



# Building on the Legacy of Vaccines in Canada: Value, Opportunities, and Challenges

# 1

## Introduction to Vaccines: The Canadian Perspective



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Vaccine Industry Committee



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# **Introduction to Vaccines: The Canadian Perspective**

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# **Introduction aux vaccins : La perspective canadienne**

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## I.1 Executive Summary / Sommaire

### I.1.1 Executive Summary

Vaccination is generally considered as one of the greatest public health achievements in industrialized countries during the 20th century, reducing morbidity and mortality from a broad range of vaccine-preventable diseases. Globally, over 5.9 million deaths are prevented annually through vaccination against nine major infectious diseases, including varicella, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (childhood), hepatitis B, measles, polio, and tuberculosis. In Canada, immunization has saved more lives over the last 50 years than any other health intervention. Indeed, the decline in incidence and death from infectious diseases as a result of vaccination is considered one of the nation's great triumphs of medical research and public health programming. In general, the ability of vaccination to increase disease resistance in both individuals and larger communities (through the phenomenon of herd immunity) speaks to the tremendous medical, social and economic value offered by vaccine technologies.

A vaccine is a substance that is introduced into the body to prevent infection or to control disease due to a certain pathogen, which is a disease-causing organism, such as a virus, bacteria or parasite. The vaccine “teaches” the body how to defend itself against the pathogen by creating an immune response. Preventive vaccines work to protect an individual from infection or disease by introducing a small component or a non-harmful form of the pathogen (called the foreign antigen) into the body. The body produces an immune response to the pathogen by generating antibodies (via the humoral response), killer cells (via the cell-mediated response), or both. A small group of memory B-cells and T-cells remain in the body and can quickly initiate a strong immune response, i.e. by producing antibodies, and helping the production of killer T-cells or antibodies, respectively. The next time the real pathogen is encountered, the immune system remembers it and mounts a much larger, quicker response than it would have if the individual had never received the vaccine. This is known as “immune memory”.

The fundamental approach to making vaccines is to isolate or create an organism (or component thereof) that is unable to cause full-blown disease, but that still retains the antigens responsible for inducing the host's immune response. This can be pursued in several ways, including the development of killed, inactivated vaccines; live, attenuated vaccines; subunit, acellular vaccines; conjugate vaccines; and the newer deoxyribonucleic or ribonucleic acid (DNA/RNA) vaccines and recombinant vaccines. Apart from their classification by manufacturing methods and target populations (e.g. vaccines for infants and children, adolescents and adults, and international travelers), vaccines can also be categorized in terms of preventive versus therapeutic vaccines classes. Preventive vaccines are the traditional type of vaccine described above; they prepare the immune system to respond in case of future exposure to a specific pathogen. In contrast, therapeutic vaccines are intended to treat an existing disease, and hence can be administered after infection or disease onset, with the goal of enhancing natural immunity against a specific pathogen, thereby reducing the burden of disease and/or enhancing quality of life.

With regard to the history of vaccine development, the first vaccine introduced in Canada was the smallpox vaccine in the late 1800s, based on the pioneering work of English physician Edward Jenner over two centuries ago. Toronto-based Connaught Laboratories (currently sanofi pasteur) has played a leadership role in the development of the smallpox vaccine since the early 1900s, and is credited with making a critical contribution to the eradication of smallpox, both in Canada in 1962, and on a global basis as declared by the World Health Organization (WHO) in 1979.

Initially developed by French chemist Louis Pasteur, the rabies vaccine was introduced as the next vaccine in Canada in the early 1900s. This was followed relatively quickly by the introduction of several other vaccines prior to the late 1930s, including those against diphtheria, pertussis (whole-cell), tuberculosis, tetanus, yellow fever and influenza. Beginning in the 1950s, Canada once again gained an international reputation as a world leader, this time in global polio eradication efforts and vaccine development. Notably, by 1954, Connaught Labs had cultivated poliovirus for the inactivated polio vaccine (IPV) in sufficient quantities to supply one of the largest clinical trials ever conducted in vaccination history to date, involving roughly 1.8 million children in Canada, the US and Finland. Overall, Connaught's development, production and global distribution of both IPV and the subsequent oral polio vaccine (OPV) have made an unparalleled contribution to the virtual elimination of poliomyelitis worldwide.

Since the introduction of the polio vaccine in the 1950s, the pace of development has accelerated, adding new vaccines against *Haemophilus influenzae* type b, hepatitis A and B, influenza, acellular pertussis, pneumococcal and meningococcal infection, and varicella to well-established vaccines for polio, measles, mumps and rubella. Vaccines against other infectious agents have also been approved recently in Canada (since 2006), including human papillomavirus, rotavirus, and zoster/shingles. Globally, a broad range of vaccines targeting over 25 infectious diseases are currently available, and the number of vaccine-preventable diseases continues to grow. New vaccine formulations or combinations, as well as a wide range of preventive and therapeutic vaccines, continue to be developed within the rapidly evolving field of vaccinology. Hence there is no reason to believe that the future of vaccines will be any less impressive than their remarkable past – in terms of saving lives and preventing suffering from devastating disease.

Although there is broad agreement that vaccination is one of the most significant public health interventions of the past century – and both the medical and economic benefits of immunization are very well documented – vaccines continue to be (mistakenly) undervalued and underutilized throughout the world. In industrialized countries, such underutilization is caused in part by underestimating the seriousness of vaccine-preventable diseases, underestimating the benefits of vaccination, and concerns regarding the side effects of vaccines. Overall, the world still falls short of realizing the full benefits of immunization, especially in the poorest developing countries, and for children – who are the most vulnerable to disease. These observations demonstrate the urgent need to better educate the public (and all relevant stakeholders) regarding the extensive benefits of vaccination. In summary, greater strides must be made by all members of the global immunization community to recognize and promote the fact that immunization programs are among the most cost-effective investments in protecting public health.

In Canada, immunization plays a central role in all of public health programming, hence renewed efforts to advocate the full value of vaccines will be critical to the overall ability to support the “common good”. BIOTECanada's Vaccine Industry Committee (VIC) plays an active role in increasing awareness of the value of vaccines to the Canadian health care system, as part of its broader mandate in fostering excellence in research, manufacturing, and full access to vaccines. Thus, in the spirit of collaboration, the VIC has put forward the following recommendations for consideration by federal, provincial and territorial (F/P/T) governments and other key stakeholders, in promoting vaccines for the benefit of all Canadians and future generations.

### Federal/Provincial/Territorial Recommendations

1. To create an environment that adequately values and supports vaccines, government officials and policy makers at all levels must recognize and promote the fact that investment in immunization programs represents excellent value for money spent, with tremendous medical, societal and economic impact in improving public health.
2. In efforts to strengthen public trust, public health officials in particular (at all F/P/T levels) must exhibit greater conviction in defending the pivotal role of prevention and immunization programs within the public health system.

### Stakeholder Recommendations

3. To help establish the importance and value of vaccination, stakeholders at all levels (including F/P/T government representatives, public health officials, policy makers, medical professionals, vaccine manufacturers and the general public) must take greater responsibility in becoming more knowledgeable (and educating others) regarding the various types of vaccines, their proven health benefits to both individuals and society, as well as their significant cost-effectiveness.
4. With regard to the role of industry players, vaccine researchers/developers and manufacturers should support decision-making processes for evaluating and recommending vaccines – and respond to inquiries from medical professionals, the media, the public and/or parents – by providing strong, accurate, and reliable data regarding the full benefits of vaccines, including endorsement of their profound positive effect on the Canadian population and the public health system as a whole.

## 1.1.2 Sommaire

*En matière de santé publique, la vaccination est considérée généralement comme l'une des plus grandes réalisations du XXe siècle dans les pays industrialisés, réduisant la morbidité et la mortalité dues à un vaste éventail de maladies évitables par la vaccination. Chaque année, l'immunisation contre neuf maladies infectieuses importantes, soit la varicelle, la diphtérie, le tétanos, la coqueluche, l'Haemophilus influenzae de type b (chez les enfants), l'hépatite B, la rougeole, la poliomyélite et la tuberculose, prévient plus de 5,9 millions de décès dans le monde entier. Au Canada, l'immunisation a permis de sauver plus de vies au cours des 50 dernières années que toute autre intervention de santé. En effet, la réduction de l'incidence des maladies infectieuses et des décès attribuables à celles-ci, grâce à la vaccination, est considérée comme l'une des grandes réussites de la recherche médicale et des programmes de santé publique au pays. En général, la capacité du vaccin d'accroître la résistance aux maladies chez les individus et les collectivités élargies (par le phénomène d'immunité collective) témoigne de la valeur exceptionnelle des technologies vaccinales sur le plan médical, social et économique.*

*Un vaccin est une substance qui, introduite dans l'organisme, sert à prévenir une infection ou une maladie attribuable à un agent pathogène (virus, bactérie ou parasite). Le vaccin « enseigne » à l'organisme à se défendre contre l'agent pathogène en créant une réaction immunitaire. Les vaccins préventifs empêchent l'apparition d'une infection ou d'une maladie en introduisant dans l'organisme une petite partie ou une forme inoffensive de l'agent pathogène (appelée antigène étranger). L'organisme développe une réaction immunitaire contre l'agent pathogène en sécrétant des anticorps (au cours de la réaction humorale), des cellules K (au cours de la réponse à médiation cellulaire), ou les deux. Un petit groupe de lymphocytes B et lymphocytes T à mémoire demeurent dans l'organisme et peuvent rapidement déclencher une réaction immunitaire forte, notamment en libérant des anticorps et en contribuant à la production de lymphocytes T cytotoxiques ou d'anticorps, respectivement. Quand l'agent pathogène réel réapparaîtra, le système immunitaire le reconnaîtra et déclenchera une réaction beaucoup plus grande et plus rapide qu'il ne l'aurait fait si le sujet n'avait jamais été vacciné. C'est ce qu'on appelle la « mémoire immunitaire ».*

*La fabrication de vaccins consiste fondamentalement à isoler ou à créer un organisme (ou un élément constitutif) qui est incapable de provoquer l'éclosion d'une maladie, mais qui garde quand même en mémoire les antigènes responsables de l'induction de la réaction immunitaire de l'hôte. On peut procéder de diverses façons, notamment à l'aide de vaccins morts ou inactivés, de vaccins vivants ou atténués, de vaccins sous-unitaires ou acellulaires, de vaccins conjugués et des nouveaux vaccins à acide désoxyribonucléique (ADN) ou à acide ribonucléique (ARN) et vaccins recombinants. En plus d'être classés selon les méthodes de fabrication et les populations cibles (p. ex., vaccins destinés aux bébés et aux enfants, aux adolescents et aux adultes, et aux voyageurs internationaux), les vaccins peuvent également être classés selon qu'ils sont préventifs ou thérapeutiques. Les vaccins préventifs sont les vaccins traditionnels décrits précédemment. Ils préparent le système immunitaire à réagir en cas d'intrusion d'un agent pathogène particulier. En revanche, les vaccins thérapeutiques visent à traiter une maladie existante et peuvent donc être administrés après l'éclosion de l'infection ou de la maladie afin d'accroître l'immunité naturelle contre un agent pathogène particulier et ainsi réduire le fardeau de la maladie et(ou) d'améliorer la qualité de vie.*

*Sur le plan historique, c'est à la fin des années 1800 qu'est apparu le premier vaccin au Canada – le vaccin antivariolique –, fruit des travaux innovateurs du physicien anglais Edward Jenner. Les Laboratoires Connaught de Toronto (appelés aujourd'hui Sanofi Pasteur) ont joué un rôle de premier plan dans le développement du vaccin antivariolique depuis le début des années 1900 et contribué d'une manière importante à l'éradication de la variole tant au Canada en 1962 qu'à l'échelle mondiale, comme l'a déclaré l'Organisation mondiale de la Santé (OMS) en 1979.*

Développé à l'origine par le chimiste français Louis Pasteur, le vaccin antirabique a ensuite fait son apparition au Canada au début des années 1900. Plusieurs autres vaccins sont apparus par la suite avant la fin des années 1930, dont les vaccins contre la diphtérie, la coqueluche (à germe entier), la tuberculose, le tétanos, la fièvre jaune et la grippe. Au début des années 1950, le Canada s'est de nouveau mérité une réputation de chef de file mondial, cette fois dans le cadre d'efforts mondiaux d'éradication de la poliomyélite et du développement de vaccins antipoliomyélitiques. En 1954, notamment, les Laboratoires Connaught ont produit une quantité suffisante de fluide viral pour permettre de créer un vaccin antipoliomyélitique inactivé (VPI) afin de réaliser un essai clinique d'une portée sans précédent, visant environ 1,8 millions d'enfants au Canada, aux États-Unis et en Finlande. En général, grâce au développement, à la production et à la distribution mondiale du VPI et, par la suite, du vaccin antipoliomyélitique oral (VPO), les Laboratoires Connaught ont apporté une contribution inégalée à la quasi-éradication de la poliomyélite dans le monde.

Depuis l'apparition du vaccin antipoliomyélitique dans les années 1950, des vaccins ont été développés à un rythme accéléré, ajoutant de nouveaux vaccins contre l'*Haemophilus influenzae* de type b, l'hépatite A et B, la grippe, la coqueluche (vaccin acellulaire), la méningite à pneumocoques et à méningocoques, et la varicelle aux vaccins bien établis contre la poliomyélite, la rougeole, les oreillons et la rubéole. Au cours des dernières années (depuis 2006), Santé Canada a aussi approuvé des vaccins contre d'autres agents infectieux, dont le virus du papillome humain, le rotavirus et le virus zona-varicelle. Sur la scène internationale, une vaste gamme de vaccins visant plus de 25 maladies infectieuses est actuellement offerte et le nombre de maladies évitables par la vaccination ne cesse de croître. En vaccinologie, secteur connaissant une évolution rapide, on poursuit le développement de nouvelles préparations ou combinaisons vaccinales, ainsi que d'un vaste éventail de vaccins préventifs et thérapeutiques. Pour ce qui est de sauver des vies et de prévenir la souffrance causée par des maladies dévastatrices, il n'y a donc pas lieu de croire que l'avenir des vaccins sera moins impressionnant que le passé remarquable qu'ils ont connu.

Bien qu'il y ait un consensus général selon lequel la vaccination est l'une des interventions de santé publique les plus importantes du siècle dernier – et les avantages médicaux et économiques de l'immunisation sont très bien documentés – les vaccins sont encore (à tort) sous-évalués et sous-utilisés dans le monde entier. Dans les pays industrialisés, la sous-utilisation des vaccins est en partie due au fait que l'on sous-estime la gravité des maladies évitables par la vaccination et les avantages de la vaccination, et que l'on craigne les effets secondaires des vaccins. En général, le monde ne réalise pas combien l'immunisation est avantageuse, surtout dans les pays en développement les plus pauvres et pour les enfants – qui sont les plus exposés aux maladies. Ces observations démontrent le besoin urgent de mieux informer la population (et tous les intervenants concernés) des nombreux avantages de la vaccination. Bref, tous les acteurs mondiaux de la vaccination doivent réaliser des progrès plus importants afin de reconnaître et de promouvoir la réalité selon laquelle les programmes d'immunisation sont parmi les investissements les plus rentables dans la protection de la santé publique.

Au Canada, l'immunisation joue un rôle crucial dans tous les programmes de santé publique; le renouvellement des efforts visant à promouvoir la valeur des vaccins sera donc essentiel à la capacité générale de faire valoir le « bien commun ». Dans le cadre de son mandat visant à promouvoir l'excellence dans la recherche, la fabrication et l'accès aux vaccins, le Comité de l'industrie des vaccins (CIV) de BIOTECanada contribue activement à sensibiliser les intervenants à l'importance des vaccins pour le système de santé du Canada. Ainsi, dans un esprit de collaboration, le CIV a formulé les recommandations suivantes à l'intention des gouvernements fédéral, provinciaux et territoriaux, et d'autres intervenants clés, afin de promouvoir la vaccination au profit de tous les citoyens canadiens et des générations futures.

### Recommandations à l'intention des gouvernements fédéral, provinciaux et territoriaux

1. *Afin de créer un environnement qui valorise les vaccins et en fait la promotion adéquatement, les fonctionnaires et décideurs de tous les échelons doivent reconnaître et promouvoir la réalité selon laquelle les programmes d'immunisation représentent un investissement rentable, ayant des répercussions médicales, sociales et économiques considérables, qui améliorent la santé publique.*
2. *Dans le cadre d'efforts visant à renforcer la confiance du public, les responsables de la santé publique (de tous les paliers FPT), notamment, doivent défendre, avec une conviction accrue, le rôle essentiel des programmes de prévention et d'immunisation au sein du système de santé publique.*

### Recommandations à l'intention d'autres intervenants

3. *Afin de contribuer à promouvoir l'importance de la vaccination, tous les intervenants (y compris les représentants des gouvernements fédéral, provinciaux et territoriaux, les responsables de la santé publique, les décideurs, les professionnels de la santé, les fabricants de vaccins et le grand public) doivent assumer une responsabilité plus grande en étant mieux informés (et en informant les autres) des divers types de vaccins, de leurs avantages reconnus pour la santé des individus et de la société, et de leur rentabilité considérable.*
4. *Quant au rôle que doit jouer l'industrie, les spécialistes de la recherche et du développement de vaccins, ainsi que les fabricants, doivent contribuer aux processus décisionnels visant à évaluer et recommander des vaccins – et répondre aux demandes de renseignements des professionnels de la santé, des médias, du public et(ou) des parents – en fournissant des données rigoureuses, exactes et fiables sur tous les avantages de la vaccination, et en faisant la promotion de ses répercussions positives profondes sur la population canadienne et l'ensemble du système de santé publique.*

## I.2 A Vaccine Primer

### I.2.1 What is a Vaccine?

A vaccine is a substance that is introduced into the body to prevent infection or to control disease due to a certain pathogen (a disease-causing organism, such as a virus, bacteria or parasite). The vaccine “teaches” the body how to defend itself against the pathogen by creating an immune response.<sup>1</sup> Unlike traditional pharmaceuticals, vaccines are biologics since they are made from living organisms (biological sources).<sup>2</sup> Specifically, vaccines are preparations of components derived from (or related to) a pathogen; they can typically induce a protective effect through one to three very small doses, in the range of micrograms to milligrams.<sup>3</sup> Immunity lasts for an extended period, from one year up to lifetime protection, including prevention of disease and/or related sequelae.

### I.2.2 How do Vaccines Work in the Body?

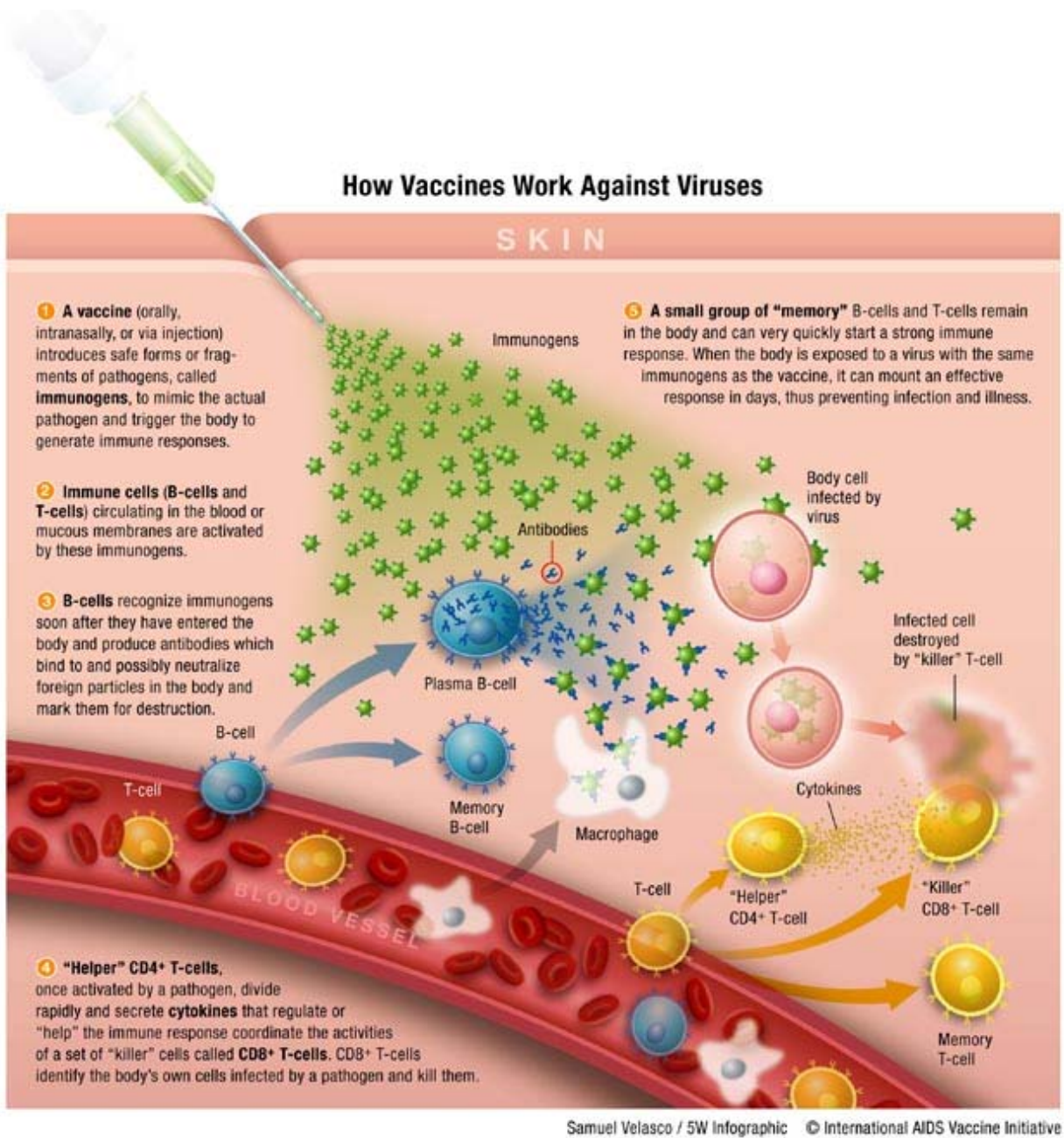
Disease-causing organisms have at least two distinct types of effects on the body. The first are the obvious effects manifested by symptoms such as fever, nausea, vomiting, diarrhea, rash and many others. The second, less obvious, effects are those underlying the immune system’s response to the infection. As the immune response increases in strength over time, the infectious agents are slowly reduced in number until symptoms disappear and recovery is complete. In general, vaccines are designed to imitate the second effect without the consequences of the first.<sup>4</sup>

The following steps summarize how a preventive vaccine can protect an individual from infection or disease:<sup>5,6</sup>

1. The vaccine introduces a small component or a non-harmful form of the pathogen into the body. This is called the foreign antigen or immunogen.
  - “Foreign” indicates that the antigen is not from the person’s own body.
  - An antigen is defined as any substance that is recognized by a component of the immune system, i.e. antibodies, cells. Antigens are often agents such as invading bacteria or viruses.
  - Similarly, immunogens are substances capable of provoking an immune response.
2. The body’s immune system produces an immune response to the pathogen by generating antibodies, killer cells, or both.
  - In the first type of immune response (known as the humoral response), the body’s B-cells produce antibodies that neutralize and help eliminate antigens in the blood, on epithelial surfaces, and in the fluid that bathes tissues.
  - In the second type of immune response (termed the cell-mediated response), specific killer cells called cytotoxic T-cells attack cells in the body that have become infected.
3. A small group of “memory” B-cells and T-cells remain in the body and can quickly initiate a strong immune response, i.e. by producing antibodies, and helping the production of killer T-cells or antibodies, respectively. The next time the real pathogen is encountered, the immune system remembers it and mounts a much larger, quicker response than it would have if the individual had never received the vaccine. This is called “immune memory”.
4. This larger, quicker immune response can act in several ways to fight infection and/or disease:
  - by stopping replication of the pathogen, so it cannot infect more cells, or
  - by producing antibodies that attach to the pathogen, rendering it harmless (humoral response), or
  - by producing immune cells that attack and kill other cells that have been infected with the pathogen (cell-mediated response).

Figure 1.1 illustrates these steps in further detail, showing how vaccines work against viruses, as one example of protection from infectious disease.

Figure 1.1 – How vaccines work against viruses



Source: Vaccine Science, International AIDS Vaccine Initiative (IAVI); [www.iavi.org/viewpage.cfm?aid=1682](http://www.iavi.org/viewpage.cfm?aid=1682).

Once a person's immune system is “trained” to resist a specific disease, the person is said to be immune to that disease. Specific immunity refers to a response that is initiated by an antigen (e.g. derived from a pathogen), and in which the immune system remembers each antigen it has previously encountered. Thus, unlike nonspecific defense mechanisms (such as the skin barrier or mucus production), which do not distinguish one infectious pathogen from another, specific immunity permits the body to recognize and defend against invading pathogens.<sup>7</sup> Specific immunity can result from either active or passive immunization, and both modes of immunization can occur by natural or artificial processes.<sup>8</sup>

The term “**active immunity**” refers to immunity produced by the body following exposure to antigens. *Naturally acquired active immunity* occurs when the person is exposed to a live pathogen, develops the disease – with clinical or sub-clinical symptoms – and becomes immune as a result of the primary immune response (upon first exposure) to the pathogen. In contrast, *artificially acquired active immunity* can be induced by a vaccine that contains the antigen (administered in the form of live, attenuated or dead pathogens or their components). In this case, the vaccine stimulates a primary immune response against the antigen without causing symptoms of the disease. In this context, it should be emphasized that vaccines are highly specific to the particular disease agent from which they are derived. While active immunity takes longer to develop than passive immunity (see below), it also lasts much longer, and is often lifelong.

In the case of “**passive immunity**”, immunity is acquired without the immune system being challenged with an antigen, but rather, by transfer of antibodies from an immune donor (human or animal) to a non-immune individual. Alternatively, immune cells from an immunized individual may be used to transfer immunity. *Naturally acquired passive immunity* occurs during pregnancy, in which certain antibodies, e.g. immunoglobulin G (IgG), are passed through the placenta (from the maternal into the fetal bloodstream), or via colostral (first-milk) transfer of immunoglobulin A (IgA). In contrast, *artificially acquired passive immunity* can be achieved by the injection of antibodies (such as gamma-globulins from other individuals or gamma-globulin from an immune animal) that are not produced by the recipient's cells. This type of approach can provide very rapid, although short-lived, resistance to infection, and is generally used when there is no time to wait for the development of active immunity, or when no effective active vaccine exists. For example, artificial transfer of immunity is practiced in numerous acute situations of infections (diphtheria, tetanus, measles, rabies, etc.), poisoning (insects, reptiles, botulism), and as a prophylactic measure (hypogammaglobulinemia).

With regard to the ability of vaccines to confer active protective immunity to the recipient, several factors contribute to the relative effectiveness of any vaccination protocol – in ways which are often poorly understood.<sup>9</sup> First, the effectiveness of active immunization naturally depends on the ability of the host to mount a normal immune response. Second, the route, dose and schedule of immunization can significantly influence vaccine effectiveness. Vaccines are generally administered via injection, e.g. into the muscle (intramuscularly), bloodstream (parenterally) or into or under the skin (intradermally or subcutaneously), or are taken orally, and boosters may be needed to develop and maintain immunological memory. Vaccines can also be given by topical application to the skin (transdermally) and by inhalation via the nose (nasally).<sup>10</sup> Third, the physical nature of the vaccine antigen, which depends on how the vaccine is made, also impacts vaccine effectiveness. In general, live, attenuated vaccines provide a more potent immune response, but may also pose greater safety risks relative to killed, inactivated vaccines (see Section 1.2.3 below).<sup>11</sup> Adjuvants (such as aluminum salts, or oil and water emulsions) can also be used to increase vaccine effectiveness, i.e. by enhancing the immune response or eliciting a specific type of immune response, either cell-mediated or humoral.<sup>12</sup>



While vaccines can protect individuals – by inducing an artificially acquired active immune response – vaccines can also protect entire communities. For example, when a critical number of people in a particular community are vaccinated against an infectious disease, even those who are not vaccinated within that community may also acquire some protection from the disease, due to the phenomenon known as “herd immunity”.<sup>13</sup> In essence, if enough people in the community are vaccinated, there is less chance that the infectious disease will spread from person to person, and unvaccinated individuals may be less likely to become infected because there is a lower risk of exposure. The ability of vaccination to increase disease resistance in both individuals and larger communities speaks to the tremendous medical, social and economic value of vaccines, and their critical role in achieving the broad public health goal of preventing infectious disease.<sup>14</sup>

### 1.2.3 How are Vaccines Made?

A live, virulent organism cannot be used as a vaccine because it would induce the very disease it is being used to prevent. Hence, the first step in making a vaccine is to isolate or create an organism (or component thereof) that is unable to cause full-blown disease, but that still retains the antigens responsible for inducing the host’s immune response. This general approach can be pursued in several ways (Table 1.1).<sup>15,16</sup>

In some cases, bacteria or viruses are killed with chemicals or heat-inactivated (killed, inactivated vaccines) or grown in cell culture in order to disable their virulent properties (live, attenuated vaccines). In other cases, the entire pathogen is not required; only the antigens that best stimulate the immune system such as proteins or polysaccharides are used (subunit, acellular vaccines).<sup>17</sup> This strategy also includes the use of toxoids (inactivated toxins), i.e. for certain pathogens that secrete harmful chemical toxins that cause illness. Other more recently developed subunit vaccines are known as conjugate vaccines, in which antigens (such as bacterial polysaccharides) are linked to a carrier protein in order to evoke a stronger immune response. Finally, newer investigative approaches involve the use of deoxyribonucleic (or ribonucleic) acid coding for a component of the agent in the vaccine (DNA/RNA vaccines). The DNA or RNA can be transferred using a viral vector in which a non-pathogenic form of a virus is used (recombinant vaccines).<sup>18</sup> Advantages and limitations of each of these approaches in developing vaccines for human use have been discussed in the literature.<sup>19,20,21</sup> An overview of ongoing research strategies in vaccine design, particularly including newer technologies, is presented in Paper 3.

**Table 1.1 – Vaccine Types and Immune Responses**

Vaccine Type	Definition	Immune Response	Examples
Killed, inactivated	Pathogen is killed, usually through a chemical process such as formalin	Evokes a robust immune response that mimics most of the responses seen during an infection	<ul style="list-style-type: none"> <li>• Typhoid vaccine</li> <li>• Salk polio vaccine</li> <li>• Hepatitis A vaccine</li> </ul>
Live, attenuated	Pathogen is weakened by genetic manipulations such that growth in the host is limited and does not cause disease; other version of live vaccine is using an organism that is related to the pathogen, but grows poorly, naturally, in humans	Evokes a broad immune response similar to that seen by the host infected with a natural pathogen	<ul style="list-style-type: none"> <li>• Oral Sabin polio vaccine</li> <li>• Nasal influenza vaccine</li> <li>• Bacille Calmette-Guerin (BCG) vaccine</li> <li>• Varicella vaccine</li> <li>• Rotavirus vaccine</li> </ul>

Vaccine Type	Definition	Immune Response	Examples
Subunit, acellular	Well-defined part(s) of the organism is purified and used as an antigen (e.g. proteins, peptides, polysaccharides, inactivated toxins)	A fragment of the “whole agent” vaccine can create an immune response	<ul style="list-style-type: none"> <li>• Acellular pertussis vaccine</li> </ul>
Conjugate	Poorer antigens (such as bacterial polysaccharides) are chemically linked to a carrier protein	Addition of other proteins (via conjugation) confers the immunological attributes of the carrier to the antigen, and thus evokes a stronger immune response; effective approach for younger children	<ul style="list-style-type: none"> <li>• <i>Haemophilus influenzae</i> type b (Hib) conjugate vaccine</li> <li>• Pneumococcal conjugate vaccine</li> <li>• Meningococcal C conjugate vaccine</li> <li>• Meningococcal (A, C, Y, W-135) conjugate vaccine</li> </ul>
DNA/RNA	Genetic material from the pathogen enter into human cells and use the cell’s “equipment” to produce some protein(s) of the pathogen encoded by the gene(s)	Immune system detects protein as a foreign or harmful antigen, produces an immune response, also will prepare a response against whole pathogen	<ul style="list-style-type: none"> <li>• AIDS vaccine (in development)</li> </ul>
Recombinant	Defined genes are incorporated into plasmid vehicle to allow for the production of large quantities of well-defined proteins, which are then used as vaccines	Immune response can be modified and targeted by insertion of specific genetic sequences	<ul style="list-style-type: none"> <li>• Hepatitis B vaccine</li> <li>• Human papillomavirus (HPV) vaccine</li> <li>• AIDS vaccine (in development)</li> </ul>

Adapted from:

i) Landry, S and Heilman, C. Future Directions in Vaccines: The Payoffs of Basic Research, Health Affairs, 2005, Vol. 24, No. 3, Exhibit 1; and

ii) Types of HIV Vaccines, International AIDS Vaccine Initiative (IAVI), [www.iavi.org/viewpage.cfm?aid=1689](http://www.iavi.org/viewpage.cfm?aid=1689).

## 1.2.4 Major Vaccine Classes

While vaccines are frequently categorized by the manufacturing approach taken (as described in Section 1.2.3), vaccines can also be classified by the target group for immunization. For example, childhood vaccines (for pediatric immunization) dominate the global vaccine market, whereas demand for adolescent and adult vaccines tends to be less concentrated and weaker, relative to pediatric vaccines.<sup>22</sup> Vaccines that are used in certain high-risk situations, including international travel, are also frequently designated as a separate class. Current recommendations for Canadians – as put forward by the National Advisory Committee on Immunization (NACI) – for infants and children, adults, and travellers are publicly available, as presented in Paper 5, Table 5.1. Notably, the financing of vaccines is also quite different for childhood, adolescent and adult immunization programs (see Paper 6, Section 6.5.1). Apart from their classification by manufacturing methods and target populations, vaccines can also be categorized in terms of preventive versus therapeutic vaccine classes.

Preventive vaccines are the traditional type of vaccine; they prepare the immune system to respond in case of future exposure to a specific pathogen. These vaccines work prophylactically to prevent a specific infectious disease by delivering an immunogenic antigen derived from the pathogen, resulting in immunity against that infectious agent.<sup>23</sup> Preventive vaccines are therefore intended for people who have not yet been infected with the foreign organism, and they do not act as a treatment or cure for an individual who is already infected with the specific pathogen.<sup>24</sup> Common examples of preventive vaccines include polio, measles, hepatitis B and tetanus vaccines. Indeed, the vast majority of vaccines currently marketed worldwide are preventive vaccines.

Historically, emphasis has been placed on preventing infectious diseases, yet researchers are now seeking to extend vaccination to the treatment of a wide range of diseases. Recent advances in immunology and biotechnology have led to the development of several therapeutic vaccines.<sup>25</sup> In contrast to preventive vaccines, therapeutic vaccines are intended to treat an existing disease rather than provide preventive protection. Hence therapeutic vaccines can be administered after infection or disease onset, with the goal of enhancing natural immunity against a specific pathogen, thereby reducing the burden of disease and/or enhancing quality of life.<sup>26</sup> Therapeutic vaccines also differ dramatically from preventive vaccines since they are often specifically formulated for individual patients, relying on clinical specimens from the patient, such as white blood cells, to create the vaccine. Although these vaccines stimulate an immune response, they do not currently have broad, population-wide application.<sup>27</sup> At present, therapeutic vaccines are currently being evaluated to treat a wide range of human disorders, including chronic infectious diseases (such as AIDS), as well as non-infectious diseases such as cancer (colorectal, breast), metabolic diseases (diabetes, hypertension), neurodegenerative diseases (Alzheimer's, stroke), and autoimmune diseases (multiple sclerosis, rheumatoid arthritis).<sup>28</sup> A discussion of potential funding mechanisms for emerging therapeutic vaccines is presented in Paper 6, Section 6.6.2.

### 1.3 Brief History of Vaccine Development – A Canadian Perspective

The foundations of modern vaccinology were laid over 200 years ago, when English physician Edward Jenner discovered a way to vaccinate against smallpox, after noticing that milkmaids who had suffered from cowpox were subsequently immune to the deadly smallpox. In 1796, he administered the first vaccine by using material (containing live virus) from cowpox pustules to immunize an eight year-old boy against the related, but much more dangerous smallpox virus. Thus the word vaccine originates from the Latin term *vaccinus*, which means “pertaining to cows”, and this first vaccine was known as “vaccinia”.<sup>29</sup> Jenner’s work was the first scientific attempt to prevent and control an infection using a deliberate systematic inoculation,<sup>30</sup> and his discovery formed the basis of one of the fundamental principles of immunization – that a relatively harmless foreign substance could evoke an immune response to protect an individual from infectious disease.

The smallpox vaccine was introduced to Canada in the late 1800s, and Connaught Laboratories (currently sanofi pasteur) has played a leadership role in the development of the smallpox vaccine since the early 1900s. Through these efforts at Connaught Labs, Canada is credited with making a critical contribution to the eradication of smallpox,<sup>31</sup> both in Canada in 1962,<sup>32</sup> and on a global basis as declared by the World Health Organization (WHO) in 1979.<sup>33</sup> Indeed, worldwide eradication of smallpox has been deemed to be the greatest public health achievement to date.<sup>34</sup> Recently, there has been renewed interest in the smallpox vaccine, i.e. since the “9/11” (September 11th 2001) attacks in the United States, when threats emerged of using smallpox as a potentially devastating bio-terrorist weapon. These threats have prompted efforts in many countries to prepare new supplies of smallpox vaccine, including Canada, for which sanofi pasteur has been processing smallpox vaccine (from frozen vaccinia pulps) since 2002.

Almost a century after Jenner’s initial discovery, French chemist Louis Pasteur developed what he called the rabies vaccine in 1885. Although what Pasteur actually produced was a rabies antitoxin that functioned as a post-infection antidote (only because of the long incubation period of the rabies germ), he expanded the term vaccine beyond its association with cows and cowpox to include all inoculating agents.<sup>35</sup> In essence, Pasteur proved that disease could be prevented by exposure to weakened germs (laboratory-attenuated live virus) that cause silent, relatively harmless infection.<sup>36</sup> The rabies vaccine was followed relatively quickly by a vaccine for the plague in 1897, and then – all before World War II in the late 1930s – vaccines against diphtheria, pertussis (whole-cell), tuberculosis (BCG), tetanus, yellow fever and influenza.<sup>37</sup> In Canada, Connaught researchers worked on the production and testing of rabies treatments, diphtheria antitoxin and influenza vaccines, and the early 1940s discovery that the pertussis vaccine acted as an adjuvant to diphtheria toxoid led to the creation of polyvalent<sup>1</sup> childhood vaccines.<sup>38</sup>

From 1910 to the 1950s, Canada was among those nations hardest hit by major epidemics of yet another infectious disease – paralytic polio. Once again however, Canada gained an international reputation as a world leader, this time in global polio eradication efforts and vaccine development, particularly beginning in the 1950s. Specifically, under the direction of Dr. Andrew J. Rhodes, Connaught researchers developed Medium 199, a synthetic nutrient base that was ideal for cultivating poliovirus because it was non-allergenic; this medium permitted Jonas Salk of the University of Pittsburgh to develop his renowned inactivated polio vaccine (IPV). A further development, known as the “Toronto technique” of rocking Povitsky bottles to grow the vaccine, enabled large scale production.<sup>39</sup>

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<sup>1</sup> A polyvalent (or multivalent) vaccine is designed to immunize against two or more strains of the same microorganism, or against two or more microorganisms.

By 1954, Connaught Labs had cultivated poliovirus in sufficient quantities to supply one of the largest clinical trials ever conducted in vaccination history to date, involving roughly 1.8 million children in Canada, the US and Finland.<sup>40</sup> The success of these efforts led to funding for a national all-Canadian trial that began in April 1955, using the same “Salk” vaccine produced by Connaught. In an unfortunate turn of events, parallel trials in the US were halted when several American children (given the polio vaccine produced by Cutter Laboratories in California) contracted polio. At this critical juncture, Canada’s Minister of National Health and Welfare, Paul Martin Sr., himself a polio victim and father of another (future prime minister Paul Martin Jr.), decided to continue with the Canadian trials, knowing the Canadian-produced vaccine had been triple-tested prior to distribution.<sup>41</sup> Martin’s confidence in the vaccine was well-justified; immunized Canadian children were well protected during the upcoming polio season, and the difficult gamble had paid its dividends.

Indeed, Canada was one of the first countries to successfully eliminate polio, and since 1993, no cases of wild polio have occurred across the country. Based on extensive experience using both the Salk IPV and the Sabin attenuated live oral polio vaccine (OPV, introduced in Canada in 1962), polio immunization in Canada has been considered an unqualified public health success. Overall, Connaught’s development, production and global distribution of both the Salk IPV and the Sabin OPV – and their subsequently enhanced formulations – have made an unparalleled contribution to the virtual elimination of poliomyelitis and its devastating consequences worldwide.<sup>42</sup> A polio-free world will be, in part, a testament to the great Canadian scientists who helped to develop the world’s first polio vaccine, and who have worked hard to bring Canada’s freedom from polio to the rest of the world.

Since the introduction of the polio vaccine in the 1950s, the pace of development has accelerated, adding new vaccines against *Haemophilus influenzae* type b (Hib), hepatitis A and B, influenza, acellular pertussis, pneumococcal and meningococcal infection, and varicella to well-established vaccines for polio, measles, mumps and rubella, i.e. as the list of approved products continued to expand in Canada and in other countries worldwide. (The pace of vaccine development and delivery in the developing world has proved a different matter.<sup>43</sup>) In Canada, vaccines against other infectious agents – including human papillomavirus, rotavirus, and zoster/shingles – have also been approved very recently, since 2006. A detailed list of vaccines currently approved for use in Canada (as of March 2008) is provided by the Public Health Agency of Canada (PHAC).<sup>44</sup> Against this backdrop of vaccine development, an overview of the history of vaccine program implementation in Canada is presented briefly in Papers 5 (Section 5.7) and 6 (Section 6.3).

Figure 1.2 presents a timeline of key milestones and additional information regarding the history of vaccination and immunization in Canada.<sup>45</sup> It should be emphasized that the terms vaccination and immunization are often used interchangeably, yet the latter is more inclusive, since it implies that the administration of an immunological agent actually results in the development of adequate immunity.<sup>46</sup> Other sources have also presented comprehensive timelines for vaccine introduction in Ontario,<sup>47</sup> the U.S.<sup>48</sup> and worldwide.<sup>49</sup> Globally, a broad range of vaccines targeting over 25 infectious diseases are currently available, based primarily on investment in research and development by the pharmaceutical industry, and the number of vaccine-preventable diseases is growing.<sup>50</sup>

In summary, although it was not long ago that serious infirmity and death from infectious disease (including smallpox, diphtheria, influenza and polio) was accepted as a fact of life, mankind has now benefitted from vaccination against many communicable diseases for over two centuries. Vaccines pioneered by (or based upon the initial research of) a handful of scientists such as Jenner, Pasteur and Salk have prevented illness or death for millions of individuals every year. While most vaccines of the 19th and 20th centuries were developed by the stimulation of the immune system to produce antibodies, recent advances in immunology have provided a deeper understanding of cell-mediated immunity, which will be essential to the successful development of future vaccines.<sup>51</sup> Newer technologies in genetic engineering and molecular biology may also provide stronger, broader, and more durable immune responses than those induced by earlier vaccines.<sup>52</sup> On the global stage, new vaccine formulations or combinations, as well as a wide range of preventive and therapeutic vaccines, continue to be developed within the rapidly evolving field of vaccinology (see Paper 3). Hence there is no reason to believe that the future of vaccines will be any less impressive or far-reaching than their remarkable past, particularly in terms of saving lives and preventing suffering from devastating disease.

Figure 1.2 – Vaccination and Immunization Timeline (Canada)

Year	Event
1882	Smallpox vaccine is made available in Canada.
1910	Rabies vaccine treatment is introduced in Canada.
1930	Routine immunization with diphtheria toxoid begins in Canada.
1941	Connaught Laboratories (now sanofi pasteur) pioneers the development of combined vaccines to immunize against diphtheria, pertussis (whooping cough) and tetanus in one shot.
1943	Routine immunization for pertussis is implemented in Canada.
1955	Jonas Salk's poliomyelitis vaccine is licensed in North America.
1962	Canada introduces the Sabin oral polio vaccine (OPV), preventing over 20,000 cases of polio per year, and is one of the first countries in the world to eradicate polio.
1967	Wyeth partners with the World Health Organization to eradicate Smallpox, providing 200 million vaccine doses annually.
1969	Rubella vaccine is introduced in Canada, decreasing incidence by 60,000 cases per year.
1979	The World Health Organization announces the worldwide eradication of Smallpox.
1982	Canada introduces the Immunization of School Pupils Act. First recombinant DNA vaccine for livestock is developed.
1988	Genetically engineered Hepatitis B vaccine is licensed for use in Canada. Vaccines for the prevention of bacterial meningitis caused by <i>Haemophilus influenzae</i> type b are introduced in Canada, decreasing the number of cases in children by nearly 97%.
1997	Since 1986, Canada has contributed \$96 million in donations towards universal immunization in developing countries.
1998	The first public immunization programs for varicella (chickenpox) are introduced in Canada.
2000	Successful immunization of mice against Alzheimer's is achieved by Dr. Peter St. George-Hyslop at the University of Toronto.
2001	Prevnar, the heptavalent conjugate pneumococcal vaccine against invasive disease, pneumonia and otitis media, is introduced for infants and children in Canada.
2003	Aventis Pasteur opens a state-of-the-art facility dedicated to the development of cancer vaccines in Toronto, home to their global cancer vaccine research program.
2005	The Canadian government announces a donation of \$160 million to the Global Alliance for Vaccines and Immunization (GAVI).
2006	Merck's quadrivalent human papillomavirus (HPV) vaccine for the prevention of cervical cancer and genital warts caused by HPV is approved for use in Canada. Canada approves the first oral pentavalent rotavirus vaccine for the prevention of rotavirus gastroenteritis in infants.
2007	Canada announces \$111 million in funding to the Canadian HIV Vaccine Initiative.
2008	Merck's vaccine for the prevention of herpes zoster (shingles) is licensed for use in Canada.

Sources: i) Canada's Vaccine Industry Committee, Leadership in Global Health, BIOTECanada 2007; and ii) Merck Press Release, August 26, 2008.

## 1.4 Value of Vaccines

### 1.4.1 Value of Vaccination Worldwide

Vaccines have recently been recognized by the British Medical Journal as one of the greatest medical advances of the past 160 years, having saved hundreds of millions of lives since their introduction.<sup>53</sup> Indeed, vaccination is generally considered as one of the greatest public health achievements in industrialized countries during the 20th century, reducing morbidity and mortality from a broad range of vaccine-preventable diseases.<sup>54</sup> With the exception of clean, safe drinking water, no treatment has rivaled immunization in reducing mortality rates.<sup>55</sup> Along with enormous improvements in sanitation and hygiene, immunization is also credited with the significant increase in life expectancy observed in the past century.<sup>56</sup> Vaccine use has resulted in the global eradication of smallpox and regional elimination of polio and measles, and has essentially eliminated most infectious diseases causing mortality in infants and children.<sup>57,58</sup> An impressive list of global statistics is presented below to describe the profound positive impact that vaccines have made on the quality of public health on a worldwide basis.

Global Benefits of Vaccination:

- In 1974, only 5% of the world's children received vaccination(s); by 2005, 75% were immunized, saving about three million lives a year.<sup>59</sup>
- Collectively, over 5.9 million deaths are prevented annually through vaccination against nine major infectious diseases [varicella, diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b (childhood), hepatitis B, measles, polio, and tuberculosis].<sup>60</sup>
- An unprecedented global vaccination campaign against smallpox has spared the global community of over 350 million new smallpox victims and some 40 million deaths from the disease.<sup>61</sup> Other than for recent concerns regarding bio-terrorism, the relative balance of benefits and risk indicates there is no longer a need for smallpox vaccination in the post-smallpox-eradication era.
- Since 2001, more than 190 countries and territories have been polio-free and the disease now exists in only about 20 countries, all in the regions of Southeast Asia and Sub-Saharan Africa. Since 1988, the number of cases reported to WHO has declined by 99%.<sup>62</sup>
- In the period from 2000 to 2006, targeted immunization campaigns helped reduce the number of global deaths caused by measles by 68%, from 757,000 to 242,000, with a corresponding 91% reduction in Africa.<sup>63</sup>

While vaccines have played a vital role in preventing infectious diseases – thereby improving individual well-being and quality of life – vaccines also offer tremendous value to society as a whole. In essence, immunization does more than just protect individuals; it protects entire populations by preventing the spread of disease from one person to another (see Section 1.2.2 regarding the concept of herd immunity). Hence vaccination is a collective activity that can protect an entire group of people, and can also cross boundaries between countries and continents, resulting in a global impact. High immunization rates in one country benefit other countries, and high rates in one generation benefit the next generation to follow.<sup>64</sup> The social value of vaccines also includes reductions in disease outbreaks, and population (and thus economic) growth through reduced mortality.<sup>65</sup>

Immunization provides not only immense medical benefits (both at the individual and societal level), as outlined above, immunization programs have been widely recognized as among the best investments in health, based on extensive analyses of both cost-savings<sup>66</sup> and cost-effectiveness.<sup>67</sup> As presented in detail in Paper 6, Section 6.4, the economic value of vaccination is well documented. Vaccines are also known to offer additional economic benefits, through reduced hospitalization and/or decreased need for expensive treatment (resulting from infection), and by improving workplace productivity.<sup>68</sup> Thus vaccines play a pivotal role in the sustainability of healthcare systems, while helping to realize the full economic growth potential of a population free of disease. In particular, since many vaccines save the lives of infants, children and young adults – who represent our greatest resource and hope for the future – immunization offers tremendous potential for maximizing economic prosperity in the decades to come.

## 1.4.2 Value of Vaccination in Canada

In the last 50 years, immunization has saved more lives in Canada than any other health intervention.<sup>69</sup> Indeed, infectious diseases – once a leading cause of death in Canada – now account for less than 5% of this country’s mortality.<sup>70</sup> Moreover, the decline in incidence and death from infectious diseases as a result of vaccination is considered one of the great triumphs of medical research and public health programming in Canada.<sup>71</sup> Table 1.2 illustrates the impact of childhood vaccines on infectious diseases; current (2000–2004) statistics on the Canadian incidence of vaccine-preventable diseases reflect the eradication of polio and diphtheria, and huge reductions in annual incidence (and peak number of cases) of *Haemophilus influenzae* type b, measles, mumps, pertussis, and rubella, compared to those prior to the introduction of the relevant vaccine.<sup>72</sup>

As one compelling example to illustrate the impressive impact of childhood vaccination in Canada, the number of reported annual cases of Hib disease had increased steadily from just over 200 cases in 1979 to roughly 700 cases in 1988, when the first Hib vaccines were introduced (Figure 1.3).<sup>73</sup> By 2002, the rate of Hib infection in Canada had dropped to under 50 cases – a staggering achievement for the near eradication of an infectious disease.<sup>74</sup> In this context, it is noteworthy that up to the mid-1980s, Hib disease was the leading cause of meningitis in children. Hence childhood Hib vaccination is considered incredibly effective, and has been acknowledged as one of the key success stories (among others, such as smallpox and polio vaccination) on the “honours list” of immunization programs in Canada.<sup>75</sup>

During his plenary address at the opening session of the 2008 Canadian Immunization Conference,<sup>76</sup> Dr. Scheifele, Professor of Pediatrics at the University of British Columbia, has proudly dubbed the trend curves that demonstrate the significant decline in the incidence of infectious disease as “disappearograms” (examples include Figure 1.3 for Hib, and graphs for other vaccines presented in Table 1.2, as provided by the PHAC).<sup>77</sup> Other newer vaccines that are also substantially decreasing childhood infectious disease rates include the meningococcal vaccine, the pneumococcal vaccine and the varicella vaccine.

**Table 1.2 – Incidence of Select Vaccine-Preventable Diseases in Canada: Pre-vaccine Era Compared with Five Most Recent Years**

Disease	Details	Pre-vaccine era*		2000-2004**	
		5-year average annual incidence per 100,000	Peak annual number of cases	5-year average annual incidence per 100,000	Peak annual number of cases
Diphtheria	Diphtheria toxoid introduced in 1926, routine infant immunization since 1930, national notifiable diseases reporting began in 1924	1925-1929 84.2	1925-1929 9,010	0.0	1
Invasive <i>Haemophilus influenzae</i> type b (Hib) in children < 5 years of age	PRP vaccine introduced in 1986, currently approved Hib PRP-T and PRP-OMP conjugate vaccines introduced in 1991/92, national notifiable diseases reporting of invasive Hib disease began in 1986	1986-1990 22.7	1986-1990 526	0.9	17

Disease	Details	Pre-vaccine era*		2000-2004**	
		5-year average annual incidence per 100,000	Peak annual number of cases	5-year average annual incidence per 100,000	Peak annual number of cases
Measles	Live vaccine approved in 1963, MMR universal infant program implemented in 1983, 2 dose MMR introduced 1996/97, no notifiable diseases reporting from 1959-68	1950-1954 369.1	1950-1954 61,370	0.2	199
Mumps	Vaccine approved in 1969, MMR universal infant program implemented in 1983, 2 dose MMR introduced 1996/97, no notifiable diseases reporting from 1960-85	1950-1954 248.9	1950-1954 43,671	0.3	202
Pertussis	Whole cell pertussis vaccine approved in 1943, acellular pertussis vaccine replaced whole cell in 1997-98, adolescent/adult acellular formulation approved in 1999	1938-1942 156.0	1938-1942 19,878	10.4	4,751
Paralytic poliomyelitis	IPV approved in 1955, OPV approved in 1962 and in use in Canada until 1997, IPV used exclusively from 1998-present	1950-1954 17.3	1950-1954 1,584	0	0
Rubella	Rubella vaccine introduced 1969, MMR universal infant program implemented in 1983, 2 dose MMR introduced 1996/97	1950-1954 105.4	1950-1954 37,917	0.1	29
Congenital rubella syndrome (CRS)	See Rubella above. National notifiable diseases reporting of CRS began in 1979	1979-1983 2.4†	1979-1983 29	0.5†	3
* Five years preceding vaccine introduction ** Provisional numbers from National Disease Reporting System 2002-2004 † per 100,000 live births					

Source: Public Health Agency of Canada, Part One, General Guidelines, The Benefits of Vaccines, Canadian Immunization Guide, Seventh Edition, 2006. [Additional data documenting the recent success of immunization programs against hepatitis B is also available; see epidemiology section in the chapter on *Hepatitis B Vaccine*.]

**Legend:**

PRP = polyribosylribitolphosphate

MMR = measles mumps rubella vaccine

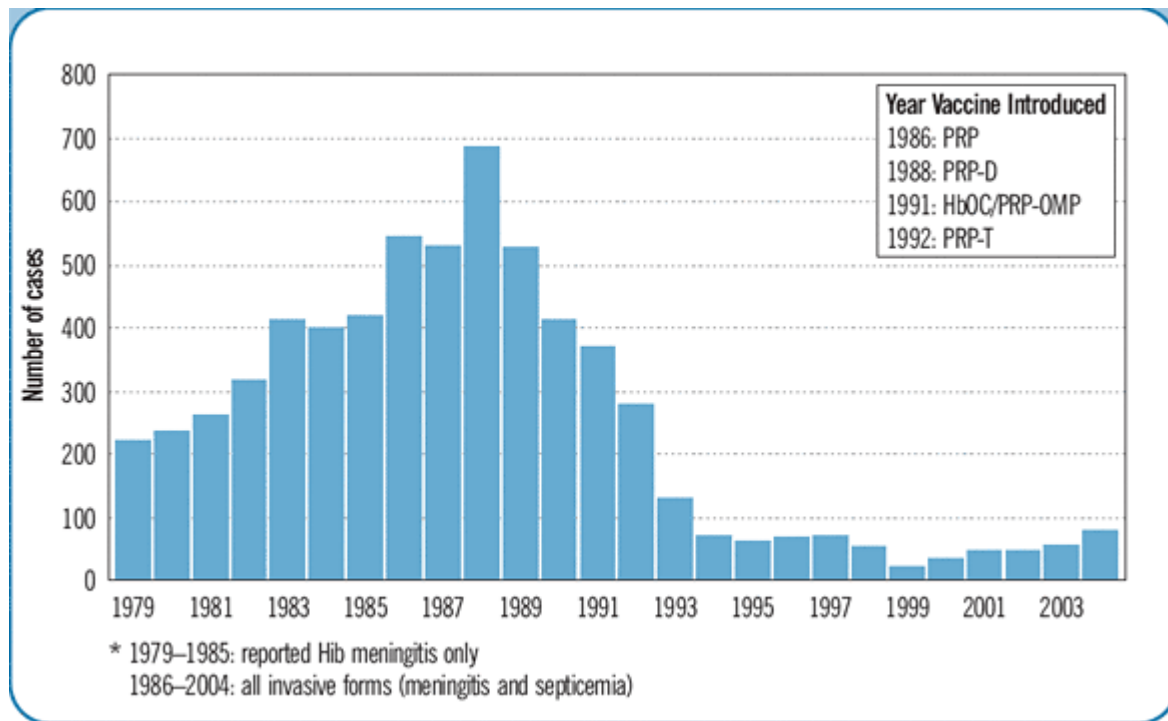
PRP-T = PRP-tetanus toxoid conjugate

IPV = inactivated polio vaccine

PRP-OMP = PRP-meningococcal protein conjugate

OPV = oral polio vaccine

**Figure 1.3 – *Haemophilus influenzae* type b (Hib) disease – Reported Cases, Canada, 1979-2004\***

Figure 1.3 – *Haemophilus influenzae* type b (Hib) disease – Reported Cases, Canada, 1979-2004\*

Source: Public Health Agency of Canada, Part One, General Guidelines, The Benefits of Vaccines, Canadian Immunization Guide, Seventh Edition, 2006.

#### Hib Conjugate Vaccines:

PRP-D = Diphtheria Toxoid Conjugate

HbOC = Diphtheria CRM<sub>197</sub> Protein Conjugate

PRP-OMP = Meningococcal Protein Conjugate

PRP-T = Tetanus Protein Conjugate

### 1.4.3 Realizing the Full Value of Immunization

Although there is broad agreement that vaccination is one of the most significant public health interventions of the past century – and both the medical and economic benefits of immunization are very well documented – vaccines continue to be (mistakenly) undervalued and underutilized throughout the world. In industrialized countries, the underutilization of vaccines is caused in part by underestimating the seriousness of vaccine-preventable diseases, underestimating the benefits of vaccination, and concerns regarding the side effects of vaccines.<sup>78</sup> Those who have witnessed the dreadful disabilities and deaths caused by smallpox and polio often viewed vaccines against these diseases as nothing short of a miracle. However, much of today's population has never experienced the devastation caused by these and other vaccine-preventable diseases, thanks to immunization programs. In addition, when there is no longer an imminent fear of contracting a disease, the public tends to forget about the limitations of cures and can become apathetic towards available prevention strategies, including vaccination.<sup>79</sup> The concept that immunization may have become (to a certain degree) the victim of its own success is described in further detail in Paper 8, in the context of vaccine awareness and education issues.

On the international stage, there is great disparity across individual countries regarding the severity of disease, availability of vaccines, and the quality of vaccination programs. Unfortunately, a child in a developing country has more than a 10-fold greater chance of dying of a vaccine-preventable disease than a child in an industrialized country. As just one example of the disparity in access to immunization, in some countries in sub-Saharan Africa, up to 70% of children do not receive the full set of vaccines.<sup>80</sup> Thus in general, while vaccination currently saves up to three million children's lives each year, another three million lives are lost worldwide from diseases that are preventable with existing vaccines. It has also been estimated that more widespread use of vaccines could prevent an additional 1.6 million deaths a year among children under the age of five.<sup>81</sup> More broadly, with sustained effort and sufficient financial resources, WHO has projected that vaccines can save an additional 10 million lives over the next decade.<sup>82</sup>

Globally, a renewed commitment has been made to immunization, and is currently being addressed by public-private partnerships such as the Global Alliance For Vaccines and Immunization (GAVI), which includes funding from the Bill and Melinda Gates foundation, as well as other substantial grants from additional donors.<sup>83</sup> The GAVI Alliance has initiated programs to address some of the most important factors that impact access to vaccines. These initiatives include improving the local healthcare infrastructure needed to deliver immunization, and establishing a number of financing initiatives such as Advance Market Commitments – designed to create market-based incentives to encourage the development of new vaccines for use in the world's poorest countries (see Paper 6, Section 6.7.3).

Overall, as the first decade of the 21st century draws to a close, vaccines continue to be underused and undervalued, and vaccine-preventable diseases remain a threat to global health. Hence the world still falls short of realizing the full benefits of immunization, especially in the poorest developing countries, and for children – who are the most vulnerable to disease. In addition, since poor vaccine coverage still exists in some parts of industrialized countries such as Canada (particularly as evidenced by sub-optimal adult immunization rates), many individuals and communities remain vulnerable to vaccine-preventable diseases.<sup>84</sup> These observations demonstrate the urgent need to better educate the public (and all relevant stakeholders) regarding the extensive benefits of vaccination. In summary, greater strides must be made by all members of the global immunization community to recognize and promote the fact that vaccines provide excellent value for money spent, specifically in terms of their broad medical, social and economic impact. Paper 6 revisits this key theme, by focusing specifically on the economic value of vaccines, and the need for predictable and sustained funding mechanisms for immunization programs in Canada.

## I.5 Recommendations

Vaccines are unquestionably one of the greatest (and most cost-effective) medical advances of the past century, yet vaccination remains undervalued and underutilized throughout the world. Since vaccination is considered to represent the single greatest promise of biomedicine – disease prevention – it is critical for all stakeholders, including international agencies, governments, policymakers, health care professionals and the general public to keep this preventive measure in the spotlight.<sup>85,86</sup> In addition, as the emerging class of therapeutic vaccines begins to enter the marketplace, it will be essential to promote the value of these newer vaccines in targeting a broad range of infectious and chronic diseases. In Canada, as for other countries, immunization plays a central role in all of public health programming, hence renewed efforts to advocate the full value of vaccines will be critical to the overall ability to support the “common good”. BIOTECanada’s Vaccine Industry Committee (VIC) plays an active role in increasing awareness of the value of vaccines to the Canadian health care system, as part of its broader mandate in fostering excellence in research, manufacturing, and full access to vaccines. Thus, in the spirit of collaboration, the VIC has put forward the following recommendations for consideration by federal, provincial and territorial (F/P/T) governments and other key stakeholders, in promoting vaccines for the benefit of all Canadians and future generations.

### Federal/Provincial/Territorial Recommendations

1. To create an environment that adequately values and supports vaccines, government officials and policy makers at all levels must recognize and promote the fact that investment in immunization programs represents excellent value for money spent, with tremendous medical, societal and economic impact in improving public health.
2. In efforts to strengthen public trust, public health officials in particular (at all F/P/T levels) must exhibit greater conviction in defending the pivotal role of prevention and immunization programs within the public health system.
  - Such proactive endorsement must be consistently demonstrated on an ongoing basis, especially in light of the recent “anti-vaccine” movement, and never more importantly than during times of controversy that often surround the introduction of new vaccines.

### Stakeholder Recommendations

3. To help establish the importance and value of vaccination, stakeholders at all levels (including F/P/T government representatives, public health officials, policy makers, medical professionals, vaccine manufacturers and the general public) must take greater responsibility in becoming more knowledgeable (and educating others) regarding the various types of vaccines, their proven health benefits to both individuals and society, as well as their significant cost-effectiveness.
  - All stakeholders need to recognize the benefits of immunization as a lifelong preventive measure, and not something that ceases after childhood.
4. With regard to the role of industry players, vaccine researchers/developers and manufacturers should support decision-making processes for evaluating and recommending vaccines – and respond to inquiries from medical professionals, the media, the public and/or parents – by providing strong, accurate, and reliable data regarding the full benefits of vaccines, including endorsement of their profound positive effect on the Canadian population and the public health system as a whole.

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