Module 3
Vaccine Development and Evaluation

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1. Competency
Integrates into practice knowledge about the main steps in vaccine development and evaluation

2. Learning Objectives
By the end of this module you will be able to:

- Describe in general terms, the process to obtain marketing approval for vaccines in Canada.
- Describe what can be learned about vaccines after they are approved for marketing via surveillance activities and more formal post marketing studies.
- Characterize in broad terms, the key roles and responsibilities for various stakeholders in post marketing assessment of vaccine safety and effectiveness.

3. Introduction
Vaccine safety is of the highest importance and concern for all vaccine stakeholders. Knowledge of vaccine development, clinical trials, and the surveillance system will help health care providers communicate the safety of vaccines which in turn will build public confidence in vaccinations.

4. History of Vaccinations

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1796</td>
<td>Edward Jenner demonstrated that inoculation with cowpox virus produced protection from infection with smallpox.</td>
</tr>
<tr>
<td></td>
<td>(Hence Vaccination: taken from vacca the Latin word for cow)</td>
</tr>
<tr>
<td>1860's - 1890</td>
<td>Louis Pasteur produced vaccines against chickenpox, cholera, diphtheria, anthrax and rabies.</td>
</tr>
<tr>
<td>Early 20th Century</td>
<td>Toxoid vaccines against diphtheria and tetanus were produced following the discovery of effective inactivation with chemicals.</td>
</tr>
<tr>
<td>Post World War 2</td>
<td>Successful live viral vaccines were developed using cell culture techniques.</td>
</tr>
<tr>
<td>Present and Future</td>
<td>New technologies are constantly developing: recombinant protein vaccines, DNA and conjugate vaccines.</td>
</tr>
</tbody>
</table>

For the history of immunizations in Nova Scotia refer to:
Nova Scotia Department of Health and Wellness, Chapter 1, Introduction, N.S. Immunization Manual
http://www.gov.ns.ca/hpp/cdpc/info-for-professionals.asp
5. Vaccine Development and Approval

Vaccines must be thoroughly tested before they can be called safe and effective for human use. It can take up to 10 years to test and develop a vaccine. Here are the sages of vaccine development from the lab to Health Canada approval.

**Figure 1 - Stages of Vaccine Development**

- **GOALS**
  - Immunogenicity *
  - Challenge studies in animal models
  - Safety studies *
  - Immunogenicity
  - Local/systemic reactions
  - Safety assessment
  - Optimal dose/schedule in target population
  - Efficacy in target populations

**Step 1:** Lab Studies
- Infectious agent
- Epidemiology
- Antigen Research

**Step 2:** Animal Studies

**Step 3:** Human Studies

**Clinical Phase I**

**Clinical Phase II**

**Clinical Phase III**

Immunogenicity * - the immune response needed to prevent disease

Safety studies * - no toxicity that would prevent their use in people

When a pharmaceutical company has successfully conducted lab studies, animal studies, and human studies, the vaccine must meet Canadian licensing standards before the vaccine can be considered for use in Canada. The Biologics and Genetics Therapies Directorate (BGTD) is the Canadian authority that regulates biological drugs (products derived from living sources) for human use (see figure 2).
6. Post Marketing Assessment of Vaccine Safety

After Canadian licensing, vaccine safety is continually monitored. This post marketing data helps to refine the benefit-risk assessment of a given vaccine as well as add to key information regarding contraindications, warnings and concomitant use with other vaccines. Information is obtained by adverse event surveillance and post marketing studies.

6.1 Adverse Event Surveillance

This surveillance occurs at the local level:

- Vaccine providers use standardized forms to report adverse events (for more details see Module 9 - Adverse Reactions Following Immunizations).
- Health care providers who don’t give vaccines but may see adverse events in practice
- Vaccine recipients/caregivers are informed at the time of vaccination to contact vaccine provider if an adverse event occurs.

Active adverse event surveillance is conducted in the following ways:

- **Active surveillance:**
  Immunization Monitoring Program Active (IMPACT) is hospital based and reports serious adverse events to the Canadian Adverse Event following Immunization Surveillance System (CAEFISS).
- **Ad hoc studies:**
  Undertaken by public health or academic investigators to assess possible causal link (e.g., oculorespiratory syndrome [ORS] following influenza vaccination).
6.2 Post Marketing Studies

Post marketing studies may provide the following information:
- Immunogenicity/efficacy in not yet studied populations
- Possible interactions with other vaccines
- Expanded safety assessment

The following is an example of a post marketing study:
A BC Human Papillomavirus Vaccine (HPV) study examined whether two doses are as effective as three doses when the vaccine is given to girls 9 - 13 years of age.

7. Skills Assessment

- Integrates into practise knowledge about the main steps in vaccine development and evaluation

8. Summary

As vaccine-preventable infections have decreased, the spotlight of public and mass media concern has shifted to vaccine safety. Since vaccines are usually given to healthy people, especially children, tolerance for adverse events is low.

Vaccines are thoroughly tested before licensure, and are continually monitored for safety by vaccine recipients, vaccine providers, hospitals and Health Canada.

9. Required Reading

Public Health Agency of Canada (2006) Vaccine safety and adverse events following immunization (7th ed.). Canadian immunization guide (7th ed.).

- Introduction
  - Vaccine evaluation and regulation
  - Vaccine safety surveillance and assessment in Canada

10. Optional Reading

- N.S. Department of Health and Wellness Chapter 1, Introduction, N.S. Immunization Manual
  http://www.gov.ns.ca/hpp/cdpc/info-for-professionals.asp

11. References

12. Quiz

**Question #1**
Which one of the following is NOT necessary during vaccine development?

A. Human testing  
B. International testing  
C. Animal testing  
D. Lab studies

**Question #2**
During vaccine development, how many subjects are involved in the Clinical Phase III trials?

A. < 10  
B. 10 - <100  
C. 50 – 500  
D. 300 – 30,000

**Question #3**
Which one of the following describes the role of the Biologics and Genetic Therapies Directorate (BGTD)?

A. Regulates drugs for human use  
B. Conducts vaccine research funded by the pharmaceutical company  
C. Monitors serious adverse events following vaccinations  
D. Markets drugs for human use

**Question #4**
A parent reporting an adverse vaccine event to Public Health is an example of what type of post marketing assessment?

A. Active Surveillance  
B. Ad hoc Study  
C. Post Marketing Study  
D. Passive Surveillance
13. Quiz Answers

Question #1
Answer: B
International testing is not necessary during vaccine development. Human, Animal and Lab studies are necessary for vaccine development.

Question #2
Answer: D
Clinical Phase III trials target the immunogenicity of vaccines in large targeted populations

Question #3
Answer: A
The BGTD regulates drugs for human use in Canada.

Question #4
Answer: D
An example of Passive Surveillance is the reporting of an immunizing agent reaction to an immunization provider who, in turn, enters the data into the electronic reporting system