Vaccines have a life cycle too!

A case study using Meningococcal Vaccines

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  • Immunization and Respiratory Infections Division, Public Health Agency of Canada
Disclosure of Potential for Conflict of Interest

Barbara Law, MD

Vaccines have a life cycle too! A case study using meningococcal vaccines

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- Grants/Research Support
  - none
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  - none
- Consulting Fees
  - none
- Other
  - Government (PHAC) employee
Vaccines have a life cycle too!

Objectives

1. Define the life cycle of vaccines and immunization programmes
2. Describe the process to obtain marketing approval for vaccines in Canada
3. Describe what can be learned about vaccines after they are approved
4. Characterize key ‘postmarket’ roles and responsibilities of:
   • Vaccine manufacturers
   • Canada’s vaccine regulatory authority
   • Public Health Agency of Canada
   • Provincial / Territorial Health
   • Vaccine providers
   • Other Healthcare providers
   • Vaccine recipients or their parents / caregivers
5. Summarize the current status of meningococcal disease and current and developing vaccines
Vaccine Life Cycle

1. Drug Discovery
2. Pre-Clinical Studies
3. Clinical Trials
4. Drug Submission
5. Licensing
6. Early Post-market Period
7. Increasing Knowledge
8. Evolution of Product and Knowledge

Key:
- GLP (Good Laboratory Practice)
- GCP (Good Clinical Practice)
- Review
- Market Authorization (NOC & DIN)
- New Drug Submission Authorization
Shared Responsibility for Vaccine Life Cycle Management
## Vaccine Development: a Manufacturing Perspective

1-30+ year timeline, depending on vaccine

<table>
<thead>
<tr>
<th>Phase</th>
<th>Subjects</th>
<th>Key Study Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>10-&lt;100</td>
<td>- Immune response pattern</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Very common reactions (&gt;10%)</td>
</tr>
<tr>
<td>II</td>
<td>50-500</td>
<td>- Optimal schedule in target group</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Common (≥ 1%) reactions</td>
</tr>
<tr>
<td>III</td>
<td>300-30,000</td>
<td>- Efficacy in target population(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Uncommon (0.1%) reactions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Frequency of events “attributable” to vaccine</td>
</tr>
</tbody>
</table>
Regulatory Standards to Ensure Safety & Efficacy
'Good Practices'= international quality management standards

### Good Laboratory Practice
Goal: uniformity, consistency, reliability, reproducibility, quality & integrity of chemical pre-clinical safety testing

### Good Clinical Practice
- Standards for how clinical trials should be conducted
- Regulatory approval
  - All new product clinical studies
  - All new lots used in clinical trials

### Good Manufacturing Practice

Starting materials must be:
- characterized
- defined origin
- acceptable quality

Validated production process
- all specifications of all steps met at least 3 times in a row

Consistent production
- each lot has characteristics of lots used in pre-licensure clinical trials to establish safety and efficacy

Licensed establishment
- to ensure adherence to GMP

Goal: uniformity, consistency, reliability, reproducibility, quality & integrity of chemical pre-clinical safety testing
Vaccine Life Cycle: Regulatory Roles & Responsibilities

Health Canada’s Health Products & Food Branch (HPFB)

- **Biologics and Genetic Therapies Directorate (BGTD)**
  - Approval of pre-market clinical trials and vaccines for marketing
  - Lot-release program
  - Review/approval of any product changes that could impact quality, safety, efficacy or effectiveness

- **Inspectorate**
  - Licences Manufacturing Facilities
  - Ensures compliance with Good Manufacturing Practices
  - Audits compliance with Food and Drug Act Regulatory reporting

- **Marketed Health Products Directorate (MHPD)**
  - Health portfolio lead on consistent approach to post-approval safety surveillance for all marketed health products
  - Conduct risk / benefit assessments of marketed health products
  - Manage Canada Vigilance monitoring program
  - Overview regulatory activities re product advertising
Shared Responsibility for Vaccine Life Cycle Management

Vaccine Researchers

Manufacturer

Health Canada (Regulator)

Public Health Agency of Canada

National Advisory Committee on Immunization
Shared Responsibility for Vaccine Life Cycle Management

An Advisory Committee Statement (ACS)

National Advisory Committee on Immunization (NACI) †

UPDATE ON THE INVASIVE MENINGOCOCCAL DISEASE AND MENINGOCOCCAL VACCINE CONJUGATE RECOMMENDATIONS

Public Health Agency of Canada

National Advisory Committee on Immunization

www.phac-aspc.gc.ca/naci-ccni
Shared Responsibility for Vaccine Life Cycle Management

No program?
Universal program?
Targeted program?
Catch-up program?
Optimum age(s)?
Public health or private clinic delivery?

TOUGH DECISIONS AHEAD

Provinces + Territories

Public Health Agency of Canada
Analytic framework for immunization programs in Canada

Erickson et al, Vaccine 2005; 23:2470-6

1. Burden of disease
2. Characteristics of the vaccine
3. Optimal program strategy
4. Program cost-effectiveness
5. Program acceptability
6. Program feasibility
7. Ability to evaluate coverage, safety, effectiveness
8. Key research questions for program implementation
9. Equitable accessibility of vaccine for all target groups
10. Ethical concerns re program implementation addressed
11. Legal concerns re program implementation addressed
12. Conformity of planned program to other regional pgms
13. Political considerations: controversy immediate benefits
What is **NOT** known about the vaccine profile prior to licensure?

**Vaccine Benefit**
- Effectiveness - in general population
- Immunogenicity and effectiveness in special populations
- Duration of immunity, need for boosters
- Community immunity?

**Vaccine Risk**
- Rare reactions (≤ 1 per 1000 vaccine doses)
- More frequent reactions in non-target group
- Delayed onset reactions (>30 days)
- Special population issues, if any

**Vaccine Acceptability and Uptake**
- Likelihood for adoption as public programme
- Public and Health Care Professional perceptions
1960s Thalidomide disaster
WHO called world nations to take action resulting in global post-market surveillance systems

Pharmacovigilance

- pharmakon (Greek): ‘drug’
- vigilare (Latin): ‘to be awake’......‘to keep watch’

Vaccine pharmacovigilance The science and activities relating to the detection, assessment, understanding, prevention, and communication of adverse events following immunization, or of any other vaccine- or immunization-related issues

www.cioms.ch/finalvpvdef.pdf
Vaccine Life Cycle

Good Laboratory Practice

Good Clinical Practice

Good Pharmacovigilance Practice

Risk Management Plans
Special Post-Marketing Studies

Good Manufacturing Practice
<table>
<thead>
<tr>
<th>Vaccine /Healthcare Provider</th>
<th>Local Health Units and Central P/T Health</th>
<th>Federal Government HC and PHAC</th>
<th>World Health Organization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inform and Counsel re risks/benefits</td>
<td>Case management regarding VPD / AE clusters</td>
<td>Regulatory Monitoring &amp; Actions</td>
<td>International Health Regulations</td>
</tr>
<tr>
<td>Correct vaccine administration</td>
<td>Regional Surveillance</td>
<td>National Surveillance</td>
<td>Global VPD/AEFI Surveillance</td>
</tr>
<tr>
<td>Manage/Report AEFI/VPD</td>
<td>Public Health Action</td>
<td>Update Expert Advice</td>
<td>Expert Advisory Groups</td>
</tr>
</tbody>
</table>
Vaccine Life Cycle

1. Drug Discovery
   - Good Laboratory Practice
2. Pre-Clinical Studies
   - Good Clinical Practice
3. Clinical Trials
4. Drug Submission
   - New Drug Submission Authorization
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6. Early Post-market Period
7. Increasing Knowledge
8. Evolution of Product and Knowledge

- Good Immunization Practice
- Good Manufacturing Practice
- Good Pharmacovigilance Practice

Immunization Competencies for Health Professionals
Immunization Programme Life Cycle

1. Prevaccine
2. Increasing Coverage
3. Adverse events following immunization
4. Loss of Confidence
5. Outbreak
6. Resumption of Confidence

Robert Chen, CDC
1. 1950, no vaccine: more than 100,000 cases per year
2. 1974, 90% coverage: 200-400 cases & 2-3 deaths per year
3. 1975: 2 infants died post DPT; vaccine program suspended for 2 months, then re-initiated at 2 years instead of infancy
4. Public confidence plummeted; coverage fell under 40%
5. 1976-79: annual pertussis outbreaks with 13,000 cases and 41 deaths in 1979 alone
Vaccine Safety Crises: UK Experience

**DTP (whole cell pertussis) & brain damage**

- 1973: British neurologist, Dr Wilson appears on UK TVs “This Week” after his case series report to Royal Society of Medicine: “every year about 100 children are brain damaged” alleging due to DTP
- Media barrage
- Parental concern
  - Association of Parents of Vaccine Damaged Children
- University professors echo parental concern
  - Epidemiologist (Gordon Stewart), Microbiologist (Gordon Dick) & Statistician (David Kerridge)
- Many GPs stopped vaccinating → pertussis epidemics
- 1976–1979: National Childhood Encephalopathy study
  - estimates risk of ~1 case / 100,000 doses of DTP
- 1985–88: many high profile court cases
Vaccine Safety Crises

Brain damage & whole cell pertussis vaccine

**Europe - United Kingdom**
- 73: Wilson discusses case series report on TV
- Media barrage
- Parental concerns leads to new lobby group (Association of Parents of Vaccine Damaged)
- Scientists echo concerns
- 76-79 National Encephalopathy Study: 1/100,000 damaged
- GPs reduce immunizations
- Major pertussis epidemics
  - Ø Over 100000 infections
  - Ø Over 1000 hospitalizations
  - Ø Over 100 deaths

**North America - United States**
- Apr 82: Vaccine roulette airs
- Media barrage
- Dissatisfied Parents Together created (becomes NVIC)
- Specialist MDs echo concerns
- May 82: Senate hearings
- 82-86: 17 to 255 DTP lawsuits/yr
- 82-85: DTP price-12cents to $4.29/dose
- Apr 86: Last DTP manufacturer gives notice of plans to quit (had been 7 in 1960)
- Oct 86: Childhood Vaccine Injury Act passed
Vaccine Safety

“Perfect Storm” Pattern

1. ‘Popularized’ alert to potential harm
   - High profile interview after medical publication
   - Popular TV show with an ‘exposé’: eg Vaccine Roulette
   - Controversial publication + press conference
   - Fast spreading rumour of ‘sabotage’

2. Media outcry in support of victims

3. Story stays in the news
   - advocacy group(s) formed
   - ‘Experts’ found to support both sides
   - Celebrities get involved
   - Legal actions initiated
   - Ineffective ‘official’ response

Even when storm dissipates, clouds remain on the horizon
Lessons Learned re Mitigating Risk Associated With Vaccine Safety Scares

- Can’t ignore rumours or allegations
- Good risk management practices essential
- Risk communication is both an art and a science
- Need to be proactive
  - Think ahead - anticipate types of allegations to arise
  - Develop a relationship with key media people
  - Communicate what is known and what is being done
  - Update regularly
  - Share results of investigations

- Crisis response enabled IF routine infrastructure in place
  - Signal detection via spontaneous reporting systems
  - Local investigation capacity
  - Hypotheses testing capacity
Think ahead!

- optimal schedule protects before period of risk but....
- Poorly understood diseases / adverse events with variable age-specific incidence may be blamed on immunization

- **Infants:** Febrile seizures
- **Toddlers:** Autism
- **Children:** Seizure disorders, asthma
- **Adolescents:** Diabetes
- **Young adults:** MS, thyroiditis
- **Pregnant women:** fetal loss
- **Elderly:** Guillain-Barré Syndrome

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**The Pediatric Infectious Disease Journal** • Volume 26, Number 11, November 2007

**Human Papilloma Virus Immunization in Adolescent and Young Adults**

* A Cohort Study to Illustrate What Events Might be Mistaken for Adverse Reactions

Claire-Anne Siegrist, MD,* Edwin M. Lewis, MPH,† Juhani Eskola, MD,‡ Stephen J. W. Evans, MSc,§ and Steven B. Black, MD¶
Vaccines have a life cycle too!

Case study: meningococcal vaccines

- Of Humans and Meningococci
- Meningococcal vaccine development
- Prospects for a meningococcal B vaccine
US

THEM
• **Infection age dependent:**
  - ↑ in infants

• **Clinical picture highly variable:**
  - Colonization: ~10% pop’n
  - Febrile illness to meningitis
  - Fulminant: fatal in <24 hours
  - Chronic: weeks to months

• **Varied risk of infection:**
  - Complement
  - Factor H
  - Mannose-binding lectin
  - Toll-like receptor 4

• **Varied severity of infection:**
  - Splenic function
  - Neutrophil IgG2/3 receptors
  - IL-1, IL10, TNF-alpha, ACE genes

• **Strictly human pathogen**

• **Environmental niche:**
  - Human nasopharynx only

• **only ‘epidemic’ meningitis**

• **13 types, but most disease:**
  - A, B, C, Y, W135
  - Distinct geographic distribution

• **Genetic makeup unique for:**
  - Antigenic / phenotypic variability
  - Small no. of hypervirulent strains

• **Among gram negative pathogens, notable ability to cause:**
  - rapidly progressive skin hemorrhage & necrosis
  - DIC and shock
# Meningococcal Vaccines

**Groups A, C, Y, W135**

<table>
<thead>
<tr>
<th>Property</th>
<th>Polysaccharide</th>
<th>Conjugate</th>
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</thead>
<tbody>
<tr>
<td><strong>Immunogenicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adults</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Children</td>
<td>Poor</td>
<td>High</td>
</tr>
<tr>
<td><strong>Quality of antibody</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Avidity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Bactericidal activity</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Response to booster</td>
<td>Poor</td>
<td>High</td>
</tr>
<tr>
<td>Induction of immunologic memory to capsule</td>
<td>No</td>
<td>High</td>
</tr>
<tr>
<td>Effect on colonization</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Canadian Variation in Meningococcal Vaccine Programmes

Men-C-C: 2, 4, 12 mo
Men-C-C: 2, 12 mo
Men-C-C: 12 mo
Men-C-A,C,Y,W: 1 adolescent dose

Immunization and Respiratory Infections Division, Centre for Infectious Disease Prevention and Control
Incidence of IMD in Canada by serogroup and year and year of vaccine introduction, 1995 to 2010*. 

*2007 to 2010 data are preliminary.
Percentage of IMD cases in each age group by serogroup in Canada, 2005 to 2010*.

*2007 to 2010 data are preliminary.
Gap: Meningococcal B Vaccine

• Now the predominant cause of meningococcal disease in Canada

• Several problems with vaccine development
  ▶ B capsular polysaccharide cross reacts with human foetal neural cell adhesion molecule
  ▶ Poorly immunogenic

• New Zealand 2004 – unique Group B outer membrane vesicle (OMV) vaccine developed to counter ongoing epidemic disease
Novel vaccine developed to deal with New Zealand Meningococcal B Epidemic

- Crude bacterial extracts (Outer Membrane Vesicles or OMV) successful to Eliminate the Epidemic in New Zealand

- 3 million doses used in 2004

proof of principle that MenB vaccines can work and can be safely used

Solution: design a vaccine with broader coverage of Men B strains

Problem: vaccine worked but limited primarily to new Zealand strain

Meningococcal Disease Northern Region

Cumulative cases

Jan Feb Mar Apr May Jun Jul Aug Sep Oct Nov Dec

0 10 20 30 40 50 60 70 80 90

2002 2003 2004 2005 2006

Auckland
REVERSE VACCINOLOGY
Uses Genomics to Develop ‘SMART’ Vaccines

- Pioneered by Rino Rappiolo
- First use: Conjugate Meningococcal B vaccine
In silico vaccine candidates identified 600 potential vaccine candidates

Express recombinant proteins

350 proteins successfully expressed in E.coli

91 novel surface-exposed proteins identified

28 novel proteins have bactericidal activity

VACCINE CANDIDATES

'SMART VACCINES'

Use Reverse Genomics to Develop Vaccines
Antigenic Components of the 4CMenB: Important for Meningococcal Survival, Function, or Virulence

- **NadA: neisserial adhesin A**
  - Promotes adherence to and invasion of human epithelial cells\(^1\)\(^-\)\(^3\)
  - Antibodies could interfere in colonization

- **fHbp: factor H binding protein**
  - Binds factor H, which enables bacterial survival\(^5\)\(^,\)\(^6\) in the blood
  - Binds the bacterial siderophore enterobactin (*in vitro*)\(^4\)

- **NHBA: neisserial heparin-binding antigen**
  - Present in virtually all strains
  - Binds heparin, which may increase the serum resistance of bacteria\(^7\)\(^,\)\(^9\)

- **NZ PorA 1.4: porin A**
  - Major outer membrane vesicles protein – induces strain specific bactericidal response

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Vaccine Life Cycle

'4CMenB'  
- Developed by Novartis  
- Currently at phase 4 – under review by Health Canada  
- Demonstrated immunogenicity and safety in phase 2 trials  
  - Some increased fever seen when with other infant vaccines  
- Immune correlates of protection posed as proxies for efficacy  
- Post-market studies planned  
  - Effectiveness  
  - Safety  
    - Febrile seizures
LIFE CYCLE

QUESTIONS?
Supplementary Slides
**Good Pharmacovigilance Practice:** WHO quality indicators for post-marketing activities including AEFI surveillance

1. Institutional regulations / guidelines for post-marketing surveillance including monitoring and management of AEFI
2. Quality Management System for post-marketing activities
3. Roles and responsibilities of the key players defined (NRA, Central Laboratory, surveillance staff, immunization staff)
4. Human resource management in place (including training)
5. Routine and functional system for regular review of safety and efficacy of the vaccine product for regulatory action including a process to review and share relevant data between key players and taking appropriate action
6. Capacity to detect and investigate significant vaccine safety issues
7. Regulatory outcome regarding vaccine performance
8. System for providing feedback on AEFI from the national to all levels
Vaccine pharmacovigilance [www.cioms.ch/finalvpvdef.pdf]

- The science and activities relating to the detection, assessment, understanding, prevention, and communication of adverse events following immunization, or of any other vaccine- or immunization-related issues.

AEFI - general definition

- Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the administration of the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding symptom or disease.
### Optimal AEFI Surveillance and Pharmacovigilance Systems

#### WHO-CIOMS WG on Vaccine Pharmacovigilance

#### AEFI - general definition

<table>
<thead>
<tr>
<th>AEFI - root cause specific definitions</th>
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<tbody>
<tr>
<td><strong>Vaccine product related reaction</strong></td>
<td><strong>AEFI that is</strong></td>
</tr>
<tr>
<td>➢ caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product</td>
<td></td>
</tr>
<tr>
<td><strong>Vaccine quality defect related reaction</strong></td>
<td><strong>AEFI that is</strong></td>
</tr>
<tr>
<td>➢ caused or precipitated by a vaccine that is due to one or more quality defects of the vaccine product including its administration device as provided by the manufacturer</td>
<td></td>
</tr>
<tr>
<td><strong>Immunization error related reaction</strong></td>
<td><strong>AEFI that is</strong></td>
</tr>
<tr>
<td>➢ Caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable</td>
<td></td>
</tr>
<tr>
<td><strong>Immunization anxiety related reaction</strong></td>
<td><strong>AEFI that is</strong></td>
</tr>
<tr>
<td>➢ Anxiety about the immunization</td>
<td></td>
</tr>
<tr>
<td><strong>Coincidental event</strong></td>
<td><strong>and AEFI that is</strong></td>
</tr>
<tr>
<td>➢ Caused by something other than the vaccine product, immunization error or immunization anxiety</td>
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</tbody>
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Vaccine Safety Surveillance in Canada

ACTIVE

Immunization Monitoring Program - ACTive

PASSIVE (spontaneous adverse event reports)

Parent/Client/Patient

Vaccine Providers

Healthcare Providers

Provincial and Territorial Health Units
Local and Central

Public Health Agency of Canada
Centre for Immunization and Respiratory Infectious Diseases
Vaccine Safety Unit

Vaccine Manufacturers

World Health Organization (WHO) Drug Monitoring Program

Health Canada
Vaccine Safety Surveillance in Canada

ACTIVE

Immunization Monitoring Program—ACTive

PASSIVE (spontaneous adverse event reports)

Parent/Client/Patient

Vaccine Providers

Healthcare Providers

Vaccine Manufacturers

P/T Health Units

PHAC Vaccine Safety Unit

WHO Drug Monitoring Program

- paid for by PHAC and administered by the Canadian Pediatric Society
- 12 pediatric hospitals in 8 provinces serving all regions for tertiary care
- RN monitor/MD investigator at each site
- monitor reviews admissions for adverse event targets, files reports
- targets: neurologic events, anaphylaxis, thrombocytopenia, severe local reactions and miscellaneous others as appropriate
Definition of Safety Signal

“Information that arises from one or multiple sources ... which suggests a new potentially causal association, or a new aspect of a known association, between an intervention and an event... either adverse or beneficial, that is judged to be sufficient likelihood to justify verificatory action.”

Hauben and Aronson
Drug Safety 2009, 32(2)

Three dimensions

- Novelty
- Suspicion
- Evaluation
World’s First Vaccine for the Poor

MenAfriVac

- Epidemic serogroup A meningococcal infection in sub-Saharan Africa
  - 25 countries
  - 1997: 250,000 infected, 25,000 died
- Serogroup A rare outside Africa
- MenAfriVac vaccine development
  - WHO
  - PATH
  - Serum Institute of India (<50cents/dose)
  - Bill and Melinda Gates Foundation
MenAFriVac
Burkino Faso 2010

- Population roll out in Burkino Faso, Mali, Niger
- September 2010 - 400,000 doses / country
- December 2010 - mass campaign launch
- 19.5 million doses to date