20e Journée de pathologie infectieuse pédiatrique ambulatoire

LA VACCINATION, C'EST DIFFICILE !

LE CAS DE LA GRIPPE

Robert Cohen
Catherine Weil-Olivier

Sachant que

- depuis le 6 octobre 2016, la campagne de vaccination contre la grippe a été lancée officiellement par la ministre de la santé
- que le vaccin vivant nasal atténué quadrivalent (Fluenz tetra®) est disponible en pharmacie, au prix de 35 €, mais non remboursé, qu'il est recommandé 2 doses la première année

Quel vaccin allez-vous proposer aux patients suivants ?

Raphaël 25 mois, asthme du nourrisson en crèche, 6 épisodes, pas vacciné l'année dernière, sous Flixotide® et Ventoline®.

- Pas de vaccin grippe
- Vaccin injectable trivalent remboursé
- Uniquement le Fluenz tetra®
- Fluenz tetra® si les parents refusent le VI

Sacha 18 mois, asthme du nourrisson en crèche, 6 épisodes, pas vacciné l'année dernière, sous Flixotide® et Ventoline®.

- Pas de vaccin grippe
- Vaccin injectable trivalent remboursé
- Uniquement le Fluenz tetra®
- Fluenz tetra® si les parents refusent le VI

Roxane 7 ans, asthme récurrent sous Seretide® et Ventoline®, vaccinée les années précédentes à plusieurs reprises.

- Pas de vaccin grippe
- Vaccin injectable trivalent remboursé
- Uniquement le Fluenz tetra®
- Fluenz tetra® si les parents refusent le VI

Articles

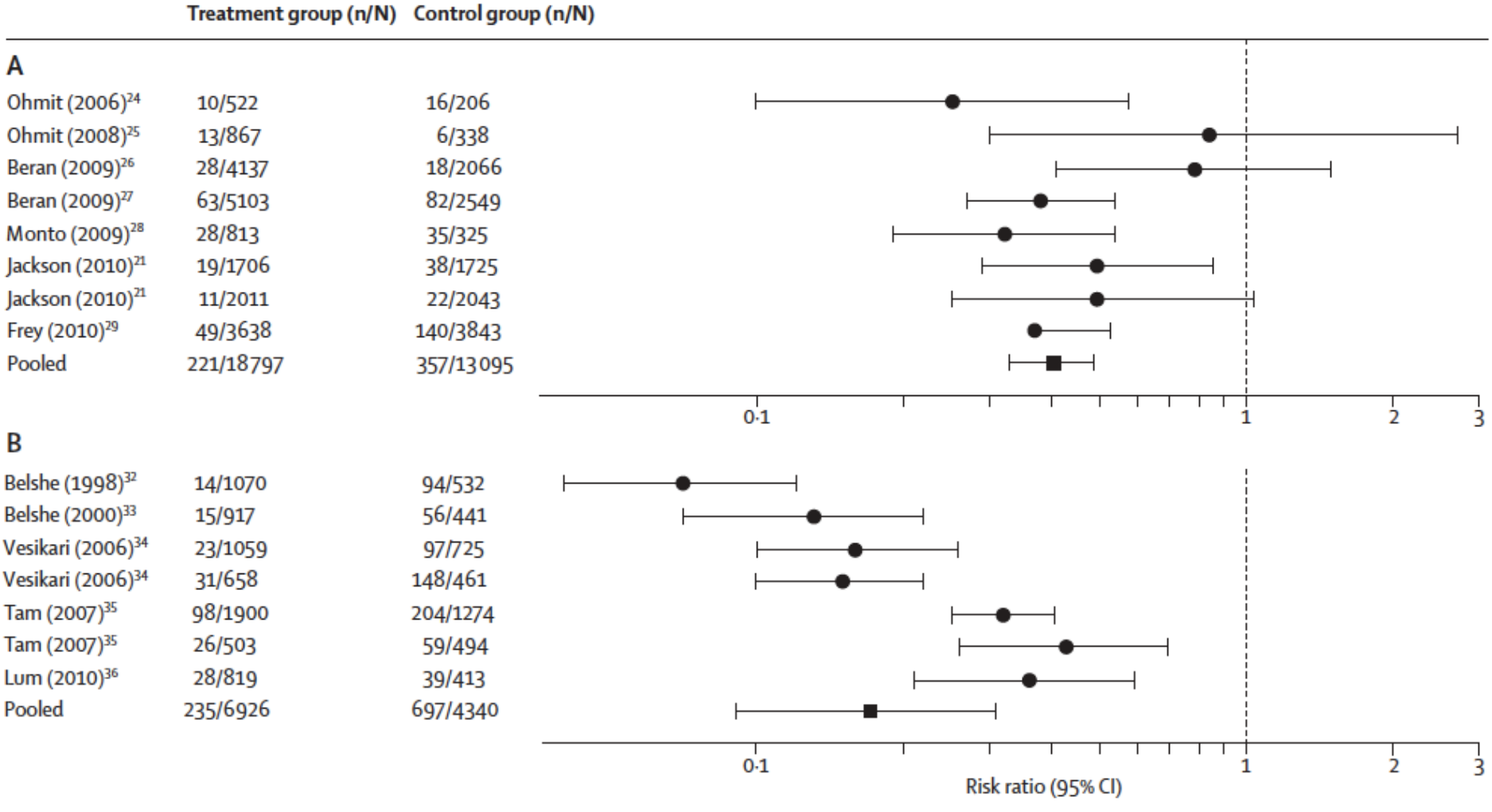
Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis

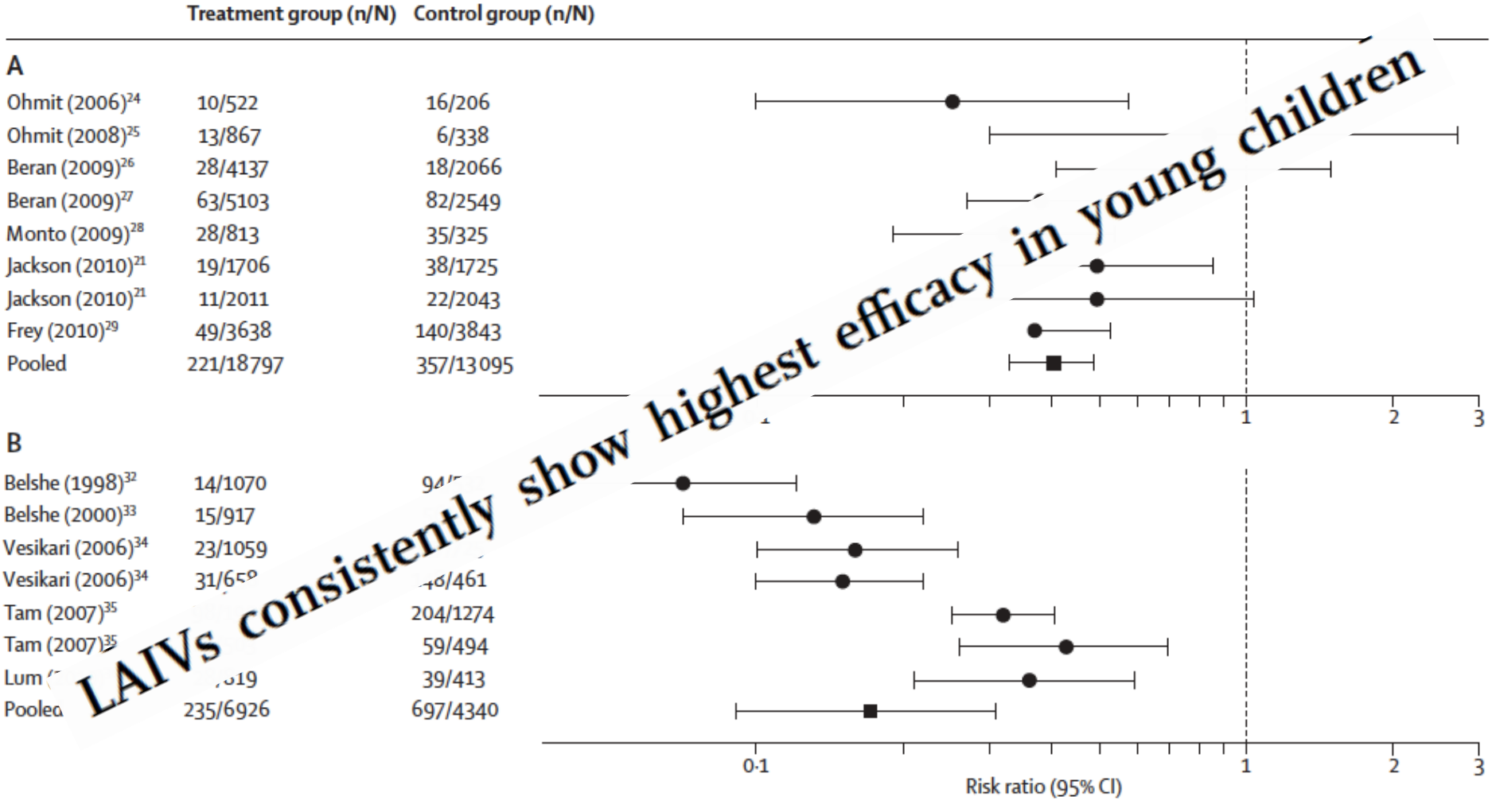
Michael T Osterholm, Nicholas S Kelley, Alfred Sommer, Edward A Belongia

Lancet Infect Dis 2012; 12: 36-44

Summary

Background No published meta-analyses have assessed efficacy and effectiveness of licensed influenza vaccines in the USA with sensitive and highly specific diagnostic tests to confirm influenza.


Treatment group (n/N)
Control group (n/N)
A
Ohmit (2006)[24] 10/522 16/206
Ohmit (2008)[25] 13/867 6/338
Beran (2009)[26] 28/4137 18/2066
Beran (2009)[27] 63/5103 82/2549
Monto (2009)[28] 28/813 35/325
Jackson (2010)[21] 19/1706 38/1725
Jackson (2010)[21] 11/2011 22/2043
Frey (2010)[29] 49/3638 140/3843
Pooled 221/18797 357/13095
0·1
1
2
3
B
Belshe (1998)[32] 14/1070 94/532
Belshe (2000)[33] 15/917 56/441
Vesikari (2006)[34] 23/1059 97/725
Vesikari (2006)[34] 31/658 148/461
Tam (2007)[35] 98/1900 204/1274
Tam (2007)[35] 26/503 59/494
Lum (2010)[36] 28/819 39/413
Pooled 235/6926 697/4340
0·1
1
2
3
Risk ratio (95% CI)


Treatment group (n/N)
Control group (n/N)
A
Ohmit (2006)[24] 10/522 16/206
Ohmit (2008)[25] 13/867 6/338
Beran (2009)[26] 28/4137 18/2066
Beran (2009)[27] 63/5103 82/2549
Monto (2009)[28] 28/813 35/325
Jackson (2010)[21] 19/1706 38/1725
Jackson (2010)[21] 11/2011 22/2043
Frey (2010)[29] 49/3638 140/3843
Pooled 221/18797 357/13095
B
Belshe (1998)[32] 14/1070
Belshe (2000)[33] 15/917
Vesikari (2006)[34] 23/1059
Vesikari (2006)[34] 31/659
Tam (2007)[35] 204/1274
Tam (2007)[35] 59/494
Lum 39/413
Pooled 235/6926 697/4340
LAIVs consistently show highest efficacy in young children
0·1
1
2
3
Risk ratio (95% CI)

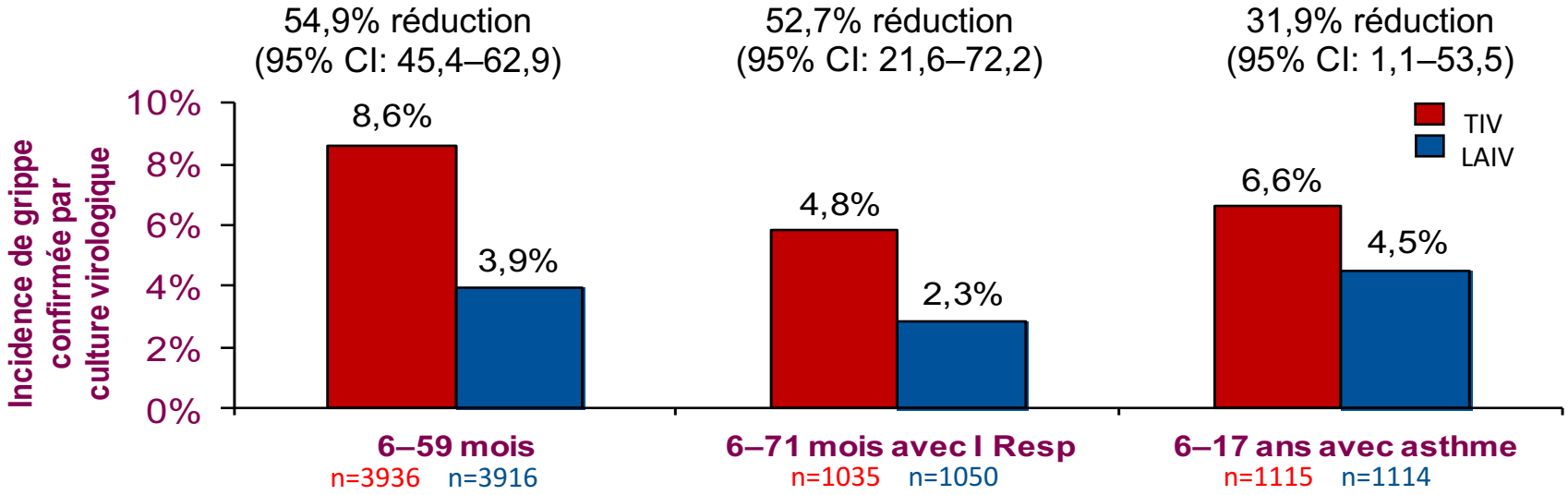
	Population (dates)	Patients randomly allocated to receive LAIV and placebo	Vaccine efficacy (95% CI)	Reported antigenic match
Children (6 months–7 years)				
Belshe et al (1998)[32]	Healthy children aged 15–71 months (1996–97)	1602	93% (88 to 96)	Type A: similar H3N2; type B: lineage match
Belshe et al (2000)[33]	Healthy children aged 26–85 months (1997–98)	1358	87% (78 to 93)	Type A: drifted H3N2; type B: not reported (1 isolate)
Vesikari et al (2006)[34]	Healthy children aged 6–<36 months attending day care (2000–01)	1784	84% (74 to 90)	Type A: similar H3N2 and H1N1; type B: lineage match
Vesikari et al (2006)[34]	Healthy children aged 6–<36 months attending day care (2001–02)	1119	85% (78 to 90)	Type A: similar H3N2 and H1N1; type B: mixed lineage
Bracco Neto et al (2009)[38]	Healthy children aged 6–<36 months (2000–01)	1886	72% (62 to 80)	Majority of strains were similar (not reported by type)
Tam et al (2007)[35]	Healthy children aged 12–<36 months (2000–01)	3174	68% (59 to 75)	Type A: similar H3N2 and H1N1; type B: lineage match
Tam et al (2007)[35]	Healthy children aged 12–<36 months (2001–02)	2947	57% (30 to 74)	Type A: similar H3N2 and H1N1; type B: mixed lineage
Lum et al (2010)[36]	Healthy children aged 11–<24 months (2002–03)	1233	64% (40 to 79)	Type A: similar H1N1 and mixed H3N2; type B: mixed lineage

	Population (dates)	Patients randomly allocated to receive LAIV and placebo	Vaccine efficacy (95% CI)	Reported antigenic match
Children (6 months–7 years)				
Belshe et al (1998)[32]	Healthy children aged 15–71 months (1996–97)	1602	93% (88 to 96)	Type A: sim… …age match
Belshe et al (2000)[33]	Healthy children aged 26–85 months (1997–98)	1358	87% (78 to 93)	…, type B: not reported (1 isolate)
Vesikari et al (2006)[34]	Healthy children aged 6–<36 months attending day care (2000–01)	1784	84% (74 to 90)	…similar H3N2 and H1N1; type B: lineage match
Vesikari et al (2006)[34]	Healthy children aged 6–<36 months attending day care (2001–02)	1119		Type A: similar H3N2 and H1N1; type B: mixed lineage
Bracco Neto et al (2009)[38]	Healthy children aged 6–<36 months (2000–01)		72% (62 to 80)	Majority of strains were similar (not reported by type)
Tam et al (2007)[35]	Healthy children aged 12–<36 mo…		68% (59 to 75)	Type A: similar H3N2 and H1N1; type B: lineage match
Tam et al (2007)[35]	Healthy children aged …–02)	2947	57% (30 to 74)	Type A: similar H3N2 and H1N1; type B: mixed lineage
Lum et al (2010)[36]	Healthy … …onths (2002–03)	1233	64% (40 to 79)	Type A: similar H1N1 and mixed H3N2; type B: mixed lineage

LAIVs consistently show highest efficacy in young children

Efficacité versus TIV

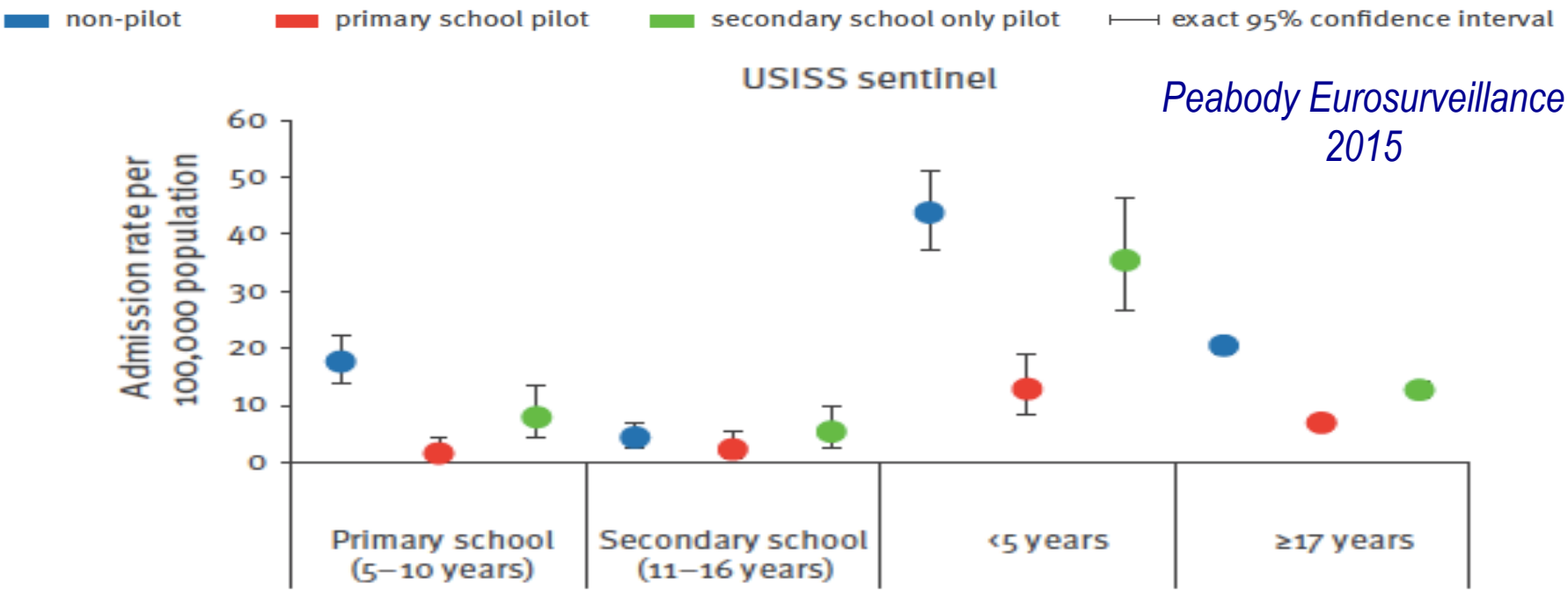
3 études randomisées ; toutes souches confondues



CI, confidence interval; LAIV, live attenuated influenza vaccine; I Resp : infection respiratoire; TIV, injectable vaccine

Belshe RB et al. *N Engl J Med* 2007;356:685–696.
Ashkenazi S et al. *Pediatr Infect Dis J* 2006;25:870–879.
Fleming DM et al. *Pediatr Infect Dis J* 2006;25:860–869.

Effet de groupe plus marqué ?



Peabody Eurosurveillance 2015

Coup de tonnerre dans un ciel (presque) serein

POLICY STATEMENT Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

Recommendations for Prevention and Control of Influenza in Children, 2016–2017

3. Quadrivalent live attenuated influenza vaccine (LAIV4) should not be used in any setting during the 2016–2017 influenza season in light of the evidence for poor effectiveness of LAIV4 in recent seasons, particularly against influenza A (H1N1)pdm09 viruses.

TABLE 2 Vaccine Effectiveness Against Any Influenza in Children, by Age and Vaccine Type

Season (Predominant Strain) and Age Range	Adjusted Vaccine Effectiveness, % (95% CI)	
	LAIV4	IIV3/IIV4
2013–2014 (H1N1pdm09)		
2–17 years	2 (–53 to 37)	61 (42 to 74)
2–8 years	–39 (–156 to 25)	60 (32 to 76)
9–17 years	36 (–31 to 69)	62 (30 to 80)
2014–2015 (H3N2)		
2–17 years	9 (–18 to 29)	31 (16 to 44)
2–8 years	9 (–28 to 35)	26 (2 to 44)
9–17 years	17 (–27 to 46)	33 (9 to 51)
2015–2016 (H1N1pdm09)		
2–17 years	3 (–49 to 37)	63 (52 to 72)
2–8 years	–3 (–76 to 40)	58 (40 to 70)
9–17 years	20 (–78 to 64)	71 (52 to 82)

Source: CDC.

En Angleterre…

(même vaccin 2015-2016)

Population	N	Cases: unvac; vaccinated	Controls: unvac; vaccinated	Adjusted VE by scheme, age, month, gender (CI**)
All ages	3841	990; 165	1959; 727	52.4% (41, 61.6)
2-17 years*	729	212; 26	402; 89	57.6% (25.1, 76)
18-44 years	1551	486;43	862;160	55.3% (34.2, 69.6)
45-64 years	908	223;49	432;204	55.4% (34.6, 69.5)
65+ years	409	24;39	105;241	29.1% (-31.4, 61.8)

Au Canada
(même vaccin 2011-2014)

Live Attenuated Versus Inactivated Influenza Vaccine in Hutterite Children: A Cluster Randomized Blinded Trial

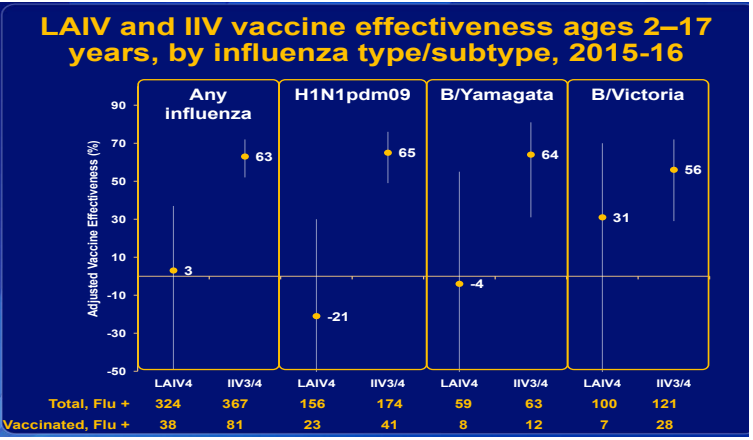
ONLINE FIRST

Mark Loeb, MD; Margaret L. Russell, MD, PhD; Vanessa Manning, BSc; Kevin Fonseca, PhD; David J.D. Earn, PhD; Gregory Horsman, MD; Khami Chokani, MD; Mark Vooght, MD; Lorne Babiuk, PhD; Lisa Schwartz, PhD; Binod Neupane, PhD; Pardeep Singh, BSc; Stephen D. Walter, PhD; and Eleanor Pullenayegum, PhD

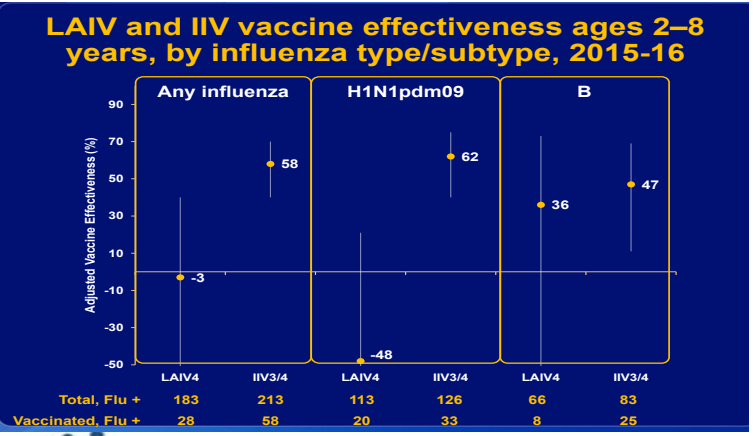
[+] Article, Author, and Disclosure Information

Ann Intern Med. Published online 16 August 2016 doi:10.7326/M16-0513

Efficacité comparable au vaccin injectable > 50%



Brendan Flannery , ACIP, June 2016

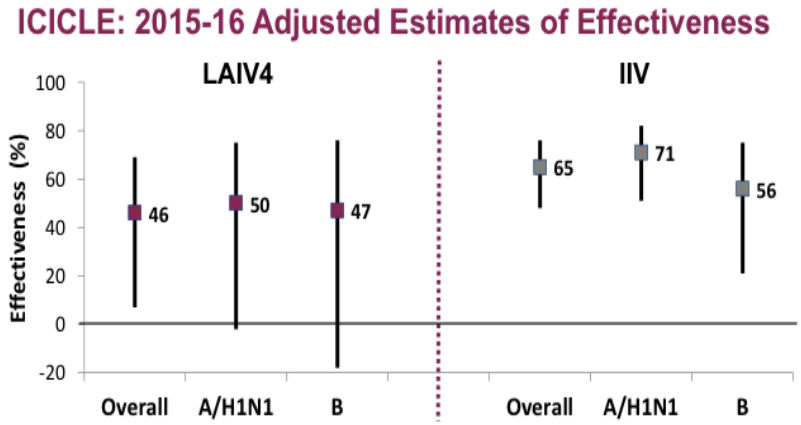


Dans toutes les études publiées,
1) l'efficacité du LAIV n'apparaît plus > au TIV
2) C'est sur AH1N1qu'il est le moins bon

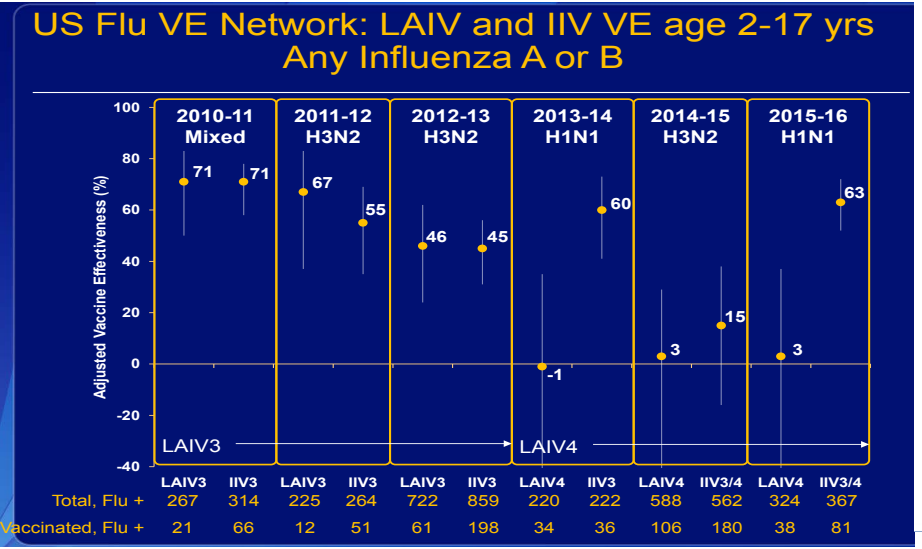
Finlande

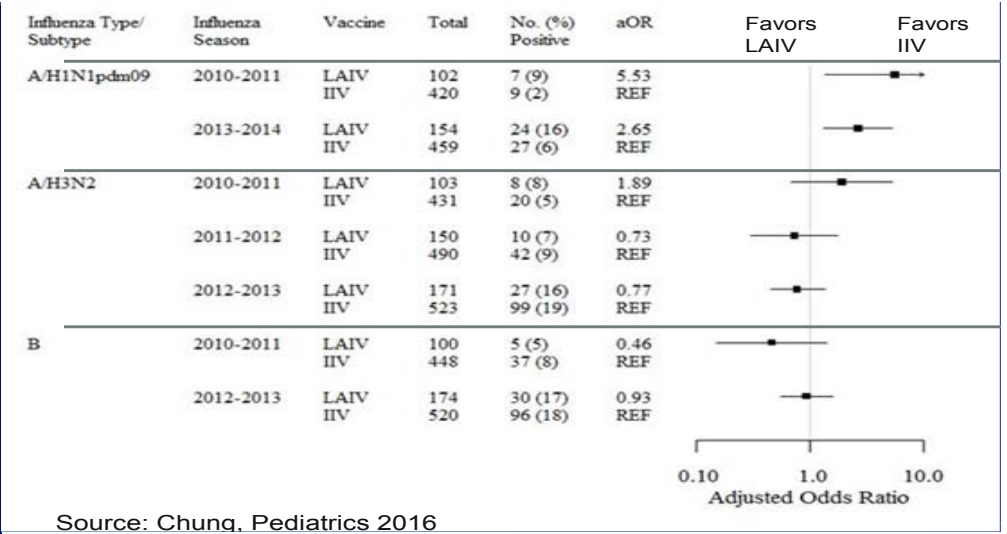
Unadjusted VE LAIV4 (95% CI)	Unadjusted VE IIV (95% CI)
46.2 (22, 63)	59.7 (27, 78)
46.7 (20, 65)	77.7 (46, 91)
35 (-56, 73)	-20.2 (-179, 48)

Chris Ambrose,Astra-Zeneca, ACIP, June 2016



Perte d'efficacité dans le temps
Plus de supériorité significative / TIV





Source: Chung, Pediatrics 2016

Pourquoi ces différences ???

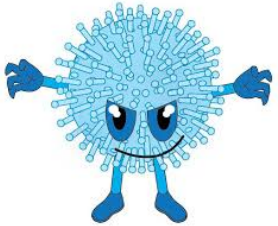
Moindre efficacité des doses répétées de vaccins dans le temps du fait de l'immunité antérieure?

Problèmes méthodologiques dans les ≠ études IC large

Diminution de la qualité du vaccin entrainant une modification des possibilités de réplication de ce vaccin vivant ?

Rôle de l'immunité antérieure

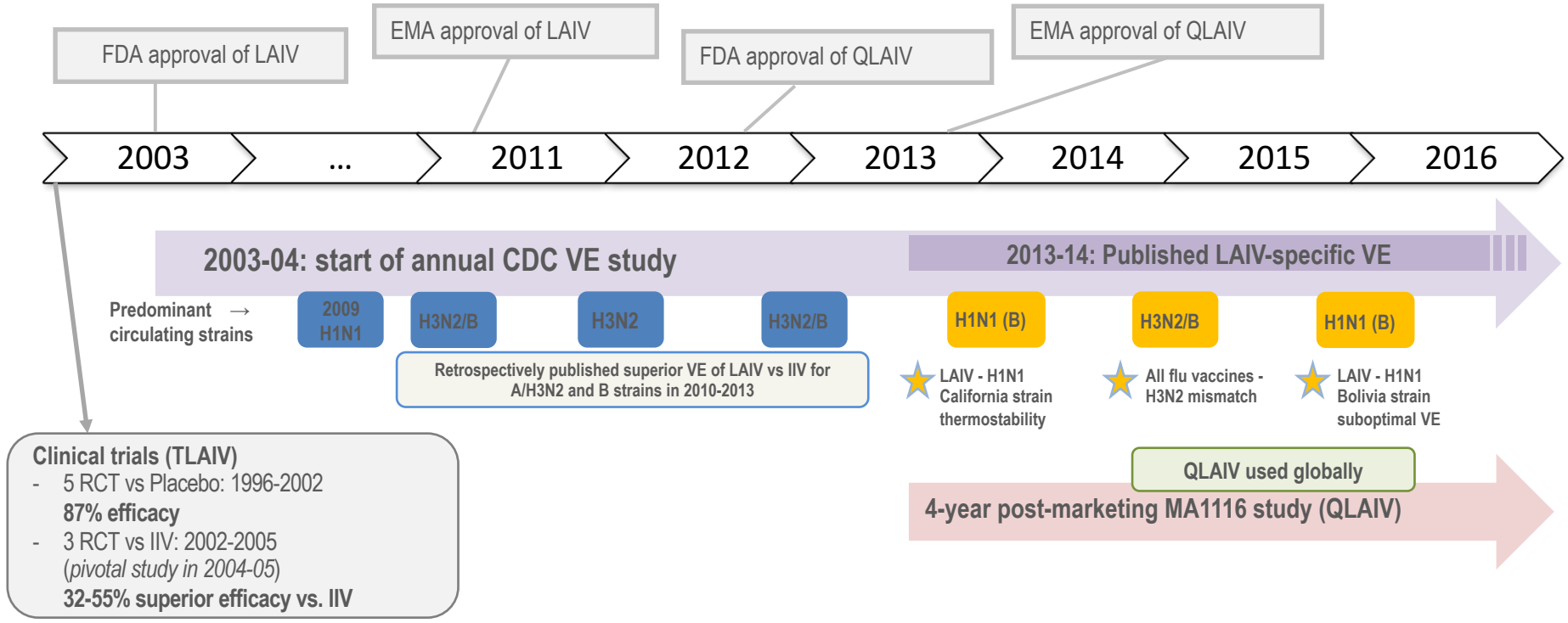
- Chez les déjà immunisés par la maladie naturelle ou vaccinés plusieurs années successives, il est probable que le vaccin soit **de moins en moins efficace.** En effet, son efficacité dépend de ses capacités à se répliquer
  - S'il y a des Ac…il ne se replique pas ou moins bien
  - Si le vaccin actuel est moins répliquant…



- **C'est ce qui explique que**
  - **Le vaccin vivant était - efficace chez l'adulte que les vaccins inactivés**
  - **Que la moindre efficacité soit apparu en premier aux USA premier pays à vacciner avec ce vaccin**

	Population (dates)	Patients randomly allocated to receive LAIV and placebo	Vaccine efficacy (95% CI)	Reported antigenic match
Children (6 months–7 years)				
Belshe et al (1998)[32]	Healthy children aged 15–71 months (1996–97)	1602	93% (88 to 96)	Type A: similar H3N2; type B: lineage match
Belshe et al (2000)[33]	Healthy children aged 26–85 months (1997–98)	1358	87% (78 to 93)	Type A: drifted H3N2; type B: not reported (1 isolate)
Vesikari et al (2006)[34]	Healthy children aged 6–<36 months attending day care (2000–01)	1784	84% (74 to 90)	Type A: similar H3N2 and H1N1; type B: lineage match
Vesikari et al (2006)[34]	Healthy children aged 6–<36 months attending day care (2001–02)	1119	85% (78 to 90)	Type A: similar H3N2 and H1N1; type B: mixed lineage
Bracco Neto et al (2009)[38]	Healthy children aged 6–<36 months (2000–01)	1886	72% (62 to 80)	Majority of strains were similar (not reported by type)
Tam et al (2007)[35]	Healthy children aged 12–<36 months (2000–01)	3174	68% (59 to 75)	Type A: similar H3N2 and H1N1; type B: lineage match
Tam et al (2007)[35]	Healthy children aged 12–<36 months (2001–02)	2947	57% (30 to 74)	Type A: similar H3N2 and H1N1; type B: mixed lineage
Lum et al (2010)[36]	Healthy children aged 11–<24 months (2002–03)	1233	64% (40 to 79)	Type A: similar H1N1 and mixed H3N2; type B: mixed lineage
Adults (18–49 years)				
Ohmit et al (2006)[24]	Healthy adults aged 18–46 years (2004–05)	725	48% (–7 to 74)	Type A: drifted H3N2; type B: mixed lineage
Ohmit et al (2008)[25]	Healthy adults aged 18–48 years (2005–06)	1191	8% (–194 to 67)	Type A: drifted H3N2; type B: lineage mismatch (1 isolate)
Monto et al (2009)[28]*	Healthy adults aged 18–49 years (2007–08)	1138	36% (0 to 59)	Type A: drifted H3N2; type B: lineage mismatch

LAIV / QLAIV licensing and VE studies



Environ 10 ans d'écart entre les premières utilisation aux US et les premières en Europe

Qualité du vaccin

- Changement de la souche AH1N1
  - Callifornia → A/Bolivia/559/2013 moins répliquante
- Ajout d'une 4^{éme} souche (interférence dans les réplications ?)
- Sensibilité à la chaine du froid → importance de la logistique et de la chaine du froid

Raphaël 25 mois, asthme du nourrisson en crèche, 6 épisodes, pas vacciné l'année dernière, sous Flixotide® et Ventoline®.

~~Pas de vaccin grippe~~

~~Vaccin injectable trivalent remboursé~~

~~Uniquement le Fluenz tetra®~~

Fluenz tetra® si les parents refusent le VI

Sacha 18 mois, asthme du nourrisson en crèche, 6 épisodes, pas vacciné l'année dernière, sous Flixotide® et Ventoline®.

- ~~Pas de vaccin grippe~~
- Vaccin injectable trivalent remboursé
- ~~Uniquement le Fluenz tetra®~~
- ~~Fluenz tetra® si les parents refusent le VI~~

Roxane 7 ans, asthme récurrent sous Seretide® et Ventoline®, vaccinée les années précédentes à plusieurs reprises.

- ~~Pas de vaccin grippe~~
- Vaccin injectable trivalent remboursé
- ~~Uniquement le Fluenz tetra®~~
- ~~Fluenz tetra® si les parents refusent le VI~~