An Advisory Committee Statement (ACS) National Advisory Committee on Immunization (NACI)

Research Priorities for COVID-19 Vaccines to Support Public Health Decisions

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PREAMBLE

The National Advisory Committee on Immunization (NACI) provides the Public Health Agency of Canada (PHAC) with ongoing and timely medical, scientific, and public health advice relating to immunization.

NACI generally issues guidance on immunization programs and research priorities for immunizing agents that have been authorized by Health Canada. However, in this exceptional circumstance of the coronavirus disease (COVID-19) pandemic, PHAC has requested rapid guidance from NACI on research priorities for COVID-19 vaccine candidates to support public health decision-making.

PHAC acknowledges that the advice and recommendations set out in this statement are based upon the best current available scientific knowledge and is disseminating this document for information purposes. NACI members and liaison members conduct themselves within the context of PHAC's Policy on Conflict of Interest, including yearly declaration of potential conflict of interest.

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I. POLICY OBJECTIVE

The following recommendations were developed to inform clinical trials of candidate COVID-19 vaccines to protect against infection, serious illness, and deaths caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The findings of these trials will be used to inform vaccine recommendations made by NACI and public health program decisions that will be made by Canadian jurisdictions once a COVID-19 vaccine or vaccines become available in Canada.

Clinical trials in Canada are governed by the regulator (Health Canada), and the regulator will have ultimate authority to determine whether proposed studies are appropriate in Canada. All clinical trials in Canada require approval from an independent Research Ethics Board. Regulators from around the world (including Health Canada) have identified the need for high quality observational research as an important complement to the evidence on the safety and effectiveness of vaccines for COVID-19 generated from randomized clinical trials, and have agreed to collaborate on priority areas on observational research during COVID-19 including vaccine safety and effectiveness monitoring, as well as studies in priority populations including in pregnancy [(1)]. This collaboration on observational studies of real-world data will be an important component of the evidence-base considered when making evidence-informed vaccine recommendations.

II. METHODS

To develop these recommendations over the month of May 2020, NACI reviewed available epidemiological summaries from national analyses of federal/provincial/territorial surveillance data reported to PHAC [(2)]; summaries of the COVID-19 vaccine product landscape from clinical trial registry data; the Vaccine Annex of the Canadian Pandemic Influenza Preparedness: Planning Guidance for the Health Sector [(3)]; materials on the draft research and development blueprint of the World Health Organization (WHO) Vaccine Solidarity Trial [(4)]; and literature on emerging risk factors for severe disease and mortality from COVID-19. NACI deliberated on the evidence and proposed recommendations on May 11, 2020, provided feedback through to May 20, 2020, and approved the revised recommendations on June 2, 2020.

III. RECOMMENDATIONS

The goals of Canada's pandemic response are to: 1) minimize serious illness and overall deaths (due to all causes), and 2) to minimize societal disruption, including reducing the burden of health care resources. Pandemic vaccine is expected to play an important role in achieving this goal.

An objective of Canada's pandemic vaccine strategy is to provide a safe and effective vaccine for all Canadians as quickly as possible. The earlier the vaccine is available, the greater its impact. Obtaining timely clinical trial data of candidate COVID-19 vaccines is crucial for eventual regulatory review and potential authorization. To guide the judicious use of scarce research resources, NACI recommends the prioritization of certain groups for clinical trials, recognizing that not all population groups can be feasibly trialed at once.

Individuals with ***social vulnerabilities*** (e.g., due to lower socioeconomic status, residence in long-term care facilities or crowded/remote locations, homelessness, tobacco/alcohol/drug use disorder, race/ethnicity, immigration or refugee status, international travel) as well as ***occupational vulnerabilities*** (e.g., healthcare workers, emergency workers, workers who have a high degree of social contact, international business travelers) may experience a higher burden of illness due to COVID-19 in part due to differential exposures or access to health care during a pandemic and should not be excluded a priori from clinical trials. ***As such, individuals with these vulnerabilities should be included in clinical trial groups when possible.***

The evidence base for COVID-19 is evolving and must be monitored, with adjustments to clinical trials as necessary. All potential biological, social, and occupational risk factors, some of which are still uncertain (e.g., increased disease severity in those with chronic kidney disease or cerebrovascular disease), should be investigated as part of COVID-19 surveillance and special studies to inform future clinical trials. Please see NACI's Equity Matrix in Appendix A for a summary of potential sources of inequity and risk factors. Information on NACI's EEFA (Ethics, Equity, Feasibility, and Acceptability) Framework with details on its development and application of evidence-informed tools including the Equity Matrix is available elsewhere [5].

III.1 CONSIDERATIONS FOR EARLY PHASE CLINICAL TRIALS

Primary priority populations

NACI recommends that the following groups be prioritized for early phase clinical trials when studying COVID-19 vaccines:

- healthy adults (18 to <60 years of age) in the initial phases of clinical trials to establish vaccine safety, immunogenicity, and efficacy (per typical clinical trial protocols); and
- adults 60 years of age and older without underlying health conditions as special populations for clinical trial investigation (due to increased risk of disease severity based on available epidemiological and scientific evidence to date and the possibility of reduced response to the vaccine due to immunosenescence, or changes in the immune system associated with age, in this population).

Table 1. Priority PICO parameters for primary priority populations for early phase clinical trial investigation to establish vaccine safety, immunogenicity, and efficacy of COVID-19 vaccines

Population[1]	Intervention	Comparator	Outcome[2]
Adults 18 to <60 years of age without underlying health conditions * (* As per typical clinical trial protocols where initial phases test the intervention in healthy volunteers. NACI acknowledges that these groups will be critical to accelerate the timely investigation of vaccines through large trials, and present minimal ethical complexities).	Candidate COVID-19 vaccine	No vaccine	Safety[3], immunogenicity, and efficacy against COVID-19
Adults 60 years of age and older without underlying health conditions * (* Stratification of age groups is recommended to determine the relative immunogenicity and efficacy of the intervention in the context of immunosenescence)	Candidate COVID-19 vaccine	No vaccine	Safety, immunogenicity, and efficacy against COVID-19

[1] NACI recommends that inclusion criteria for all populations include adequate numbers of both those who are COVID-19 naïve as well as those with evidence of previous infection based on virological or serological confirmation to determine the outcomes of the intervention in both situations.

[2] Possible primary outcomes of interest include: safety and immunogenicity. Possible secondary outcomes of interest include: confirmed infection with SARS-CoV-2, as determined by PCR and/or culture for active infection, or retrospectively through serology (differential serologic assay would be required to distinguish vaccine effect from natural infection); viral shedding; mechanical ventilation; ICU stay; hospitalization; mortality; correlates of risk; and durability of vaccine protection.
[3] Systematic collection of pregnancy-specific safety data arising from participants unknowingly pregnant at the time of vaccination or who become pregnant within a pre-determined window following vaccine administration should be in place.

Secondary priority populations

Due to safety concerns, potential suboptimal immune response to vaccination related to immature or altered immune systems, and potential for severe illness from COVID-19, NACI recommends that the following groups should also be considered for early phase clinical trial investigation as soon as it is feasible after safety, immunogenicity, and efficacy have been established in healthy adults:

- children and adolescents;
- immunocompromised adults; and
- pregnant women.

Pregnancy has traditionally been an exclusion criterion for clinical trials of vaccines and has not been included among clinical trials for COVID-19 vaccines at the time of writing. Therefore, there is a need for the safe inclusion of pregnant individuals in clinical trials of candidate COVID-19 vaccines to ensure that this population has equitable access to COVID-19 vaccine options informed by robust safety, immunogenicity, and efficacy data. Considerations for COVID-19 vaccine investigation during pregnancy include: prioritizing platforms and adjuvants suitable for use in pregnancy; ascertainment of pregnancy-specific indicators of safety; conducting non-clinical studies, such as reproductive toxicology studies, early in the clinical development of vaccine candidates; and working with regulatory agencies to determine the types of reproductive and developmental toxicology data required to enroll pregnant women in late phase trials.

Table 2. Priority PICO parameters for secondary priority populations for early phase clinical trial investigation due to safety concerns, potential suboptimal immune response to vaccination against COVID-19, and potential for severe illness from COVID-19

Population[1]	Intervention	Comparator	Outcome[2]
Children and adolescents <18 years of age without underlying health conditions * (* Stratification of age groups is recommended to determine the relative immunogenicity and efficacy of the intervention)	Candidate COVID-19 vaccine	No vaccine	Safety, immunogenicity, and efficacy against COVID-19
Immunocompromised children, adolescents, and adults * (* Stratification of age groups and level of immunocompromise is recommended to determine the relative immunogenicity and efficacy of the intervention)	Candidate COVID-19 vaccine	No vaccine	Safety, immunogenicity, and efficacy against COVID-19

Population[1]	Intervention	Comparator	Outcome[2]
During pregnancy (any trimester)	Candidate COVID-19 vaccine	No vaccine	Safety, immunogenicity, and efficacy against COVID-19 (* In the case of vaccination during pregnancy, studies will ideally include assessment of antibodies in umbilical cord blood, and vaccine efficacy in both mother and infant during the first year of life. Stratification of efficacy results for newborns according to trimester of vaccine administration could help inform optimal timing of vaccine delivery during pregnancy.)

[1] NACI recommends that inclusion criteria for all populations include adequate numbers of both those who are COVID-19 naïve as well as those with evidence of previous infection based on virological or serological confirmation to determine the outcomes of the intervention in both situations.

[2] Possible primary outcomes of interest include: safety and immunogenicity. Possible secondary outcomes of interest include: confirmed infection with SARS-CoV-2, as determined by PCR and/or culture for active infection, or retrospectively through serology (differential serologic assay would be required to distinguish vaccine effect from natural infection); viral shedding; mechanical ventilation; ICU stay; hospitalization; mortality; correlates of risk; and durability of vaccine protection.

Concomitant administration with other vaccines

After adequate immune response of the candidate COVID-19 vaccine has been established, consider the investigation of the safety, immunogenicity, and efficacy/effectiveness of concomitant administration of the COVID-19 vaccine and other recommended vaccines (e.g., routine childhood vaccinations in children; seasonal influenza, pneumococcal, zoster, and Tdap vaccinations in adults) in the above-mentioned primary and secondary priority populations. These data will be informative for public health program decision-making.

III.2 CONSIDERATIONS FOR LATE PHASE CLINICAL TRIALS AND POST-MARKET STUDIES

Individuals with certain pre-existing conditions – either potentiating health conditions such as asthma or other conditions identified through epidemiological studies of risk factors for COVID-19 (e.g., diabetes, hypertension, chronic lung disease, cardiovascular disease) – may be at increased risk of severe illness from COVID-19. Individuals with social or occupational vulnerabilities may also be at increased risk of illness due to differential access to health care or differential disease exposure, susceptibility, severity, or consequences. As these populations may not necessarily be included or studied with adequate sample size in early phase clinical trials, NACI recommends that the following groups be prioritized for late phase clinical trial and post-market investigation:

- individuals with pre-existing health conditions; and
- individuals with social and/or occupational vulnerabilities.

Table 3. Priority PICO parameters for priority populations for late phase clinical trial and post-market investigation due to increased risk of illness from COVID-19

Population[1]	Intervention	Comparator	Outcome[2]
Adults 18 to <60 years of age with at least one of the following pre-existing health conditions: hypertension, diabetes mellitus, cardiovascular disease, and chronic lung disease	Candidate COVID-19 vaccine	No vaccine	Safety[3], immunogenicity, and effectiveness against COVID-19
Adults 60 years of age and older with at least one of the following pre-existing health conditions: hypertension, diabetes mellitus, cardiovascular disease, and chronic lung disease * (* Stratification of age groups is recommended to determine the relative immunogenicity and efficacy of the intervention in the context of immunosenescence)	Candidate COVID-19 vaccine	No vaccine	Safety, immunogenicity, and effectiveness against COVID-19
Children and adolescents <18 years of age with at least one pre-existing health condition (e.g., potentiating health conditions such as asthma, or other conditions identified by the evolving epidemiology of COVID-19 in pediatrics) * (* Stratification of age groups is recommended to determine the relative immunogenicity and efficacy of the intervention)	Candidate COVID-19 vaccine	No vaccine	Safety, immunogenicity, and effectiveness against COVID-19
Individuals with social and/or occupational vulnerabilities	Candidate COVID-19 vaccine	No vaccine	Safety, immunogenicity, and effectiveness against COVID-19

[1] NACI recommends that inclusion criteria for all populations include adequate numbers of both those who are COVID-19 naïve as well as those with evidence of previous infection based on virological or serological confirmation to determine the outcomes of the intervention in both situations.

[2] Possible primary outcomes of interest include: safety and immunogenicity. Possible secondary outcomes of interest include: confirmed infection with SARS-CoV-2, as determined by PCR and/or culture for active infection, or retrospectively through serology (differential serologic assay would be required to distinguish vaccine effect from natural infection); viral shedding; mechanical ventilation; ICU stay; hospitalization; mortality; correlates of risk; and durability of vaccine protection.

[3] Systematic collection of pregnancy-specific safety data arising from participants unknowingly pregnant at the time of vaccination or who become pregnant within a pre-determined window following vaccine administration should be in place.

IV. ADDITIONAL CONSIDERATIONS

Please refer to NACI's EEFA (Ethics, Equity, Feasibility, and Acceptability) Framework for details on its development and application of evidence-informed tools including the Ethics Integrated Filters, Equity Matrix (included as Appendix A), Feasibility Matrix, and Acceptability Matrix.[5]

Ethics

- Key universal ethical standards for research involving humans should be adhered to during a public health emergency such as the COVID-19 pandemic, including the need for scientific validity, social value, and individual informed consent. It may be challenging for prospective participants to weigh the potential risks and benefits of research participation in the current situation given uncertainties around COVID-19, social vulnerabilities resulting from the public health response, and the potential perception that an experimental vaccine is better than nothing. Efforts must be made to ensure all prospective clinical trial participants are informed of any additional risks associated with an expedited trial and understand that benefits are uncertain before providing consent to participate in research. The need for Research Ethics Board review of clinical trials without exclusion of approval steps remains; transparency with adequate assessment of outcomes cannot be compromised.

- Some outstanding questions for COVID-19 vaccines (e.g., correlates of protection, rates of asymptomatic transmission, vaccine impact on viral shedding) could potentially be answered by human challenge studies. While these studies are ethically complex and would have to be carefully navigated with Research Ethics Boards and the federal regulator, WHO has outlined key criteria for the ethical acceptability of COVID-19 human challenge studies [6], which should be followed when undertaking such studies.

Equity/Feasibility

- In order to support NACI's evidence-informed decisions, which include equity analyses to identify and limit potential inequities that may arise with recommendations, vaccine outcome results disaggregated by potential factors contributing to biological inequities such as sex, age, and health status will be important. Trials should endeavour to power their groups to allow analyses by demographic variables. In addition, potential factors contributing to inequities related to social vulnerabilities (e.g., due to lower socioeconomic status, residence in long term care facilities or crowded/remote locations, homelessness, tobacco/alcohol/drug use disorder, race/ethnicity, immigration or refugee status, international travel) as well as occupational vulnerabilities (e.g., healthcare workers, emergency workers, workers who have a high degree of social contact, international business travellers) should be considered in late clinical trial and post-market investigation. Please refer to NACI's Equity Matrix for vaccine decision-making (Appendix A).

- To facilitate the deployment of the candidate vaccine(s), feasibility issues, which are assessed by NACI when making recommendations, are important to address (e.g., strive for limiting number of doses required for long term protection, ease of storage and handling requirements, preferred route(s) of administration, alignment with existing immunization schedules). All segments of the population are susceptible to and can transmit infection, and could potentially benefit from vaccine. In consideration of the socio-economic and health impacts that the COVID-19 pandemic has had worldwide, a cost-effective vaccine will likely be needed to eventually deploy beyond the priority target groups.

Health economics

- NACI's decision-making is also informed by health economics, including economic evaluations. Such analyses examine the value of interventions, and provide insight on opportunity costs and the efficient allocation of resources. During a pandemic, clinical and ethical considerations likely supersede cost-effectiveness considerations for policy decision-making. Nonetheless, trialists should consider collecting the following data alongside clinical trials, which can be used in subsequent model-based analyses:

    - Health-related quality of life, specifically health utilities;
    - Patient-reported outcomes (PROs) (i.e., functional status associated with the health care or treatment received); and/or
    - Patient-reported experiences measures (PREMs) (i.e., patients' experience with their care or a health service).

V. KNOWLEDGE GAPS

NACI has identified the need for further research to address current knowledge gaps where data are absent or limited that may inform the design of clinical trials and downstream public health decision-making. NACI recognizes that there are studies already in progress that may address many of these gaps but the findings of these studies were not yet available at the time of writing. Identified knowledge gaps include the following research questions:

1. Are IgA/IgG/IgM antibodies protective against SARS-CoV-2?

2. Is there a cell-mediated immunity correlate of protection against SARS-CoV-2?

3. Is SARS-CoV-2 natural infection (symptomatic or asymptomatic) associated with protection against re-infection or severe disease? What is the duration of natural protection against re-infection or severe disease from SARS-CoV-2?

4. What is the duration of vaccine protection against re-infection or severe disease from SARS-CoV-2?

5. Does vaccination following prior SARS-CoV-2 infection or vaccination of SARS-CoV-2 naïve individuals elicit enhanced disease upon subsequent infection?

6. Are any other vaccines (e.g., BCG) protective against COVID-19 through off-target effects?

7. Does a high level of demand or acceptability exist for candidate vaccines in various target groups in different epidemiological contexts across the country?

8. What is the epidemiological profile of COVID-19 (e.g., communicable period, all risk groups)?

    a. What is the disease distribution and spectrum of clinical illness for COVID-19, including burden of illness and risk by age, gender and other demographic variables, and risk groups?
    b. What are the transmission dynamics of COVID-19, including degree of asymptomatic transmission, role of children in transmission, vertical transmissibility, onset and duration of viral shedding and communicable period, impact of changing weather conditions, and trends over time?
    c. What are the rates of COVID-19 co-infections with other respiratory pathogens and impact on pathogenesis and clinical outcomes?

   d. Is there cross-protection or interference from antibodies/exposure to human seasonal coronaviruses when exposed to SARS-CoV-2 or vaccinated against SARS-CoV-2?

9. Are there any emerging safety signals with COVID-19 vaccination that are not predicted by the current understanding of the safety profile of similar vaccines?

LIST OF ABBREVIATIONS

COVID-19	Coronavirus disease 2019
ICU	Intensive care unit
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
NACI	National Advisory Committee on Immunization
PCR	Polymerase chain reaction
PHAC	Public Health Agency of Canada
PREM	Patient-reported experiences measure
PRO	Patient-reported outcome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
WHO	World Health Organization

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APPENDIX A

NACI Equity Matrix

This tool is used by NACI to identify potential distinct inequities that may arise with a recommendation, reasons for inequities, as well as interventions to reduce inequity and improve access. The identification of key health inequity factors for vaccine decision-making is ideally supported by clinical trial data.

Factors that may contribute to health inequity	**Why inequity may exist (differential access or differential disease exposure, susceptibility, severity or consequences)**	**Interventions to reduce inequity and improve access**
Pre-existing condition (e.g. chronic disease, immunocompromised, pregnancy)		
Place of residence (remote, overcrowding, homeless, institutionalization)		
Race/ethnicity/culture/ language/ Immigration/refugee status		
Occupation		
Gender Identity/Sex		
Religion/Belief system		
Education/Literacy level		
Socioeconomic status (SES) (including income/coverage of cost of vaccination)		
Social capital (social support/networks/trust)		
Age		
Other factors (risk behaviours – drug and alcohol use disorders, smoking)		