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Requested supplement to the notice *Strategy for Vaccination Against COVID-19: Postponement of the Second Dose in a Context of Shortage*

NOTICE FROM THE COMITÉ SUR L'IMMUNISATION DU QUÉBEC

January 15, 2021

Question

Recently, various strategies have been recommended in a number of jurisdictions regarding the time interval between the two doses of COVID-19 vaccines. The Ministère de la Santé et des Services sociaux (MSSS) has asked the Comité sur l'immunisation du Québec (CIQ) to explain the basis of these different intervals. The MSSS also inquired whether the CIQ has maintained the recommendations that it put forward in a recent scientific notice (1), in particular, the recommendation to offer an initial dose of the vaccine to the greatest number of individuals belonging to the first six priority groups[1] before administering the second dose.

Response

Data on certain approved vaccines

The Phase 3 trials on COVID-19 vaccines were carried out in a context where the objective was to very quickly obtain protection that meets the authorization criteria of the Food and Drug Administration and the World Health Organization (WHO): that is, at least 50% efficacy in preventing cases of COVID-19, confirmed by polymerase chain reaction (PCR) tests, with the lower bound of the 95% confidence interval being greater than 30% (2). As a result, schedules with more than one dose with short intervals were consistently used by the main manufacturers, with the sole exception of Johnson & Joshnson (Janssen), for which only a single dose is planned (3).

In the Phase 3 trial of the now-approved Pfizer-BioNTech messenger RNA vaccine, BNT162b2, the recommended interval between the two doses was 21 days (4). In actual fact, the second doses were administered with an interval ranging from 19 to 42 days. We do not know how many of the 19,965 participants received their second dose of BNT162B2 at a 42-day interval, but it must be a small proportion as the specified interval was 19 to 23 days.

In the Phase 3 trial of Moderna's now-approved messenger RNA vaccine, mRNA-1273, the recommended interval between the two doses was 28 days (5), and the second doses were administered at an interval ranging from 21 to 42 days (4). As in the previous study, we do not know how many people actually received the second dose 42 days after the first dose, but it must also be a small proportion of the 14,134 participants in the mRNA-1273 group included in the per-protocol analysis.

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[1] CHSLD residents, healthcare workers, individuals living in private seniors' residences, residents of isolated and remote communities, individuals in the community aged 80 and above, and individuals in the community aged 70 to 79.

A third vaccine from AstraZeneca (AZD1222), based on viral vector technology, has been approved in the United Kingdom but is not yet approved in Canada. We do not yet have all of the details of its efficacy studies. In the four clinical trials for this vaccine involving a total of 23,848 participants, the recommended interval between the two doses was 28 days (6). For logistical reasons, some of the participants in the study conducted in Brazil (N=1,459) received the second dose of AZD1222 12 weeks after the first. Efficacy from 21 days after a single dose of the vaccine (maximum follow-up of 12 weeks) was similar to the efficacy of two doses of vaccine (7). Data on the immune response after the second dose as a function of the time between the two doses have also been published; these data are included in Table 1(8). It is clear that antibody titres are higher when the second dose is given later, which may suggest longer-term protection.

Table 1. Serological response to the ADZ1222 vaccine.

Population	Prior to vaccination	28 days after dose 1	28 days after dose 2
	GMT (95% CI)	**GMT (95% CI)**	**GMT (95% CI)**
Total	(N=882) 57.2 (52.8; 62.0)	(N=817) 8,386.5 (7,758.6; 9,065.1)	(N=819) 29,034.7 (27,118.2; 31,086.7)
Interval between doses			
< 6 weeks	(N=481) 60.51 (54.1; 67.7)	(N=479) 8,734.08 (7,883.1; 9,676.9)	(N=443) 22,222.73 (20,360.50; 24,255.3)
6-8 weeks	(N=137) 58.02 (46.3; 72.6)	(N=99) 7,295.54 (5,857.4; 9,086.7)	(N=116) 24,363.10 (20,088.5; 29,547.3)
9-11 weeks	(N=110) 48.79 (39.6; 60.1)	(N=87) 7,492.98 (5,885.1; 9,540.2)	(N=106) 34,754.10 (30,287.2; 39,879.8)
≥ 12 weeks	(N=154) 52.98 (44.4; 63.2)	(N=152) 8,618.17 (7,195.4; 10,322.3)	(N=154) 63,181.59 (55,180.1; 72,343.4)

N = Number of subjects per group; GMT = Geometric mean titre; CI = Confidence interval.
Source:
https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/950250/Information_for_UK_healthcare_professionals_on_COVID-19_Vaccine_AstraZeneca.pdf

In general, shorter intervals for vaccines requiring more than one dose do not generate an optimal immune response, and an increase in the interval between the first and second doses generally results in higher serum antibody levels as well as greater and, above all, longer protection (9,10). A similar phenomenon has been observed with an experimental mRNA vaccine against the avian viruses H10N8 and H7N9. A six-month interval between the first and second doses multiplied the geometric mean titres of serum antibodies by 2.6 to 10.1 compared to a 21-day interval (11).

Recommendations in some jurisdictions on the interval between doses and the underlying rationale

In a notice issued on December 18, 2020, the CIQ recommended offering an initial dose to the maximum number of individuals belonging to the first six targeted priority groups before offering a second dose (1). This recommendation is based on the following:

- The high efficacy (92%) of the BNT162b2 and mRNA-1273 vaccines 14 days after the first dose.
- The strong probability that the decline in vaccine-conferred immunity is gradual and slow, as has been demonstrated for several vaccines, despite uncertainties about the duration of efficacy after the first dose.
- The high incidence of COVID-19, where any delay in vaccinating certain highly vulnerable groups would cause many deaths and hospitalizations and where a strategy offering an initial dose of the vaccine to twice as many vulnerable people appears essential to the objective of preventing serious illness set by the Programme d'immunisation contre la COVID-19 au Québec, which is the Quebec program for immunization against COVID-19, and the ethical values supporting this objective.
- The generally better immunity with a longer interval between vaccine doses (9,10).
- Modelling data that suggests that postponing the administration of the second dose is an advantageous strategy for the prevention of COVID-19, even in pessimistic scenarios in which the efficacy of the first dose rapidly declines (12,13).

Since the CIQ's notice was issued, other organizations have proposed longer intervals than those recommended by the manufacturers of the approved vaccines. Based on the data available, the Joint Committee on Vaccination and Immunisation in the UK has recommended an interval of 3 to 12 weeks for the BNT162b2 vaccine and 4 to 12 weeks for ADZ1222, in order to rapidly ensure protection against COVID-19 for the greatest possible number of individuals with an initial dose (13). The choice of a possible 12-week interval seems to come from the analysis showing that protection persists for at least 12 weeks with the ADZ1222 vaccine. The objective was also to harmonize the recommendations regarding these two vaccines, since there is no robust data suggesting a different duration of efficacy in the case of messenger RNA vaccines.

Based on the same data, the National Advisory Committee on Immunization (NACI) has recommended an interval of 21 or 28 days for the BNT162b2 vaccine and 28 days for the mRNA 1273 vaccine, specifying, however, that a province may decide to maximize the number of individuals benefiting from an initial dose by delaying the administration of the second dose to a time preferably not exceeding 42 days (6 weeks) after the administration of the first dose (4). No maximum interval between the doses has been specified. The NACI noted that some participants in the clinical trials received the second dose 42 days after the first dose. The suggestion to not exceed 42 days is therefore not based on data showing decreased efficacy after this period of time.

Similarly, the WHO recommends an interval of 21 to 28 days between the two doses of the BNT162b2 vaccine, the only vaccine against COVID-19 that the organization has approved at present. However, they mention that this interval could be extended to 42 days (6 weeks) depending on the epidemiological situation (14), since data from the Phase 3 clinical trials include people who received their second dose with an interval of 42 days. The WHO also specifies that the proposed maximum interval could be revised depending on the availability of data on longer intervals between doses. In other countries like Denmark, an interval of 6 weeks between the two doses has also been permitted. Once again, these recommendations of a maximum interval of 42 days are not based on decreased efficacy after this interval, but rather on the absence of available data beyond this period for the two vaccines currently approved for use in Canada.

CIQ recommendations

In line with the data presented, the CIQ maintains its recommendation that the strategy for vaccination against COVID-19 in Quebec, in a context of vaccine 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.

The CIQ notes that the administration of a second dose is important to ensure long-term protection and must be provided. The administration of the second dose could be moved up if efficacy studies show a rapid decline in protection after the initial dose. If, conversely, the studies show high, sustained protection, the second dose could perhaps be further postposed so that other priority groups may be vaccinated sooner. For example, individuals 60 to 69 years old would be a group to vaccinate quickly, considering that, from September to December 2020 in Quebec, they made up 16% of hospitalizations, 28% of admissions to intensive care, and 6% of deaths. Finally, the CIQ reiterates its recommendation for 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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The French version is entitled *Demande complémentaire pour l'avis 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/3103-vaccination-2e-dose-contexte-penurie-covid19

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