Infezioni respiratorie ricorrenti.

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Caserta, 2 giugno 2008

- Respiratory infections are a serious problem worldwide
- Some children as a group are predisposed to high morbidity
- Recurrent respiratory tract infections: definition and risk factors
- Efficacy of immunostimulants

Respiratory infections in children during winterseason

- a cohort study of healthy Melbourne children
- age 12 - 71 months
- Influenza-like ilnesses during winterseason
- 118 children → 137 ILI episodes over 12 weeks
- 0.53 ILI episodes per child-month
- Risk factors:

a. younger age

b. structured exposure to other children

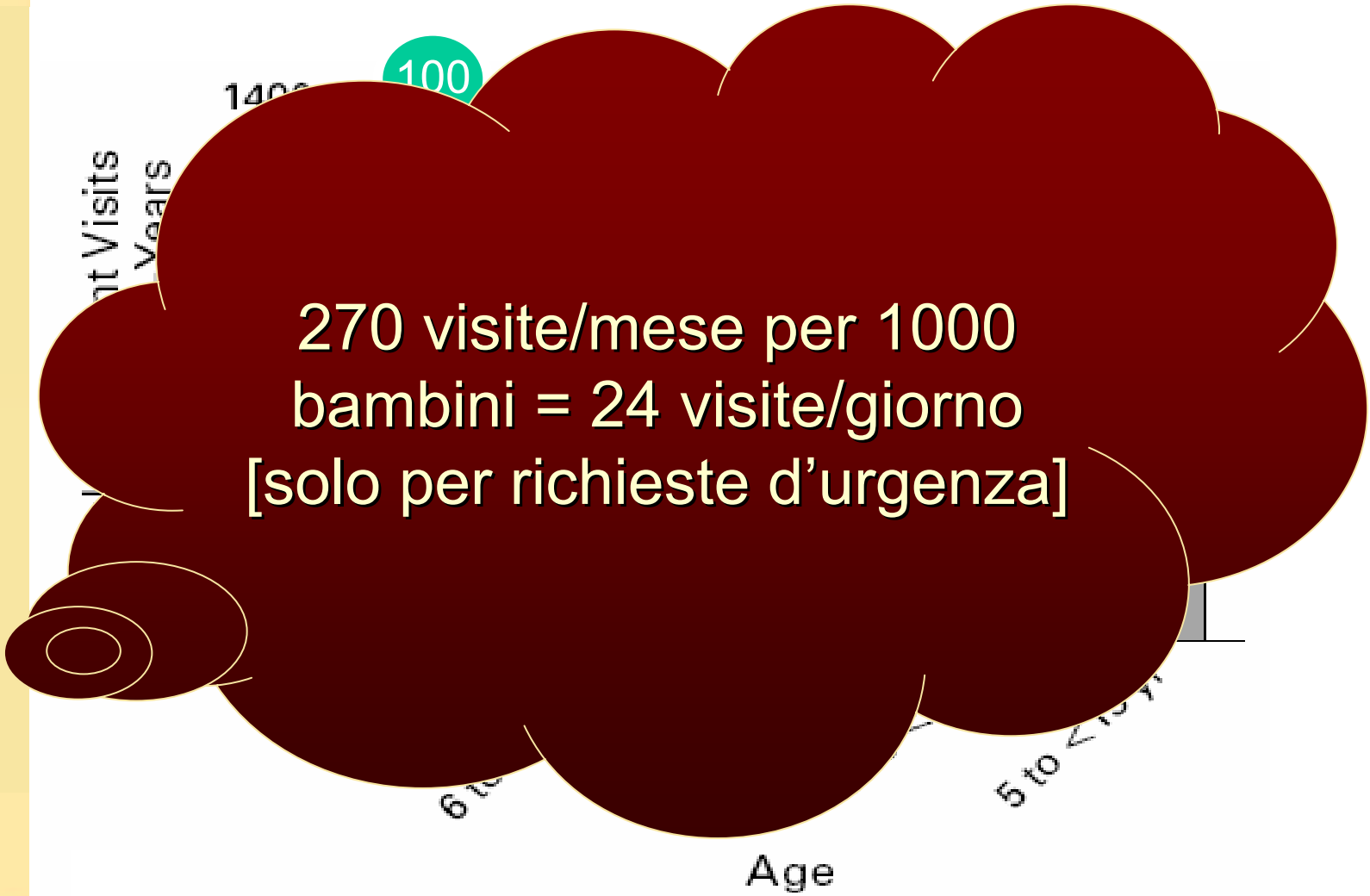
Leder K. Respiratory illness during winter: a cohort study of urban children from temperate Australia. J Paediatr Child Health. 2005; 41:125-9

Respiratory infections in children during winterseason

- mean duration 10.4 days
- 46.7 GP visits/100 episodes
- 19.7 antibiotic courses / 100 episodes
- 2.2 admissions /100 episodes
- average 11.7 h excess time spent caring for child /episode.

Leder K. Respiratory illness during winter: a cohort study of urban children from temperate Australia. J Paediatr Child Health. 2005; 41:125-9

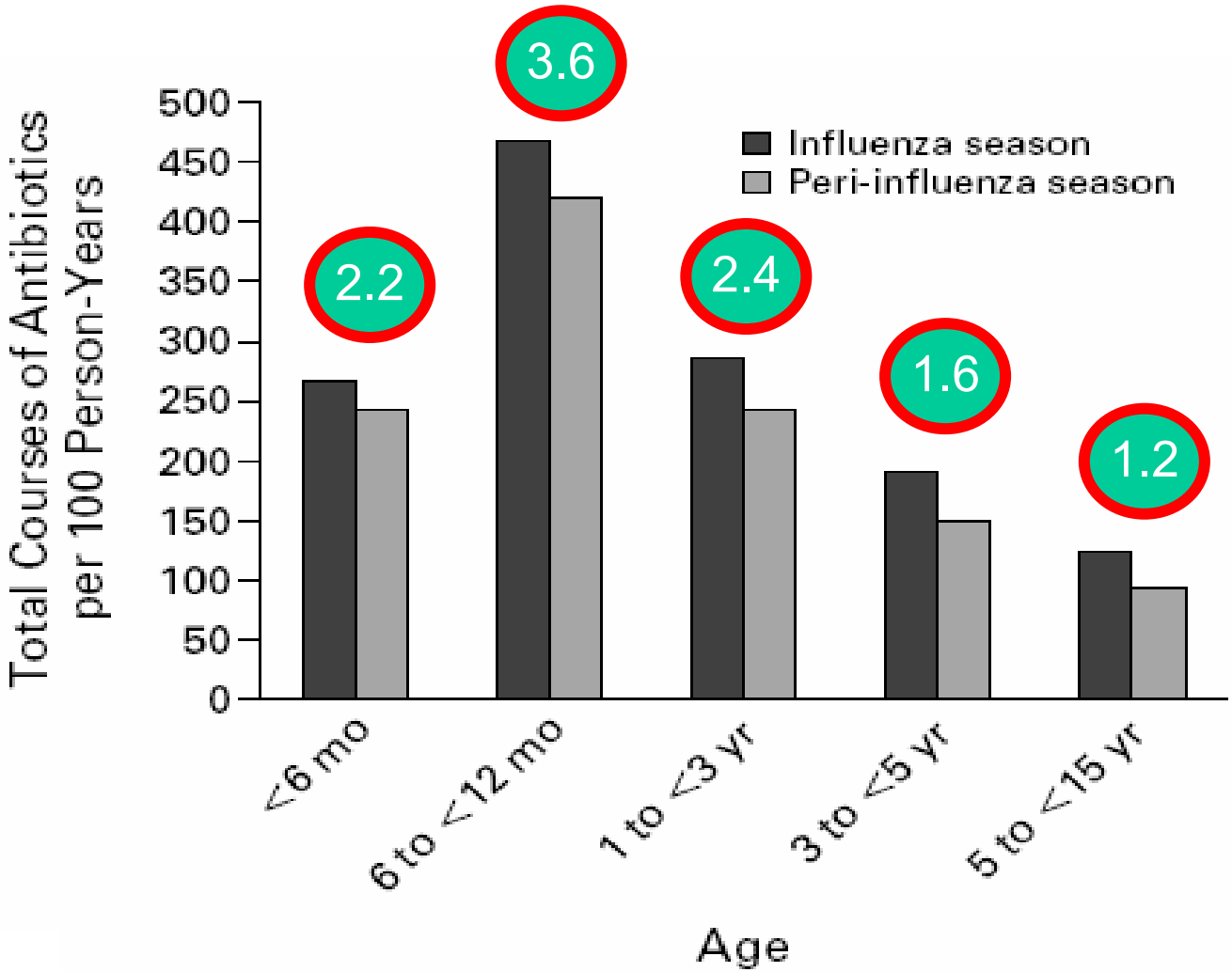
N° visite per 100 persone in un anno



270 visite/mese per 1000 bambini = 24 visite/giorno [solo per richieste d'urgenza]

Neuzil KM. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med. 2000;342:225-31

N° cicli antibiotici per 100 persone in un anno



Neuzil KM. The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med. 2000;342:225-31

N° visite di pronto soccorso per 100 bambini < 7 anni in un anno

	Mean Rate in ED Population per 1000 Visits (95% CI)
ARI	398 (366–429)
RSV	149 (137–163)
Influenza	37 (31–43)
PIV	11 (9–14)
Adenovirus	18 (14–24)
Enterovirus	5 (3–8)

Values represent rounded numbers. NA indicates not applicable.

Bourgeois FT. Influenza and other respiratory virus-related emergency department visits among young children. Pediatrics. 2006 118:e1-8

Direct and indirect costs are substantial

- A health diary from 600 families in Melbourne
- 80% at least one respiratory episode/15 months
- 2.2 respiratory episodes / person / year
- mean episode duration: 6.3 days
- children < 2 years:
  - most likely to have at least one respiratory episode
  - greater number of episodes per person
  - the longest episode duration (6.8 days)
- 28.7% respiratory episodes → doctor's visit
- 23% → time off school

Leder K. A community-based study of respiratory episodes in Melbourne. Aust N Z J Public Health. 2003; 27:399-404

The cost of seasonal respiratory illnesses in children

Children surveyed	118
Age, months	12-71
Time	July-December, 2001
Influenza-like episodes	202
Medical visits	89
Antibiotic prescriptions	42
Average cost, $ (95% CI)	241 (191 -291)

Lambert S. The cost of seasonal respiratory illnesses in Australian children: the dominance of patient And family costs and implications for vaccine use. Commun Dis Intell. 2004;28:510-6

Younger children and those with siblings may be less susceptible to illness associated with daycare

- 185 newborns - Prince Edward Island, Canada
- Follow-up 2 years
- Telephone interviews of the parent
- daycare vs. non-daycare: >>> at 15 months of age
- daycare vs. non-daycare: > at 3 months of age
- daycare vs. non-daycare: > children without siblings

- Lower family income > higher family income

Dales RE. Respiratory illness in children attending daycare. Pediatr Pulmonol. 2004;38:64-9.

Health impact of exposure to environmental tobacco smoke in Italy

Patologia	Numero di casi stimati
Basso peso alla nascita	2033
SIDS	87
Infezioni vie aeree < 2 anni	77.000
Asma	27.000
Sintomi respiratori cronici	48.000
Otite media sierosa	64.000

Forastiere F. Health impact of exposure to environmental tobacco smoke in Italy Epidemiol Prev. 2002; 26:18-29

“Io fumo solo in balcone dottore!”

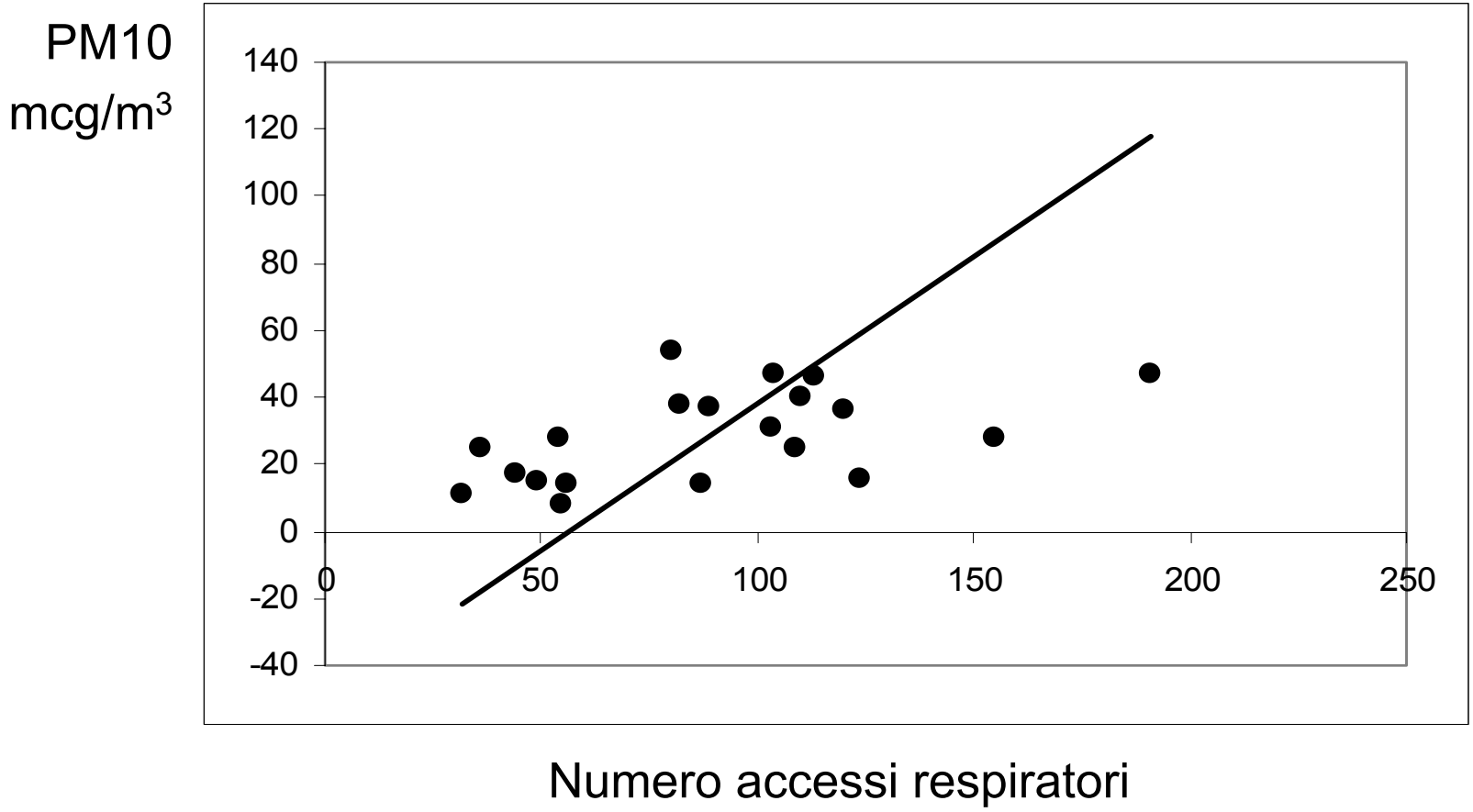
- **Numerosi studi dimostrano che anche quando i genitori dicono di fumare all’aperto l’esposizione del bambino al fumo passivo non viene ridotta.**
- **Perché?**

Johansson A et al. Indoor and outdoor smoking: impact on children's health. Eur J Public Health. 2003; 13:61-6

Nelson R. Smoking outside still causes second-hand smoke exposure to children.Lancet 2002;359:1675

Bahcecilier N. Parental smoking behaviour and the urinary cotinine level of asthmatic children. J Asthma 1999;36:171-5

PM10 ed accessi in PS per sintomi respiratori
R2 = 0.28; P < 0.02



Caddeo A. Impatto dell'esposizione al PM10
sulla frequenza di visite per patologie respiratorie in un pronto soccorso pediatrico.
Dal Mito alla Realtà, 31 gennaio – 1 febbraio 2008

Regimen Sanitatis Salerni
Secolo XI

Che l'aria sia pura, tersa e luminosa,
che non sia infetta o graveolente.

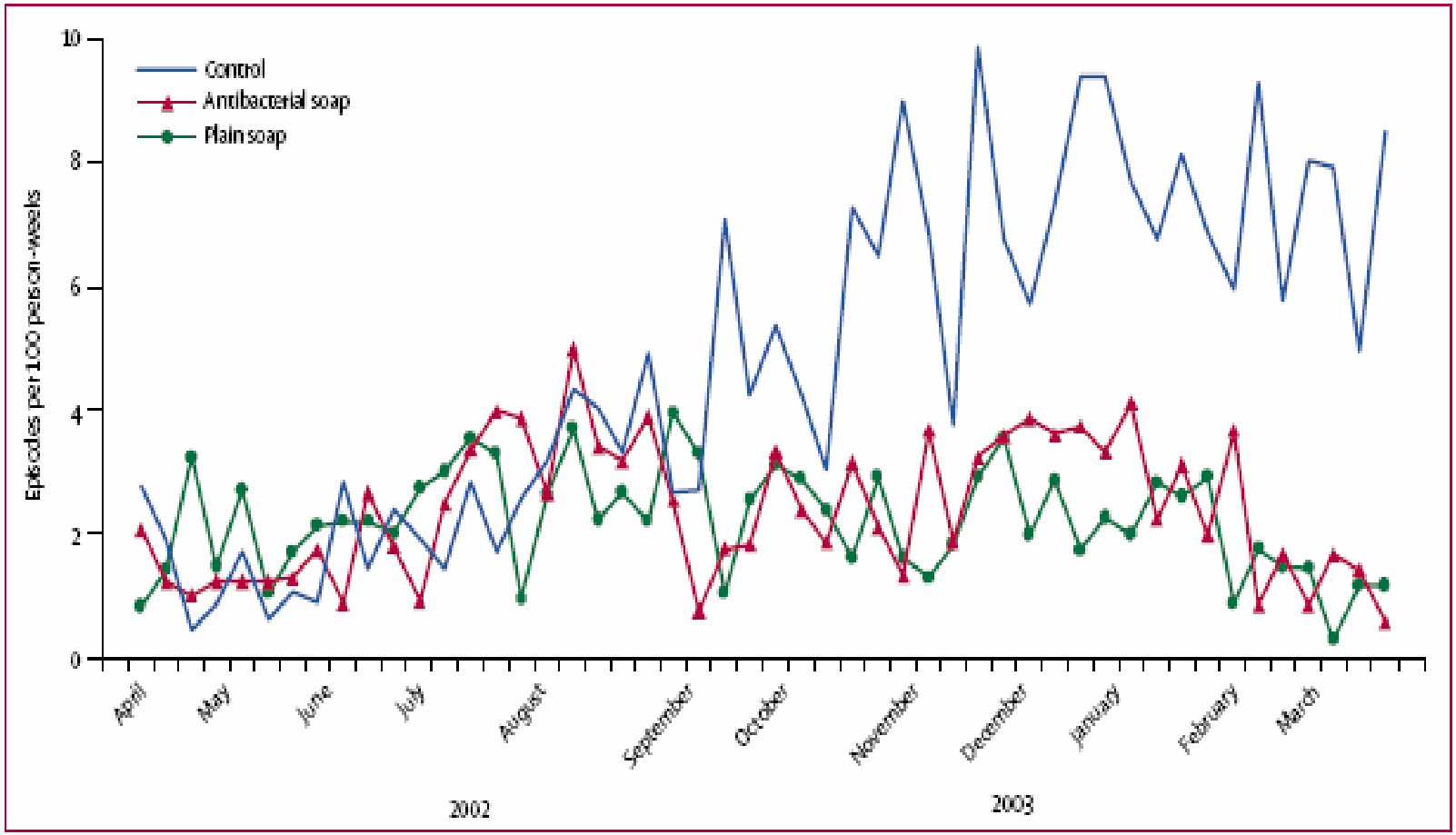


Figure 2: Incidence of pneumonia in children younger than 5 years

Luby SP. Effect of handwashing on child health: a randomised controlled trial. Lancet 2005;366:225-33

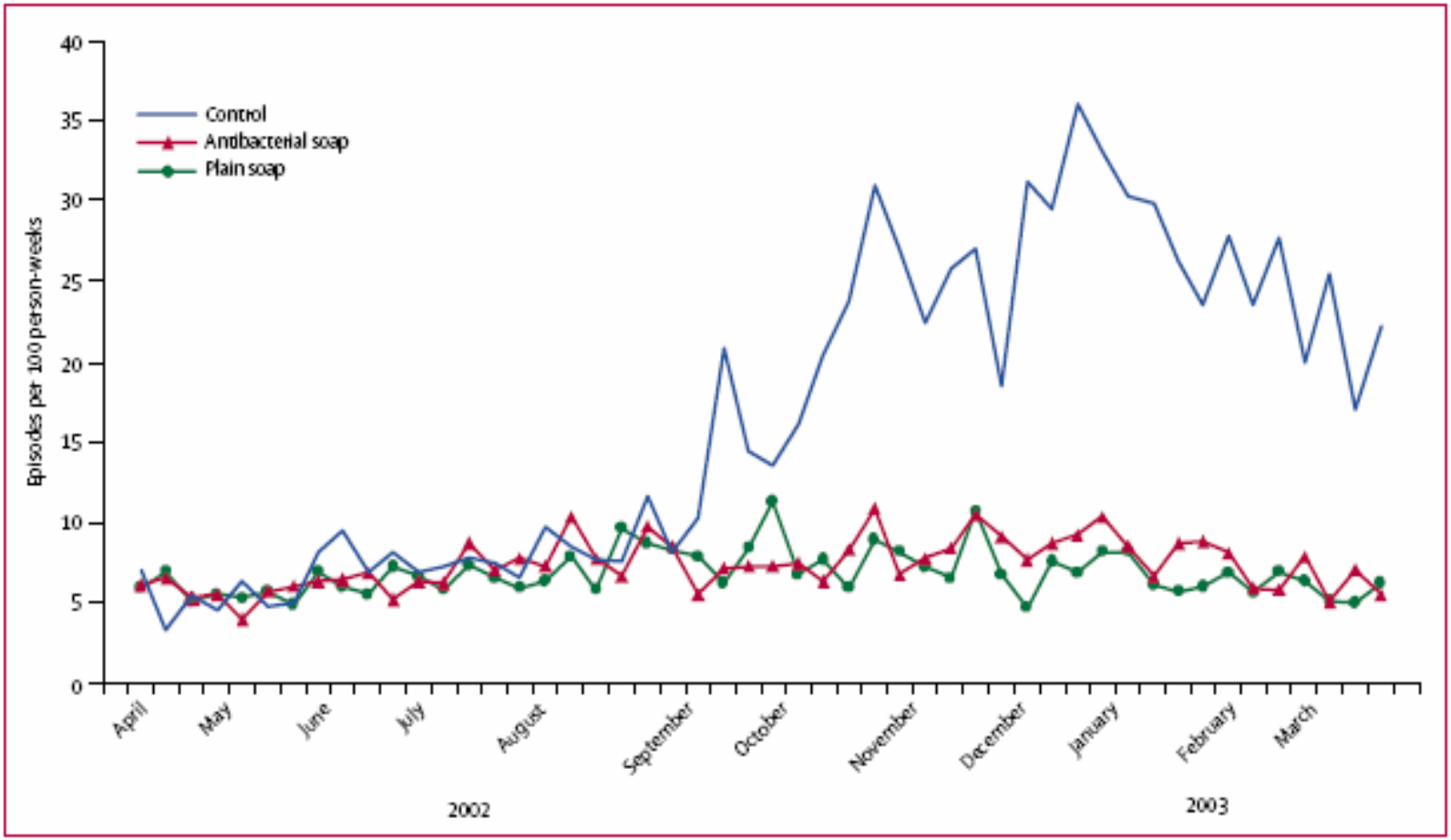


Figure 4: Incidence of congestion and coryza in children younger than 15 years

Luby SP. Effect of handwashing on child health: a randomised controlled trial. Lancet 2005;366:225-33

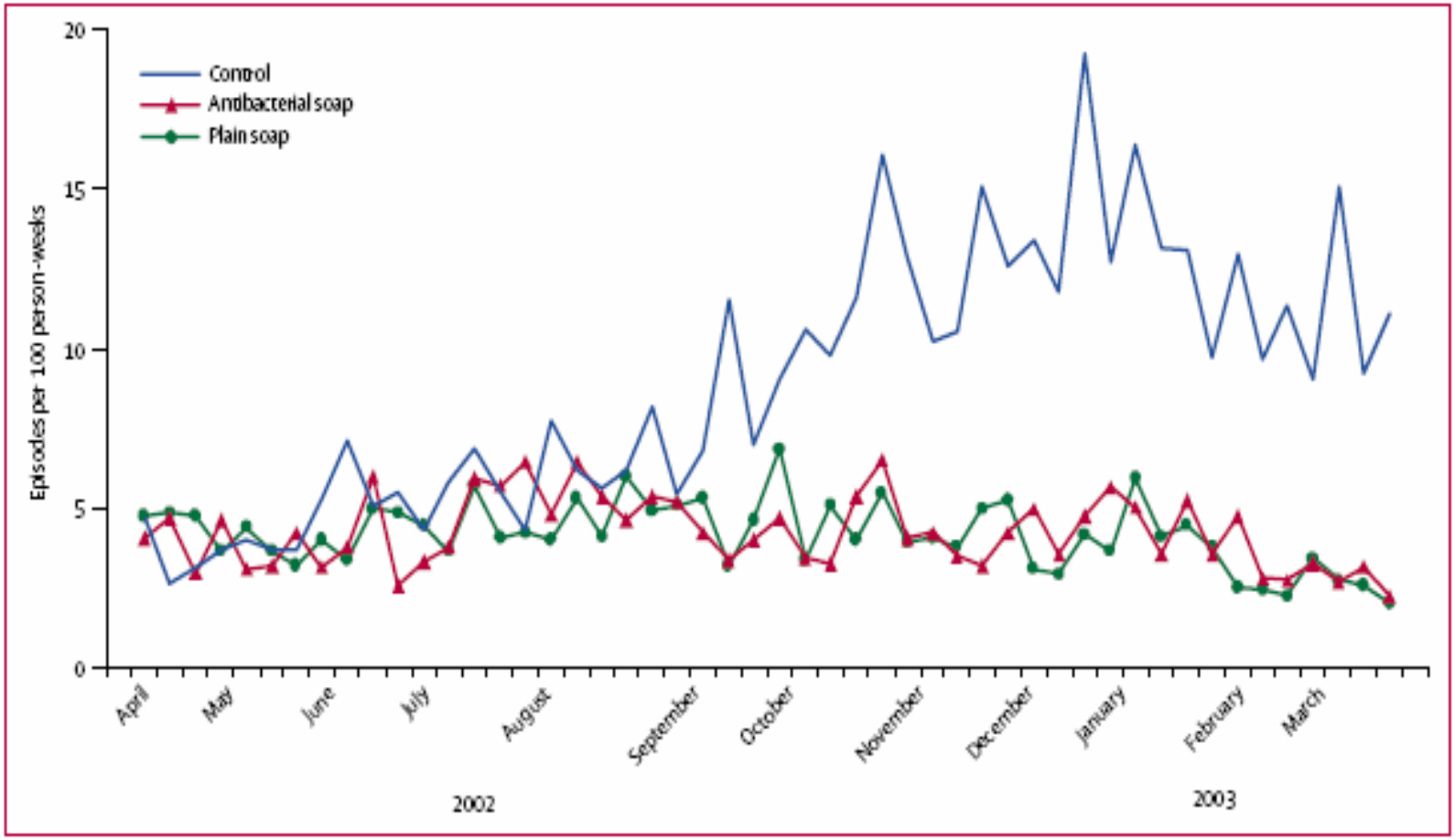


Figure 3: Incidence of cough and difficult breathing in children younger than 15 years

Luby SP. Effect of handwashing on child health: a randomised controlled trial. Lancet 2005;366:225-33

Regimen Sanitatis Salerni
Secolo XI

Se vuoi vivere sano a lungo
lavati spesso le mani.

- Respiratory infections are a serious problem worldwide
- Some children as a group are predisposed to high morbidity
- Recurrent respiratory tract infections: definition and risk factors
- Efficacy of immunostimulants

Allergic children have more numerous and severe respiratory infections than non-allergic children

Number and duration of RI in children with RRI		
# RI	Non allergic (n=71)	Allergic (n=46)
Total RI # (p=0.0001)	0.94±1.37	1.26 ± 073
Mild RI # (p<0.000001)	0.53±.64	1.02±0.70
Total RI duration (days; p=0.009)	4.85±5.24	8.92±9.64
Mild RI duration (days; p=0.0007)	2.99±3.91	7.82±9.87

Ciprandi G. Pediatr Allergy Immunol 2006: 17: 389–91

Some children as a group show high morbidity

- 41 school-age children with RRTIs [antibiotics] as preschoolers (a)

vs.

- 29 children (same age and socio-economic background) without RRTIs as preschoolers (b)

Two-year follow-up:

- RTI episodes a>b ($p < 0.01$)
- RTI duration a>b ($p < 0.01$)

Soderstrom M. Respiratory tract infections in children with recurrent episodes as preschoolers. Acta Paediatr Scand. 1991;80:688-95

Certain children constitute a group with high morbidity

Annual incidence of bacterial RTI:

Age	Group A	Group B	P
2 yrs	6.2	1.4	< 0.001
7 yrs	3.1	1.2	< 0.01
8 yrs	2.4	0.8	< 0.05

→ **Children with high morbidity are susceptible to RTIs and other illnesses over a long period of years**

Soderstrom M Respiratory tract infections in children with recurrent episodes as preschoolers. Acta Paediatr Scand. 1991;80:688-95

Recurrent respiratory infections and immune defects

- IgG2 subclass deficiency → pneumonia, sinusitis, invasive pneumococcal disease
- IgA deficiency → pneumonia, otitis, diarrhoea
- G2m(n) allotype of IgG2 → susceptibility to encapsulated bacteria
- Fc receptor IIa: H131 high affinity, FcRIIa-R131 low affinity for IgG2
- Heterozygotic C2 deficiency in 1%–1.5% of the general population
- Homozygous deficiency of C4A or C4B in 3% of the population
- Mannose-binding lectin (MBL2) activates the complement system

Bossuyt X. Coexistence of (partial) immune defects and risk of recurrent respiratory infections. Clin Chem. 2007;53:124-30

Recurrent respiratory infections and immune defects

Number of (partial) Immune defects	Patients (n=55)	Control (n=43)
0	6	27
1	20	10
2	21	3
3	8	1

Bossuyt X. Coexistence of (partial) immune defects and risk of recurrent respiratory infections. Clin Chem. 2007;53:124-30

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Recurrent Respiratory Tract Infections: a clinical score

Variable		October 1 – 15	October 16-31	November 1 – 15…	…March 16 - 31
Tonsillitis, otitis, pharyngitis	Present	1	1	1	1
	Absent	0	0	0	0
Bronchitis, pneumonia	Present	2	2	2	2
	Absent	0	0	0	0
Medical visit	Yes	1	1	1	1
	No	0	0	0	0
Number of episodes of illness	1	1	1	1	1
	2	2	2	2	2
	> 2	3	3	3	3

De Martino M, Vierucci A. Il bambino con infezioni respiratorie ricorrenti. Immunol. Pediatr. 1981; 1:76 -9

Recurrent Respiratory Tract Infections: a clinical score

Variable		October 1 – 15	October 16-31	November 1 – 15…	…March 16 - 31
Duration of episodes	3 days	1	1	1	1
	3 – 6 days	2	2	2	2
	> 6 days	3	3	3	3
Treatment	None	0	0	0	0
	Symptomatic	1	1	1	1
	Antibiotics	2	2	2	2
Time off school	None	0	0	0	0
	0 – 3 days	1	1	1	1
	> 3 days	2	2	2	2

De Martino M, Vierucci A. Il bambino con infezioni respiratorie ricorrenti. Immunol. Pediatr. 1981; 1:76 -9

Recurrent Respiratory Tract Infections: a clinical score

Scoring recurrent respiratory infections recorded every 15 days in winter (October-March)

Children with a score > 30 points in 6 months ⇒ five episodes of URTIs or three episodes of LRTIs requiring antibiotic therapy, medical visit and/or time off school

De Martino M, Vierucci A. Il bambino con infezioni respiratorie ricorrenti. Immunol. Pediatr. 1981; 1:76 -9

Treatment of children suffering from recurrent respiratory infections with Immucytal

Inclusion criteria:

a. Children from 3 to 12 years.

b. Children suffering recurrent RRTIs defined as 30 points in Vierucci clinical score, corresponding to five episodes of severe respiratory infection per winter season requiring antibiotic therapy, a medical visit and absence from school.

Endpoint and period considered:

Monthly clinical score + immunological parameters

6 months

Fiocchi A. et al. Ped. Prev. Soc. 1988

Pierre Fabre Pharma

Reduction of the number and severity of respiratory tract infections in children by oral immunostimulation

Inclusion criteria:

a. Children aged 4 - 9 years, history of 10 RRTIs in the last year
b. Children from 4 to 6 years must have 8 severe RRTIs lasting more than 2 weeks in this period
c. Children from 7 to 9 years must have 4 severe RRTIs lasting more than 2 weeks in this period

Endpoint and period considered:

Total number of infections

14 weeks

Riedl-Seifert R.J. et al.: Adv. Exp. Med. Biol. 1995

Use of a polyvalent bacterial lysate in patients with recurrent respiratory tract infections: results of a prospective, placebo-controlled, randomized, double-blind study

Inclusion criteria:

a. History of recurrent RRTIs.
b. Children 4 to 6 years: >10 RRTIs in the last year.
c. Children 7 to 11 years: > 8 RTIs in the last year.
d. Patients suffering 4 RRTIs lasting more than 2 weeks were included too.

Endpoint and period considered:

% of patients without infectrion
6 months

Rutishauser M. et al. Adv. Ther. 1998

Immunotherapy with an oral bacterial extract (OM 85 BV) for upper respiratory infections

Inclusion criteria:

a. Children from 0.5 to 19 years.
b. History of $\geq$ 3 upper RTIs in the last 6 months

Endpoint and period considered:

% of patients without infections

6 months

Paupe J. Respiration 1991

Evalutation of RU 41740 (Biostim) for the prevention of recurrent nasopharyngeal infections in pediatric patients

Inclusion criteria:

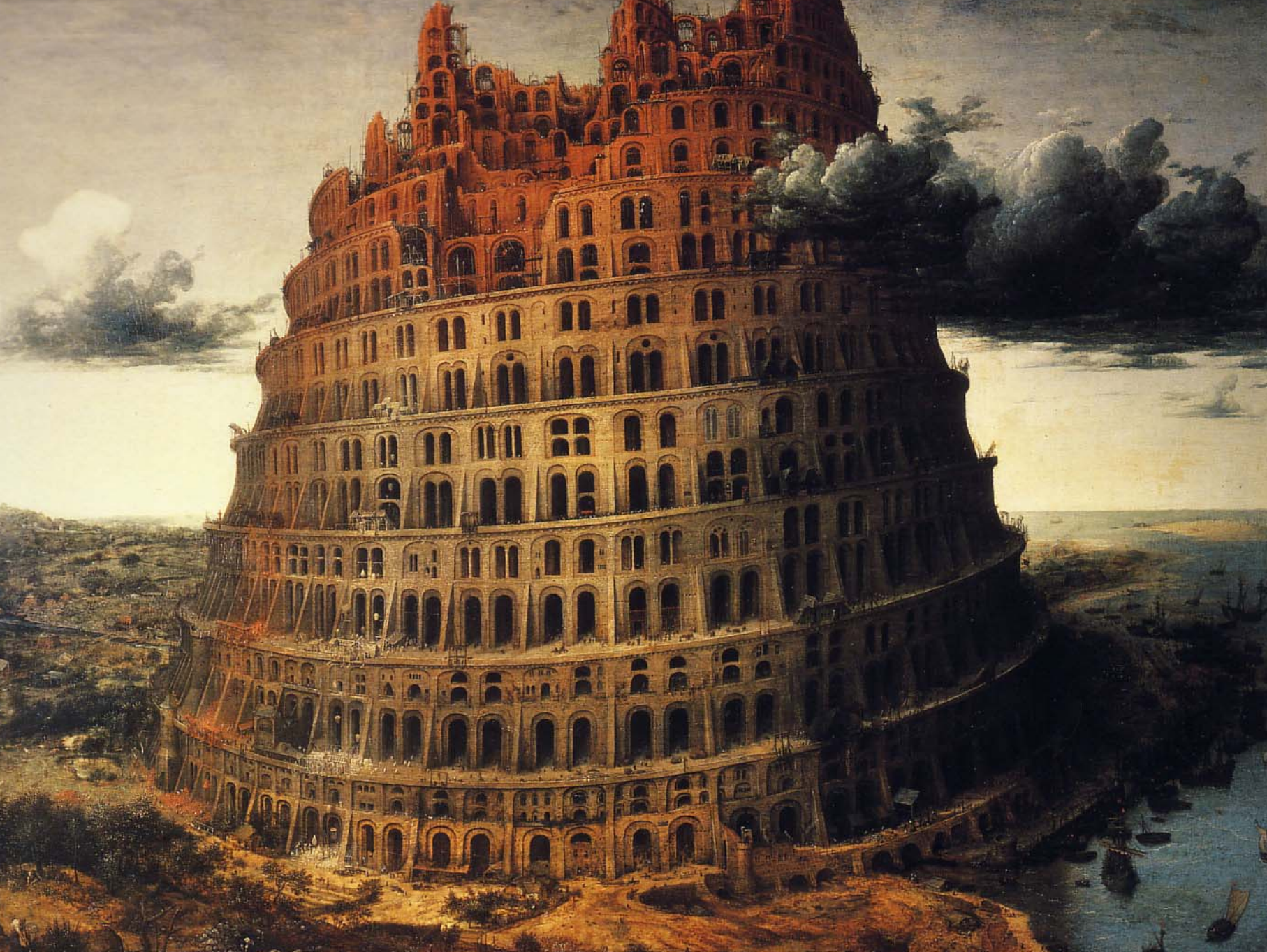
a. Children from 1 to 13 years
b. Children with history of recurrent rhinopharynx infections with at least 3 infections of this kind during the year before the study

Endpoint and period considered:

Mean ± SD, number of infections

6 months

Reinert P. Ann. Pediatr. (Paris) 1995



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Levels of evidence

Level I a	meta-analysis of randomised controlled trials (RCT)
Level I b	at least one RCT
Level II a	at least one controlled study without randomisation
Level II b	at least one other type of study
Level III	non-experimental descriptive studies
Level IV	expert committee reports or opinions or clinical experience of respected authorities

Shekelle PG. Clinical guidelines: Developing guidelines.
BMJ, 1999; 318: 593 -6

Immunostimulants and ARTIs: a meta-analysis

RESULTS: Four of five RCTs with Jadad's score > 3 showed significant reduction of ARTIs in immunostimulant groups
- 42.64%, (95% confidence - 45.19 / - 40.08%);
- 60% mean number of ARTIs in treated vs. placebo group.

CONCLUSIONS: immunostimulants are an effective treatment for the prevention of ARTI. Further high-quality RCTs are required

Berber A.J, A meta-analysis of randomized placebo-controlled clinical trials on the prevention of respiratory tract infections in children using immunostimulants. Investig Allergol Clin Immunol. 2001; 1: 235-46

Ribosomal immunostimulation
3 months' duration

	Number of recurrences	Duration of infection	Antibacterial requirement
ENT	- 27-68%	- 28-66%	-29-60%
Otitis media	- 10-53%	- 16-56%	- 18-47%
ENT + LTRI	- 32-61%		

These results clearly demonstrate that ribosomal immunostimulant is effective in preventing and in reducing upper and lower respiratory tract infections in children and adults

Bellanti J. Ribosomal immunostimulation: assessment of studies evaluating its clinical relevance in the prevention of upper and lower respiratory tract infections in children and adults. BioDrugs. 2003; 17: 355-67

Conclusioni

1. Il problema delle IRR ha un notevole peso sul bambino, sulla famiglia e sulla società in termini di morbilità, qualità della vita, costi sociali ed economici
2. Esistono bambini che sia per fattori immunologici che per stile e condizioni di vita hanno un rischio aumentato di IRR
3. E' possibile influire sullo stile di vita per ridurre il rischio di IRR
4. L'efficacia degli immunomodulatori è validato da diverse metanalisi
5. E' auspicabile un utilizzo integrato di interventi volti a modificare lo stile di vita "a rischio" insieme ad un uso mirato dei modulatori della risposta immune