Module 3: Vaccine Development and Evaluation

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**Competency:** Integrates main steps of vaccine development and evaluation into practice knowledge.

**Learning Objectives**
Upon successful completion of this continuing education lesson, you will be better able to:

1. Describe, in general terms, the process to obtain marketing approval for vaccines in Canada.
2. Describe what can be learned about vaccines after they are approved for marketing, via surveillance activities and more formal post-marketing studies.
3. Characterize, in broad terms, the key roles and responsibilities for each of the following relative to the post-marketing assessment of vaccine safety and effectiveness:
   - Vaccine manufacturers
   - Canadian regulatory authority (Biologics and Genetic Therapies Directorate)
   - Public Health Agency of Canada
   - Provincial/territorial health departments
   - Vaccine providers
   - Health care providers who don’t administer vaccines
   - Vaccine recipients or their parents/caregivers

**Test Your Current Knowledge**
Based on your current knowledge, determine if the following statements are true or false.

1. One of the key roles for the biologics and genetic therapies directorate is to approve new vaccines on the market.
   a. True
   b. False
2. The National Advisory Committee on Immunization is made up of government officials.
   a. True
   b. False
3. The National Advisory Committee on Immunization writes updates to the Canadian Immunization Guide and these updates are published online.
   a. True
   b. False
4. A patient reporting an adverse vaccine-related event to Public Health is an example of passive surveillance.
   a. True
   b. False
Vaccines in Canada

Vaccines are a medical preventive measure to support and increase the health status of a population. Immunization programs are one of the most cost-effective disease prevention strategies available today, both in reducing mortality and morbidity. With the ever increasing number of vaccines being introduced into the Canadian market, it is crucial that all healthcare professionals understand and can communicate the vaccine development and approval process to their patient population.

Vaccine Development

Clinical Note

Unlike pharmaceutical agents, vaccines are primarily used in large numbers of healthy individuals. For this reason, vaccine safety is of paramount importance and there is much less tolerance for adverse effects with the products.

The first step in the development of a vaccine is identification of the microorganism or toxin that causes an illness. Once the microorganism is identified, scientists interested in the condition can initiate research in the possibility of a vaccine to reduce the incidence of the disease or its consequences and complications. The development of vaccines has become a global activity, with vaccines being researched and produced internationally at specialty sites with vaccine safety and efficacy being of the highest concern for all. Module 6 and Module 13 discuss many of the communication and questions that will be asked by your patients about vaccine safety.

Vaccines are developed based on the burden of the disease, the complications of infection and the suitability of a vaccine in relation to its target disease. The development of a new vaccine is a rigorous process starting with pre-clinical laboratory testing to ensure that vaccine candidates produce the immune response needed to prevent disease and have no toxicities that would prevent their use in people. Human studies then proceed through several phases involving progressively more subjects. The clinical trial phases are listed in Table 1.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Number of subjects</th>
<th>Key study objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>10-&lt;100</td>
<td>• Immunogenicity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Local/systemic reactions</td>
</tr>
<tr>
<td>II</td>
<td>50-500</td>
<td>• Optimal dose/schedule in target population(s)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Ongoing safety assessment</td>
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### Immunization Competencies Education Program

Module 3: Vaccine Development and Evaluation

**III**

<table>
<thead>
<tr>
<th>Number</th>
<th>Cost Range</th>
<th>Key Activities</th>
</tr>
</thead>
</table>
| 300-30,000 | | • Immunogenicity/efficacy in target population(s)  
• Ongoing safety assessment |

**IV**

<table>
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<tr>
<th>Number</th>
<th>Cost Range</th>
<th>Key Activities</th>
</tr>
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</table>
| Varies with study objectives (100 to many thousands) | | • Immunogenicity/efficacy in not yet studied populations  
• Possible interactions with other vaccines  
• Expanded safety assessment |

**Post-marketing passive or active surveillance**

<table>
<thead>
<tr>
<th>Number</th>
<th>Population</th>
<th>Key Activities</th>
</tr>
</thead>
</table>
| General population | | • “Real world” effectiveness  
• Rare or unexpected adverse events (signals) |

**The Biologics and Genetic Therapies Directorate (BGTD)**

Once the vaccine manufacturer has completed all the clinical trials necessary they submit their data to the biologics and genetic therapies directorate (BGTD) of Health Canada. BGTD is the Canadian federal authority that regulates biological drugs (products derived from living sources) and radiopharmaceuticals for human use.  

This regulatory authority is responsible for verifying the safety, efficacy and quality of all biologics for human use, including vaccines. BGTD reviews the clinical and chemistry/manufacturing information of vaccine submissions and conducts on-site evaluations of manufacturing facilities and laboratory analysis of vaccines. The clinical information includes data from clinical trials, and post-marketing safety and efficacy information. BGTD will grant a marketing authorization for the vaccine if the evidence to support the safety, efficacy and quality of the vaccine is considered adequate and sufficient.

Once approved by BGTD the vaccine will be given notice of compliance (NOC) and issued a drug identification number (DIN). BGTD will also approve the vaccine’s product monograph. A product monograph is the official labelling document for a vaccine and must be approved by Health Canada when the vaccine is first authorized for marketing and each time the information is updated. It is a factual, scientific document that, devoid of promotional material, describes the properties, claims, indications, conditions and any other information required for optimal, safe and effective use of the vaccine. It must accurately reflect important information and results from clinical trials and other relevant information submitted to Health Canada for evaluation.

Once approved, all batches of vaccine are tested by BGTD to ensure the potency and safety is suitable for patient use. BGTD determines which safety and potency tests need to be performed and both the manufacturer and BGTD evaluate each batch of vaccine.

The key roles of the Biologics and Genetics Therapies Directorate (BGTD) are:
• Approving the vaccine and monograph and issuing a vaccine DIN
• Evaluating the production process and inspecting the production facilities to determine if they are suitable
• Testing each batch of vaccine to ensure it meets safety and potency standards
• Monitoring safety after release with the Public Health Agency of Canada (PHAC) and the manufacturers

It is important to note that while the BGTD evaluates the efficacy and safety of vaccines, they do not make recommendations on the use of individual vaccines. This is done by the National Advisory Committee on Immunization, as discussed below.

Watch Dr. Ian Gemmill’s presentation

**National Advisory Committee on Immunization (NACI)**

Once a vaccine is approved in Canada, the next step is to determine who should be immunized based on the burden of the disease, the efficacy and safety of the vaccine as well as other factors such as the economic analysis of the cost of immunization. This role is managed by the National Advisory Committee on Immunization (NACI).

NACI’s mandate is to provide the Public Health Agency of Canada (PHAC) with ongoing and timely medical, scientific, and public health advice relating to vaccines and certain prophylaxis agents. More specifically, advice may relate to the use of vaccines in humans, vaccine evaluation, and the monitoring of vaccine-associated adverse events.

NACI is composed of twelve voting members who are knowledgeable in the field of immunization practices, have multidisciplinary expertise in public health, and in the use of vaccines and prophylaxis agents for the prevention of vaccine-preventable diseases. This committee includes specialists in paediatrics, infectious disease & medical microbiology, public health, immunology and internal medicine.

The process through which NACI develops their recommendations include:

• Review of product monograph
• Thorough review of the scientific literature on:
  • The burden of disease (morbidity, mortality) in the population in general and in specific risk groups
  • Vaccine characteristics (e.g. safety, efficacy, effectiveness)
  • Additional various factors outlined in “An Analytic Framework for Immunization Programs in Canada”. Consideration will be given to the relevance, quality and quantity of published and unpublished data.
• Review of the recommendations of other groups: e.g. Advisory Committee on Immunization Practices (ACIP), American Academy of Pediatrics (AAP), Canadian Paediatrics Society (CPS).
• Grading and reporting the level of evidence associated with its recommendations. In the absence of data or when data is inadequate, the expert opinions of members and other experts will be used to make recommendations.

NACI’s recommendations are reported to both the Chief Public Health Officer of Canada (CPHO) and the Public Health Agency of Canada (PHAC). All NACI’s recommendations on vaccine use in Canada are published online in the Canadian Immunization Guide – Evergreen Edition as new information becomes available. Additional statements and updates are published in the Canada Communicable Disease Report (CCDR).

The Canadian Immunization Committee (CIC) and Provincial Bodies
NACI provides recommendations based on extensive research and literature review. The Canadian Immunization Committee (CIC) is the federal/provincial/territorial (F/P/T) body that provides leadership in immunization by giving advice and recommendations on implementation of a national immunization strategy and programmatic issues affecting immunization. The objectives of a national process for immunization program planning are to minimize duplication of effort and to move towards harmonization of immunization schedules across the country.

Health is considered a provincial responsibility and therefore each province and territory decides on its own publicly funded vaccine programmes. In most jurisdictions, it is provincial or territorial advisory committees on immunization that make recommendations to their provincial government.

The organizations involved in the approval and implementation of a vaccine are shown in Figure 1.
Monitoring Vaccines After Introduction

Vaccine safety is a paramount concern for most parents. Immunization safety is crucial to ensure the public’s trust in immunization programs. With vaccines being administered to such a large portion of our healthy population, there is little tolerance by the public for adverse effects and complications caused by immunization.

Canada has systems in place to monitor the safety of vaccines that have been approved by the BGTD.\(^5\) Canada is and has been a world leader in “post-marketing surveillance of adverse effects”.\(^5\)

Monitoring vaccine safety in Canada involves:

- Passive surveillance (spontaneous reporting of adverse events by providers or recipients)
- Active surveillance (ongoing watch and reporting of severe adverse events following childhood immunization)
- Focused epidemiology or clinical ad hoc studies, as necessary\(^3\)
Canadian Adverse Events Following Immunization Surveillance System (CAEFISS)

CAEFISS is an important and passive surveillance system under the Public Health Act and mandated by law in many provinces. It is the responsibility of everyone in the vaccine process including the manufacturer, PHAC, health care providers and the patient being immunized and their family. This type of surveillance encompasses all spontaneous adverse event reporting. If health care providers suspect an adverse reaction, they are required to complete a Report of Adverse Events Following Immunization (AEFI) form. A copy of the Report of Adverse Events Following Immunization (AEFI) form is found in the Compendium of Pharmaceuticals and Specialties (CPS) but is also available for download from PHAC.

Health care providers complete these reports and submit them to their local public health agency or Medical Officer of Health. From there, reports are sent to the central provincial/territorial health ministry, which in turn forwards them to the Immunization and Respiratory Infections Division within the Centre for Infectious Disease Prevention and Control at the Public Health Agency of Canada (PHAC). This federal office is responsible for maintaining a national database of all reported adverse events. The database also includes reports from vaccine manufacturers, which are required by law to submit all adverse event reports to PHAC and, if serious, to do so within 15 calendar days of receipt. In some jurisdictions, reports related to vaccines that are not publicly funded are submitted by vaccine providers directly to PHAC. If in doubt, it is best to check with the provincial/territorial public health department to verify where the report should be sent.

PHAC receives about 4,000 reports each year. Most reports concern minor events such as a fever or local injection site reactions.

Active Surveillance

Canada has a unique program called IMPACT (Immunization Monitoring Program ACTive). In this program, a nurse at each of the main children’s teaching hospitals in Canada actively reviews all admissions to the hospital for certain serious illnesses such as seizures, encephalitis, encephalopathy and acute paralysis.

In their reports, the nurse records details about the illness and obtains a written immunization history from the parents, family doctor or immunization clinic to determine whether the illness happened after vaccination. These reports are sent to the IMPACT data centre and are analyzed for causal relationships. IMPACT has confirmed that severe neurological illness post immunization is very rare. Although seizures have been reported, no cases of encephalitis, encephalopathy or acute paralysis have been linked to vaccination.

Visit Canadian Paediatric Society’s IMPACT - Immunization Monitoring Program ACTive website for more information on IMPACT and access to the IMPACT newsletter.

Ad Hoc Studies

In addition to monitoring for adverse effects, additional surveillance, as well as epidemiologic or clinical studies may be undertaken by public health or academic investigators to further characterize adverse events of concern, to assess whether or not there is a causal link between the vaccine and a given
adverse event or to learn about risk factors that increase the likelihood that an adverse event will occur.³

**Causality Assessment**
Canada investigates the link between potential complications and vaccination. They are part of a global network of specialist involved in the monitoring of international immunization to ensure that it is safe, effective and not linked to any serious complications.
## From Vaccine Development to Regular Use

**Vaccine Candidate**
- Pathogen with no/limited diversity causing global infectious disease
- Infection followed by prolonged immunity to re-infection
- Vaccine response mimics natural protection
- Antigen safe, highly immunogenic, easily made

**Developing a Vaccine**
- Animal studies - Immune response and protect against viral challenge
- Phase 1 (10-<100) immune response and safety
- Phase 2 (50-500) Best dose, safety, level of immune response
- Phase 3 (300-30,000) Does the vaccine work?, and safety
- Limited Canadian trials due to being a small % of global vaccine market

**Making a Vaccine**
- Manufactured in specific, government inspected and approved plant
- Every ingredient and step is scripted and double-checked
- Multiple in-process quality assurance tests
- Multiple final checks on purity, potency and consistency
- Typical production cycle 9-12 months

**Vaccine Licensure**
- BGTD reviews plant, process, and all animal/trial data
- BGTD independently tests vaccine lots and additional trials, process takes 9-18 months
- BGTD approves product monograph
- BGTD tests every vaccine lot before release to the public and monitors safety after release
- BGTD does NOT make recommendations for use

**Recommendation for Use**
- NACI is Canada’s senior policy advisory committee. Experts volunteer to sit on committee
- NACI reviews data and evidence and publish statements on disease burden, vaccine characteristics and optimal use
- NACI publishes Canadian Immunization Guide
- Provinces through CIC decide which vaccines they will cover. Recommended vaccines may NOT always be funded
- Local public health departments distribute funded vaccines to providers
- Funding approval may be delayed for years and programs can differ between provinces

**Vaccine Safety**
- Canada relies on users to report AEFIs which are reviewed locally, provincially and federally
- BGTD requires post-marketing safety studies
- PHAC funds IMPACT surveillance at pediatric hospitals
- Potential for specialized studies - GBS, egg allergy

**Evaluation and Refinement**
- Effectiveness - impact on case numbers, causes of vaccine failure, indirect benefits, ecological effects
- Public acceptance, uptake rates central to effectiveness
- Duration of protection, need for boosters, timing
- Combination vaccines, compatibility with other shots
Key Learning Points

1. Vaccines have an exceptional safety record and have to undergo extensive clinical trials before manufacturers apply for approval in Canada.

2. The Biologics and Genetic Therapies Directorate (BGTD) reviews:
   - Clinical trial data on vaccine efficacy and safety
   - Manufacturing process procedures and site inspections
   - Product monograph
   - Each batch of vaccines produced

3. The National Advisory Committee on Immunization (NACI):
   - Provides PHAC with current information on vaccines
   - Is comprised of immunization experts
   - Writes the Canadian Immunization Guide which is continually updated online as an Evergreen Edition
   - Publishes updates in the Canada Communicable Disease Report (CCDR)

4. Canadian Immunization Committee (CIC) and provincial and territorial committees make recommendations regarding the funding of vaccines on the publicly funded immunization program.

5. Monitoring of the Immunization program is paramount to maintain safety and patient trust.

6. Monitoring occurs through passive and active surveillance through CAEFISS and IMPACT respectively.

7. Everyone involved in the immunization process has a responsibility to ensure vaccines are safe and is obligated to report adverse events.
Post-Test

1. Which of the following is assessed through each of the phases of a vaccine’s clinical trials?
   a. Immunogenicity
   b. Safety of the vaccine
   c. Optimal immunization dose schedule
   d. Possible interactions with other vaccines

2. Which of the following is NOT a role of the Biologics and Genetic Therapies Directorate?
   a. Establish the safety, efficacy and quality of vaccines
   b. Inspect the manufacturing facility to ensure they meet with Canadian standards
   c. Make recommendations on vaccine use in Canada
   d. Test each batch of vaccine to ensure they meet potency and safety limits

3. Which of the following statements is true regarding the National Advisory Committee on Immunization?
   a. It is primarily made up of government officials
   b. It provides PHAC with timely information on vaccines
   c. It approves the product monograph for use in Canada
   d. It approves the use of vaccine on provincial publicly funded programs

Mrs. Hughes is in with her daughter Madeline. When you discuss Madeline’s immunization status, she mentions that she is not sure if she wants to immunize her. She mentions there have been some postings online that there is very little regulation regarding immunizations and there is very little safety net regarding immunizations in Canada.

4. What would be the MOST appropriate response to Mrs. Hughes’ concerns regarding the regulation of immunization?
   a. Mrs. Hughes, I can understand that you are concerned about vaccine safety program but you are just going to have to give the immunizations to Madeline
   b. Mrs. Hughes, although there is very little legislation, it is the law that you immunize your child
   c. Mrs. Hughes, I can understand you may have concerns about vaccine safety; however I can assure you that Canadian officials closely monitor every step of the entire vaccine process from manufacturing, right through to approval of use in the public and also after the vaccine is released
   d. Mrs. Hughes, we have a safe system but I completely understand that you do not want to administer a vaccine to your child
5. When answering Mrs. Hughes’ concerns about the safety net, which of the following statements is the MOST appropriate to use?
   a. Although vaccines are not tested extensively, our surveillance system is very good
   b. Vaccines are well tested and Canada has one of the best surveillance systems in the entire world
   c. The safety net is not that extensive but vaccines are so safe that we don’t have to worry about it
   d. Mrs. Hughes, we have done all this surveillance in the past and have never had a problem so we can probably scale down our surveillance in the future

Discussion Forum
1. Some people of the antivaccine movement have stated that vaccine approval is not heavily regulated and this alleged situation places our children at risk. Do you have any patient counselling tips or strategies that you have found helpful to use when educating patients on this myth?
2. The Canadian Immunization Guide provides a comprehensive review of immunization issues. Do you have any suggestions for information that you would wish to be in the guide?
3. Although significant adverse effects with immunizations are rare, we have an extensive adverse effect monitoring system. What do you feel are the biggest challenges to our current system and what would be your recommendations to address them?
4. Are there any additional topics on vaccine development and evaluation that you feel would be helpful?
References


