INSPQ INSTITUT NATIONAL DE SANTÉ PUBLIQUE DU QUÉBEC

Strategy for Vaccination Against COVID-19: Postponement of the Second Dose in a Context of Shortage

COMITÉ SUR L'IMMUNISATION DU QUÉBEC

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Context

The number of cases, hospitalizations, and deaths due to COVID-19 have been increasing in Quebec since August 2020. In addition to the suffering of those infected and their friends and family, caring for patients and their contacts creates a significant burden for healthcare workers, who are frequently infected, threatening the integrity of our healthcare system. The way the pandemic develops in the coming months will depend on the population's compliance with the recommendations to minimize contacts, maintain physical distancing, wear a mask, and wash hands. It will also depend on the general measures enacted by the government. Unless there is dramatic improvement in the population's compliance or there are much stricter measures implemented, we cannot expect a swift decline in the weekly number of new hospitalizations and deaths without vaccination. In the short term, the impact of vaccination will depend on the targeted groups, the vaccination coverage within these groups, and the vaccines' effectiveness.

COVID-19 burden by priority group

The Comité sur l'immunisation du Québec (CIQ) has determined a priority order for the groups to be vaccinated (1). The contribution to the number of cases, hospitalizations, admissions to intensive care units (ICUs), and deaths between September 1 and December 6, 2020 vary widely among the first six priority groups (Table 1). Individuals living in CHSLDs have the highest proportion of deaths (39.5%); individuals 70 to 79 years old living in the community have the highest rate of intensive care unit (ICU) admissions (26.7%); and the percentage of all hospitalizations is high for residents of private seniors' residences (21.6%), individuals ≥ 80 years old (19.4%), and individuals 70 to 79 years old (17.9%) living in the community. Healthcare workers make up 11.8% of COVID-19 cases in Quebec while only representing 3-4% of the total population. Together, individuals living in CHSLDs and private seniors' residences, healthcare workers, and individuals ≥ 70 years old living in the community represent 24.8% of cases, 65.3% of hospitalizations, 54.5% of ICU admissions, and 92.3% of deaths in Quebec. The expedient vaccination of these groups would substantially reduce the burden of COVID-19, especially severe cases (hospitalizations and deaths). Note that the inclusion of individuals living in isolated and remote regions is justified by a risk of outbreak that could lead to serious consequences in these environments where there is a sizable proportion of individuals who are more susceptible due to chronic illness, difficulty applying isolation measures for infected individuals, and reduced access to specialized healthcare services.

Québec

Table 1 **Order of priority for vaccination against COVID-19 in Quebec and percentages of all cases, hospitalizations, admissions to the ICU, and deaths between September 1 and December 6, 2020 by group**

Rank	Group	Estimated number	Cumulative number	COVID-19 cases N = 90,575 % (n)	Hospitalizations N = 4,460 % (n)	ICU N = 724 % (n)	Deaths N = 1 482 % (n)
1	CHSLD residents	40,000	40,000	2.8% (2,507)	3.9% (174)	2.9% (21)	39.5% (585)
2	Healthcare workers	325,000	365,000	11.8% (10,695)	2.5% (110)	2.9% (21)	0.9% (13)
3	Individuals living in private seniors' residences	136,000	501,000	3.7% (3,307)	21.6% (961)	7.9% (57)	24.9% (369)
4	Residents of isolated and remote communities	46,000	547,000	N/A	N/A	N/A	N/A
5	Individuals in the community aged ≥ 80	418,000	965,000	2.8% (2,547)	19.4% (864)	14.1% (102)	16.5% (244)
6	Individuals in the community aged 70-79	768,000	1,733,000	3.7% (3,375)	17.9% (798)	26.7% (193)	10.5% (156)
	Total of groups 1 to 6	1,733,000		24.8%	67.9%	54.5%	92.3%

Source: Taken from the database Trajectoire de santé publique ([TSP], MSSS), December 6, 2020. N/A = not available.

Vaccination schedule and predictable vaccine supply

The first Pfizer-BioNTech BNT162b2 mRNA vaccine has been authorized in Canada with a schedule for two doses spaced a minimum of 21 days (2) apart and the mRNA-1273 vaccine from Moderna may soon be authorized with a schedule of two doses spaced a minimum of 28 days apart.

Assuming 85% vaccine coverage in the groups mentioned above, around 3 million vaccine doses would be required to vaccinate these six initial priority groups if we are to expect a significant impact on deaths, ICU admissions, and hospitalizations while protecting healthcare workers. The real, short-term epidemiological impact will be much lower due to the context of vaccine shortage and an upcoming vaccine rollout that will be very gradual. The number of doses to be delivered to Quebec by March 21, 2021 is unknown but will be substantially lower than 3 million; it could likely be around 1.3 million. This number would allow for the vaccination of 650,000 individuals with 2 doses, which covers those in the first four groups but very few individuals aged 70 or older living in the community, who represented 27% of deaths, 40.8% of ICU admissions, and 37.3% hospitalizations from September 1 to December 6, 2020.

While there is a shortage, we could maximize the health impact of the available doses by using a strategy where a first dose is administered to all individuals in the six initial priority groups before administering the second dose.

Vaccine efficacy after 1 and 2 doses

There is no immunological correlate of protection in humans, but experimental studies done on rhesus macaques with the BNT162b2 vaccine have demonstrated protection through low levels of neutralizing antibodies in the serum (3).

The schedule using 2 doses of the BNT162b2 vaccine has demonstrated short-term 95% efficacy, measured during the period starting on the 7th day following administration of the second dose with an average follow-up of around 2 months after this date (4,5). However, the clinical trial that demonstrated this high efficacy also showed that the vaccine offers very good protection with the first dose, with this protection appearing around the 12th day and lasting until at least the administration of the second dose and until the one-week period that is usually required for the booster effect.

The data from the clinical trial presented in Figure 3 in the article published in the New England Journal of Medicine shows that the occurrence of COVID-19 in the vaccinated group is similar to that of the placebo group in the first 10-12 days, after which occurrence in the vaccinated group abruptly diverges and remains stable thereafter (4). After the first dose and before the second dose, there were 39 cases in the vaccinated group and 82 in the placebo group, for 52% efficacy. This figure greatly underestimates the protection provided by the first dose as it includes the first days following the first dose during which efficacy is not expected as this is the latency period during which the immune response is activating. In their documents submitted to the United States FDA, the manufacturer also published the cumulative number of cases up to day 7 and up to day 14 after the first dose for each group (5). The vaccine efficacy can be calculated using these figures while excluding the cases occurring before day 7 (21 vaccinated and 25 placebo) or before day 14 (37 vaccinated and 55 placebo), periods during which immunity from the vaccine is not yet fully active (Table 2).

Table 2 Vaccine efficacy from one and two doses by observation period following each dose

Observation period	Vaccine N = 21,669 Cases	Placebo N = 21,686 Cases	Vaccine efficacy	95% CI
After dose 1				
Between dose 1 and dose 2	39	82	52.4%	30%-68%
7 days after dose 1 up until dose 2 (excluding cases occurring before day 7)	18 (21)	57 (25)	68.3%	46%-81%
14 days after dose 1 up until dose 2 (excluding cases occurring before day 14)	2 (37)	27 (55)	92.3%	69-98%
After dose 2				
Between dose 2 and 7 days after dose 2	2	21	90.5%	61-99%
Starting 7 days following dose 2 (primary analysis of the study)	9	172	94.8%	90-98%

When the cases occurring within 14 days of the first dose are excluded, the vaccine efficacy is 92.3%, which is equivalent to the 90.5% efficacy measured during the 7 days following the second dose and to the 95% for the entire monitoring for after 7 days following the second dose. The 95% confidence intervals for vaccine efficacy between day 14 after the first dose and up until the second dose range from 69% to 98%, suggesting high protection (69%) from a single dose during this observation period, even in the worst-case scenario.

The Phase 3 trial of Moderna's mRNA-1273 vaccine also showed excellent efficacy after a single dose. In the documents submitted by Moderna to the FDA for approval of their vaccine in the United States, information is provided on the vaccine efficacy after one dose and two doses of the vaccine (6). In the interim analysis of Phase 3 of the P301 trial, the vaccine's efficacy at preventing COVID-19 in the period starting 14 days after administration of the second dose was 94.5% (95% CI: 86.5% to 97.8%) with 100% efficacy against illness defined as serious: no cases in the experimental group versus 11 cases in the control group. Comparison of the cumulative frequency of COVID-19 cases in the experimental group and control group revealed a divergence that began on the 13th day after the randomization and continued monotonically. The vaccine efficacy for participants who received a single dose of the vaccine was 50.8% (95% CI: -53.6% to 86.6%) during the first 14 days and then 92.1% (95% CI: 68.8% to 99.1%) after that. In the experimental group, 2 cases classified as serious, based on oxygen desaturation in the blood, but without any other complications, were counted versus 4 in the control group. In another analysis, participants who were seronegative at the administration of the first dose were given a PCR test at the administration of the second dose. In the experimental group, SARS-CoV-2 infection was documented in 14 of the 14,134 participants versus 38 of the 14,073 participants in the control group. This result suggests that one dose of the vaccine reduces the risk of infection by 63% four weeks after its administration. All these data indicate good short-term efficacy from a single dose of mRNA-1273 to prevent both infection and the disease.

These results showing very high efficacy from the first dose of the vaccine are unsurprising. For many vaccines with schedules that include more than one dose, the first dose by far provides the greatest share of the protection. This phenomenon has been demonstrated by the vaccines against pertussis, measles, rubella, mumps, varicella, pneumococcus, and hepatitis A (7-12). The additional doses mainly serve to ensure long-term protection.

The duration of efficacy for Pfizer and Moderna's vaccines against COVID-19 is unknown for both one dose and two doses as the participants in Phase 3 of the clinical trials were monitored over a four-month maximum. If the studies are to continue, it is not possible to document the efficacy of an initial dose only over multiple months since the majority of participants received a second dose between 19 and 42 days following the first. However, it will be possible to document the medium-term efficacy of a schedule including 2 doses spaced 21 or 28 days apart as is recommended by the manufacturers. It is possible that the protection provided by a single dose will decrease gradually but more quickly than with 2 doses. It is still unlikely that the protection provided by an initial dose would end abruptly and quickly.

Although the duration of efficacy from a single dose of the vaccine remains unknown, one thing is certain: as long as individuals are unvaccinated, they remain at risk of contracting COVID-19 and developing complications. As the incidence of COVID-19 will remain high in the early months of 2021, the lack of vaccination for individuals 70 or older living in the community will lead to hundreds of hospitalizations and deaths due to COVID-19.

Given the current prevailing epidemiological situation in Quebec and the efficacy of a single dose of the vaccine, the strategy that should prevent the greatest number of cases would be to offer an initial dose of the vaccine to individuals in the first six priority groups, without reserving received vaccine doses for use as second doses 3 or 4 weeks after the first as is recommended by the manufacturers. The second dose would be offered according to vaccine availability and to the observed duration of effectiveness. This strategy requires close monitoring of the vaccine's effectiveness to quickly identify any sign of decreased effectiveness from the first dose in certain groups or, conversely, adopting a "wait and see" approach for a decision on the timing of the second dose.

This strategy also raises the question of interchangeability between vaccines. The Pfizer and Moderna vaccines both comprise messenger RNA that encodes the spike protein that ultimately generates an immune response. Even though the two products differ in their composition and exact mRNA genetic sequence, it is likely that a mixed schedule using both vaccines would produce a booster effect. This *may* also be the case for a mixed schedule comprised of two products using different technology platforms but that both aim to produce antibodies against the S spike protein. It will be necessary to monitor the scientific data on the interchangeability of COVID-19 vaccines to ensure that vaccinated individuals receive optimal protection.

Objectives of the COVID-19 vaccination strategy and ethical aspects

The objectives of the COVID-19 program that is now starting are the following:

1) Protect the most vulnerable individuals and prevent serious illness and death.
2) Prevent healthcare worker illness and absenteeism to ensure that healthcare services function properly.

These objectives, outlined in the notice from the CIQ on the vaccination priority groups (1), are based on the values of compassion, equality, justice, equity, and mutual support. Even though the vaccine was approved based on a schedule of two closely spaced doses, a single dose of the mRNA COVID-19 vaccine has demonstrated very high short-term protection. In the current epidemiological context where any delay in vaccinating certain highly vulnerable groups would cause a major risk of serious illness or death, a strategy offering an initial dose of the vaccine to twice as many highly vulnerable people appears essential to the objectives and ethical values of the Programme d'immunisation contre la COVID-19 au Québec, which is the Quebec Program for Immunization Against COVID-19.

Program compliance

Technical committees on vaccines around the world recommend administering 2 doses of the vaccine against COVID-19 at a 21-day interval, as this interval was examined in a Phase 3 study. In Canada, the National Advisory Committee on Vaccination (NACI) recommends administering 2 doses of the Pfizer-BioNTech BNT162b2 mRNA vaccine (2) with an interval of 21 or 28 days between the 2 doses. This interval must be a minimum of 19 days, but no maximum interval is proposed. This is intended to give the provinces and territories maximum flexibility in how they implement their programs depending on the operational constraints of vaccination services and vaccine supply. The recommendation made below is, therefore, in line with that of NACI.

Recommendation for the Programme d'immunisation contre la COVID-19 au Québec (Quebec Program for Immunization Against COVID-19)

The Comité sur l'immunisation du Québec recommends that the strategy for vaccination against COVID-19 in Quebec, in a context of shortage while the virus is spreading widely, be to offer an initial dose of the vaccine to the greatest possible number of individuals belonging to the first six priority groups. Once all of these individuals have had the opportunity to receive their first dose, we can then begin offering the second dose if the studies on effectiveness demonstrate a decline in protection after the first dose. If, conversely, the studies show high, sustained protection, the second dose can be postponed so that other groups of the population may be vaccinated.

The Comité sur l'immunisation du Québec also recommends close, continuous monitoring of the vaccine's effectiveness in near-real time throughout 2021 so that, if necessary, adjustments to the vaccination strategy proposed here may be made quickly.

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AUTHOR

Comité sur l'immunisation du Québec.

WRITERS

Gaston De Serres
Philippe De Wals
Direction des risques biologiques et de la santé au travail

LAYOUT

Marie-France Richard, Administrative Officer
Direction des risques biologiques et de la santé au travail

TRANSLATION AND REVIEW

Emily Wilson
Claire Maryniak

The French version is entitled *Stratégie de vaccination contre la COVID-19 : report de la 2e dose en contexte de pénurie* is also available on the website of the Institut national de santé publique du Québec at: www.inspq.qc.ca/publications/3098-strategie-vaccination-2e-dose-covid

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