort study
  - Case-control study
  - Times series study
- **3**
  - Before/after study
  - Cross-sectional study
- **4**
  - Non-comparitive study(case-series, focus groups descriptive epidemiology)
- **5** expert opinion

Level of evidence - *Research Design*

I	Evidence from randomized controlled trial(s)
II-1	Evidence from controlled trial(s) without randomization
II-2	Evidence from cohort or case-control analytic studies, preferably from more than one center or research group
II-3	Evidence from comparisons between time and places with or without the intervention; dramatic results from uncontrolled experiments would be included here
III	Opinions of respected authorities, based on clinical experience; descriptive studies or reports of expert committees

Limitations of ranking evidence only according to Research Design

- Does not consider how well the study was done, ie internal validity
  - *Example: Case-control studies*
    - Accurate ascertainment of cases
    - Nonbiased selection of cases/controls with exclusion criteria applied equally to both
    - Response rate
    - Diagnostic testing procedures applied equally to each group
    - Appropriate attention to potential confounding variables

Clinical guidelines in 2006: characteristics

- High level of rigour with which evidence is identified, appraised, summarized
- Explicit linkage between the recommendation and the evidence supporting it

CTFPHC as a model – Schema for ranking evidence

- Systematic procedure for literature retrieval and synthesis
- Levels of evidence assigned based on *Research design*
- Levels of evidence – *Quality* (Internal Validity) rating
- Recommendation *grades* for preventive actions

Evidence – Quality (Internal validity) rating

Good A study that meets all design-specific criteria
**(includes meta-analyses or systematic reviews)*

Fair A study that does not meet (or it is not clear that it meets) at least one design-specific criterion
**(includes meta-analyses or systematic reviews)*

Poor A study that as at least one design-specific* "fatal flaw", or an accumulation of lesser flaws to the extent that the results of the study are not deemed able to inform recommendations

Harris et al, 2001

CTFPHC as a model – Schema for ranking evidence

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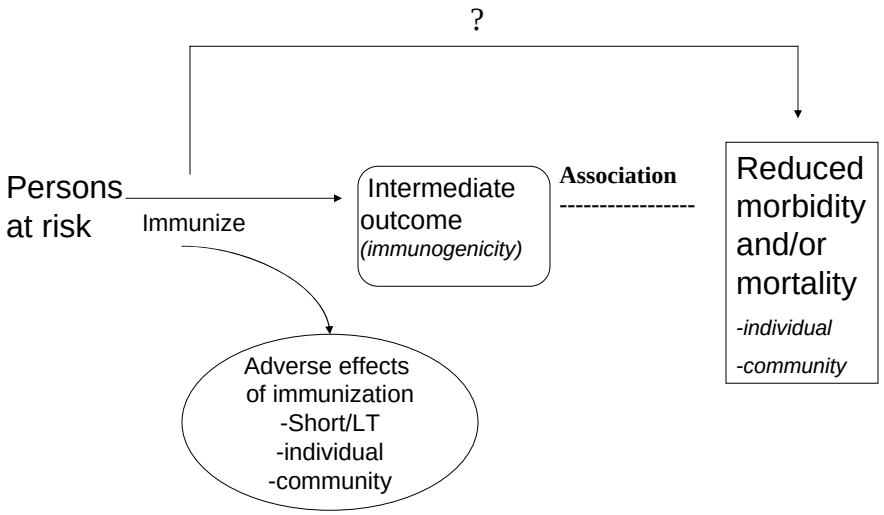
What is considered in making a recommendation “grade”?

- Types of evidence
- Quality of evidence
- Magnitude of benefit and harm

CTFPHC(US) Recommendation grades

A	Good evidence to recommend *(US:strongly recommends)*
B	Fair evidence to recommend *(US:recommends)*
C	Existing evidence is conflicting,doesn’t allow recommendation for or against,other factors may influence decision-making *(US: no recommendation)*
D	Fair evidence to recommend against *(US:recommends against)*
E	Good evidence to recommend against (US: 0)
I	Insufficient evidence to (quality and/or quantity) to make a recommendation, however other factors may influence decision-making *(US: insufficient)*

Analytic framework for immunization
(after USTFPHC)



Steps to reviewing evidence

- Literature retrieval and syntheses
- Summary tables with data relevant to populations of interest:
  - Level of evidence
  - Rating of internal validity
  - Consideration of external validity (extent to which data applies to populations not studied)
- Consider overall consistency and coherence of data
- Weigh magnitude of benefit and harms
- Apply recommendation grade

Development process for NACI statements *(a work in progress…)*

- Identification of populations, interventions, outcomes of interest by working group
- Literature review
  - Explicit search strategy (electronic databases, reviews, Cochrane, ?request monograph?)
- Summary of evidence on benefit (efficacy and effectiveness of intervention) and harm (safety)
  - Research design ranking
  - Quality ranking
  - Consideration of magnitude of benefit, harm
- Recommendations developed and brought to NACI for discussion, vote

Proposed recommendation grades for NACI

A	Good evidence to recommend preventive action (immunization or prophylaxis)
B	Fair evidence to recommend immunization
C	Existing evidence is conflicting, doesn't allow recommendation for or against immunization, however other factors may influence decision-making
D	Fair evidence to recommend against
E	Good evidence to recommend against
I	Insufficient evidence (quality and/or quantity) to make a recommendation, however other factors may influence decision-making

Presentation of evidence

- Literature syntheses (tables, methods, narrative); published on web
- Recommendation statement shorter version, published
- Recommendation statement (full) archived archived by NACI secretariat with all references embedded to assist in preparing future statements, responding to correspondence.

Challenges to making evidence based vaccine recommendations:

- This is a human resource-intensive process (searching, synthesis, librarian)
- NACI members without previous experience in this methodology will go through a(n) (uncomfortable) learning curve
- Different schema are in use (CATMAT, NACI, provincial etc)
- large number of "C" and "I" Recommendations (due to insufficient, inconclusive, or conflicting evidence in subpopulations), leading to “expert” advice - may be unsatisfying

Challenges to making evidence based vaccine recommendations (continued):

- a "C" or "I" recommendation may be misinterpreted as evidence against, when more research needs to be done
- Immunogenicity outcomes are variably well developed for humoral immunity, not at all for cell-mediated immunity. Minimal incentive to develop these if the product is approved/licensed in the general population
- Public health benefits and harms may not be known at the time of the recommendation
- need to consider all varieties of benefit and harm associated with immunization (e.g. confidence in vaccine programs, improved quality or length of life, anxiety relieved, avoided effort for other public health interventions). These are not easily measured.
- Costs not considered by NACI because of lack of content expertise

….Through intellectual and intelligent inquiry science is the discoverer of all things. It unites present and past…. and confers upon man today the essence of all human knowledge….

Thank you !!!!

Internal validity: *Randomized controlled trials (RCTs) and cohort studies*

- Initial assembly of comparable groups:
  - RCTs: adequate randomization, including concealment and whether potential confounders were distributed equally among groups
  - Cohort studies: consideration of potential confounders; consideration of inception cohorts
- Maintenance of comparable groups (includes crossovers, adherence, contamination)
- Important differential or high loss to follow-up
- Measurements: equal, reliable, and valid, masking