Seasonal Influenza vaccines Efficacy /effectivenes in children

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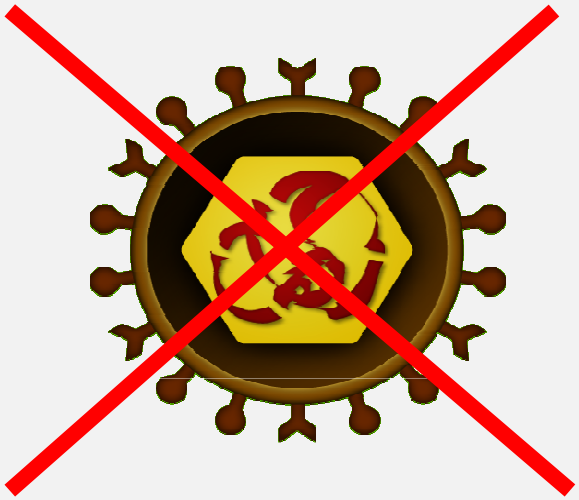
GEIG, 2008, Strasbourg

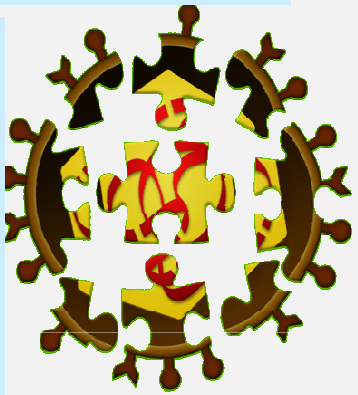
Influenza Vaccines in Europe are inactivated, injectable (TIV)

Whole Virus, inactivated



Split virion inactivated

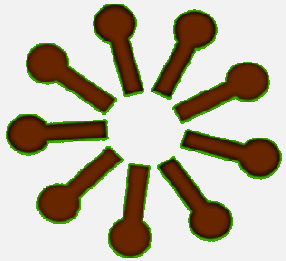
- Vaxigrip®/mutagrip® SP-MSD
- Immugrip ® PierreFabre
- Fluarix® GSK
- Previgrip® Chiron



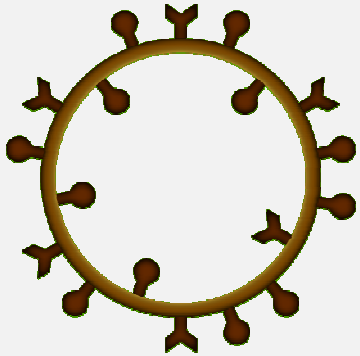
Sub-unit

Surface antigens

- Influvac ® Solvay
- Fluvirine® Evans vaccines
- Agrippal® Chiron
- Gripguard® Chiron



Virosomal



BUT….Flu TIV in Europe

- Have been registrated

  & are yearly evaluated in subjects > 18 yoa

  Is « analogy » in children feasible ?

- CHMP biological criteria utilized to evaluate immunogenicity are thus for subjects > 18 yoa

  Are those criteria adequate for children ?

- ❑ Immuno-immaturity in young children
- ❑ A need for specific pediatric trials before registration (PIP)

Rationale of influenza vaccination in children

Reduce morbidity

- Infection
- Complications
- Hospitalisation rate
- Absenteeism

Reduce transmission of virus

- Propagation of epidemics
- In household
- In the community

Direct effect
Individual benefit

Indirect effect
Herd immunity

Safety of flu vaccines TIV is fine !! in children

- **Egg allergy (anaphylaxis) : contra-indication**

- **Asthma / influenza vaccines**

  No increase of post-vaccination bouts

Which efficacy/effectiveness of registered Flu vaccines TIV in children?

Efficacy/effectiveness of Flu inactivated vaccines

Healthy children / adolescents (all ages ≤ 18 ys)

Meta-analysis including randomized clinical studies for preventing naturally occurring influenza and/or acute otitis media cases

	Overall Vaccination efficacy % *(95% CI)*	N of RCT, N patient
Clinically diagnosed illnesses URSS studies excluded	**36** *(31–40)* **61** *(49–70)*	19 N=247,517
Laboratory confirmed cases	**67** *(51–78)* Effectiveness 45% *(33-55)*	18 N =8574
Acute otitis media	**51** *(20–70)*	11 N =11,349

RCT: randomized clinical trials

Manzoli L et al. Pediatric Infect Dis J 2007;26:97–106

Assessing the efficacy / effectiveness of Flu vaccines in healthy children/adolescents

Negri meta-analysis

- **Efficacy: lab confirmed cases**
- **Effectiveness: against clinical illness**

	Efficacy	Effectiveness
	% (95% CI)	*% (95% CI)*
Inactivated injectable	**65%** *(45% - 77%)*	**33%** *(22% - 42%)*

- **NO evidence of reduction of AOM episodes RR=1.00 (95%CI: 79-1.26)**

Ref : CDC's Advisory Committee recommends influenza vaccination forchildren 6 moa through 18 yoa, 27 February 2008, Press release

Assessing the efficacy / effectiveness of Flu vaccines in healthy children/adolescents

(age < & >2 yrs)

	Efficacy	Effectiveness
> 2 yrs	% (95% CI)	% (95% CI)
Live attenuated Intra-nasal	**79%** *(48% - 92%)*	**33%** *(28% - 38%)*
Inactivated injectable	**59%** *(41% - 71%)*	**36%** *(24% - 46%)*
< 2yrs Inactivated injectable	**= placebo**	**NA**

51 studies
(17 from Russia)
= 263,987 children

Analysis of vaccine efficacy & effectiveness in children > 2 ys
14 RCTs & 11 cohort studies compared with placebo or no intervention

Vaccines for preventing influenza in healthy children
Cochrane Database of Systematic Reviews 2007 Issue 4

Jefferson, Cochrane 2008 issue 2 (extensive metanalysis)

… « No convincing evidence that vaccines reduce

- Mortality
- Hospitalisation admissions
- Serious complications
- Community transmission of influenza »

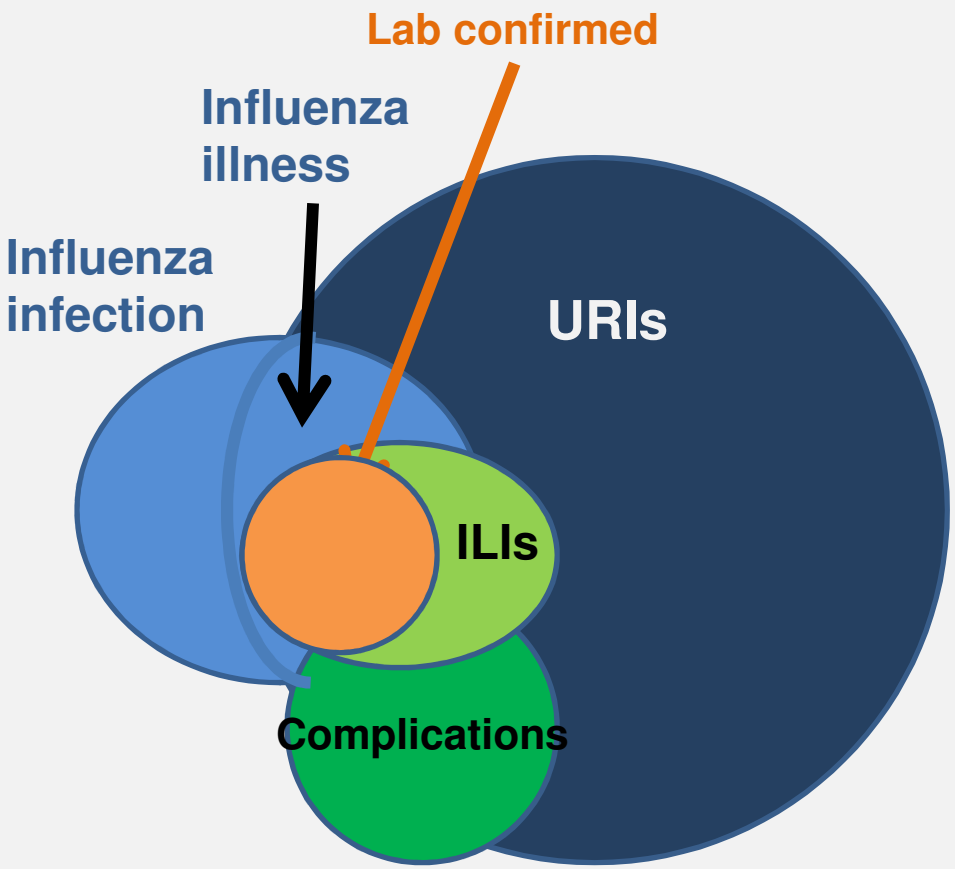
BUT….Effectiveness estimation

A problem of outcome or cases definitions

- Large variety of outcomes (interdependent)

how to interpret them?

- Highly specific (lab confirmed cases) leads to higher RR reduction
- Highly sensitive (e.g. clinical respiratory illness) associated with lower RR reduction & higher Absolute Risk reduction



ILI: febrile cough illness
URI: upper respiratory illness

K.Nichol ,Vaccine 2008, 26, supplt 4

TIV Effectiveness in children 6-23 moa

Shay D & al CDC, USA

presented at ESWI Sept 2008

- **Emerging Infection program**
- **9 states dispatched through the US**
- **3 season year study 2005/06, 06/07, 07/08**
- **Case control study : mean 3.7 controls/case**
- **Powered for a 40% vaccine effectiveness (1 dose TIV)**
- **Diagnostic by rapid test, direct fluorescence A+B, viral culture, RT-PCR**

TIV Effectiveness, children 6-23 moa

Shay D & al CDC,USA

presented at ESWI Sept 2008

- 176 /290 eligible patients in 3 seasons
- 651 controls
- Boys 62% / Girls 39%

Virus Dg	05/06	06/07	07/08
A	72%	84%	65%
A + B	2%	-	-
B	15%	10%	25%
unknown	11%	6%	10%

Influenza A virus was predominant

Age Group (moa)	Vaccinees	controls
6-11	41%	40%
12-17	34%	34%
18-23	25%	26%

3 in 4 children under 18 moa

TIV Effectiveness, children 6-23 moa

Shay D & al CDC,USA

presented at ESWI Sept 2008

Vaccination Coverage rate	Full	Partial	NO
05/06	9%	24%	67%
06/07	13%	23%	65%
07/08	23%	21%	56%

Vaccination effectiveness 3 seasons, 6-23 moa	Full	Partial
Crude VE	64% (42-78)	33% (-4, 57%)
Adjusted VE	69% (45-82)	32% (-11,x%)

Adjustment : high risk groups, low birth weight…

Influenza Vaccine effectiveness

Ontario,Canada

presented at ESWI, Sept 2008

- **Population based study, « ecological »**
- **Decrease in mortality, healthcare ?**

	Pre vaccination program	Post vaccination program	Reduction of hospitalization
Overall ages	33.4%	8.5%	75%
<5 yrs	44.5%	23.8%	45%

Some effectiveness,driven by increase of uptake in the younger age groups

Is TIV utilization optimal in young children ?

Inactivated influenza Vaccine Schedule in children

Age	Dose	N dose
6 – 35 mo	0.25 mL	1 – 2 doses*
	(*3x7.5 mcg/dose*)**	
3 – 8 ys	0.5 mL	1 – 2 doses*
	(*3x15 mcg/dose*)	
≥ 9 ys	0.5 mL	1

* Children never vaccinated previously

** HA content per strain included in the trivalent vaccine

- ❑ Injectable !
- ❑ Annual booster !!

France, BEH 2008, N°16-17

Two questions to think about

Why start the schedule at 6 moa?

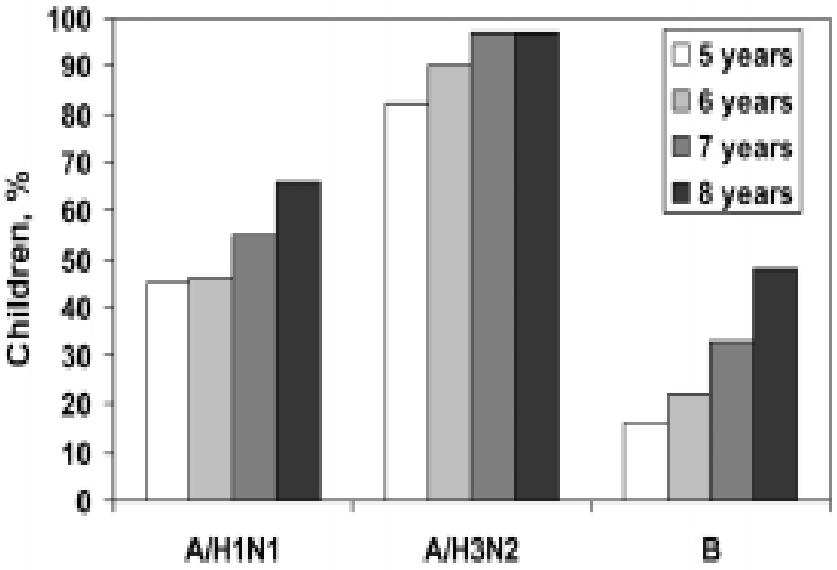
Why ½ doses in children < 36 moa?

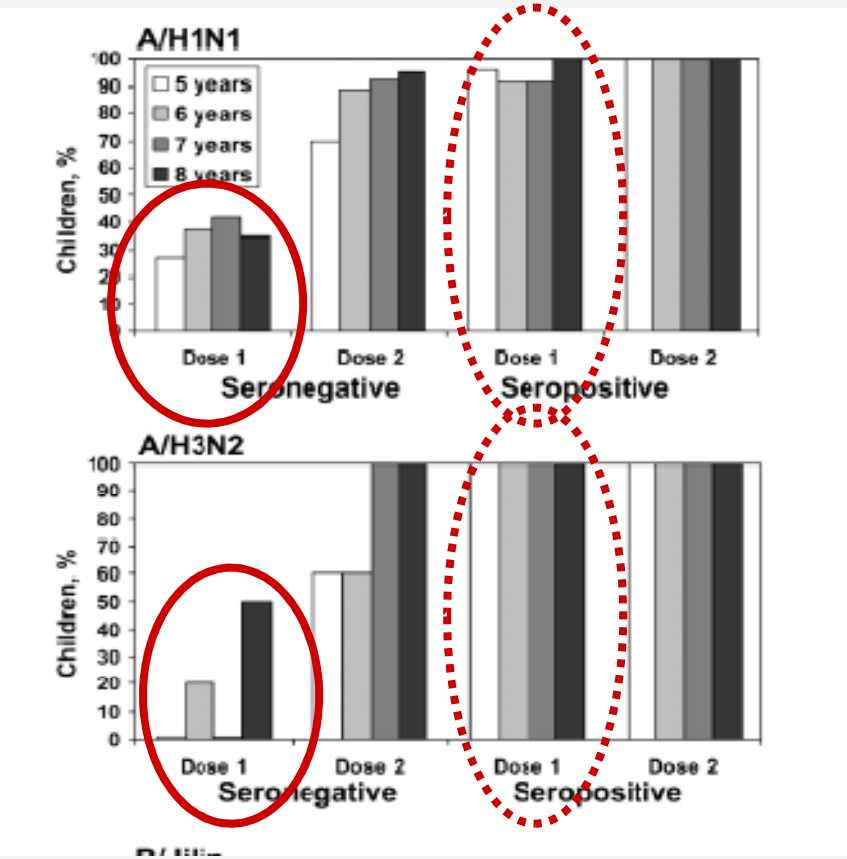
Immunogenicity and Reactogenicity of 1 versus 2 Doses of Trivalent Inactivated Influenza Vaccine in Vaccine-Naive 5–8-Year-Old Children

Kathleen M. Neuzil,[1,2] Lisa A. Jackson,[4] Jennifer Nelson,[2,4] Alexander Klimov,[5] Nancy Cox,[5] Carolyn B. Bridges,[7]

JID 2006:194 (15 October)

2 doses are needed in naïves



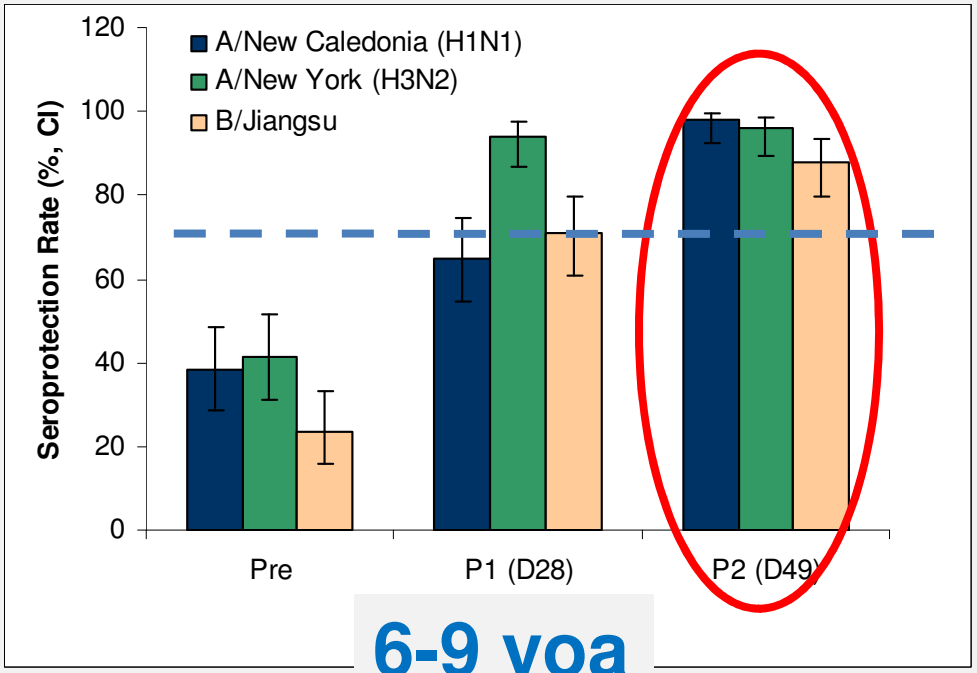


% seropositive children before vaccination

≥1:40 depending on statute (+ / -), age, dose

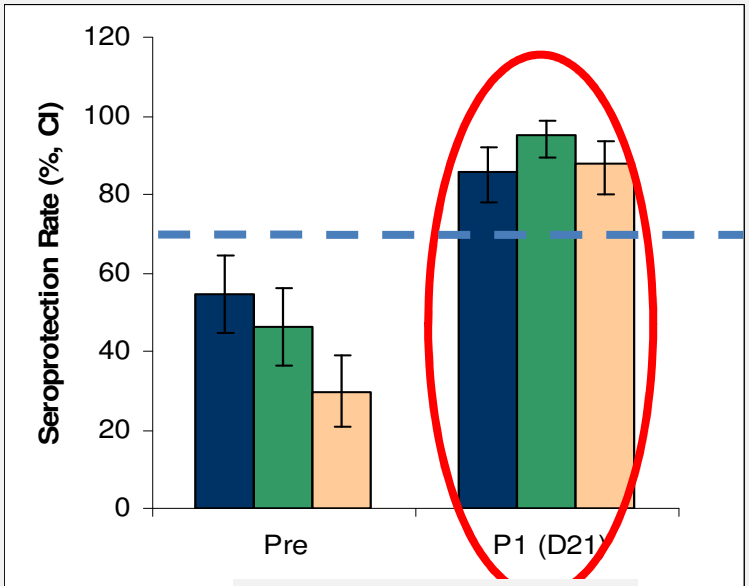
A reality :
TIV Efficacy in children < 9 yoa needs TWO doses !!

When vaccinated for the first time



6-9 yoa

SPR after 2 doses



10-13 yoa

SPR after 1 dose

Jackson LA et al. Pediatrics 2006;118:2032–2037; Schuster V et al. 25th ICP, Athens 2007. Poster presented.

Consequences in children < 9 years of age

- When **vaccinated for the first time a need for 2 doses** of TIV

- **Non-compliance with the TIV 2-doses** may be associated with **suboptimal protection** against infection

How to trigger a 2 doses full vaccination schedule ?

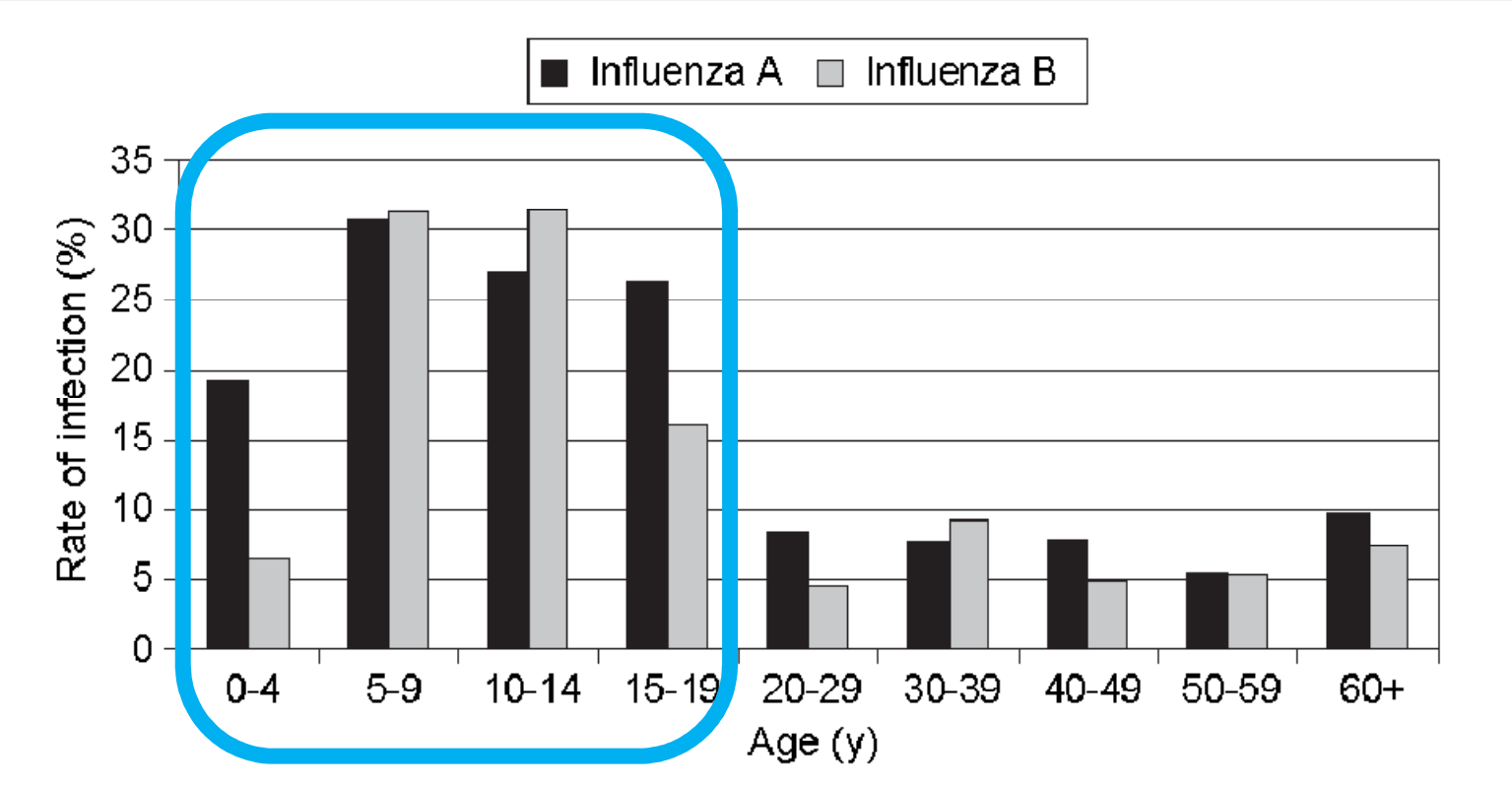
Jackson LA et al. Pediatrics 2006;118:2032–2037

Adequacy between Flu burden in children (< 2 yrs) & TIV efficacy ?

Children at any age ….
During every seasonal Influenza

- ❑ Are at risk of
  - being infected by the virus
  - influenza disease
- ❑ Have a high attack rate
  a high hospitalization rate
- ❑ Are a major vector
  of influenza transmission

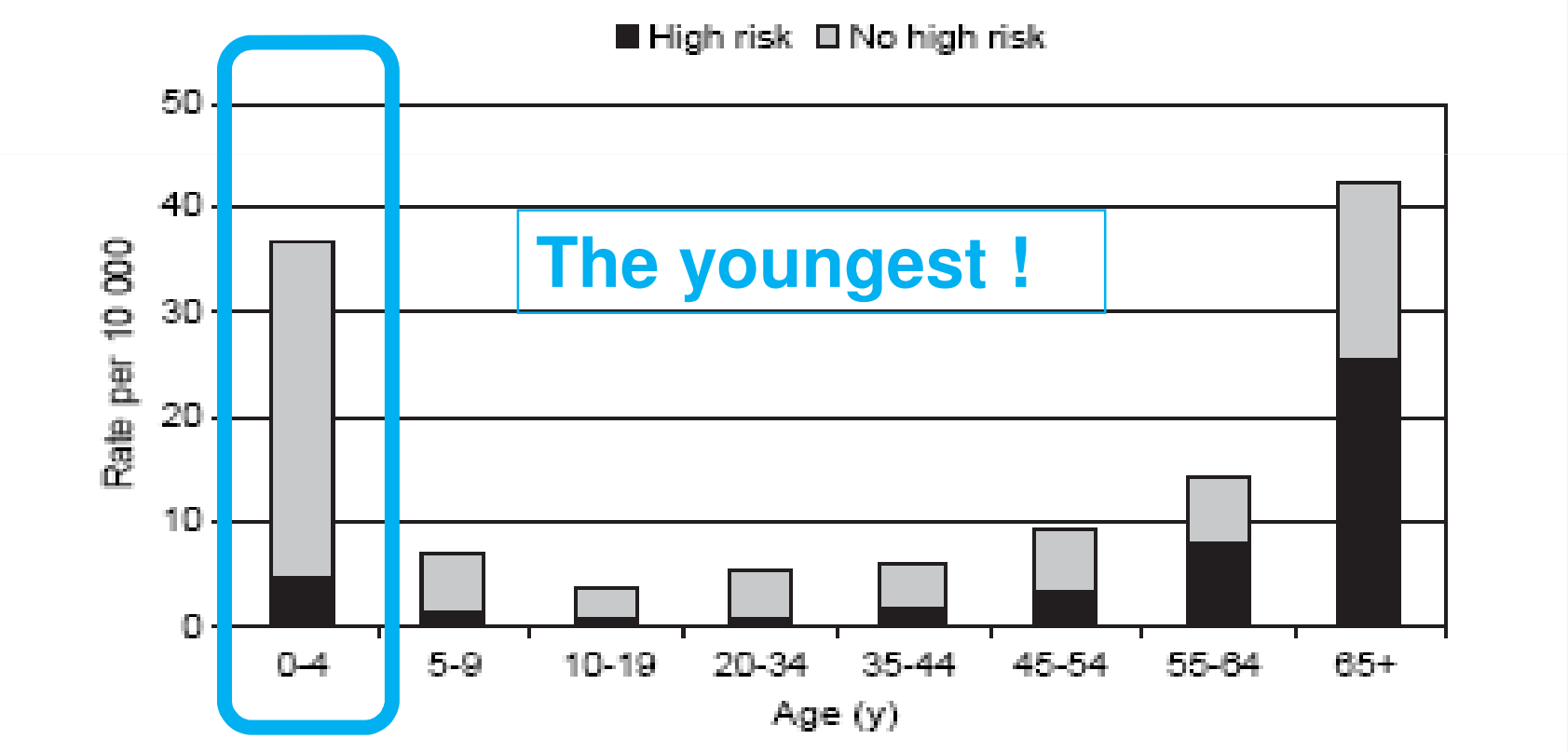
Influenza epidemics
A high attack rate in children



Heikkinen T., Acta Paediatr. 2006;95:778–784

Age-specific rates of hospitalization

Hospitalization with acute respiratory disease during three consecutive influenza epidemics (1978-1981) Houston, USA.



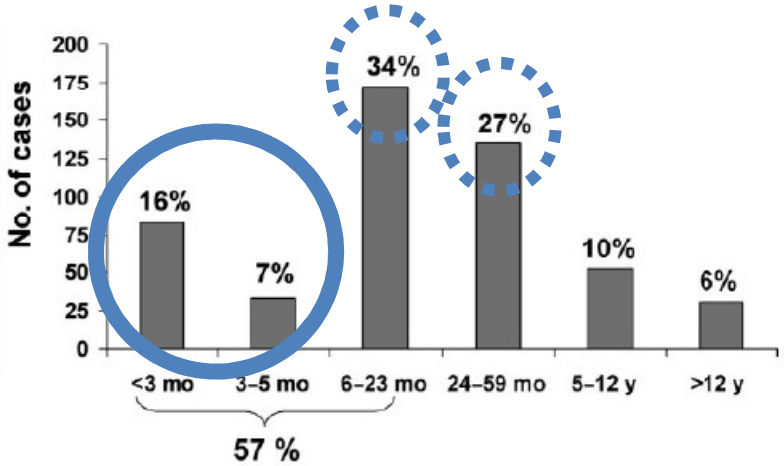
Glezen WP et al. Am Rev Respir Dis 1987, 136:550–555

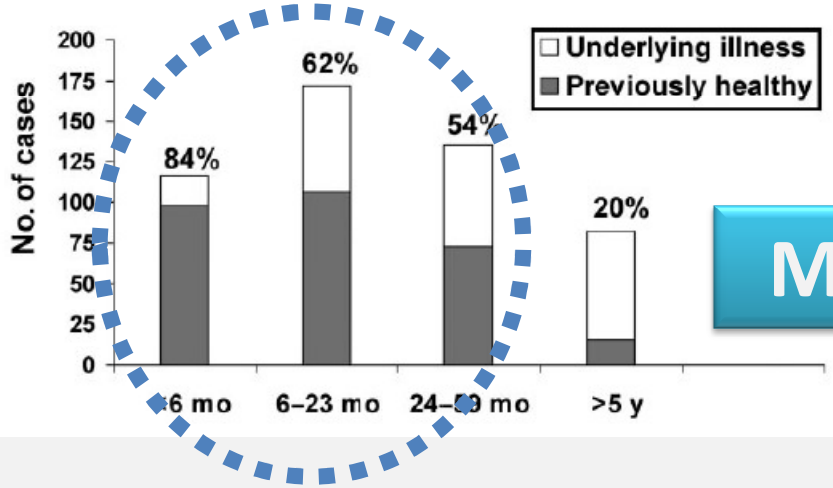
Children hospitalized for influenza admissions

Canadian Immunization Monitoring Program Active Centres, 2003-2004

Many young children

23% under 6 moa
57% under 2 yoa
84% under 5 yoa



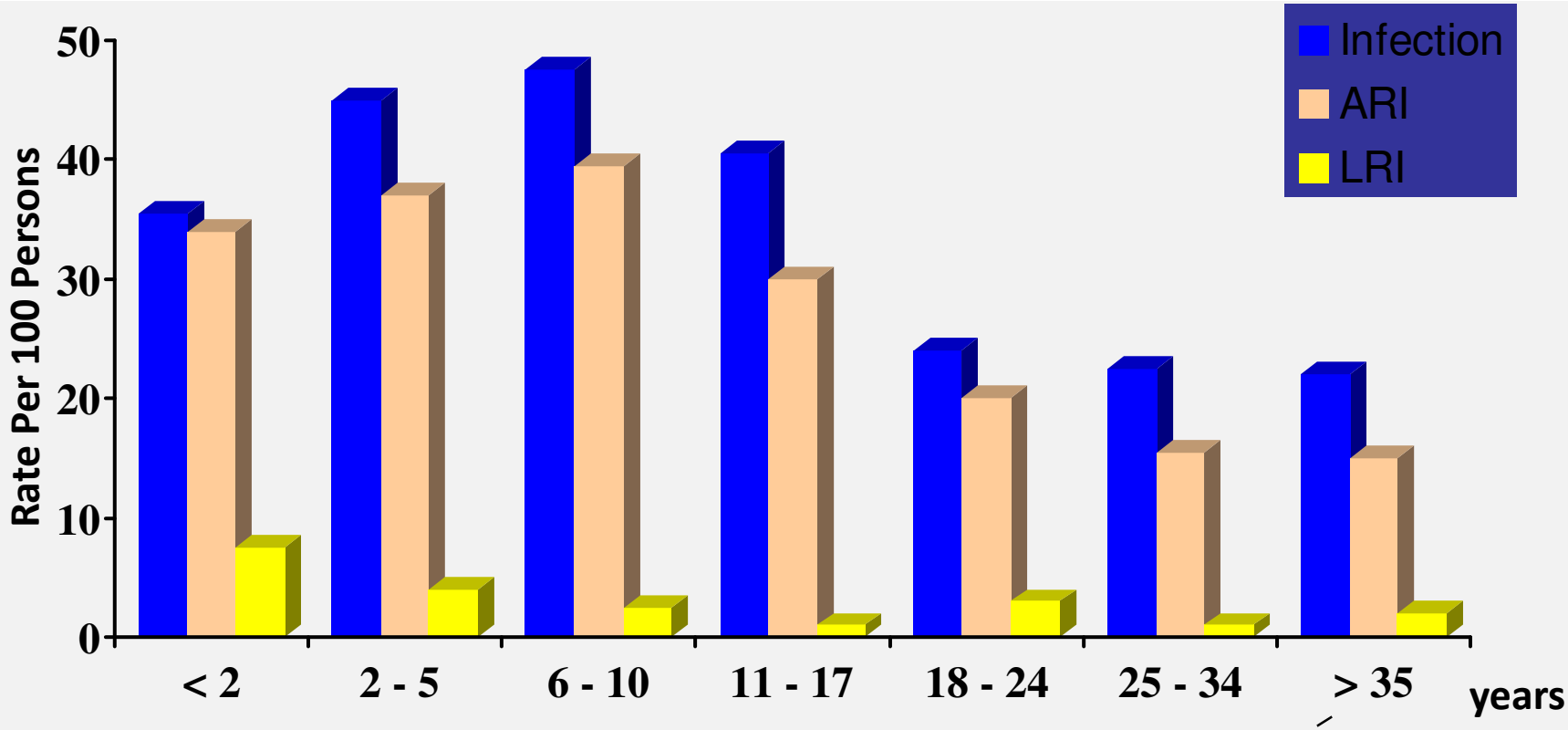


Many healthy children

Moore, et al. Pediatrics 2006;118(3):e610

Influenza is -mainly- a respiratory disease

URT & LRT in children

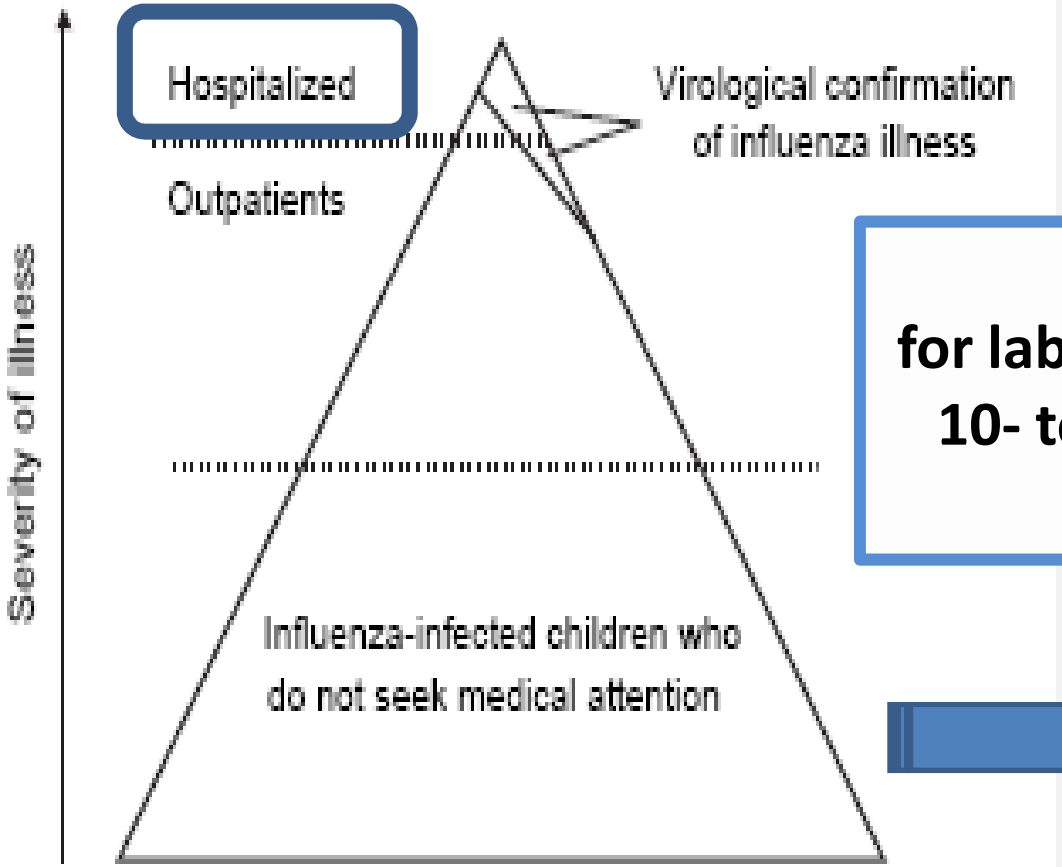


URT = high risk of transmission

Houston Family Study, 1976 to 1984. D'après Glezen W.P.

Influenza "iceberg" in children in community

Flu burden is still underestimated



Outpatient visits for laboratory-confirmed influenza 10- to 250-times more common than hospitalizations.

SPREAD

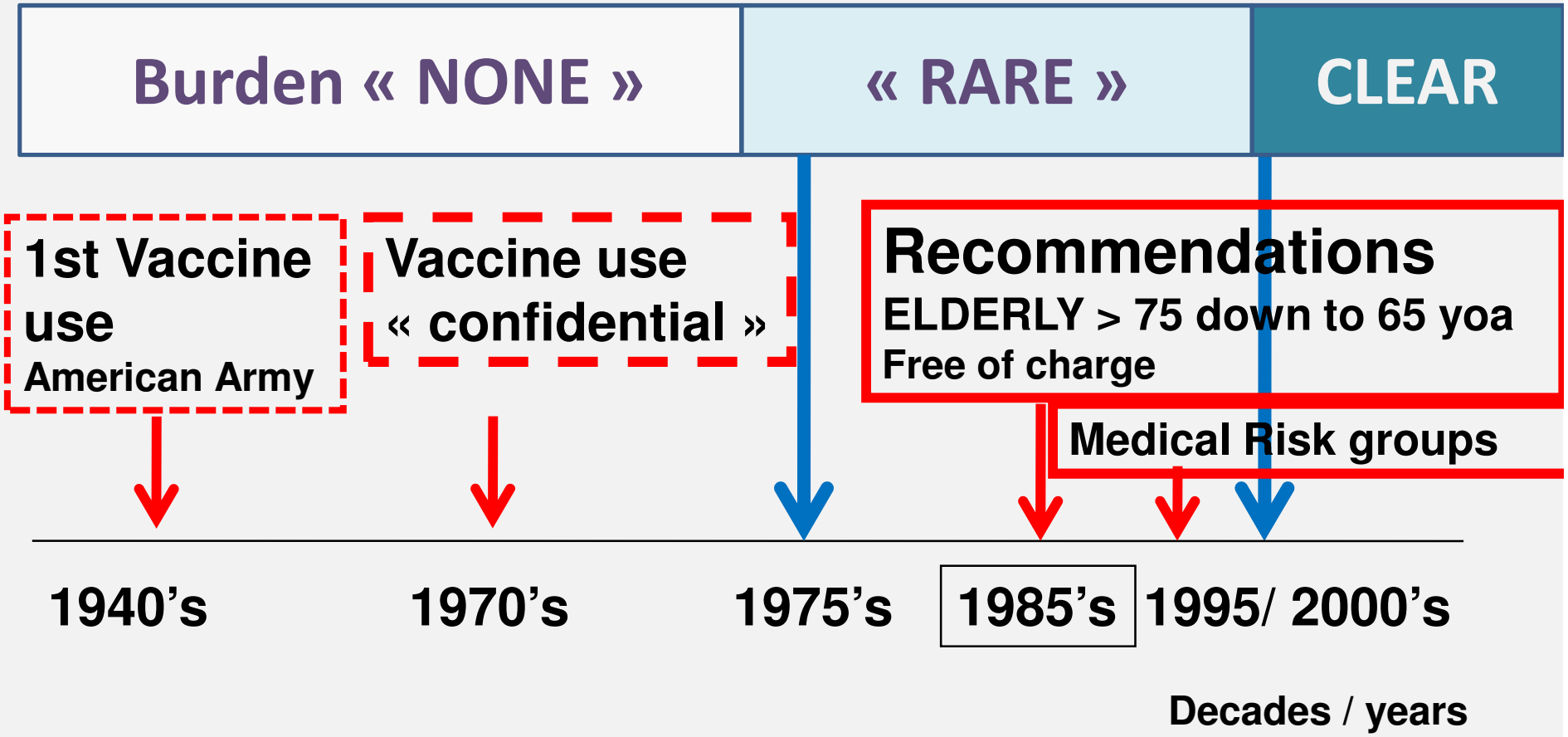
Ohmit SE, et al. Clin Infect Dis 2006;43:564–568; Poehling KA, et al. N Engl J Med;2006;355:31–40; Heikkinen T et al. Acta Paediatr 2006;95:778–784

Summary

Influenza in children is

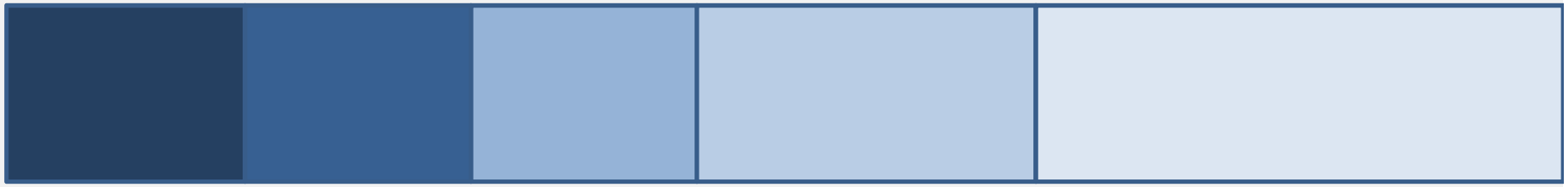
- **clearly admitted since…10 years**
- **still (largely??) underestimated**
- **a huge burden in < 2 yrs**
  & especially in < 6 moa (NO vaccine available)
- **a healthy child disease**
- **though more severe in medical high risk groups**
- **AND a major source of transmission**
  in households & communities

Recognition of the burden in children / TIV use / recommendations



Flu Burden in children / TIV

Influenza (nowadays) identified burden



NO vaccine	NO studies	One Study *	Several studies Some efficacy	Efficacy Adults= children

Age

< 6 moa < 1 yr < 2 yrs < 5 yrs > 5 yrs

*: recent studies comparing LAIV / TIV

Summary

- TIV are « old » vaccines

  EU evaluation: requests / needs are no more what they were !

- Interest in vaccinating against Flu is recent (20- 30 years)

- Interest (need) fo vaccinating (young) children is - even more recent (5-10 years)

  - limited to high risk groups

A strong will to enlarge programs
How to go further with flu vaccines & policies in children?

A need for “stronger” & safe flu vaccines

Future in Flu vaccines

- ❑ **Existing intra nasal live attenuated vaccine**
- **Recommended in the US**

  BUT…… for <u>healthy</u> children > 2 yrs
- **Soon in Europe?**

- ❑ **Ongoing research for other vaccines**
- **Adjuvanted (benefit from H5N1 vaccines)**
- **Intra dermal**
- **…….**

One of the hopes: live attenuated intra-nasal influenza vacccines LAIV

- **Safety : OK (BUT….)**

- **Efficacy LAIV 79%** *(48% - 92%)***> TIV 59%** *(41% - 71%)*
  Persistent 2nd season even with mismatched strains
  Efficacious on Flu AOM

- Schedule: 1 spray twice with a 4 w interval.

Besche NEJM 2007; MMWR 2008

Belshe R comparative study TIV / LAIV

- **54.9% fewer cases of cultured-confirmed influenza in the LAIV group than in the TIV group**

  153 vs. 338 cases, *p<0.001*
- **Attack rate LAIV / TIV**

  3.9% / 8.6% *p<0.001*
- **Relative efficacy LAIV / TIV in reduction of AOM & LRTI**

  50.6% p 0.004 & 45.9% p= 0.046
- **Superior efficacy of LAIV / TIV observed for both antigenically well-matched & drifted viruses**

N Engl J Med. 2007;356:685-96.

Methods

- *Children 6 to 59 moa*
- *Safety and efficacy*
- *Influenza-like illness monitored with cultures*
- *throughout the 2004-2005 influenza season*

BUT with LAIV / TIV among children 6 - 11 moa

- **wheezing within 42 days post dose 1 more common**
- **higher rates of hospitalization (6.1% / 2.6% *p= 0.076*)**

Belshe R comparative study TIV / LAIV

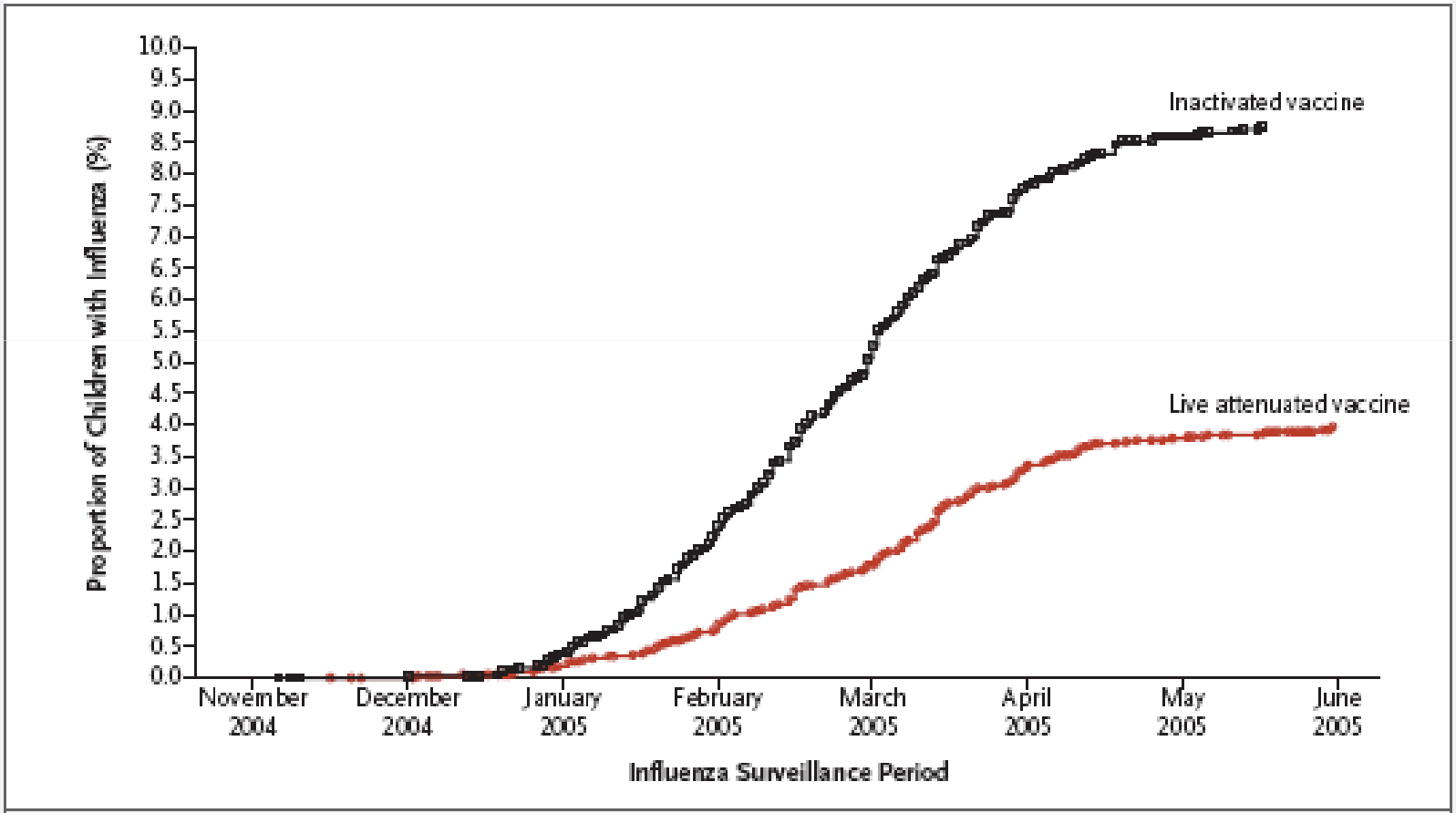


Figure 1. Kaplan–Meier Curves for the Time to the First Culture-Confirmed Report of Influenza in the Two Vaccine Groups.

N Engl J Med. 2007;356:685-96.

Belshe R comparative study TIV / LAIV

Table 2. Influenza Attack Rates in the According-to-Protocol Population.*

Variable	Similarity to Vaccine†	Live Attenuated Vaccine (N=3916)‡		Inactivated Vaccine (N=3936)§		Reduction in Attack Rate with Live Vaccine¶
		Cases	Attack Rate	Cases	Attack Rate	
		no.	%	*no.*	%	% (95% CI)
Virus	Well matched	53	1.4	93	2.4	44.5 (22.4 to 60.6)
A/H1N1		3	0.1	27	0.7	89.2 (67.7 to 97.4)
A/H3N2		0	0	0	0	—
B		50	1.3	67	1.7	27.3 (−4.8 to 49.9)
Age at first vaccination (any influenza virus)	Well matched					
6–23 mo		23	1.3	32	1.7	29.1 (−21.2 to 59.1)
24–35 mo		17	1.3	24	1.8	32.6 (−25.8 to 64.5)
36–59 mo		13	1.7	37	4.7	65.6 (36.3 to 82.4)
Previous vaccination (any influenza virus)	Well matched					
Yes		18	1.9	29	3.1	39.3 (−9.2 to 66.9)
No		35	1.2	64	2.1	46.9 (20.0 to 65.2)
Virus	Not well matched	102	2.6	245	6.2	58.2 (47.4 to 67.0)
A/H1N1		0	0	0	0	—
A/H3N2		37	0.9	178	4.5	79.2 (70.6 to 85.7)
B		66	1.7	71	1.8	6.3 (−31.6 to 33.3)

N Engl J Med. 2007;356:685-96.

Belshe R comparative study TIV / LAIV
wheezing /hospitalization

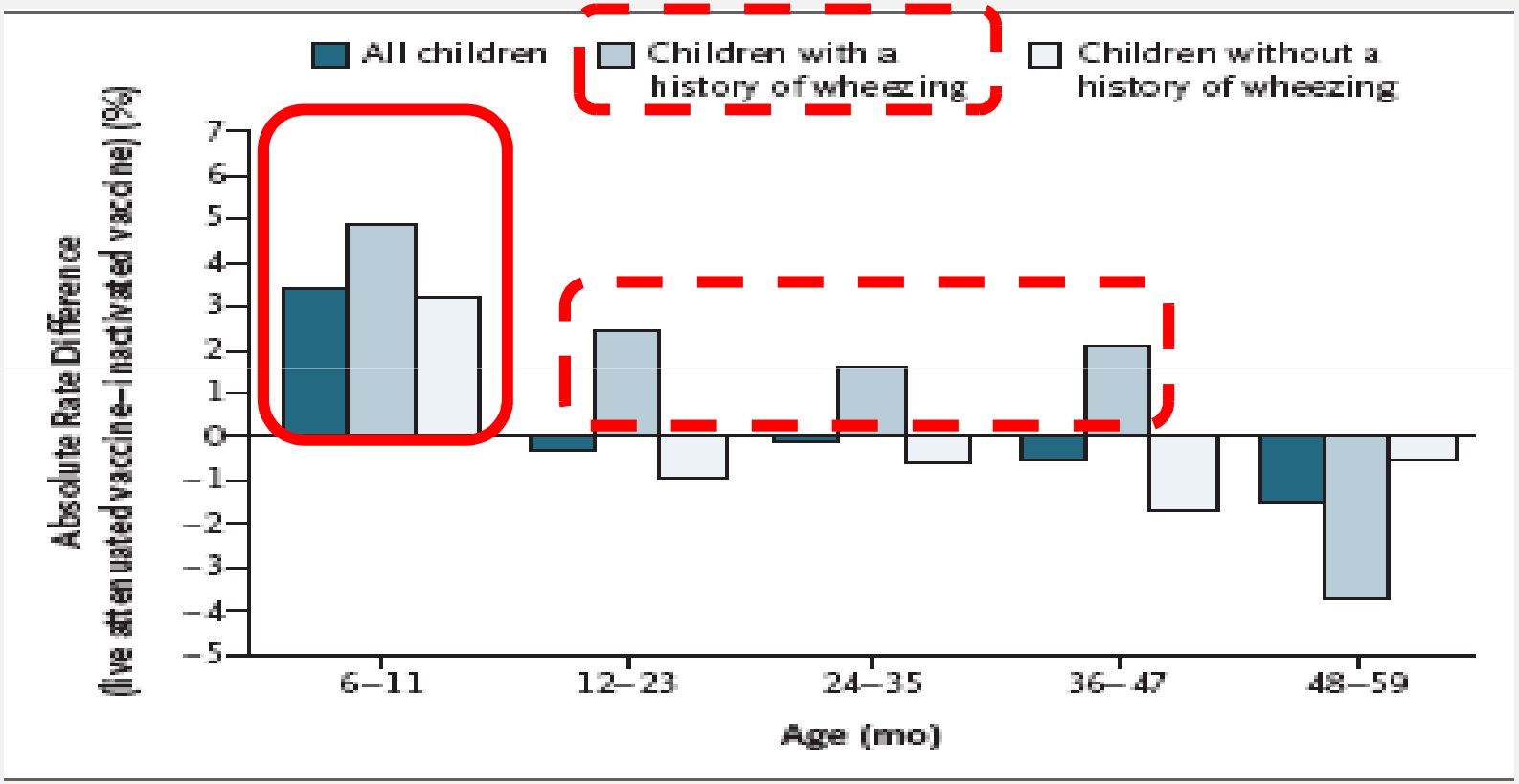


Figure 2. Difference in Rates of Hospitalization between the Two Vaccine Groups, According to Age and the Presence or Absence of a History of Wheezing Illness before Vaccination.

N Engl J Med. 2007;356:685-96.

A need for flu vaccines studies

- adequate design
- specific to children

A need for strategies to improve vaccination coverage (with existing recommendations)

Vaccination coverage in recommended groups

Remains < 50%

among high risk groups

health-care personnel

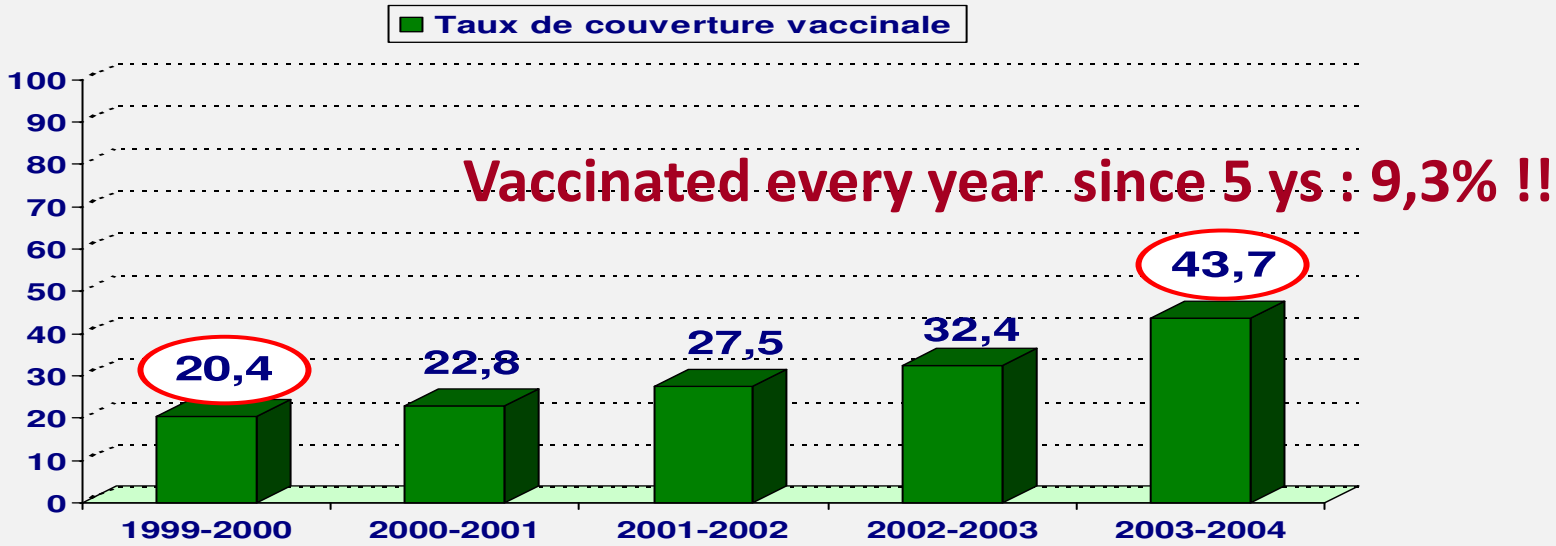
& pregnant women

Fiore AE, el al. MMWR Recomm Rep. 2007;56(RR-6):1–54

(Very) High risk children

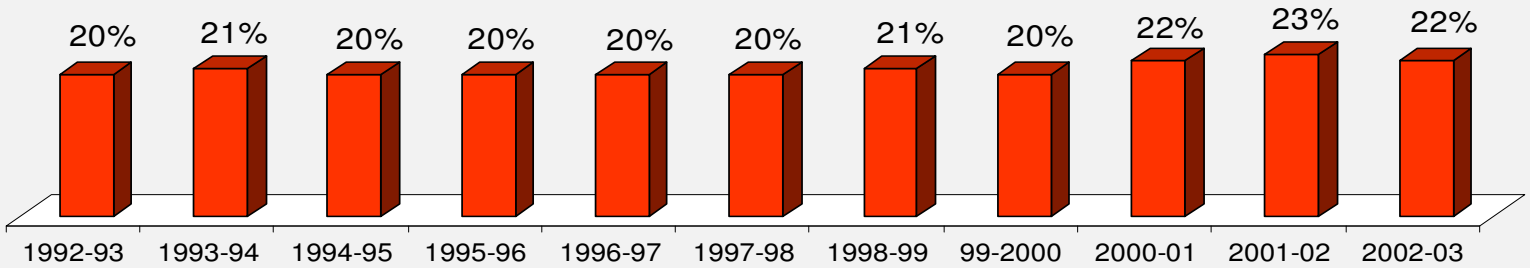
snapshot in Parisian Region

prospective survey in 7 pediatric hospitals



Vaccinated every year since 5 ys : 9,3% !!

General Population , France *Sofres survey*



Weil-Olivier et al. Arch Pediatr 2007 Oct 4; Epub

Asthmatic children

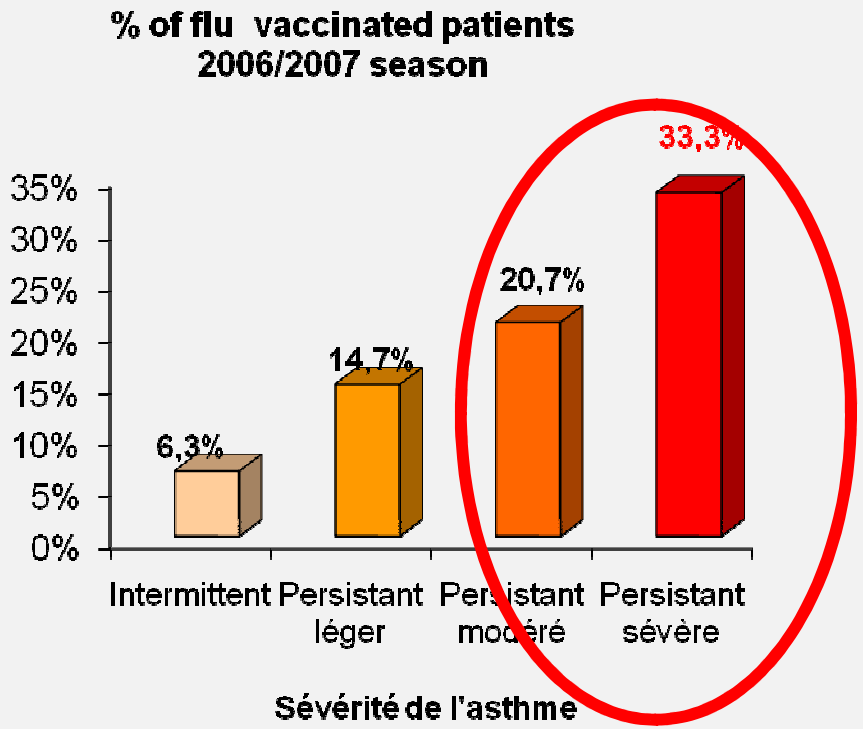
Coverage rate

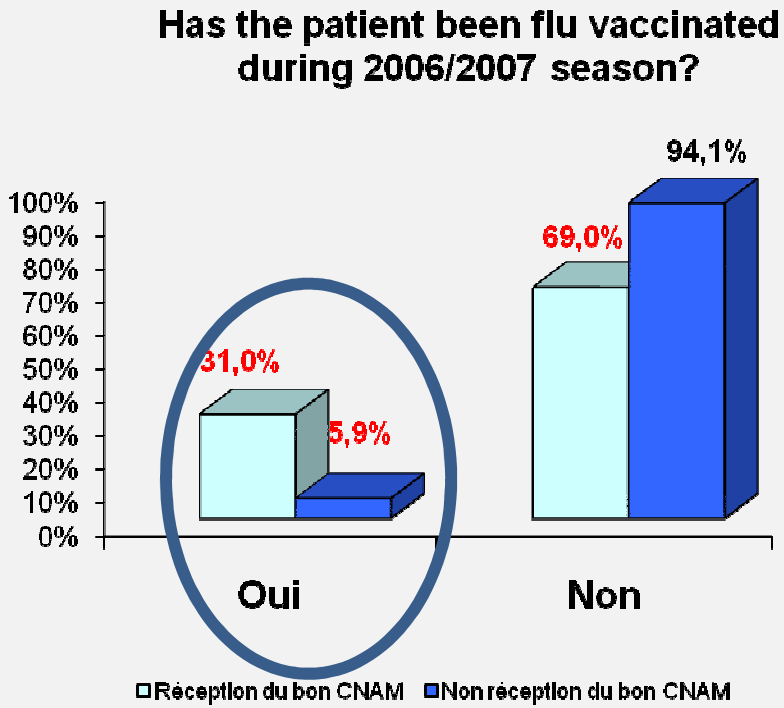
2006/2007 : 15,7%

2005/2006 : 13,9%

2004/2005 : 10,9%

French national survey *(in press)*
8 pneumo-pediatric wards
N=433 children





GAP between
EU recommendations (75% coverage rate)
& current vaccination coverage

Low vaccination coverage

Public health consequences

- **High morbidity**
- **Hospitalizations**
- **& influenza-related mortality**

(& NO indirect benefit)

There is a need to increase coverage of influenza vaccination in children

Vaccination is the primary approach in the prevention of influenza

From 6 months of age

❑ **Most European countries*** recommend TIV

- for children ≥ 6 moa
- Only at medical high risk (chronic pulmonary, cardiac or metabolic diseases, ..) for complications from influenza

❑ **North America**** recommends TIV / LAIV

- to any child
- > 6 moa up to 18 yrs

LAIV: live attenuated vaccine
Only for healthy > 2 yrs

****Finland, Austria : universal recommendation for < 2yoa***

***** MMWR_2008_RR 57***

Recommended Influenza Vaccination in Children

	USA	EU
> 6 months of age	**Recommended for all with high risk conditions**	**Recommended for all with high risk conditions**
6 moa up to 18 yoa (*Canada 6-23 moa*)	**Recommended for healthy children**	**NO *except Austria, Finland (up to 2yoa)***
Elderly	Recommended	Recommended
HCPs, household contacts, care givers	Recommended	Recommended for all HCPs
Pregnant women	Recommended	NO
All Other	Recommended	NO

MMWR, RR 57, 2008

Report of the Committee on Infectious Diseases. Pediatrics 2007;19:846–51; BEH 2008, N °16-17

European Readiness for Universal Immunization of children of different age groups?

Relies on estimation of effectiveness in the (few) available studies !!!

Estimation of this strategy is still imprecise

Due to…

- problems in study design
- different vaccine types
- different target age groups for immunisation
- different matching profiles vaccine strain/ wild circulating strain
- outcomes' definition variation

Infant and children seasonal immunisation against influenza on a routine basis during inter-pandemic period
ECDC technical report Jan 2007

To Increase awareness !!!! towards influenza vaccination in children

- **Recommendations consulted…& followed…..**

- **Vaccination of high risk persons contacts health care professionals /households**

  Patient safety quality program

- **Annual boosters**

www.sante.gouv.fr ; MMWR Recomm Rep. 2007;56(RR-6):1–54

Recommended vaccination season

Start date & end date

- **Influenza vaccines are available**

From the end of September (or beginning of October depending on the producers)

At the same time (official date) in every pharmacy

Presented to the press by GEIG roughly 15-21 days before

- **End date** preferably before the end of December

Later is feasible & beneficial !!

France

Reasons
for the vaccination season ending campaign

Early start due to

The probability & unpredictability of epidemics occurrence (from Nov/ Dec)

The **need for 2 doses** (primo-vaccination) in children < 9 yoa

The need for **15 days for antibodies to raise & achieve a protective level**

Late ending

From a pragmatic point of view

- no harm vaccinating during a current epidemics
- but less benefit & lower benefit / risk ratio

Potential benefits for extending the flu vaccination season

- ❑ advantages
- To raise coverage rates in targeted populations
- Children may get the "missed" 2nd dose
- Awareness for influenza of the population

- ❑ & To get better prepared for a pandemics

Sustain flu vaccination seasonal campaign

- Think about Influenza vaccine out-patients & hospitalized ones
- Late recall / reminders
- Official late campaigns newspapers, TV, radio
- Second “vaccination day”

Child flu seasonal vaccination

Strong conviction that as a primary prevention, a large Flu vaccination would benefit

- children

  decreasing disease burden

- & the society

  reducing transmission.

Conclusion

Needs

- ❑ Children better adapted vaccines
  & better evaluation & better use

- ❑ Increased
  - awareness of disease in children
  - coverage & compliance
  - & campaigns to be implemented

Nuage de particules créé quand la personne éternue. (Davidhazy, 2007)

Influenza virus Transmission

Direct respiratory

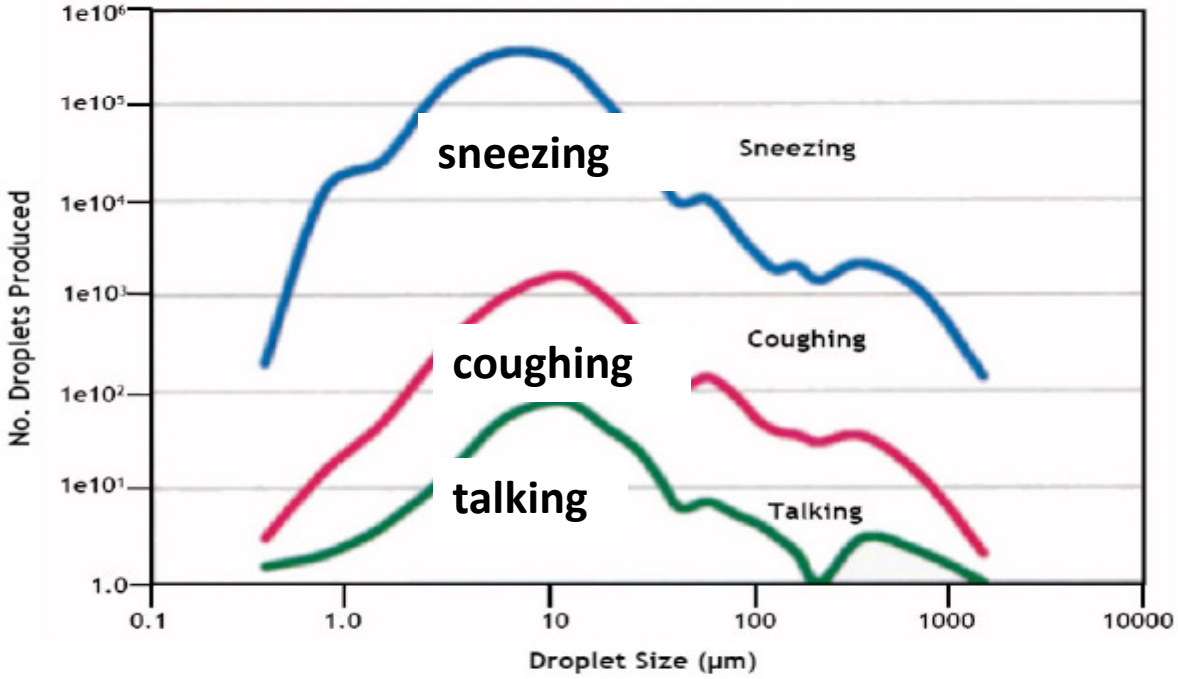


Figure 1. Size distribution of droplets formed upon sneezing (blue), coughing (pink) and talking (green) * Note: log scale (Kowalski & Bahnfleth, 1998)

Children are major disseminators during epidemics

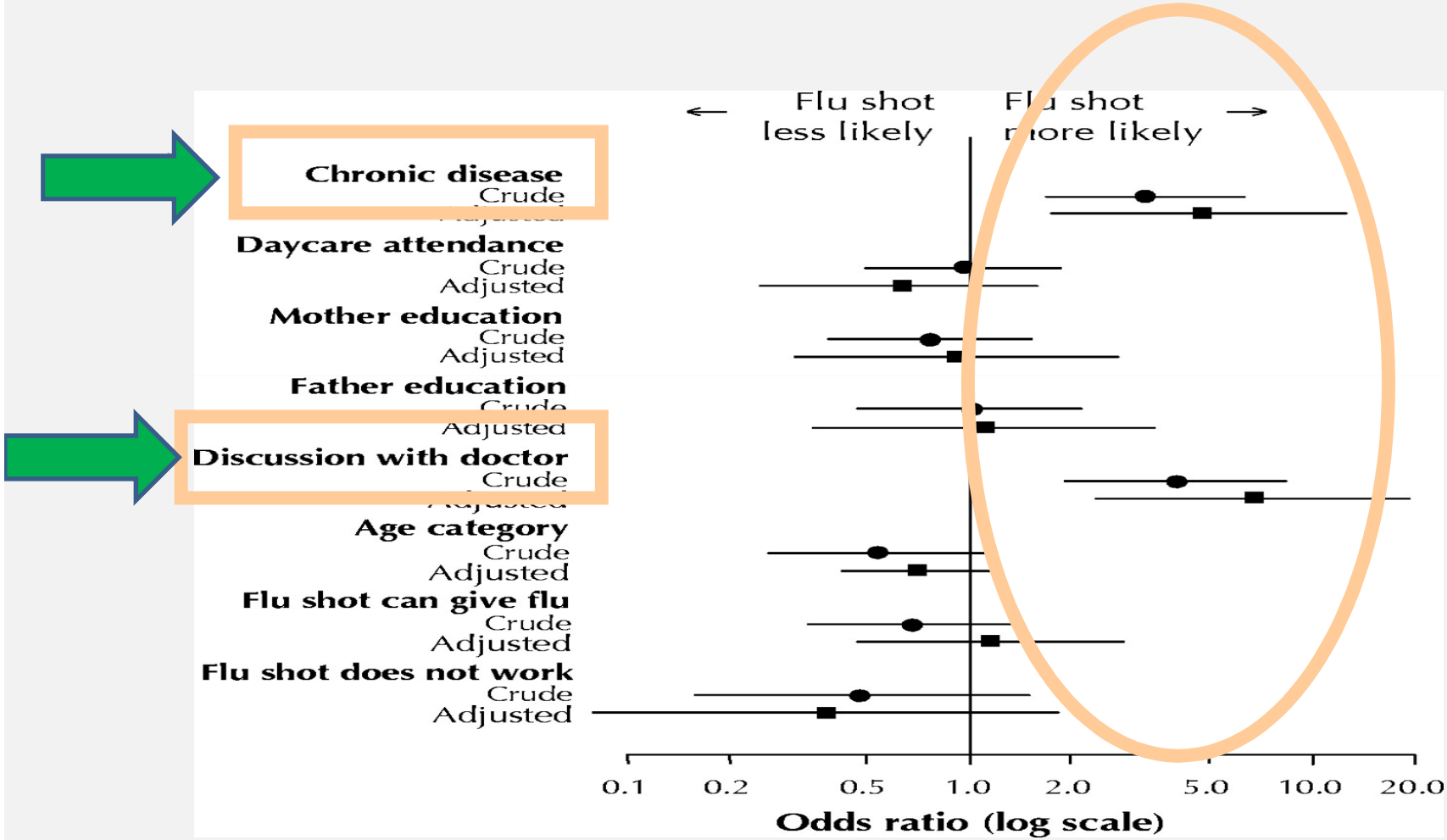
- **High attack rates**
- **Duration of viral shedding**

  children >>> adults, up to 10-14 d post symptoms onset
- **High titres of viruses** in naso-pharynx
- **Promiscuity** (DCC, schools)

Transmission of influenza both in the household and the entire community; including the elderly

Nicholson Textbook of Influenza. Oxford: Blackwell Science; 1998.
Longini IM, et al. Am J Epidemiol 1982;115:736–751

Influenza Vaccine Acceptance



Grant V; CMAJ 2003;168 (1)

Recommendations for influenza immunization of children, AAP, 2006-2007

Update recommendations for routine use

(1) **Children with high-risk conditions** who are 6 months and older

(2) **Healthy children 6 through 59 months of age**

(3) **Household contacts & out-of-home caregivers** of children with high-risk conditions and all healthy children younger than 5 years

(4) **Health care professionals**

(5) Other children, adolescents, and adults can be immunized to decrease the impact of influenza

American Academy of Pediatrics ; Red Book: 2006 Report of the Committee on Infectious Diseases. Pediatrics 2007;19:846–51

Influenza Vaccination
European Union Recommendations

Mostly based on individual protection*
Protection of high risk subjects + HCW

to prevent high frequency of complications / deaths

- **Persons aged 65 ys and over**
- **Any age ≥ 6 mois ; chronic diseases** -respiratory, cardiac, renal, neurological,…- , diabetes or immunological

NO impact on influenza epidemics

*** except Austria, Finland**

Seasonal Influenza vaccines Efficacy /effectivenes in children

Catherine Weil-Olivier

University Paris VII, France

GEIG, 2008, Strasbourg