1.2 A Vaccine Primer

1.2.1 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.[1] Unlike traditional pharmaceuticals, vaccines are biologics since they are made from living organisms (biological sources).[2] 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.[3] Immunity lasts for an extended period, from one year up to lifetime protection, including prevention of disease and/or related sequelae.

1.2.2 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.[4]

The following steps summarize how a preventive vaccine can protect an individual from infection or disease:[5,6]

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.

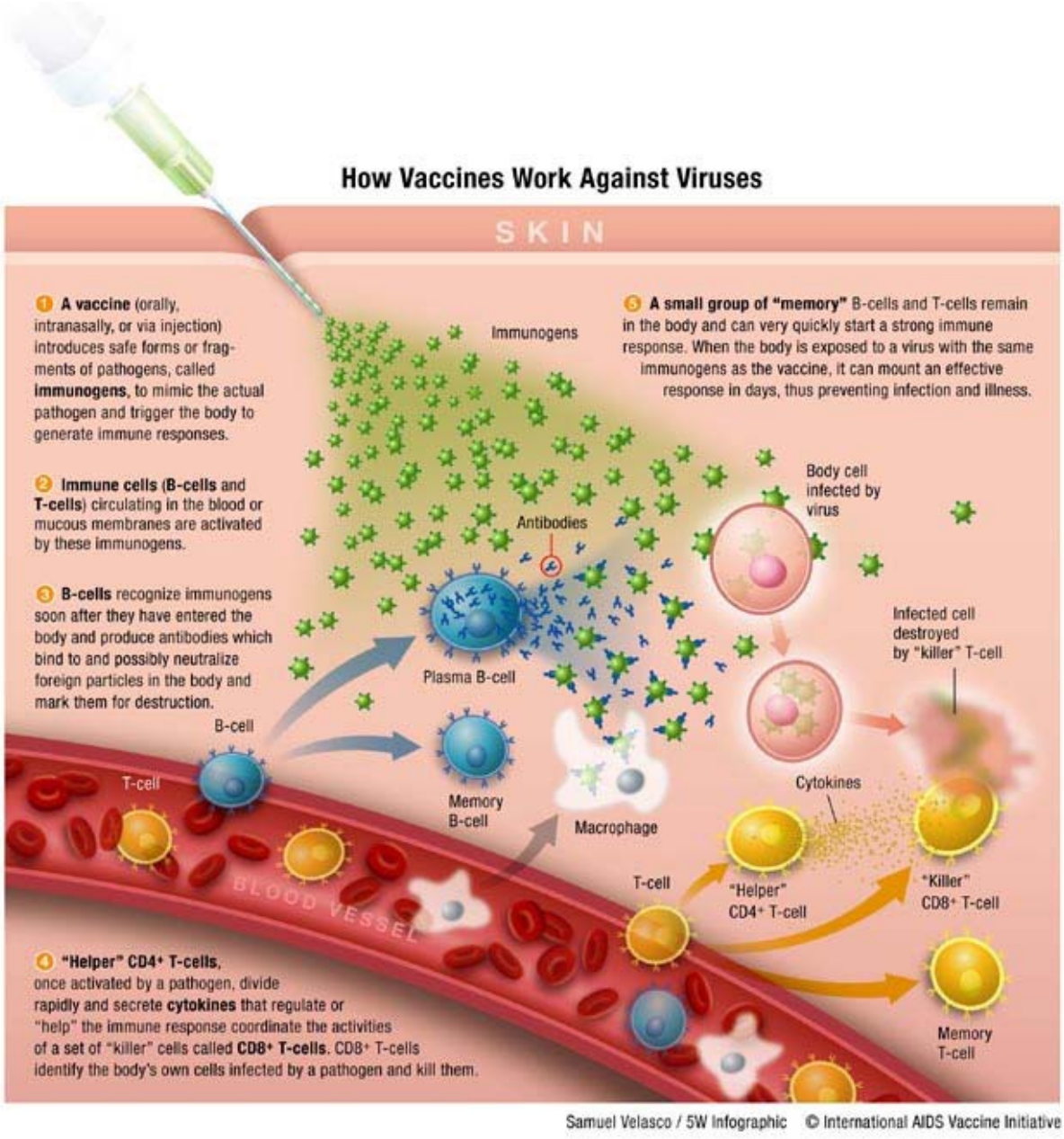
2. The body's immune system produces an immune response to the pathogen by generating antibodies, killer cells, or both.
    - In the first type of immune response (known as the humoral response), the body's B-cells produce antibodies that neutralize and help eliminate antigens in the blood, on epithelial 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.

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.[7] Specific immunity can result from either active or passive immunization, and both modes of immunization can occur by natural or artificial processes.[8]

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.[9] 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).[10] 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).[11] 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.[12]

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".[13] 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.[14]

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).[15,16]

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).[17] 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).[18] Advantages and limitations of each of these approaches in developing vaccines for human use have been discussed in the literature.[19,20,21] 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	• Typhoid vaccine • Salk polio vaccine • Hepatitis A vaccine
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	• Oral Sabin polio vaccine • Nasal influenza vaccine • Bacille Calmette-Guerin (BCG) vaccine • Varicella vaccine • Rotavirus vaccine

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	• Acellular pertussis vaccine
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	• *Haemophilus influenza* type b (Hib) conjugate vaccine • Pneumococcal conjugate vaccine • Meningococcal C conjugate vaccine • Meningococcal (A, C, Y, W-135) conjugate vaccine
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	• AIDS vaccine (in development)
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	• Hepatitis B vaccine • Human papillomavirus (HPV) vaccine • AIDS vaccine (in development)

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.

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.[22] 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 vaccines 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.[23] 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.[24] 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. [25] 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.[26] 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.[27] 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).[28] 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".[29] Jenner's work was the first scientific attempt to prevent and control an infection using a deliberate systematic inoculation,[30] 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,[31] both in Canada in 1962,[32] and on a global basis as declared by the World Health Organization (WHO) in 1979. [33] Indeed, worldwide eradication of smallpox has been deemed to be the greatest public health achievement to date. [34] 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.[35] In essence, Pasteur proved that disease could be prevented by exposure to weakened germs (laboratory-attenuated live virus) that cause silent, relatively harmless infection.[36] 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.[37] 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[i] childhood vaccines.[38]

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.[39]

[i] 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.[40] 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.[41] 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.[42] 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.[43]) 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).[44] 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.[45] 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.[46] Other sources have also presented comprehensive timelines for vaccine introduction in Ontario,[47] the U.S.[48] and worldwide.[49] 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.[50]

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.[51] Newer technologies in genetic engineering and molecular biology may also provide stronger, broader, and more durable immune responses than those induced by earlier vaccines.[52] 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 *Haemophilus influenzae* 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.[53] 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.[54] With the exception of clean, safe drinking water, no treatment has rivaled immunization in reducing mortality rates.[55] Along with enormous improvements in sanitation and hygiene, immunization is also credited with the significant increase in life expectancy observed in the past century.[56] 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.[57,58] 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.[59]
- 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].[60]
- 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.[61] 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-Sahara Africa. Since 1988, the number of cases reported to WHO has declined by 99%.[62]
- 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.[63]

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.[64] The social value of vaccines also includes reductions in disease outbreaks, and population (and thus economic) growth through reduced mortality.[65]

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[66] and cost-effectiveness.[67] 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.[68] 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.