



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

## 3

### Research and Development: Fostering Vaccine Innovation in Canada



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Vaccine Industry Committee



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Vaccine Industry Committee

# **Research and Development: Fostering Vaccine Innovation in Canada**

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**Recherche et développement : Favoriser l'innovation dans l'industrie des vaccins au Canada**

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Ce document forme une partie de la série, *Les vaccins au Canada, un héritage à faire fructifier : Valeur, possibilités et défis*. Pour lire la série entière, veuillez visiter [www.biotech.ca/vaccines](http://www.biotech.ca/vaccines).  
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## 3.1 Executive Summary / Sommaire

### 3.1.1 Executive Summary

Vaccine research and development (R&D) has been quietly undergoing a renaissance in recent years, particularly as health care authorities increasingly acknowledge the benefits and cost-effectiveness of vaccination. Canada continues to make significant contributions to vaccine R&D; these accomplishments have saved lives, decreased human suffering, and reduced health care costs, thus protecting the well being of individuals and societies in Canada and around the world. Globally, renewed or expanded research efforts have been fueled by several factors, including the lack of vaccines currently available for several major infectious diseases (e.g. malaria, hepatitis C, and acquired immunodeficiency syndrome, AIDS); the need for viable alternatives to antibiotics to help fight infection; concerns regarding emerging infectious diseases as well as potential threats such as pandemic influenza and bioterrorism; and the recent growth and “blockbuster” revenues observed in the global vaccine market. Collectively, these factors underscore the crucial need for vaccine R&D to remain a priority, both in Canada and worldwide.

While recent innovation in vaccine research has been widely acknowledged, the unique characteristics and challenges of the vaccine R&D environment are less well recognized. Specifically – unlike traditional pharmaceuticals – vaccines are complex biological medicines, thus developing a new vaccine can take (on average) 15-20 years, costing in the range of \$US 500-800 million, and may require clinical testing in 15-20 times as many subjects as for traditional pharmaceutical drugs. Since vaccine development usually takes longer and requires more capital than for other medicines, supportive public health policies that recognize the true value of vaccination are needed to attract and sustain adequate investment in new vaccines.

A diverse range of factors and criteria guide the R&D process, although initial priority setting is focused primarily upon selection of vaccines that target pathogens or diseases of major public health importance. The vaccine R&D process itself represents a broad continuum of investigative efforts, from basic and discovery research (including testing in animal/preclinical models) through to Phase I/II/III clinical trials in humans. If a candidate vaccine is deemed effective in Phase III clinical studies, then an application for licensure is submitted to regulatory bodies such as Health Canada’s Biologics and Genetic Therapies Directorate (BGTD). Following regulatory approval, post-licensure trials (e.g. Phase IV studies) are often performed to assess long-term vaccine safety and effectiveness, e.g. under “real world” conditions.

Recent advances in immunology, genetic engineering and molecular biology techniques are enabling the application of a diverse range of new strategies in vaccine development, which in turn have advanced the ability of researchers to create both preventive and therapeutic vaccines, or target new diseases, not thought possible before. Therapeutic vaccines are intended to treat an existing disease, rather than provide prophylactic protection. At present, therapeutic vaccines are being evaluated to treat a wide range of human disorders, including certain chronic infectious diseases (AIDS, hepatitis C), as well as non-infectious diseases such as cancer; metabolic disorders (hypertension, diabetes); neurodegenerative diseases (stroke, Alzheimer’s); and autoimmune diseases (multiple sclerosis, rheumatoid arthritis). Other recent advances in vaccine technology include the development of new combination vaccines, which target a series of diseases or multiple strains of a pathogen. In addition, new adjuvants (which enhance the immune response and hence may reduce the need for booster shots), and novel vaccine delivery methods (i.e. via oral, intranasal,

transdermal, or transcutaneous routes) – that may help to minimize the pain and logistical constraints associated with current needle-based delivery – are also being evaluated.

At present, the leading vaccine companies in Canada include GlaxoSmithKline Canada, Merck Canada Ltd., Novartis Canada, Pfizer Canada (formerly Wyeth Pharmaceuticals Canada), and Sanofi Pasteur Ltd. Collectively, these companies are engaged in a broad range of R&D activities in Canada – encompassing basic, clinical, epidemiological, and outcomes-based research – to help build the body of evidence supporting the complete vaccine R&D life-cycle. These leading vaccine manufacturers are also involved in many international research initiatives, e.g. through partnerships with the World Health Organization (WHO), GAVI, and the Bill and Melinda Gates Foundation. Smaller, emerging companies presently engaged in early-stage vaccine R&D in Canada include Amorfix Life Sciences Ltd., Bioniche Life Sciences Inc., Generex Biotechnology, Immunovaccine Inc., Medicago, PlantForm Corporation, TheraCarb Inc., and Variation Biotechnologies Inc.. The Canadian vaccine research community also encompasses a broad array of players at academic, hospital, and government laboratories and research institutions. An important new non-profit organization within the Canadian vaccine research landscape is the Pan-Provincial Vaccine Enterprise (PREVENT), established in February 2008.

The 2008 Canadian Institutes of Health Research (CIHR) report entitled “Vaccines for the 21st Century” confirms Canada’s strong track record in leading vaccine R&D efforts. Current strengths exist in basic research (including development of methods for antigen delivery and enhancing immune responses to vaccines), as well as in the areas of epidemiology, vaccines for special populations, and vaccine evaluation research. At present, over 25 infectious agents or disease targets are under investigation in Canada. Notwithstanding these strengths, the CIHR report has also identified specific vaccine-related challenges in Canada, as follows: i) research efforts need to be better coordinated; ii) vaccine R&D is costly; iii) vaccines for many diseases and new formulation/delivery methods are needed; iv) the public lacks accurate knowledge regarding the safety and efficacy of vaccines; v) there is a gap between basic research and Phase I/II clinical trials; and vi) there are many clinical research questions that require public funding.

Since vaccines are widely recognized as essential tools in maintaining public health, an adequately supported R&D environment will be critical in enabling development of novel vaccine technologies to protect the future health of all Canadians. At present, key players involved in funding vaccine R&D in Canada (as in other industrialized countries) include vaccine companies, universities, research institutes, government agencies and private/public investors – all of whom need incentives to continue to invest in high-risk, innovative technologies. In essence, the availability of R&D funding depends largely upon sales revenues, which are typically a function of the prevailing vaccine policy environment, including licensure, recommendation, and reimbursement mechanisms. Thus in order to fuel the vaccine innovation cycle, enhanced and sustained R&D investments, as well as supportive public policies, are urgently required.

In general, policy mechanisms that aim to promote investment in R&D by reducing the burden of research risks and costs (e.g. via grant funding or tax incentives) are referred to as “push” strategies. In contrast, “pull” strategies encourage R&D investment by helping to ensure adequate return on investment (e.g. by strengthening demand volumes or product pricing, or through favourable procurement policies), particularly in uncertain markets – i.e. for vaccines targeting diseases linked to poverty, bioterrorism or other emerging threats, in Canada or abroad. Overall, enhanced “push” and “pull” policies are required to encourage greater investment in R&D in the vaccine sector. Finally, to foster continued stability and future innovation in vaccine research, long-term partnerships

among industry players, government agencies, public health authorities, and policy makers will also be crucial. Such collaboration should span across academic, public and private sector researchers, and should ideally involve philanthropic organizations. The collective efforts of all relevant stakeholders will be required to enable new vaccines to become fully developed and accessible to the populations in need as efficiently as possible, thus ensuring that vaccination remains one of the world's most important and cost-effective public health measures.

In the spirit of such collaboration, and to help maintain the recent momentum in vaccine R&D, the following recommendations are put forward by BIOTECanada's Vaccine Industry Committee (VIC) for consideration by federal, provincial, and territorial governments and other key stakeholders.

### Federal/Provincial/Territorial (F/P/T) Recommendations

1. In view of the unique (complex, lengthy, risky and costly) nature of the vaccine R&D environment, F/P/T government policy approaches to developing an efficient vaccine marketplace should aim to encourage long-term investment in R&D in the vaccine sector.
2. Government officials at all F/P/T levels need to establish and promote policies that will expand incentives for vaccine research by removing barriers for developers/manufacturers to risk investment capital to discover vaccines needed in Canada and worldwide.
3. Both “push” and “pull” investment incentives should be further developed to more aggressively encourage future investment in vaccine R&D, i.e. by effectively decreasing research costs and increasing vaccine demand, respectively.
  - Current “push” strategies, including grant funding and tax incentive programs (e.g. Canada's Scientific Research and Experimental Development, SR&ED, program), should be expanded or enhanced to attract additional funding for vaccine research in Canada.
  - “Pull” strategies should also be advanced to promote investment in vaccine R&D (via strategic procurement policies, guaranteed-purchase agreements and/or stockpiling) to help offset market uncertainty, e.g. for vaccines targeting diseases of poverty, bioterrorism or other emerging threats.

### Stakeholder Recommendations

4. To maintain and build upon the recently renewed interest in vaccine R&D, it is essential that stakeholders at all levels, including researchers, government agencies, public health authorities, industry representatives, and investors seek to align common interests in fostering long-term innovation in the vaccine sector.
5. To maximize the health benefits of novel vaccines for all Canadians – and to successfully develop new vaccines that target diseases endemic in the developing world (e.g. malaria, tuberculosis, AIDS) – it will be critical to cultivate long-term collaborative research-oriented agreements among relevant stakeholders, both within Canada and on the international stage.
6. To better coordinate vaccine research efforts in Canada, the CIHR and its partners should organize and facilitate vaccine research workshops and facilitate communication among vaccine researchers, foster linkages among all stakeholders, and establish a vaccine research network.

7. Partnerships across Canadian stakeholder groups (e.g. including funding organizations, industry, academic institutions, and governments) – established primarily to drive vaccine R&D – should also be leveraged to promote potential new sources of funding, while encouraging academic and corporate scientists to focus their research activities.
8. To help bridge the gap between basic science and Phase I/II clinical trials (e.g. to gain insight regarding preclinical vaccine development), academic researchers should partner with industry, potentially through an industry-funded strategic initiative under the direction of the CIHR.
9. In the specific context of clinical research, Canadian researchers must strive to remain internationally competitive to continue to attract industry sponsored pre-licensure vaccine clinical trials to Canada.
  - Clinical trialists should consistently provide excellent value in executing clinical studies.
  - Canadian vaccine clinical study sites should meet the research standards of all major regulatory agencies, e.g. Health Canada, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA).

### 3.1.2 Sommaire

*On assiste, depuis quelques années, à un regain d'intérêt pour les activités de recherche et développement (R et D) liées aux vaccins, en raison notamment du fait que les autorités en matière de soins de santé reconnaissent de plus en plus les avantages et la rentabilité de la vaccination. Le Canada continue de contribuer de façon importante à ces activités. Ces réalisations ont permis de sauver des vies et de réduire la souffrance humaine et le coût des soins de santé, protégeant ainsi le bien-être des sociétés canadiennes et internationales, et de leurs membres. À l'échelle mondiale, les efforts renouvelés ou accrus des chercheurs sont alimentés par divers facteurs, y compris l'absence actuelle de vaccins contre plusieurs maladies infectieuses importantes (p. ex., le paludisme, l'hépatite C et le sida), la nécessité de trouver des solutions de rechange viables aux antibiotiques afin de combattre les infections, les préoccupations que suscite l'apparition de nouvelles maladies infectieuses et de menaces possibles (p. ex., pandémie de grippe et bioterrorisme), de même que la croissance récente du marché mondial des vaccins et des recettes faramineuses qu'il génère. Tous ces facteurs soulignent le besoin essentiel de préserver le caractère prioritaire des activités de R et D liées aux vaccins, au Canada comme ailleurs dans le monde.*

*Alors que les récentes innovations de l'industrie de la recherche sur les vaccins sont reconnues à grande échelle, les traits et défis uniques qui la caractérisent le sont moins. Par exemple, les vaccins, contrairement aux produits pharmaceutiques traditionnels, sont des produits biologiques complexes. Le développement d'un nouveau vaccin peut donc s'échelonner (en moyenne) sur 15 à 20 ans, coûter de 500 à 800 millions de dollars américains et nécessiter la tenue d'études cliniques sur 15 à 20 fois plus de sujets que les médicaments traditionnels. Étant donné que le développement des vaccins nécessite plus de temps et de capitaux que d'autres médicaments, les autorités en matière de santé publique doivent adopter des politiques qui reconnaissent la vraie valeur de la vaccination afin d'obtenir des investissements suffisants dans les nouveaux vaccins et de les conserver.*

*Le processus de R et D repose sur divers facteurs et critères, mais l'étape initiale d'établissement des priorités vise principalement à sélectionner des vaccins destinés à combattre des agents pathogènes ou des maladies d'importance capitale pour la santé publique. Les activités de R et D liées aux vaccins forment un continuum, allant de la recherche fondamentale et de la découverte (y compris la tenue d'essais précliniques sur des animaux) aux essais cliniques de phase I, II et III sur des sujets humains. Si le candidat-vaccin est jugé efficace au terme des essais cliniques de phase III, une demande d'homologation est alors présentée à un organisme de réglementation, tel la Direction des produits biologiques et des thérapies génétiques (DPBTG) de Santé Canada. Au terme de l'approbation réglementaire, des études post-homologation (de phase IV, par exemple) sont souvent menées afin d'évaluer l'innocuité et l'efficacité à long terme du vaccin, notamment dans des conditions réelles.*

*Les récentes percées réalisées dans les domaines de l'immunologie, du génie génétique et de la biologie moléculaire ont permis d'appliquer diverses stratégies nouvelles au développement des vaccins, ce qui, en retour, a accru la capacité des chercheurs de créer des vaccins préventifs et thérapeutiques, ou de cibler de nouvelles maladies, jusqu'ici insoupçonnées. Les vaccins thérapeutiques visent à combattre des maladies existantes plutôt qu'à conférer une protection prophylactique. On en évalue actuellement l'efficacité contre un vaste éventail de troubles humains, y compris certaines maladies infectieuses chroniques, dont le sida et l'hépatite C, et des maladies non infectieuses comme le cancer, les troubles métaboliques (hypertension, diabète), les maladies neurodégénératives (accidents vasculaires cérébraux, maladie d'Alzheimer) et les maladies auto-*

*immunes (sclérose en plaques, polyarthrite rhumatoïde). Le développement de nouvelles combinaisons vaccinales, destinées à combattre diverses maladies ou de multiples souches d'un agent pathogène, fait aussi partie des percées récentes de la technologie vaccinale. De nouveaux adjuvants (qui améliorent la réaction immunitaire et peuvent donc réduire le recours à des doses de rappel) et méthodes d'administration des vaccins (notamment par voie orale, intranasale, transdermique ou transcutanée) – pouvant contribuer à réduire la douleur et les contraintes logistiques causées par la méthode actuelle d'administration à l'aide d'une seringue – sont aussi évalués.*

*Actuellement, GlaxoSmithKline Canada, Merck Canada Ltée, Novartis Canada, Pfizer Canada (Wyeth Pharmaceuticals Canada) et Sanofi Pasteur Ltée sont les principaux fabricants de vaccins au Canada. Ensemble, ces compagnies exercent une vaste gamme d'activités de R et D au Canada – y compris des travaux de recherche fondamentale, clinique et épidémiologique, et des études de résultats –, qui contribueront à constituer un ensemble de données destinées à étayer le cycle complet de recherche et de développement des vaccins. Elles participent également à de nombreux projets de recherche internationaux, notamment dans le cadre de partenariats avec l'Organisation mondiale de la Santé (OMS), l'Alliance GAVI et la Fondation Bill et Melinda Gates. De nouvelles compagnies de plus petite envergure, dont Amorfix Life Sciences Ltée, Bioniche Life Sciences Inc., Generex Biotechnology, Immunovaccine Inc., Medicago, PlantForm, TheraCarb Inc. et Variation Biotechnologies Inc., mènent actuellement des travaux préliminaires de recherche et développement de vaccins au Canada. Le milieu canadien de la recherche sur les vaccins englobe également un vaste éventail d'intervenants œuvrant dans des laboratoires universitaires, hospitaliers et gouvernementaux, et des établissements de recherche. Le Pan-Provincial Vaccine Enterprise (PREVENT), fondé en 2008, est un important organisme à but non lucratif au sein de l'industrie canadienne de la recherche sur les vaccins.*

*Le rapport des Instituts de recherche en santé du Canada (IRSC) intitulé Des vaccins pour le 21e siècle, publié en 2008, confirme la contribution importante du Canada dans le passé aux activités de R et D axées sur les vaccins. Le pays excelle actuellement dans la recherche fondamentale (notamment sur les méthodes d'administration d'antigènes et les moyens de susciter certains types de réponses immunitaires) et d'autres secteurs, tels l'épidémiologie, les vaccins destinés à des populations particulières et les études d'évaluation. Plus de 25 agents infectieux ou maladies infectieuses sont à l'étude. Malgré ces points forts, le rapport des IRSC cite également des défis à relever quant aux activités de R et D liées aux vaccins, et formule les suggestions suivantes : i) Les efforts de recherche doivent être mieux coordonnés; ii) Les activités de recherche et développement liées aux vaccins sont coûteuses; iii) Il n'existe pas encore de vaccins contre plusieurs maladies importantes. En outre, on a besoin de meilleures méthodes pour formuler et administrer les vaccins; iv) La population n'est pas assez bien informée sur l'innocuité et l'efficacité des vaccins; v) Il y a un fossé entre la recherche fondamentale et les essais cliniques de phase I et II; vi) Des fonds publics sont requis pour l'étude de nombreuses questions en recherche clinique.*

*Les vaccins étant considérés comme des outils essentiels de protection de la santé publique, il sera primordial de bien soutenir les activités de R et D afin de mettre au point de nouvelles technologies vaccinales capables de protéger la santé de tous les Canadiens dans les années à venir. Actuellement, les activités de R et D liées aux vaccins au Canada (comme dans d'autres pays industrialisés) sont principalement financées par des fabricants de vaccins, des universités, des établissements de recherche, des organismes gouvernementaux et des investisseurs privés et publics. Tous ces intervenants ont besoin qu'on leur propose des mesures les incitant à continuer d'investir dans des technologies innovatrices, présentant des risques élevés. Fondamentalement, le financement des activités de R et D repose en grande partie sur les recettes de ventes, qui sont*

*habituellement tributaires du contexte politique existant en matière de vaccins, y compris des mécanismes d'homologation, de recommandation et de remboursement. Afin d'alimenter le cycle d'innovation dans l'industrie des vaccins, il est donc urgent d'accroître les investissements dans la R et D, de les préserver et d'adopter des politiques publiques qui y sont favorables.*

*En général, on appelle « stratégies de pression » les mécanismes politiques destinés à promouvoir les investissements en R et D en réduisant le fardeau que représentent les risques et les coûts associés à la recherche (p. ex., par des programmes de subventions ou des incitatifs fiscaux). En revanche, les « stratégies d'attraction » sont ces mécanismes qui encouragent les investissements en R et D en garantissant un rendement suffisant du capital investi (p. ex., par une augmentation du volume de la demande ou du prix des produits, ou par l'adoption de politiques d'approvisionnement favorables), notamment dans des marchés incertains, dont celui des vaccins servant à combattre des maladies liées à la pauvreté, au bioterrorisme ou à d'autres menaces émergentes, au Canada ou ailleurs dans le monde. On doit, en général, adopter des stratégies de pression et d'attraction qui favorisent les investissements accrus dans les activités de R et D liées aux vaccins. Enfin, pour favoriser la stabilité continue et l'innovation future dans la recherche sur les vaccins, il faudra également encourager l'établissement de partenariats à long terme entre les intervenants de l'industrie, les organismes gouvernementaux, les autorités en matière de santé publique et les décideurs. Une collaboration de cette nature devra également être établie entre les chercheurs des secteurs universitaire, public et privé, et viser idéalement des organismes philanthropiques. Tous les intervenants concernés devront s'efforcer de faire en sorte que les nouveaux vaccins soient pleinement développés et mis à la disposition des populations dans le besoin le plus efficacement possible, pour qu'ainsi la vaccination continue d'être l'une des interventions de santé publique les plus importantes et les plus rentables au monde.*

*Dans cet esprit de collaboration et afin de contribuer à maintenir le récent regain d'intérêt pour les activités de R et D liées aux vaccins, le Comité de l'industrie des vaccins (CIV) de BIOTECanada a formulé les recommandations suivantes à l'intention des gouvernements fédéral, provinciaux et territoriaux, et d'autres intervenants clés.*

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

1. *Compte tenu du caractère unique (complexes, longs, risqués et coûteux) des travaux de R et D liés aux vaccins, les approches politiques des gouvernements fédéral, provinciaux et territoriaux à l'égard du développement d'un marché des vaccins efficace doivent viser à encourager les investissements à long terme en R et D dans l'industrie des vaccins.*
2. *Les représentants gouvernementaux de tous les paliers doivent établir et promouvoir des politiques qui augmenteront les mécanismes incitatifs favorisant la recherche sur les vaccins en abolissant les barrières auxquelles se heurtent les entreprises de développement et de fabrication de vaccins pour obtenir le capital de risque nécessaire à la découverte des vaccins dont on a besoin au Canada et ailleurs dans le monde.*
3. *Des stratégies « de pression » et « d'attraction » doivent être élaborées plus clairement afin d'encourager, d'une manière plus dynamique, les investissements futurs dans les activités de R et D liées aux vaccins, notamment en réduisant efficacement les coûts de la recherche et en augmentant la demande à l'égard des vaccins.*
  - *On doit améliorer les stratégies de pression actuelles, y compris les programmes de subventions et incitatifs fiscaux (p. ex., le programme canadien de crédits d'impôt pour la recherche scientifique et le développement expérimental [RS&DE]) ou en élaborer de nouvelles, afin d'obtenir des investissements additionnels dans la recherche sur les vaccins au Canada.*
  - *On doit également améliorer les stratégies d'attraction visant à promouvoir les investissements dans les activités de R et D liées aux vaccins (par l'établissement de politiques d'approvisionnement stratégiques, de contrats d'achat garanti et/ou la constitution de réserves) afin de compenser les marchés incertains, dont celui des vaccins servant à combattre des maladies liées à la pauvreté, au bioterrorisme ou à d'autres menaces émergentes.*

## Recommandations à l'intention d'autres intervenants

4. *Afin de préserver le récent regain d'intérêt pour les activités de R et D liées aux vaccins et d'en tirer profit, il est essentiel que tous les intervenants, y compris les chercheurs, les organismes gouvernementaux, les autorités en matière de santé publique, les représentants de l'industrie et les investisseurs, tentent de concilier leurs intérêts afin de favoriser l'innovation à long terme dans l'industrie des vaccins.*
5. *Afin de maximiser les avantages des nouveaux vaccins pour la santé de tous les Canadiens – et développer avec succès de nouveaux vaccins visant à combattre les maladies endémiques qui frappent les pays en développement (p. ex., le paludisme, la tuberculose et le sida) – il sera important de promouvoir auprès des intervenants concernés, tant au Canada qu'à l'étranger, l'établissement d'accords de collaboration à long terme, axés sur la recherche.*
6. *Afin de mieux coordonner les efforts de recherche sur les vaccins au Canada, les IRSC et leurs partenaires doivent organiser et animer des ateliers de recherche sur les vaccins, faciliter la communication entre les chercheurs, favoriser l'établissement de liens entre tous les intervenants et établir un réseau de recherche sur les vaccins.*
7. *Les partenariats établis entre des groupes d'intervenants canadiens (p. ex., organismes de financement, représentants de l'industrie, établissements d'enseignement et gouvernements) – principalement dans le but de promouvoir les activités de R et D liées aux vaccins – doivent également viser à promouvoir de nouvelles sources possibles de*

*financement, tout en encourageant les chercheurs universitaires et l'industrie à concentrer leurs activités de recherche.*

8. *Afin de combler le fossé qui existe entre la recherche fondamentale et les essais cliniques de phase I et II (et mieux comprendre, par exemple, le développement préclinique des vaccins), les chercheurs universitaires doivent s'associer à l'industrie, dans le cadre, par exemple, d'une initiative stratégique financée par l'industrie, sous la direction des IRSC.*
9. *Dans le contexte particulier de la recherche clinique, les chercheurs canadiens doivent s'efforcer de demeurer compétitifs à l'échelle internationale afin de pouvoir continuer d'effectuer au Canada des essais cliniques sur les vaccins avant leur homologation, parrainés par l'industrie.*
  - *Les chercheurs doivent constamment rechercher l'excellence dans la réalisation d'essais cliniques.*
  - *Les centres canadiens où sont réalisés des essais cliniques sur les vaccins doivent se conformer aux normes de recherche de tous les principaux organismes de réglementation, dont Santé Canada, la Food and Drug Administration (FDA) des États-Unis et l'Agence européenne du médicament (EMA).*

## 3.2 Recent Rejuvenation of Vaccine Research

Since the discovery of modern vaccination more than 200 years ago, vaccines have proved to be one of the most successful and cost-effective public health interventions.<sup>1</sup> Globally, investment in research and development (R&D) – largely by the pharmaceutical industry – has resulted in a broad range of vaccines targeting over 25 infectious diseases.<sup>2</sup> Building on past momentum, vaccine research has been quietly undergoing a renaissance in recent years, particularly as health care authorities increasingly acknowledge the benefits and cost-effectiveness of vaccination. Canada continues to make significant contributions to vaccine R&D; these accomplishments have saved lives, increased life expectancy, decreased human suffering, and reduced health care costs, thus protecting the well being of individuals and societies in Canada and around the world. Indeed, in its Strategic Plan for 2007-2012, the Canadian Institutes of Health Research Institute of Infection and Immunity (CIHR-III) has identified “Vaccines of the 21st Century” as a top research priority.<sup>3</sup>

Apart from the proven impact of vaccination in protecting public health, the recent rejuvenation in vaccine research has been fueled by various other factors. Unmet medical need remains a principal driver, as there are no vaccines currently available for several major infectious diseases – including malaria, hepatitis C, and acquired immunodeficiency syndrome (AIDS) – and some existing vaccines are not completely protective.<sup>4</sup> In addition, for diseases caused by certain bacteria, vaccines are viewed as a viable alternative to antibiotics, for which increasing antibiotic resistance and declining development efforts have hampered recent scientific breakthroughs.

It is also widely recognized that reducing the infectious disease burden is one of the most promising opportunities in enabling developing countries to escape from poverty, and vaccination represents a highly effective tool in achieving this goal. Currently, the Global Alliance for Vaccines and Immunization (GAVI) and the Bill and Melinda Gates Foundation, among others, are taking important steps to address these challenges, initially targeting malaria, tuberculosis, the human immunodeficiency virus (HIV) that causes AIDS, and other diseases.<sup>5</sup> (It should be noted that in the specific case of tuberculosis, the currently available Bacille Calmette-Guérin, BCG, vaccine is a live, attenuated vaccine that is not sufficiently effective for widespread population use. It also presents a risk of tuberculosis infection, particularly in individuals who are immunocompromised.<sup>6</sup>) Furthermore, concerns regarding emerging infectious diseases such as severe acute respiratory syndrome (SARS), the possible emergence of a pandemic influenza virus, and recent threats of bioterrorism have also heightened awareness by policymakers regarding the importance of vaccine research in the context of global health and security.<sup>7,8</sup> Collectively, these factors underscore the crucial need for vaccine R&D to remain a priority both in Canada and worldwide.

The resurgence of interest in vaccine research has also been underpinned by the rapidly expanding body of knowledge in the fields of microbial pathogenesis and immunology (described in further detail in Section 3.5), which in turn has advanced the ability of researchers and developers to create both preventive and therapeutic vaccines, or target new diseases, not thought possible before.<sup>9</sup> In contrast to preventive vaccines, therapeutic vaccines are intended to treat an existing disease, rather than provide prophylactic 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>10</sup>

In addition to these scientific advances, the recent growth observed in the global vaccine market and the ability to achieve “blockbuster” status through robust sales revenues (as summarized in Paper 2) have provided a strong impetus for vaccine manufacturers to renew and/or expand research efforts, i.e. with a view toward increasing public health impact while achieving commercial success. Overall, current industry estimates suggest there are approximately 150-200 candidates in the vaccine pipeline worldwide (in various stages of clinical development), and intensified interest in vaccine R&D is anticipated to generate a three-fold increase in available vaccines over the next few decades.<sup>11,12,13</sup>

### 3.3 Vaccine Research and Development Overview

#### 3.3.1 R&D Environment

Although great scientific achievements are technically feasible in today's vaccine R&D environment, the unique nature of the vaccine R&D process suggests there may be limits in terms of translating science into approved products for use in preventing and treating disease. Unlike traditional pharmaceuticals, vaccines are biological medicines based on living organisms, and are therefore considered technology-intensive products, not commodities. Thus while traditional drug development takes many years and involves major investment risk, vaccine R&D can take even longer and involve higher costs. This is often due to the fact that vaccines are ultimately used in very large populations, and target diseases that – despite presenting a public health threat – may have a relatively low incidence.<sup>14</sup> In addition, vaccines must also meet specific, extensive regulatory requirements throughout their development, scale-up and post-launch monitoring cycles. As a result, developing a new vaccine takes (on average) 15-20 years, costs in the range of \$US 500-800 million, and can require testing in tens of thousands of individuals – potentially enrolling 15-20 times as many subjects as for traditional pharmaceutical drugs.<sup>15,16,17</sup> Overall, the development of new vaccines is a complicated, time-consuming, risky, expensive, and competitive process; the unique and challenging nature of this process is often not fully appreciated. In particular, these challenges are not well understood by academics, clinicians and public health officials, many of whom (unfortunately) continue to refer to vaccines as “expensive”, rather than promoting the intrinsic value of vaccines as primary prevention tools.

An important difference between developing preventive vaccines and most other therapeutic medicines is that vaccines are typically administered not only to large populations, but also to otherwise healthy individuals to protect against potential future disease. When viewed through the lens of the fundamental medical principle that stipulates, “First, do no harm”, this shifts the balance of benefits versus risks, such that greater value is placed on patient safety.<sup>18</sup> Thus prophylactic vaccines are held to high, exacting safety standards (with lower tolerance for adverse events) in today's risk-averse society.<sup>19</sup> Consequently, one of the key challenges faced within the current vaccine research environment is the requirement for enrolling healthy volunteers into very large clinical trials, which frequently means that recruitment efforts must be directed more towards the community, rather than towards health care programs and facilities (which are commonly targeted in recruiting patients into conventional drug trials).<sup>20</sup> Fortunately, in light of the tremendous potential for vaccination in terms of contributing to “public good”, preventive vaccines have a good safety record; most side effects are minor and serious complications are rare. It is also anticipated that the emerging class of therapeutic vaccines will offer significant opportunities to satisfy unmet medical needs, while demonstrating satisfactory risk-benefit profiles. Hence the development of safe and effective therapeutic vaccines (including appropriate formulation and delivery methods) is expected to play an increasing role in shaping the future R&D environment.

Given that the vaccine R&D process is difficult, lengthy and expensive, manufacturers need incentives to invest in such high-risk, innovative technologies – in essence, to prevent companies from abandoning the vaccine marketplace (frequently in favour of developing traditional drugs). Hence policy approaches to developing an efficient vaccine marketplace should encourage long-term investment in R&D in the vaccine sector (see Section 3.7.2). More generally, it is critical that decision makers in Canada and abroad recognize and defend the unique characteristics of the vaccine R&D environment when formulating regulatory and public health policies that impact vaccine research and large-scale production, which ultimately support successful vaccine program implementation.

### 3.3.2 R&D Process

The vaccine R&D process represents a broad continuum of investigative efforts from basic research through to clinical trials, and usually includes subsequent post-licensure studies to monitor longer-term vaccine safety and effectiveness (e.g. under “real world” conditions).<sup>21</sup> A diverse range of factors and criteria guide the R&D process, although initial priority setting is focused primarily upon selection of vaccines that target pathogens or diseases of major public health importance.<sup>22</sup> Hence the study of new vaccines typically begins with the recognition of an infectious disease burden worth preventing.<sup>23</sup> In general, disease burden determination encompasses the evaluation of medical and social burden<sup>24</sup> (including disease incidence and prevalence, mortality and morbidity rates, and disease impact on quality of life) as well as economic burden,<sup>25</sup> including direct medical costs (often measured in terms of health care resource utilization) and indirect costs (such as lost productivity in the workplace). Estimation of disease burden is further supported by disease surveillance programs providing epidemiological data. However, publicly available epidemiology data and standardized detection methods for disease-causing agents tend to be lacking in Canada, as in other countries. Thus in many cases, comprehensive vaccine research programs targeting a specific pathogen or disease must also include the study of epidemiological patterns and associated health burden.<sup>26</sup>

Aside from addressing public health concerns and unmet medical needs, vaccine developers also place a high priority on vaccine candidates and/or markets with promising future growth opportunities and potential return on investment. In addition, technical feasibility is another key factor that guides decisions regarding new vaccine research. Specifically, it can be a considerable challenge to translate basic research into a scaled-up production process, while meeting all of the safety and manufacturing requirements. Hence decisions regarding product design need to be carefully aligned with operational strategy, and the economic impact (including cost and capacity implications) of design changes (such as alternative dosages or adjuvants) must be taken into consideration early in the development cycle.<sup>27</sup> Other drivers that influence which vaccines will be pursued in research programs (and/or the selection of vaccine candidates to carry forward into clinical trials) include anticipated regulatory hurdles, recommendations by key opinion leaders, public opinion, and unexpected threats or emerging diseases.<sup>28</sup>

As a major early step in the vaccine R&D process, the basic research phase is usually initiated by identifying an infectious agent linked to a specific disease, and investigation of the causes and mechanisms of disease transmission and pathogenesis. Thus basic research studies explore the physiological and genetic composition of pathogens (including strain categorization and typing), the human immune response to infection, and the ways in which pathogens interact with human host cells. This type of basic research lays the foundation for “vaccine discovery” efforts to identify and test potential antigens that could represent targets for a vaccine-induced immune response. Such early-stage research also aids the development of techniques for producing and isolating potential antigens, and for assessing the immune protection offered by vaccine candidates. Once specific

antigens have been chosen, methods to formulate and deliver the vaccine, including evaluation of dosing and schedules, are developed and tested in animal (preclinical) models.<sup>29</sup> To further advance basic research successes achieved in the laboratory setting – and to prepare for clinical studies in humans – subsequent “process development” research efforts focus on the design of commercial products (and methods transfer) to support industrial scale manufacturing (see Paper 7).

As an excellent example of the significant contribution of basic scientific research to vaccine development, Dr. Harald zur Hausen of the German Cancer Research Centre (Heidelberg, Germany) was recently awarded the 2008 Nobel Prize in Medicine for the “discovery of the causative role of papilloma viruses in cancer of the cervix”.<sup>30</sup> Notably, Dr. zur Hausen discovered multiple genotypes of the human papillomavirus (HPV), molecularly cloned HPV types 16 and 18, and demonstrated that HPV deoxyribonucleic acid (DNA) is present in a majority of cervical cancers. He was able to implicate HPV types 16 and 18 as the principal viral oncogenes, and suggested their continued expression contributed to the tumorigenic phenotype.<sup>31</sup> Hence this important body of research has played a pivotal role in the development of commercially available HPV vaccines to help prevent cervical cancer (and which also protect against a wide range of other HPV-related diseases). In recognition of his pioneering work regarding the linkage between HPV and cervical cancer, Dr. zur Hausen was also awarded the Canadian Gairdner Award in April 2008.<sup>32</sup>

In general, if a promising vaccine candidate emerges from discovery research – with demonstration of suitable purity, safety, potency, immunogenicity (ability to stimulate the immune system) and protectiveness in animal models – clinical trials are then conducted in human subjects to test the safety and effectiveness of the potential vaccine. The four phases of clinical research (which mirror the structure of clinical research programs for traditional pharmaceutical compounds) are described in Paper 4, in the context of regulatory oversight by Health Canada and/or other regulatory authorities. To briefly summarize the clinical research process, Phase I trials examine safety of the vaccine in a small number (up to 100) of healthy individuals, whereas Phase II trials examine safety and immunogenicity in a larger number of individuals (e.g. several hundred). In Phase III trials, the vaccine is administered to a significantly larger group of individuals (e.g. several thousand) to gather additional information regarding vaccine safety and immunogenicity. Completion of Phase I, II, and III clinical trials may require six to 10 years (or possibly longer), depending upon the time required for protocol development, subject enrollment, data collection and analyses, as well as regulatory submission and approval at each successive stage.

If a candidate vaccine is deemed effective in Phase III clinical trials, then an application for licensure is submitted to regulatory bodies such as Health Canada’s Biologics and Genetic Therapies Directorate (BGTD) and the U.S. Federal Drug Administration (FDA). Following regulatory approval, post-licensure trials (e.g. Phase IV studies) are often performed to assess long-term vaccine safety and effectiveness, as well as the social and economic effects of the vaccine. It is noteworthy that all vaccines produced for human trials in Canada must be manufactured according to good manufacturing practices (GMP). Sponsors must also conduct all clinical trials, including Phase IV trials, in accordance with the principles of good clinical practices (GCP).<sup>33</sup>

## 3.4 Major Research Players in Canada

### 3.4.1 Leading Vaccine Companies

As summarized in Paper 1, Canada is well recognized as a global leader in vaccine research, with its significant contribution during the 20th century (led by Connaught Laboratories, currently sanofi pasteur) towards the development of pertussis, diphtheria, and polio vaccines, as well as its pioneering work on combination vaccines, including diphtheria, pertussis, tetanus, polio, and *Haemophilus influenzae* type b (Hib) combinations. At present, the “top tier” vaccine companies in Canada include GlaxoSmithKline (GSK) Canada, Merck Canada Ltd., Novartis, Pfizer Canada (formerly Wyeth Pharmaceuticals Canada), and Sanofi Pasteur Ltd. These players represent Canadian divisions of the respective multinational companies headquartered in Europe (GSK, Novartis, sanofi aventis) or the United States (Merck, Pfizer). Collectively, these companies are engaged in a broad range of R&D activities in Canada, with highlights summarized briefly below.<sup>34</sup>

Vaccines that are currently in the advanced pipeline stage (i.e. in Phase III in Canada or under BGTD review for market approval) include GSK’s HPV 16/18 cervical cancer vaccine (Cervarix) and Pfizer’s 13-valent pneumococcal conjugate vaccine (Prevnar 13).<sup>35,36</sup> Although other global R&D activities funded by big pharma players fall outside the scope of the current report, these companies have extensive vaccine pipelines targeting a wide range of diseases (as reviewed elsewhere).<sup>37,38,39</sup> These leading vaccine manufacturers are also involved in many international research initiatives, e.g. through partnerships with the World Health Organization (WHO), GAVI, the Bill and Melinda Gates Foundation, and/or the United Nations Children’s Fund (UNICEF).

GlaxoSmithKline Canada is currently conducting clinical research to support new vaccine products, as well as epidemiological research regarding the health and economic burden of vaccine-preventable diseases. GSK’s Laval site serves as an R&D hub for North America, supporting early-stage research projects, and the development of technology platforms for candidate vaccines.<sup>40</sup> Recent clinical trials in Canada have evaluated the company’s HPV vaccine, and vaccines targeting diphtheria/pertussis and rotavirus. Both in Canada and globally, GSK is engaged in research programs to support the development of influenza vaccines, including preparation for the possible emergence of a pandemic influenza virus. In this context, GSK has initiated (in mid-2007) the first North American pre-pandemic vaccine trials in the company’s global pre-pandemic influenza program, and has enrolled subjects in two provinces in Canada, as well as in seven states in the U.S. These Phase I/II trials will evaluate GSK’s proprietary adjuvanted H5N1 vaccine produced at the company’s manufacturing facility in Quebec.<sup>41</sup> GSK also supports several external research projects, including a collaboration with the University of Toronto in the development of high throughput assays for the identification of serological correlates of protection in pneumococcal disease.

Merck Canada is currently working with several Canadian clinical and academic researchers to build the body of evidence supporting the completion of the vaccine R&D life-cycle. This work includes epidemiologic research and outcomes-based research to document disease-related burden of illness and health care resource utilization (e.g. for rotavirus, HPV and zoster vaccines); clinical research studies (Phase I/II/III trials) to evaluate vaccine safety and efficacy; and post-licensure surveillance and evaluation of immunization programs. Merck Canada Ltd currently conducts several of these projects under the direction of James Mansi, Director Vaccine Medical & Scientific Affairs, and Martin Sénécal, Health Economics and Outcomes Research Manager. The company also supports a number of external research collaborations, including projects at McGill University, Université de Montreal, Université Laval, Dalhousie University, University of Toronto, and University of British Columbia – as well as with key public health research teams at CancerCare Manitoba and the Médecin Conseil et Conseillere Scientifique, Institut National de Santé Publique du Québec.

As another leading company involved in vaccine R&D, sanofi pasteur is currently conducting research on novel vaccines for seasonal and pandemic influenza, including novel delivery systems, doses and adjuvants. In addition, sanofi pasteur is engaged in epidemiological surveillance of annual influenza patterns to evaluate the effectiveness/benefit of universal influenza vaccination programs. The company is completing a vaccine research development centre (as part of its \$Cdn 100 million state-of-the-art research facility at its Connaught campus in Toronto),<sup>42,43</sup> and is conducting Phase II clinical trials for therapeutic cancer vaccines for melanoma<sup>44</sup> and colorectal cancer, with additional research efforts being directed at breast cancer. Vaccines developed by sanofi pasteur using modified canary pox viral vectors (ALVAC) to deliver tumor-associated antigens or other immunomodulatory molecules are currently in Phase II clinical trials in Canada and abroad. Sanofi pasteur also has a number of collaborative partnership agreements, with research projects at the University of Ottawa, Dalhousie University, University of Toronto, and the University of British Columbia (U.B.C.). Sanofi pasteur also supports research regarding infectious disease epidemiology as conducted through Canada's active surveillance network, called the Immunization Monitoring Program ACTIVE (IMPACT) system.

Pfizer Canada is also devoted to vaccine R&D, with a current focus on conducting ongoing surveillance studies of invasive and non-invasive pneumococcal disease, as well as ongoing participation in global Phase III clinical studies – with a new (13-valent) pneumococcal conjugate vaccine for infants, children and adults, and a vaccine for the treatment of Alzheimer's disease. In addition, Pfizer Canada continues its support of excellence in Canadian vaccine research, and has recently announced – along with the CIHR – renewed funding of the Canadian Clinical Research Chair in Vaccines to facilitate cross-country collaboration in innovative vaccinology development. David Scheifele is the current CIHR/Pfizer Chair in Clinical Vaccine Research at the British Columbia Children's Hospital and U.B.C.; his research efforts include evaluation of mechanisms involved in local reactions to child booster vaccinations.

As the fifth largest vaccine player on the global stage, Novartis has recently been recognized as having the industry's "Best Vaccine Pipeline", with vaccines targeting more than 20 viral and bacterial diseases.<sup>45</sup> Although Novartis is not engaged in discovery vaccine research in Canada, the company is conducting late-stage, multinational clinical trials with its quadrivalent meningococcal vaccine, Menveo, including enrollment in Canada.<sup>46</sup>

It is noteworthy that several major corporate deals have been announced in the North American vaccine sector since 2007, including the acquisition of MedImmune by AstraZeneca, the purchase of Acambis by sanofi pasteur, and the acquisition of both Coley Pharmaceutical and Wyeth by Pfizer.<sup>47,48,49,50</sup> While these corporate deals testify to the renewed interest in vaccines by traditional big pharma companies, these players have not publicly announced specific plans to date for short- or longer-term vaccine research initiatives in Canada.

### 3.4.2 Emerging Canadian Companies

Smaller, emerging companies presently engaged in vaccine R&D in Canada include Bioniche Life Sciences Inc., Immunovaccine Inc. (IMV), Medicago, PlantForm Corporation, and Variation Biotechnologies Inc. (VBI); see Table 3.1.<sup>51,52</sup> These companies are Canadian-based, and are currently conducting early-stage (preclinical and Phase I clinical) research to advance the development of a wide range of preventive vaccines (against influenza, hepatitis B & C, HIV/AIDS, salmonella, campylobacter, listeria, cryptosporidiosis and other infectious agents or diseases) and/or therapeutic vaccines (targeting prostate, breast and other cancers). These companies are also developing innovative enabling technologies to enhance vaccine design (e.g. through the use of virus-like particles, VLP, and liposomes) and to improve antigen presentation, as well as to facilitate vaccine manufacturing (e.g. via plant-based methods). Bioniche also has a Canadian-licensed cattle vaccine against *Escherichia coli* O157:H7 to help prevent animal-to-human transmission of *E. coli*. Bioniche is publicly traded on the Toronto Stock Exchange (TSX); Medicago is publicly traded on the TSX Venture Exchange; and IVT, VBI, and PlantForm are all privately-held companies financed primarily by venture capital investors.

Other Canadian companies involved in vaccine research include Amorfix Life Sciences Ltd., Genorex Biotechnology, and TheraCarb Inc. Amorfix, which is publicly traded on the TSX, is currently engaged in preclinical development of vaccines to treat amyotrophic lateral sclerosis (ALS), commonly referred to as Lou Gehrig's disease.<sup>53</sup> Genorex is publicly traded on the U.S. NASDAQ exchange; the company is developing immune regulating technologies for therapeutic vaccines targeting influenza, HIV and cancer indications. Genorex has initiated Phase II clinical trials in breast cancer and Phase I clinical trials in prostate cancer with its AE37 vaccine candidate.<sup>54</sup> TheraCarb Inc. is a private Canadian biotechnology company developing and commercializing technologies derived from the Alberta Ingenuity Center for Carbohydrate Sciences (AICCS). TheraCarb's lead vaccine candidate is designed to treat infections from *Candida albicans*, and is being advanced through a strategic alliance with Wellstat Vaccines (Gaithersburg, Maryland, U.S.).<sup>55</sup>

**Table 3.1 – Emerging Canadian Companies Conducting Vaccine R&D**

Company	Description
Bioniche Life Sciences Inc.	Bioniche is a research-based, technology-driven biopharmaceutical company focused on the discovery, development, manufacturing, and marketing of proprietary products for human and animal health markets worldwide. The fully-integrated company has three operating divisions: Human Health, Animal Health, and Food Safety. In addition to its Canadian licensed cattle vaccine against <i>E. coli</i> O157:H7 (trademarked Econiche), Bioniche Food Safety has a pipeline of vaccines in development, including vaccines against <i>Salmonella</i> , <i>Campylobacter</i> and <i>Listeria</i> , all of which are diseases harboured by animals that can cause human illness; <a href="http://www.bioniche.com">www.bioniche.com</a> .

Company	Description
Immunovaccine Inc. (IMV)	<p>IMV is the owner of the patented VacciMax and DepoVax vaccine delivery platforms that deliver long-duration enhanced immunity to a variety of antigens in a single dose, without boosting or significant side effects. VacciMax achieved 100% tumor elimination in three independent pre-clinical cancer models and significant increase in antibody responses in pre-clinical infectious disease models. IMV is anticipated to enter Phase 1 clinical trials in a therapeutic cancer indication and a prophylactic infectious disease indication in the near future; <a href="http://www.immunovaccine.com">www.immunovaccine.com</a>.</p>
Medicago	<p>Medicago is committed to providing highly effective and affordable vaccines based on proprietary virus-like particle (VLP) and manufacturing technologies. Medicago is developing VLP vaccines to protect against H5N1 pandemic influenza, using a transient expression system which produces recombinant vaccine antigens in non-transgenic plants.</p> <p>This technology has potential to offer the advantages of speed and reduced cost over competitive technologies. It could deliver a vaccine for testing in about a month after the identification and reception of genetic sequences from a pandemic strain. This production time frame has the potential to allow vaccination of the population before the first wave of a pandemic strikes and to supply large volumes of vaccine antigens to the world market; <a href="http://www.medicago.com">www.medicago.com</a>.</p>
PlantForm Corporation	<p>PlantForm is focused on providing low cost therapeutic drugs to improve quality of life. The company aims to create value for investors using proprietary technology licensed from the University of Guelph to manufacture antibody and protein drugs in tobacco plants. The company's first product will be a biosimilar version of an internationally marketed monoclonal antibody drug. The company's second product is a vaccine for the fatal diarrheal disease Cryptosporidiosis. The company will develop and market these, and future innovative drugs, under strategic alliance agreements; <a href="http://www.plantformcorp.com">www.plantformcorp.com</a>.</p>
Variation Biotechnologies Inc. (VBI)	<p>VBI pioneers research in the bioinformatic design of vaccines. The company's Variosite technology addresses the issue of "antigenic variation," which allows viral pathogens to escape detection by the human immune system. This technology can be applied to viruses such as HIV, hepatitis C, SARS, dengue and influenza, VBI's current vaccine focus. VBI is also actively acquiring innovative vaccine adjuvant and delivery technologies from Canadian &amp; international research institutions. VBI's goal is to create next generation vaccines with significant safety, breadth of reactivity, stability and production efficiencies over traditional vaccine approaches; <a href="http://www.variationbiotech.com">www.variationbiotech.com</a>.</p>

Adapted from: Canada's Vaccine Industry Committee, Leadership in Global Health, BIOTECanada, 2008; and corporate information presented at [www.bioniche.com](http://www.bioniche.com), [www.immunovaccine.com](http://www.immunovaccine.com), and [www.plantformcorp.com](http://www.plantformcorp.com).

### 3.4.3 Other Canadian Research Initiatives

Broadly speaking, the Canadian vaccine research community encompasses the discovery and clinical research departments of the top-tier and emerging industry players mentioned above, as well as a broad array of players engaged in early-stage vaccine R&D at academic, hospital, and government laboratories and research institutions. An impressive roster of early-stage research programs – as led by prominent scientists in the latter group – is presently underway, including research initiatives at several vaccine-related organizations in Canada, e.g. the Canadian Food Inspection Agency (CFIA); the Canadian HIV Vaccine Initiative (CHVI); the Canadian HIV Trials Network (CTN); Defence Research and Development Canada (Department of National Defence); McMaster Centre for Gene Therapeutics; National Research Council of Canada (NRC) Institute for Biological Sciences; and the Public Health Agency of Canada (PHAC) National Microbiology Laboratory. Current vaccine-related research activities at these organizations are concisely summarized in the recent comprehensive CIHR report.<sup>56</sup>

An important new player within the Canadian vaccine research landscape is the Pan-Provincial Vaccine Enterprise (PREVENT), established in February 2008. Based at the University of Saskatchewan, PREVENT is one of 11 new Centres of Excellence for Commercialization and Research (CECRs) established through the Networks of Centres of Excellence program.<sup>57</sup> PREVENT has been incorporated as a non-profit company that will help bridge the gap between basic science and licensed vaccines by partnering with Canadian stakeholders, and by shouldering the risk of early-stage vaccine development. By keeping manufacturing and clinical trials in Canada, PREVENT aims to accelerate the rate at which essential vaccines reach the Canadian marketplace, resulting in earlier patient access. PREVENT will leverage existing vaccine expertise through partnerships with other key Canadian research organizations and facilities, including the Vaccine and Infectious Disease Organization (VIDO) and the International Vaccine Centre (InterVac), both at the University of Saskatchewan, as well as the Canadian Center for Vaccinology (CCfV) in Halifax, and the British Columbia Centre for Disease Control (BCCDC) in Vancouver; see Table 3.2.<sup>58</sup> Ultimately, the fundamental purpose of PREVENT is to strengthen Canada's vaccine industry through enhanced public/private partnerships, thus promoting growth, investment and improved global competitiveness.<sup>59</sup>

**Table 3.2 – Organizations Working in Partnership with PREVENT**

Organization	Vaccine-related Research Activities
British Columbia Centre for Disease Control (BCCDC)	Performs vaccine research from antigen discovery to preclinical studies, as well as the evaluation of the impact of vaccines; <a href="http://www.bccdc.org">www.bccdc.org</a>
Canadian Center for Vaccinology (CCfV) and Clinical Trials Research Center	Includes scientists and experts in diverse fields who conduct research programs to develop, evaluate and generate new vaccines and vaccine technologies; <a href="http://www.centerforvaccinology.dal.ca">www.centerforvaccinology.dal.ca</a>
Vaccine and Infectious Disease Organization (VIDO) and the International Vaccine Centre (InterVac)	Conducts research and develops vaccine and immunity enhancing technologies for humans and animals. Works to ensure that discoveries are commercialized; <a href="http://www.vido.org">www.vido.org</a>

Source: French, M. Vaccines for the 21st Century, Taking Canada to the Next Level, Canadian Institutes of Health Research (CIHR) Institute of Infection and Immunity, 2008.

With specific regard to vaccine clinical research, clinical trials are typically sponsored by vaccine manufacturers and conducted jointly with teams at well-recognized vaccine clinical research centres in Canada, including the Vaccine Evaluation Centre at U.B.C. and the B.C. Children’s Hospital; the CCfV affiliated with Dalhousie University in Halifax; and the Institut National de Santé Publique du Quebec, based in Montreal and Quebec City.<sup>60</sup> Clinical studies conducted at these evaluation centres may also be used to support other global vaccine licensure applications, i.e. through regulatory agencies outside Canada. The vaccine trial community within Canada is relatively small; most researchers in academic and public health settings belong to the Canadian Association for Immunization Research and Evaluation (CAIRE), a nonprofit collaboration and research advocacy initiative. Several small and larger contract research organizations (CROs) also assist vaccine manufacturers as service providers in conducting vaccine clinical research.

In the context of public/private partnerships and vaccine clinical research, it should be noted that Sanofi Pasteur recently announced a \$Cdn 3.8 million donation to the CCfV to support human vaccine research.<sup>61</sup> Of this donation, \$Cdn 1 million will be used to support the construction of the Sanofi Pasteur Human Vaccine Challenge Unit at the CCfV; the purpose of this facility is to conduct early-stage clinical trials on candidate vaccines. This unique facility will be a 5,400 square foot, ten-bed, inpatient facility with isolation rooms, including full disease containment and physiological monitoring equipment. The remaining \$Cdn 2.8 million of the donation will support the Canadian Maternal Immunization Study at the CCfV, which will investigate whether immunization of pregnant women against pertussis can protect newborns from developing whooping cough. The Sanofi Pasteur Human Vaccine Challenge Unit is the first of its kind in Canada and, with less than a handful of such facilities worldwide, it will be at the leading edge of global vaccine research.

### 3.5 Emerging Vaccine Technologies

Throughout the 19th and 20th centuries, most vaccines were developed by stimulating the immune system to produce antibodies. More recently however, advances in immunology have provided a deeper understanding of cell-mediated immunity, and novel genetic engineering and molecular biology techniques are enabling the application of a diverse range of new strategies in vaccine development.<sup>62</sup> Current approaches to support vaccine discovery – which encompass reverse vaccinology (requiring genomics and bioinformatics), structure-based design (including virus-like particles), cell culture methods, and peptide-based strategies – are well reviewed in the literature.<sup>63,64,65</sup> Recently developed second-generation vaccines include (among others): conjugate vaccines for *Haemophilus influenzae* type b, meningococcal disease and pneumococcal disease; genetically engineered subunit vaccines for Streptococcus and HPV; and recombinant vector vaccines targeting HIV and hepatitis B.<sup>66</sup> Continued progress in genome sequencing, as well as increased knowledge of both the humoral (antibody-based) and cell-mediated (T-cell-based) arms of immune system, will be essential in developing future vaccines – particularly to conquer difficult disease targets (and leading global killers) including HIV/AIDS, tuberculosis and malaria.<sup>67</sup>

As described in Section 3.2, the recent biotechnology revolution has led to the development of the emerging class of therapeutic vaccines. With regard to the underlying mechanism of action for these novel vaccine technologies, an immune response – when correctly targeted – can be used to eliminate cells with aberrant behaviour or aberrant genomic function, or to reduce the extent of inflammation affecting a specific organ. It is this general approach that raises the possibility of developing vaccines against diseases not known to be related to infectious agents,<sup>68</sup> including cancer and autoimmune disorders as summarized below. Interestingly, recent research (regarding HIV, hepatitis B, and other pathogens) generally seems to suggest that while antibody-based

vaccines are excellent in providing protection from infection, T-cell-based vaccines are unable to prevent infection, but may be important in controlling an established infection. Hence therapeutic vaccines, including those against cancer, are generally based on inducing cytotoxic T-cells – although proof-of-principle that a pure T-cell vaccine is protective on its own is still lacking.<sup>69</sup>

At present, therapeutic vaccines are being evaluated to treat a wide range of human disorders, including certain chronic infectious diseases (AIDS, hepatitis C, chlamydia), as well as non-infectious diseases such as cancer (melanoma, colorectal, breast, prostate, leukaemia); metabolic diseases (atherosclerosis, hypertension, diabetes); neurodegenerative diseases (stroke, Alzheimer's, ALS); and autoimmune diseases (multiple sclerosis, rheumatoid arthritis).<sup>70,71,72</sup> In addition, therapeutic vaccines are presently in development to treat allergies, asthma, and drug addictions (e.g. to nicotine and cocaine), and to maintain contraception (by immunization against specific hormones).<sup>73</sup>

Another recent advance in vaccine technology has been the development of new combination vaccines. Historically, combination vaccines have been defined as the mixing of several vaccines against a series of diseases (for example, the DTaP vaccine is a mixture of vaccines used to prevent diphtheria, tetanus and pertussis), thus facilitating administration by reducing the number of separate inoculations required.<sup>74</sup> In addition, combination vaccines may also include multi-antigen constructs that target multiple strains of a given pathogen (e.g. multi-valent<sup>i</sup> HPV vaccines, and 7-valent or 13-valent pneumococcal conjugate vaccines). More recently, the concept of requiring both arms of the immune system to effectively combat many diseases has led to a broader definition of combination vaccines, which now also encompasses the “prime boost” approach to maximize the immune response to a single disease. Using the latter strategy (e.g. in developing new malaria and HIV vaccines), the first vaccine is used to prime the immune system, and then at the appropriate time, the second vaccine is used to either direct or expand (“boost”) the immune response.<sup>75</sup>

As an example of a childhood combination vaccine, GSK's Infanrix-hexa is a single injection to immunize against diphtheria, tetanus, pertussis, polio, *Haemophilus influenzae* type b and hepatitis B. Effective February 1, 2009, British Columbia has become the first province – and indeed the first jurisdiction in North America – to offer Infanrix-hexa, which results in three fewer injections in the B.C. infant vaccine schedule.<sup>76</sup> Overall, as early childhood vaccination schedules become more crowded, and as disease syndromes with multiple causes become better understood, there will be increased pressure to develop new combination vaccines, i.e. to minimize the number of injections required. However, next generation combination vaccines will not be simple to develop, as the immunologic “rules of interference” among vaccines are not yet well described.<sup>77</sup>

In addition to the introduction of therapeutic and new combination vaccines, new adjuvant technology is also revolutionizing the vaccine field. Adjuvants are critical components of vaccines; they enhance the immune response to an antigen and help trigger specific types of immune responses. Adjuvants also play a role in creating antigen-specific immunological memory. Until recently, adjuvants contained in human vaccines licensed in North America were limited to mineral (e.g. aluminum) salts. However, vaccine and adjuvant developers are currently looking to new adjuvants for a range of potential benefits, not only to heighten immune responses, but also to lengthen the effectiveness of vaccines and to trigger a different set of protective responses beyond the traditional antigen/antibody approach.<sup>78</sup> Emerging adjuvant technologies currently encompass oil-in-water emulsions (including MF59, used in Novartis' meningococcal B vaccine and pre-

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<sup>i</sup> Valence is the number of different antigens in the vaccine; a trivalent vaccine has three antigens, for example.

pandemic influenza vaccine), liposomes, toll-like receptor (TLR) agonists (such as monophosphoryl lipid A, known as MPL; and CpG oligodeoxynucleotides), cytokines, and other substances that help stimulate a T helper type 1 (T<sub>H</sub>1) immune response.<sup>79,80</sup> An effective adjuvant may ultimately lead to a cheaper vaccine, since less of the expensive active ingredient is needed to generate the desired immune response. This can be vital in cases where vaccines are in short supply, since adjuvants act to efficiently “extend” the limited vaccine stock.<sup>81</sup> Certain adjuvants may also help reduce overall health care costs by decreasing the number of required visits to physicians or clinics for booster immunizations, i.e. due to heightened immune response and immunological memory subsequent to initial vaccination.

New routes of vaccine delivery (e.g. oral, intranasal, transdermal) are also playing an important role in the development of future vaccine technologies – and may be useful in administering new adjuvanted<sup>82</sup> or combination vaccines.<sup>83</sup> Although injections into the skin (subcutaneous) and muscle (intramuscular) have traditionally served as the means to deliver vaccines into humans, there are limitations to the feasibility of numerous injections. In addition to pain reduction, there are several theoretical reasons for preferring other routes of immunization, including minimization of logistical constraints associated with needle disposal, storage, and mass immunization strategies.<sup>84,85</sup> Hence alternative routes of immunization are being introduced, e.g. the new live, attenuated influenza vaccine is given intranasally, thus inducing both systemic and local responses and providing broader protection against antigenically drifted strains. Other promising examples in the development pipeline include aerosol administration (inhalation) of measles and rubella vaccines, oral delivery of vaccines (e.g. against hepatitis B surface antigen) derived from edible transgenic plants, and transcutaneous administration (via patches, microneedles or powder applied to the skin) of hepatitis B and anthrax vaccines.<sup>86</sup>

### 3.6 Current Strengths and Challenges in Canadian Vaccine Research

As introduced in Section 3.2, the CIHR Institute of Infection and Immunity (CIHR-III) has selected “Vaccines of the 21st Century” as a research priority in its Strategic Plan for 2007-2012. To help build an action plan to support this strategic initiative, the Institute recently surveyed individual vaccine researchers as well as representatives from vaccine-related organizations and funding agencies in Canada. Participants were asked to: i) summarize their accomplishments and/or investments in research; ii) identify challenges; and iii) make suggestions for facilitating and supporting research and translating knowledge into new products and services. In the context of reviewing current strengths and challenges in Canadian vaccine research, several key findings from the comprehensive 2008 CIHR report are presented below. Topline suggestions and recommendations for improving future vaccine research in Canada (as reported in the CIHR survey results, and generally linked to identified challenges) are captured in the general recommendations presented in Section 3.9.

According to the CIHR report, Canada has a strong track record of making significant contributions to vaccine research and development. Major accomplishments over the past decade include:

- Developing an acellular pertussis vaccine from basic research to manufacture by sanofi pasteur;
- Developing vaccine technology to prevent meningitis by Dr. Howard Jennings at the National Research Council of Canada;

- Preparing for and assessing the impact of HPV immunization in Canada by Dr. Babak Pourbohoui at the BCCDC, Dr. Marc Brisson at Laval University and Dr. Eduardo Franco at McGill University;
- Assessing and making recommendations for influenza immunization programs by Dr. Noni Macdonald at the CCfV and Dr. Jeff Kwong at the Institute for Clinical Evaluative Sciences;
- Developing a vaccine candidate for SARS by the SARS Accelerated Vaccine Initiative led by Dr. Brett Finlay and Dr. Robert Brunham at the BCCDC;
- Developing and licensing a cattle vaccine against *E. coli* O157:H7 by Dr. Andrew Potter at VIDO and Dr. Brett Finlay at the BCCDC;
- Developing candidate vaccines against hemorrhagic fevers by Dr. Heinz Feldmann and Dr. Steven Jones at the PHAC National Microbiology Laboratories;
- Researching and developing adjuvants, which are added to vaccines to enhance immune responses, by GlaxoSmithKline Inc. and several individual researchers at universities; and
- Developing therapeutic cancer vaccines by manufacturers and researchers at universities including Dr. Jonathan Bramson at McMaster University.

Overall, these accomplishments showcase Canada's specific strengths in vaccine research. Across the country, there are strong research programs to support development of novel adjuvants and methods of antigen delivery, as well as to investigate mechanisms to evoke specific types of immune responses. Other areas of strength among vaccine researchers in Canada include epidemiology, vaccines for special populations, and evaluation research. Across all geographic jurisdictions and academic/government/industry laboratories, over 25 different infectious agents or disease targets are under investigation in Canada (with the most common being influenza, HPV and HIV), and efforts are also being directed towards the development of therapeutic cancer vaccines.

With regard to vaccine-related challenges in Canada, the CIHR report has also summarized relevant responses by survey participants. Specifically, participants were asked to comment on vaccine-related scientific challenges requiring attention in Canada, and ways in which CIHR-III might facilitate vaccine-related research and/or translation of research accomplishments into new products or health services; key results are presented in Table 3.3.

**Table 3.3 – Challenges in Canadian Vaccine Research**

Challenge	Rationale/Description
Research efforts need to be better coordinated.	There are a number of excellent vaccine researchers and specialists in Canada in a number of organizations, but their efforts are fragmented and there is a general lack of communication among different groups.
Vaccine research and development is costly.	It costs \$Cdn 750 million to \$Cdn 1 billion to develop a vaccine. Even early-stage research, which is performed by both academic and industry researchers, requires millions of dollars and must be sustained for longer than the typical research grant of three to five years.

Challenge	Rationale/Description
<p>There are still several major diseases for which there currently are no vaccines, and improved methods to formulate and deliver vaccines are also needed.</p>	<p>Vaccines developed in the last century were generally relatively easy to make. The tough ones remain. Survey respondents identified the following infectious agents and diseases for which vaccines are needed for humans: West Nile virus, methicillin-resistant <i>Staphylococcus aureus</i> (MRSA), HIV, hepatitis C, cancer, avian influenza, meningococcal group B, respiratory syncytial virus, plague, tuberculosis, SARS, dengue and prions. A vaccine targeting equine encephalitis is also needed.</p>
<p>The public lacks accurate knowledge regarding the safety and efficacy of vaccines.</p>	<p>Public concern regarding vaccine safety has increased over the past ten to 15 years. Paradoxically, part of the problem has been the success of vaccines. Health care professionals and public health experts need to do a better job of educating the public (and, in some instances, other health care providers) regarding the safety and efficacy of vaccines.</p>
<p>There is a gap between basic research and Phase I/II clinical trials.</p>	<p>Many academic researchers become stalled relatively early in vaccine development because they lack the resources, expertise, funds and, in some cases, the desire to take their discoveries through pre-clinical trials. Road blocks arise because the vaccine must be produced under stringent and costly good manufacturing practices (GMP) for human trials and regulatory approval must be sought.</p>
<p>There are many clinical research questions that require public funding.</p>	<p>Many vaccine-related clinical research questions are of more interest to public health and governments than industry. Examples include:</p> <ul style="list-style-type: none"> <li>• Are fewer doses of a vaccine effective?</li> <li>• Why are there low coverage rates in certain groups?</li> <li>• Would it be possible to develop delivery methods that combine vaccines?</li> </ul> <p>Public funding is needed to support research to answer these and other questions. The answers will help governments and others make informed decisions regarding the purchase of vaccines and delivery of immunization programs.</p>
<p>Adapted from: French, M. Vaccines for the 21st Century, Taking Canada to the Next Level, Canadian Institutes of Health Research (CIHR) Institute of Infection and Immunity, 2008. (Additional details provided in report.)</p>	

Apart from the recent CIHR survey findings – and in the broader context of basic research challenges faced by Canadian scientists (as well as by vaccine researchers in other countries) – a number of technical hurdles must still be overcome in the pursuit of novel vaccine technologies. Indeed, while more vaccines are being developed than ever before, the challenges faced by researchers in designing new vaccines (and moving beyond the “low hanging fruit”) are becoming ever more daunting. These challenges include the inherent ability of many viruses to evolve (through antigenic variation, as seen with HIV and influenza); strain diversity of certain bacteria and viruses (requiring effective multi-valent vaccines, e.g. targeting pneumococcal or rotavirus disease); and the need to

develop vaccines that rely on T-cell-based immunity for protection (e.g. for infections such as tuberculosis).<sup>87</sup>

Furthermore, in the development of certain live, attenuated vaccines (e.g. against Shigella), finding the balance between attenuation and immunogenicity represents a significant challenge, and designing the right cocktail of multiple strains to provide immunity against all components simultaneously – and also to work in infants through to adults, regardless of background gut flora – is a difficult task.<sup>88</sup> In general, addressing population and age diversity (among children, young adults, and the elderly), and achieving duration of protection following immunization remain key challenges in the evolving vaccine R&D field.

Apart from the technical obstacles faced in performing basic vaccine research, another major challenge voiced by vaccine clinical trial researchers is the increasing difficulty of attracting clinical studies to Canada. Notably, recent trends towards globalization and consolidation within the vaccine industry have forced Canadian clinical trialists to adapt to remain competitive, i.e. for fewer industry-sponsored clinical research projects with ever tighter budgets.<sup>89</sup> For example, some of the key challenges in building an international reputation for Canadian trialists and ensuring ongoing attractiveness to large international companies include the following: clinical study costs are relatively high in Canada (due to wage rates for Canadians versus those at trial centres in Eastern Europe and Asia); data from domestic clinical trials must support licensure applications in many countries (requiring more complex, harmonized review processes); and Canadian centres that depend upon project-to-project funding for survival (as opposed to those with consistent, subsidized funding for research infrastructure) are becoming increasingly fragile. Overall, to continue to attract pre-licensure clinical trials, Canadian researchers need to demonstrate outstanding quality, reliability and efficiency (including rapid ethics review) in executing domestic arms of multinational clinical studies.

## 3.7 Funding Vaccine R&D

### 3.7.1 Key Funding Organizations

In Canada, as in other industrialized countries, key players involved in funding vaccine R&D include vaccine companies, universities, research institutes, government agencies and private/public investors. Basic research regarding pathogens and immune responses is supported by a cross-section of industry, academic and government organizations, whereas development-related and clinical research programs are primarily funded by industry players. For multinational companies engaged in vaccine research in Canada, funding is derived chiefly from corporate R&D budgets – which may represent 15-40% of sales revenues.<sup>90</sup> In the case of smaller Canadian-based vaccine companies, funding for vaccine research is typically driven by financing from the Canadian public financial markets and the Canadian/U.S. venture capital communities (e.g. Clarus Capital Partners, Arch Venture Partners, 5AM Ventures, Genesys Capital).<sup>91</sup> For both top-tier (global) pharma players and emerging Canadian-based companies, additional funding partnerships are also sought with Canadian and international research granting agencies.

At the international level, potential funding organizations for Canadian vaccine research encompass the U.S. National Institutes of Health (NIH),<sup>92</sup> and several nongovernmental organizations (NGOs), including GAVI; the Bill and Melinda Gates Foundation; the Rockefeller Foundation; and the Wellcome Trust. In Canada, major research funding agencies include the CIHR; the National Research Council of Canada (NRC); the Natural Sciences and Engineering Research Council

(NSERC); the Industrial Research Assistance Program of Canada (IRAP); the Canada Foundation for Innovation (CFI); the National Cancer Institute of Canada (NCIC); and the Canadian HIV Vaccine Initiative (CHVI).<sup>93,94</sup> Other funding sources include the International Development Research Centre (IDRC), a Canadian Crown corporation; the Alberta Heritage Foundation for Medical Research (AHFMR); the Michael Smith Foundation for Health Research (MSFHR); and Genome Canada and its six Genome Centres. In addition, provincial government departments or initiatives (e.g. the Ontario Ministry of Research and Innovation, MRI; and the Market Readiness program of the Ontario Centres of Excellence)<sup>95</sup> – as well as a range of charitable organizations and medical associations in Canadian health care – provide other funding opportunities. A detailed list of international, federal, provincial, and private sector vaccine funding organizations is presented in Appendix 4 of the 2008 CIHR report.

### 3.7.2 Encouraging Investment in Vaccine Innovation

Since vaccines are widely recognized as essential tools in maintaining public health, an adequately supported R&D environment will be critical in enabling development of novel vaccine technologies to protect the future health of all Canadians. In essence, vaccine innovation is driven primarily by R&D funding, which in turn depends largely upon sales revenues – which are typically a function of the prevailing vaccine policy environment, including licensure, recommendation, and reimbursement mechanisms (refer to Papers 4, 5, and 6).<sup>96</sup> Thus in order to fuel the vaccine innovation cycle, enhanced and sustained R&D investments, as well as supportive public policies and positive public opinion, are urgently required.

Currently, vaccine researchers/developers in Canada face several challenges in terms of attracting adequate investments for vaccine innovation. For example, the vaccine business has become increasingly competitive, and concerns have been expressed regarding the need to compete for investment dollars within the global economy.<sup>97</sup> Specifically, the multinational nature of many vaccine companies means that the needs of individual countries such as Canada (considered a small part of the global market) may often be ignored. In addition, Canadian vaccine prices traditionally have been among the lowest in the industrialized world, due to bulk purchasing contracts, so there is less incentive to develop vaccines for the Canadian market. On the whole, since investment decisions for vaccines development are based on market potential and projected profits, Canadian priorities for vaccine research are less likely to be considered.

Furthermore, as described in Section 3.3.1, the cost of research for new vaccines has markedly increased in recent years – and the development process typically takes longer than for other medicines – thus manufacturers need incentives to invest in such high-risk, innovative technologies. Research grants, subsidies, and funding programs (such as those offered by organizations summarized in Section 3.7.1) act as primary vehicles to encourage vaccine research, although there remains an urgent need to maintain and augment such programs in Canada. In particular, it has been suggested that Canadian initiatives to introduce infrastructure awards (such as those announced recently by the CFI) should be expanded.<sup>98</sup> Unfortunately, the federal government's Budget 2009 offered no new funding for research operating grants at the CIHR, NSERC and the Social Sciences and Humanities Research Council (SSHRC) - Canada's three federal funding agencies, which directly or indirectly impact vaccine research. The national debate on science funding has recently escalated, particularly as the U.S. National Institutes of Health will receive a \$US 3.9 billion increase to its budget as part of U.S. President Obama's 2009 economic stimulus package.<sup>99,100</sup>

In general, policy mechanisms to address supply-side issues by reducing the burden of R&D costs (e.g. via grant funding) are referred to as “push” strategies. Other “push” strategies include tax incentives, such as Canada’s Scientific Research and Experimental Development (SR&ED) program, which provides tax credits as a percentage of eligible R&D expenses.<sup>101</sup> Indeed, SR&ED tax rebates are critical funding mechanisms for emerging vaccine developers, who may not yet have sales revenues to support research programs. However, the current SR&ED program is viewed by many as insufficient; BIOTECCanada (as one of several industry organizations in the biopharmaceutical sector) has recently renewed its call for enhanced government support of scientific innovation, i.e. via proposing various options for increasing refundable SR&ED credits.<sup>102</sup>

In contrast to “push” mechanisms, “pull” strategies aim to promote investment in R&D by enhancing demand-side conditions, i.e. via increasing demand volumes or through stronger product pricing. For example, companies may be reluctant to invest in a robust R&D program for certain vaccines due to market uncertainty, i.e. for vaccines against: i) emerging diseases (such as SARS); ii) biological weapons (such as anthrax, plague, smallpox, Ebola); or iii) diseases mainly affecting underdeveloped countries. Against the backdrop of these concerns, the U.S. has recently led the way in terms of implementing “pull” strategies to encourage vaccine R&D, particularly through stockpiling and guaranteed-purchase agreements – including Advanced Market Commitments (AMC) – which help to reduce the risk associated with unpredictable future demand or ability to pay (see Paper 6, Section 6.7.3).<sup>103,104</sup>

While Canada has recently announced a pilot pneumococcal AMC program to help support vaccine research to benefit the world's poorest nations,<sup>105</sup> the federal government has been less actively engaged in implementing “pull” strategies to attract private sector vaccine investment in the development of vaccines to protect against bioterrorist threats or emerging diseases. However, it is hoped that in the near term future, additional “push” funding or other “pull” incentive programs to promote vaccine R&D may be announced in Canada to support the goals of the Pandemic Influenza Preparedness Program.<sup>106</sup> In general, Canadian government “pull” policies, including favourable procurement policies, are required to ensure a positive market environment and to foster continued innovation in new vaccine technologies.<sup>107,108,109,110</sup> It should be noted, however, that the Patented Medicine Prices Review Board (PMPRB) – as described in Paper 6 – and the current federal/provincial/territorial (F/P/T) vaccine procurement process act in synergy to place downward pressure on vaccine prices. Hence current PMPRB review mechanisms and F/P/T procurement policies tend to be viewed as counterproductive to the development of “pull” initiatives. These current mechanisms and policies are also believed to play a role in stifling innovation in vaccine technology, thus jeopardizing Canada’s competitive positioning in vaccine research and commercialization.

Given the highly favourable public health impact of vaccination programs, investment in the development of new vaccines is generally considered suboptimal, particularly in Canada. In this context, it is noteworthy that Canada ranks very poorly in the area of innovation (13th among 17 “wealthy” countries of the Organisation for Economic Cooperation and Development, OECD) – scoring a “D” (the lowest of four possible grades), according to a recent performance Report Card compiled by The Conference Board of Canada.<sup>111</sup> In this report, innovation is defined as “the ability to turn knowledge into new and improved goods and services.” Interestingly, the report notes that almost all countries leading the OECD innovation scores have government programs that encourage innovation in alignment with national interests, i.e. via high priority “push-pull” programs supported by the highest level of government. Hence to help promote greater scientific innovation in Canada, significant work remains to be done to further develop both “push” and “pull” strategies to provide investment incentives, especially for private sector organizations. In theory, implementation of such

government programs should positively impact vaccine innovation in Canada by enhancing investments in vaccine R&D.

Overall, achieving sustainable funding for vaccine R&D will require long-term commitment and reasonably predictable future demand, as well as government policies (e.g. that oversee licensure, recommendation, procurement and reimbursement mechanisms) that recognize the full value of vaccination. In general, while policy approaches that encourage sustained investment in vaccine research should assist in driving future innovation in the development of life-saving (preventive) and therapeutic vaccines, such policies should also help to prevent manufacturers from exiting the vaccine market, thus ensuring continued vaccine supply both domestically and globally.

### 3.8 Fostering Collaborations to Support Vaccine R&D

To ensure continued stability and future innovation in vaccine research – and particularly to provide a supportive environment for ongoing investment in novel vaccine technology – long-term partnership and collaboration among industry players, government agencies, public health authorities, and policy makers will be crucial. Collaborations in vaccine research can take many forms, including partnerships among academic, public sector and private sector researchers. For example, developing networks of skilled, cross-disciplinary clinical trial centres may help give identify to Canadian vaccine research communities, while favouring international competitiveness for Canadian clinical sites. Such collaborative efforts would also facilitate readiness to respond to national threats or other emerging opportunities and would foster dialogue between clinical trialists and governments (e.g. regarding national expertise requirements) and between trialists and vaccine manufacturers (e.g. including methods to improve sponsored research studies).<sup>112</sup> As one example, the CIHR has funded and facilitated the development of the Canadian HIV Trials Network, to support research including clinical studies in vaccine development for HIV.

Collaborative opportunities within the vaccine research landscape also span across the public, private, and philanthropic sectors; these stakeholders also need to join forces to ensure that new or improved vaccines are fully developed and become accessible to the populations in need as efficiently as possible. Internationally, there has also been renewed interest in vaccine R&D, as summarized in Section 3.2. Recent international initiatives have been useful in helping to leverage funds from national sources. In this context, it appears unlikely that the Canadian HIV Vaccine Initiative would have been established without significant support from the Bill and Melinda Gates Foundation.<sup>113</sup> As another notable example of Canadian/international research partnerships, the PHAC has recently contributed resources and expertise to the International Infectious Disease Centre in Kenya, a state-of-the-art research centre (accessible to researchers from all contributing countries) that is able to respond quickly to outbreaks of infectious disease.<sup>114</sup> Global partnerships of this nature offer immense benefits to populations in developing nations that are in need of shared resources. CIHR and other stakeholders should continue to establish partnerships with funding organizations, industry, academic institutions and government to drive vaccine R&D to help meet the needs of Canadians and those in developing countries.

Interestingly, in his presentation delivered at the 8th Canadian Immunization Conference (CIC) in December 2008, Neil Cashman, Canada Research Chair in Neurodegeneration and Protein Misfolding Diseases at the University of British Columbia, expressed his view that Canada appears naturally adept at developing partnership opportunities, including collaboration within the vaccine research field.<sup>115</sup> He remarked that PREVENT – the recently created Canadian nonprofit organization (see Section 3.4.3) – provides an excellent example of Canada's ability to collaborate

effectively,  
i.e. by leveraging existing vaccine expertise through its partnerships with VIDO, InterVac, CCfV, and BCCDC. Dr. Cashman's research collaborations with PREVENT include investigation of the role of misfolded proteins in prion-mediated and neurological diseases (e.g. ALS and Alzheimer's), and development of potential therapeutic vaccines, currently being tested in animal models. His personal belief is that PREVENT represents the “flavour of things to come” in terms of strengthening Canada's vaccine research sector through enhanced public/private partnerships that encourage investment, innovation, and global competitiveness.

Overall, it remains vital to foster a supportive vaccine research environment, i.e. to continuously develop new vaccines and to improve existing technologies. Hence the coordinated actions of industry, academic and government researchers, along with national and international funding agencies (including nonprofit foundations and NGO/humanitarian organizations) will be critical in harnessing existing research potential, and to accelerate new technology platforms – not only via enhanced vaccine safety, efficacy, and/or delivery methods, but also through improved downstream implementation of immunization programs. The vaccine sector is a vibrant area in which the goals of industry and government often overlap, i.e. to maximize public health benefits of biopharmaceutical innovation. Working together in cooperative partnership, the collective efforts of all relevant stakeholders will go a long way toward advancing novel research opportunities, thus helping to ensure that vaccination remains one of the world's most important and cost-effective public health measures.

### 3.9 Recommendations

Canadian scientists and companies have a strong track record of making significant contributions to vaccine research, and – as part of the renewed global interest in vaccine R&D – Canada continues to drive the discovery of new vaccines that reduce human mortality and morbidity, thus decreasing health care costs. While recent innovation in vaccine research is generally well recognized, the unique characteristics and challenges of the vaccine R&D environment are less well understood. Specifically, since vaccine development usually takes longer and requires more capital than for other medicines, supportive public health policies that recognize the true value of vaccination are required to attract and sustain adequate investment in new vaccines. Unfortunately, in the absence of a favourable policy environment (e.g. including effective investment incentives to pursue high-risk technologies), inadequate funding for vaccine R&D may delay the availability of new vaccines that can prevent future disability and death.

Furthermore, to maintain the resurgence of interest and recent momentum in vaccine R&D, all relevant stakeholders will need to work together with cohesive, coordinated efforts to succeed in maximizing the full benefits of introducing new vaccine technologies. In the spirit of such collaboration, the following recommendations are put forward by BIOTECanada’s Vaccine Industry Committee (VIC) for consideration by federal, provincial, and territorial governments and other key stakeholders. It should be acknowledged that the 2008 CIHR report, entitled “Vaccines for the 21st Century”, provides an excellent overview of recommendations for vaccine-related R&D in Canada, as compiled from survey responses by researchers and representatives of relevant organizations and funding agencies involved in vaccine research across the country. Recommendations from the CIHR report – which help to address the specific challenges presented in Section 3.6, Table 3.3 – are incorporated (in bold) within the general recommendations presented below.

#### Federal/Provincial/Territorial (F/P/T) Recommendations

1. In view of the unique (complex, lengthy, risky and costly) nature of the vaccine R&D environment, F/P/T government policy approaches to developing an efficient vaccine marketplace should aim to encourage long-term investment in R&D in the vaccine sector. These initiatives should assist in sustaining and enhancing vaccine research in Canada, thus driving future innovation in the development of life-saving (preventive) and therapeutic vaccine technologies.
2. Government officials at all F/P/T levels need to establish and promote policies that will expand incentives for vaccine research by removing barriers for developers/manufacturers to risk investment capital to discover vaccines needed in Canada and worldwide. While such incentives are particularly critical for smaller, Canadian-based vaccine companies, they will also promote Canadian research initiatives at major (multinational) vaccine developers.
3. Both “push” and “pull” investment incentives should be further developed to more aggressively encourage future investment in vaccine R&D, i.e. by effectively decreasing research costs and increasing vaccine demand, respectively.

- Current “push” strategies, including grant funding and tax incentive programs (e.g. SR&ED), should be expanded and/or enhanced to attract additional funding for vaccine research in Canada. Specific recommendations for “push” mechanisms include the following:
  - i. The federal government should continue to fund vaccine R&D primarily through the CIHR (with supplementary funding through other F/P/T funding agencies), in collaboration with industry and the PHAC;
  - ii. Canadian funding agencies should provide additional infrastructure awards (e.g. to fund state-of-the-art laboratories and equipment and/or specific operating costs), particularly for emerging vaccine companies and clinical trial evaluation centres, i.e. to increase their stability and competitiveness, and to indirectly contribute to projects funded by other organizations;
  - iii. **The CIHR should continue to support basic research – particularly in the areas of microbiology, immunology, and vaccinology – to facilitate advances in preventing/treating diseases for which vaccines are not yet available. Development of strategic vaccine research initiatives (e.g. focused on two to three areas in which Canada can become a world leader) should also be considered;**
  - iv. **The CIHR and affiliated partners should support behavioral, social and ethics research, including public perceptions concerning vaccines and best methods to educate the public regarding the safety, efficacy and value of vaccination;**
  - v. **To facilitate the advance of vaccine discoveries from basic science towards Phase I/II clinical trials, a transitional GMP facility (as well as guidelines) should be established. New funding mechanisms should also be created (e.g. by CIHR and potential partners) to help bridge the gap between basic science and clinical trials, i.e. a separate funding envelope should be considered to support translational research with a view towards vaccine commercialization; and**
  - vi. **The CIHR should provide additional and ongoing support for preclinical and post-licensure vaccine trials, e.g. to address research questions that are of greater interest to public health and governments officials than to vaccine manufacturers.**
- “Pull” strategies should also be advanced to promote investment in vaccine R&D (via strategic procurement policies, guaranteed-purchase agreements and/or stockpiling) to help offset market uncertainty, e.g. for vaccines targeting diseases linked to poverty, bioterrorism or other emerging threats, in Canada or abroad.

## Stakeholder Recommendations

4. To maintain and build upon the recently renewed interest in vaccine R&D, it is essential that stakeholders at all levels, including researchers, government agencies, public health authorities, industry representatives, and investors seek to align common interests in fostering long-term innovation in the vaccine sector.
5. To maximize the health benefits of novel vaccines for all Canadians – and to successfully develop new vaccines that target diseases endemic in the developing world (e.g. malaria, tuberculosis, HIV/AIDS) – it will be critical to cultivate long-term collaborative research-oriented agreements among relevant stakeholders, both within Canada and on the international stage.
6. To better coordinate vaccine research efforts in Canada, the CIHR and its partners should:
  - Organize workshops to facilitate communication/collaboration among vaccine researchers and stakeholders, i.e. to identify gaps and set vaccine research priorities;
  - Foster linkages among all stakeholders, e.g. groups such as the CIHR, PHAC, Health Canada, industry and others could work jointly (as a collaborative consortium) to identify sources of infection and morbidity, and determine the best approach to deal with each disease or potential threat; and
  - Establish a network of centres of excellence for vaccine R&D, ideally as a formal, integrated, vaccine research centre with a full spectrum of research capabilities encompassing basic science, clinical trials, and population and public health research.
7. Partnerships across Canadian stakeholder groups (e.g. including funding organizations, industry, academic institutions, and governments) – established primarily to drive vaccine R&D – should also be leveraged to promote potential new sources of funding, while encouraging academic and corporate scientists to focus their research activities.
8. To help bridge the gap between basic science and Phase I/II clinical trials (e.g. to gain insight regarding preclinical vaccine development), academic researchers should partner with industry, potentially through an industry-funded strategic initiative under the direction of the CIHR (see “push” strategies iii & v of Recommendation 3 above).
9. In the specific context of clinical research, Canadian researchers must strive to remain internationally competitive to continue to attract industry sponsored pre-licensure vaccine clinical trials to Canada.
  - To ensure ongoing attractiveness to large international companies, clinical trialists should consistently provide excellent value, i.e. by demonstrating outstanding quality and efficiency (including rapid contract approval and ethics review) in executing clinical studies.
  - To help build an international reputation, Canadian vaccine clinical study sites should meet the research standards of all major regulatory agencies, e.g. Health Canada, the U.S. FDA, and the European Medicines Agency (EMA).

## 3.10 References

- <sup>1</sup> World Health Organization (WHO) Weekly Epidemiological Record, No. 19, 2006, 81, p189-196.
- <sup>2</sup> The Value of Vaccines: Two Centuries of Unparalleled Medical Progress, International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), May 2008.
- <sup>3</sup> French, M. Vaccines for the 21st Century, Taking Canada to the Next Level, Canadian Institutes of Health Research (CIHR) Institute of Infection and Immunity, 2008.
- <sup>4</sup> Kieny, M.P., Excler, J.-L., and Girard, M. Research and Development of New Vaccines Against Infectious Diseases, American Journal of Public Health, Vol. 94, No. 11, 2004, p1931-1935.
- <sup>5</sup> Almond, J. Vaccine Renaissance (Foreword), Nature, Vol. 5, July 2007, p478-481.
- <sup>6</sup> Behr, M. Evil Synergy Between HIV and Tuberculosis Dictates Need for More Effective Vaccine, 8th Canadian Immunization Conference, Toronto, December 2, 2008, INFO-Vaccine, Tuesday Edition; [www.phac-aspc.gc.ca/cnic-ccni/2008/pdf/info-vac3-eng.pdf](http://www.phac-aspc.gc.ca/cnic-ccni/2008/pdf/info-vac3-eng.pdf).
- <sup>7</sup> Landry, S. and Heilman, C. Future Directions in Vaccines: The Payoffs of Basic Research, Health Affairs, 2005, Vol. 24, No. 3, p758-769.
- <sup>8</sup> Rogers, T. Risky Business: Building, Managing, and Working in High-Containment Laboratories, BioBusiness December 2008 / January 2009, p25-30.
- <sup>9</sup> Coleman, M., Sangruejee, N., Zhou, F., and Chu, S. Factors Affecting U.S. Manufacturers' Decisions to Produce Vaccines, Health Affairs, 2005, Vol. 24, No. 3, p635-642.
- <sup>10</sup> Thomas, J. Unmet Ethical Concerns of the Proposed Preventive HIV Vaccine Trials in India, Indian J Med Ethics. 2004;12(3); [www.ijme.in/123vp087.html](http://www.ijme.in/123vp087.html).
- <sup>11</sup> Salinsky, E., and Werble, C. The Vaccine Industry: Does It Need a Shot in the Arm? National Health Policy Forum, Background Paper, January 2006.
- <sup>12</sup> From Polio to Cancer: The New Face of Vaccine Technology, BIOTECCanada Vaccine Industry Committee (VIC), BIOTECCanada, Spring 2008.
- <sup>13</sup> The Value of Vaccines: 2 – Yesterday, Today, Tomorrow, Aventis Pasteur Limited, 2002.
- <sup>14</sup> The Unique Challenges of Vaccine Research, Development and Manufacture, International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), Influenza Vaccine Supply International Task Force, June 2008.
- <sup>15</sup> The Value of Vaccines: Two Centuries of Unparalleled Medical Progress, International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), May 2008.
- <sup>16</sup> Plotkin, S. Why Certain Vaccines Have Been Delayed or Not Developed at All, Health Affairs, 2005, Vol. 24, No. 3, p631-634.
- <sup>17</sup> Werble, C. Vaccines Enter the New Age of Adjuvants, The RPM report, September 2006.
- <sup>18</sup> Vaccine Renaissance, An Interview with Dr. Gary Nable, Director of the Vaccine Research Center, National Institute for Allergy and Infectious Disease, National Institutes of Health; [www.ngpharma.com/pastissue/article.asp?art=271782&issue=225](http://www.ngpharma.com/pastissue/article.asp?art=271782&issue=225), accessed June 24, 2008.
- <sup>19</sup> Almond, J. Vaccine Renaissance (Foreword), Nature, Vol. 5, July 2007, p478-481.
- <sup>20</sup> Scheifele, D., Halperin, S., Ward, B, and Duval, B. The Challenges Facing Canadian Trialists in an Increasingly Competitive Global Market: What Can Be Done to Remain Competitive?, Can J. Infect Dis Med Microbiol., Vol. 18, No. 3, May/June 2007, p205-208.
- <sup>21</sup> Law, B. Vaccine Safety Pre and Post Licensing, 2005/2006 Public Health Works Speaker Series, April 18, 2006.
- <sup>22</sup> Burt, D. What Drives New Vaccine Development: Who Gets to Decide What Conditions are Targeted? 8th Canadian Immunization Conference, Toronto, December 1, 2008.
- <sup>23</sup> Orenstein, W. A., Douglas, et al. Immunizations in the United States: Success, Structure and Stress, Health Affairs, 2005, Vol. 24 (3), p599-610.
- <sup>24</sup> Michaud, C., Murray, C., Bloom, B. Burden of Disease – Implications for Future Research, JAMA Vol. 285, No. 5, Feb. 7, 2001.
- <sup>25</sup> Institute of Health Economics (IHE), Economics of Childhood Immunizations in Canada: Data Book, May 2007.
- <sup>26</sup> Blouin, C. Issues and Challenges with New Vaccines, Perspective from the Industry, Canadian Public Health Association (CPHA) Conference, September 2007.
- <sup>27</sup> Structural Shift: Promising Yet Challenging New Markets for Vaccines, Mercer Management Consulting, 2006.

- <sup>28</sup> Parrington, M. Vaccines in the Pipeline, Canadian Public Health Association (CPHA) Conference, September 2007.
- <sup>29</sup> Orenstein, W. A., Douglas, et al. Immunizations in the United States: Success, Structure and Stress, Health Affairs, 2005, Vol. 24 (3), p599-610.
- <sup>30</sup> Merck Congratulates Nobel Laureate for Research Leading to Development of Gardasil, Merck Canada Press Release, October 7, 2008.
- <sup>31</sup> Colucci, R., Hryniuk, W., Savage, C. HPV Vaccination Programs in Canada – Are We Hitting the Mark? In: Report Cancer in Canada, 2008, p6-9.
- <sup>32</sup> Professor Harald zur Hausen, Professor Emeritus and Recent Chairman and Scientific Director, German Cancer Research Centre, Heidelberg, Germany, 2008 Gairdner International Awardee; [www.gairdner.org/awards/awardees2/2008/2008awarde/haraldzurh](http://www.gairdner.org/awards/awardees2/2008/2008awarde/haraldzurh).
- <sup>33</sup> Overview of the Clinical Trial Application Process; Health Canada; [www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clin/cta\\_overview-eng.php](http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clin/cta_overview-eng.php).
- <sup>34</sup> French, M. Vaccines for the 21st Century, Taking Canada to the Next Level, Canadian Institutes of Health Research (CIHR) Institute of Infection and Immunity, 2008.
- <sup>35</sup> EP Vantage Therapeutic Focus - Vaccines Set for Rapid Growth, PartneringNEWS, Special Edition for BioPharm America Sept. 9-10 2008, published June 30, 2008.
- <sup>36</sup> BIOTECCanada, Issue Brief, Sustainable Funding for Vaccines in Canada, September 2008.
- <sup>37</sup> Structural Shift: Promising Yet Challenging New Markets for Vaccines, Mercer Management Consulting, 2006.
- <sup>38</sup> 13th Annual Report, Top 10 Pipelines: Novartis, Best Vaccines Pipeline, MedAdNews Vol. 28, No. 1, January 2009.
- <sup>39</sup> Wyeth Pharmaceuticals Development Pipeline (as of October 16, 2008); [www.wyeth.com](http://www.wyeth.com).
- <sup>40</sup> Canadian Vaccines Leader, GlaxoSmithKline Canada, 2008.
- <sup>41</sup> First North American Clinical Trials with GSK's Candidate Pre-Pandemic Vaccine to Start, GlaxoSmithKline Press Release, August 3, 2007.
- <sup>42</sup> The Value of Vaccines: 2 – Yesterday, Today, Tomorrow, Aventis Pasteur Limited, 2002.
- <sup>43</sup> BioBusiness Magazine, Newsletter Number 15, May 2008.
- <sup>44</sup> A Shot in the Arm to Fight Skin Cancer, sanofi pasteur Press Release, January 15, 2009.
- <sup>45</sup> 13th Annual Report, Top 10 Pipelines: Novartis, Best Vaccines Pipeline, MedAdNews Vol. 28, No. 1, January 2009.
- <sup>46</sup> New Data Show Menveo(TM) to be the First Quadrivalent Meningococcal Vaccine to Provide Immunogenicity in Infants, Novartis Press Release, January 9, 2008.
- <sup>47</sup> Almond, J. Vaccine Renaissance, Nature Reviews, Microbiology, July 2007, Volume 5, p478-481.
- <sup>48</sup> EP Vantage Therapeutic Focus - Vaccines Set for Rapid Growth, PartneringNEWS, Special Edition for BioPharm America Sept. 9-10 2008, published June 30, 2008.
- <sup>49</sup> Frizell, A. Sanofi Buys Acambis for £276 Million, The Independent, July 26, 2008.
- <sup>50</sup> Arnst, C. Pfizer CEO: Wyeth Takeover Will be Different, BusinessWeek, January 26, 2009.
- <sup>51</sup> Canada's Vaccine Industry Committee, Leadership in Global Health, BIOTECCanada, 2008.
- <sup>52</sup> PlantForm Corporation, Subunit Vaccines; [www.plantformcorp.com/products/sub-vac.html](http://www.plantformcorp.com/products/sub-vac.html).
- <sup>53</sup> Amorfix Life Sciences Develops Two Vaccines That Extend Life in Amyotrophic Lateral Sclerosis (ALS) Animal Model, Amorfix Life Sciences Ltd. News Release, October 9, 2007.
- <sup>54</sup> Generex Biotechnology, Corporate Fact Sheet, Q1-2009; [www.generex.com/index.php](http://www.generex.com/index.php).
- <sup>55</sup> Research & Development, TheraCarb Inc.; [www.theracarb.com/research.php](http://www.theracarb.com/research.php).
- <sup>56</sup> French, M. Vaccines For the 21st Century, Taking Canada to the Next Level, Canadian Institutes of Health Research (CIHR) Institute of Infection and Immunity, 2008.
- <sup>57</sup> The Pan-Provincial Vaccine Enterprise, Overview; [www.vido.org/news/prevent/index.php](http://www.vido.org/news/prevent/index.php).
- <sup>58</sup> Pan-Provincial Vaccine Enterprise (PREVENT) Announces Board Members, Vaccine Targets, Vaccine Infectious Disease Organization (VIDO) Press Release, May 2, 2008.
- <sup>59</sup> Potter, A. The Pan-Provincial Vaccine Enterprise (PREVENT) – A New Paradigm for Accelerating Vaccine Commercialization, 8th Canadian Immunization Conference, Toronto, December 2, 2008.
- <sup>60</sup> Gemmill, I. The Canadian Immunisation System, 2008 Canadian Pediatric Society (CPS) Immunisation Provider Training Course, Toronto, November 28, 2008.

- <sup>61</sup> Sanofi Pasteur Donates Nearly \$4 Million to Fund Vaccine Research that is Unique in Canada, sanofi pasteur Press Release, February 7, 2008.
- <sup>62</sup> Plotkin, S. Vaccines: Past, Present and Future, *Nature Medicine Supplement*, Vol. 11, No. 4, April 2005, ps5-s11.
- <sup>63</sup> Vaccine Renaissance, An Interview with Dr. Gary Nable, Director of the Vaccine Research Center, National Institute for Allergy and Infectious Disease, National Institutes of Health; [www.ngpharma.com/pastissue/article.asp?art=271782&issue=225](http://www.ngpharma.com/pastissue/article.asp?art=271782&issue=225), accessed June 24, 2008.
- <sup>64</sup> Rappuoli, R. Bridging the Knowledge Gaps in Vaccine Design, *Nature Biotechnology*, Volume 25, No. 12, December 2007, p1361-1366.
- <sup>65</sup> Diaz-Mitoma, F. Introduction and Overview of New Vaccines: New Biotechnology, Canadian Public Health Association (CPHA) Conference, September 2007.
- <sup>66</sup> From Polio to Cancer: The New Face of Vaccine Technology, BIOTECCanada Vaccine Industry Committee (VIC), BIOTECCanada, Spring 2008.
- <sup>67</sup> Landry, S. and Heilman, C. Future Directions in Vaccines: The Payoffs of Basic Research, *Health Affairs*, 2005, Vol. 24, No. 3, p758-769.
- <sup>68</sup> Poland, G.A., Murray, D. Bonilla-Guerrero, R. Science, Medicine, and the Future: New Vaccine Development, *British Medical Journal* 2002; 324; p1315-1319.
- <sup>69</sup> Rappuoli, R. Bridging the Knowledge Gaps in Vaccine Design, *Nature Biotechnology*, Volume 25, No. 12, December 2007, p1361-1366.
- <sup>70</sup> Poland, G.A., Murray, D. Bonilla-Guerrero, R. Science, Medicine, and the Future: New Vaccine Development, *British Medical Journal* 2002; 324; p1315-1319.
- <sup>71</sup> Cancer Vaccine Fact Sheet, National Cancer Institute (NCI); [www.cancer.gov/cancertopics/factsheet/cancervaccine/print?page=&keyword](http://www.cancer.gov/cancertopics/factsheet/cancervaccine/print?page=&keyword).
- <sup>72</sup> Cashman, N. Protein Misfolding-Specific Epitopes – New Targets for Immunotherapy, 8th Canadian Immunization Conference, December 2, 2008, Toronto.
- <sup>73</sup> Plotkin, S. Vaccines: Past, Present and Future, *Nature Medicine Supplement*, Vol. 11, No. 4, April 2005, ps5-s11.
- <sup>74</sup> Landry, S. and Heilman, C. Future Directions in Vaccines: The Payoffs of Basic Research, *Health Affairs*, 2005, Vol. 24, No. 3, p758-769.
- <sup>75</sup> Plotkin, S. Vaccines: Past, Present and Future, *Nature Medicine Supplement*, Vol. 11, No. 4, April 2005, ps5-s11.
- <sup>76</sup> Picard, A. BC Babies Get 6-in-1 Vaccine, *The Globe and Mail*, February 27, 2009.
- <sup>77</sup> Plotkin, S. Vaccines in the 21st Century, In: *Lifesaving Vaccines*, Journal USA, Global Issues: Vol. 12, No. 3, March 2007, p29-30.
- <sup>78</sup> Werble, C. Vaccines Enter the New Age of Adjuvants, *The RPM Report*, September 2006.
- <sup>79</sup> Glenn, G. and O'Hagan, D. Adjuvants: Progress, Regress and Pandemic Preparedness, *Expert Rev. Vaccines*, Vol. 6 (5), 2007, p651-652.
- <sup>80</sup> Werble, C. Vaccines Enter the New Age of Adjuvants, *The RPM Report*, September 2006.
- <sup>81</sup> New Adjuvants Helping Vaccines Work Better, Industrial Research Limited, 2008.
- <sup>82</sup> Babiuk, L. Novel Adjuvants and Delivery Systems for Improving Vaccines, 8th Canadian Immunization Conference, December 2, 2008, Toronto.
- <sup>83</sup> Igietseme, J., Eko, F. et al. Combination Vaccines: Design Strategies and Future Trends, *Expert Rev. Vaccines*, Vol. 5 (6), 2005, p739-745.
- <sup>84</sup> Plotkin, S. Vaccines in the 21st Century, In: *Lifesaving Vaccines*, Journal USA, Global Issues: Vol. 12, No. 3, March 2007, p29-30.
- <sup>85</sup> Landry, S. and Heilman, C. Future Directions in Vaccines: The Payoffs of Basic Research, *Health Affairs*, 2005, Vol. 24, No. 3, p758-769.
- <sup>86</sup> Plotkin, S. Vaccines: Past, Present and Future, *Nature Medicine Supplement*, Vol. 11, No. 4, April 2005, ps5-s11.
- <sup>87</sup> Diaz-Mitoma, F. Introduction and Overview of New Vaccines: New Biotechnology, Canadian Public Health Association (CPHA) Conference, September 2007.
- <sup>88</sup> Almond, J. Vaccine Renaissance, *Nature Reviews, Microbiology*, July 2007, Volume 5, p478-481.

- <sup>89</sup> Scheifele, D., Halperin, S., Ward, B., and Duval, B. The Challenges Facing Canadian Trialists in an Increasingly Competitive Global Market: What Can Be Done to Remain Competitive?, *Can J. Infect Dis Med Microbiol.*, Vol. 18, No. 3, May/June 2007, p205-208.
- <sup>90</sup> The Value of Vaccines: 2 – Yesterday, Today, Tomorrow, Aventis Pasteur Limited, 2002.
- <sup>91</sup> Nascimento, E., Variation Biotechnologies Inc., Personal Communication, February 2009.
- <sup>92</sup> Immunovaccine (IMV) Signs Agreement with National Institutes of Health to Explore Vaccines for HIV and Malaria, ImmunoVaccine Technologies Inc. Press Release, February 25, 2009.
- <sup>93</sup> Variation Biotechnologies – Partners; [www.variationbiotech.com/vbi\\_partners.html](http://www.variationbiotech.com/vbi_partners.html).
- <sup>94</sup> Canadian Foundation for Innovation Invests in Research Infrastructure, *Biotechnology Focus*, January 2009.
- <sup>95</sup> Current Investors, Platform Corporation; [www.platformcorp.com/About Us/current-invst.html](http://www.platformcorp.com/About Us/current-invst.html).
- <sup>96</sup> Brenders, P. Collaboration for Solutions, Presentation at BIO Chicago, April 2006.
- <sup>97</sup> French, M. Vaccines For the 21st Century, Taking Canada to the Next Level, Canadian Institutes of Health Research (CIHR) Institute of Infection and Immunity, 2008.
- <sup>98</sup> Scheifele, D., Halperin, S., Ward, B., and Duval, B. The Challenges Facing Canadian Trialists in an Increasingly Competitive Global Market: What Can Be Done to Remain Competitive?, *Can J. Infect Dis Med Microbiol.*, Vol. 18, No. 3, May/June 2007, p205-208.
- <sup>99</sup> Bailey, I. Federal Budget Impact: Nobel Scientist Criticizes Tories over Funding, *The Globe and Mail*, January 31, 2009.
- <sup>100</sup> Werble, C. Vaccine Incentives in the Obama Administration, *The RPM Report*, January 12, 2009.
- <sup>101</sup> Scientific Research and Experimental Development (SR&ED) Tax Incentive Program, [www.cra-arc.gc.ca/sred/](http://www.cra-arc.gc.ca/sred/).
- <sup>102</sup> Canadian Biotech Jobs and Innovation at Risk As 50% of Firms Report Cash Shortage, *Biotechnology Focus*, February 2009.
- <sup>103</sup> Grabowski, H. Encouraging the Development of New Vaccines, *Health Affairs*, 2005, Vol. 24, No. 3, p697-700.
- <sup>104</sup> The Unique Challenges of the Vaccine Market and Vaccination Policies, International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), Influenza Vaccine Supply International Task Force, June 2008.
- <sup>105</sup> Canada's New Government Doubles Its Contribution to the Global Efforts to Develop and Produce Vaccines for Diseases in Developing Countries, Press Release, Feb. 9, 2007; [www.fin.gc.ca/news07/07-011e.html](http://www.fin.gc.ca/news07/07-011e.html).
- <sup>106</sup> Scheifele, D., Halperin, S., Ward, B., and Duval, B. The Challenges Facing Canadian Trialists in an Increasingly Competitive Global Market: What Can Be Done to Remain Competitive?, *Can J. Infect Dis Med Microbiol.*, Vol. 18, No. 3, May/June 2007, p205-208.
- <sup>107</sup> Allen, B. Tailored to Fit, Strategic Public Procurement Stimulates the Economy, drawn from Highlights of Discussions and Record of Proceedings – Consultation Roundtable, Summit April/May 2006, p10.
- <sup>108</sup> Allen, B. Putting the Squeeze on Procurement: Procurement Policy As a Lever for Innovation, Science and Environment, ISE Chapter 11, *Canadian Policies and Performance 2007-08*, Ed. Doern, B. McGill-Queen's University Press, p219-239.
- <sup>109</sup> Research Canada: An Alliance For Health Discovery, Understanding the Functional Innovation System: Achieving a Critical Balance, Submission to House of Commons Standing Committee on Finance, August 15, 2008.
- <sup>110</sup> Innovation Nation, Department for Innovation, Universities & Skills, Presented to Parliament by the Secretary of State for Innovation, Universities & Skills, the Chancellor of the Exchequer and the Secretary of State for Business Enterprise and Regulatory Reform by Command of Her Majesty, March 2008.
- <sup>111</sup> How Canada Performs: A Report Card on Canada, The Conference Board of Canada, 2008; [www.conferenceboard.ca/HCP/default.aspx](http://www.conferenceboard.ca/HCP/default.aspx).
- <sup>112</sup> Scheifele, D., Halperin, S., Ward, B., and Duval, B. The Challenges Facing Canadian Trialists in an Increasingly Competitive Global Market: What Can Be Done to Remain Competitive?, *Can J. Infect Dis Med Microbiol.*, Vol. 18, No. 3, May/June 2007, p205-208.
- <sup>113</sup> French, M. Vaccines For the 21st Century, Taking Canada to the Next Level, Canadian Institutes of Health Research (CIHR) Institute of Infection and Immunity, 2008.

<sup>114</sup> Butler-Jones, D. The Health of the Public Is the Foundation of Prosperity: the Work of the Public Health Agency of Canada at Home and Around the World, CMAJ, October 23, 2007, 177 (9), p1063-1064.

<sup>115</sup> Cashman, N. Protein Misfolding-Specific Epitopes – New Targets for Immunotherapy, 8th Canadian Immunization Conference, December 2, 2008, Toronto.

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