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Use of Live-Attenuated Influenza Virus Vaccine (LAIV), Flumist® in children and adolescents aged 2-17 years of age with chronic conditions

Québec

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Context

The live attenuated influenza virus vaccine (LAIV), Flumist®, administered by intranasal spray, is approved for people aged 2-59 years. The National Advisory Committee on Immunization (NACI) recommended in its statement for the 2011-2012 season that, given its efficacy and immunogenicity, LAIV should be used preferentially for healthy children and adolescents aged 2 to 17 years[1]. NACI also indicates that LAIV can be used for children with chronic diseases, other than immune compromising conditions or severe asthma, but that there were insufficient data to recommend the preferential use of LAIV over trivalent inactivated vaccine (TIV)[2]. The Comité sur l'immunisation du Québec (CIQ) also recommended, at its June 2011 meeting, that LAIV should be used preferentially in healthy children aged 2-17 years, particularly among household contacts of people at high risk for complicated influenza infection.

At the December 2011 CIQ meeting, the question of LAIV preferential use in children and adolescent with chronic conditions was discussed again and, despite the absence of data demonstrating superior efficacy of LAIV in this group, members of the CIQ felt that there was no reason to believe that the immune response would be different from that obtained in healthy children. In order to ensure harmonization of vaccines for use in the paediatric population and to ensure equity, the Ministère de la Santé et des Services sociaux du Québec (MSSS) asked the CIQ to reconsider this issue and justify the merits of LAIV preferential use in children aged 2 to 17 years with chronic diseases without immune compromise.

Efficacy and Immunogenicity of LAIV in healthy children and adolescents

An extensive literature review was produced by NACI in 2011, detailing the immunogenicity and efficacy of LAIV compared to TIV[2]. The meta-analysis of Ambrose and colleagues summarizes the current data[3]. The five randomized controlled trials evaluating the efficacy of the LAIV vaccine included 4,288 children aged 24 to 71 months who were enrolled in efficacy studies comparing LAIV to placebo and 7,986 children and adolescents aged 2-17 years who were enrolled in studies comparing LAIV to TIV. The vaccine efficacy (VE) of 2 doses of LAIV compared to placebo during the first influenza season was 83% (95% CI: 78, 87) against antigenically similar strains. VE was 87% (95% CI: 78, 93) against strains of influenza A/H1N1, 86% (95% CI: 79, 91) against influenza A/H3N2 and 76% (95% CI: 63; 84) against influenza B. The VE was 93% (95% CI: 83, 97) when only B strains of similar lineage were analyzed. During a second season of vaccination), the VE was 87% (95% CI: 82, 91) against antigenically similar strains of influenza A and B.

The three studies comparing the vaccine efficacy of LAIV compared to TIV showed that subjects who were vaccinated with LAIV had 44% (95% CI: 28, 56) fewer infections (vaccine relative efficacy) caused by antigenically similar strains and 48% (95% CI: 38, 57) fewer infections caused by all strains of influenza, regardless of matching with vaccine strains. Analysis by type and subtype showed a vaccine relative efficacy of LAIV compared to TIV of 97% (95% CI: 78, 100) for infections caused by strains of Influenza A/H1N1, 55% (95% CI: 38, 67) for influenza A/H3N2 and 32% (95% CI: 14, 46) for influenza type B, regardless of antigenic match with vaccine strains.

As detailed in the NACI statement[2], the safety of LAIV was evaluated in multiple clinical studies with more than 28,500 healthy children and adolescents aged 2 to 17 years. The Adverse events following immunization (AEFI) most often reported, regardless of age, were nasal congestion and rhinorrhea. The AEFI passive surveillance system in the U.S. (VAERS) reported that among those 24 to 59 months old, 222 significant events were identified between 2007 and 2009. Of these, fever (47%), vomiting (28%), and rhinorrhea (21%) were most common[4]. Six cases of asthma exacerbation in children with known asthma and 8 reports of wheezing in children without a prior history of asthma were identified. Although wheezing had been reported as a possible AEFI following LAIV during the initial studies, Belshe and colleagues reported that in over 7,800 children aged 6 to 59 months followed prospectively, 3.9% of those vaccinated with LAIV and 3.1% of those vaccinated with TIV had clinically significant wheezing. The proportion of children with wheezing was, however, significantly different in those 6 to 23 months old (5.9% vs 3.1% after LAIV and TIV, respectively) during the second, third and fourth weeks after vaccination. This difference was not found in those aged 24 months and older[5].

Efficacy and safety of LAIV in asthmatics

Given the potential risk of asthma exacerbation in patients previously known as asthmatics, a Cochrane systematic review assessed vaccination against influenza in this population[6]. The group identified a study of quality conducted by Redding et al.[7] in 48 children with asthma, which demonstrated no significant difference between the group receiving LAIV and placebo with respect to change in forced expiratory volume (FEV_1), the number of asthma exacerbations, the number of participants with a reduction in peak expiratory flow rate of 15% or 30%, or the number of participants who used β-agonists as a rescue measure. Combining the results of this study with that of Atmar and colleagues, published in 1989 (n = 17 children with asthma)[8], the authors of the Cochrane review reported no difference in risk of decreased FEV_1 2-4 days post vaccination (RD: 0.01, 95% CI: -0.12, 0.15). It should be noted that the LAIV vaccines used in both studies were different (trivalent[7] vs monovalent)[8].

Fleming and colleagues randomized over 2,000 asthmatic children and adolescents aged 6 to 17 years to receive either TIV or LAIV. The study population consisted of an equal proportion of subjects who had been admitted for asthma (31% for each group) or who had received systemic corticosteroids (44% for LAIV vs 43% for VTI). Moreover, a similar proportion of subjects were receiving, at the time of the study, inhaled steroids (69.3% for LAIV vs. 68.8% for VTI) or systemic corticosteroids (1.9% for LAIV vs. 1.3% for VTI). The effectiveness of LAIV was 34.7% (95% CI: 3.9, 56) higher than that of TIV. The proportion of subjects who reported an AEFI was similar in both groups, except for rhinorrhea / nasal congestion in a higher proportion of those who received LAIV (66.2% for LIAV vs. 52.5% for TIV; $p < 0.001$) and wheezing found in a greater proportion of subjects who received TIV (19.5% for LAIV vs. 23.8% for TIV; $p = 0.02$)[9].

Gaglani and colleagues followed over 2,000 children and adolescents aged between 1.5 and 18 years with intermittent wheezing vaccinated with LAIV during four influenza seasons. No differences in consultation rates for respiratory symptoms were identified in 0-42 days after vaccination compared to the reference period in the four age groups[10].

Safety and immunogenicity in LAIV in subjects with cystic fibrosis

A Cochrane systematic review assessed influenza vaccination in patients with cystic fibrosis[11]. The authors reported that both vaccines (LAIV and TIV) were immunogenic in patients with cystic fibrosis. However, in the absence of randomized trials comparing the two vaccines, the relative effectiveness of LAIV compared to TIV is unknown. The proportion of AEFI was 24% (48/201) for LAIV, 43% (13/30) for influenza split-virus vaccine and 27% (57/210) for TIV. AEFIs were not severe or persistent. In terms of AEFI, no difference was found between types of influenza vaccine but a low statistical power could have explained this lack of difference.

Safety and immunogenicity of LAIV in subjects with mild immunosuppression

Halasa and colleagues randomized children and adolescents with cancer, aged 5-17 years, to receive either placebo or LAIV. Of the 20 subjects enrolled in the study, 10 had solid tumors and 10 had hematological malignancies. Subjects were excluded if they had asthma and if they were receiving inhaled steroids. During the 10 days following vaccination, only nasal congestion / rhinorrhea (77% for LAIV vs. 20% for placebo, $p = 0.02$) and vomiting (33.3% for LAIV vs. 10% for placebo, $p > 0.5$) were reported more frequently with LAIV. One child in each group reported a temperature between 37.8 and 38.3 ^{0}C during the first 10 days after vaccination. Following vaccination, 78%, 89% and 78% of subjects who received LAIV and 60%, 90% and 40% who received placebo had an antibody titer ≥ 1/40 by microneutralization against influenza A/H1N1, A/H3N2 and B respectively. The subjects who received placebo had, however, lower antibody titers (HAI and microneutralization)[12].

Carr and colleagues[13] randomized 55 subjects aged between 2 and 21 years with hematologic malignancy (n = 25) or solid tumor (n = 30) to receive either LAIV (n = 28) or TIV (n = 27). Total AEFIs reported between 0 and 10 days post-vaccination were similar in both groups. However fever was reported more frequently following TIV (0% for LAIV vs 7.4% for TIV), as was cough (7.1% with LAIV vs. 18.1% for TIV), whereas rhinorrhea

was reported equally in both groups (35.7% for LAIV vs. 33.3% for TIV). Immunogenicity (HAI) was better after TIV. Table 1 summarizes immunogenicity data from this study.

These two studies, taken together, include a limited number of subjects receiving LAIV (n = 36), whose underlying diseases and treatments varied, resulting in immunosuppression and immune responses that were highly variable. Results of serological and cellular immunity (ELISPOT)[13] are therefore difficult to compare. It is thus impossible to draw conclusions on the immunogenicity of LAIV and TIV for this group of patients, given the limited data currently available.

Table 1 Immunogenicity of LAIV and TIV in patients with mild immunosuppression (Adapted from Carr et al.)[13]

	LAIV (n = 26)	TIV (n = 26)	P
A (H3N2)			
Pre-vaccination			
• GMT (IC95%)	80 (5-1,244)	126 (5-2,920)	0.30
• % seroprotection	84%	80.7%	> 0.999
Post-vaccination			
• GMT (IC95%)	82 (7-976)	228 (18-6,286)	< 0.001
• % seroprotection	80.7%	92.3%	0.41
• % seroconversion	7.6%	46.1%	< 0.004
A (H1N1)			
Pre-vaccination			
• GMT (IC95%)	24 (3-216)	38 (3-456)	0.19
• % seroprotection	34.6%	53.8%	0.26
Post-vaccination			
• GMT (IC95%)	17 (4-80)	89 (6-1,336)	< 0.001
• % seroprotection	34.6%	73.0%	0.01
• % seroconversion	7.6%	26.9%	0.13
B (Flor) – matched strains			
Pre-vaccination			
• GMT (IC95%)	11 (2-66)	13 (1-131)	0.51
• % seroprotection	15.3%	23	0.73
Post-vaccination			
• GMT (IC95%)	14 (3-68)	21 (2-274)	0.41
• % seroprotection	19.2%	30.7%	0.52
• % seroconversion	3.8%	11.5%	0.60
B (Bris) – mismatched strains			
Pre-vaccination			
• GMT (IC95%)	20 (3-153)	12 (2-81)	0.05
• % seroprotection	30.7%	19.2%	0.52
Post-vaccination			
• GMT (IC95%)	8 (2-29)	11 (2-53)	0.15
• % seroprotection	3.8%	15.3%	0.34
• % seroconversion	0%	3.8%	< 0.999

Note: GMT: Geometric Mean Titer; Seroprotection: Titre HAI ≥ 40; Seroconversion: Four-fold increase in HAI titre pre- and post-vaccination or titers post-vaccination ≥ 40 if < 10 pre-vaccination.

Economic considerations and acceptability of LAIV

LAIV will likely be more expensive than TIV. At this time, it is estimated that the cost of LAIV would be between 1.5 and 2 times higher than that of TIV. We have not undertaken an incremental cost-effectiveness analysis associated with a change to use this vaccine in the Province of Québec. However, the literature reports studies on the cost-effectiveness of LAIV vs. TIV in children aged 24 to 59 months in the U.S.[14] and Canada[15]. The authors conclude that, from an economic standpoint, the additional cost associated with

the use of LAIV could be partly offset by the superior efficacy of LAIV compared to TIV, with an increased reduction in direct and indirect costs of influenza infections.

In addition to the anticipated gains in vaccine efficacy, ease of administration of the intranasal vaccine and the anticipated decrease in fear of injections in children and adolescents may help improve influenza vaccine acceptability among both parents and health professionals. One could thus hope for a better coverage.

Synthesis

The literature review demonstrates superior efficacy of LAIV compared to TIV in healthy and asthmatic children and adolescents. The few data on immunogenicity, which we know is not an ideal marker of efficiency, in children with most chronic illnesses other than immune compromising states shows good immunogenicity with LAIV. As no efficacy study has been done in children with chronic illness, it is impossible to generalize the results demonstrating superior efficacy of LAIV compared to TIV observed in healthy children to this population. However, the Comité sur l'immunisation du Québec considers that the LAIV is likely to be at least as effective as TIV in children with chronic diseases without immunosuppression.

From the standpoint of safety, LAIV is generally well tolerated. Some studies have cast doubt on its safety in patients with previous history of asthma. However, more recent studies show that the proportion of subjects with asthma exacerbations or episodes of wheezing is similar after LAIV and TIV.

From an economic standpoint, the additional cost of the vaccine should be offset by reduced costs associated with the treatment of influenza in the pediatric population. One can also expect the intranasal vaccine to be more acceptable than the injectable vaccine and thus hope for a better coverage.

Recommendation

In this context, the Comité sur l'immunisation du Québec recommends the preferential use of LAIV for all children and adolescents aged 2 to 17 years, including those with underlying chronic diseases, except for those with immunosuppression or other contraindication for the use of LAIV[16].

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