Western Canadian Immunization Forum
2011

Perspectives on Evaluating Immunization Programs

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Conflict of Interest Disclosures

David Scheifele:

Passionate about vaccines

Conducted many vaccine trials sponsored by various vaccine companies

Occasional consultant to industry and governments

Carol LaJeunesse:

None to declare, except passion

Canadian Immunization Programs

- How would you rate Canada's vaccination programs to date, compared to other affluent nations such as the USA and UK?

Adequate?

Pretty Good?

World Class?

ANSWER

- Canada's programs are truly world class!
- Canada's programs have rated among the top 3 among developed nations, historically and currently
- World class doesn't mean perfect – lots of room for improvement

RECENT "HONOURS LIST"

- Pertussis – early adoption of acellular vaccines (1995) and combos
- Influenza – outstanding uptake in seniors (1990's), inclusion of young children (2004)
- Pneumococcal and meningococcal C conjugates, early disease control (2002)
- HPV vaccines – early adoption, school programs (2007)

Research as Means to Success

- The successful establishment of new programs and subsequent disease control did not happen by accident
- Providers were key partners in success
- Much research was required:
  - To demonstrate the need for a vaccine
  - To evaluate the new vaccine
  - To evaluate and fine tune the new programs

New Vaccines are a Work in Progress

- "With vaccines, we are building our boat and sailing it at the same time"
- David Heymann, World Health Organization

Vaccine Research and the PHN

- Why are groups like the VEC important?
- What types of things do we do?
- How does the VEC facilitate PHN immunization practice?
- Working together as a team

VACCINE EVALUATION CENTER

- First Canadian academic vaccine research unit (established in 1988)
- Multi-investigator, broad scope, shared infrastructure model
- Capable surveillance, field, laboratory and data management teams
- Multiple concurrent studies, various funding sources (academic grants, gov't contracts, industry)

VACCINE EVALUATION CENTER

- Within Vancouver we have a network of experienced investigators and staff with capability with all phases of vaccines testing and access to all ages.
- Demonstrated ability to plan, implement and manage large multi-center studies that are clinical, surveillance, epi or laboratory based
- Completed >200 studies to date

VEC Background

- One of a network of vaccine/immunity evaluation centres across Canada
- 41 on staff currently; scientist investigators, clinical investigators (MD), clinical team, data team, laboratory team, epidemiologist, behaviourist (PhD)
- Many are part-time
- All are biased – pro-vaccine

Background and Qualifications

- Requires that individuals conducting trials involving humans have the appropriate background, education and training
- Investigators for most clinical trials are MDs, they are all paediatricians and ID specialists on staff at C&W. Some are dermatologists, medical directors, epidemiologists etc.
- CRC & Nurses are extensively trained in research, have public health background and are vaccine certified

VEC Investigators

- Dr. David Scheifele: CT, Epidemiology, Programmatic Evaluation
- Dr. Simon Dobson: CT, AEFI investigation
- Dr. Julie Bettinger: Epidemiology, KAB
- Dr. Tobias Kollmann: Immunology, CT
- Dr. David Speert: Microbial Pathogenesis & Host Defense, International Collaborations
- Dr. Laura Sauve: Epidemiology, CT
- Dr. Janet McElhaney: Immunology, CT
- Dr. Jan Dutz: Immunology, Dermatology, CT
- Programmatic Partners: Drs Skowronski, Naus, Dawar, Van Buynder

RECENT VEC CT HIGHLIGHTS

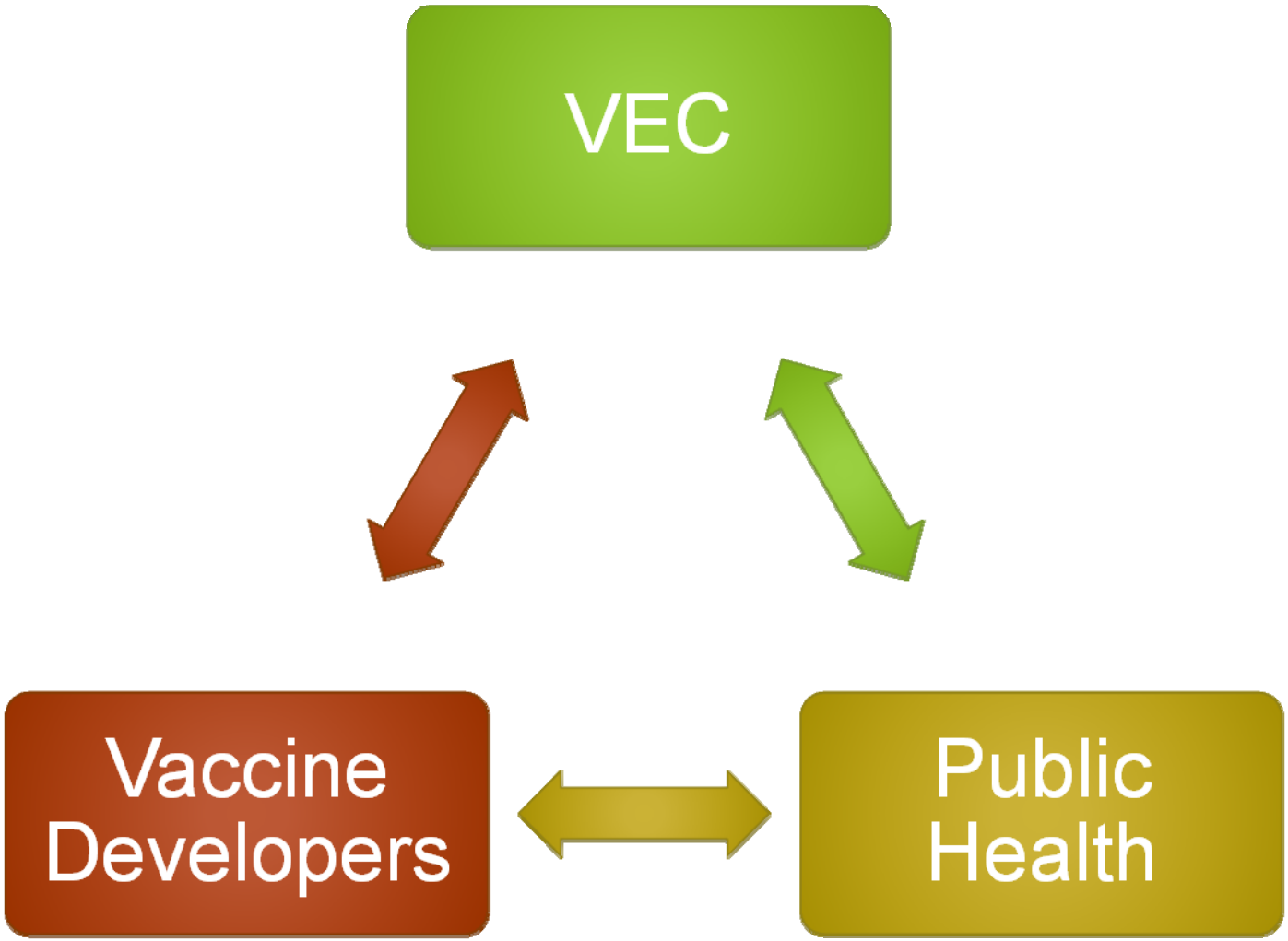
- Led Rapid Trials group of PCIRN
  (8 trials, 4 during the pandemic)
- 1st vaccine studies in Aboriginal children (Infanrix hexa), adults (H1N1 influenza)
- Led large multi-center study of alternative dosing schedule for HPV vaccine in young girls
- Men C schedules in Canada - comparison

VEC Non-CT HIGHLIGHTS

- Serve as data center for IMPACT pediatric hospitals active surveillance project and as 1 of 13 surveillance centres
- Province wide survey of physicians to determine challenges of vaccine delivery
- Province wide survey of parents of young children to determine “up to date” status and understand attitudes and beliefs

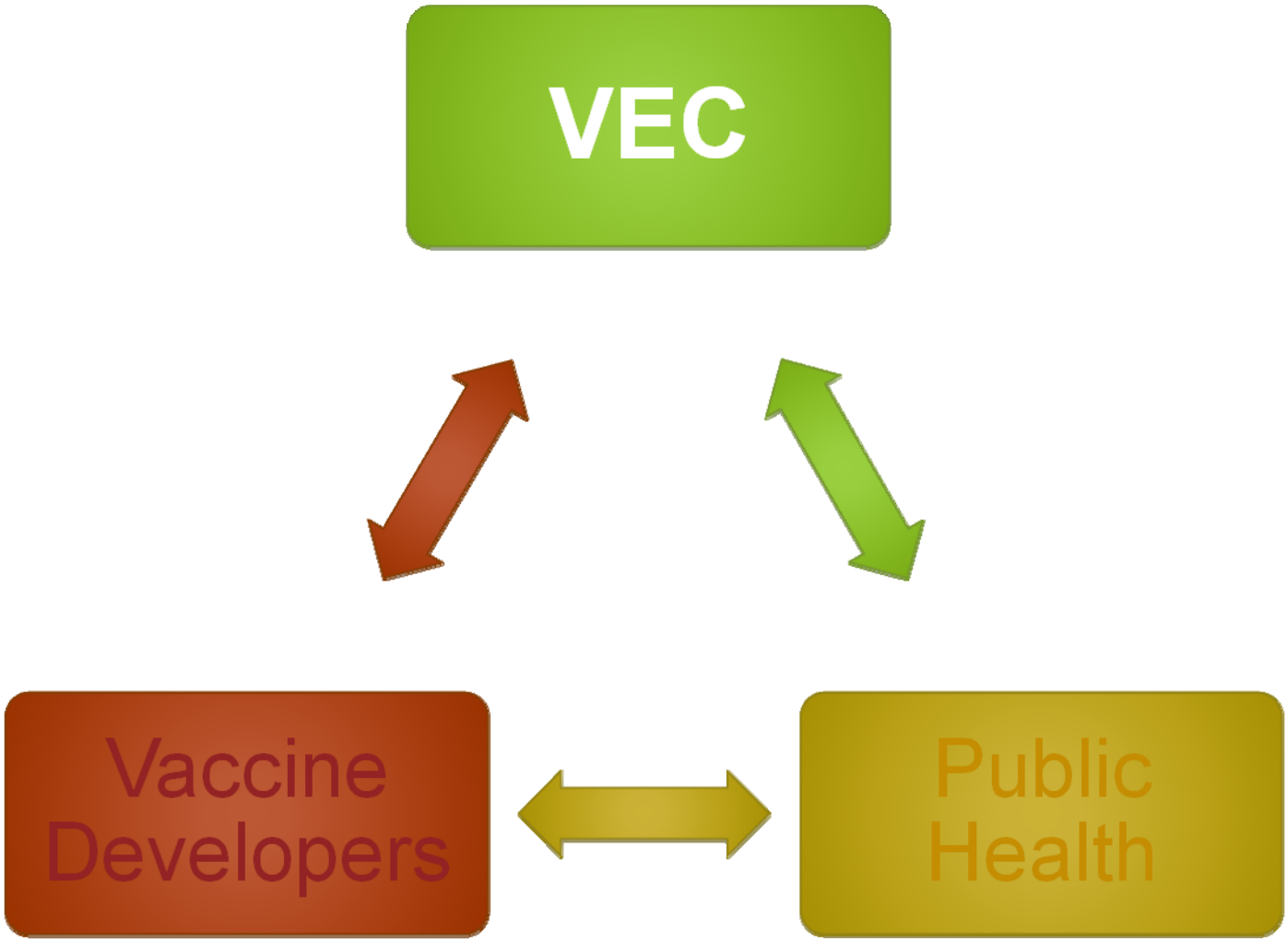
DATA MANAGEMENT

- Operates with a web-based EDC platform providing real-time data which facilitates national and global studies
- Applies industry level QA/QC standards
- Proven rapid turn around of results
- STAR - Ability to track all participants, reminders, letters, recruitment, electronic vaccination registry


VEC
Vaccine Developers
Public Health

Independent Research

- Vaccine safety and effectiveness
- Vaccine product comparisons
- Vaccine preventable infections
- Assessment or Enhancement of Public Immunization programs
- Monitoring and Surveillance
- Development of the Immune System


VEC
Vaccine Developers
Public Health

Changing Immunization Programs

- Changing face of disease
- **New vaccines, Complexity of the program, Schedule**
- Cost
- 'Sophistication' of vaccinees

IDEAL PROGRAM EVALUATION PLAN

- Each province would have means to assess uptake, safety and disease control, by similar methods
- Collaborative planning, joint funding of cross-cutting questions would occur
- Need new funding models for evaluation
- Need willing, skilled researchers and centers

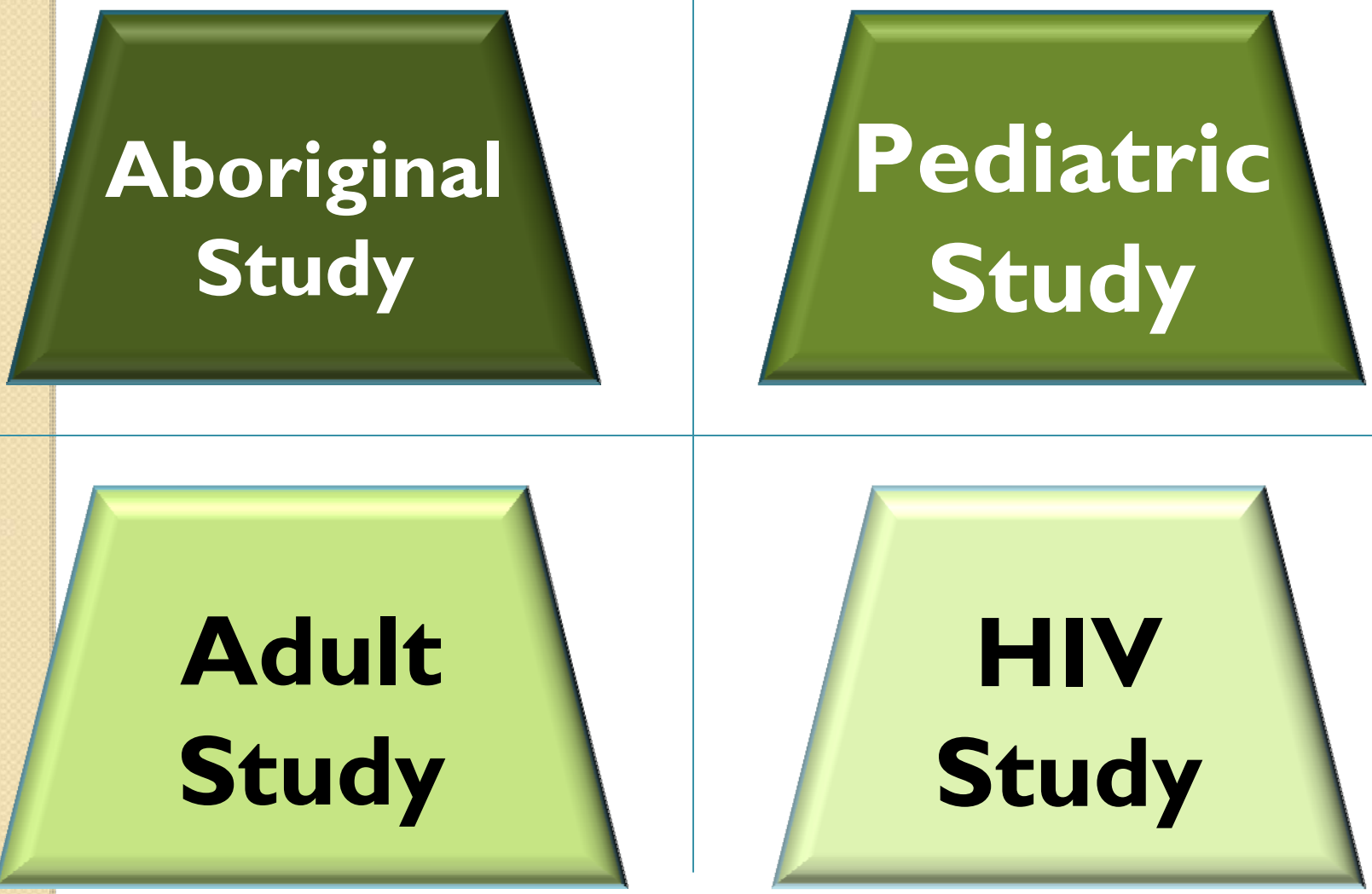
Public Health Agency of Canada (PHAC) and Canadian Institute for Health Research (CIHR) Influenza Research Network (PCIRN)

Rapid Trials Theme PI, Dr. David Scheifele MD

PCIRN Network Background

- Established to "prepare" for pandemic vaccine research studies
- Several Themes
  - VEC leads the Rapid Trial theme
- 3 year program
- 2009 = 4 Trials during the pandemic
- 2010 = 2 Trials
- 2011 = 1 Trial (2 sub-trials)

2009: Four Trials in the Pandemic Year



2009 Results – Aboriginal and Pediatric Studies

Aboriginal Study

- Robust antibody responses
- Response rates and GMT were higher than in non-aboriginal adults

Pediatric Study

- 2nd dose increased titers substantially
- Adverse effects were frequent but tolerable

2009 Results – Adult and HIV Studies

Adult Study

- Responses to vaccine were robust
- Responses were unaffected by concurrent TIV administration

HIV Study

- One dose was quite immunogenic, however, a second "booster" dose significantly increased protection

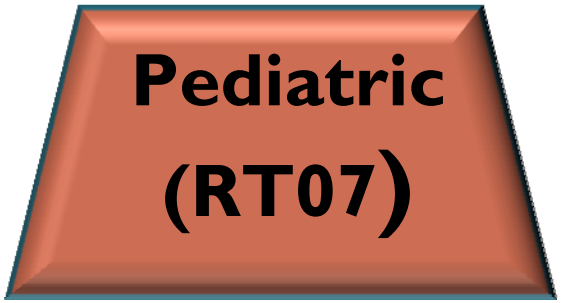
2010 : Conducting a rapid clinical trial

PCIRN's Adult TIV Study was the first of its kind in Canada.

- Pre licensure trial of Fluviral vaccine
- Goal was to inform public program
- Five Centres, 325 subjects
- First visit completed in one week
- All safety follow-ups within 4 weeks
- Report issued to Public Health September 2010, widely disseminated

Rapid Trials 2010: Pediatric Study

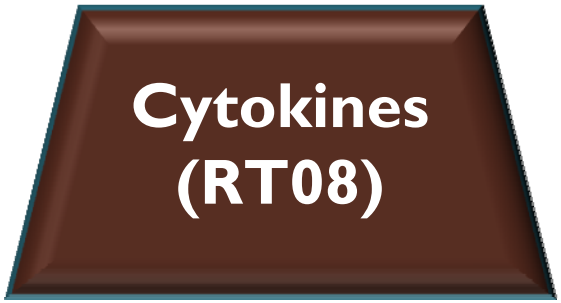
Public health had a keen interest in a pediatric study following reports of AE from Australia.



- No safety signal from Adult trial gave go-ahead
- Goal was to again inform public program
- Four centres, 200 subjects
- First visit mid-September
- All safety follow-ups within 8 weeks
- Initial findings are consistent with Adult study

2010 : ORS

ORS symptoms …
What causes them, can we predict who will get them?



- Exploratory
- Goal was look and see if cause definable
- Two Centres, 48 participants
- Immunological markers - cytokine
- Genetics – DNA

2011 = Seniors; 4 vaccines compared

Several new Formulations of Flu vaccine available for seniors.

- Seniors – protective levels harder to attain
- Goal was to ascertain if one vaccine was better in older population
- Eight centres, 942 participants
- First visit mid-September
- All safety follow-ups within 5 weeks
- Current status

Changing Immunization Programs

- Changing face of disease
- New vaccines, Complexity of the program, Schedule
- Cost
- 'Sophistication' of vaccinees

Changing face of disease

- Is the target organism disappearing? Becoming less susceptible?
- Are the strains swapping?
- How do we keep tabs on that?
- Are we preventing disease in one age group but moving it to an older group?
- Surveillance
  - CASPER
  - IMPACT

SOME NOTABLE BEGINNINGS

CASPER project in Calgary, re Pneumococcal Control has been an ideal model:

- Established baseline rates IPD, all ages (program rationale)
- Tracked effects of PCV7 vaccination program (Alberta 1st to use, influenced others to start programs)
- First Cdn report of effectiveness, indirect protection
- Recent report of eradication (!) of PCV7 disease cases, rapid effect of PCV13

IMPACT Active Surveillance

- 12 pediatric centers across Canada
- Monitoring Adverse Events following immunization and Vaccine-preventable disease admissions
- Existed since1992 to supplement passive reporting of AEFI's and VPDs
- Numerous reassuring safety reports
- Valuable data in support of newer vaccine programs (Hib, VZ, PNC, MenC/B, RV)

Changing Immunization Programs

- New vaccines, Complexity of the program, Schedule
- Cost
- 'Sophistication' of vaccinees

Changing Immunization Programs

- Become complex, with 15 current target infections and increasing
- New vaccines, revised vaccines, combination vaccines
- Boosters
- Schedules
- Dosage changes

QUESTIONS NEEDING ANSWERS

Regarding NEW vaccine:

- Is it meeting safety expectations?
- Is it gaining public acceptance?
- Is it working as well as expected?
- Is it working better than expected?

  (providing indirect protection)

QUESTIONS RE NEW VACCINE

- What is the most cost-effective dosing schedule? Best choice among products?
- Any detrimental effects of using with other vaccines?
- How long does protection last? Booster needed?
- Do some vaccinees fail to respond? Why?
- Choosing between competing product

Vaccine Development Process

- 10-20 years
- Identification of antigen
- 5-10 years of lab development (lab and animal)
- Phase 1: first humans (small 10+, close observation for immunogenicity and AE)
- Phase 2: dosage, schedule, safety (50-500)
- Phase 3: immunogenicity and reactogenicity - 500-30,0000
- Phase 4: post-licensure (efficacy)

New vaccine/combinations studies

- Pentavalent (1992)
- Hep B (1992)
- Hep A/B (1993)
- DPTaP-IPV, HIB (1994)
- Men C, Herpes (1996)
- Varicella (1997)
- Pentacel (2000)
- MMR-V (2001)
- MenACWY (2001)
- HPV (2005)
- Hexavalent (2010)

Evaluation of Meningococcal C Conjugate Vaccine Programs in Canadian Children

Co-ordinating Centre - PI, Dr. Julie Bettinger PhD

BC Site - PI, Dr. David Scheifele MD

CIHR-FUNDED STUDY LED BY VEC

- Investigators: J Bettinger, D Scheifele, J Kellner, O Vanderkooi, A Schryvers, S Halperin
- Compares programs: AB vs BC vs NS
- Infants enrolled at 12 months, for 12 mo dose
- Blood tests at 12, 13, 36 and 60 months for antibody assay re protection

Rationale

- Meningococcal disease is endemic in Canada (~200 cases a year)
- Serogroup C strains cause a substantial proportion of cases and deaths (30%-50%)
  - For every 100 children who get sick 15 will die
- Disease risk is highest in young children and adolescents
  - Ideal vaccine would provide protection throughout life
- Meningococcal disease starts with non-specific (flu-like) symptoms, difficult to diagnose, difficult to treat

Rationale

- MenC vaccines safe and effective
  - Provide an opportunity to prevent serogroup C infections
- The “best practice” for the administration of these vaccines is not known
- Duration of protection for MenC vaccines is not known
- At $80 per vaccine dose, the cost implications of multiple dosing are significant

Background

- Introduction of MenC universal infant vaccination in 2002-2005
  - The recommended 3 dose infant immunization schedule was adopted in only one province (AB)
  - Other provinces adopted a single dose at 12 months as a cost saving measure (NS), without evidence for effectiveness or duration of protection
  - British Columbia (BC) adopted a 2 and 12 month schedule, without evidence for effectiveness or duration of protection
- 3 different vaccines are used
  - Alberta, BC and Nova Scotia use a meningococcal C-tetanus toxoid conjugate (MenC-TT) vaccine (NeisVac-C)
  - Other provinces used two different meningococcal C-diphtheria toxin conjugate (MenC-CRM) vaccines

MENINGOCOCCAL C VACCINE FOR INFANTS

- Provinces chose 3 different infant schedules in absence of data:

  Alberta: 3 doses (2, 4, 12 months)

  BC : 2 doses (2 and 12 months)

  Others: 1 dose (12 months)

- Which provides best value?

Objective

- Compare the different infant MenC immunization programs currently in place in Canada by assessing protection levels at 1, 3 and 5 years of age afforded by MenC-TT in 3 different MenC infant immunization programs
  - Nova Scotia (one dose at 12 months),
  - British Columbia (doses at 2 and 12 months) and
  - Alberta (doses at 2, 4 and 12 months).
- To examine the immunological outcomes during the peak years of risk

Timeline

Jul 2009 – 2011 Visit 1 and Visit 2

2011 - 2014: Visit 3

2013 - 2015: Visit 4

MENC PROGRAMS: EARLY RESULTS

- AB infants all retained protection to 12 months, boosted well after 12 mo dose
- BC infants close 2nd : most (84%) had protection at 12 months, boosted well with 12 month dose
- NS infants susceptible to 12 months, weaker response to 12 mo dose

Significance of MenC Study

- Canada is the only country using different infant schedules
- The 2 and 12 month schedule is of great interest to UK, other countries as the optimal infant schedule

Changing Immunization Program

NEW REALTY OF HIGH VACCINE COSTS

- Newest vaccines are very expensive, $75-$150/dose
- Reflects rising costs of vaccine development, from requirements for more, larger pre-licensure studies
- Also higher production costs for new technologies
- Less marketplace competition, fewer companies globally

Cost Drivers

- Become expensive: cost to fully immunize

  Boy - $850 Girl - $1,300

Will be higher with rotavirus vaccine, second dose varicella added

- New vaccines will continue to be costly

COPING WITH HIGH VACCINE COSTS

- "Recommend but don't supply free"

  Examples: zoster, FluMist

- Determine most cost-effective deployment

  Consider: age of use, number of doses

  Examples: 2 dose HBV in adolescents

  2 dose PCV7 in infants

BCGov01
2 dose versus 3 HPV Vaccine Study

PI, Dr. Simon Dobson MD

Outline

1. Background
2. HPV vaccines
   Study vaccine
3. Case for a two dose trial
4. Research question
5. Trial Details and Outcome

Human papillomaviruses

DNA viruses (>100)

>40 infect the genital tract

- **High Risk**

  16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, 82

- **Low Risk**

  6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81

Acquisition

- Most common sexually transmitted infection
- 60% of girls will have acquired genital HPV at 48 months from first intercourse
- Point prevalence of active infection decreases with age from a peak of 23% at 20-24 yrs to a low of 4% at 45-59 yrs

Burden of HPV – cervical cancer the tip of the iceberg

- HPV causes 470 000 cases of cervical cancer per year worldwide
- >200,000 deaths annually (WHO)
- 35 000 die from cervical cancer per year in Europe & USA

HPV prevalence (before vaccine)

- Approx. 2 million Canadians infected
- Approx 550,000 new infections per year in Canada
- Highest direct medical costs of all STI'S other than HIV

Natural history

- Infection to release of virus – about 3 weeks
- Infection to appearance of lesions may be weeks to months

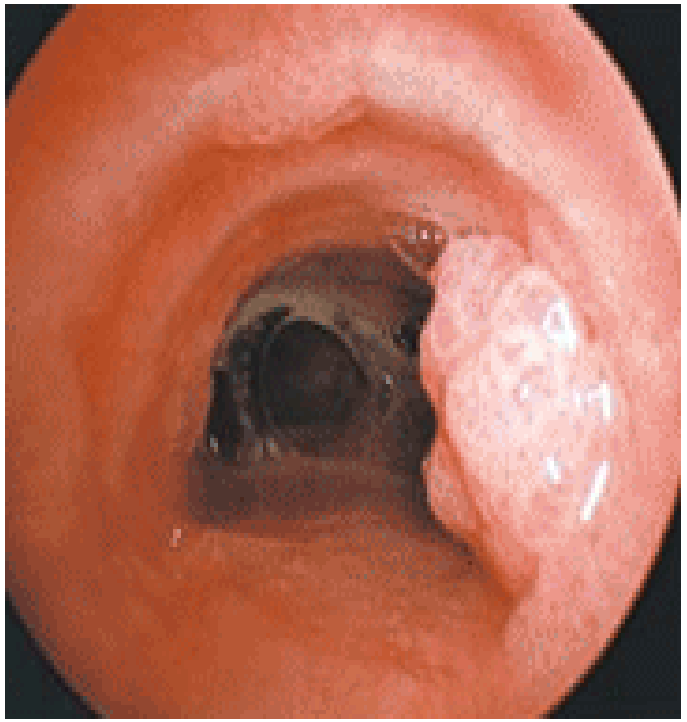
- 15-20% of HPV 6 and 11 infection results in clinically visible lesions
- Infection usually clear in 5-6 months for 6 and 11, 8-14 months for HR subtypes

Non malignant disease

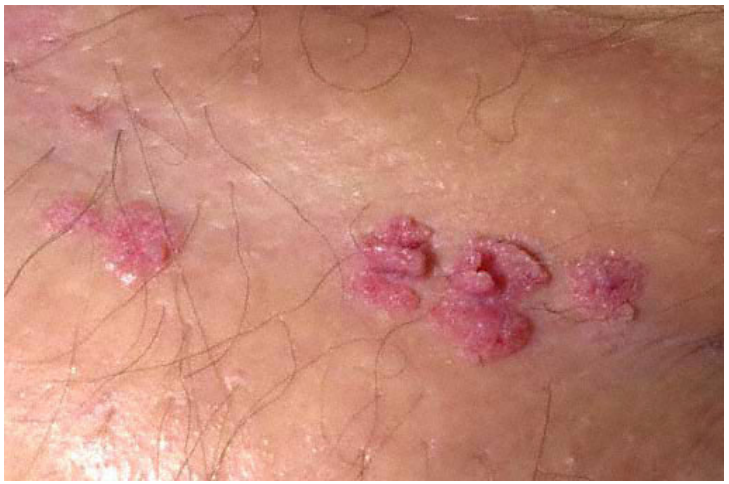
- Respiratory presentation: RRP
- Genital disease: warts

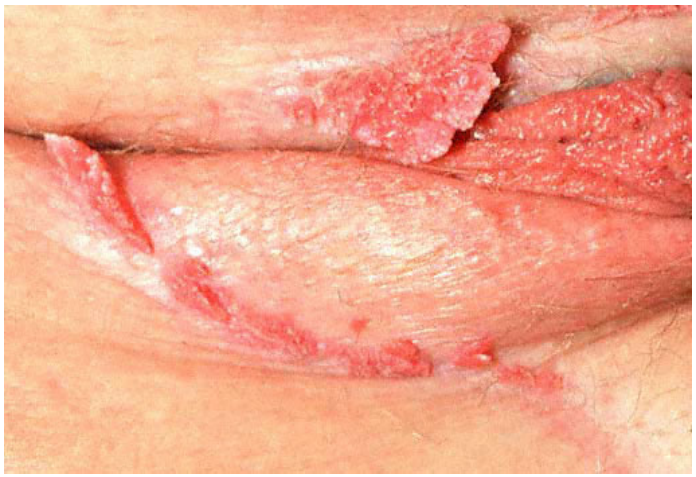
Recurrent Respiratory Papillomatosis (RRP)

- **Age distribution is bimodal**
- Usually caused by **HPV types 6 or 11**
- **RRP is rare**
- **Numerous OR visits for debulking of warts**

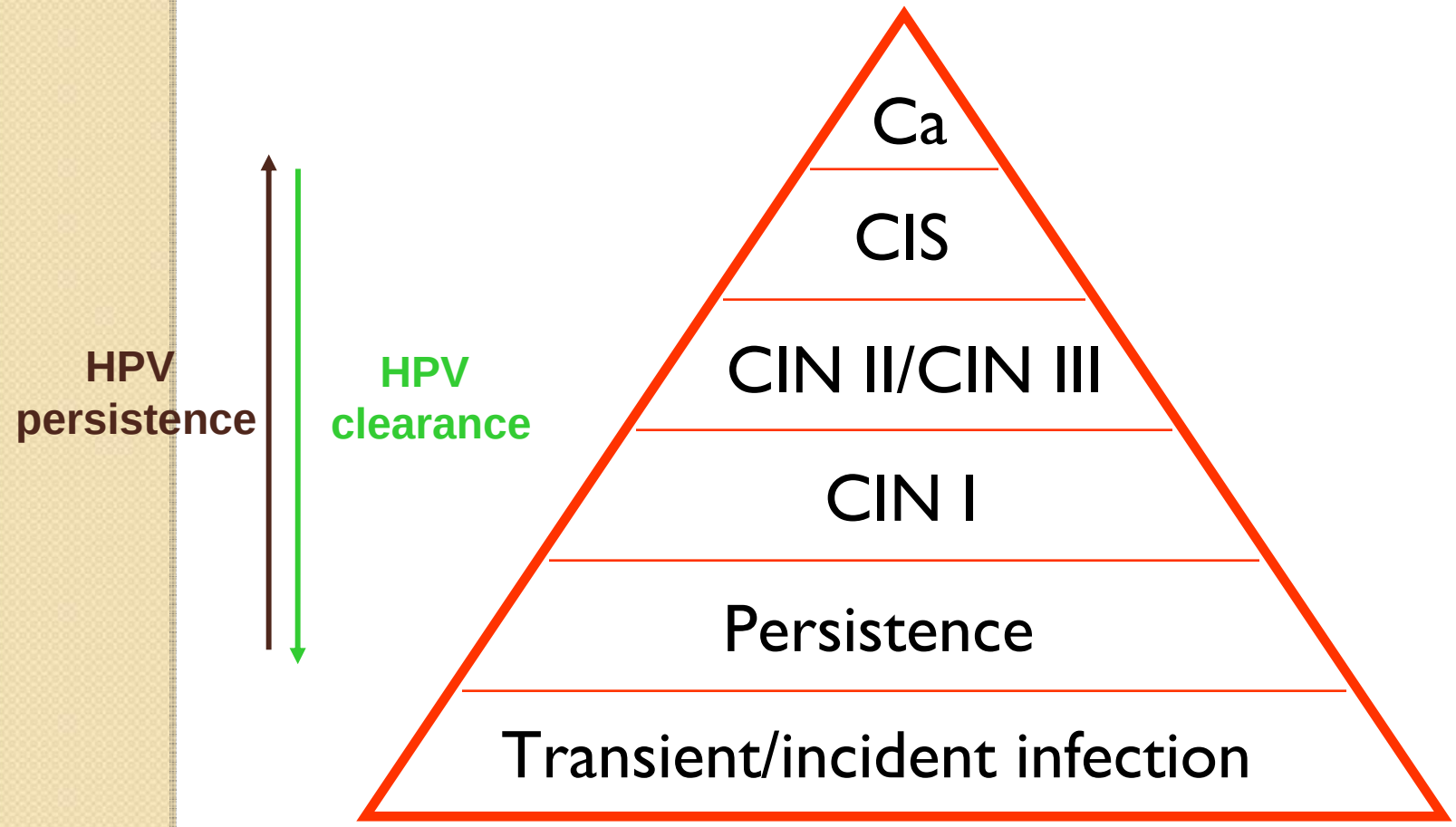


Anogenital warts





Persistent HPV infections



Ca = carcinoma

CIS = carcinoma *in situ*

Progression or Resolution of HPV

- Most people are exposed to the high-risk types of HPV at some point, but not everyone will develop abnormal cell changes
- The majority (over 80%) of HPV infections are transient, asymptomatic and resolve spontaneously
- Persistent infection is the first stage in the progression from HPV infection to cervical cancer

HPV Vaccines

	Gardasil™	Cervarix™
Company	Merck	GSK
Type of vaccine	Prophylactic vaccines consisting of virus-like particles containing L1 capsid proteins	
Antigens	Quadrivalent: HPV 6, 11, 16, 18 at 20/40/40/20 µg	Bivalent: HPV 16, 18 at 20/20 µg
Expression system	Yeast	Baculovirus
Adjuvant	Alum: 225 µg aluminum hydroxyphosphate sulfate	ASO4: 500 µg $Al(OH)_3$ & 50 µg MPL
Dose & schedule	0.5 mL IM at 0, 2, 6 months	0.5 mL IM at 0, 1, 6 months
Licensed	Yes	Yes

Study vaccine: Gardasil™

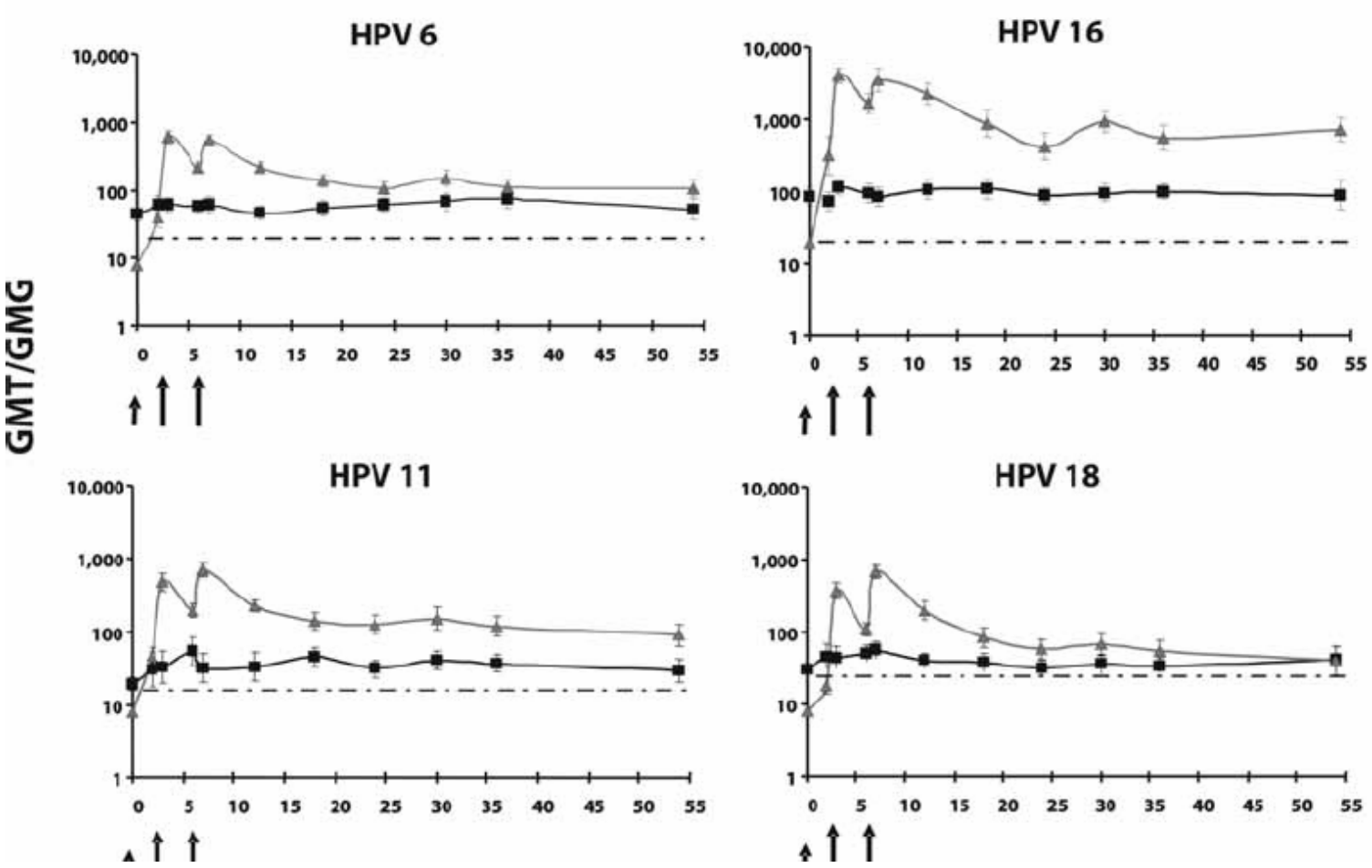
- Safe
- Immunogenic

  sera and mucosal immunity

  > 99% seroconversion

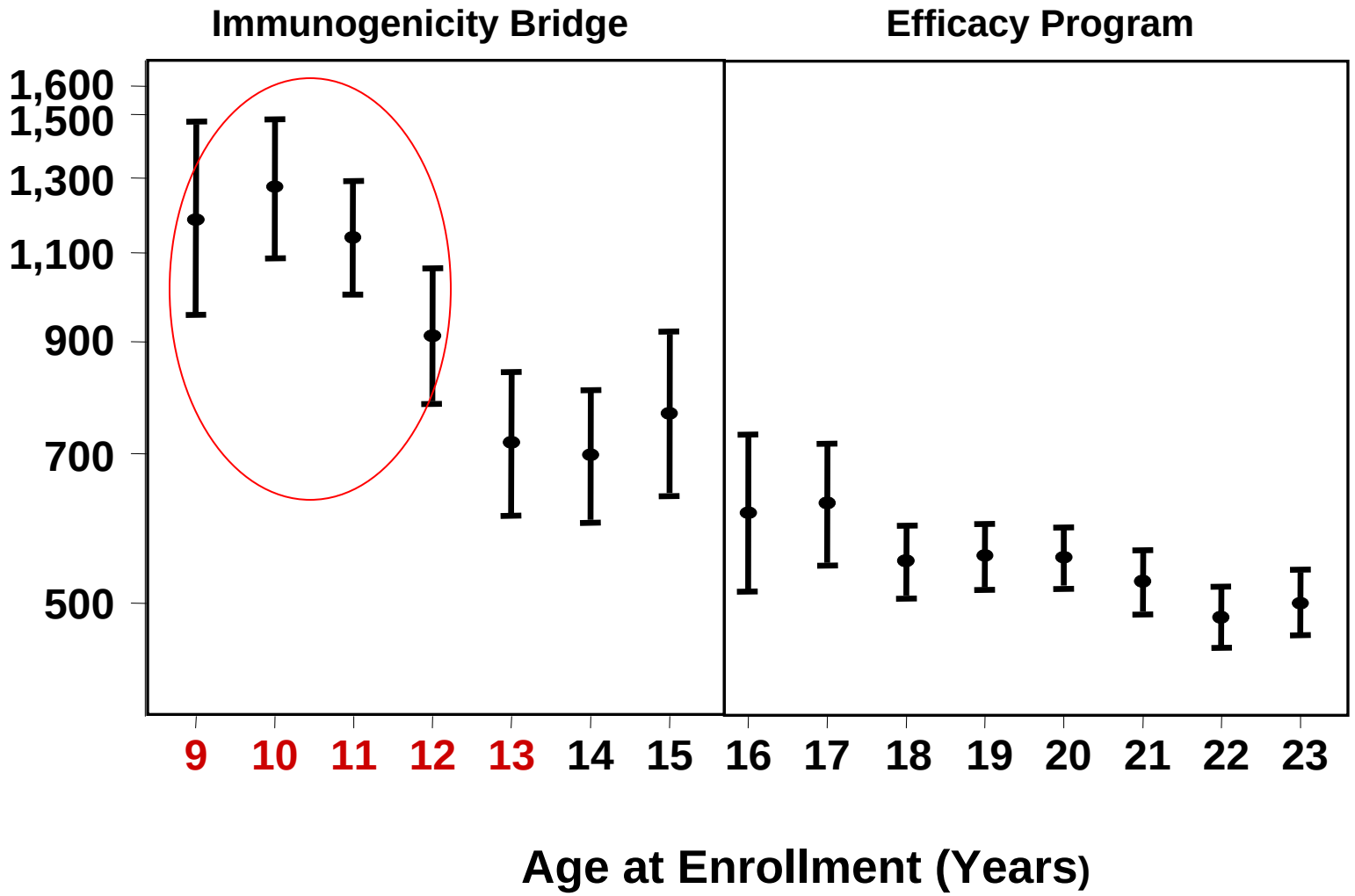
  Durable antibody response to 5 yrs at 3 doses
- Efficacious
- Effective

Antibody response at 4.5 yrs



Anti-HPV 6 antibodies by age

(3-dose Q-HPV vaccine)



Building the case for a two-dose trial

- Immune response in adolescents is superior to any other age group
- Examples of a pediatric vaccine dosage (Hepatitis A and B)
- Align with current school based hepatitis B program

Clinical trial components

Three sites: Vancouver, Halifax, Quebec

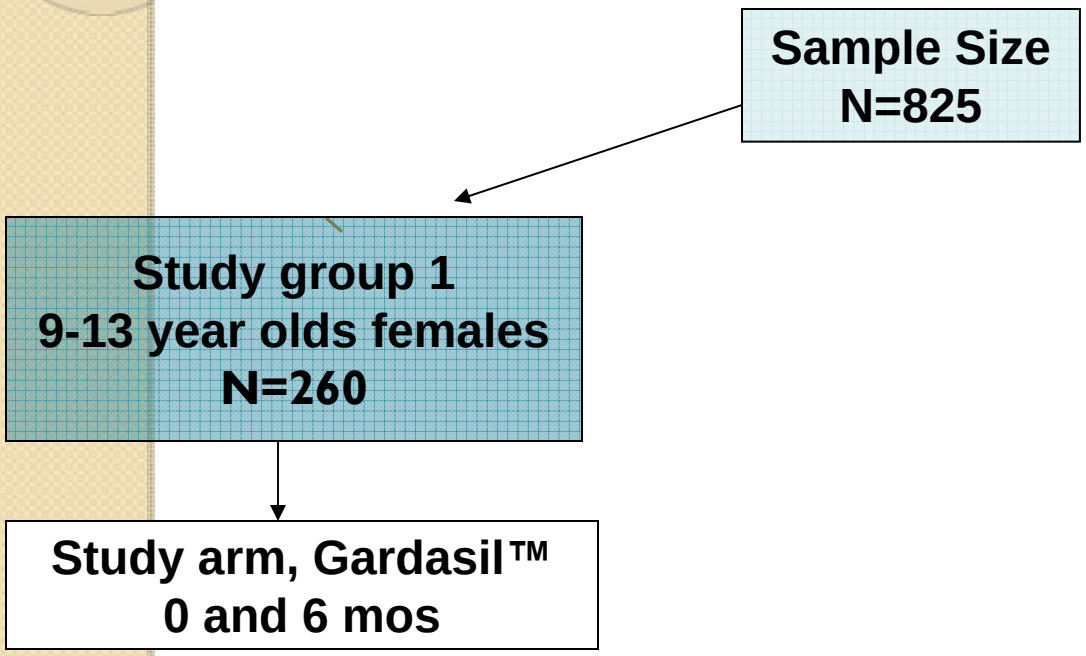
Study part 1: time period 0-7 months

Objective: to assess peak immune response

Study part 2: time period 14-36 months

Objective: to assess durability of immune response

Trial design



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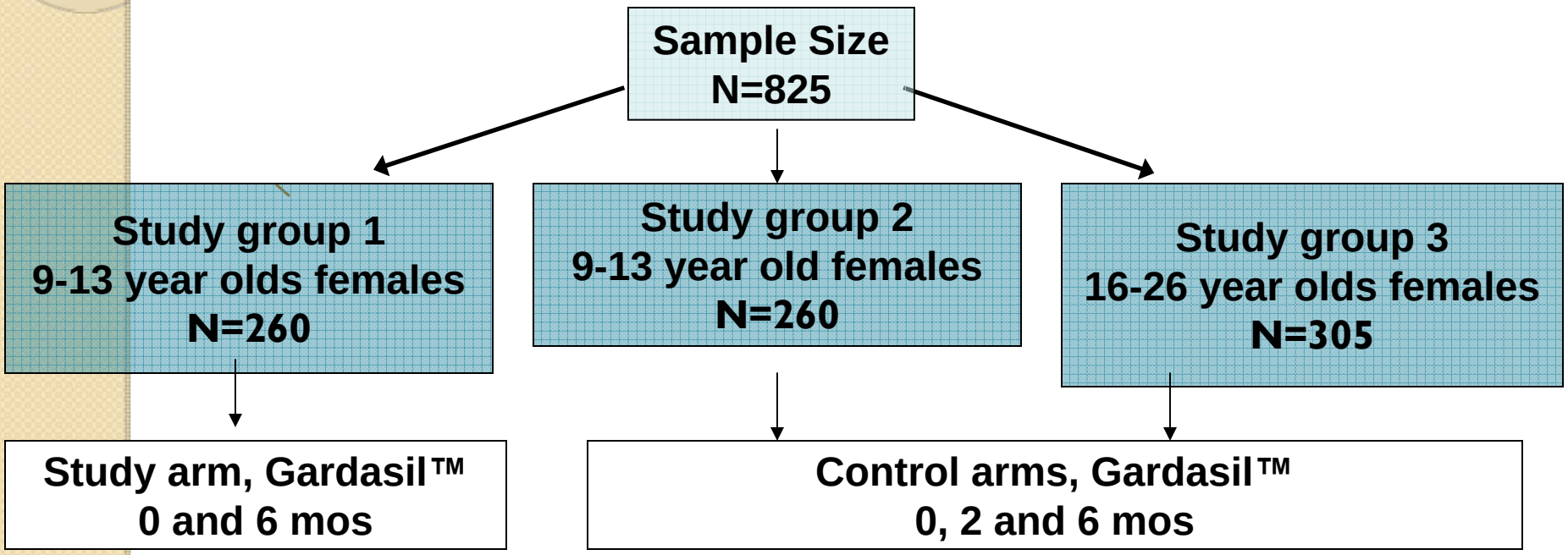

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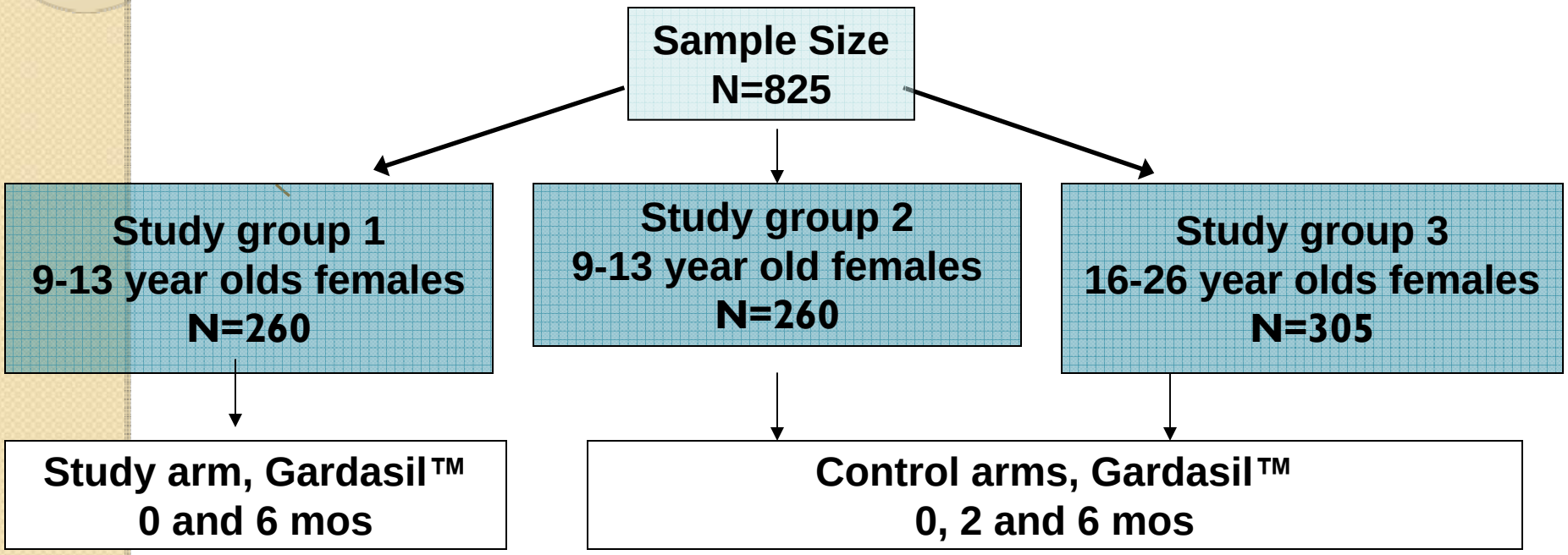


Primary outcome: **Anti-HPV 16 and 18 GMT, t =7 months**

Secondary outcomes

- **2-dose adolescents/ 3-dose adults**

Anti-HPV 6, 11

t =7 mos

durability of antibody response

t = 18, 24, and 36 mos

Seroconversion rates

B and T cell response

t = 0 and 7 mos

Time line

- Enrolment start Part 1:
  - Aug 7 2007 Centre 1
  - 6 months
- Last Visit Last Subject (Part 1)
  - End of August 2008
- FVFS (Part 2)
  - March 2009 (18mth)
- LVLS = end Nov 2010

Visit Summary
Part 1

Group	Vaccine Schedule	Bloods	Total Visits
1	Month 0 and 6	0 and 7	3
2	Month 0,2 and 6	0 and 7	4
3	Month 0,2 and 6	0 and 7	4

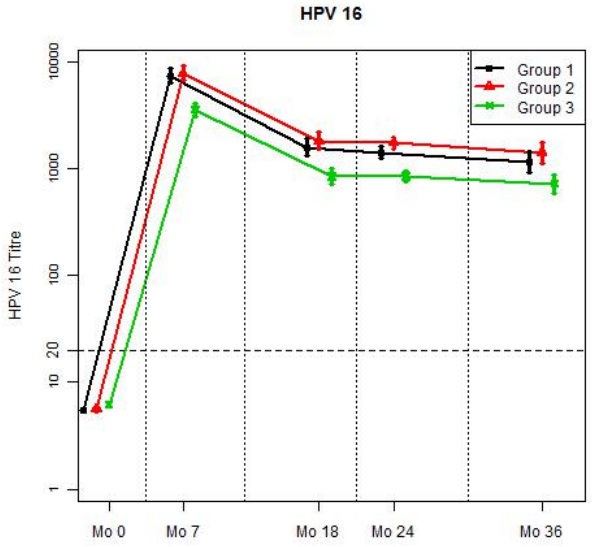
Visit Summary
Part 2

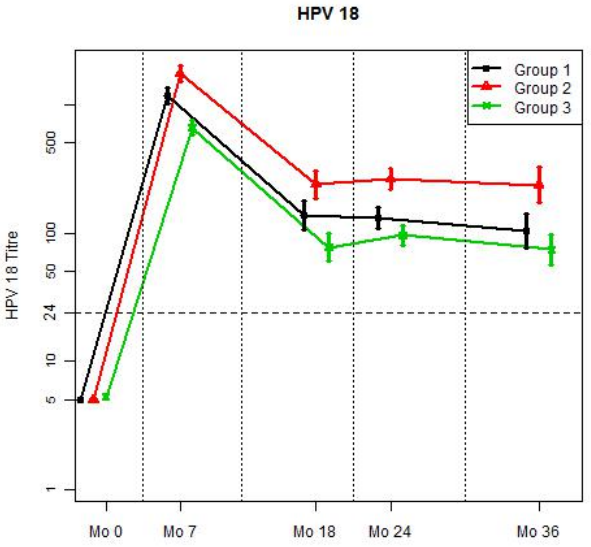
Group	Vaccine Schedule	Bloods	Visits at
A	Month 0 and 6 or Month 0,2 and 6	2	18 and 24 mth
B	Month 0 and 6 or Month 0,2 and 6	2	24 and 36 mth

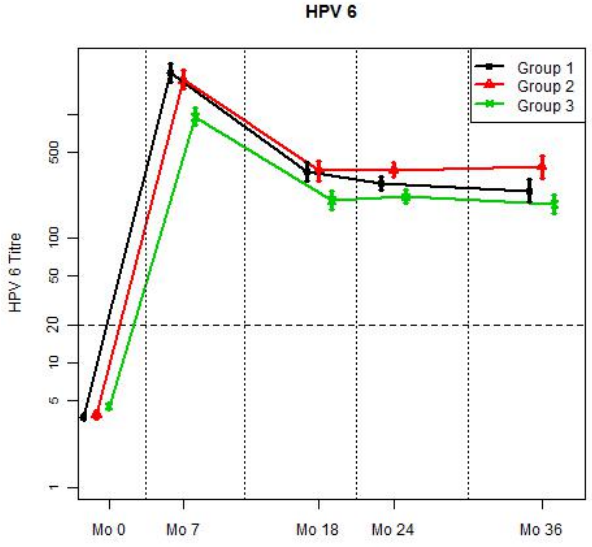
Results 7 mth

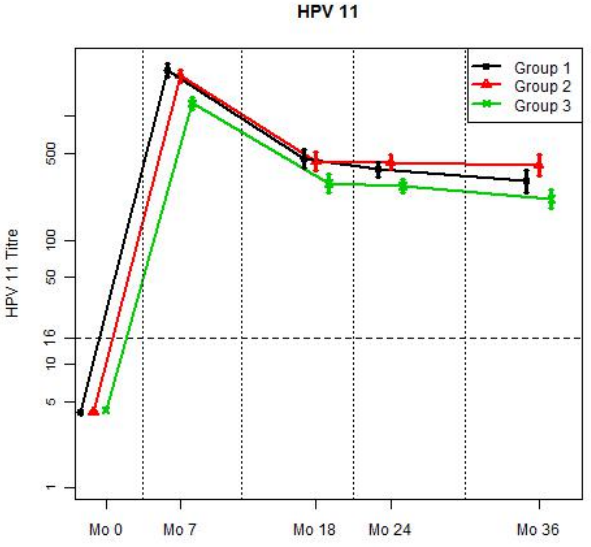
- Following a 2 dose regimen in 9-13 year old girls, antibody responses to HPV-16,-18, -6,-11 were **non-inferior** through 7 months, as compared to a 3-dose regimen in young adult women

Geometric Mean Titres in the Intention To Treat Population









Conclusions

- Following a 2 dose regimen in 9-13 year old girls, antibody responses to HPV-16,-18,-6,-11 were **non-inferior** through 36 months, as compared to a 3-dose regimen in young adult women

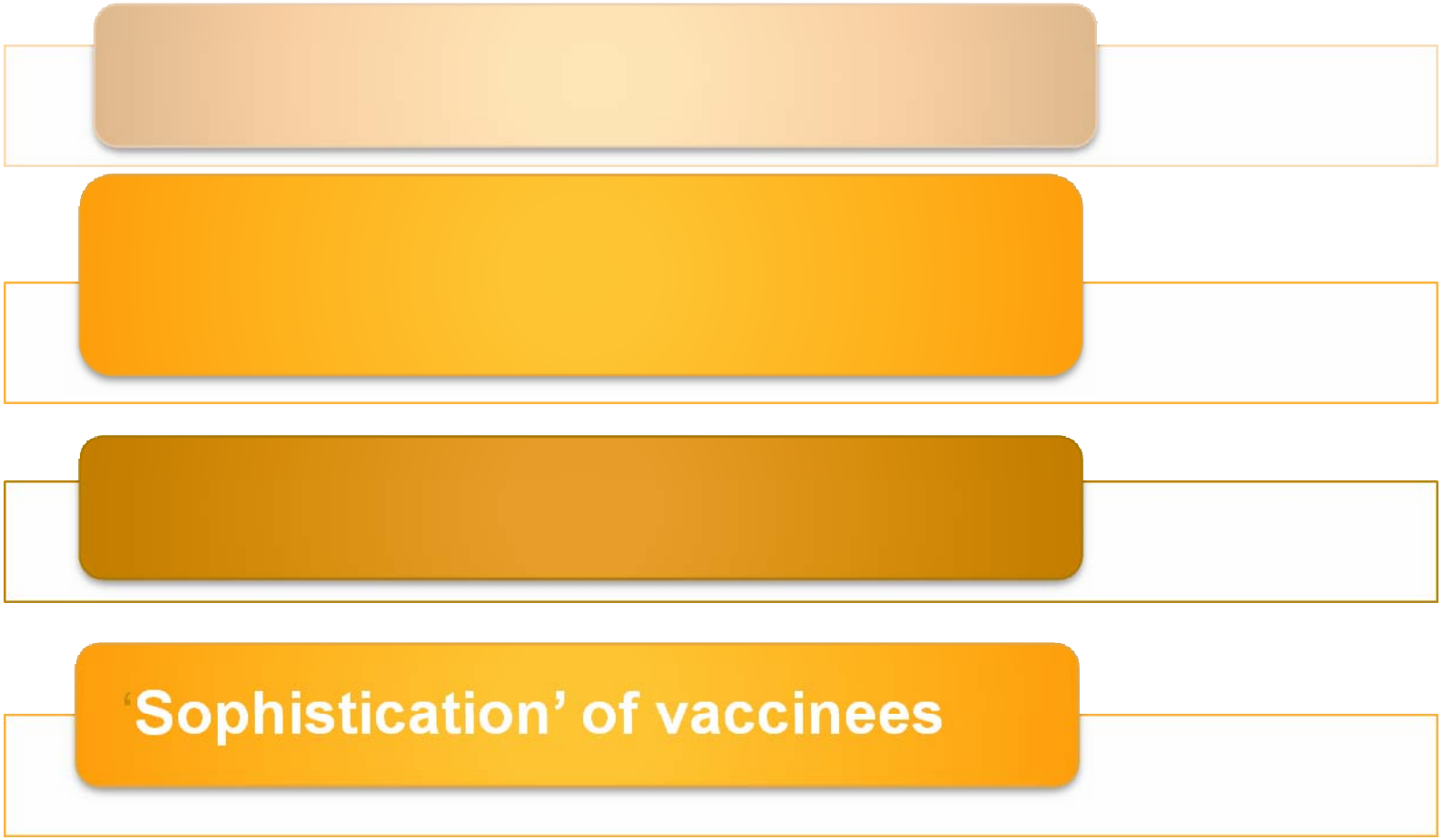
Outcome

- In 2008/09 British Columbia implemented a 2 dose schedule for Grade 6 with an option for a booster dose in highschool
- In September 2010, a 0, 6 month two dose schedule in its HPV immunization program for 11 year old girls

Next steps

- Alternative schedules have been used (Quebec and BC)
- Evaluation of the programs has to be in place (immunogenicity and effectiveness studies)
- High levels of support from government, health care providers and public

Changing Immunization Program



'Sophistication' of the Vaccinees

- Decision-making influenced by the internet
- Insistence on higher safety standards
- Never seen disease as motivator
- Less consistent relationship with FMD as trusted advisor
- Mistrust of governments, authorities
- RESULT: suboptimal uptake of vaccines

Studies of Public Receptivity

- Social marketing of new vaccines requires greater sophistication, evidence base
- Studies of public knowledge, attitudes and beliefs are increasingly necessary to shape education/promotion plans
- Recent VEC studies: Pregnant women and adjuvanted pandemic vaccine, attitudes to HPV vaccine

Back to the Honour's List

- Recent improvements in childhood vaccination programs that were aided by VEC research studies:
  - Feasibility of MenB vaccine program, based on studies of the IMPACT isolate collection
  - Adoption of hexavalent vaccine to reduce injections per visit
  - Adoption of PCV13 vaccine
  - 2-dose HPV program

Basic Project Management

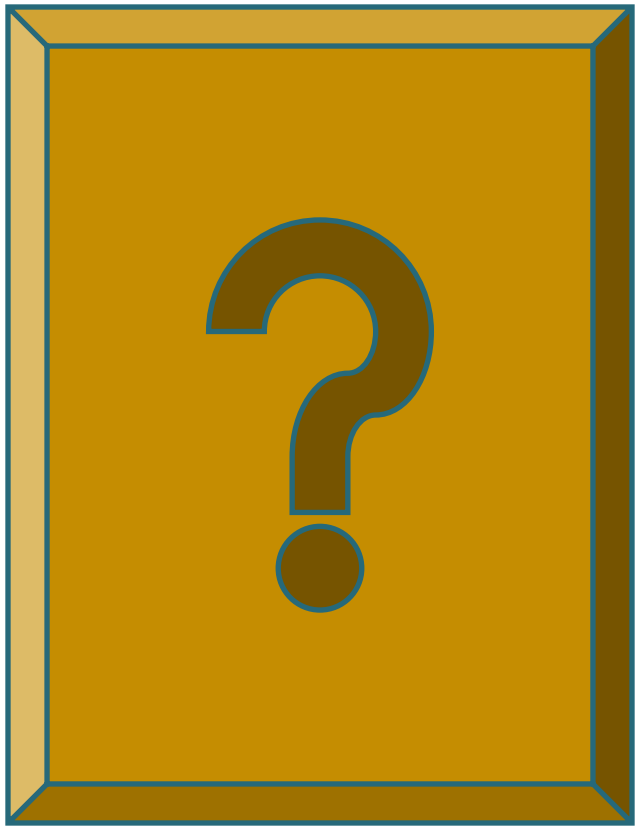
- Recruit potential participants – the biggest challenge for vaccine studies
- Enroll participants, with informed consent
- Retain participants
- Distribute results (knowledge translation)

PHNs and Research Nurses – a team

- Understanding and enhancing the flow of information
  - What can you do for us?
  - What can we do for you?
  - How can we accomplish this?

HELPING THE VEC

- May be opportunities to refer potential participants for new studies
- Need to be aware of subjects who follow non-standard schedules (and don't make them ineligible for our follow-up by giving non-study vaccines)
- Moral support is always welcome, as it aids public credibility and acceptance



Pearls

- The successful establishment of new vaccine programs and subsequent disease control did not happen by accident. Much research was required.
- The Vaccine Evaluation Center (VEC) was the first Canadian academic vaccine research unit (established in 1988). It is a multi-investigator, shared infrastructure model capable of surveillance; clinical, laboratory and data management teams execute multiple concurrent studies from various funding sources (academic grants, gov't contracts, industry) without core funding

Recent Accomplishments

- Leads Rapid Trials group of Influenza Research Network; (8 trials, 4 during the pandemic)
- 1st vaccine studies in Aboriginal children, adults
- Leads large multi-center study of alternative dosing schedule for HPV vaccine in young girls (2 doses versus 3): Outcome is that BC has changed to a 2 dose plan
- Leads a Men C schedules in Canada – comparison study that is demonstrating that a 2 dose schedule (as in BC) is most cost-effective

The VEC needs help from PHNs

The VEC needs PHNs to be a part of the process of assisting in research by:

1. Understanding central role of research in the success of public programs
2. Championing the VEC and what we do (recruiting, retaining kids on study)
3. Not overriding study execution plans by rendering kiddies ineligible
4. Disseminating results of key studies