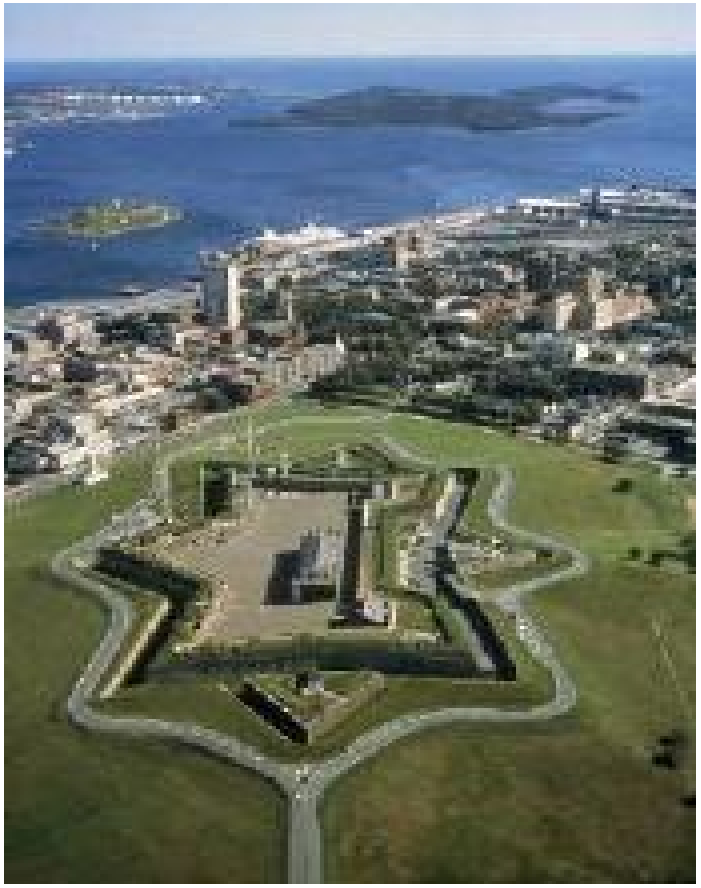
Canada's National Advisory Committee on Immunization (NACI): Current methods and experiences in developing evidence-based recommendations



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Canadian Center for Vaccinology

Chair NACI (2007-2011)

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Immunization recommendations in Canada: background

- *NACI*, a scientific committee, makes recommendations on vaccine use to the Chief Public Health Officer of Canada
- *Canadian Immunization Committee*, a federal-provincial-territorial committee, issues recommendations for publicly funded program implementation
- Provinces decide which vaccines to fund and how they will deliver them

Our current process:

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Canada Communicable Disease Report CCDR

Volume 35 • ACS-1
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An Advisory Committee Statement (ACS)
National Advisory Committee on Immunization (NACI)†

PDF Version
10 Pages - 160 KB

Evidence-based recommendations for immunization – Methods of the National Advisory Committee on Immunization

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada with ongoing and timely medical, scientific and public health advice relating to immunization. The Public Health Agency of Canada acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. NACI

History of Current Methods:

- Weren't we always evidence-based?
  - Yes, but:
    - No explanation of method for literature synthesis/review
    - No evaluation of quality of evidence
    - No explicit linking of evidence to recommendation
    - Not clear how final recommendation grade was related to "evidence" presented
- 2004: NACI working group formed
  - Tasks: review EBM for immunization recommendations, prepare options for consideration
  - Develop templates for evidence retrieval, summary, recommendation preparation in effort to make the process more transparent, subject to reader critical appraisal
  - Goal: more explicit, transparent process so that reader can see primary data, determine rationale for recommendations

- Process approved, but there was a recognition that program resources were required to support this methodology

Overview: steps in NACI immunization recommendation:

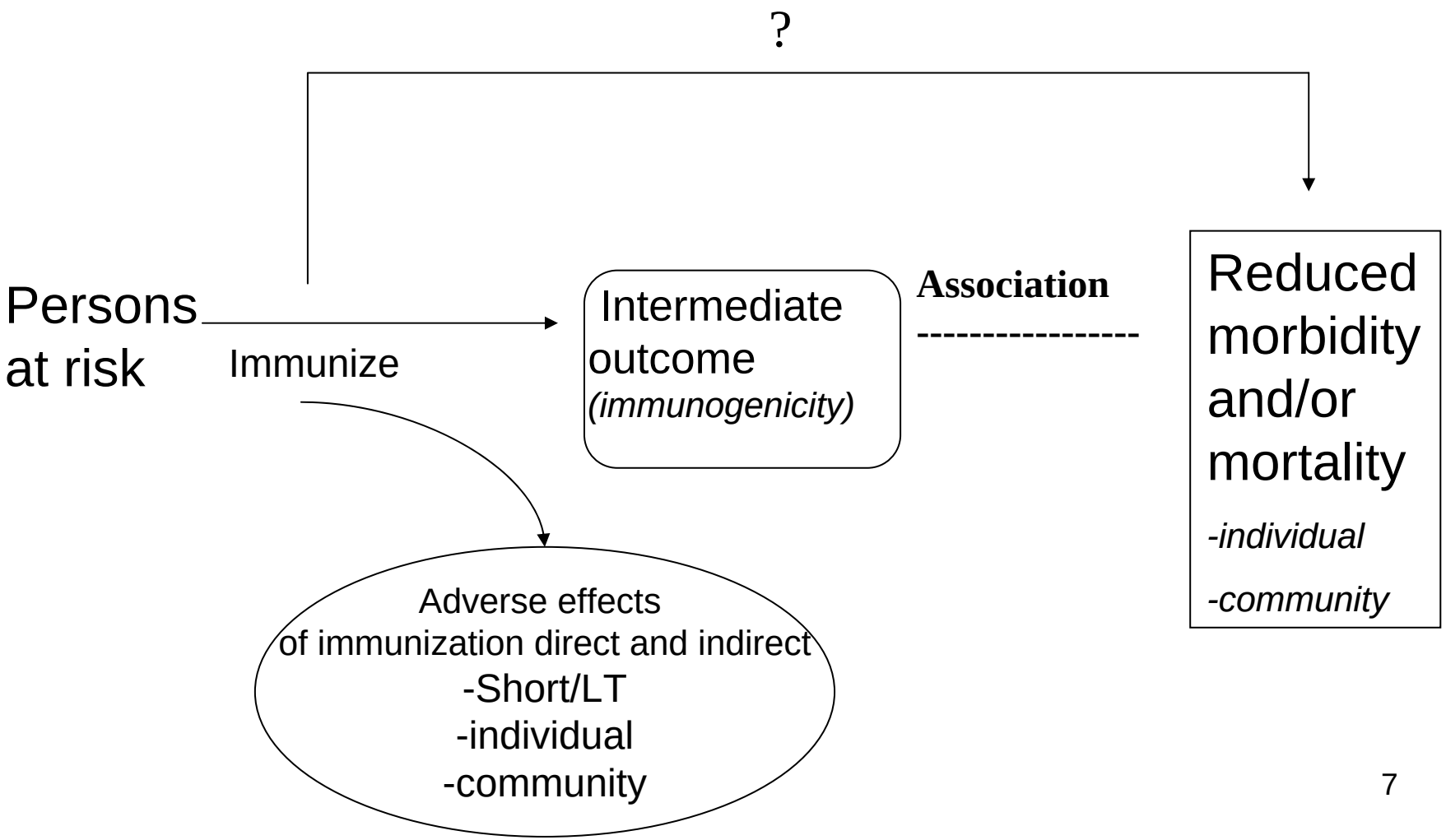
1. Literature retrieval and syntheses
2. Review of assembled evidence
    1. Burden of illness in Canadians
    2. Evidence tables with individual studies, research design and quality
    3. Assessment of overall direction of evidence, magnitude of benefits/harms, potential population v individual health outcomes, other considerations…
3. Discuss options for recommendations and rationale for potential grade assignment (letter corresponding with a descriptor)

assign grade, which is accompanied by short narrative that explains the rationale

NACI recommendation: Overview of process (1)

- Stimulus to prepare/revise recommendations (e.g. new vaccine, new evidence about authorized vaccine efficacy/safety)
- Working group struck, with member “lead” and PHAC “lead”, internal and external experts
- Steps
  - Plan scope of lit review (populations/outcome measures for safety/efficacy/effectiveness in individual, population etc)
  - Lit review is contracted out or done internally
  - Work plan over time
  - Report on progress to NACI, bring options to full committee

Analytic framework for immunization
(after USTFPHC)



NACI recommendation: Overview of process *(2)*

- Literature retrieval
  - Databases, languages, inclusion/exclusion criteria etc.

- Literature summary (tabular format)
  - Individual study level of evidence
  - Individual study quality of evidence
  - Individual studies grouped as appropriate (e.g. immunogenicity in a subpopulation)

Variables used in evidence tables

Table 1. Evidence retrieval and synthesis - examples of variables to be extracted from primary studies of vaccine efficacy, effectiveness and safety.

i	Population studied (e.g. age, health status, setting, gender).
ii	Intervention (e.g. vaccine dose(s), route, schedule, concomitant vaccines or medications).
iii	Sample size.
iv	Outcome measures (laboratory confirmed, clinical, surrogate) and method of detection (active/passive). Where surrogate outcome measures are used evidence must be available that directly links the measure with clinical outcomes.
v	Length of follow-up/duration of protection.
vi	Results in treatment and control arm providing confidence intervals and/or statistical tests of significance as appropriate.
vii	Reactogenicity, method(s) for detecting these.
viii	Adverse events, method(s) for detecting these.
ix	Ranking of *level of evidence* (study design) of each individual study (e.g. randomized controlled trial).
x	Evaluation of *quality of the study.*

Level of evidence of individual studies based on 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

Evaluation of quality (internal validity) of individual studies

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

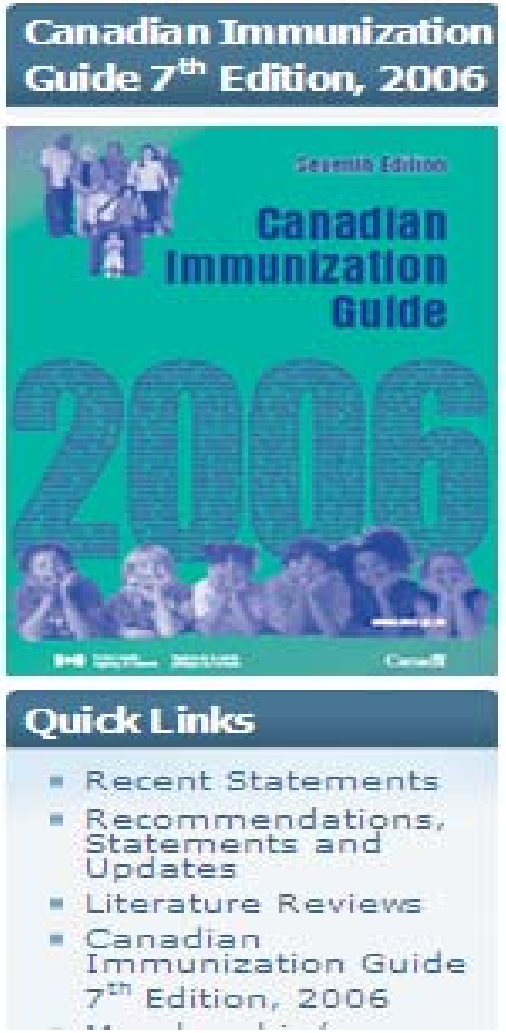
Overall Recommendation

- Based on evidence regarding burden of illness in Canadians

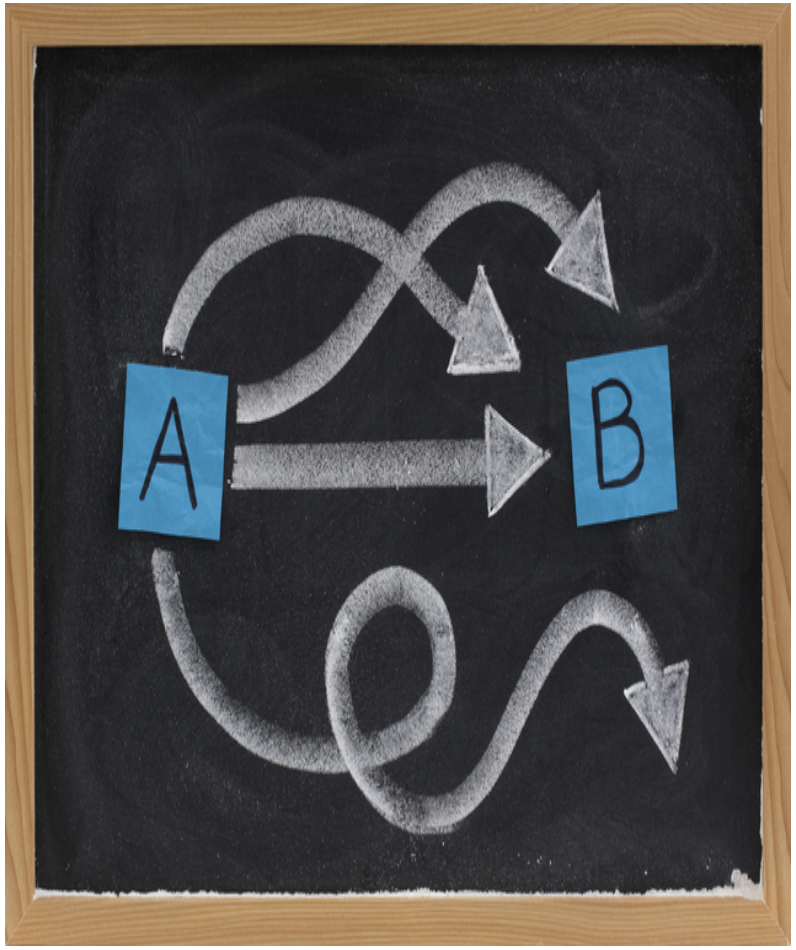
- Based on evidence about individual and public health outcomes associated with the vaccine
  - individual studies (with ranking of level and quality of evidence, summarized in tables in statement AND (+/-) literature review document published
  - Overall direction of evidence, magnitude of benefit and harm,

Accessibility of evidence to reader

- Literature reviews (tables, methods, narrative); published on NACI web site
- Recommendation statement with full references, on web
- Canadian Immunization Guide (aimed at immunization provider, shorter, few references)



What is the method for getting from the explicit evidence to the recommendation?



- There is no quantitative method
- What is considered:
  - Overall direction, magnitude and quality of evidence about safety and immunogenicity/efficacy quality of the vaccine
  - Burden of illness in Canadians and potential benefit (absolute risk, Number needed to vaccinate)
  - Analytic framework factors *(deWals, Erickson, Farand Vaccine 2005*)

Analytic framework for immunization programs in Canada

- Burden of disease
- Vaccine characteristics (safety, efficacy)
- Immunization strategy and program
- Cost-effectiveness of program
- Acceptibility of program
- Feasibility of program
- Ability to evaluate programs
- Equity of the program
- Ethical considerations
- Legal considerations
- Conformity of program
- Political considerations

NACI

CIC, provinces, territories

Vaccine 2005;23:2470-2476


Seems overwhelming ?

Challenges to making evidence based vaccine recommendations:

- This is a human resource-intensive process (searching, extraction from primary literature, synthesis of data)
- Committee members without previous experience in this methodology will go through a learning curve
- Different evaluation schemata are in use for various Health department advisory committees
- When there are "C" (conflicting) or "I" (insufficient) evidence recommendations, “expert” advice may be given – this is unsatisfying to participants and may raise concern about the credibility of recommendations

Challenges to making evidence based vaccine recommendations (continued):

- Assignment of a "C“ (conflicting evidence) or "I" (Insufficient evidence) grade may be misinterpreted as evidence “against” the intervention. However a recommendation to vaccinate or not is not being made *at that time* because more evidence is required

- Immunogenicity outcomes are variably well developed for humoral immunity, and not at all for cell-mediated immunity. These intermediate outcomes are less strong than efficacy or effectiveness outcomes, and,
  - There is little incentive to develop these if the product is approved/licensed in the general population
  - Immunogenicity outcomes (intermediate) will be increasingly used with newer vaccines

Challenges to making evidence based vaccine recommendations (continued):

- Public health benefits (e.g. indirect protection) and harms (rare AEs) may not be known at the time of the recommendation (not a new issue), so recommendations need to be regularly revisited

- Committee members concerned that costs should be explicitly integrated into NACI process ….governance/functional review of immunization advisory committees underway, will report to Canadian Public Health Network Council

- 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.

Solutions: Desire in many jurisdictions to avoid duplication of (this enormous) effort required for evidence based decision making : SIVAC and other like-minded collaborative ventures may be a solution so that we are using resources wisely across borders, sharing our learning