

Preparing for the Pandemic Vaccine Response

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Summary of Significant Changes:

- The scope of the Annex has been expanded to provide a more comprehensive tool for health sector planners and, by doing so, support a Pan-Canadian approach to the operational issues identified as part of a pandemic vaccine strategy. A Background and Assumptions section provides information on Canada's current pandemic influenza vaccine contract with a domestic manufacturer and key assumptions used in planning. Also key cross-cutting issues have been addressed.
- The "priorities for vaccination" listing has been removed and replaced with a discussion of when prioritization might be needed. Included are considerations in the event that prioritization is needed and the implications for planners, with special emphasis on the requirement for flexibility in operational plans.
- The status of federal and national preparedness activities with respect to the pandemic vaccine strategy is summarized along with key actions for planners.

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1.0 Introduction

1.1 Purpose of the Annex

Immunization with a safe and effective pandemic vaccine has always been considered the cornerstone of the health response to pandemic influenza in Canada. The federal government has made a commitment to secure enough pandemic vaccine for every person in Canada in order to help prevent illness due to the pandemic virus. In addition, the federal government is committed to working with the provincial and territorial governments to ensure that the pandemic vaccine is made available to as many people as possible as quickly as possible. There are many challenges associated with this goal. This annex identifies those challenges that are currently being addressed at the pan-Canadian and federal level with an eye to improving general awareness and specific planning activities across Canada.

This version of Annex D replaces the version first published with the Canadian Pandemic Influenza Plan for the Health Sector (CPIP) in 2004 and subsequently in 2006. The previous version consisted mainly of a priority list for planners to use when considering how to deliver a priority-based immunization program. This guidance was intended to help focus operational plans geared towards identifying, accessing and immunizing subgroups of the population at the time of the pandemic. The provision of a numbered priority list may have unintentionally served to distract from operational planning activities. This version of Annex D is intended to focus on the need for flexible response plans and to re-emphasize that prioritization decisions (if required) will need to be based, in part, on data that will not be available until the pandemic virus has started circulating. Although this fact was identified in the previous version of the annex and in public communications, it was decided that removal of the priority list was the best way to shift emphasis. This decision should not necessitate any alteration to operational planning activities, which should, for the most part, be independent of the order in which population subgroups might be accessed.

Annex A (*Planning Checklists*) of the CPIP provides a preliminary list of planning activities for the pandemic vaccine program that were developed to facilitate planning at provincial and territorial (P/T) and local levels. The purpose of this annex (Annex D) is to ensure that all pandemic planners and potential responders are aware of both the preparations for the pandemic vaccine program that are under way at the federal and pan-Canadian level and the key cross-cutting planning issues. A secondary purpose is to provide information to members of the public who are seeking additional information regarding the pandemic vaccine program.

1.2 Background

With the creation of the pandemic readiness vaccine contract in 2001, Canada took a large step forward on the world stage in terms of pandemic preparedness. This investment clearly established the pandemic vaccine strategy as the cornerstone of the response to pandemic influenza in Canada and highlighted the need for attention to the issue internationally. Since

the establishment of this 10-year contract with a domestic manufacturer of influenza vaccine, planning has advanced on all fronts. However, the need for a safe and effective pandemic vaccine as early as possible in the global outbreak has remained the ultimate means to achieve the goals of reducing morbidity, mortality and societal disruption due to an influenza pandemic.

Canada's public health community is reasonably well integrated, each jurisdiction being familiar with its respective roles and responsibilities. In general, provision of services occurs primarily at the regional level with P/T governments overseeing, advising and funding these services. The federal government is responsible for ensuring that services are in place for specific populations, such as First Nations on reserve, the military and those incarcerated in federal penitentiaries. The federal government also has a role in coordinating and supporting initiatives for which there is a desire for national consistency across Canada or for which a single national point of contact is advantageous. Therefore, both orders of government have a role and responsibilities that pertain to a pandemic vaccine program.

1.3 Assumptions

In order to facilitate nationwide planning for an event that in many ways is unpredictable, it is useful to use a common set of assumptions as a starting point. The Pandemic Influenza Committee (PIC) has included a set of assumptions in the Background section of the CPIP. The following subset of the complete list is presented here because these assumptions have specific implications for the pandemic vaccine program in Canada:

- The next pandemic will first emerge outside of Canada.

Implication: The virus to be used for the pandemic vaccine will be isolated outside of Canada and sent to the manufacturer as a "primary seed lot". The government does not have control over when this will occur.

- The next pandemic virus will be present in Canada within three months after it emerges in another part of the world, but it could be much sooner because of the volume and speed of global air travel.

Implication: There will likely be cases of pandemic influenza in Canada prior to the availability of vaccine (see section 3.1 for more details regarding vaccine manufacturing timelines). While the extent of spread in Canada cannot be predicted, the vaccine may not be available until after the first wave of illness in this country.

- The first peak of illness in Canada could occur within two to four months after the virus arrives here. The first peak in mortality is expected to be approximately one month after the peak in illness.

Implication: There will likely be deaths due to pandemic influenza in Canada before the availability of vaccine.

- The impact of the pandemic in terms of severity, age distribution and extent of spread may be different from annual influenza; however, this will not be known until the novel virus starts spreading efficiently in the human population.

Implication: It will not be possible to identify in advance of the pandemic the individual risk factors for poor outcome of infection with the specific pandemic influenza virus.

- Individuals who recover from illness caused by the pandemic strain will be immune to further infection by that strain.

Implication: Those with a history of illness attributed to the pandemic virus may be considered at lower priority for immunization if prioritization is necessary. Criteria for determining who might be immune at the time the vaccine becomes available in Canada would need to be developed and consistently applied. It would not be feasible or advisable to use laboratory testing to identify all these individuals.

In addition, the Pandemic Vaccine Working Group of PIC suggests using the following vaccine-specific assumptions:

- A pandemic vaccine will become available in time to have an effect on the impact of the pandemic in Canada. The extent of the effect will largely depend on the timing of vaccine availability in comparison to pandemic activity in Canada.
- Two doses of vaccine will be needed in order to optimize protection (i.e. more protection will be provided by a second dose of pandemic vaccine). The two doses would be given approximately one month apart.
- Vaccine efficacy estimates developed before population distribution (e.g. in clinical trials) will translate into equal vaccine effectiveness once used in the general population.
- Because of cross-protection, a vaccine developed from a strain isolated early in the pandemic will still be beneficial should the pandemic virus “drift” over the course of the pandemic.
- The new pandemic vaccine is not likely to be 100% effective, but even a vaccine with relatively low efficacy (e.g. 30%) will help curb the effect of the pandemic.
- There will be limited information regarding vaccine safety before the rollout of the immunization campaign.
- Concern regarding vaccine safety and reactogenicity will likely be inversely proportional to the severity of the pandemic in Canada.
- Depending on the timing of the pandemic and availability of the pandemic vaccine, seasonal influenza immunization programs may not be initiated or completed, as the pandemic vaccine program is the priority.

2.0 The Pandemic Vaccine Program

2.1 Challenges

Universal vaccination has the advantage of creating a population that is highly resilient to the pandemic virus because of both individual protection and potential herd immunity. This requires a relatively simple intervention (i.e. one or two injections) over a relatively short period of time. While public health authorities are well versed in delivering mass immunization programs, challenges regarding the pandemic influenza vaccine strategy remain.

One of the key challenges is planning for, and successfully managing, the unprecedented uncertainty that will characterize the pandemic vaccine program. Those involved in pandemic planning are well aware that it is not possible to predict the timing, severity, viral characteristics, virus strain or epidemiology of an influenza pandemic in advance. Furthermore, there are the uncertainties regarding when a pandemic vaccine might be available, what the dose and

schedule will be, how effective it will prove to be and what the safety profile will be when the vaccine is used for the entire population. The reaction of the public to both the pandemic and the new pandemic vaccine also cannot be determined in advance. The severity of the pandemic, timing of vaccine availability during the pandemic, and real and perceived safety profile of the vaccine will likely be key drivers of the public reaction. This reaction will influence demand for the vaccine and consequently communication regarding the organization and implementation of the vaccine program.

Obviously, there are many communication issues that will need to be addressed as the pandemic evolves globally, and arrives and spreads across Canada. However, the expectation for, and availability of, a brand new pandemic vaccine for the Canadian population will create additional communication challenges. Since the entire population cannot be immunized simultaneously there will be a need to determine where those first batches of vaccine are sent and who gets the injections first.

There are several potential “rate-limiting steps”^{*} in the delivery of a population-wide pandemic vaccine program. If the new vaccine, which will become available in batches, were to be produced rapidly in sufficient batch sizes to allow for concurrent national distribution, then the rate-limiting step would shift closer to the front lines, where operational issues will ultimately determine the rate of administration to the public. However, if the vaccine supply were insufficient to meet the national vaccine administration rate (estimated on the basis of feedback from planners in advance of the pandemic) there would be a need to prioritize specific groups of people to receive the vaccine before others. Determining priority lists for immunization at the time of the pandemic will be challenging, because several factors will need to be considered, and it is possible that key information (e.g. comprehensive epidemiological data applicable to Canada) may be lacking. The rationale and measures taken to prioritize the supply will need to be communicated to the public.

2.2 Federal and F/P/T Preparations

As stated in the CPIP, the objectives of the pandemic vaccine program are as follows:

- To provide a safe and effective vaccine program to all Canadians as quickly as possible.
- To allocate, distribute and administer vaccine as rapidly as possible to the appropriate groups of people.
- To monitor the safety and effectiveness of immunization programs.

The following tables summarize the federal and national preparations to meet these objectives. In order to do this it will be critical for P/T and local plans to incorporate nationally agreed upon principles and recommendations, and translate these into comprehensive operational plans.

Legend for Tables:	
FPT = Federal/Provincial/Territorial	PHAC = Public Health Agency of Canada
HC = Health Canada	P/T = Provincial/Territorial
NACI = National Advisory Committee on Immunization	VVTAC = Vaccine Vigilance Technical Advisory Committee
PIC = Pandemic Influenza Committee	WG = Working Group

^{*} A rate-limiting step is a step in a sequential process that may be slow compared with those steps that follow but nonetheless must be completed first. An example of a rate-limiting step for the pandemic vaccine program could be the delivery of the vaccine to a remote location.

Table 1. Objective: provision of a safe and effective vaccine program to all Canadians as quickly as possible

Focus	Lead Group (i.e., point of contact for these actions)	Actions	Status
Pandemic vaccine production readiness	<i>Federal:</i> Centre for Immunization and Respiratory Infectious Diseases, PHAC	<ul style="list-style-type: none"> ▪ Maintain and revise as necessary vaccine readiness contract with manufacturer. ▪ Monitor status of clinical trials from contracted and other manufacturers to assess and optimize use of new technologies. 	<ul style="list-style-type: none"> ▪ Contract in place until March 2011, currently based on egg-based technology, ensures that domestic manufacturer can initiate production of pandemic vaccine at any time. ▪ Manufacturer has exceeded capacity target of 8 million monovalent doses per month. This capacity may further increase if use of new adjuvant permits a lower antigen content (e.g. 3.8 ug as opposed to 15 ug per dose); however two-dose schedule will likely be necessary.
Timely review of pandemic vaccine candidate(s)	<i>Federal:</i> Biologics and Genetic Therapies Directorate, HC	<ul style="list-style-type: none"> ▪ Ensure that mechanisms are in place that can be used to review and authorize a safe and efficacious vaccine for use in Canada within the shortest time frame possible. ▪ Ensure that trained staff are in place for the timely testing and release of pandemic vaccine lots after authorization for use. 	<ul style="list-style-type: none"> ▪ HC is prepared to perform an expedited review of any New Drug Submission for a pandemic vaccine. ▪ HC has examined other access mechanisms, including the Special Access Program, the use of interim orders and a clinical trial, to facilitate timely access to pandemic vaccine.
Prototype vaccine production to “test system” and potentially expedite review process	<i>Federal:</i> Centre for Immunization and Respiratory Infectious Diseases, PHAC	<ul style="list-style-type: none"> ▪ Funding allocated by federal government for development of prototype (“mock”) vaccines to facilitate testing and streamlining of the pandemic vaccine strategy. ▪ Meetings with contracted domestic manufacturer to monitor progress and finalize details. 	<ul style="list-style-type: none"> ▪ H5N1 adjuvanted vaccine being produced in Canada has been allocated to this initiative. ▪ Potential vaccine for New Drug Submission.

Focus	Lead Group (i.e., point of contact for these actions)	Actions	Status
	Biologics and Genetic Therapies Directorate, HC	<ul style="list-style-type: none"> ▪ Inspection of facilities and development of methods to test vaccine. ▪ Review Clinical Trial Applications to ensure that they are in accordance with Part C Division 5 of the <i>Food and Drug Act</i> and Regulations. 	<ul style="list-style-type: none"> ▪ Prototype vaccine has been produced, and methods for testing are under development. ▪ Clinical trial sponsored by manufacturer allowed to proceed.
Safety and efficacy testing	<p><i>Federal:</i> Centre for Immunization and Respiratory Infectious Diseases, PHAC</p> <p><i>National:</i> Pandemic Vaccine WG of the PIC</p> <p><i>Federal:</i> Biologics and Genetic Therapies Directorate, HC</p>	<ul style="list-style-type: none"> ▪ Facilitate and build clinical trial and vaccine evaluation capacity in Canada, and test using prototype vaccine. ▪ Review Clinical Trial Applications to ensure that they are in accordance with Part C Division 5 of the <i>Food and Drug Act</i> and Regulations. 	<ul style="list-style-type: none"> ▪ Have met with the manufacturer to hear and provide feedback on their plans for clinical trials. ▪ Clinical trials of vaccine produced in Canada planned for 2008/09. ▪ Canadian sites engaged in enhanced surveillance network for annual influenza vaccine.
Indemnity of vaccine manufacturer	<i>Federal:</i> PHAC	<ul style="list-style-type: none"> ▪ Secure indemnity agreement in order to prevent delays in release of new vaccine at time of pandemic. 	<ul style="list-style-type: none"> ▪ Current supply contract contains provisions stipulating that, until the vaccine is fully licensed under Canada's food and drug laws, Canada will compensate the manufacturer for any claims or lawsuits brought by third parties against it. Once vaccine is fully licensed, Canada's obligations to indemnify will end.

Table 2. Objective: allocate, distribute and administer vaccine as rapidly as possible to the appropriate groups of people

Focus	Lead Group	Actions	Status
Allocation of pandemic vaccine within Canada	<i>National:</i> PIC	<ul style="list-style-type: none"> ▪ Develop preliminary agreement on how vaccine will be distributed within Canada. 	<ul style="list-style-type: none"> ▪ Principle of equitable access agreed upon. ▪ Per capita distribution favored in absence of more details regarding the epidemiology of the pandemic.
Distribution of product	<p><i>Federal:</i> Public Works and Government Services Canada (as contracting authority, once allocation was agreed upon)</p> <p><i>National:</i> Vaccine Supply WG of the Canadian Immunization Committee</p>	<ul style="list-style-type: none"> ▪ Secure agreement with vaccine manufacturer for distribution of pandemic vaccine from manufacturing site to specified depots. ▪ Coordinate with P/T and federal government divisions as necessary to ensure that plans are in place for transportation of vaccine from depot to administration sites and identify any security concerns. 	<ul style="list-style-type: none"> ▪ Distribution plan from manufacturer to as many as 80 destinations across Canada. Preliminary destinations (1-2 per province and territory) have been specified; additional delivery points still to be identified. ▪ Centre for Immunization and Respiratory Infectious Diseases (PHAC) has plans to look at feasibility and implementation issues regarding a “lot distribution map” for annual influenza vaccine. Purpose is to facilitate investigation of any clusters of adverse events following immunization that may be due to a specific vaccine lot. Could potentially be applied to distribution of the pandemic vaccine (for the same purpose).

Focus	Lead Group	Actions	Status
Other supplies required for vaccine program	<i>National:</i> Vaccine Supply WG of the Canadian Immunization Committee	<ul style="list-style-type: none"> ▪ Support national discussion regarding the quantity and availability of other supplies (e.g. syringes and needles) that would be needed to deliver the pandemic vaccine program; whether stockpiling is necessary; and how that might be managed (e.g. feasibility of stock rotation), given the uncertainty of pandemic arrival. ▪ Identify supplies for which bulk purchase may be desirable. 	<ul style="list-style-type: none"> ▪ P/Ts have primary responsibility and have, so far, acted on their own behalf; some P/T stockpiles exist. ▪ Preliminary lists of supplies have been developed. ▪ Some manufacturers of these supplies have been contacted and have provided information of projected availability at time of pandemic. ▪ Federally coordinated bulk purchase has been provided as an option to P/Ts (has not been implemented at this time).
Vaccine recommendations	<i>National:</i> Pandemic Vaccine WG of the PIC (together with NACI representation)	<ul style="list-style-type: none"> ▪ Make recommendations regarding the vaccine dose, schedule, contraindications and route of administration for the pandemic vaccine. 	<ul style="list-style-type: none"> ▪ The Pandemic Vaccine WG includes members of NACI (including the Chair of NACI and the NACI subgroup that is responsible for seasonal influenza vaccine recommendations), in addition to experts on clinical trials, laboratory science and pandemic influenza. This group is prepared to make these recommendations when necessary.

Focus	Lead Group	Actions	Status
Prioritized use of pandemic vaccine	<i>National:</i> Pandemic Vaccine WG of the PIC	<ul style="list-style-type: none"> ▪ Divide Canadian population into subgroups that may be used if vaccine administration must be prioritized, in order to facilitate planning (i.e. identification, communication and access) at the P/T and local level. ▪ Consider the order of administration to these population subgroups and what variables might result in re-ordering the groups. 	<ul style="list-style-type: none"> ▪ Subgroups have been identified, but order of receipt of vaccine will ultimately depend on many factors, including the epidemiology and dynamics of the pandemic. ▪ See section 3.3 below for further discussion of this key issue.
Public communication plans	<i>National & Federal:</i> Communications Working Group of PIC & PHAC Communications Directorate	<ul style="list-style-type: none"> ▪ Facilitate coordinated and consistent messaging regarding the pandemic vaccine across Canada with the international community, and stakeholders. 	<ul style="list-style-type: none"> ▪ Preliminary key messages have been developed. More refined key messages are in development.

Table 3. Objective: monitor the safety and effectiveness of vaccination programs

Focus	Lead Group	Actions	Status
Post-release safety monitoring	<p><i>Federal:</i> Centre for Immunization and Respiratory Infectious Diseases, PHAC</p> <p>Biologics and Genetic Therapies Directorate, HC</p>	<ul style="list-style-type: none"> ▪ Develop guidelines for monitoring of vaccine use during a pandemic and identify issues related to tracking of adverse events following immunization and to liability. ▪ Develop system for timely analysis of received reports and dissemination of data back to P/Ts. ▪ Support new VVTAC activities. ▪ Develop communication plans to involve FPT health and immunization programs and the public. ▪ Appropriate regulatory action if required. 	<ul style="list-style-type: none"> ▪ Plans: pilot testing of a strategy to capture self-reported vaccine safety information from a cohort of those first to be immunized; testing strategies for rapid early collection and integration of data from multiple sources (e.g. clinics, Web-based reporting, phone lines, hospital-based sentinel sites); and weekly analyses of safety information with a mechanism in place for independent expert review and advice. ▪ Pilot testing of a rapid, shared communications strategy. ▪ Explore VVTAC role in making recommendations regarding cessation of immunization due to safety concerns.
Vaccine effectiveness evaluation <i>(Note: Currently there is no way to evaluate effectiveness of an influenza vaccine against death; this remains an outstanding issue with surveillance implications)</i>	<i>National:</i> Pandemic Vaccine WG of PIC	<ul style="list-style-type: none"> ▪ Develop protocol that can be implemented at the time of the pandemic to give vaccine effectiveness estimates. 	<ul style="list-style-type: none"> ▪ Potential groups for participation in evaluation have been identified. ▪ Methodology is being rehearsed using seasonal data from sentinel sites (i.e. against infection and hospitalization).

3.0 Cross-cutting Planning Issues

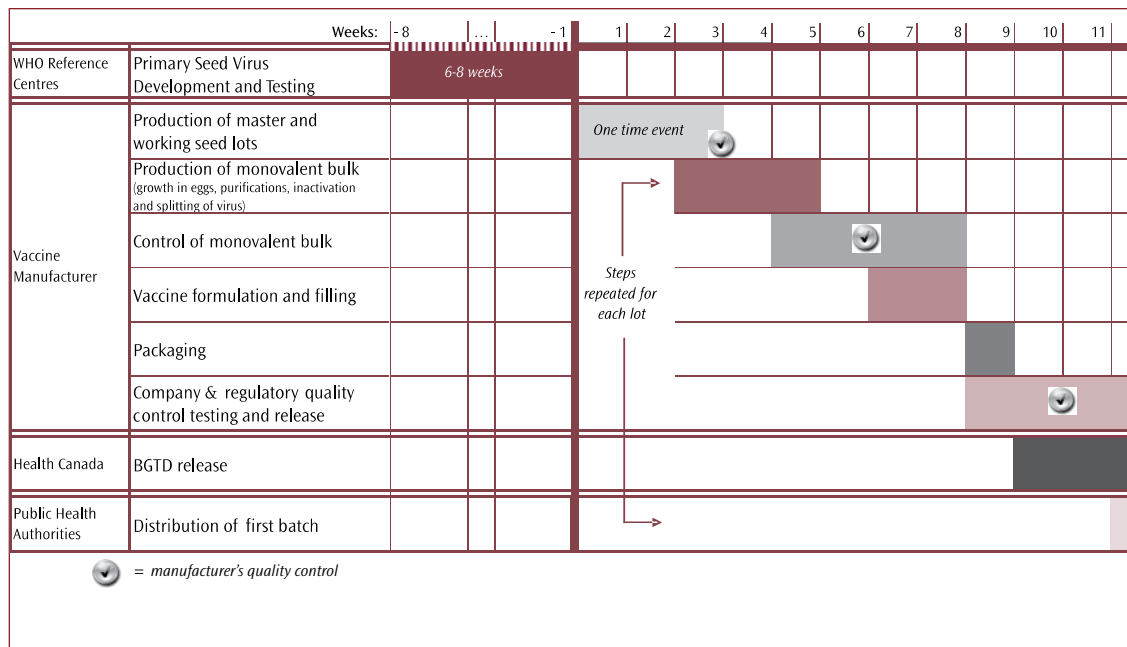
The following sections are intended to highlight issues that affect planning at all levels. These issues are key items on the agenda at the national and federal planning tables, but, like most other national or federal pandemic planning issues, the ultimate impact will occur at the level of program implementation.

3.1 Vaccine Manufacturing Timeline

Influenza vaccine is manufactured every year according to a predetermined timeline. Typically, the World Health Organization (WHO) confirms the recommended virus strains for the Northern Hemisphere vaccine in February, and national/regional strain selection occurs in March. This is followed by seed lot production in April, various production and quality control steps throughout the summer months resulting in a product ready for regulatory approval in August, and batch release occurring in August, September and October. This schedule is designed to provide vaccine for administration starting prior to the typical influenza season in Canada (i.e. November-April). However, even though this is a tried and tested annual process, there can be uncontrollable delays or complications in the manufacturing process that result in delays in product availability and, rarely, vaccine shortages.

It is important to keep in mind that although a great deal of effort is being put into streamlining and shortening this timeline for production of a pandemic vaccine, the process will still be vulnerable to the uncontrollable delays or complications that have been experienced with the annual influenza vaccine. Therefore, whenever the timeline for pandemic vaccine manufacturing is presented, it should be considered as a “best case scenario”. The following diagram represents the current “best case” timeline for production of the first batch of a pandemic vaccine in Canada. At this time it is expected that the product will be a split virus adjuvanted vaccine manufactured in Canada using egg-based technology.

Figure 1. Pandemic Vaccine Manufacturing Timelines



The development of the primary seed with full safety testing by WHO collaborating laboratories can take 6-8 weeks. This may be shortened somewhat if the seeds are forwarded to the manufacturer before the safety testing is complete; however, the manufacturers must work under biosafety level 2+ conditions. The timeline presented in Figure 1 is for the first lot of vaccine. After this, lots could be produced on a routine basis because the process is continuously repeated. Note that the production of the seed lots occurs once, whereas the subsequent steps are repeated for each lot.

The production process consists of growth of the virus in eggs, purification, inactivation and splitting of the virus to produce the monovalent bulk, followed by the formulation and filling into vials. There are quality control tests performed at a minimum on the seed lots, the monovalent bulk and the final product. The manufacturer could perform some of the quality control testing in parallel, although this carries a risk of formulating and filling a lot that could subsequently be useless if the product fails “upstream” testing.

This timeline of 10-12 weeks to obtain the first batches will only be possible if a production process for the pandemic vaccine is in place and parallel testing by the Biologics and Genetic Therapies Directorate (BGTD) occurs. Manufacturers are working through production process requirements by developing prototype vaccines, specifically the process to manufacture H5N1 vaccine. If the product currently manufactured in Canada is submitted for and receives regulatory approval, it may be possible to streamline the approval of future novel influenza vaccines if, as with the annual vaccines, the only change is the use of a different virus strain.

As described previously, BGTD is working to ensure that mechanisms are in place for review and authorization of a safe and efficacious vaccine for use in Canada within the shortest time frame possible, and that trained staff are available for the timely testing and release of pandemic vaccine lots after authorization for use. The Centre for Immunization and Respiratory Infectious Diseases, PHAC, will continue to support the development of a clinical trial network to facilitate rapid in-Canada evaluation of a new pandemic vaccine and, with the Pandemic Vaccine Working Group of PIC, will monitor research regarding novel vaccine development and new technologies aimed at improving production timelines. Dose-sparing strategies will also be monitored for potential application to the Canadian plans.

3.2 Vaccine Production and Administration Rate

In the current vaccine readiness contract the vaccine manufacturer is committed to a production rate target of 8 million monovalent doses of pandemic vaccine per month (i.e. approximately 2 million doses per week). This target was created when the contract was first developed in 2001, with the working assumption that each monovalent dose would contain 15 ug of antigen. In an effort to accelerate the potential production rate the domestic manufacturer developed and added a novel adjuvant to test batches of a new H5N1 vaccine. Clinical trials with a similar product in Europe have suggested that a dose containing 3.8 ug of antigen with the novel adjuvant is sufficient to induce a significant immunological response to H5N1 in the vaccine recipient. Specifically, early testing suggests that a schedule of two doses of this vaccine would be sufficient to induce a protective response in approximately 80% of healthy adult recipients.¹

These results are promising but are specific to the H5N1 product, which uses 3.8 ug of antigen per dose; it is not known whether 3.8 ug of antigen will be sufficient when developing vaccines with different novel influenza strains. There could also be a difference in yield with new influenza strains. Finally, the production of monovalent bulk is only one step in the manufacturing process,

and currently other limitations would preclude the production of a final product at a rate of 32 million doses per month (i.e. 8 million doses per week).

Ideally, the rate at which vaccine is administered to the population should keep up with the production rate of vaccine. Previously, planners were asked to be prepared to vaccinate the entire Canadian population (approximately 32 million people) over the course of four months, corresponding to the production rate of 8 million doses per month (or 2 million doses per week). Given the promising results with the lower antigen content in the current H5N1 vaccine, it is now prudent for planners to consider how they might administer vaccine more rapidly to the population if the pandemic vaccine is produced at a faster rate than previously expected.

Planners are now encouraged to consider what their maximum vaccine administration rate would be based on current plans and whether this could be increased to a maximum of 25% of their population per week should the production of pandemic vaccine be accelerated to that level. The implication is that flexible (or a range of) strategies for vaccine administration should be in place to deliver vaccine at a rate that matches the vaccine production rate. For planning purposes, this range should be considered to be 6.25% to a maximum of 25% of the population per week.

Assuming that two doses of vaccine given approximately one month apart will be necessary for optimal protection, a key planning question becomes, at what point do the operational issues related to delivering a program based on priority groups become an impediment to achieving the optimal administration rate? A simple illustration of this concept is a family consisting of a health care worker, a healthy spouse, one school-age child and one child under 2 years of age. Each of these family members could be given different priority for immunization and directed to different clinic locations, since they are all in different subgroups of the population. For the clinic administrators and for the family it would likely be more efficient and expedient to simply immunize the whole family (or at least the non-health care worker and the children) at one session and ask them all to come back at the appropriate interval for the second dose. This approach could eliminate the need for the clinic team to verify eligibility to receive the vaccine based on priority group, simplify public messaging, potentially reduce confusion and public aggravation at clinic sites, and likely make clinic planning more efficient by making clinic attendance more predictable. In geographically isolated communities the potential efficiency of this approach would be even more evident, as immunization teams could schedule clinics in a way that would reduce the number of community visits required to deliver the population-based program.

3.3 Prioritization

Although enough vaccine will be made to immunize all Canadians, the new pandemic vaccine will still become available in batches, necessitating decisions regarding how these doses will be distributed across Canada and whether to prioritize certain subgroups of the population ahead of others. As indicated earlier, the degree to which prioritization is needed will be linked to the vaccine production and administration rate.

At this time there is no policy decision regarding distribution of the first doses of vaccine across Canada. While a per capita approach seems to be the most equitable approach and should be used for planning purposes, there are other factors that may influence this decision at the time. For example, if the vaccine becomes available as first wave activity appears to be subsiding in some provinces but escalating in others, perhaps the first doses should be sent to the area where activity is escalating in an effort to mitigate the impact of the first wave in those locations. Alternatively, the provinces with subsiding activity might be in the best position to deliver mass immunization programs, as human resources could be shifted away from patient care, given the declining

number of new cases, and into vaccine administration. Mathematical modeling and feedback from pandemic planning exercises may provide some insight with respect to this issue, but there are other factors that will also need to be considered. Final allocation decisions, therefore, may not be made until the pandemic is under way and the vaccine becomes available.

In order to assist with preparations for implementation of a priority-based strategy at the local level, the Pandemic Vaccine Working Group of PIC developed priority groups (i.e. subgroups of the entire population) for planning purposes, which were published as a numbered list in Annex D, both with the 2004 and the 2006 edition of the CPIP. This document is now replacing that version of Annex D.

The subgroups of the population identified in the previous version of Annex D have been retained, as each group has commonalities, such as a role in contributing to the pandemic planning goals and potential access strategies, which make the groupings logical from a planning perspective. These existing subgroups of the Canadian population can be classified into occupation-based groups, high-risk groups and healthy adults and children (i.e. those not a part of the occupational groups identified). Table 4 lists the working definition for each of the subgroups and gives examples of who might be included in each group. The subgroups are intended to be mutually exclusive but, together, to cover the entire Canadian population. Most of these definitions can also be found in the Glossary for the Plan. **The groups are presented in alphabetical order: this table does not represent a priority list.**

Table 4. Population subgroups

Population Subgroup (NOT priority order)	Definition (for the purposes of this process)	Examples of who would make up the group and how they might be accessed
Health care workers	Persons who work in settings where essential health care is provided	Nurses, physicians, laboratory workers, pharmacists, emergency medical services <ul style="list-style-type: none"> • Might be accessed through work-place-based clinics
Healthy adults	All individuals, 18 years of age and over, who do not have a medical condition or fit into an age category that would qualify them for inclusion in the high-risk group and who do not fall into one of the other occupation-based groups <i>(Note: if adults 65 years and over are considered to be at “high risk of poor outcome”, as they are on a seasonal basis, then they would not be included in this group)</i>	<ul style="list-style-type: none"> • Might be accessed through community-based clinics
Healthy children	All individuals, 2-17 years of age, who do not have a medical condition that would qualify them for inclusion in the high-risk group	<ul style="list-style-type: none"> • Might be accessed through school or community-based clinics

Population Subgroup (NOT priority order)	Definition (for the purposes of this process)	Examples of who would make up the group and how they might be accessed
High risk (of poor outcome)	Those groups in which epidemiological evidence indicates that there is an increased risk of poor outcome due to the disease	This would have to be determined according to the epidemiology of the pandemic** <ul style="list-style-type: none"> • Might be accessed through dedicated clinics at locations convenient for the particular groups (e.g. nursing homes for residents)
Key health decision makers*	Persons whose decision-making authority is necessary for implementing and maintaining the health sector response to pandemic influenza	Medical officers of health, hospital Chief Executive Officers and Chiefs of Staff, Ministers of Health <ul style="list-style-type: none"> • Might be accessed through workplace-based clinics)
Key societal decision makers*	Persons whose decision-making authority will be necessary at the time of the pandemic to minimize societal disruption	Mayors, police chiefs, fire chiefs, judges, other government ministers <ul style="list-style-type: none"> • Might be accessed through workplace-based clinics
Public health responders*	Persons who are essential to the implementation and maintenance of the public health response to pandemic influenza and who would not be expected to come within 1 meter of a known influenza case in their work setting	Public health nurses not involved in patient care, other public health staff, public health administrators <ul style="list-style-type: none"> • Might be accessed through workplace-based clinics
Pandemic societal responders*	Persons who are trained or primarily involved in the provision of an essential service that, if not sustained at a minimal level, would threaten public health, safety or security	Police officers, firefighters, corrections officers, utility workers, mortuary staff <ul style="list-style-type: none"> • Might be accessed through workplace-based clinics
<p>* These definitions were developed to facilitate pandemic planning regarding the identification of specific groups that may be targeted as part of specific public health interventions and therefore may not be well recognized outside of the public health sector. Also note that where the third column in the table includes occupational groups, this has been provided as an example and is not intended to be inclusive or to convey that the entire occupational group would meet the criteria for inclusion in this defined population subgroup for immunization.</p> <p>** For planning purposes the high-risk groups for annual influenza (as identified by the National Advisory Committee on Immunization) have been used:</p> <ul style="list-style-type: none"> • Adults and children with selected chronic health conditions if significant enough to require regular medical follow-up or hospital care. These high-risk conditions include the following: <ul style="list-style-type: none"> • cardiac or pulmonary disorders (including bronchopulmonary dysplasia, cystic fibrosis and asthma), diabetes mellitus and other metabolic diseases, cancer, immunodeficiency, immunosuppression (due to underlying disease and/or therapy), renal disease, anemia or hemoglobinopathy, conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration, children and adolescents with conditions treated for long periods with acetylsalicylic acid. • People of any age who are residents of nursing homes and other chronic care facilities. • People ≥ 65 years of age • Healthy children aged 6 to 23 months • Pregnant women 		

Determining the order in which these subgroups of the population would receive vaccine is a much more difficult task and one that experts concur must take into consideration several

factors, many of which will not be known until the pandemic occurs. The following are examples of these factors and considerations:

- **Impact on pandemic goals** (i.e. minimizing serious illness, overall deaths and societal disruption): minimizing serious illness and overall deaths would suggest giving high-risk groups and health care workers priority over others. However minimizing societal disruption may favor prioritization of the critical infrastructure occupational groups and perhaps healthy adults.
- **Operational considerations** (e.g. size of the group, ease of identification and accessibility): depending on the amount of vaccine available it may be easiest to prioritize smaller groups that can be easily located and identified, for example, health care workers, or to immunize everyone in a remote community at once.
- **Severity/epidemiology of the pandemic:** a severe pandemic may result in public pressure to immunize children first. Similarly if the pandemic virus is similar to one that has circulated previously (e.g. H2N2) it may make sense to prioritize the age groups that would not be expected to have been exposed to a similar virus previously.
- **Difference in vaccine effectiveness between groups** (e.g. if vaccine effectiveness is significantly lower in the elderly and immunocompromised): this may favour prioritizing the “healthy” over some of the high-risk groups.
- **Timing of vaccine availability** (e.g. end of first wave, inter-wave period, start of second wave): availability between waves may favour prioritization of the occupational groups in preparation for the next wave or those in high transmission settings like school-age children, in an effort to flatten the epidemic curve of the second wave. Vaccine availability at the start of a second wave may lead to prioritizing those at high risk, especially if a significant proportion of the other groups are expected to have developed immunity during the first wave.
- **Public opinion and risk perception as a consideration** (e.g. perceived severity of the pandemic and risks of the vaccine): the public may want children to be immunized first if the pandemic is severe. Alternatively, if the pandemic is perceived as relatively mild and the vaccine is highly reactogenic, the public may wish to delay immunizing children until more is known about the long-term effects of the new vaccine.

Conceptualizing how all these variables might interact in order to present a menu of priority lists for each possible contingency is not an efficient use of time or resources. There are simply too many potential combinations of factors and considerations, and many of these (e.g. public opinion) may not be “static” over the course of the pandemic. Such lists would run the risk of derailing planning efforts: with focus on the order of the population subgroups, many planners would be forced to spend time justifying the lists instead of working on how the specific groups of people would be identified and accessed should it be necessary to prioritize them as part of the pandemic vaccine program.

It is envisioned that at the time of the pandemic the Pandemic Vaccine Working Group would make recommendations regarding whether prioritization of the vaccine supply is necessary and, if necessary, the order in which the subgroups of the population would be immunized and whether any subgroups should be targeted at the same time. The Pandemic Vaccine Working Group of PIC is dedicated to developing a prioritization decision-making strategy or tool that would encompass the factors and considerations listed previously. This strategy/tool would be made publicly available for educational purposes, but ultimately it is expected to be used by the Working Group to make recommendations regarding prioritization to PIC and subsequently to the Public Health Network Council. The national policy decision regarding the order in which the

population subgroups should be immunized across Canada would likely be made by Ministers of Health on the advice of the Chief Medical Officers of Health and the Public Health Network Council, with the strong recommendation that the order decided on would be consistently applied across Canada.

3.4 New Influenza Vaccine Developments

In an effort to improve global preparedness for pandemic vaccine production, the WHO encourages research and development for new influenza vaccines² (i.e. prototype novel influenza vaccines) and approaches that may decrease production timelines (e.g. cell culture). Asian-strain H5N1 virus seed lots were made available for this initiative. Recently, there have been several forums (WHO meetings, vaccine conferences etc.) at which the manufacturers have provided information and clinical trial data on their prototype vaccines. As a result of promising efficacy data and evidence suggesting that some products may provide cross-protection against different clades* of the same virus, some manufacturers have proceeded to submit these vaccines for approval by various regulatory authorities.

In addition, the concept of using these new H5N1 vaccines to “prime” individuals in preparation for an H5N1 pandemic has been introduced. The intention would be to ultimately decrease the time to vaccine-induced protection by administering a vaccine with a strain similar to that expected to be responsible for the next pandemic and then to administer a specific pandemic strain vaccine to these individuals as soon as it becomes available. The expectation is that the first dose (the “pre-pandemic” vaccine) would serve to prime the individual’s immunological response, and the second pandemic strain-specific dose would serve as a booster, eliciting specific protection against the pandemic virus.

Some countries are now considering, or are actually stockpiling, pre-pandemic vaccine, which at this time is available only for the Asian-strain H5N1 virus.

Other vaccines under investigation include whole virus vaccines, other adjuvanted vaccines (e.g. alum adjuvanted), vaccines targeting internal proteins (as opposed to the H and N surface proteins) and vaccines that can be administered using different routes (e.g. intradermal and transdermal). The Pandemic Vaccine Working Group will continue to monitor new influenza vaccine developments and potential implications for planning in Canada.

3.5 Stockpiling

Technology has now advanced to the point at which pre-pandemic influenza vaccines against novel influenza viruses are starting to become available for purchase by governments. Some countries have already stockpiled or have committed themselves to stockpiling a new Asian H5N1 vaccine as part of preparedness activities for an H5N1 influenza pandemic. Canada does not have a stockpile of H5N1 vaccine and is continuing to focus on strategies to increase general preparedness against pandemics of any influenza subtype. However, the Pandemic Vaccine Working Group will continue to review the science related to H5N1 vaccines to inform further decision making. This review will include ongoing monitoring for evidence of the effectiveness of priming with novel influenza vaccines.

* The term “clade” is defined as “related organisms descended from a common ancestor”, see www.medterms.com. At this time at least three clades of the highly pathogenic H5N1 virus have been identified.

It is important for planners at the P/T and local level to determine whether it will be necessary to stockpile supplies that would be required to implement mass immunization clinics targeting the entire Canadian population once a pandemic vaccine becomes available. This work is being supported nationally by the Vaccine Supply Working Group of the Canadian Immunization Committee. However, these discussions need to be informed by P/T and local level planners, who are in the best position to plan with those delivering health care, as key issues such as stock rotation are more conducive to local arrangements.

4.0 Action Items

The following list is a summary of key action items that have been derived from the content of this annex. This list is intended to supplement the list already provided in Annex A of the CPIP and to highlight areas in which national and/or federal preparedness activities are linked to operational planning issues.

- Planners need to determine whether (and how) they could administer one dose of vaccine to their entire population within one month. If this is not feasible, they need to determine what the fastest achievable and sustainable administration rate is for the community they serve in the context of a pandemic, when human and other resources may be limited.
- Planners need to be prepared to implement both a non-prioritized and prioritized pandemic immunization program, recognizing that they may be notified which is to be implemented at very short notice and that, regardless of the strategy, they will ultimately be trying to immunize essentially the entire population.
- Planners need to determine whether using a non-priority-group based strategy makes the most sense for any segments of the population in their jurisdiction. An example may be remote, isolated communities.
- Planners need to develop methods of identifying the numbers for each population subgroup and how best to confirm inclusion in a particular subgroup at the level of the immunization clinic.
- Planners need to ensure that the appropriate communication channels are in place to
 - update key players at the local level regarding the implications of the latest science and technology and the status of plans for the pandemic vaccine program as part of ongoing preparedness;
 - provide the public with the information they will need regarding the pandemic vaccine program;
 - facilitate implementation of the program as consistently as possible across Canada (based on nationally agreed upon recommendations and policies);
 - mobilize the resources required to rapidly implement mass immunization clinics (including sources and training of “surplus” immunizers).
- With respect to the pandemic vaccine strategy, planners need to stockpile the medical supplies (e.g. syringes) that will be integral to the implementation of mass immunization clinics.
- Currently, pandemic planning at the P/T and local level should include the following:
 - consideration that the 10-12 week timeline for pandemic vaccine production is a best-case scenario;

- recognition that expected delivery dates for pandemic vaccine may be delayed;
- a feedback loop for timely notification of any suspected serious or unusual adverse events following immunization.

5.0 Research

Research will play a key role in informing both preparedness and response activities. The PHAC and the Canadian Institutes of Health Research (CIHR) hosted a meeting in September 2005 to identify research priorities and develop a strategic, multi-year research agenda for influenza. Proceedings from this meeting are available at: <http://www.cihr-irsc.gc.ca/e/30967.html>.

The pandemic vaccine strategy could benefit from research conducted during annual influenza seasons. There is also a need to have research protocols ready for implementation at the time of the pandemic in order to better inform decision making and post-pandemic evaluation.

In response to this need, PHAC and CIHR launched a Request for Applications (RFA) for Catalyst Grants for Pandemic Preparedness to mobilize the research community for an outbreak response (see: <http://www.researchnet-recherchenet.ca/rnr16/viewOpportunityDetails.do?prog=312&view=browseArchive&browseArc=true&progType=CIHR-1&type=AND&resultCount=25>). Catalyst Grants allow for the planning and preparatory phase of research projects that will be essential for pandemic control during an outbreak. The vaccine-relevant research areas addressed depend on the outcome of peer review, but the evaluation of vaccine effectiveness and investigation of adverse events following immunization are expected to be included.

In addition to research activities currently under way, a PHAC/CIHR RFA for Team Grants (see: <http://www.cihr-irsc.gc.ca/e/32804.html>) called for applications related to vaccines and immunization programs, such as research into the optimal use and efficiency of existing vaccines and the development of novel vaccination technologies, including means of vaccine delivery. It is expected that successfully peer reviewed projects will be under way by the spring of 2008.

Finally, PHAC and CIHR launched a Funding Opportunity for the establishment of an Influenza Research Network (IRN) in December 2007. The IRN will mobilize nation-wide research experience and talent in vaccine evaluation in order to develop and test methodologies/methods related to the safety, immunogenicity and effectiveness of influenza vaccines in persons of all ages before and after release of the vaccines for general use. It is expected that the successfully peer-reviewed project will be under way by the spring of 2009.

As pandemic preparedness activities and research continue to be a global priority, it is important that research findings and new technologies from outside Canada are monitored, shared and used to inform future plans. At this time there are many vaccine-related research activities being undertaken. Another area of interest is mathematical modeling, which might shed further light on the potential impacts of different prioritization strategies.

6.0 Conclusions

Optimal planning for the pandemic vaccine program requires the development of flexible plans at all levels of government. F/P/T planning activities have been identified according to the usual roles and responsibilities (i.e. with respect to the delivery and organization of health care) but also with consideration of when a centralized approach is most efficient – for example, when securing a vaccine contract for the production of pandemic vaccine. Planning at these levels must be informed by the operational realities of what can be expected when implementing such a massive undertaking at a time of stretched resources and intense public awareness and scrutiny.

No plan is or will be perfect; in fact, it may only be in hindsight that areas of improvement can be identified. Given the uncertainties and changing context that are characteristic of pandemic planning, the most that planners can do for Canadians is to make sure that plans are based on the best information available at a given time and that they continue to evolve. They should be based on the best available science, technology, and resources, and ensure that public needs and expectations are managed through education of the public by experts and through education of experts regarding public values and expectations.

1. GlaxoSmithKline. *GSK reports significant advance in H5N1 pandemic flu vaccine programme*. Press release. London, England, and Rixensart, Belgium, July 26, 2006.
2. World Health Organization. *Global pandemic influenza action plan to increase vaccine supply*. September 2006. Available at: http://www.who.int/csr/resources/publications/influenza/CDS_EPR_GIP_2006_1.pdf.

