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Preferential LAIV use in children with chronic underlying conditions?

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Disclosure of Relationship	Company/Organization
I am a member of an Advisory Board or equivalent with a commercial organization.	NO
I am a member of a Speaker Bureau.	NO
I have received payment from a commercial organization (including gifts or other consideration or 'in kind' compensation).	NO
I hold a patent for a product referred to in the CME/CPD program or that is marketing by a commercial organization	NO
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I hold investments in a pharmaceutical organization, medical devices company or communications firms.	NO
I am currently participating in or have participated in a clinical trial within the past two years.).	NO
I have received research grants from commercial organizations	GSK, Sage, Pfizer, AbbVie

Objectives

- At the end of this session, participants will be able to:
  - Discuss the risks and benefits of LAIV use in children with cystic fibrosis
  - Discuss how influenza vaccination clinics in tertiary care centres have used the LAIV to increase influenza vaccination uptake in children with chronic conditions

Live-attenuated influenza vaccine

- Intranasally administered influenza vaccine
- Live-attenuated reassortants of 3 (4) vaccine strains:
  - Master donor strain: cold-adapted, temperature-sensitive and attenuated
- Stimulates mucosal immunity (IgA and cell-mediated immunity): able to enhance mucosal IgA avidity without increase in serum Ab concentration
- Viral shedding: 44% (5-8 years), 27% (9-17 years), 17% (18-49 years)

LAIV efficacy vs. IIV (2-17 years)

Criteria used	Relative efficacy	95% CI
Antigenically similar strains	44%	28 - 56
All influenza strains	48%	38 - 57
A/H1N1 – regardless of match	97%	78 - 100
A/H3N2 – regardless of match	55%	38 - 67
B – regardless of match	32%	14 - 46

Ashkenazi S. *Pediatr Infect Dis J* 2006; 25: 870-9
Fleming DM. *Pediatr. Infect. Dis. J.* 2006; 25: 860-9
Belshe RB. *NEJM* 2007; 356: 685-96.

IIV vs. LAIV efficacy – Age groups

Age groups	Relative efficacy (IIV/LAIV)	95%CI
18-46 years (1)	53%	-5 - 80
18-46 years (2)	50%	20 - 69
60 years +	41%	-17 - 70

Ohmit SE. *NEJM* 2006; 355: 2513-22
Monto AS. *NEJM* 2009; 361: 1260-7
Forrest BD. *Vaccine* 2011; 29: 3633-9

LAIV vs. IIV (effectiveness) - US

Season	Vaccine effectiveness		
	Overall	2-8 years	9-18 years
2011-12	4% (-105, 55)	43% (-80, 82)	-16% (-277, 64)
2012-13	4% (-40, 34)	35% (-8, 61)	-21% (-134, 38)

Clippard J. *ID Week 2014*, Philadelphia

LAIV vs. IIV - efficacy in asthmatics

Criteria	Relative efficacy (LAIV/IIV)	95% CI
Antigenic match	34.2%	3.2 – 55.7
Regardless of match[1]	32.4%	1.9 – 53.7
Regardless of match[2]	46.6%	18.6 – 65.4
Regardless of match[3]	39.9%	-25.9 – 72.3

1. Fleming DM. *Pediatr. Infect. Dis. J.* 2006; 25: 860-9
2. Belshe RB. *NEJM* 2007; 356: 685-96
3. Ashkenazi S. *Pediatr. Infect. Dis. J.* 2006; 25: 870-9.

Ambrose CS. *Eur J Clin Microbiol Infect. Dis.* 2012; 31: 2547-57

Safety

- Healthy children:
  - mainly rhinorrhea and nasal congestion
  - Wheezing: 3.9% (LAIV) vs. 3.1% (IIV) – 5.9% in 6-23 months-old
- Asthmatics:
  - Cochrane review: no difference in risk of decreased FEV1
  - Fleming et al:
    - Rhinorrhea/nasal congestion: 66.2% (LAIV) vs. 52.5% (IIV)
    - Wheezing: 19.5% (LAIV) vs. 23.8% (IIV)

Cates CJ. *Cochrane Database Syst Revl* 2013: 2: CD00364
Fleming DM. *Pediatr. Infect. Dis. J.* 2006; 25: 860-9

Children with cystic fibrosis (CF)

- Immunogenicity similar to healthy children
- Described AEFIs:

AEFI	n/N	%
Fever	4/47	8.5
Rhinorrhea	18/47	38.3
Cough	9/47	19.1
Increase in sputum	5/20	25%

Gruber WC. *J. Infect. Dis* 1994; 169: 241-7

LAIV and CF

- Children with CF followed in clinics across Canada aged 2-18 years
- LAIV and followed x 56 days
- Year 1: October 1, 2012 – January 30, 2013
- Year 2: October 1, 2013 – January 30, 2014
- <u>Exclusions:</u>
  - Systemic corticosteroids
  - Medically-attended wheezing in previous 7 days
  - Nasal polyps or significant rhinorrhea
  - Immunosuppressed

Boikos C. *Pediatr* 2014; 134 DOI: 10.1542/peds.2014-0887

Outcomes studied

- **Primary**:
  - Respiratory deteriorations: Unscheduled medical visit or hospital admission
- **Secondary:**
  - Incident oral antibiotic use for respiratory complaints
  - All-cause hospitalizations
  - Respiratory and/or systemic AEFIs

- Analysis: Self-controlled incidence rate ratios (at-risk vs. non at-risk periods)

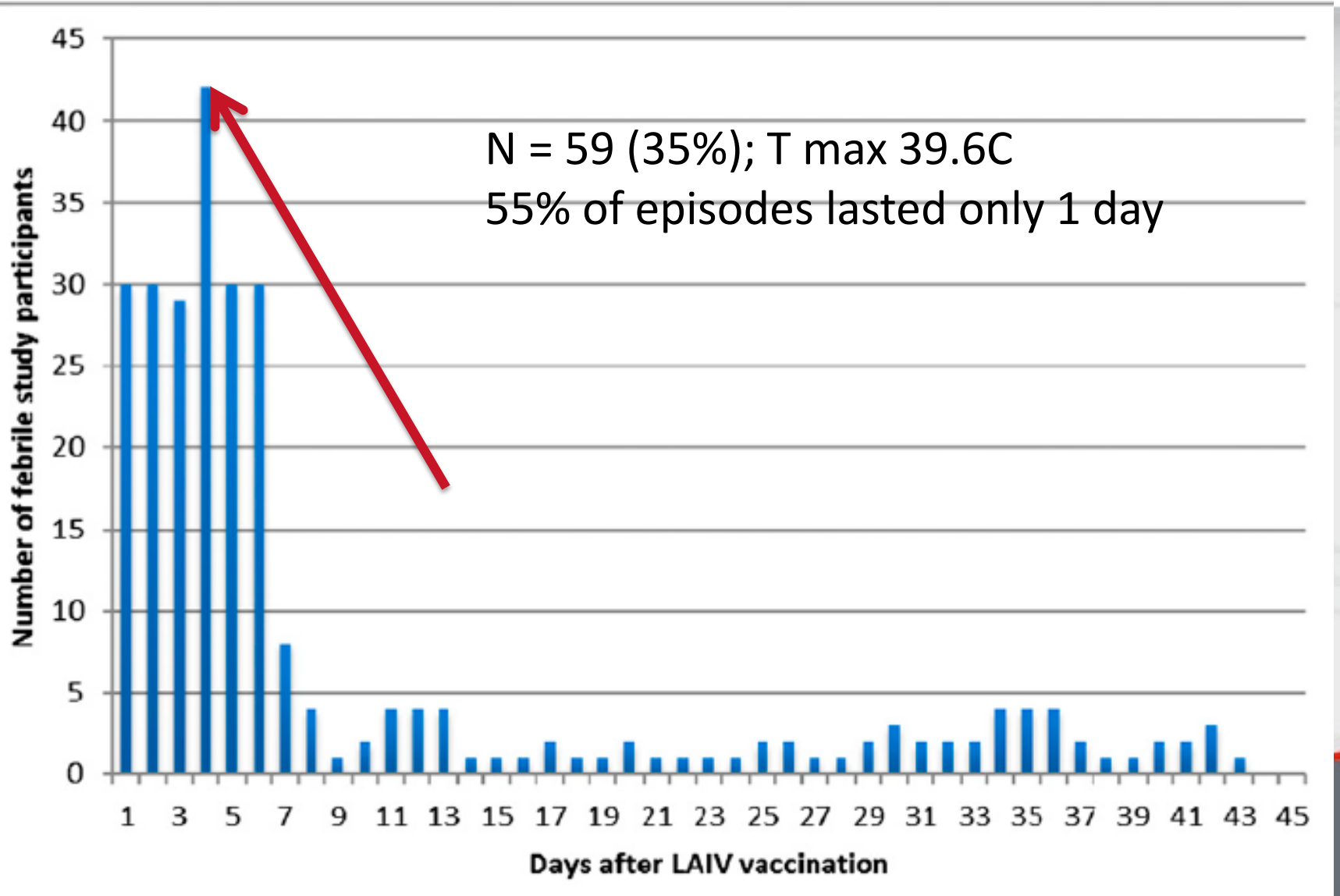
Characteristics	N=168	<9 years (n=60)
Age (years): Mean (SD), median	10.6 (4.7), 11	
Race – Caucasian (%)	161 (96.4)	
Received IIV:		
For past 2 years	110/166 (66%)	43/59 (73%)
Not in past 2 years	31/166 (19%)	10/59 (17%)
Antibiotic use (%)		
Inhaled AB	31 (18.5)	
Azithromycin	5 (3)	
Corticosteroid use (%)		
Inhaled	26 (15.5)	
Nasal	19 (11.3)	
Both	18 (10.7)	

Outcomes

Outcomes	IRR or RR	95%CI
Incident respiratory deteriorations	0.72	0.11-4.27
PO antibiotic treatments	0.32	0.03-1.80
All-cause hospitalizations	1.16	0.30-4.81
At least 1 solicited symptom – week 1 (%)	107 (64)	
Joint pain	10.5	2.5-44.1
Myalgia	9.7	3-31.1
Vomiting	7.7	2.4-25.1

Solicited symptoms after IIV (CF): 15/21 (71%)

AEFI: fever


N = 59 (35%); T max 39.6C
55% of episodes lasted only 1 day
Number of febrile study participants
0
5
10
15
20
25
30
35
40
45
1 3 5 7 9 11 13 15 17 19 21 23 25 27 29 31 33 35 37 39 41 43 45
Days after LAIV vaccination

Symptom[a]	All Study Participants (n = 168)				Days 0–28		
	Days 0–6	Days 0–28	Days 29–56	RR[b] (95% CI)	<9 y old (n = 60)	≥9 y old (n = 108)	RR (95% CI)
Runny nose	56 (33%)	74 (44%)	28 (17%)	2.64 (1.81–3.86)	35 (58%)	39 (36%)	1.62 (1.16–2.25)
Nasal congestion	48 (29%)	67 (40%)	23 (14%)	2.91 (1.91–4.45)	27 (45%)	40 (37%)	1.22 (0.84–1.76)
Headache	48 (29%)	56 (33%)	59 (35%)	0.95 (0.71–1.28)	12 (20%)	44 (41%)	0.49 (0.28–0.85)
Tiredness	46 (27%)	53 (32%)	11 (7%)	4.82 (2.61–8.90)	17 (28%)	36 (33%)	0.85 (0.52–1.38)
Worsening of cough	18 (11%)	39 (23%)	22 (13%)	1.77 (1.10–2.86)	14 (23%)	25 (23%)	1.01 (0.57–1.79)
Sore throat	36 (21%)	49 (29%)	11 (7%)	4.45 (2.40–8.26)	13 (22%)	36 (33%)	0.65 (0.37–1.13)
Increased sputum	0	0	0	—	0	0	—
Abdominal pain	27 (16%)	34 (20%)	7 (4%)	4.86 (2.22–10.65)	13 (22%)	21 (19%)	1.11 (0.60–2.06)
Muscle aches	23 (14%)	29 (17%)	3 (2%)	9.67 (3.00–31.12)	7 (12%)	22 (20%)	0.57 (0.26–1.26)
Chills	24 (14%)	26 (15%)	4 (2%)	6.50 (2.31–18.22)	7 (12%)	19 (18%)	0.66 (0.30–1.49)
Sleep disturbance	17 (10%)	23 (14%)	6 (4%)	3.83 (1.60–9.17)	10 (17%)	13 (12%)	1.38 (0.65–2.97)
Diarrhea	16 (10%)	22 (13%)	5 (3%)	4.40 (1.71–11.34)	11 (18%)	11 (10%)	1.80 (0.83–3.90)
Nausea	21 (13%)	22 (13%)	8 (5%)	2.75 (1.26–6.00)	8 (13%)	14 (13%)	1.03 (0.46–2.31)
Joint pain	17 (10%)	21 (13%)	2 (1%)	10.50 (2.50–44.08)	6 (10%)	15 (14%)	0.72 (0.29–1.76)
Vomiting	18 (11%)	23 (14%)	3 (2%)	7.67 (2.35–25.05)	13 (22%)	10 (9%)	2.34 (1.09–5.01)
Redness in both eyes	15 (9%)	15 (9%)	0	—	7 (12%)	8 (7%)	1.58 (0.60–4.13)
Difficulty breathing	15 (9%)	18 (11%)	0	—	5 (8%)	13 (12%)	0.69 (0.26–1.85)
Difficulty swallowing	17 (10%)	17 (10%)	0	—	7 (12%)	10 (9%)	1.26 (0.51–3.14)
Wheezing	13 (8%)	13 (8%)	3 (2%)	4.33 (1.26–14.93)	6 (10%)	7 (6%)	1.54 (0.54–4.38)
Facial swelling	10 (6%)	10 (6%)	0	—	4 (7%)	6 (6%)	1.20 (0.35–4.09)
Fever	59 (35%)	64 (38%)	15 (9%)	4.27 (2.54–7.18)	27 (45%)	37 (24%)	1.31 (0.90–1.93)
At least 1 symptom	107 (64%)	130 (77%)	91 (54%)	1.43 (1.22-1.68)	49 (82%)	81 (75%)	1.09 (0.93-1.28)

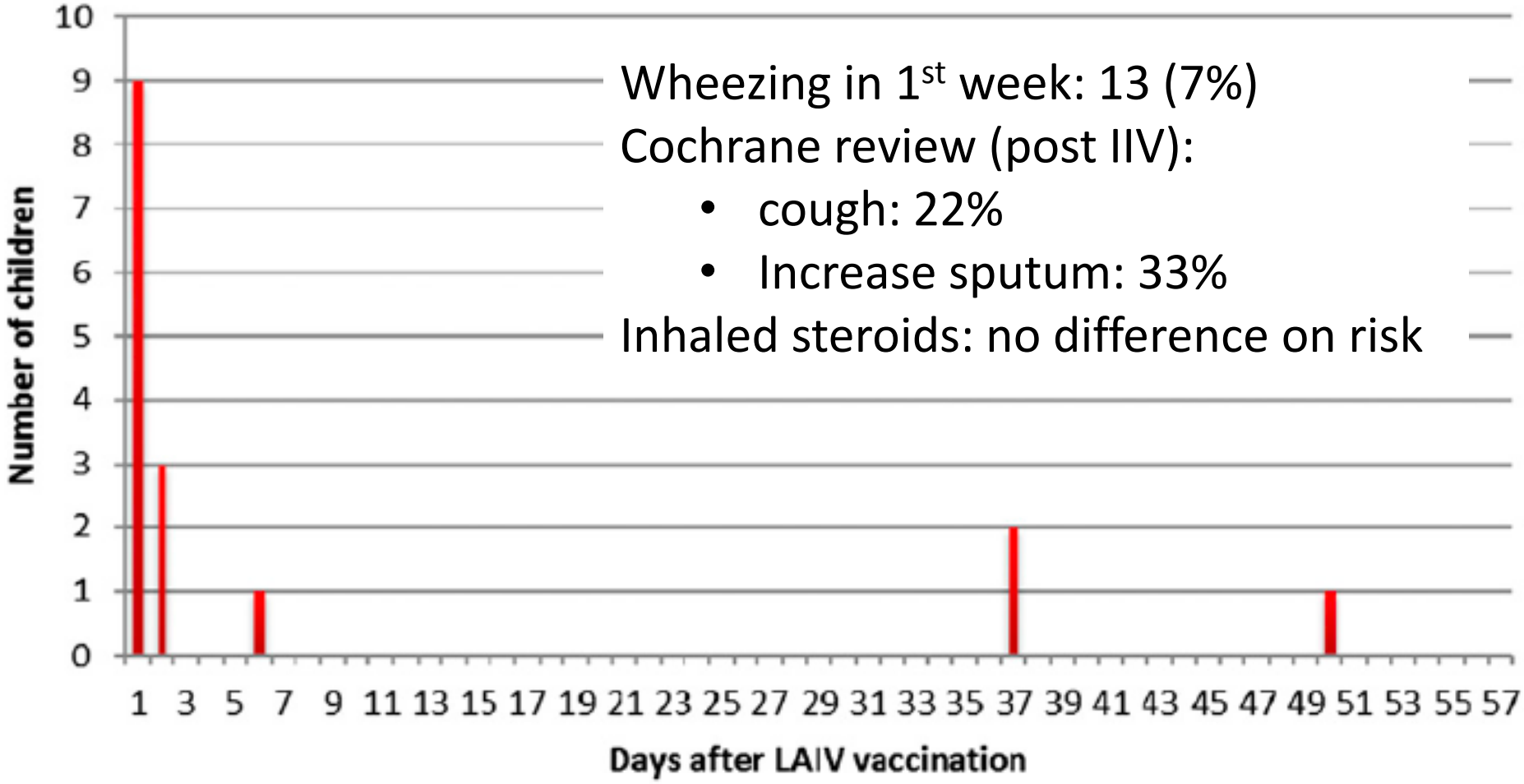
Inhaled corticosteroids use at baseline

- Runny nose:
  - + = RR 1.11 (0.51-2.42)
  - - = RR 3.37 (2.15-5.29)

Inhaled corticosteroids use at baseline

- Nasal congestion:
  - + = RR 1.63 (0.76-3.45)
  - - = RR 3.6 (2.14-6.04)

Wheezing



Wheezing in 1st week: 13 (7%)

Cochrane review (post IIV):

- cough: 22%
- Increase sputum: 33%

Inhaled steroids: no difference on risk

AEFIs (2nd year)

AEFI (%)	First LAIV (n=28)	2nd year (n=66)	Healthy (n=19)
Chills	5 (18)	2 (3)	0
Myalgia	4 (14)	2 (3)	1 (5)
Arthralgia	2 (7)	2 (3)	1 (5)
Tired	11 (39)	8 (12)	5 (26)
Headache	7 (25)	11 (17)	6 (32)
Nausea/Vomiting	3 (11)	1 (1.5)	0
Redness eyes	1 (4)	0	1 (5)
Coughing worse	6 (21)	6 (9)	2 (11)
Wheezing	1 (4)	0	0
Facial swelling	0	0	0
Fever	1 (4)	3 (5)	0

C. Quach, unpublished data

Influenza vaccination clinics

- In Quebec, funded by MSSS: Influenza vaccination clinics in tertiary care pediatric hospitals, using LAIV as preferential vaccine
  - The Montreal Children's Hospital results will be presented by Dr. Joanna Merckx – December 4th @11:00 Room 202
  - In 2012-13 and 2013-14: 630 children with chronic conditions vaccinated/year; on average 400 household members/year were also vaccinated
  - In both years, 20% of parents said that the only reason for getting their child vaccinated was because of the on-site clinic

LAIV – chronic conditions

- LAIV preferred by:
  - 403/512 parents (78.7%) *** no needle!!
  - Comparing 2012 to 2013: 12% (62/599) and 26% (125/473) of eligible children did not choose LAIV ($p<0.0001$)
  - The reason for this is unclear and needs to be further investigated.

Conclusions

- LAIV has been shown to be more effective than IIV in most influenza seasons for children aged 2-6 years
- In 2013-14, the CDC reported a lack of VE in young children for p/H1N1
- LAIV can be safely used in children with CF – its use for a second year does not seem to increase AEFIs
- LAIV has been used as the preferred vaccine in children with chronic conditions, without immunosuppression
- The trend to decrease LAIV preference needs to be followed

Questions

Additional reference

Quach C. Vaccinating High-Risk Children with the Intranasal Live-Attenuated Influenza Vaccine: the Quebec Experience. *Paediatr Resp Rev* 2014; 15: 340-7.

http://authors.elsevier.com/a/1Q1vy5Q-0lLM25

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