INFLUENZA IN CHILDREN

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OBJETIVES

Peculiarities of influenza in children

How to stratify the risk of severe disease in paediatric patients

Treatment strategies

Vaccination

FLU (INFLUENZA DISEASE)

Nonspecific clinical syndrome. Many respiratory viruses causes the same clinical syndrome.

Fever, headache, myalgia.

Respiratory manifestations: cough, sore throat and rhinitis.

Fever without source.

Main reasons for admission: Lower respiratory tract disease (bronchopneumonia) and asthma exacerbation.

COMPLICATED INFLUENZA DISEASE

Respiratory failure:

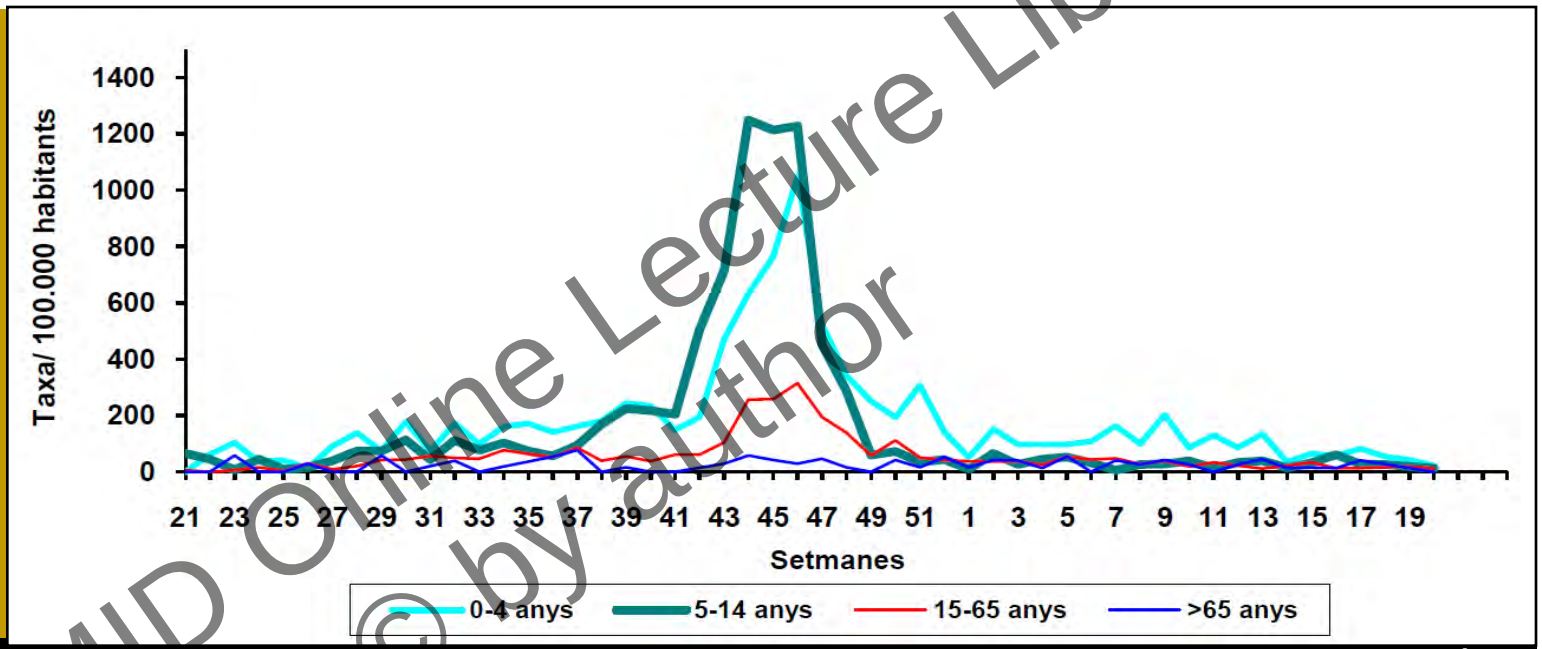
- Airway disease.
- Alveoli (bronchopneumonia, ARDS).

Bacterial superinfection (10 - 30% of severe cases). In mild disease, the most frequent, OMA.

Extrapulmonary manifestations: myocarditis, CNS disease (encephalopathy, demyelinating).

Catalonia 2009-2010

Incidence:



Age (y)	Population	Severe influenza cases (admitted cases)	Hospitalizations: Rate * 100.000 inhab
0-4	418.271	84	20,1
5-14	715.308	80	11,2
15-44	3.345.794	301	9,0
45-64	1.839.021	229	12,5
>64	1.233.465	78	6,3
TOTAL	7.551.859	772	10,2

WHY INFLUENZA DISEASE IS MORE SEVERE IN CHILDREN?

Lack of immunity to influenza viruses → Any influenza virus (old or new subtype) is "new" for children.

The severity also depends on the "virulence" of the new virus, and when the "influenza season" comes - cocirculation with other respiratory infections (viral and bacterial)-.

A general rule: all respiratory diseases are more severe in children.

IN FACT, ALL RESPIRATORY DISEASES ARE MORE SEVERE IN CHIDREN

Immature immunity? **Scarce data...**

Physical factors:

- Less muscle mass.
- Children ventilate mostly by respiratory rate (ref. < 1 y-old, 40-50 bpm).
- Smaller pulmonar-tree.
- Minor bronchial airway caliber. More resistences due to airway-cells inflamation/destruction or secretions.
- Soft chest-wall → more ineffective respiratory effort.

WHAT DOES THIS MEAN?

- Minor need of comorbidity to cause severe disease.
- Minor need of coinfection to cause severe disease.
- Although 5-10% of admitted children develop ARDS, there is no need of “bilateral opacities in chest-X-ray” to cause severe disease.

There is an absolute lack of data regarding to the role of a “immature immunity” in paediatric influenza disease.

OTHER PECULIARITIES IN CHILDREN…

Infectivity – viral shedding:

- 80% of the population at 5 days of clinical symptoms.
- 10% at 10 days.
- **In children, for 10 or more days (especially in preadolescents). Immunosuppressed, weeks.**
  - **Why did they have a worse control of viral load?**
    - **More immature immunity ????**

RISK GROUPS OF THE WHO (PRE-PANDEMIC AND PROPOSED FOR THE 2009 PANDEMIC)

Infants and children, especially < 2 years

Pregnant women.

Chronic lung disease

Chronic heart disease (heart failure and cyanotic heart disease, especially).

Metabolic Diseases.

Renal / hepatic / neurological diseases (neuromuscular, neurocognitive and epilepsy), hemoglobinopathies, primary or secondary immunosuppression.

Children treated with acetylsalicylic acid.

> 65 years.

SCORES. RISK OF HOSPITAL ADMISSION.

Pediatr Emer Care 2009; 25: 369-375

3 influenza seasons (pre-2009). 1230 children (44%, admitted).

Predictor Category	Predictor	Regression Coefficient	Multivariable Odds Ratio (95% CI)	Weight for Risk Score*
Historical	High-risk medical condition	1.40	4.06 (2.91 – 5.68)	2
Clinical	Respiratory distress on examination	0.85	2.33 (1.61 – 3.38)	1
Radiographic	Radiographic evidence of pneumonia	2.06	7.82 (3.62 – 16.92)	3
Laboratory	Influenza B infection	1.38	3.99 (2.57 – 6.21)	2

Limitations:

- You need confirmation of influenza diagnosis. You won't have it on your Emergency Department… Rapid diagnosis tests (IFI) had a low sensitivity in children (60 - 80%).
- Does this study add something really new?

RISK-FACTORS FOR ADMISSION

CIBERESP (2009 pandemia - 36 Spanish hospitals (paediatric cases)):

- Age: < 2 y-old.
- Comorbidity.
- Lower parent's educational level. ¿¿¿ Racial factor???
- *Respiratory distress, hypoxaemia, pneumonia (in fact, we should consider those "risk-factors" as outcome variables).*

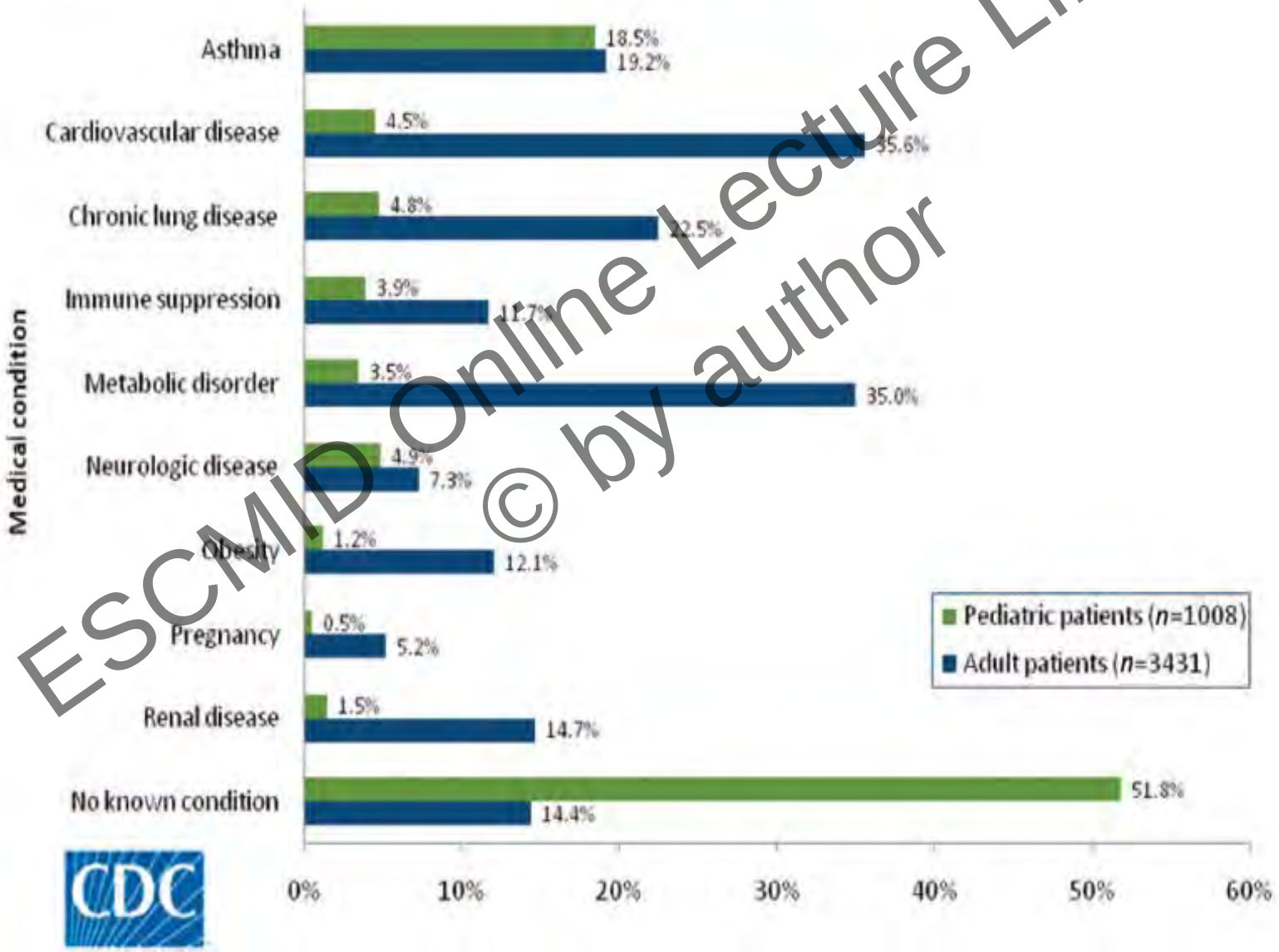
ONCE ADMITTED, WHO WILL BE AT A RISK OF A MORE SEVERE DISEASE?

Adults: Pregnancy, obesity, pulmonary chronic disease, diabetes.

Children: Neurologic, pulmonary and congenital heart diseases.

However… high rates of healthy children with severe disease were observed (2009 H1N1).

USA, 2010-2011



INCIDENCE, COMPLICATIONS, AND RISK FACTORS FOR PROLONGED STAY IN CHILDREN HOSPITALIZED WITH COMMUNITY-ACQUIRED INFLUENZA. PEDIATRICS. 2007; 119: 740-748

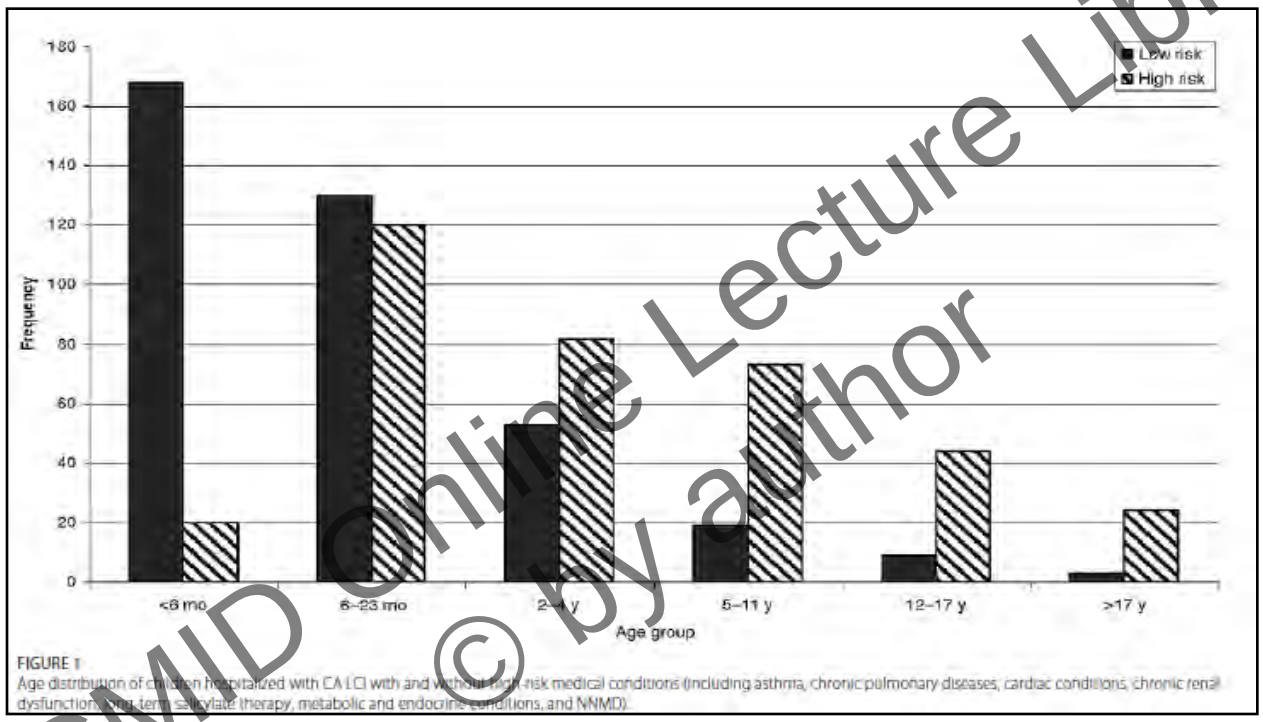


FIGURE 1
Age distribution of children hospitalized with CA LCI with and without high-risk medical conditions (including asthma, chronic pulmonary diseases, cardiac conditions, chronic renal dysfunction, long-term salicylate therapy, metabolic and endocrine conditions, and NNMD).

- Any-1 comorbidity was a risk-factor of needing for Paediatric Intensive Care Admission.
- Neurologic-neuromuscular chronic conditions and congenital heart diseases were associated with a longer hospital stay.

2009 Influenza A H1N1 Infections: Delays in Starting Treatment With Oseltamivir Were Associated With a More Severe Disease. Launes et al. *Ped Infect Dis J 2011; 30: 622-625*

PICU-admission: 24 of 127 hospitalized children

RISK FACTORS OF NEEDING PICU ADMISSION	Univariate p-value	Multivariate analysis	
		Odds-ratio (C.I. 95%)	p-value
Age	p = 0.1	1.0 (0.9 - 1.0)	p=0.9
Reactive C-protein	p < 0.05	1.0 (0.9 - 1.0)	p=0.1
Patients in whom oseltamivir was started > 72 hours after onset of symptoms	p < 0.05	3.7 (1.1 - 11.7)	p < 0.05
Confirmed co-infection	p = 0.5	-	-
Patients with a previously-known disease	p < 0.05	4.1 (1.1 - 15)	P < 0.05

More than 50% were > 5 year-old. However, median age among previously healthy children (71/127) 2 y-old.

Severe Pediatric Influenza in California, 2003–2005: Implications for immunization recommendations *Pediatrics (2006)*

- 160 cases of serious illness (PICU admission w/ 15 deceased children)).
- Median age, 1.5 years.
- **28 proven coinfection** (eg GNBs, pneumococcus, staph aureus, S. pyogenes, ...)).
- **53% with known disease** (mainly NRL and pulmonary).
- **Only 8 / 37 patients** who should had been vaccinated following the ACIP criteria for immunization were **vaccinated** ...

Influenza-associated mortality among children – United States: 2007–2008. *Influenza and Other Respiratory Viruses (2010)*

- 88 deaths. Median age, 5 years.
- **S. aureus** (infection or colonizer) in 20 of 57 children with cultures. The coinfectes patients were older and/or without comorbidity.

Paediatric mortality related to pandemic influenza A H1N1 infection in England: an observational population-based study. *Lancet (2010)*

	Number of deaths	Fatality rate per 100 000 cases of pandemic influenza A H1N1 (range)	Mortality rate per million population (95% CI)
< 1 year	9	151 (34–635)	14 (6–26)
1–4 years	15	33 (9–114)	6 (3–10)
5–9 years	22	17 (5–54)	8 (5–12)
10–15 years	15	10 (3–35)	4 (2–7)
16–17 years	9	26 (6–102)	7 (3–13)
0–17 years	70	19 (7–51)	6 (5–8)

	Deaths	Population prevalence estimates (thousands)	Age-standardised mortality rate per million population (95% CI)
Chronic respiratory disease	33	392	167 (89–268)
Chronic cardiac disease	16	72	232 (132–377)
Chronic neurological disease	35	31	1536 (988–2242)
Immunosuppression	7	38	166 (66–343)
Chronic kidney disease	3	6	449 (85–1333)
Diabetes mellitus	0	2	0 (–)
None	13	10 125	1·3 (0·7–2·2)

Table 5: Age-standardised mortality rate for deaths related to pandemic influenza A H1N1 for children

- 70 deaths.
- 15 (21%) healthy children.
- Any chronic condition (WHO), higher mortality rates.
- CAUTION WITH patients w/ neurologic diseases!

IMPLICATIONS FOR TRIAGE IN PRIMARY AND SECONDARY CARE. *J INFECT (2011)* DOI:10.1016/J.JINF.2011.07.014

Table 1 Factors reported in case series of patients with severe pH1N1/09 infection.

Demographics/Co-morbidities
- Young age[11–16]
- Pregnancy/Post partum[11,13,14,16,22]
- Chronic lung disease[11–16,34]
- Obesity[11,12,14–16,34,38]

Admission Vital Signs
- Hypotension[12,14,48]
- Tachycardia[12,14]

Laboratory parameters
- Elevated Creatine Kinase[12]
- Elevated Lactate Dehydrogenase[16]
- Thrombocytopenia[14]
- C-reactive protein[4,59]

Microbiology
- Secondary bacterial infection[11,22,60]

Radiographic
- Pneumonia[13,16,46]
- Multilobar chest radiograph involvement[16, 46]

Organ Failure
- Respiratory failure[11–13,18,22,46,48]
- Renal failure[12,14,16,18]

Marker of poor outcome in ICU admitted patients
- Refractory hypoxaemia requiring invasive ventilation or ECMO[11,13,18,22,46]
- Adult Respiratory Distress Syndrome (ARDS)[11,46,48]

In paediatric patients, we could add… too:

- Neurologic diseases.
- Congenital heart diseases. Farias et al. Intensive Care Med. 2010; 36: 1015-1022
- Other laboratory parameters: anemia, limphopenia. Da Dalt et al. Italian Journal of Pediatrics 2011, 37:24
- Lower rates of bacterial coinfection in patients who required PICU admission (10-30%). Other factors of severity.

THEN, HOW TO STRATIFY THE RISK?

Validated scoring systems to predict hospitalization do not exist.

Scores to predict mortality in critically ill children hospitalized in paediatric ICUs (Paediatric Risk of Mortality score, Paediatric Index of Mortality) had limiting utility in level-of-care decision making.

What do we use to consider?

- Respiratory distress scores (ref. World Health Organization).
- Pulse oximetry. Oxigenation index.
- Age.
- Community-acquired pneumonia criteria of severity (ref. IDSA/ATS)
- WHO risk-groups.
- Laboratory parameters and chest-X-ray.

From theory to practice

Admission criteria?

- Hypoxemia (SatHb < 93%) and/or moderate respiratory distress.
- < 4-6 w-old with signs of lower-tract respiratory infection (even viral).
- < 3 m-old with suspected bacterial coinfection.
- Apnea.
- Multilobar infiltrates.
- Pleural effusion.

Be careful with certain comorbidities: sickle-cell disease, immunosuppressed children, neuromuscular diseases,…

PICU admission?

•Needing for respiratory support: hypercarbic respiratory failure, or need of FiO2 > 40-50%. Severe respiratory distress (probably we can consider **non-invasive MV**).

•Shock. Metabolic acidosis.

•Altered consciousness.

•Other extrapulmonary manifestations: myocarditis.

RAPID DIAGNOSIS AND EARLY TREATMENT

The treatment has been proved to be **effective in reducing viral load**.

- Potential beneficial effect in children with comorbidity and pre-adolescent children (they showed a worse control of viral load).

Shorter duration →Lower transmissibility → Less ill patients at risk → Reduced mortality.

Starting treatment **within the first 48-72 hours** of clinical symptoms:

- Reduced absenteeism.
- Increased "quality of life."
- Early treatment is associated with lower complication rates during the pandemic.

Oseltamivir: Few adverse effects. Most of them were mild (gastrointestinal).

DIAGNOSTIC

Rapid diagnostic test, not useful:

- Sensitivity: 50% - 80%.
- Especificity: 90 - 95%.
- It was widely used in prepandemic seasons.

Viral culture.

- False negative results in children with > 5 d of clinical symptoms. Centralization of samples.

RT-PCR. *Gold-standard*

- Different kinetics of viral-loads between nasopharyngeal aspirates and tracheal aspirates.

DIAGNOSTIC AND ANTIVIRAL INDICATIONS

Who must be tested and treated for influenza (paediatrics) - IDSA-:

During epidemic seasons (4-6 weeks/year), independently of vaccine coverage:

- Children who do not require admission with fever and respiratory symptoms or fever without source, with risk factors for severe disease (comorbidity proposed by WHO and / or age <2 years).
- Children who require admission with fever and respiratory symptoms.
- Respiratory exacerbation in patients with lung disease.
- Healthy children with confirmed disease in who you want to reduce the duration of symptoms and transmissibility.

How many patients were we treating without influenza disease? Can we have a more accessible diagnostic tool?.

VACCINATION:

- Target population.
- How?

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

All children. 6 m-old to 18 y-old.

Why?

- 6 - 24 m-old: high risk of requiring for admission.
- 2 - 5 y-old: main transmitters and high use of health resources (consultation and treatment (antibiotics,...).
- Other children: a significant proportion of the deceased patients(52% the season 2010-2011) were previously healthy.

2 doses (4 weeks between doses).

1 dose:

- > 9 y-old
- In patients with 2-doses of previous influenza vaccination.

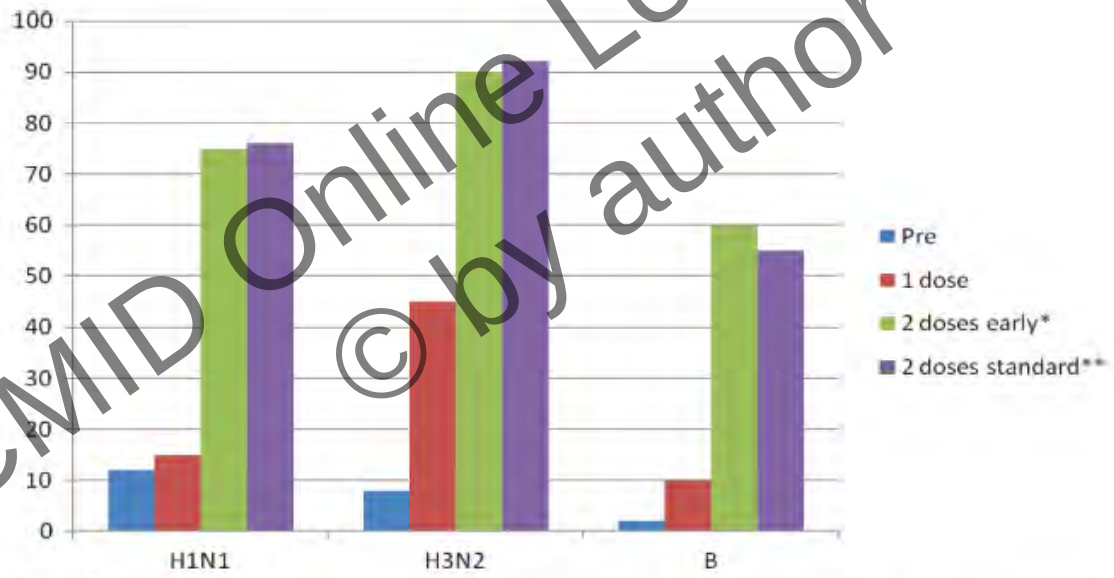


FIGURE 4
Percentage of children with titers greater than 1:32 during seasons with no change in vaccine antigen. * One dose administered in the spring; the second dose administered in the fall. ** Two doses administered 4 weeks apart in the fall. (Reprinted with permission from Englund JA, Fairchok MP, Monto AS, Neuzil KM. *Pediatrics.* 2005;115[4]:1039–1047.)

CONTROVERSES

Antibody titers getting the "protector" cut-off value is not synonymous of protection ...

Cochrane review: effectiveness in preventing influenza illness confirmed or influenza-like illness. **Jefferson T et al. Vaccines for Preventing influenza in healthy children. Cochrane Database Syst Rev. 2008; CD004879**

- About 60% of those > 2 y-old were protected.
- No protection in children < 2 y-old.

Could vaccination with attenuated virus be more effective than TIV? ***Drugs. 2011; 71:1591-622. J Infect Dis. 2011; 204:1475-82***

TO CONSIDER...

The effectiveness depends on

- Including fragments corresponding to the circulating virus or how much they resemble antigenically.
- That the disease attack rate exceeds a certain threshold.
- Virological confirmation of disease. - The vaccine protects against flu ... no other respiratory viruses.-

Vaccination with attenuated virus has important limitations (no in children < 2 y-old, no in patients with comorbidity, no in patients with recent bronchospasm).

CONCLUSIONS

- Children whith influenza are not “small adults” with influenza → Higher risk due to physical and immune differences.
- High-risk of severe disease in < 2-y old and older children with comorbidity (NRL!).
- Treat the admitted children and those with high-risk conditions.
- Vaccinate children following your health-authorities recommendations. Controversies for universal children vaccination.