

# LA PREVENZIONE DELL'INFLUENZA

Susanna Esposito

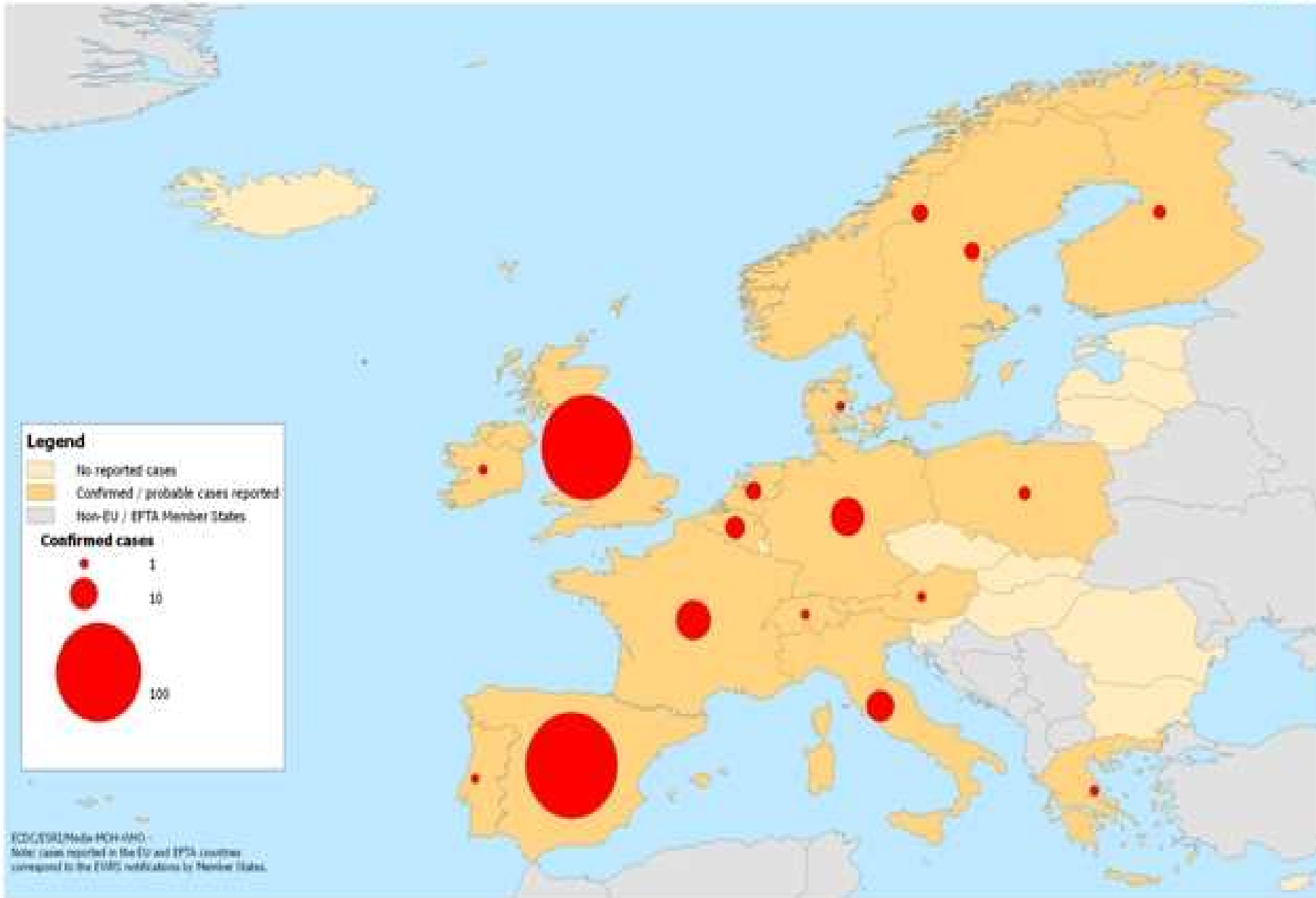
Dipartimento di Scienze Materno-Infantili  
Università di Milano

Fondazione IRCCS "Ospedale Maggiore  
Policlinico, Mangiagalli e Regina Elena"  
Milano

# INFLUENZA EPIDEMIOLOGY

- Third cause of death for infectious diseases in industrialized countries
- Ubiquitous and extremely contagious
- Caused by viral agents with high antigenic variability
- Existence of animal reservoir
- Associated with severe complications

# Reported cumulative number of confirmed cases of new influenza A(H1N1) in EU and EFTA countries, as of 21 May 2009, 17:00 hours CEST

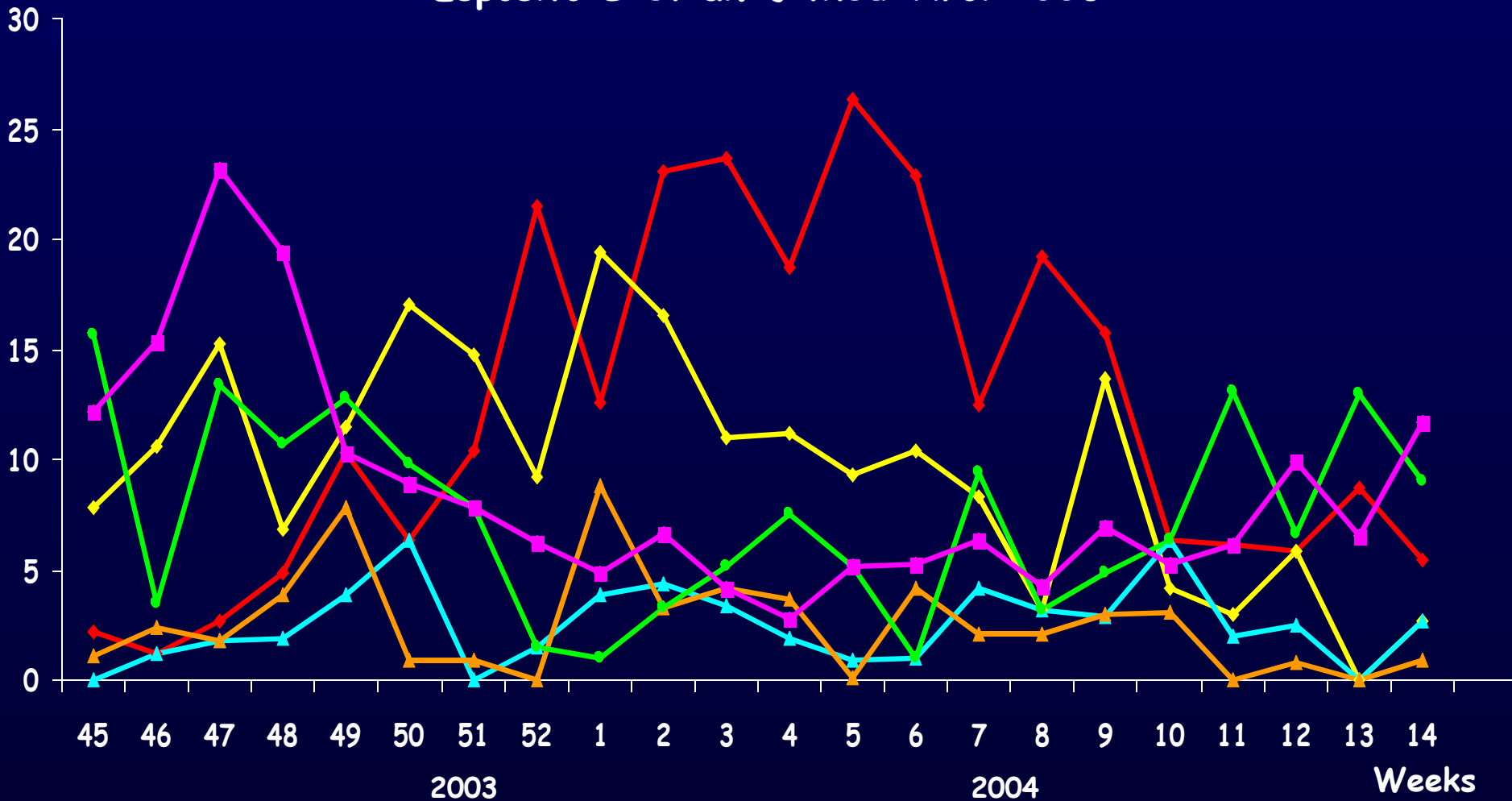


# DISTRIBUTION OF RESPIRATORY VIRUSES DURING THE WINTER SEASON 2003-2004

(Children enrolled = 2,060)

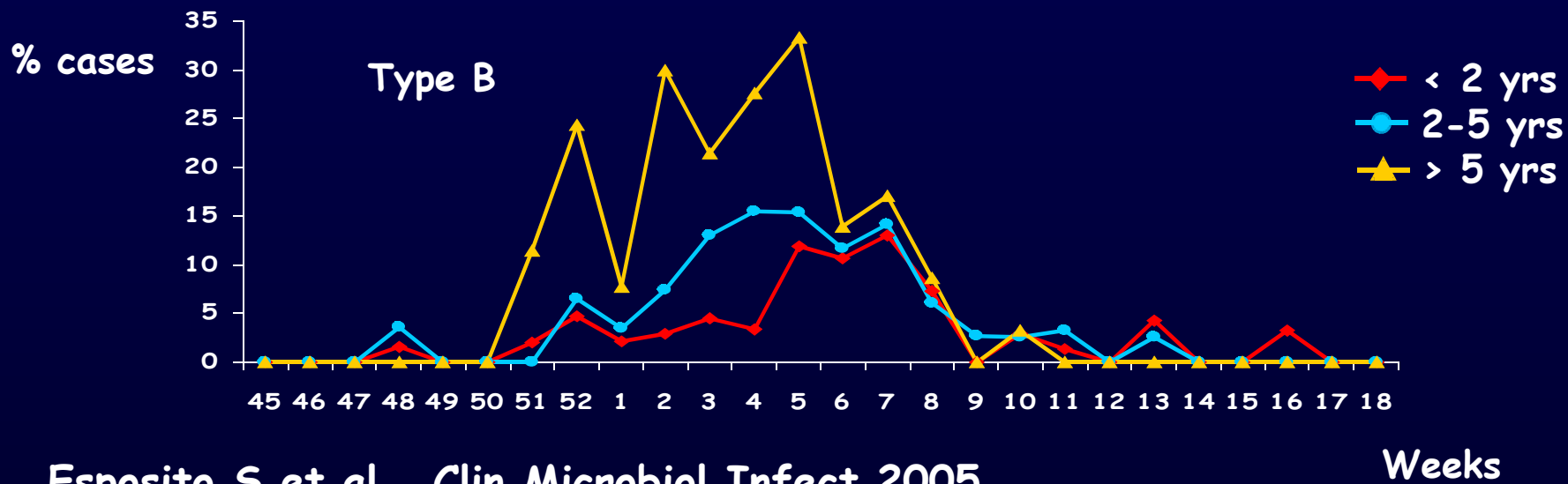
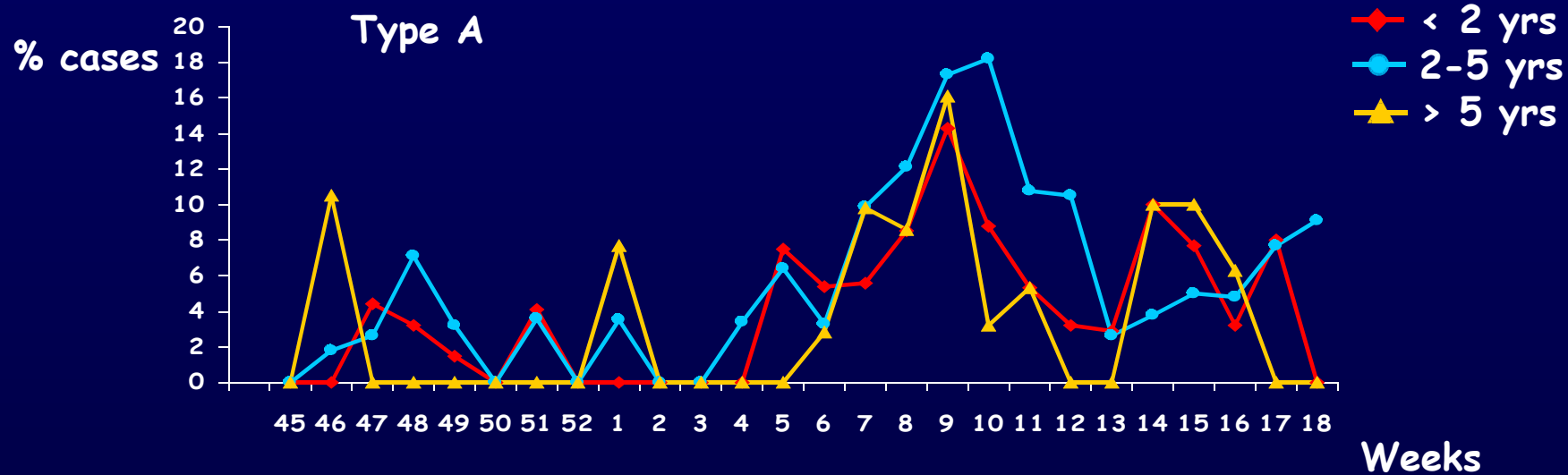
Esposito S et al. J Med Virol 2006

% cases



—◆— Influenza —◆— RSV —▲— hMPV —▲— Coronaviruses —●— Rhinovirus —■— Adenovirus

# AGE DISTRIBUTION OF SWABS POSITIVE FOR INFLUENZA A AND B VIRUSES IN STUDY CHILDREN (n=3,310)



Esposito S et al., Clin Microbiol Infect 2005

Weeks

# CLINICAL MANIFESTATIONS OF INFECTIONS DUE TO hMPV, RSV AND INFLUENZA VIRUSES IN CHILDREN

(Principi et al. NEJM 2004)

	<b>MPV (N=35)</b>	<b>RSV (N=141)</b>	<b>INFLUENZA (N=223)</b>
<b>Fever ≥ 38.5</b>	<b>28 (80.0%)*</b>	66 (46.8%)	<b>179 (80.3%)**</b>
<b>Respiratory tract infection</b>	35 (100%)	135 (95.7%)	199 (89.2%)
<b>Gastrointestinal infection</b>	0	6 (4.3%)	14 (6.3%)
<b>Fever without source</b>	0	0	10 (4.5%)

\* $p < 0.05$  and \*\* $p < 0.0001$  vs RSV

# HOSPITALIZATION DURING INFLUENZA SEASON ACCORDING TO AGE

(Da Neuzil KM et al. NEJM 2000)

AGE	No. OF PERSON-YEARS	No. OF HOSPITALIZATIONS FOR ACUTE CARDIOPULMONARY CONDITIONS PER 10,000 PERSON-YEARS				No. OF INFLUENZA-ATTRIBUTABLE HOSPITALIZATIONS PER 10,000 PERSON-YEARS*		AVERAGE EXCESS No. OF HOSPITALIZATIONS PER 10,000 CHILDREN PER YEAR (95% CI)†
		INFLUENZA SEASON	PERI-INFLUENZA SEASON	SUMMER	TOTAL	CRUDE	STANDARDIZED‡	
		<6 mo	117,205	1964	1497	608	1146	
6 to <12 mo	82,997	1117	854	403	675	263	233	49.6 (35.3–63.8)
1 to <3 yr	324,900	464	387	233	325	77	79	18.6 (14.2–23.0)
3 to <5 yr	302,344	232	193	138	173	39	43	8.6 (4.9–12.3)
5 to <15 yr	1,207,697	120	105	86	98	15	22	4.1 (2.8–5.5)

\*Values are differences in rates between the influenza season and the peri-influenza season (the base-line values).

†Values are weighted averages of annual excess hospitalizations for a population of 10,000 persons within the specified age group. The excess hospitalizations were calculated for each stratum by multiplying the stratum-specific difference in hospitalization rate by the proportion of the study year covered by the influenza season. CI denotes confidence interval.

‡The weighted average differences in rate between the influenza season and the peri-influenza season were calculated with stratum-specific person-years in all seasons as weights; strata were defined by age group, study year, race, and residence.

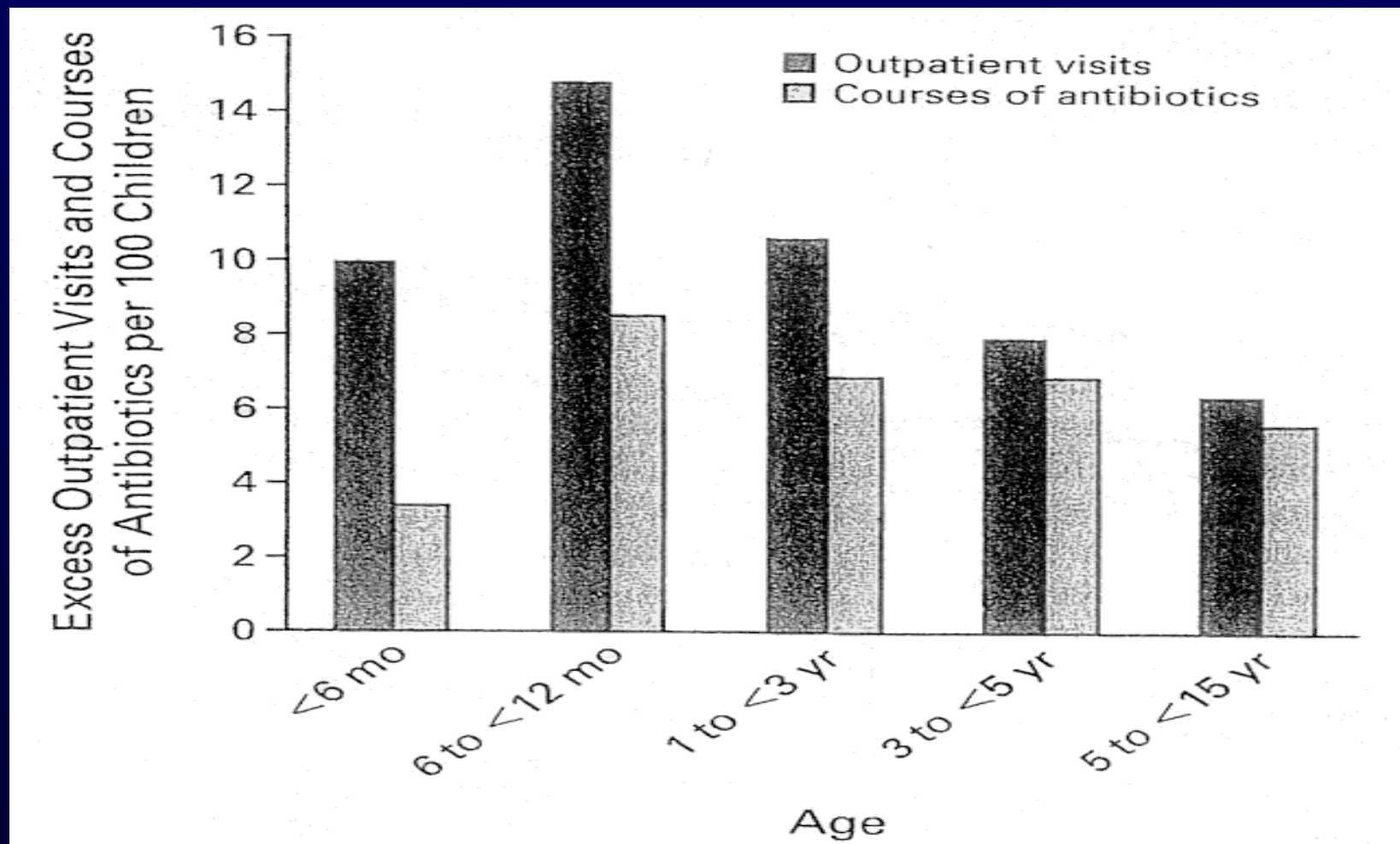
# HOSPITALIZATION DURING INFLUENZA SEASON ACCORDING TO AGE AND PRESENCE OF UNDERLYING CHRONIC DISEASE

(Izurietta HS et al. NEJM 2000)

YEARS	AGE	HOSPIT./ 100,000 HR SUBJECTS	HOSPIT./ 100,000 HEALTHY SUBJECTS
1973 - 1993	0-11 mos	1900	496 - 1038
	12-24 mos	800	186
	3 - 4 yrs	320	86
	5 - 14 yrs	92	41
1992 - 1997	0-23 mos	-	144 - 187
	2 - 4 yrs	-	0 - 25
	5 - 17 yrs	-	8 - 12
1968 - 1973	15 - 44 yrs	56 - 110	23 - 25
	45 - 64 yrs	392 - 635	13 - 23
	≥ 65 yrs	399 - 518	-
1969 - 1995	< 65 yrs	-	20 - 42 (*)
	≥ 65 yrs	-	125 - 228 (*)

(\*) without a separation between HR and healthy subjects.

# INCREASE IN OUTPATIENT VISITS AND ANTIBIOTIC COURSES DURING INFLUENZA SEASON



Neuzil KM et al., N Engl J Med 2000

# INFLUENZA ASSOCIATED DEATHS AMONG CHILDREN IN THE UNITED STATES

- 153 influenza-related deaths
- Median age of died children was 3 years (63% aged <5 yrs)
- 31% died outside hospital setting
- 29% died within three days after the onset of the illness
- 47% had previously been healthy

# NEUROLOGIC COMPLICATIONS IN CHILDREN HOSPITALIZED WITH INFLUENZA

- Of 842 patients, 72 had an influenza-related neurologic complications (INC)
- Seizures were the most common neurologic complication, whereas encephalopathy was uncommon
- An age of 6-23 months and an underlying neurologic or neuromuscular disease were independent risk factors for INC

# SOCIOECONOMIC IMPACT OF INFECTIONS DUE TO hMPV, RSV, INFLUENZA ON HOUSEHOLDS

(Principi et al. NEJM 2004)

	hMPV+ households	RSV+ households	INFLUENZA+ households
Similar disease to the study child	16 (12.5%)*	24 (4.7%)	78 (9.7%)*
Outpatient visits	16 (12.5%)**	16 (3.2%)	78 (9.7%)**
Antipyretic use	14 (10.9%)*	18 (3.6%)	104 (12.9%)**
Antibiotic use	6 (4.7%)	11 (2.2%)	36 (4.5%)
Hospitalization	0	0	3 (0.4%)
Days lost from work (median, range)	4 (2-10)*	2.5 (2-7)	4 (1-10)*
Days lost from school (median, range)	4 (3-15)*	2 (2-4)	5 (1-15)*

\* $p < 0.05$  and \*\* $p < 0.0001$  vs RSV+ households

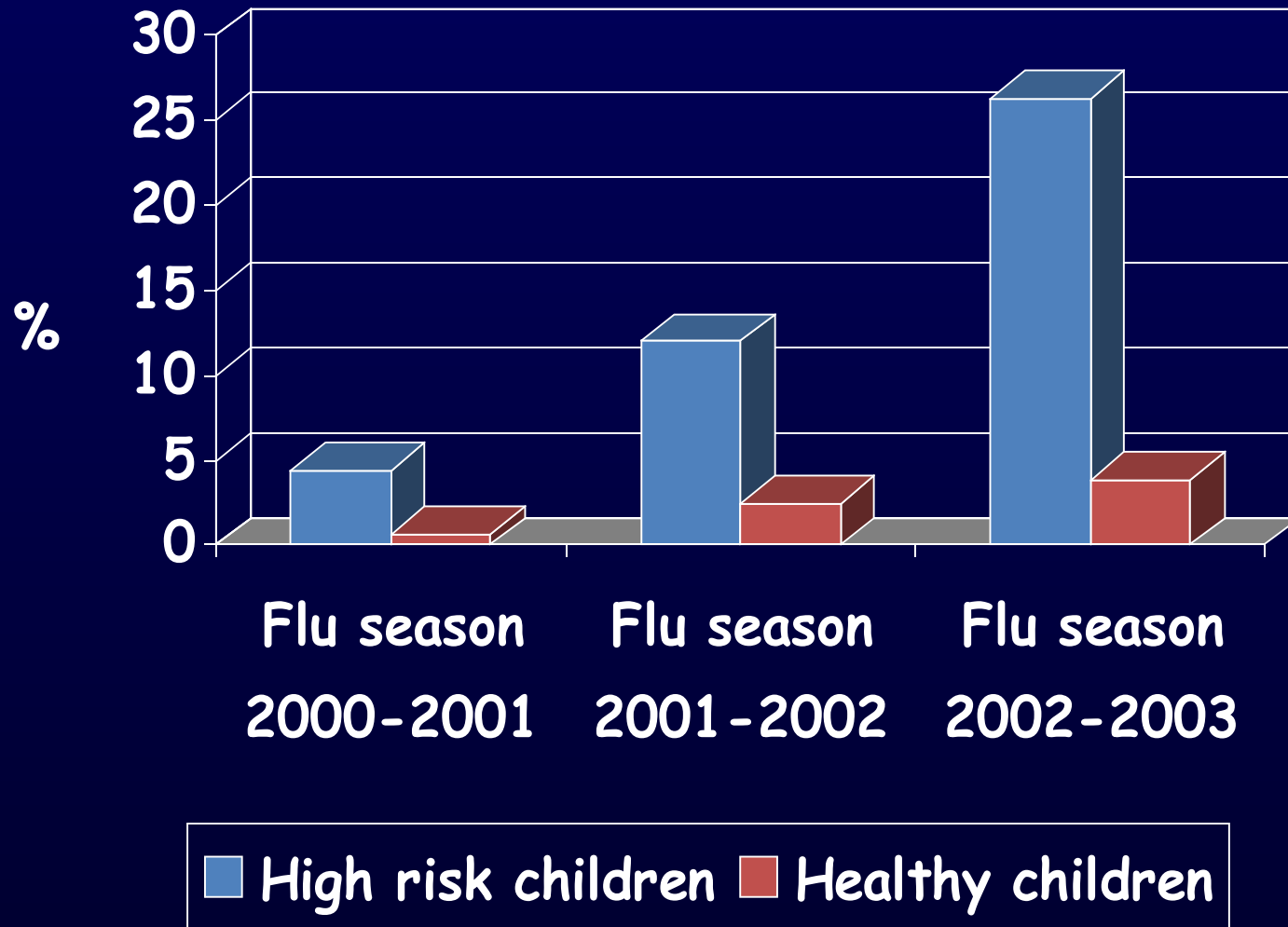
# TARGET GROUPS FOR INFLUENZA VACCINATION IN PEDIATRIC AGE

(ACIP, MMWR 2008; Italian Ministry of Health, 2008)

- CHILDREN  $\geq$  6 MONTHS WITH :
  - CHRONIC PULMONARY DISEASES (INCLUDING ASTHMA)
  - CARDIOVASCULAR DISEASE
  - RENAL, HEPATIC OR HEMATOLOGICAL DISORDERS
  - METABOLIC DISORDERS
  - IMMUNOSUPPRESSION (INCLUDING HIV)
  - ANY CONDITION THAT CAN COMPROMISE RESPIRATORY FUNCTION OR THAT INCREASE THE RISK OF ASPIRATION
- SUBJECTS AGED 6 MONTHS-18 YEARS WHO ARE RECEIVING LONG-TERM ASPIRIN THERAPY

# INFLUENZA VACCINATION RATES AMONG 5,286 ITALIAN CHILDREN

(Esposito S et al., Vaccine 2006)



# INFLUENZA VACCINATION COVERAGE IN THE STUDY CHILDREN, BY CHRONIC MEDICAL CONDITION (%)

(Esposito S et al., Vaccine 2006)

High-risk condition	2000-2001	2001-2002	2002-2003
Asthma (n=101)	1.9*	5.9*	20.8
Cystic fibrosis (n=24)	8.3*	20.8*	41.7
Bronchopulmonary dysplasia (n=12)	8.3	25.0	33.3
Cardiac disease (n=47)	0*	6.4	12.8
Diabetes (n=14)	7.1	14.2	35.7
Chronic renal dysfunction (n=25)	8.0	16.0	32.0
Hemoglobinopathies (n=12)	8.3	16.7	33.3
Primary immunodeficiency (n=11)	9.1	18.2	36.4
Cancer (n=18)	5.6	16.7	33.3
HIV infection (n=10)	10.0	30.0	40.0

# VACCINATED HIGH-RISK CHILDREN (No. =72)

Why is your child vaccinated against influenza?

ANSWER	FREQUENCY
Pediatrician's recommendation	63 (87.5%)
Protection of parents	6 (8.3%)
Protection of an elderly family members	2 (2.8%)
Previous serious influenza-like illness	1 (1.4%)

# UNVACCINATED HIGH-RISK CHILDREN (No.=202)

Why is your child not vaccinated  
against influenza?

ANSWER	FREQUENCY
Lack of awareness	173 (85.6%)
Inconvenience	11 (5.5%)
Concern about side effects	18 (8.9%)

# PEDIATRICIANS' OPINIONS CONCERNING INFLUENZA (No.=256)

If you do not recommend influenza vaccination in a child with chronic disease, what are the reasons?

ANSWER	FREQUENCY
Influenza infection not sufficiently severe	68 (26.6%)
Poor efficacy of influenza vaccines	149 (58.2%)
Concern about side effects	39 (15.2%)

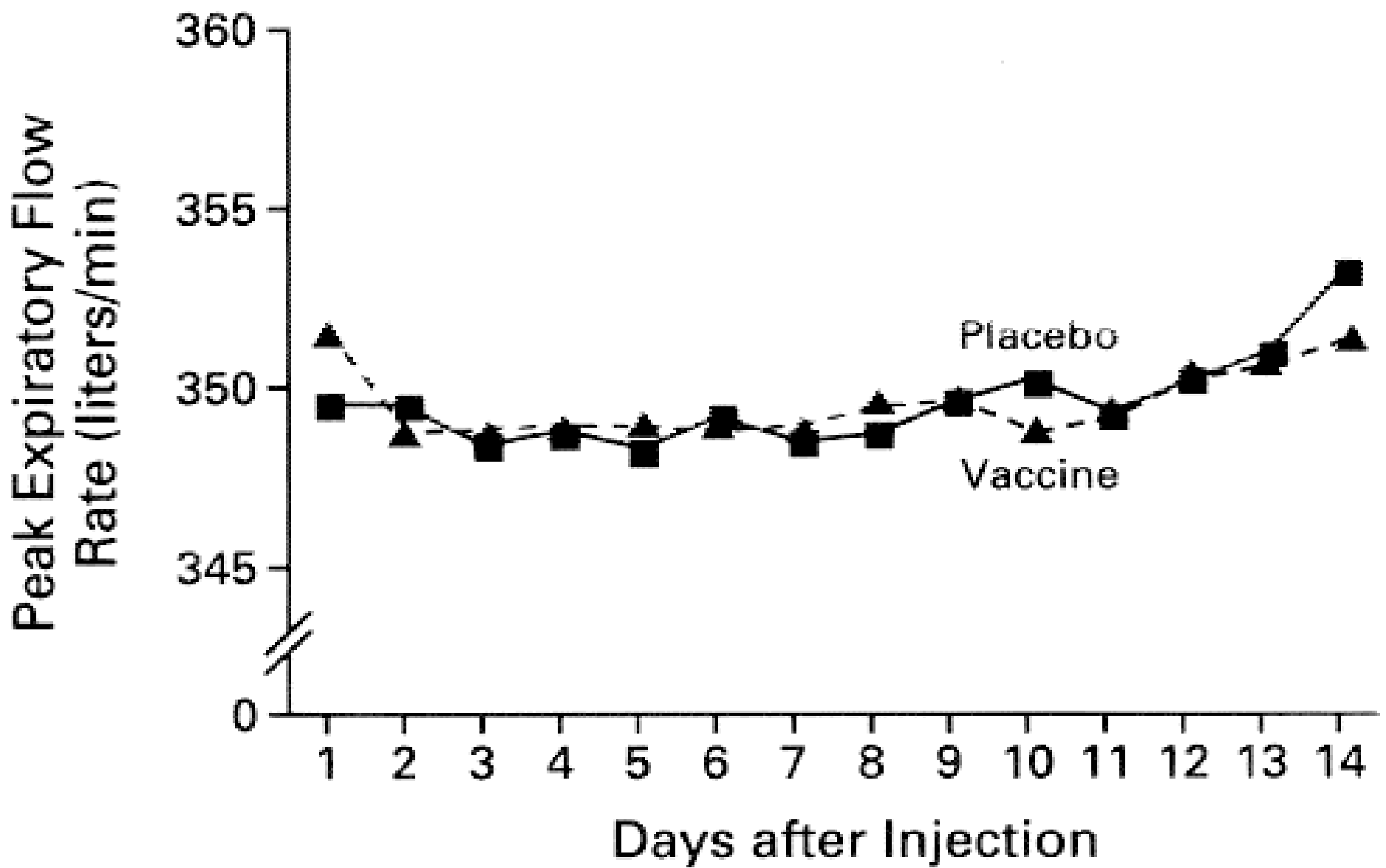
Esposito S et al., Vaccine 2006

# ASTHMA AND INFLUENZA VACCINATION

(Am Lung Ass Asthma Clin Res Centers, N Engl J Med 2001)

- 2,032 patients with chronic asthma aged 3-64 years (712 < 14 anni)
- Randomized 1:1 to receive TIV or placebo
- Asthma exacerbation in the 2 weeks after enrollment:
  - TIV **28.8%**
  - PLACEBO **27.7%**

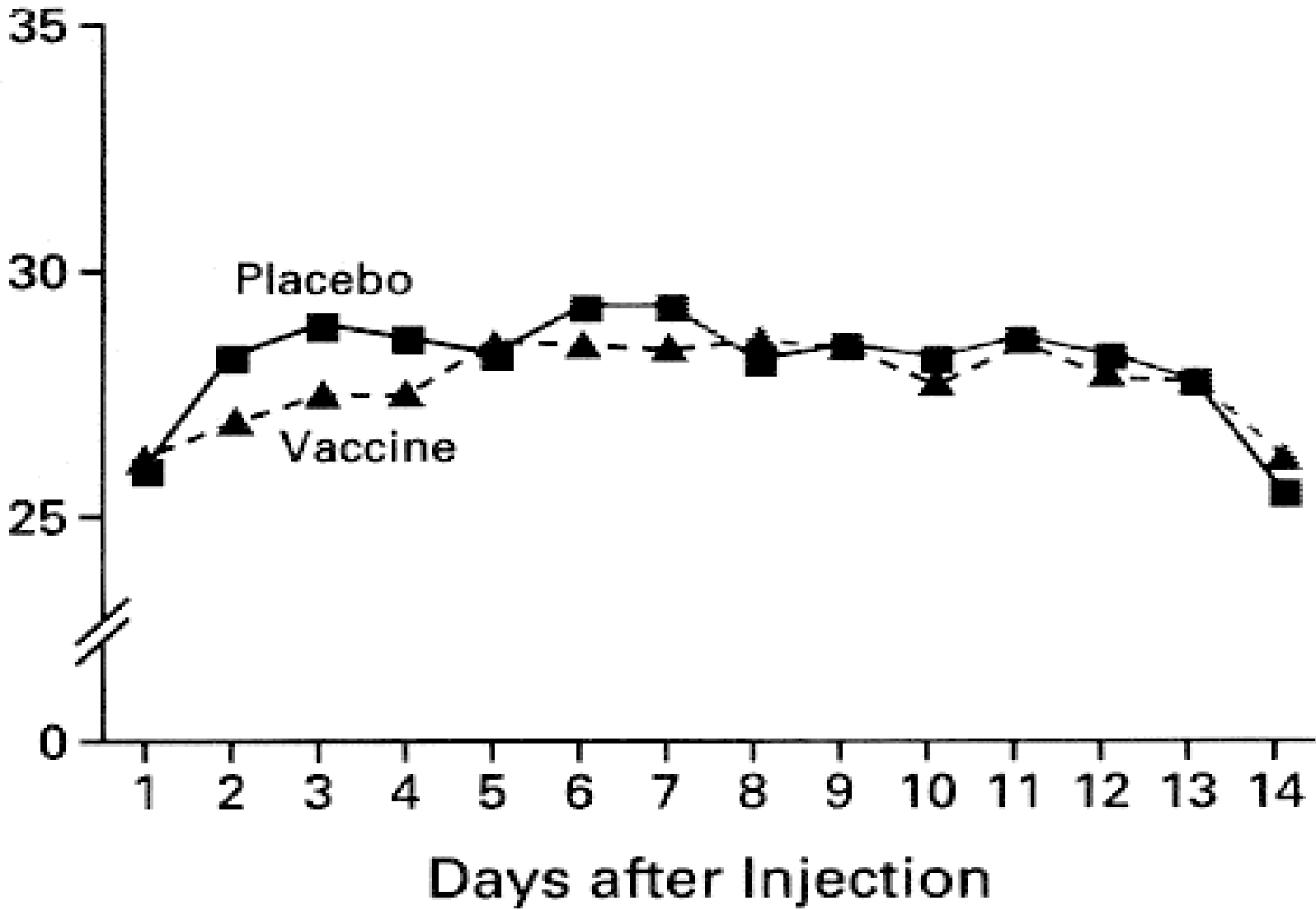
A



Am Lung Ass Asthma Clin Res Centers, N Engl J Med 2001

B

Use of Rescue Medication  
for Asthma Symptoms (%)



Am Lung Ass Asthma Clin Res Centers, N Engl J Med 2001

# INFLUENZA AND ASTHMA: EFFICACY OF THE VACCINATION

(Kramarz P et al., J Pediatr 2000)

	Influenza season		
	1993-1994*	1994-1995*	1995-1996†
No. of cases‡	577	969	2,075
No. of asthma exacerbations	710	1,146	2,564
Follow-up time (child-months)	3,904	6,520	14,067
Adjusted incidence rate ratio	0.78	0.59	0.65
(95% CI)§	(0.55-1.10)	(0.43-0.81)	(0.52-0.80)
<i>P</i> value	.15	.001	.0001

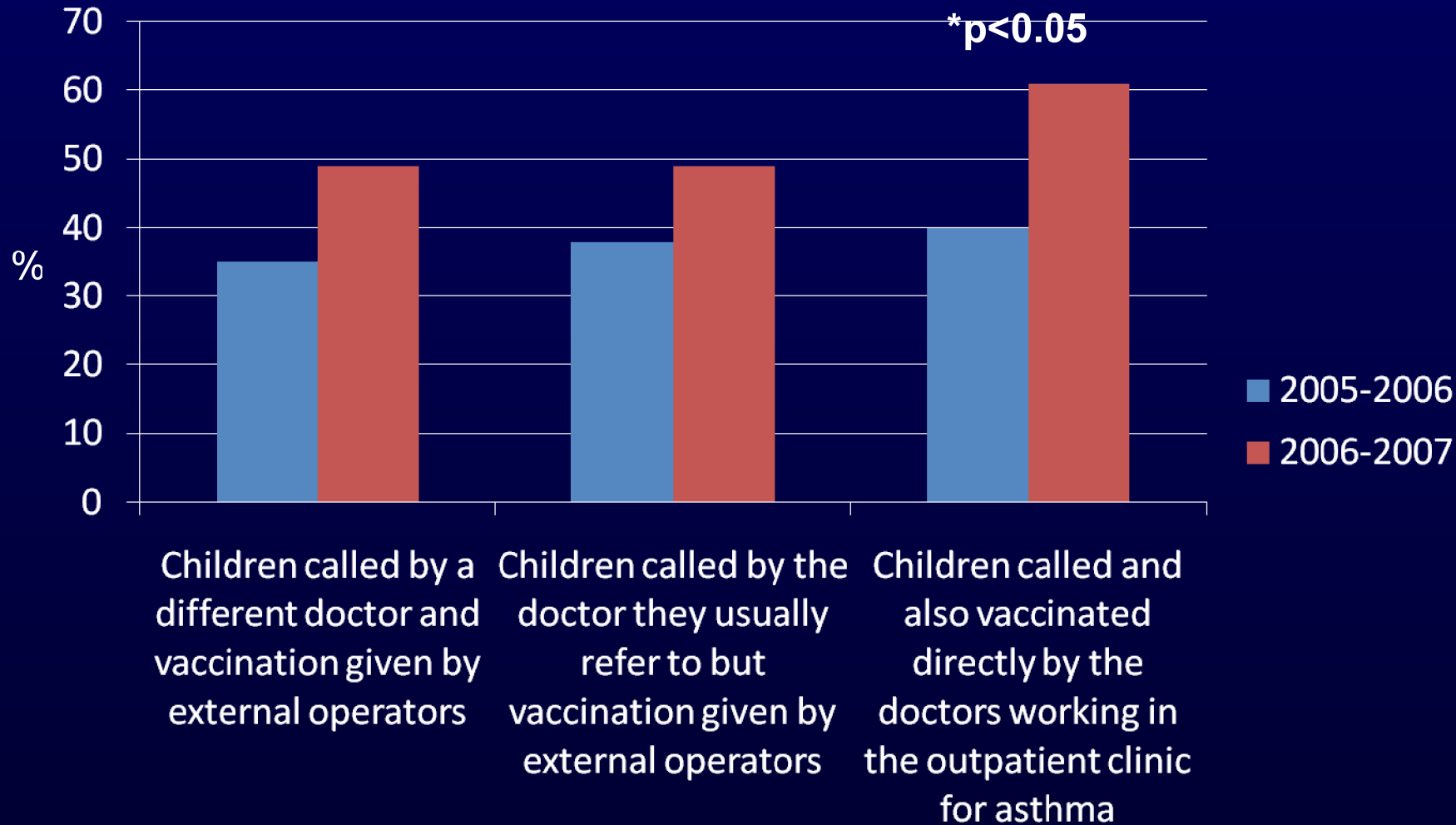
\*Three HMOs.

†Four HMOs.

‡Children with asthma who had at least one asthma exacerbation during the influenza season.

§Incidence rate ratio (95% CI) of asthma exacerbation occurring after influenza vaccination compared with the period before vaccination in the same individual; estimated by conditional Poisson regression models stratified by individual child and adjusted for 2-week periods of calendar time from October 1 through April 30 of each season.

# INTERVENTIONS TO IMPROVE INFLUENZA VACCINATION COVERAGE AMONG CHILDREN WITH CHRONIC ASTHMA



Esposito et al., Vaccine 2009

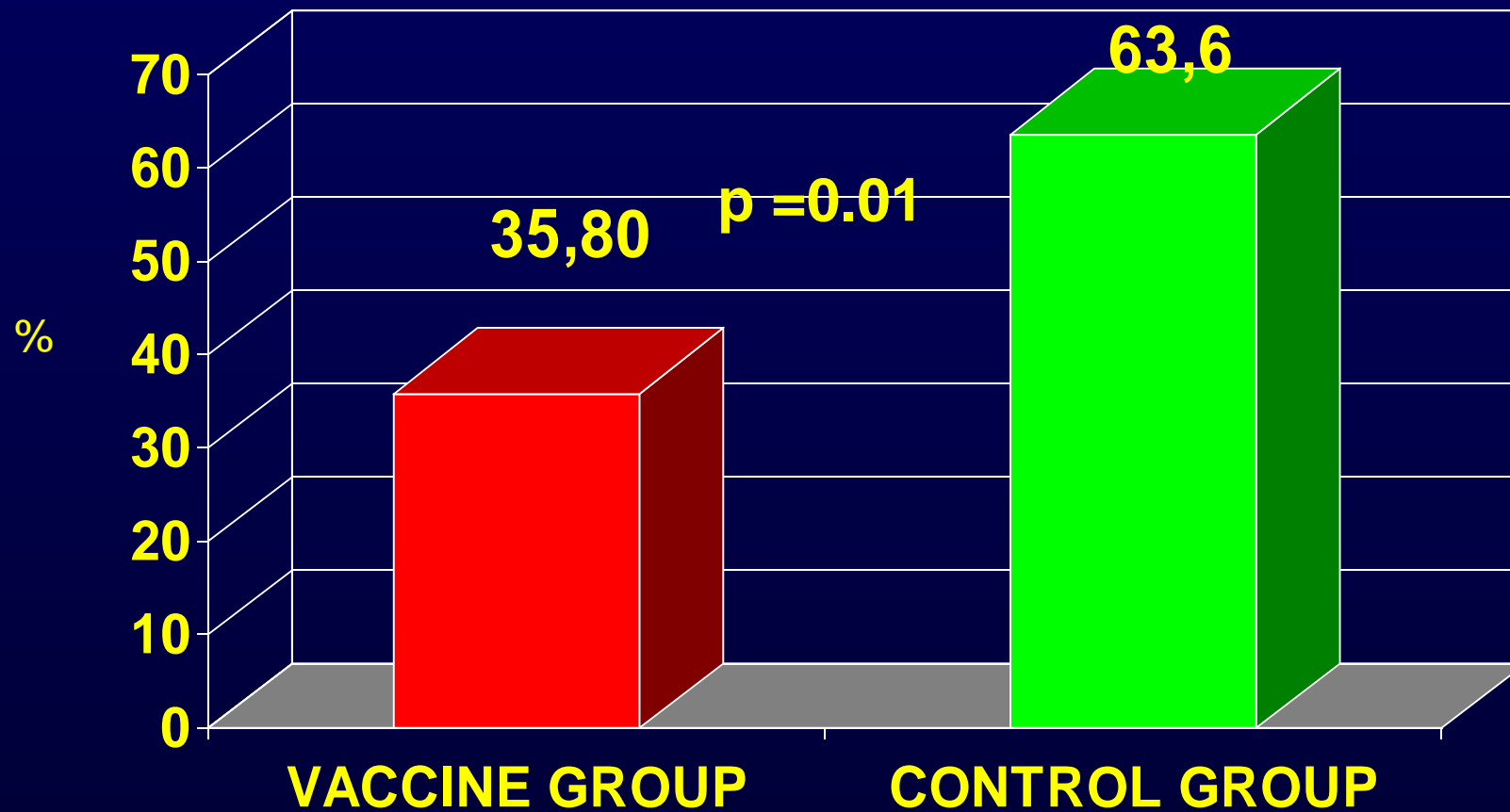
**TARGET GROUPS FOR INFLUENZA  
VACCINATION IN PEDIATRIC AGE**  
(ACIP, MMWR 2008)

**ALL CHILDREN AGED 6 MONTHS - 18 YRS**

**ALL HOUSEHOLD CONTACTS (INCLUDING  
CHILDREN) OF CHILDREN AGED  $\leq 59$   
MONTHS AND ADULTS AGED  $\geq 50$  YEARS**

**ALL HOUSEHOLD CONTACTS (INCLUDING  
CHILDREN) OF PERSONS WITH HIGH-  
RISK MEDICAL CONDITIONS**

# OCCURRENCE OF ACUTE OTITIS MEDIA ACCORDING TO INFLUENZA VACCINATION



Marchisio P et al., Clin Infect Dis 2002.

# EFFECTIVENESS FOR INFLUENZA VACCINATED AND UNVACCINATED CHILDREN WITH RECURRENT RESPIRATORY TRACT INFECTIONS

STUDY CHILDREN	VACCINATED (N=64)	CONTROLS (N=63)	P VALUE
NO. OF URTI	1.68 ± 1.62	4.52 ± 2.43	<0.0001
NO. OF LRTI	0.68 ± 0.88	1.24 ± 1.32	0.0042
NO. OF FEBRILE RESPIRATORY ILLNESSES	1.59 ± 1.49	3.87 ± 2.74	<0.0001
NO. OF HOSPITALIZATIONS	0.05 ± 0.23	0.10 ± 0.25	0.417
NO. OF ANTIBIOTIC PRESCRIPTIONS	1.32 ± 1.28	2.35 ± 1.59	<0.0001
NO. OF ANTIPYRETIC PRESCRIPTIONS	2.21 ± 2.03	3.98 ± 2.37	<0.0001
MISSED SCHOOL DAYS	3.10 ± 6.23	13.83 ± 12.50	<0.0001

Esposito S et al., Vaccine 2003.

# EFFECTIVENESS AMONG HOUSEHOLD CONTACTS OF INFLUENZA VACCINATED AND UNVACCINATED CHILDREN WITH RECURRENT RESPIRATORY TRACT INFECTIONS

HOUSEHOLD CONTACTS	VACCINATED	CONTROLS	P VALUE
LOSS OF MATERNAL WORK DUE TO CARE FOR THE ILL CHILD	0.64 ± 1.86	4.05 ± 5.34	<0.0001
LOSS OF PATERNAL WORK DUE TO CARE FOR THE ILL CHILD	0.11 ± 0.46	0.97 ± 2.24	0.001
NEED FOR HELP DUE TO CARE FOR THE ILL CHILD	53.5%	74.7%	0.012
NO. WITH RESPIRATORY ILLNESS	1.88 ± 1.68	2.90 ± 1.68	0.0005
NO. OF MEDICAL VISITS	1.22 ± 1.37	2.06 ± 1.77	0.002
NO. OF HOSPITALIZATIONS	0.01 ± 0.12	0	0.354

Esposito S et al., Vaccine 2003.

# IMMUNOGENICITY OF TWO DIFFERENT INFLUENZA VACCINES IN CHILDREN AGED 6 MONTHS - 5 YEARS

(Kanra, Marchisio et al., *Pediatr Infect Dis J* 2004)

Immune Status	Treatment	ITT Population	Seroconversion (% of Subjects)			Seroprotection (% of Subjects)			GMT (Fold Increase)		
			H1N1	H3N2	B	H1N1	H3N2	B	H1N1	H3N2	B
Total	Virusome- adjuvanted split	156	80.1	66.0	90.4	87.8	80.1	90.4	18.08	6.89	37.72
		170	75.9	62.9	89.4	82.9	78.2	89.4	15.77	6.74	35.80
<i>P</i>			0.3559	0.5612	0.7711	0.2142	0.6743	0.7711			
Unprimed	Virusome- adjuvanted split	116	88.8	69.8	94.8	88.8	77.6	94.8	26.99	7.95	49.94
		120	77.5	68.3	93.3	78.3	75.8	93.3	18.01	8.07	43.34
<i>P</i>			0.0208	0.8039	0.6271	0.0306	0.7502	0.6271			
Primed	Virusome- adjuvanted split	40	55.0	55.0	77.5	85.0	87.5	77.5	5.66	4.56	16.71
		50	72.0	50.0	80.0	94.0	84.0	80.0	11.47	4.38	22.63
<i>P</i>			0.0941	0.6370	0.7727	0.1573	0.6388	0.7727			

# Fluad general overview

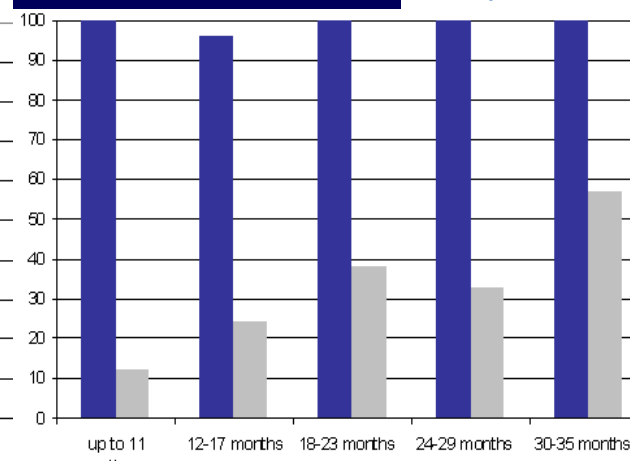
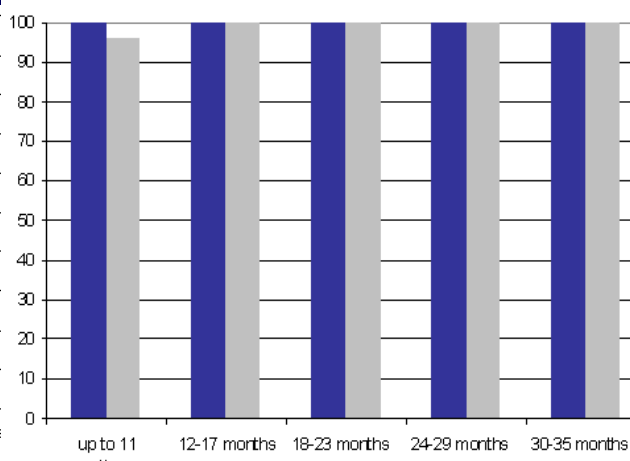
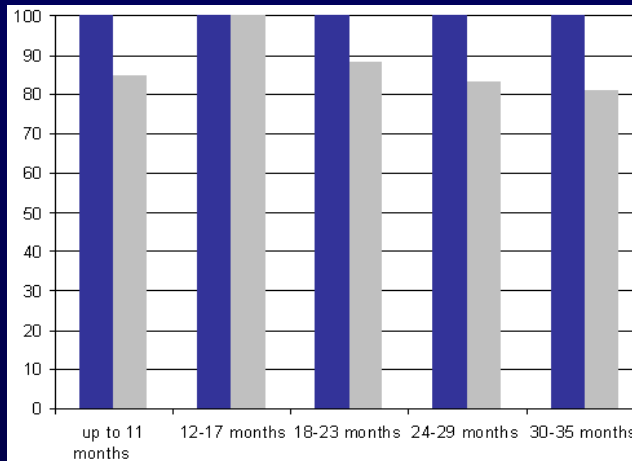
## Fluad immunogenicity in unprimed healthy children (6- <36 moa) - Study V70P2

**H1N1**

**H3N2**

**B**

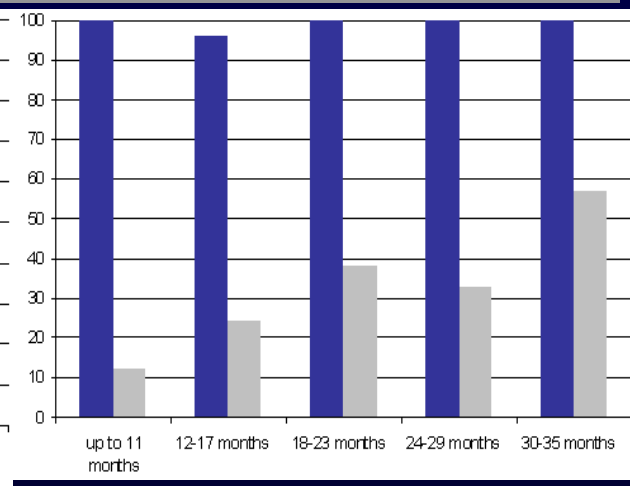
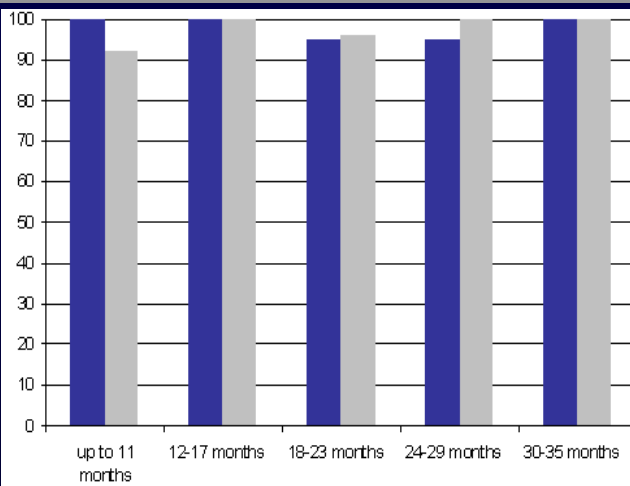
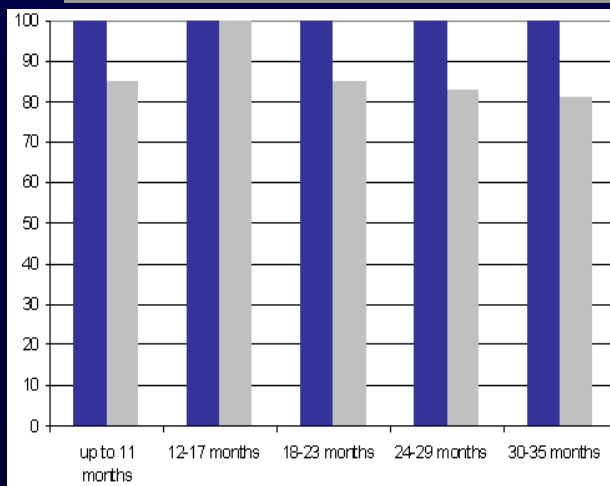
Seroprotection



**FLUAD**

**Vaxigrip**

Seroconversion or Significant Increase



Vesikari et al., ICAAC 2007 Chicago

# EFFICACY OF TIV IN OTHERWISE HEALTHY CHILDREN AGED 2-5 YEARS

(Esposito et al., Vaccine 2006)

Event	Vaccinated children ( <i>n</i> =202)	Unvaccinated children ( <i>n</i> =101)	Vaccine effectiveness (%) <sup>*</sup>	<i>p</i> -value
Number of upper respiratory tract infections	1.66 ± 0.62	2.47 ± 0.43	33	<0.0001
Number of lower respiratory tract infections	0.32 ± 0.88	0.41 ± 1.32	22	0.004
Number of febrile respiratory illnesses	2.47 ± 1.49	3.32 ± 2.74	26	<0.0001
Number of hospitalisations	0.01 ± 0.23	0.02 ± 0.25	50	0.417
Number of antibiotic prescriptions	1.36 ± 1.28	1.98 ± 1.59	32	<0.0001
Number of antipyretic prescriptions	4.70 ± 2.03	6.59 ± 2.37	29	<0.0001
Missed school days	4.61 ± 6.23	8.84 ± 12.50	48	<0.0001

Mean values ± S.D.

# IMPACT OF INFLUENZA VACCINATION IN CHILDREN AGED 2-5 YEARS ON HOUSEHOLDS

(Esposito et al. Vaccine 2006)

Event	Household contacts of vaccinated children ( <i>n</i> = 548)	Household contacts of unvaccinated controls ( <i>n</i> = 256)	Vaccine effectiveness (%) <sup>*</sup>	<i>p</i> -value
Number of influenza-like illness	3.03 ± 1.68	4.27 ± 1.68	30	0.0005
Number of medical visits for influenza-like illness	2.18 ± 1.37	3.16 ± 1.77	31	0.002
Number of hospitalisations	0	0	0	1.00
Number of antibiotic prescriptions	0.76 ± 0.99	1.40 ± 1.33	46	<0.0001
Number of antipyretic prescriptions	1.01 ± 0.76	1.99 ± 1.46	49	<0.0001
Loss of parental work (days)	1.91 ± 1.43	2.93 ± 2.31	35	0.001
Mothers	3.22 ± 1.86	4.78 ± 2.34	33	0.001
Fathers	0.56 ± 0.46	0.98 ± 1.22	43	<0.0001
Missed school days of siblings	1.43 ± 2.61	2.93 ± 4.10	51	<0.0001

Mean values ± S.D.

# COST-EFFECTIVENESS OF ADJUVANTED INFLUENZA VACCINATION

	No Vaccination of 6-60-Month- Old-Children	Vaccination of 6-24-Month- Old-Children	Vaccination of 6-60-Month- Old-Children
ILI events in Children 6-60 months	4,080,000	3,930,000	3,600,000
ILI events saved in Children 6-60 months	-	150,000	480,000
ILI events in Households	5,670,000	5,520,000	5,130,000
ILI events saved in Households	-	150,000	540,000
ILI events saved in Children and Households	-	300,000	1,020,000
Incremental QALYs	-	900	3000
Incremental costs	-	+ €12,000,000	+ € 30,000,000
incremental cost-effectiveness	-	€13,333/QALY	€10,000/QALY
Incremental costs	-	- €21,000,000	- €63,000,000
Incremental costeffectiveness	-	dominant	dominant

Marchetti et al., Hum Vaccine 2007

# INFLUENZA VACCINATION IN PEDIATRIC AGE

- **CHILDREN WITH MEDICAL PROBLEMS**  
TO URGENTLY IMPROVE INFLUENZA VACCINATION COVERAGE IN CHILDREN WITH THE TRADITIONAL CHRONIC UNDERLYING DISEASES

TO INCLUDE IN THIS GROUP CHILDREN WITH RECURRENT AOM OR RRTIs

- **OTHERWISE HEALTHY CHILDREN**  
TO CONSIDER THE UNIVERSAL INFLUENZA VACCINATION FOR MEDICAL AND SOCIOECONOMIC REASONS IN CHILDREN AGED 6-59 MONTHS