Is it time for flu vaccination in children ?

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Available vaccines in Belgium 2015-16

- Inactivated influenza vaccine (IIV) :

  -trivalent (TIIV):Influenza A/H1N1 and A/H3N2 + B Yamagata-

  ≥ 6 months of age

  (Influvac®,Intanza®,Vaxigrip® TM 5,82-6,50 E)

  -quadrivalent (QIIV): + B /Victoria *(αRix-Tetra ®TM 6,77 E)*

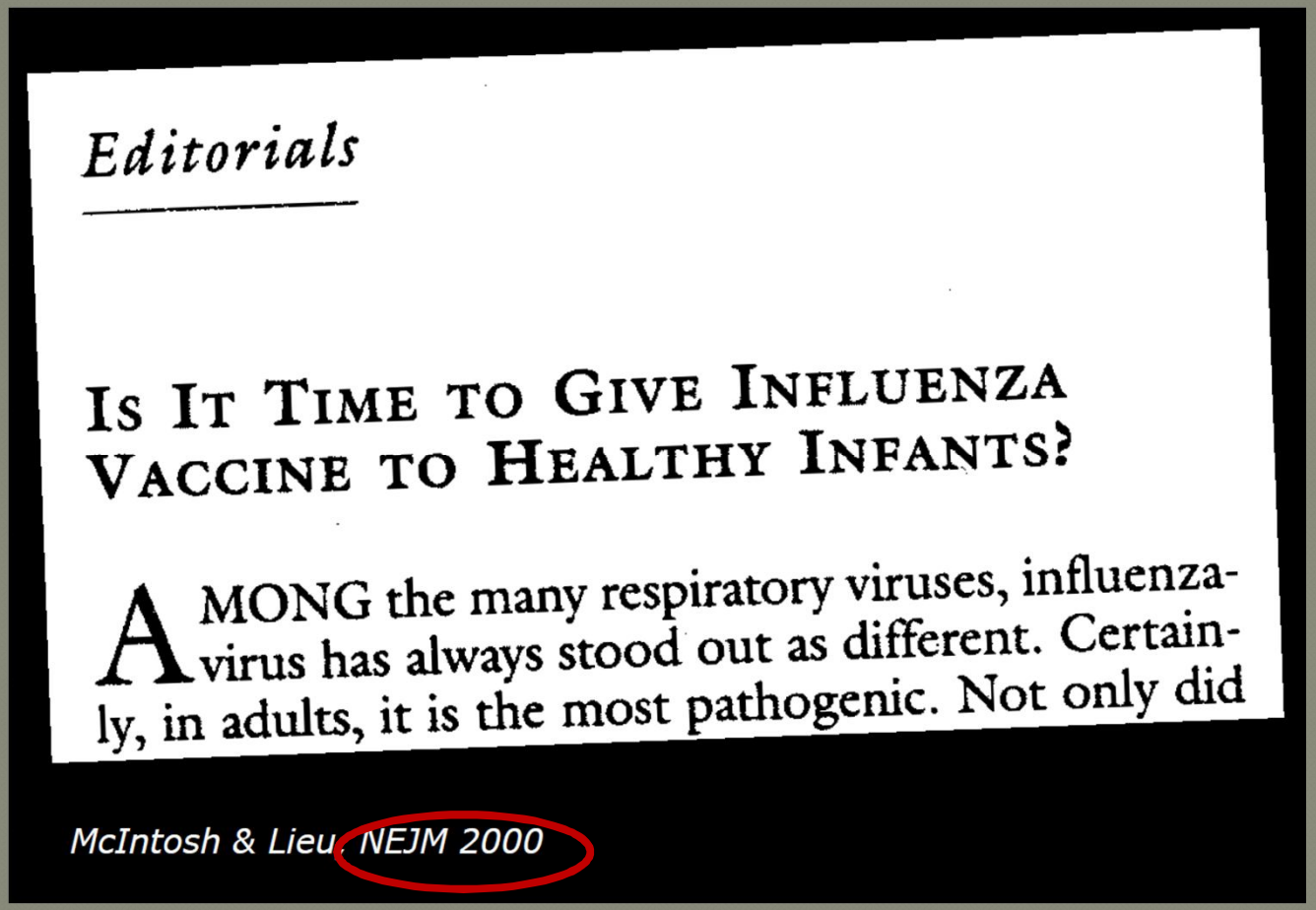
  ≥ 3 years

- Live attenuated influenza vaccine (LAIV):

  -quadrivalent (Q-LAIV): *Fluenztetra® 35,64 E*

  ≥2y to 18y- unreimbursed

2000



Editorials

Is It Time to Give Influenza Vaccine to Healthy Infants?

AMONG the many respiratory viruses, influenza virus has always stood out as different. Certainly, in adults, it is the most pathogenic. Not only did

McIntosh & Lieu, NEJM 2000

had been introduced in larger populations.[13] Ideally, in the case of influenza vaccines, randomized trials of the safety, effectiveness, and cost effectiveness of vaccination of infants and toddlers should be conducted in populations large enough to identify any risks of rare adverse events and should be continued through several epidemics — long enough to establish their worth. Multiple centers should be included, because there may be wide disparities in the rates of hospitalization for influenza in different demographic groups and different insurance systems.[4,5] Such studies would enable us to evaluate the benefits, risks, and economic effects of routine immunization of infants and toddlers against influenza on the basis of the best possible evidence, before we consider any national recommendation.

KENNETH MCINTOSH, M.D.

Vaccination strategies

- Specific high risk subpopulation:
  - most countries across Europe (>1980/1990s)
  - young age= risk factor?
  - direct effect

OR

- Universal vaccination targeting only children (UK-Finland- different age category) or the whole population (US)
  - direct and indirect effect

US 2003 (≥ 6-23m) -2010 ≥ 6m
Finland 2007: 6-26 m
UK 2013:2-17 y

Belgium 2015-16

A. Le Conseil recommande, pour la vaccination contre la grippe saisonnière 2015-2016 que, les groupes de sujets suivants soient prioritaires :

- Groupe 1 : les personnes à risque de complications à savoir :
  - les femmes enceintes qui seront au deuxième ou troisième trimestre de grossesse au moment de la saison de la grippe. Elles seront vaccinées dès le deuxième trimestre de leur grossesse ;
  - tout patient à partir de l'âge de 6 mois présentant une affection chronique sous-jacente, même stabilisée, d'origine pulmonaire (incluant l'asthme sévère[1]), cardiaque (excepté l'hypertension), hépatique, rénale, métabolique(incluant le diabète), neuromusculaire ou des troubles immunitaires (naturels ou induits) ;
  - toute personne de 65 ans et plus ;
  - les personnes séjournant en institution ;
  - les enfants de 6 mois à 18 ans compris sous thérapie à l'aspirine au long cours.
- Groupe 2 : le personnel du secteur de la santé.
- Groupe 3 : les personnes vivant sous le même toit que
  - des personnes à risque du groupe 1 ;
  - des enfants de moins de 6 mois.

Universal vaccination of healthy children

- Main reasons
  - -Age= risk factor
  - -Children = disseminators
  - -Cost effectiveness?
- Vaccine efficacy/effectiveness?

AGE= risk factor?

-US Chaves (PIDJ 2014-proven hospitalised cases ≤ 12m) :

< 3m= 50% cases -328/10^5 –sepsis work up

75%: no risk factor

ICU: < 6 m or with cardiac-pulmonary-neuromuscular

- Izunieta NEJM 2000

Table 4. Excess Rates of Hospitalization for Acute Respiratory Disease Attributable to Influenzavirus among Children without High-Risk Conditions during Periods in Which Influenzavirus Predominated.*

Study Site and Age Group	Rate in Period When Influenzavirus Predominated	Rate in Summer Base-Line Period	Excess Rate Attributable to Influenzavirus (95% CI)†	P Value	Rate in Peri-Seasonal Base-Line Period	Rate Attributable to Influenzavirus (95% CI)‡	P Value
	rate/100,000 person-months				rate/100,000 person-months		
Northern California Kaiser							
0–1 yr	231	81	151 (113 to 188)	<0.001	120	112 (73 to 150)	<0.001
2–4 yr	53	27	26 (9 to 42)	<0.002	38	15 (−2 to 33)	<0.081
5–17 yr	19	19	0 (−5 to 5)	0.951	14	5 (1 to 10)	<0.026
Group Health Cooperative							
0–1 yr	193	66	127 (82 to 171)	<0.001	107	86 (39 to 132)	<0.001
2–4 yr	21	16	5 (−9 to 20)	0.468	24	−3 (−19 to 13)	0.727
5–17 yr	17	12	5 (−3 to 10)	0.066	10	7 (1 to 12)	<0.012

*CI denotes confidence interval.

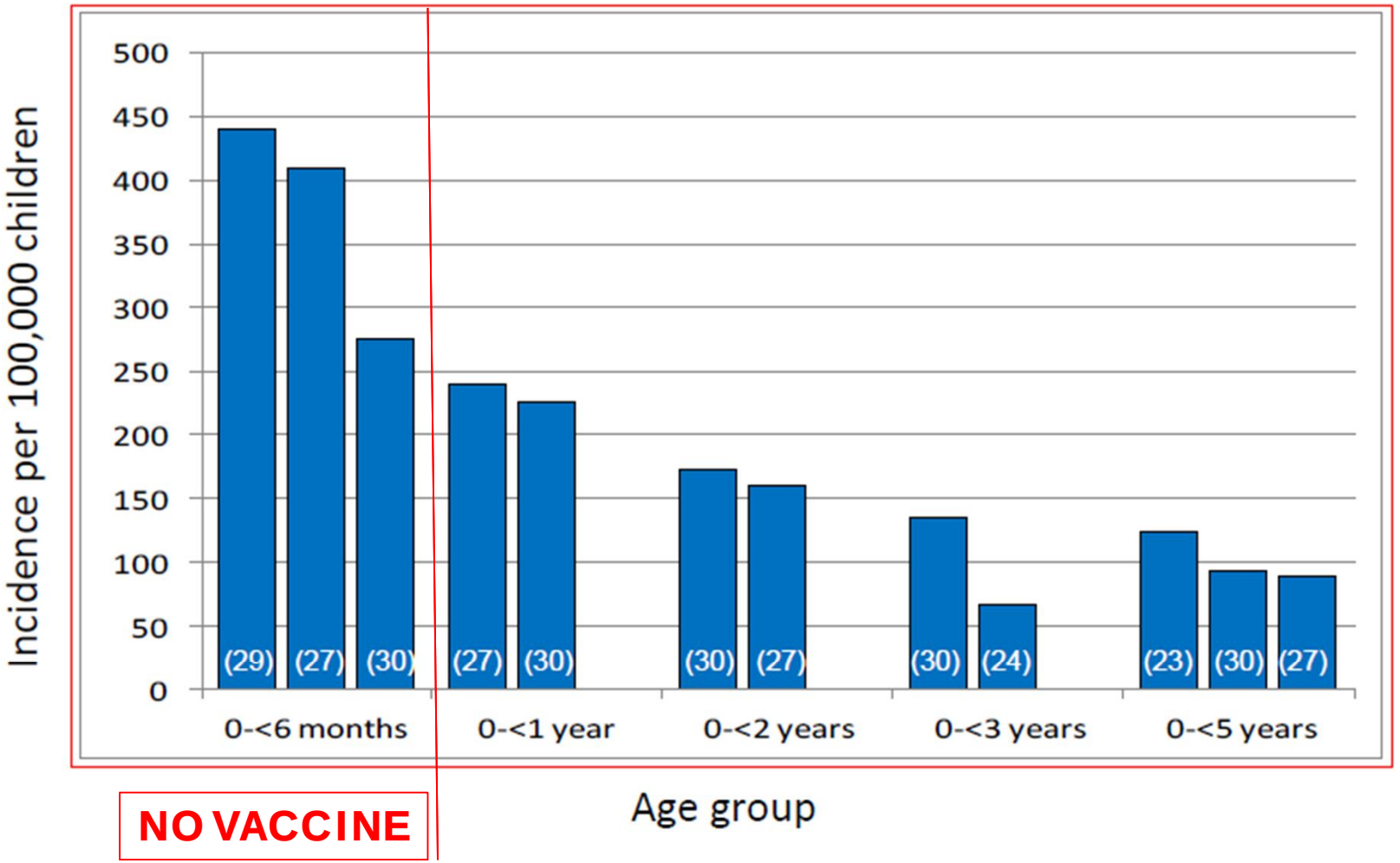
†Values are the rates during periods in which influenzavirus predominated minus the rates during the summer base-line periods.

‡Values are the rates during periods in which influenzavirus predominated minus the rates during the peri-seasonal base-line periods.

Children < 2 y without RF = same probability to be hospitalised as adult with RF

Population-based incidence of influenza hospitalizations of children

Germany[23], Spain[24,27], Finland[30], and the UK[29]



Heikkinen et al., Pediatr Infect Dis J 2013

Protection of children <6 months of age

- Household contacts vaccination
- Vaccination during pregnancy: 2 randomised trials

  Zamman (NEJM 2008 Bangladesh- TIV vs PPSV23)

  ↓53% (proven) -↓ 29% **febrile RTI in children ≤ 6 m**

  Madhi (NEJM 2014 S Africa- TIV vs placebo- mother HIV + or-)

  children ≤ 6 m

  ↓48.8% (PCR) if mother HIV – and 26.7% if HIV+

2006

Terho Heikkinen · Robert Booy · Magda Campins ·
Adam Finn · Per Olcén · Heikki Peltola ·
Carlos Rodrigo · Heinz-Josef Schmitt ·
Fabian Schumacher · Stephen Teo ·
Catherine Weil-Olivier

Should healthy children be vaccinated against influenza?

A consensus report of the Summits of Independent European Vaccination Experts

"…Considering the high rates of infection, office visits, and hospital admission, and the frequent occurrence of bacterial complications such as AOM in children younger than 3 years, these children should be regarded as a high-risk group for influenza, analogously with healthy persons aged 65 years or older. As a logical implication of this, we conclude that annual influenza vaccination should be recommended to all children aged 6 months to 3 years, with or without any underlying medical conditions."

Eur J Pediatr 2006

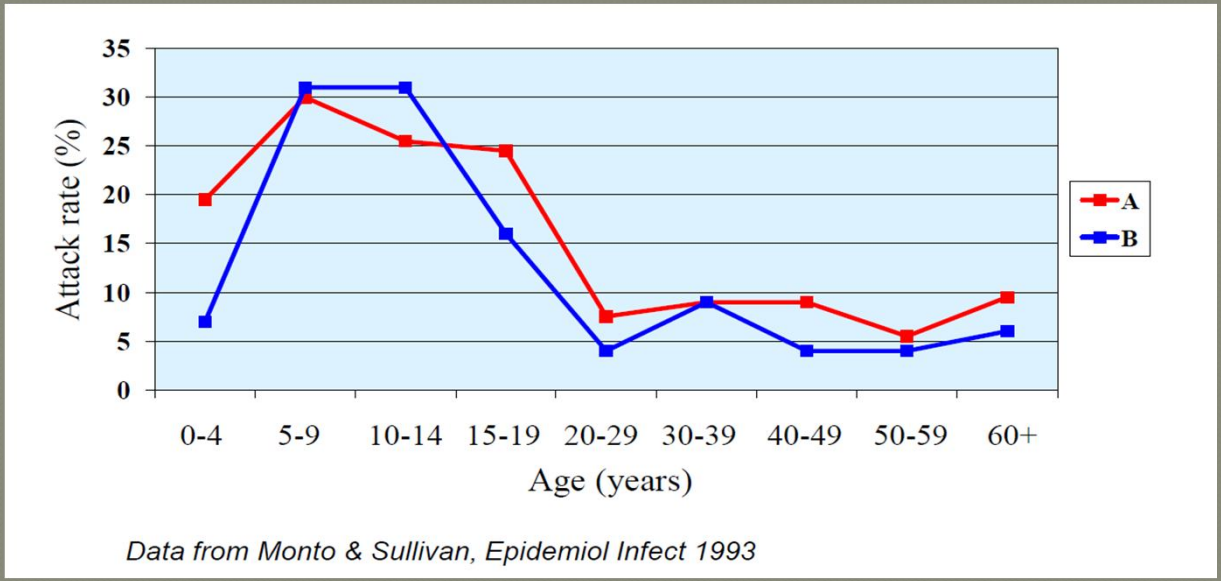
WHO 2012, 87:461-76

For countries considering the initiation or expansion of programmes for seasonal influenza vaccination, WHO recommends that pregnant women should have the highest priority. Additional risk groups to be considered for vaccination, in no particular order of priority, are children aged 6–59 months, the elderly, individuals with specific chronic medical conditions, and health-care workers. Countries with existing influenza vaccination programmes targeting any of these additional groups should continue to do so and should incorporate immunization of pregnant women into such programmes.

Universal vaccination of healthy children

High attack rates +prolonged excretion + multiple contact:

Children = the main disseminators of influenza (households and community)



Universal vaccination of healthy children

- Which pediatric age-groups to target to achieve optimal direct and indirect protection?

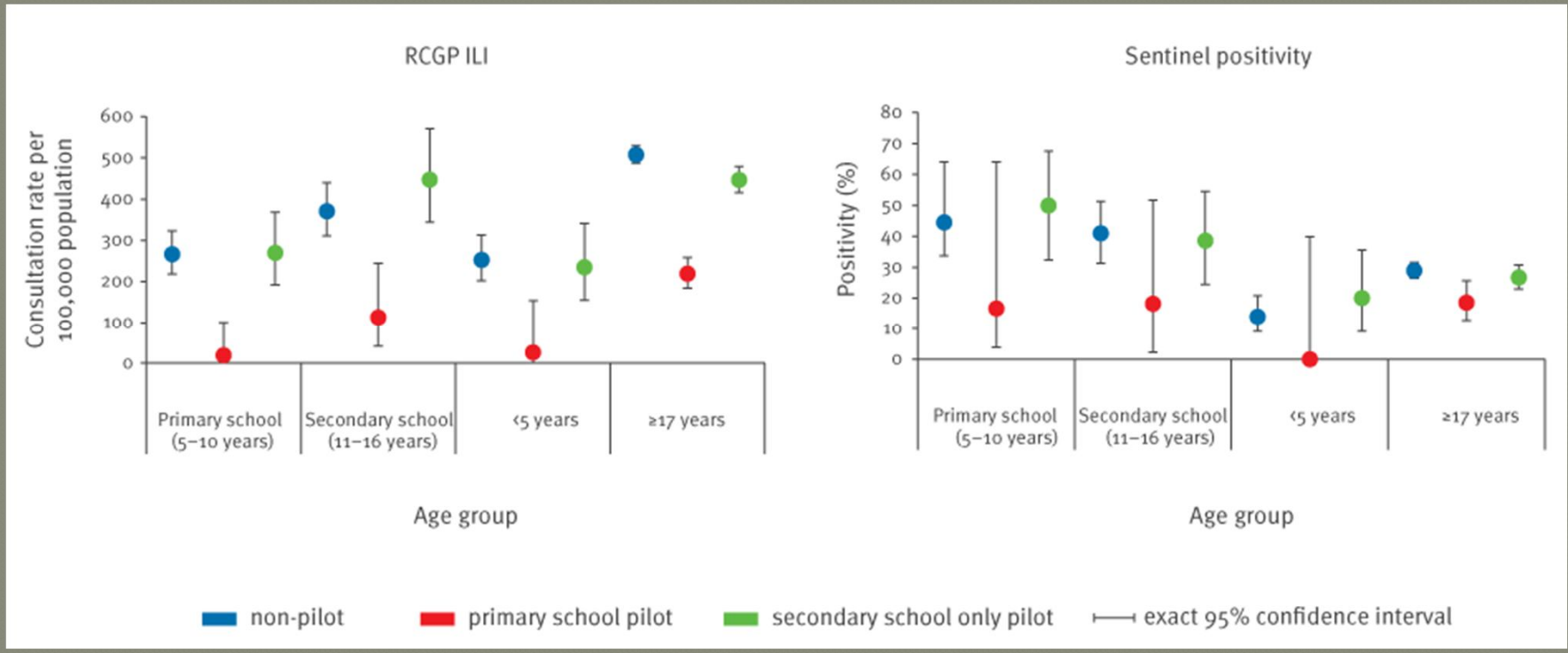
- All school age children or focus on certain groups such as primary school age children alone

UK experience

- 2013-14: first year of LAIV programme
  all healthy children 2-3 years +
  4-11 years primary school from pilots areas

- 2014-15: all 2 to 4 years-olds +
  primary school age pilots (4-11) +
  additional healthy secondary school children (11-13 years- olds) *Pebody Eurosurv oct 2015*
  dominant circulating A(H3N2) and B strains drifted

UK experience



Primary care indicators were lower in pilots areas where primary school age children were vaccinated compared with non-pilot areas (targeted and non targeted age groups),

No such differences for secondary school pilot areas

UK experience

Despite the circulation of drifted A(H3N2) and B influenza strains (2014-15):

- Vaccinating children of primary school age resulted in a significant reduction in incidence for a range of surveillance indicators.
- This effect was evident in targeted and non-targeted age groups (under 5 and > 17) compared with populations where primary school age children were not vaccinated.
- The size of the effect was less for more severe endpoints, in particular excess mortality.
- Vaccination of secondary school age children alone (11–13 years of age) failed to show conclusive evidence of such reduction in disease incidence in either targeted or non-targeted age-groups.

Pebody Eurosurv Oct 2015

Vaccine choice

- Live attenuated vs inactivated?
- Quadrivalent vs trivalent?

→ vaccine efficacy

→ vaccine effectiveness

Vaccine efficacy compared with placebo:

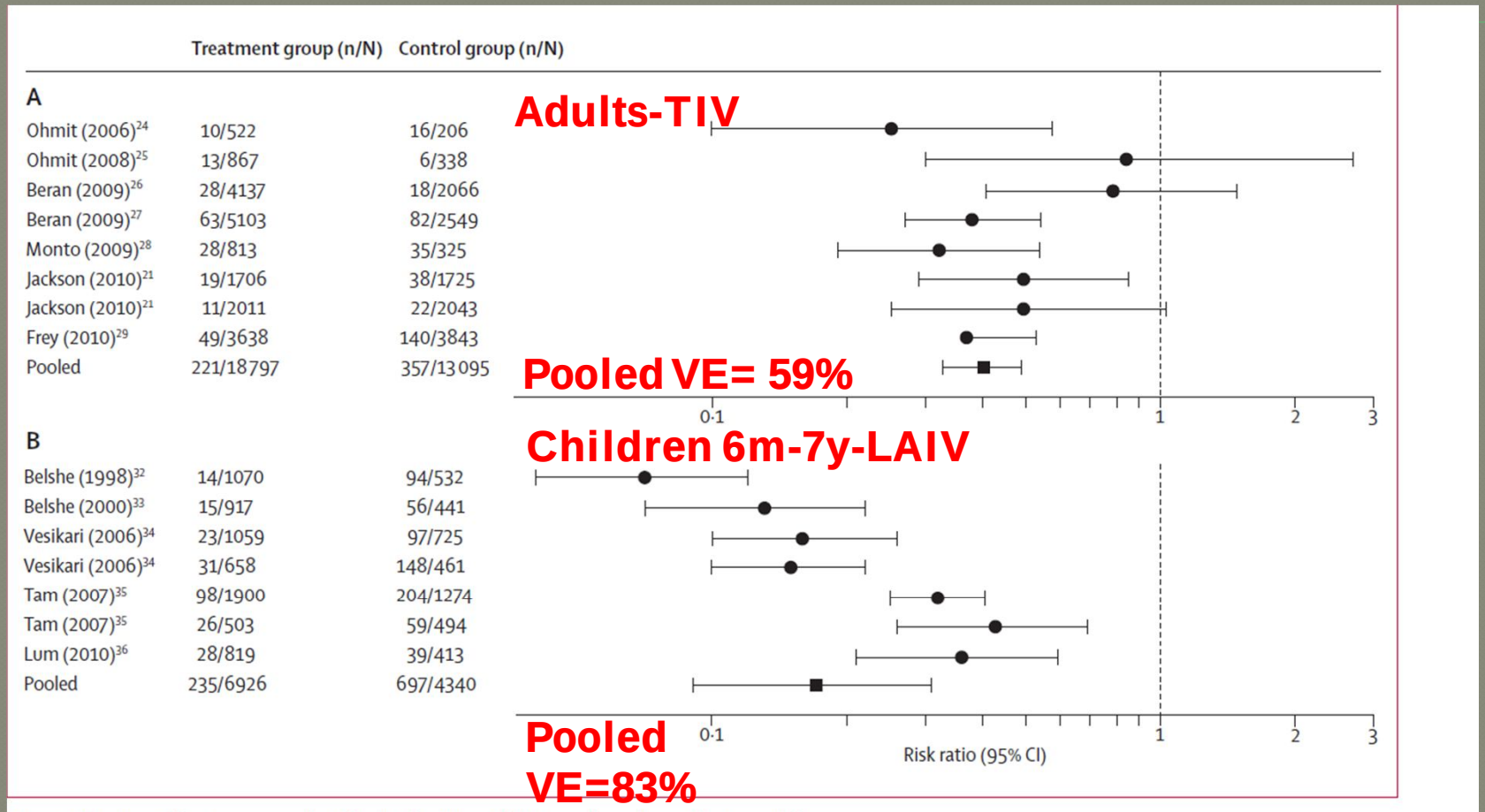


Figure 2: Vaccine efficacy compared with placebo (Mantel-Haenszel random-effects model)
(A) Trivalent inactivated influenza vaccine in adults aged 18–64 years. (B) Live attenuated influenza vaccine in children aged 6 months to 7 years. Studies were prospective (risk ratio) which are equivalent to case-control (odds ratio). n=cases of influenza. N=group size.

Relative vaccine efficacy LAIV vs TIV in children

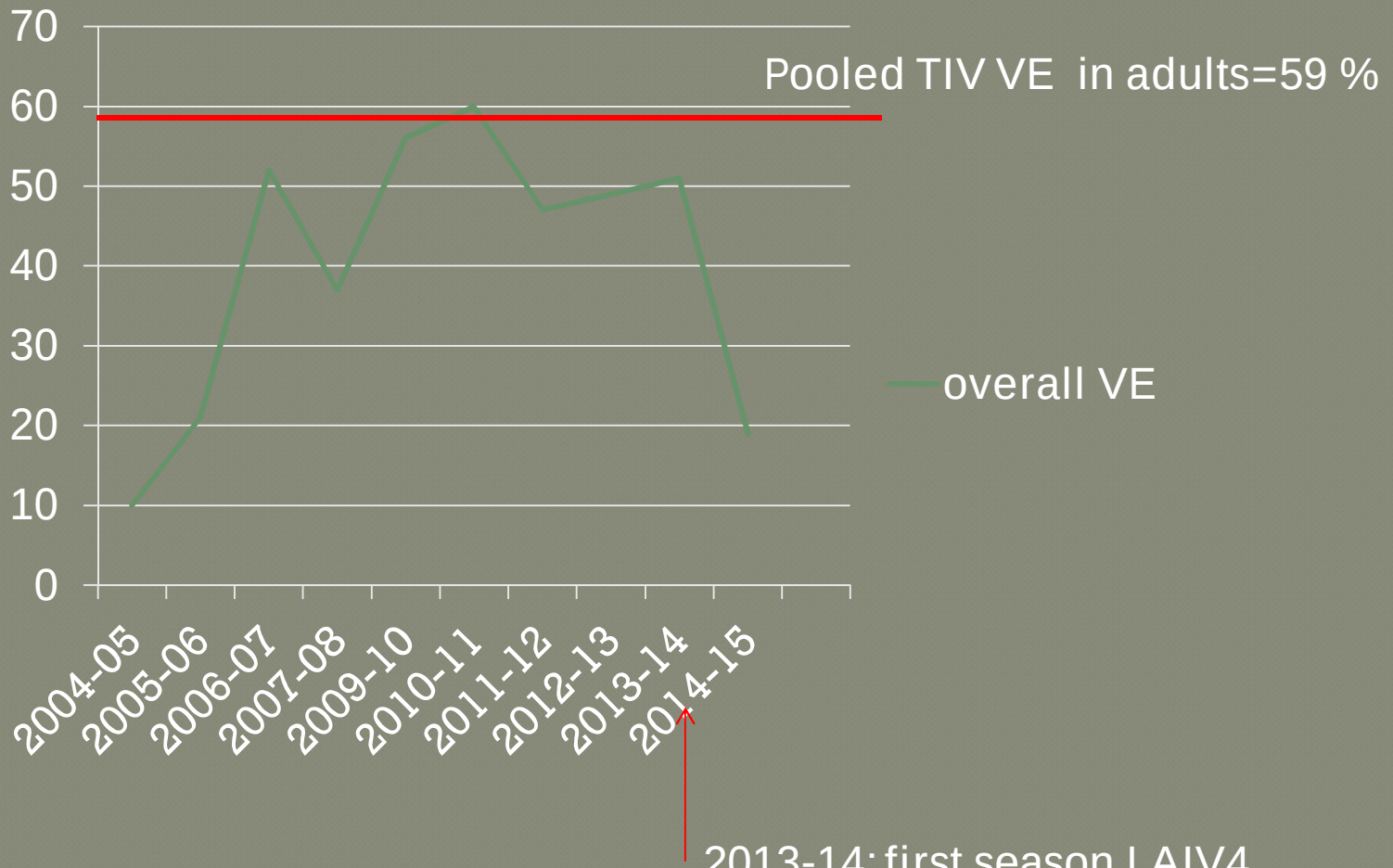
- Healthy children: relative efficacy from 44 to 52%

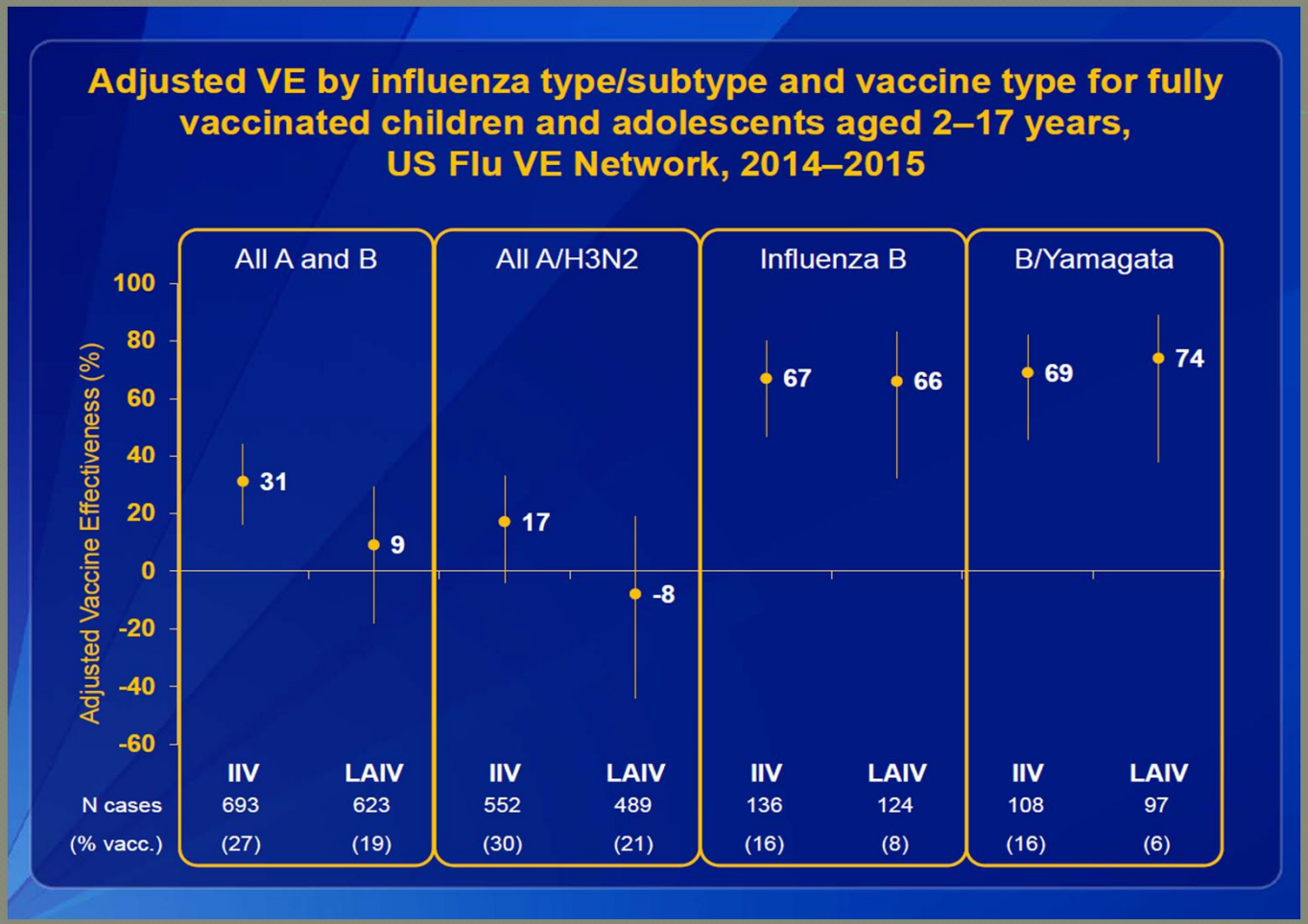
  Ambrose et al (Vaccine 2012 -2014)

- Asthmatic children and recurrent RTI : relative efficacy 35% and 53%

  Ashkenazi PIDJ 2006- PR-LAIV vs TIIV:2187 patients (6-72 m)
  Fleming PIDJ 2006-PR open-label LAIV vs TIIV: 2229 patients (6-17y)

Vaccine Effectiveness: US

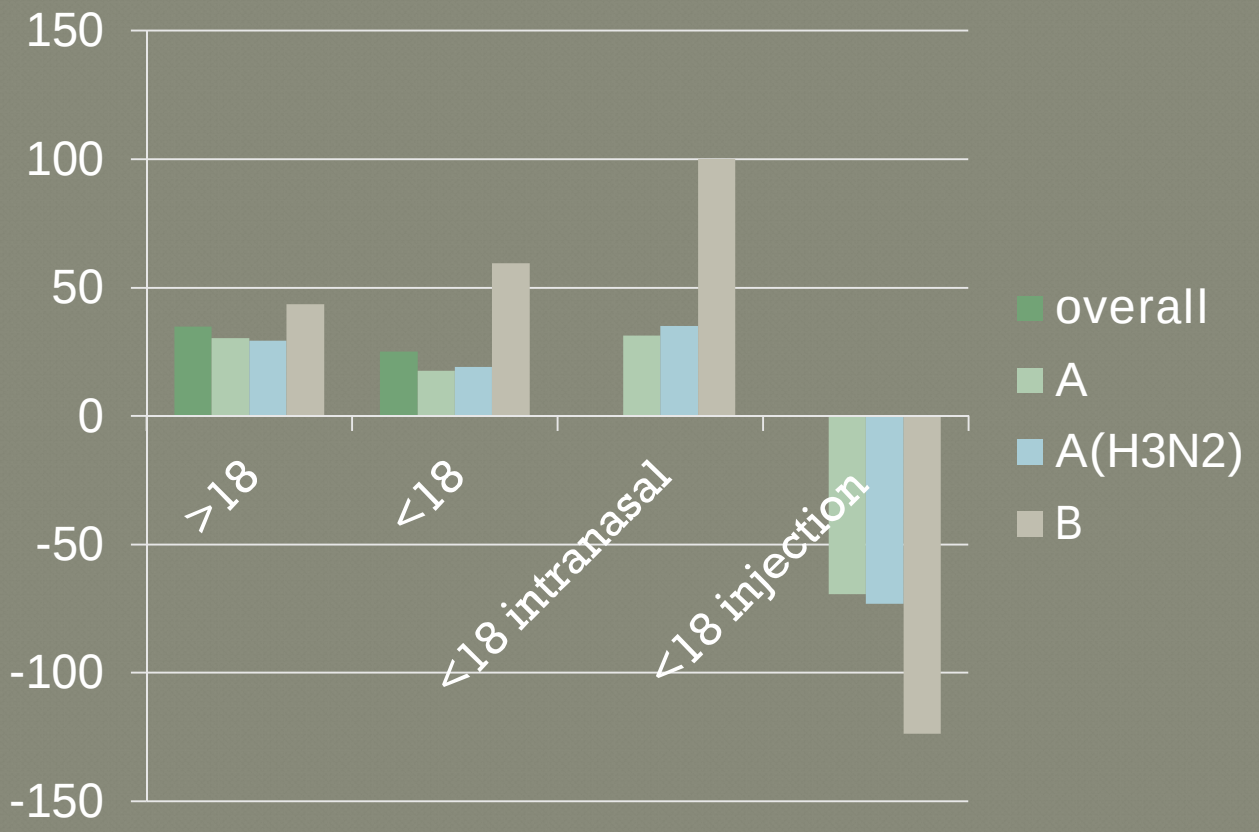




Predominance H3N2 antigenically and genetically drifted from vaccine strain

No difference between LAIV vs IIV

Vaccine Effectiveness :UK 2014/15



no significant difference between inactivated vs intranasal (wide Confidence Interva
LAIV: significant effectiveness for B (but limited numbers)

Pebody Eurosurv 2015

LAIV vs IIV ?

- LAIV: universal vaccination-relative vaccine efficacy > IIV but no difference in vaccine effectiveness
- LAIV contraindicated:
  - Children < 2 years or > 18 years
  - Moderate to severe febrile illness or nasal congestion
  - Severe asthma, active wheezing
  - Known or suspected ID, immunosuppressive ou immunomodulatory therapies or anyone in close contact with ID patient
  - Pregnancy
  - Egg allergy, other live virus vaccines within the last 4 weeks

Quadrivalent better than trivalent?

-2 antigenically distinct lineages (since 80s): B/Victoria and B/Yamagata

-Few cross-protection : specific hemagglutinin A protein

-1980s: B/Victoria , 1990s : B/Yamagata and >2000: two types

-Europe (2001-11): 1-60% type B

-Mismatch between vaccine and circulating B strains :

US: 46% (2001-2012)

Europe: 58% (2003-11)

-Australia 2015: influenza B = 67% and in children B/ Victoria (13/33) but vaccine strain (TIV) = B/Yamagata

Target groups

GROUP	RATIONALE	VACCINE
High risk group		
< 6 months	hospitalisation complications	NO-pregnant women and household contacts
6-36 months with RF		**TIV** * (LAIV *if > 2 years)
≥ 36 months with RF		**QIV*** or TIV * LAIV *
HEALTHY		
6-24 m	high risk of complications	TIV *
>2-? years	High attack rate transmission	**LAIV** * or TIV * or QIV * if ≥ 3 years

* 2 doses if first vaccination < 9 years of age

Take Home Message

- Universal vaccination of healthy chidren?:

  probably yes: children = main disseminators BUT

  how to achieve a high vaccine coverage in a short period?
  target age-group?

- High risk strategy: better coverage

  < 6 months of age: household + pregnancy

  < 24 months of age? BUT = TIV (2 doses)

- LAIV vs IIV: better relative vaccine efficacy BUT unreimbursed and several contraindications or precautions and no difference in VE(US-UK)

- Quadri or trivalent: link to the epidemiology (see preliminary data in Australia)