Vaccinology:

From Bench to Bedside to Boardroom

4th Canadian Therapeutics Congress
May 30, 2007
Halifax, Nova Scotia

Symposium Schedule

• Introduction and overview	• Scott A. Halperin, MD
• New vaccines and delivery systems	• Lorne Babiuk, PhD
• Licensing a vaccine to prevent cancer: clinical trials of Human Papilloma Virus Vaccine	• Shelly McNeil, MD
• Translation into policy: influenza vaccine during pregnancy	• Noni MacDonald, MD
• Novel vaccine providers and liability	• Lorraine Lafferty, LLM

Success of Vaccines

- US Centers for Disease Control and Prevention (CDC) named vaccination as the number one public health achievement of the 20th century
  - Eradication of smallpox
  - Near elimination of polio
  - Control or diphtheria, tetanus, pertussis, invasive *Haemophilus influenzae* b disease, measles, mumps, rubella, hepatitis B
  - Prospect of control of varicella, meningococcal disease, invasive pneumococcal disease

Ten Great Public Health Achievements — United States, 1900–1999

- **Vaccination**
- Motor-vehicle safety
- Safer workplaces
- Control of infectious diseases
- Decline in deaths from coronary heart disease and stroke
- Safer and healthier foods
- Healthier mothers and babies
- Family planning
- Fluoridation of drinking water
- Recognition of tobacco use as a health hazard

CDC, MMWR, December 24, 1999 / Vol. 48 / No. 50
http://www.cdc.gov/mmwr/PDF/wk/mm4850.pdf

Polio Successes

Impact of Vaccination 9 Diseases: Canada

Disease	Baseline 20th Century Estimates per Year	Baseline 21st Century Estimates per Year
Smallpox	5,000	0
Diphtheria	20,000	1
Pertussis	150,000	3000
Tetanus	60	3-5
Polio (paralytic)	2,000	0
Measles	300,000	<400
Mumps	90,000	90
Rubella CRS	~90	<1
H. influenzae b	2,000	<20

Tetanus successes

Cost effectiveness

Cost per Life Year Saved for Selected Life-saving Interventions (from Tengs et al)

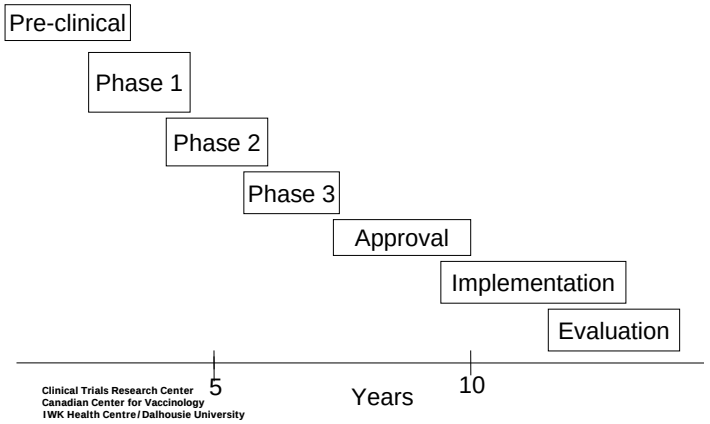
Measles, mumps and rubella immunization for children	≤0
Smoking cessation advice for pregnant women who smoke	≤0
Mandatory seat belt law	$69
Mammography for women aged 50	$810
Chlorination of drinking water	$3,100
Smoking cessation advice for people who smoke more than one pack per day	$9,800
Driver and passenger airbags/manual lap belts (vs. airbag for driver only and belts)	$61,000
Smoke detectors in homes	$210,000
Ban on products containing asbestos (vs. 0.2 fibres/cc standard)	$220,000
Low cholesterol diet for men over age 20 and over 180 mg/dL	$360,000
Crossing control arm for school buses	$410,000
Radiation emission standard for nuclear power plants	$100,000,000
Chloroform private well emission standard at 48 pulp mills	$99,000,000,000

Tengs et al. Risk Anal 1995 15: 369-90

Vaccine Development

- On average, it takes 10-15 years to bring a vaccine to market
- Vaccine development is highly pyramidal; for each success there are many failures
- Most failures occur in the pre-clinical stage and in early phase 1 clinical trials
- Vaccines that reach late stage 2 and phase 3 have an increased likelihood of reaching the market
- Timing predictions are still unstable
  - Regulatory factors
  - Corporate factors

Vaccine Gestation



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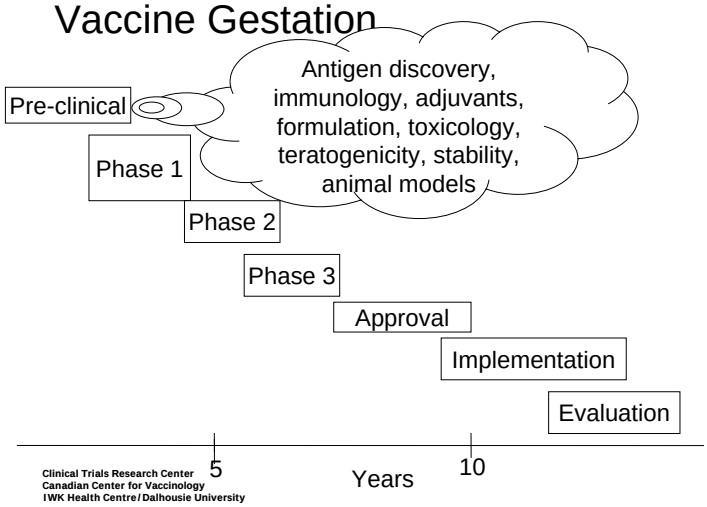

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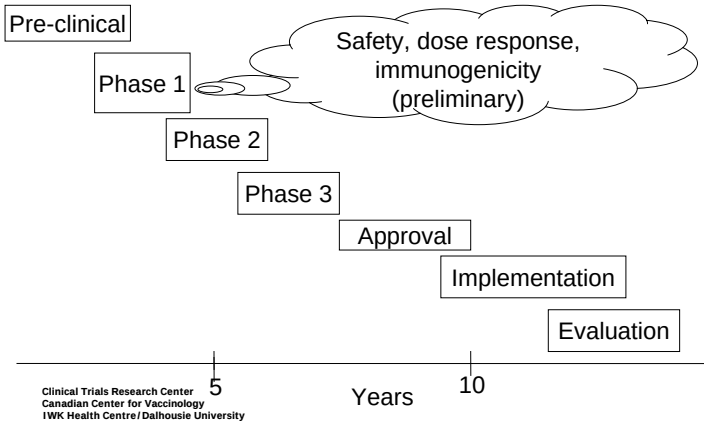
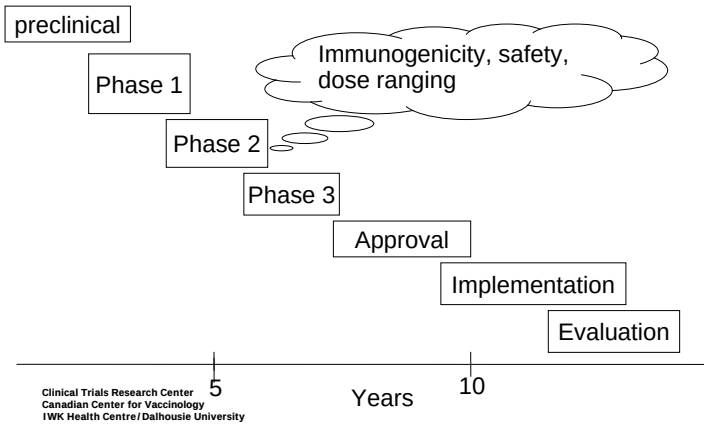


Phase 1: vaccine safety

- Small studies (n=40-50)
- Safety primary outcome
  - Injection site reactions (pain, erythema, swelling)
  - Systemic reactions (fever, anorexia, fatigue, headache, muscle ache, joint pain)
- Dose response
  - Often done with dose escalation with interval safety assessment
- Preliminary immunogenicity
  - Antibody response

Vaccine Gestation



Clinical Trials Research Center
Canadian Center for Vaccinology
IWK Health Centre/Dalhousie University

Phase 2: immunogenicity

- Larger studies (n=100-2000)
- Initial smaller studies to confirm optimal dose (dose ranging)
- Usually randomized, blinded, multicentered
- Immunogenicity primary outcome
- Late phase 2 studies can have expanded safety as primary outcome
- Lot consistency for at least one study

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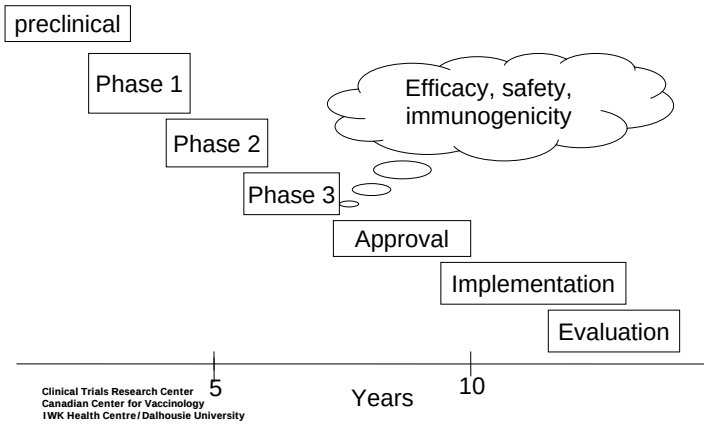

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Phase 3: Efficacy

- There are 3 options for showing vaccine efficacy:
  - Clinical endpoint
  - Immune response endpoints, if accepted by regulator (e.g., Hib vaccines, Hepatitis B vaccines)
  - "Animal Rule" (FDA), if certain criteria are met
- Expanded safety
- Immunogenicity in subset

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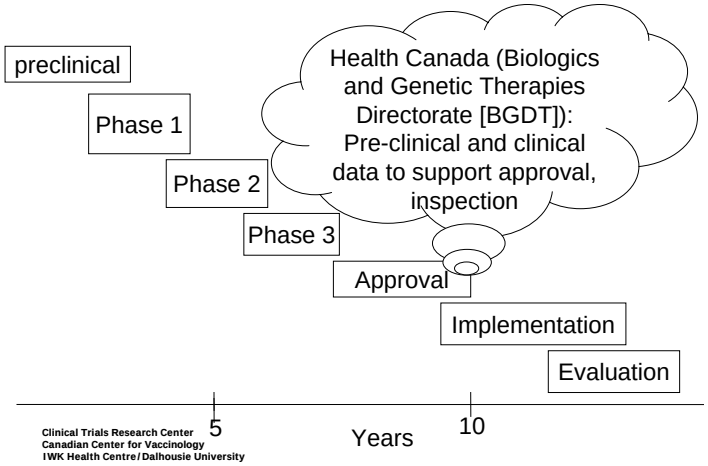

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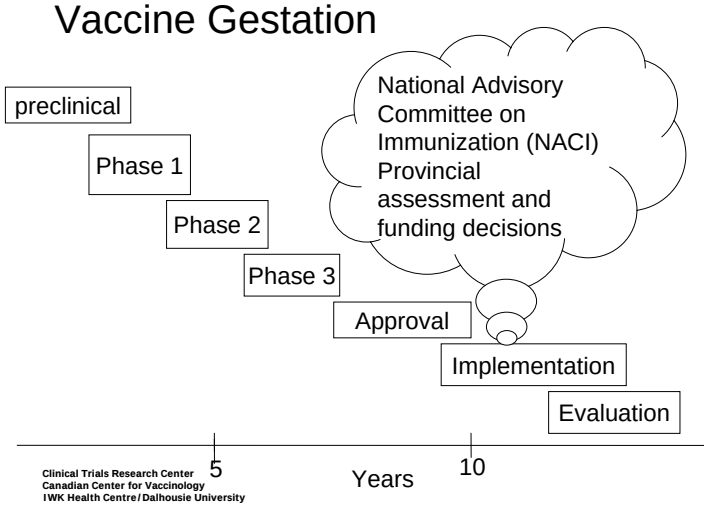

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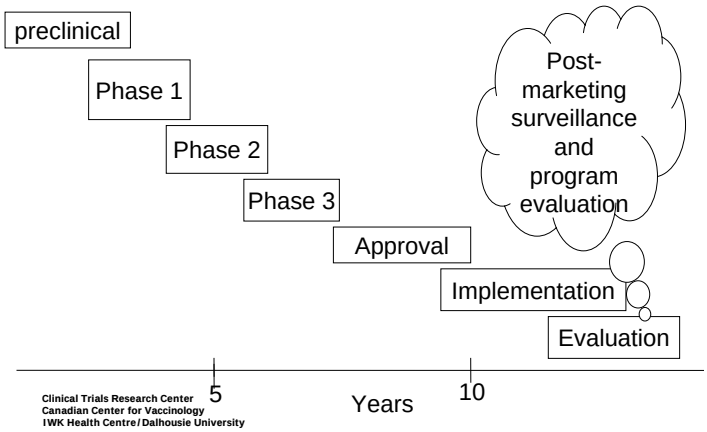
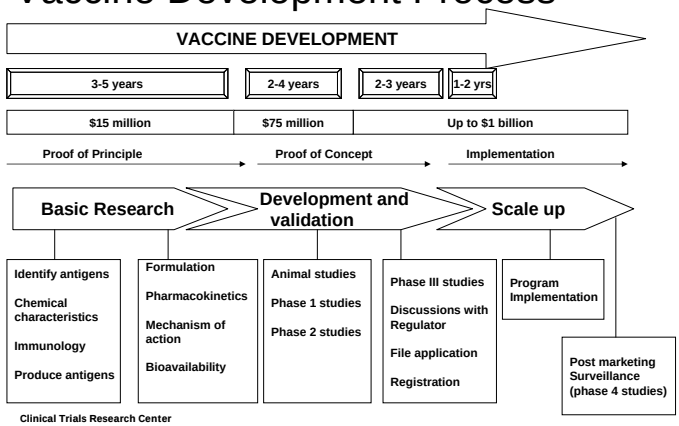


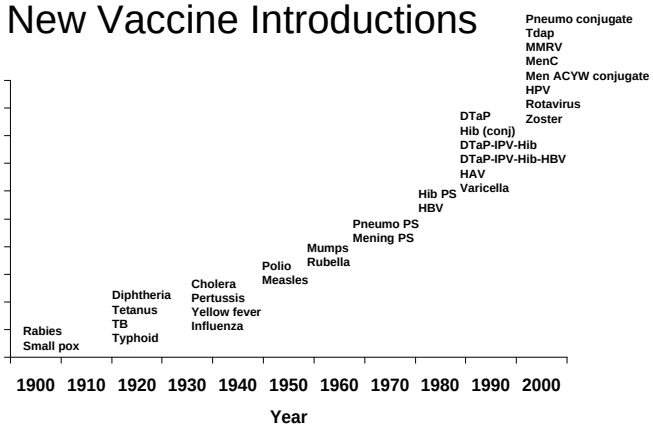
Phase 4: Effectiveness

- In contrast to phase 3 clinical trials to measure efficacy, phase 4 studies examine whether the vaccine works under normal use
- Expanded safety
  - Rare adverse events that occur at a frequency below clinical trial detection limits
- Program evaluation

Vaccine Development Process



New Vaccine Introductions



National Immunization Strategy

- Initiative of the Government of Canada and the provinces and territories
  - a comprehensive strategy to meet the current and future immunization needs of Canadians
  - The 2003 federal budget provided funding of $45 million over five years to strengthen federal infrastructure and programs for addressing immunization issues
    - vaccine safety
    - surveillance of vaccine preventable diseases and immunization coverage
    - Research
    - vaccine supply issues
    - professional and public education.

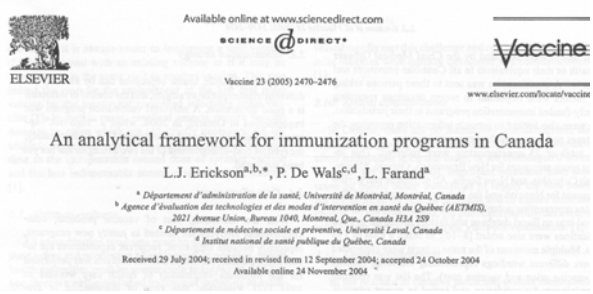
www.phac-aspc.gc.ca/media/nr-rp/2005/2005_14bk1_e.html

Goals of the NIS

- Ensure equitable and timely access to recommended vaccines
- Optimize program safety and effectiveness
- Improve co-ordination and cost-effectiveness of immunization programs
- Ensure the security of vaccine supply
- Provide rapid and effective national interventions in emergency situations and in response to international requests when required
- Promote professional and public acceptance of recommended programs.

www.phac-aspc.gc.ca/media/nr-rp/2005/2005_14bk1_e.html

Model for Program Decision-Making



Available online at www.sciencedirect.com
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An analytical framework for immunization programs in Canada

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Analytical Framework Criteria

- Disease burden
- Vaccine characteristics
- Immunization strategy and program
- Cost effectiveness
- Acceptability of vaccine program
- Feasibility of program
- Ability to evaluate programs
- Research questions
- Equity of the program
- Ethical considerations
- Legal considerations
- Conformity of the program
- Political considerations

Summary

- Vaccines, more so than drugs, require additional developmental steps at the program level in Canada
- Vaccine development is a long progress with multiple hurdles
  - Basic science
  - Epidemiology
  - Clinical trials
  - Translation
    - Knowledge, Attitudes, Behaviors and Beliefs
    - Bioethics
    - Health Law
    - Health Policy
    - Social Marketing

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