Efficacité de la vaccination antigrippale dans la population adulte et pédiatrique

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Objectifs cliniques de la vaccination et populations cibles

- Objectifs de la vaccination
  - Mortalité, complications (pneumonie)
  - Morbidité simple
    - En fonction de l'âge
    - Populations particulières (asthmatiques, immunodéprimés)
  - Vaccination « altruiste »
- Epidémiologie variable de la grippe saisonnière
  - Variabilité antigénique et adéquation vaccin/virus sauvage
  - Expression clinique infection

Expression clinique de l'infection chez des sujets adultes immunocompétents susceptibles et infectés expérimentalement - revue

- Proportion d'infections symptomatiques ***65% (95% CI 56%-73%)***

Influenza virus types and subtypes	Subgroups/parti-cipants/events	Pooled estimates (%)	95%CI
A/H1N1	11/228/158	**70.8**	50.4-85.2
A/H3N2	13/180/107	**60.5**	50.4-69.8
A/H2N2	2/44/31	**72.4**	54.8-83.2
B	6/40/25	**57.4**	35.2-76.9
All	32/492/321	**64.8**	55.5-73.1

- Proportion of **fièvre (>=100°F or 37.8°C)** ***31% (95%CI 24%-40%)***
  - ***37% (H1N1), 35% (H3N2), 7.5% (B)* (p<0.001)***

Carrat F et al. Am J Epidemiol. 2008;167:775

Critères de jugements

- Cliniques
  - Syndrome grippal
    - Toux ou mal de gorge + fièvre (>37.8°C)
  - Infection respiratoire aiguë
    - Définition très variable
    - La fièvre n'est pas un critère nécessaire
- Cliniques avec confirmation virologique
- Infection grippale
  - Séroconversion (multiplication x4 du titre HAI post/pre épidémic)

Quelques essais importants : efficacité sur la morbidité non compliquée – adultes

- Syndrome grippal: EV=25% (425 sujets par groupe, double aveugle)

Table 3. Health-Related Benefits Associated with Vaccination.*

Study Outcome	Rate per 100 Subjects		Difference (95% CI)	Vaccine Effectiveness	P Value
	Placebo Group	Vaccine Group			
				%	
Primary					
Episodes of upper respiratory illness	140	105	35 (17–53)	25	<0.001
Days of sick leave due to upper respiratory illness	122	70	52 (21–84)	43	0.001
Visits to physicians' offices for upper respiratory illness	55	31	24 (8–40)	44	0.004

Nichol KL et al. N Engl J Med 1995;333:889

Quelques essais importants : efficacité sur la morbidité non compliquée – adultes

		1997-98			1998-99	
	Vaccinés N=576	Placebo N=554	P	Vaccinés N=582	Placebo N=596	
Syndrome grippal – n (%)	161 (28)	132 (24)	0.25	82 (14)	128 (22)	<.001
Infection respiratoire aiguë – n (%)	259 (45)	232 (42)	0.57	137 (24)	156 (26)	0.32
Patients prélevés	138	137		141	137	
Syndrome grippal confirmé	3 (2)	6 (4)	0.33	2 (1)	14 (10)	0.001

EV=34%
NNV=14

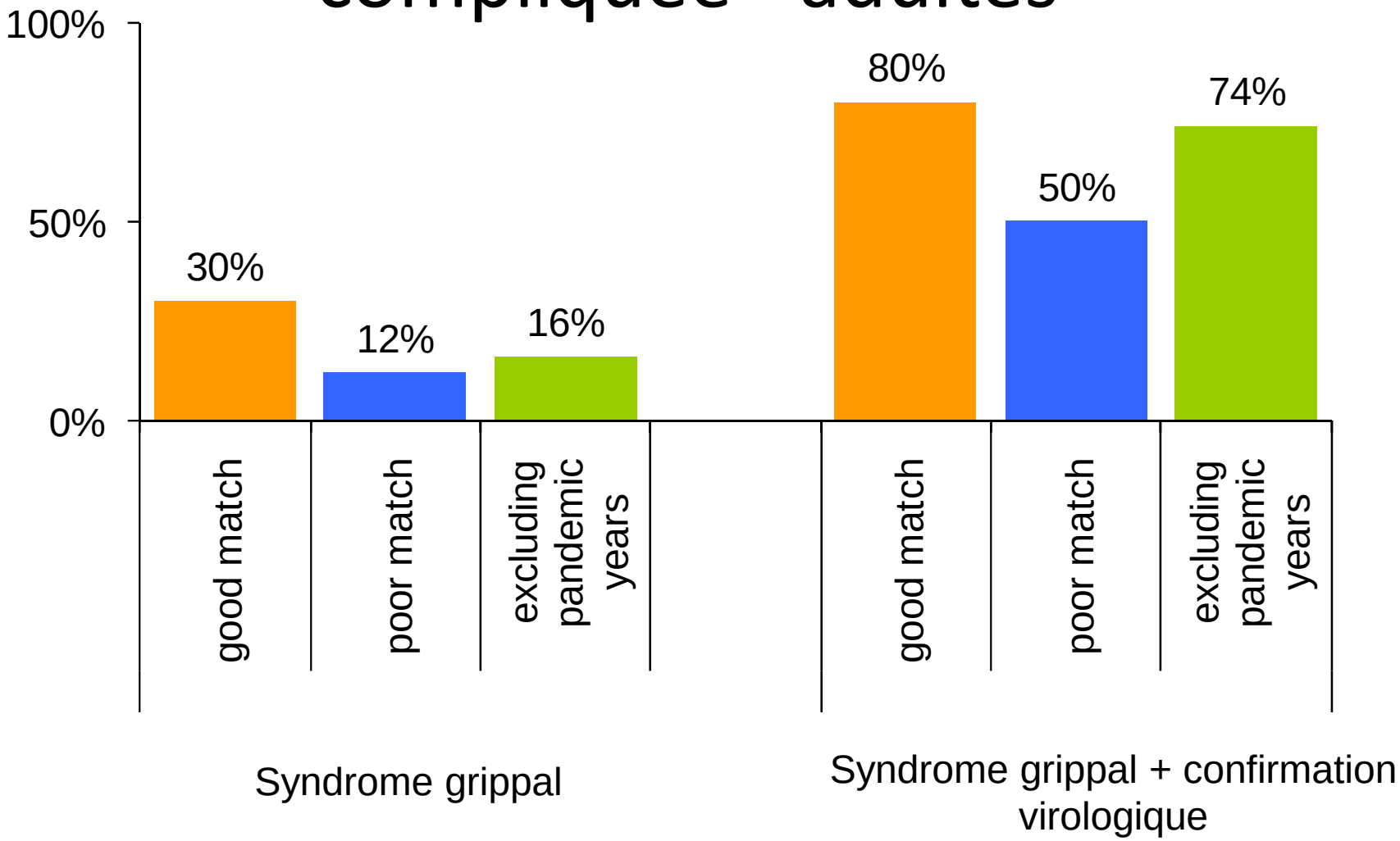
EV=86%
NNV=11

Mismatch antigénique: Variant épidémique « éloigné » de la souche vaccinale

Variant épidémique proche de la souche vaccinale

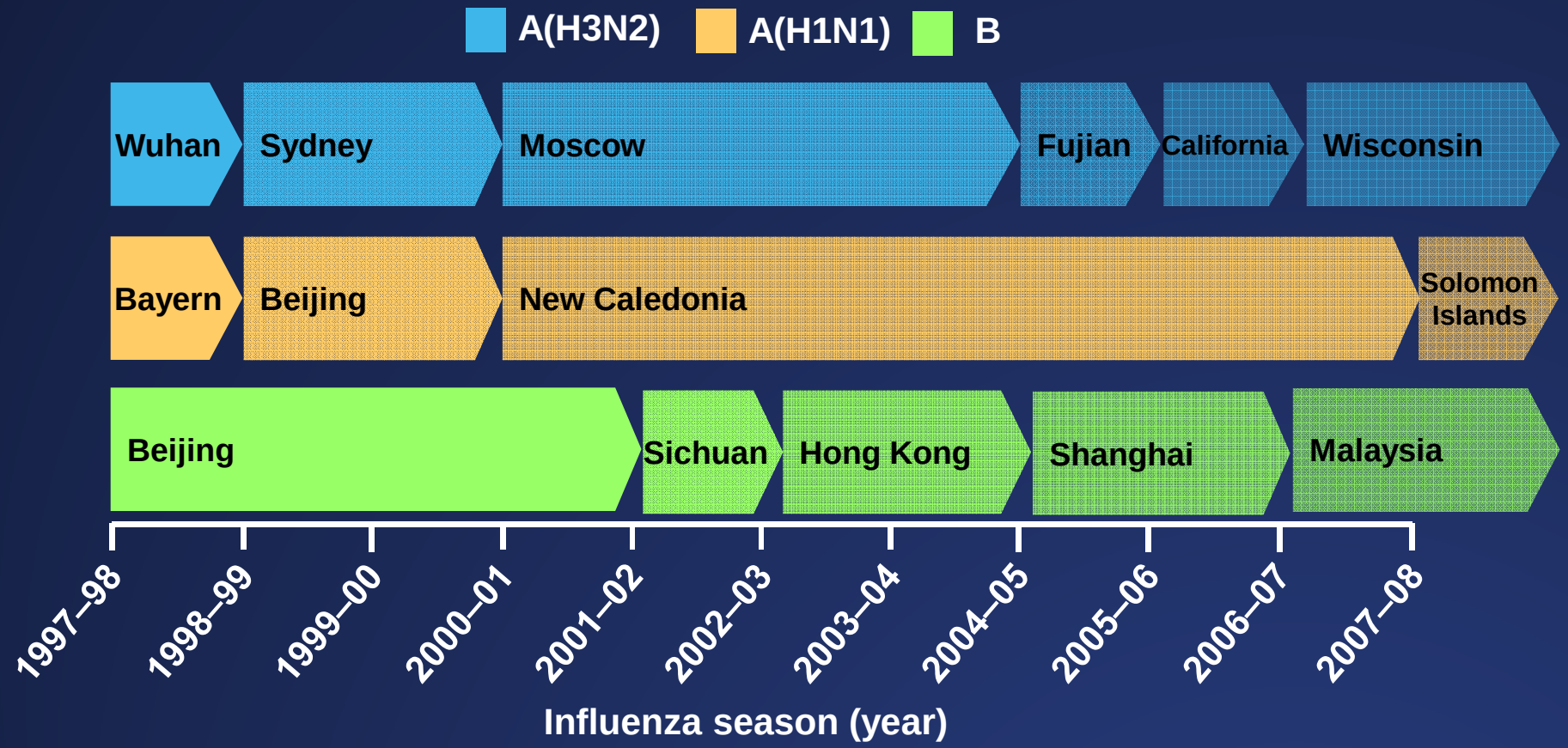
D'après Bridges CB et al. JAMA 2000;284:1655-63

Efficacité sur la morbidité non compliquée - adultes



Demicheli V et al. Cochrane Database Syst Rev 2007; CD001269

Antigenic drift



- **Recommended strains have changed 12 times since 1997–1998 due to antigenic drift**

www.who.int

Antigenic distance and vaccine efficacy

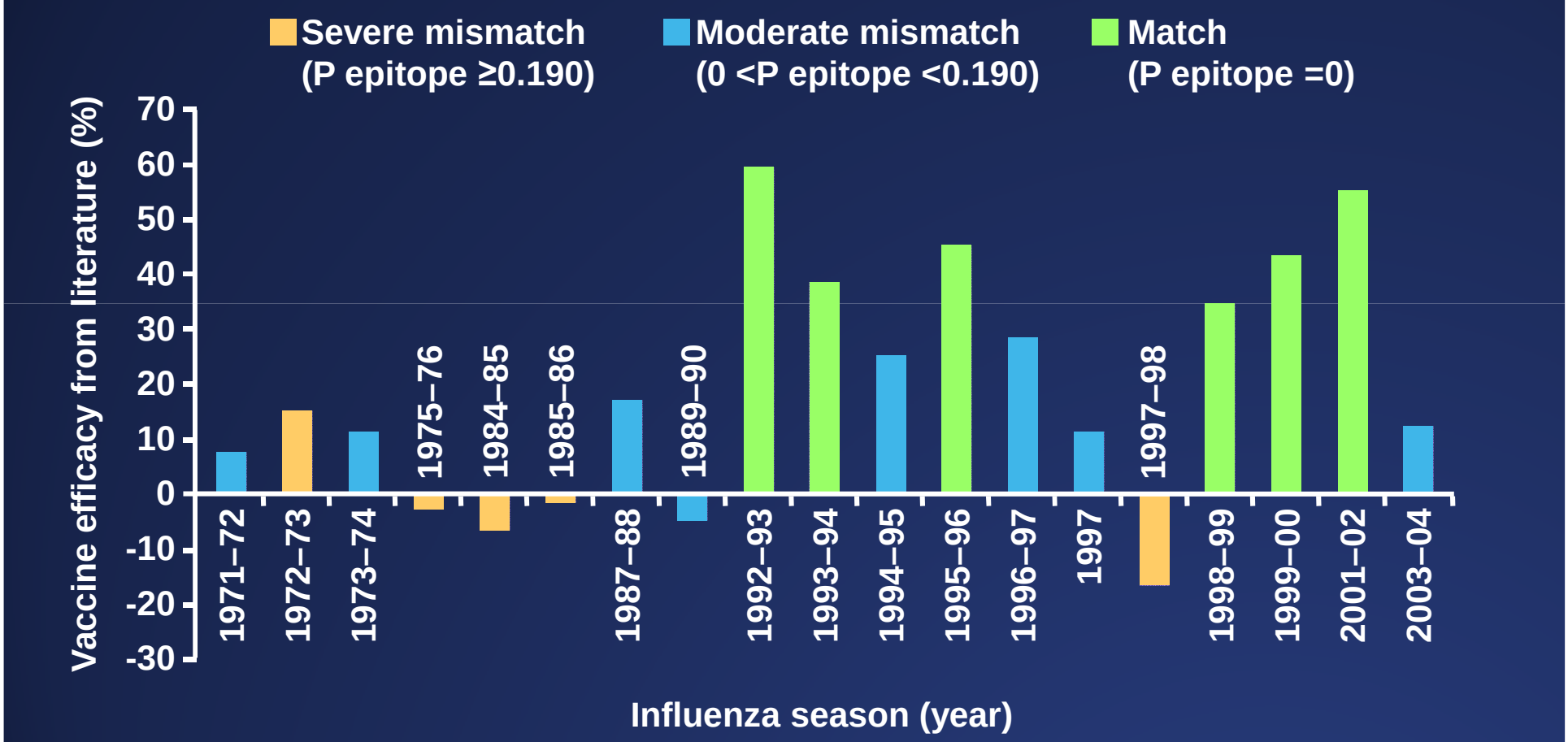
- Antigenic/sequence distance between the vaccine strain and the circulating strain = the proportion of amino acid differences in the dominant epitope

$$\text{P epitope:} \quad \frac{\text{number of amino acid differences in the dominant epitope}}{\text{total number of amino acids in the dominant epitope}}$$

- Antigenic distance and vaccine efficacy are strongly correlated

Gupta *et al. Vaccine* 2006

Strong correlation between antigenic distance and vaccine efficacy



P epitope value defines the degree of antigenic drift

Gupta *et al. Vaccine* 2006

Efficacité sur la morbidité - enfants

- Deux vaccins différents évalués
  - Inactivé
  - Vivant atténué (non commercialisé en Europe)
- 14 essais thérapeutiques contrôlés

Enfants: efficacité supérieure du vaccin vivant atténuée (< 5 ans)

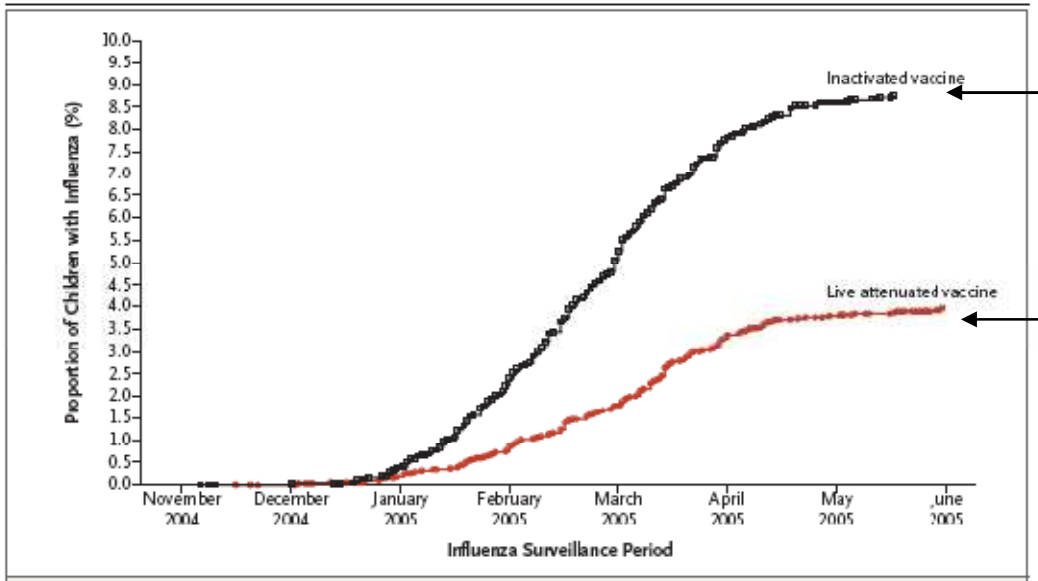


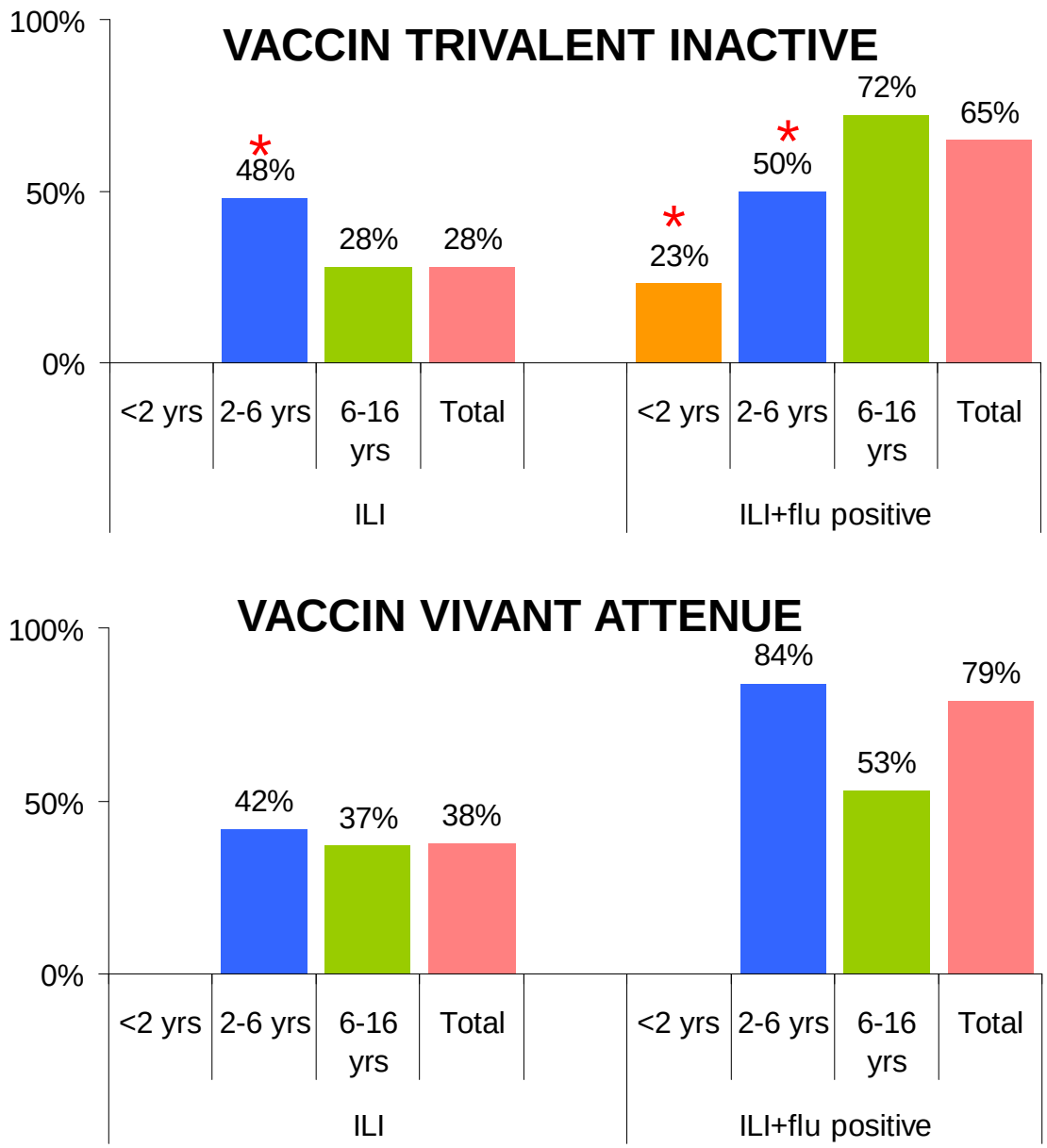
Figure 1. Kaplan–Meier Curves for the Time to the First Culture-Confirmed Report of Influenza in the Two Vaccine Groups.

Culture-confirmed influenza was caused by any wild-type influenza strain (regardless of antigenic match or mismatch to vaccine) in children who received a study vaccine according to the study protocol ($P<0.001$ by the log-rank test). Of 3936 children given inactivated vaccine, 338 had influenza, and of 3916 children given live attenuated vaccine, 153 had influenza. Each square denotes one infected child in the inactivated-vaccine group, and each circle one infected child in the live attenuated vaccine group.

338 ILI flu pos/3936

153 ILI flu pos/3916

Belshe RB et al. N Engl J Med 2007;356:685



Efficacité vaccinale chez l'enfant

* Non significativement différent de zéro

Jefferson T et al. Lancet 2005; 773

Et H1N12009 ?

Données observationnelles suggèrent efficacité clinique du vaccin pandémique sur souche 2009

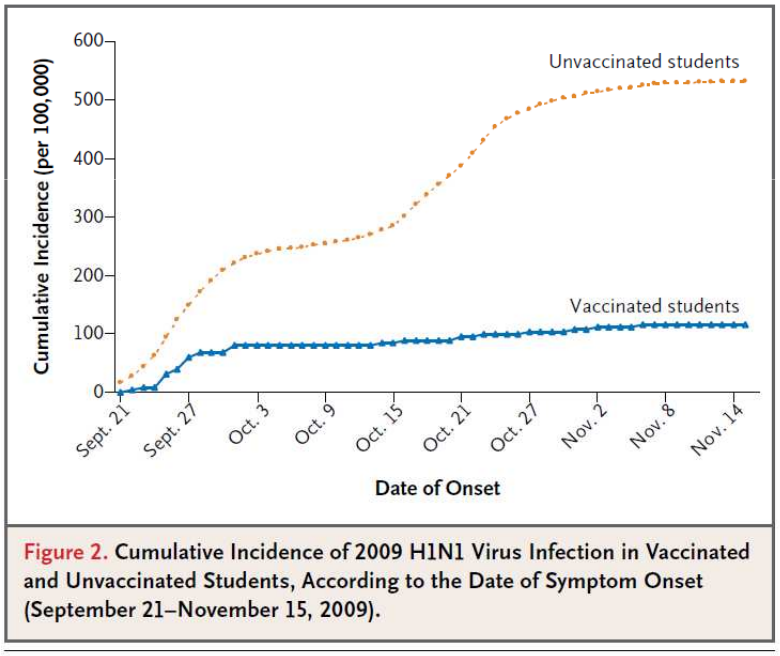


Figure 2. Cumulative Incidence of 2009 H1N1 Virus Infection in Vaccinated and Unvaccinated Students, According to the Date of Symptom Onset (September 21–November 15, 2009).

nd adjusted PIVE.

Crude and Adjusted PIVE Estimates	Included Population	*n*	Percent PIVE	95% CI
Crude[b]	All	1,502	79.0	55.8–90.0
	<65 y	1,367	83.3	61.2–92.8
	15–64 y	912	76.6	44.7–90.1
	<15 y	455	100	58.2–100.0[c]
	No chronic disease	1,190	81.5	53.0–92.7
Adjusted model[d]	All	1502	66.0	23.9–84.8
	<65 y	1,367	71.3	29.1–88.4
	15–64 y	912	65.5	12.3–86.5
	<15 y	455	100	Not calculable[e]
	No chronic disease	1,190	70.2	19.4–89.0

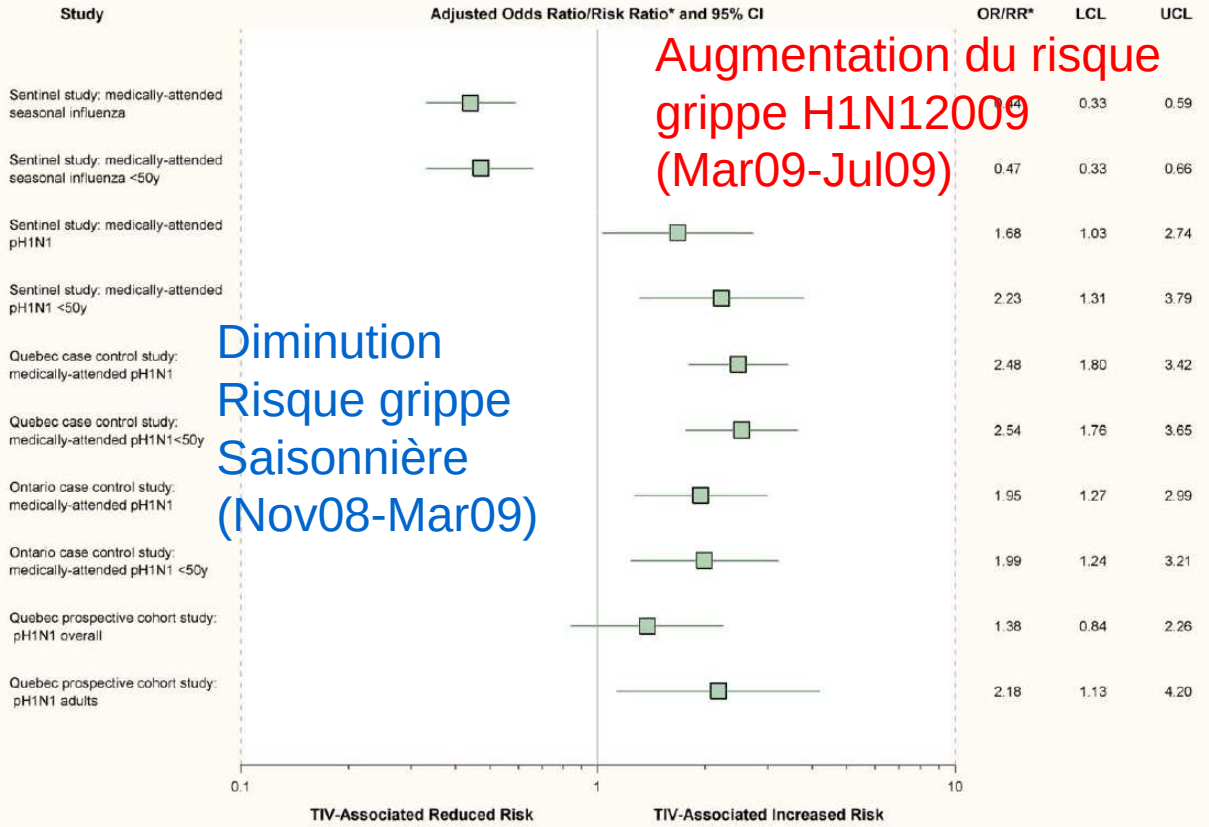
EV: 72% chez les moins de 65ans

Wu J et al. N Engl J Med 2010;363:2416-2423

Valenciano et al. PLoSMed; 8(1): e1000388.

Impact de la vaccination saisonnière sur H1N1 2009

- 4 études observationnelles (3 cas-témoin, 1 étude prospective) au Canada



Skowronski et al. PLoSMed; 8(1): e1000388.

Un essai de vaccination saisonnière vs placebo

Variable	TIV group	Placebo group	*P*
Study subjects			
No. of study subjects	71	48	
Serologically confirmed infection[a]			
Seasonal A/H1N1	0.08 (0.02–0.15)	0.21 (0.09–0.32)	.10
Seasonal A/H3N2	0.07 (0.01–0.13)	0.12 (0.03–0.22)	.49
Pandemic A/H1N1	0.32 (0.22–0.43)	0.17 (0.06–0.27)	.09
Seasonal B	0.03 (0.00–0.07)	0.08 (0.01–0.16)	.36

Factors Associated with the Risk of Laboratory-Confirmed Pandemic Influenza in household members

Risk factor	No. of study subjects	Adjusted odds ratio[a] (95% confidence interval)
Age <16 years	192	6.60 (2.17–20.13)
Age 16–45 years	163	2.53 (0.80–7.99)
Age >45 years	76	1.00
Female sex	229	1.00
Male sex	202	0.97 (0.55–1.70)
No laboratory-confirmed seasonal influenza A infection	277	1.00
Laboratory-confirmed seasonal influenza A infection	93	0.35 (0.14–0.87)
Did not receive seasonal influenza vaccine	271	1.00
Received seasonal influenza vaccine prior to 2008–2009 season	106	1.11 (0.54–2.26)
Completed study before 1 October 2009	221	1.00
Completed study between 1 October and 20 October 2009	156	2.77 (1.53–4.99)

[a] Adjusted for age, sex, laboratory-confirmed seasonal influenza A infection, receipt of TIV, and date of study completion.

Cowling B J et al. Clin Infect Dis. 2010;51:1370-1379

Femmes enceintes et … enfants

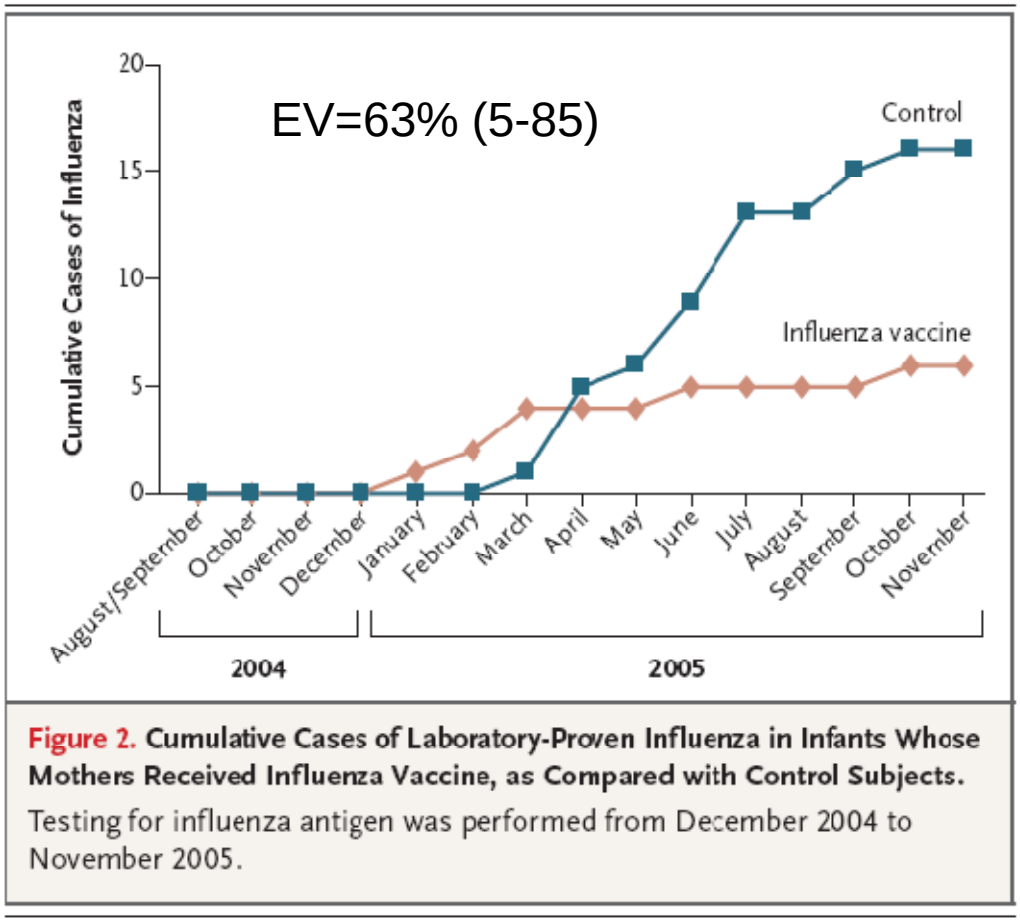


Figure 2. Cumulative Cases of Laboratory-Proven Influenza in Infants Whose Mothers Received Influenza Vaccine, as Compared with Control Subjects.
Testing for influenza antigen was performed from December 2004 to November 2005.

- 340 femmes randomisées vaccin inactivé vs vaccin pneumocoque (3ème Trimestre)
- 316 enfants suivis 1,5 ans

- EV sur Infections respiratoires aigues fébriles enfants : 29%(7-46)
- EV sur Infections respiratoires fébriles chez mère : 36% (4-57)

Zaman K et al. N Engl J Med 2008;359:1555

Femmes enceintes et … enfants

- Enquête cas témoin : les cas sont des enfants hospitalisés et confirmés virologiquement; les témoins sont des enfants hospitalisés mais négatifs

Table 4. Effectiveness of Influenza Vaccine Given to Mothers During Pregnancy in Preventing Hospitalization for Influenza among Their Infants

Measure	Subjects aged <6 months	Subjects aged ⩾6 months
No. (%) of case infants; no. (%) of control infants		
Mother was vaccinated	2 (2.2); 31 (19.9)	1 (4.6); 2 (5.6)
Mother was not vaccinated	89 (97.8); 125 (80.1)	21 (95.5); 34 (94.4)
Vaccine effectiveness (95% CI), %		
Unadjusted	90.7 (59.9–97.8)[a]	−41.4 (−2257.3 to 91.5)[b]
Adjusted[c]	91.5 (61.7–98.1)[a]	…

NOTE. CI, confidence interval.

[a] $P = .001$.

[b] $P = .809$.

[c] The adjusted model for subjects aged <6 months retained vaccination of household contacts and prematurity.

Benowitz I et al. Clin Infect Dis; 2010;51:1355-1361

Conclusion: questions en suspens

- Questions cliniques sans réponse
  - Interactions virales/vaccins et efficacité clinique à long terme d'une vaccination répétée
  - Efficacité clinique des vaccins adjuvantés vs non adjuvantés ? Protection croisée ?
- Vers la recherche d'un vaccin « universel » ?

Vaccination with a synthetic peptide from the influenza virus hemagglutinin provides protection against distinct viral subtypes

EDITORIAL COMMENTARY

Taia T. Wang[a,1], Gene S. Tan[a,1], Rong Hai[a], Natalie Pica[a], Lily Ngai[a], Damian C
Adolfo García-Sastre[a,d,e], Thomas M. Moran[a,f], and Peter Palese[a,d,2]

PNAS 2010;107:18979

Prospecting the Influenza Hemagglutinin to Develop Universal Vaccines

Ruben O. Donis and Nancy J. Cox

Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

CID 2011; 52:1010

Induction of unnatural immunity: prospects for a broadly protective universal influenza vaccine

Gary J Nabel & Anthony S Fauci

Nature Med 2010; 16:1389