

USO DEGLI ANTIBIOTICI E LE LINEE GUIDA

Nicola Principi

Principali conseguenze del cattivo uso degli antibiotici

- Aumento della pressione di selezione con più rapida emergenza di batteri resistenti
- Ridotta durata dell'efficacia terapeutica degli antibiotici
- Aumento degli eventi avversi farmaco-dipendenti
- Aumento del costo economico della terapia farmacologica e dell'assistenza per singolo episodio di malattia

Antibiotic drug
monitoring in pediatric
patients.

Principi N, Sher D, Moresco RC,
Marchisio P, Viola G, Sereni F.

Prog Clin Biol Res. 1979;35:109-17.

Antibiotic choice in selected diseases and children

(from Principi N, et al. Eur J Clin Pharmacol 1981)

Antibiotic prescriptions

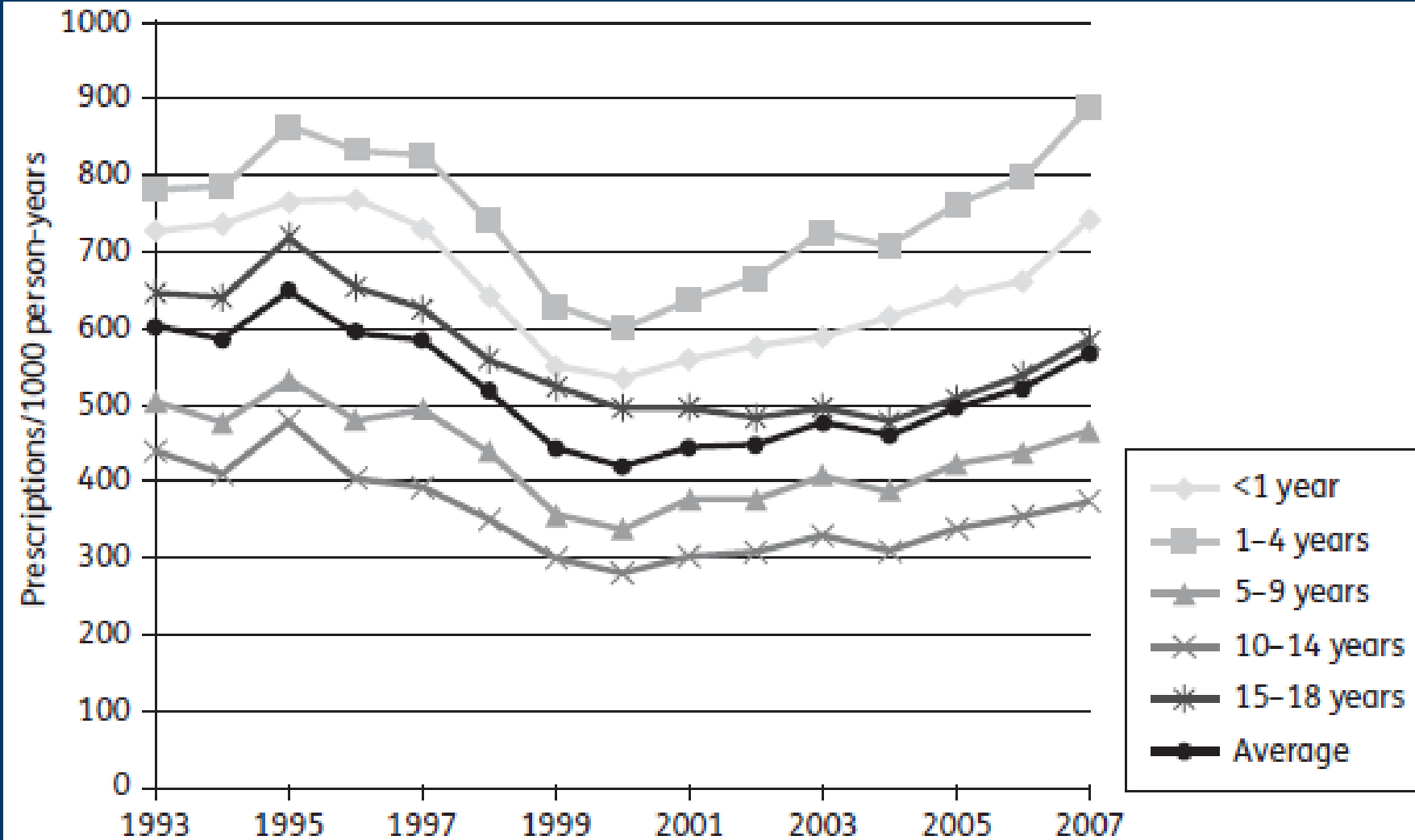
	N° cases	Adequate (%)	Justifiable (%)	Not Justifiable (%)
Otitis	39	74.3	2.6	23.1
Pneumonia	153	41.2	4.6	54.2
< 60 days	13	38.4	-	61.6
< 3 years	64	46.9	3.1	50.0
> 3 years	76	36.9	6.5	66.6
Pharyngotonsillitis	122	68.9	4.1	27.0
Total	314	56.1	4.1	39.8

CDC campaign activities and their targeted impact at various levels

<i>CDC Campaign Activities</i>	<i>Individuals</i>	<i>Groups and Social Networks</i>	<i>Institutions and Organizations</i>
Pediatric principles	Improve knowledge, attitudes, and skills of providers	Change social norms among providers to support appropriate prescribing by engaging professional organizations in development of guidelines	Codify guidelines by encouraging organizations to adopt prescribing guidelines as policy
Health education materials	Improve knowledge, attitudes, and skills of providers, patients, and parents	Facilitate communication between providers and patients	
National media campaign	Increase awareness of appropriate antibiotic use; improve knowledge and attitudes of general public and providers	Stimulate discussion among consumers and providers; change community norms to decrease demand for antibiotics	
Medical school curriculum	Improve knowledge, attitudes, and skills of medical students	Change social norms among medical students to support appropriate prescribing	Include appropriate antibiotic use as integral part of clinical training
Performance measures	Increase consumer and health care purchaser awareness of health plan performance in appropriate prescribing	Facilitate communication among consumers and among health care purchasers regarding health plan performance	Focus health plan improvement efforts based on results; encourage health care purchasers to use results in making contract decisions with health plans

Trends in antibiotic prescriptions for outpatient children in the UK GPRD, 1993-2007

(from Schneider-Lindner V, et al. JAC 2011)



Time trends in antibiotic prescriptions for outpatients children in the UK GPRD

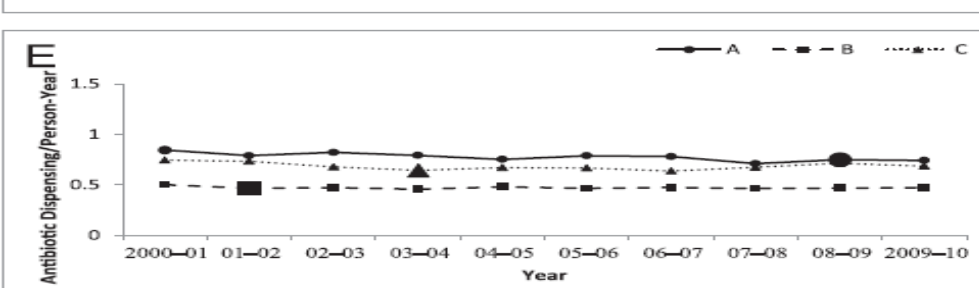
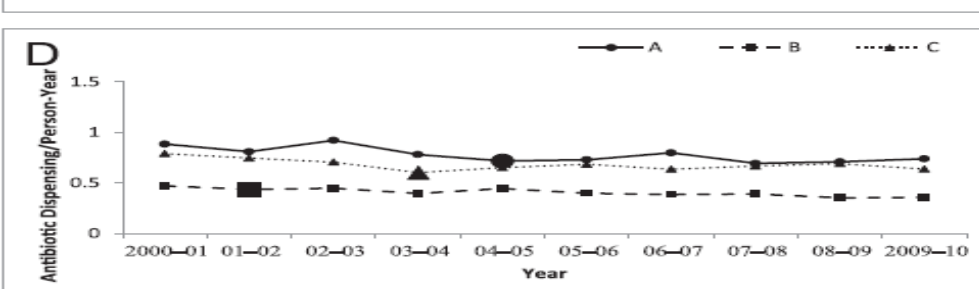
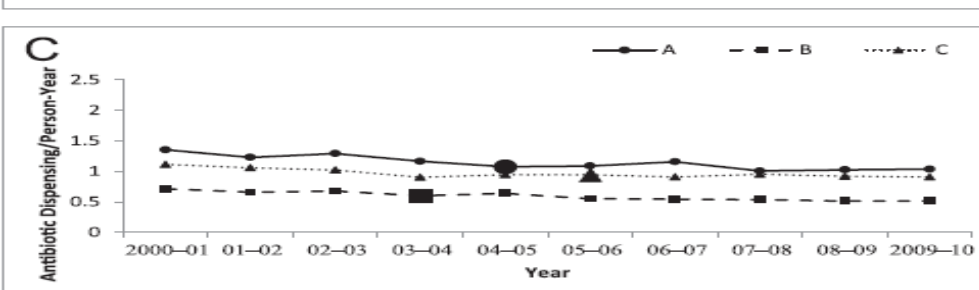
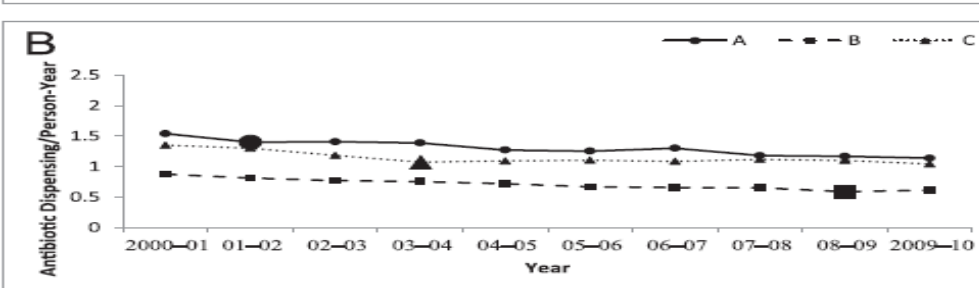
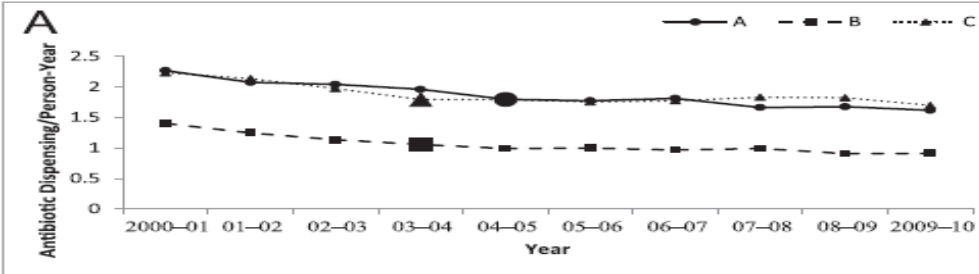
(from Schneider-Lindner, et al. JAC 2011)

Antibacterial drug class by BNF chapter	Prescription rate/1000 person-years in 2000	Prescription rate/1000 person-years in 2007	Adjusted ^a ratio of prescription rates in 2007 compared with 2000	Adjusted ^a annual change 2000–2007
Broad-spectrum penicillins	231.468	308.013	1.43 (1.35–1.52)	4.6% (4.0–5.3%)
Benzylpenicillin and phenoxymethylpenicillin	55.305	76.403	1.38 (1.31–1.46)	4.1% (3.4–4.8%)
Macrolides	55.234	71.798	1.34 (1.27–1.42)	3.7% (2.7–4.8%)
Penicillinase-resistant penicillins	44.256	62.423	1.42 (1.34–1.50)	4.8% (4.2–5.6%)
Cephalosporins and other β -lactams	28.229	37.698	1.47 (1.33–1.63)	5.0% (3.7–6.3%)
Sulphonamides and trimethoprim	24.969	34.285	1.41 (1.34–1.49)	4.9% (4.0–5.8%)
Tetracyclines	27.193	40.921	1.22 (1.16–1.29)	2.6% (1.9–3.4%)
Metronidazole and tinidazole	2.273	3.154	1.17 (1.06–1.29)	3.7% (2.2–5.2%)
Quinolones	1.962	3.996	1.87 (1.51–2.31)	9.7% (6.7–12.7%)
Nitrofurantoin methenamine hippurate and fosfomycin ^b	0.721	1.920	2.59 (2.07–3.23)	15.0% (11.8–18.2%)
Polymyxins	0.944	1.235	1.27 (0.97–1.68)	3.5% (0.1–7.0%)
Aminoglycosides	0.188	0.204	1.01 (0.61–1.68)	3.1% (–1.7 to 8.3%)
Clindamycin	0.032	0.068	1.96 (0.86–4.47)	3.5% (–5.3 to 13.2%)
Fusidic acid	0.057	0.076	1.34 (0.73–2.46)	1.3% (–6.6 to 9.8%)
Chloramphenicol	0.013	0.003	0.20 (0.04–1.01)	–23.1% (–36.8 to –6.4%)

Prescriptions of mecillinams, vancomycin and teicoplanin, linezolid and antipseudomonal penicillins were too infrequent for reliable estimation of time trends.

^aAdjusted for gender, age groups, gender-age group interactions and practice.

^bDrugs from chapter 'Urinary tract infections' not listed elsewhere in the BNF.

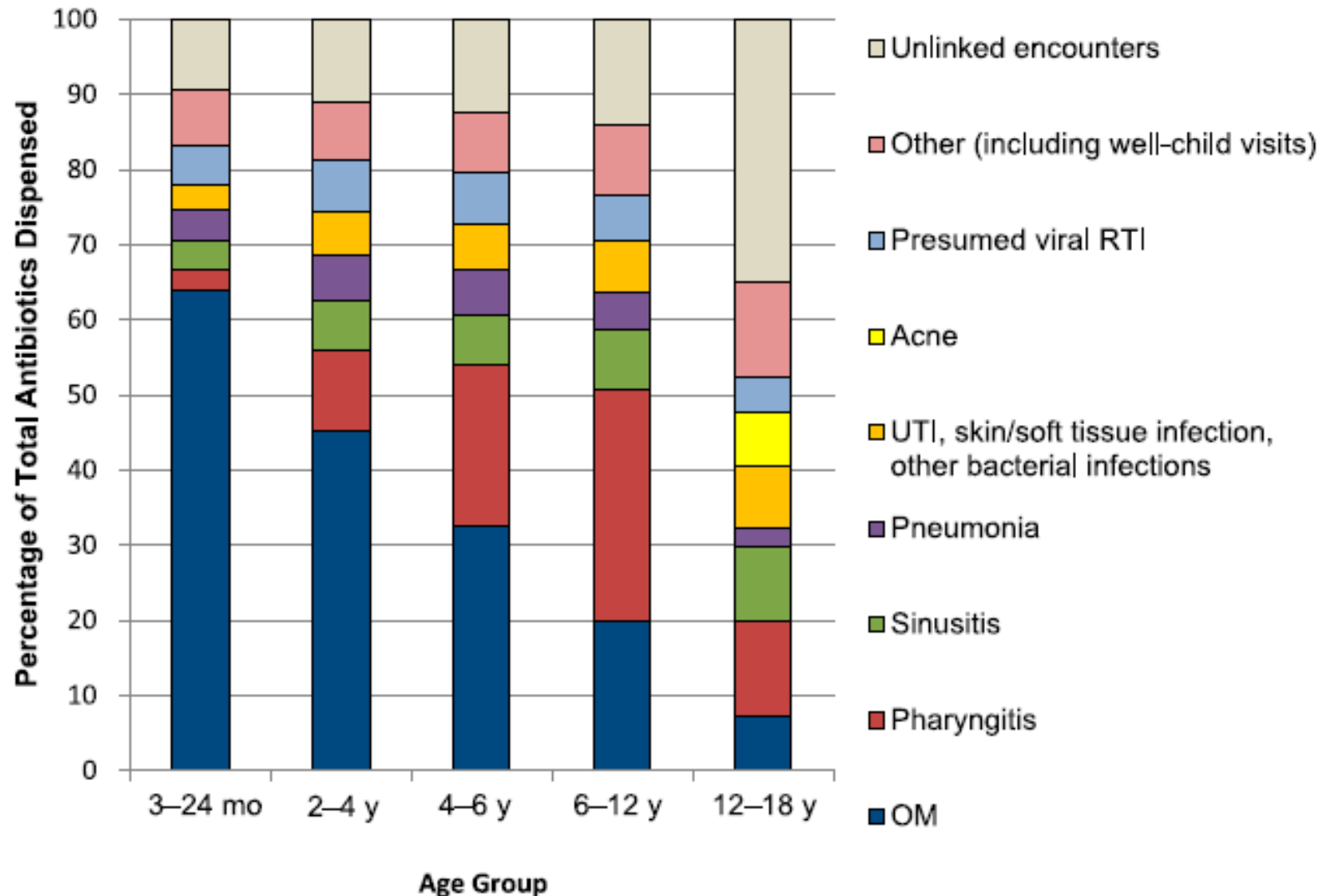


Rates of antibiotic dispensing per person year for children aged:
 A 3 to 24 months,
 B 2 to < 4 years,
 C 4 to < 6 years,
 D 6 to < 12 years,
 E 12 to < 18 years.
 Values are for
 A New England,
 B Mountain West
 C Midwest Regions

From Vaz LE, et al.
 Pediatrics 2014

Distribution of diagnosis and antibiotic prescriptions in 2009-2010 among children in 3 health plans

(from Vaz LE et al. Pediatrics 2014)





Clinical Usefulness

Rational use of antibiotics for the management of children's respiratory tract infections in the ambulatory setting: an evidence-based consensus by the Italian Society of Preventive and Social Pediatrics

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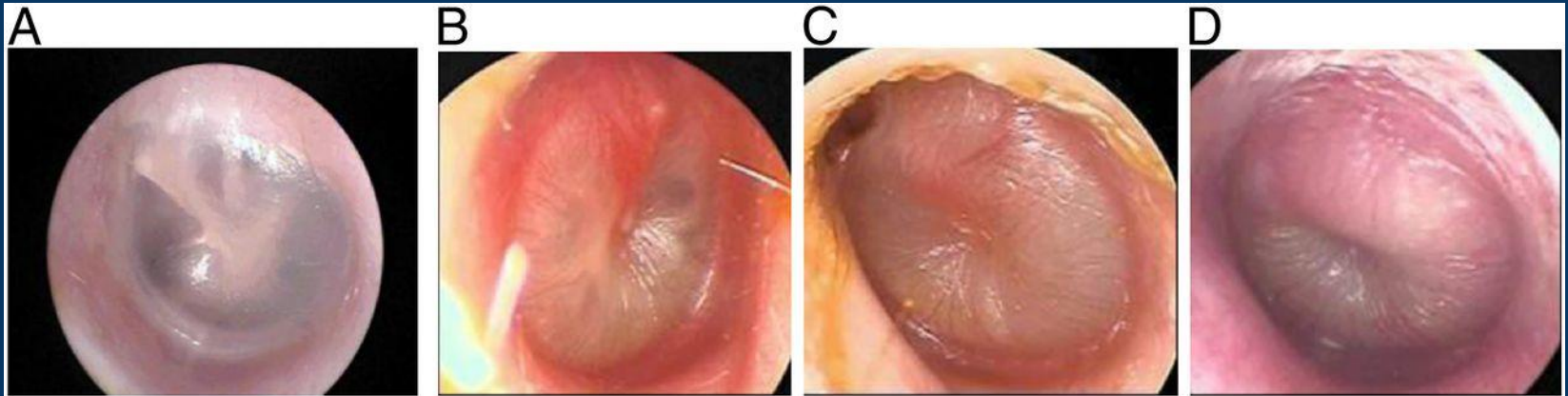
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A, Normal TM. B, TM with mild bulging.



Lieberthal A S et al. Pediatrics 2013;131:e964-e999

AOM Epidemiology in Italy

- 40 Primary Care Pediatricians
- 15176 Children
- Age between 1 and 59 months
- Observation period of about 6 months (between 18/12/2000 and 30/06/2001)
- 1530 OMA episodes in 1236 children
- *S. pneumoniae* isolated from nasopharynx in 23% of the cases
- About 30000 episodes of OMA/100000 children younger than 59 months of age/year
- In Italy, about 120000 AOM/year

INCIDENZA CUMULATIVA DI OTITE MEDIA NEI PRIMI ANNI DI VITA

(Teele DW e Klein JO, J Infect Dis 1989)

età	1 episodio	2 episodi	3 episodi
0-1 anno	62.4%	17.3%	1.0%
0-3 anni	83.9%	46.2%	16.0%
0-5 anni	91.2%	64.5%	29.9%
0-7 anni	93.4%	73.9%	39.2%




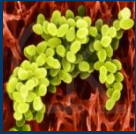
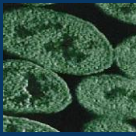

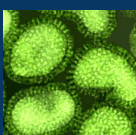
BACTERIAL PATHOGENS ISOLATED FROM CHILDREN WITH ACUTE OTITIS MEDIA

(from Schito GC et al. JAC 1999)

PATHOGEN	PERCENTAGE	
	MEAN	RANGE
<i>S. pneumoniae</i>	38	27-52
<i>H. influenzae</i>	27	16-52
<i>M. catarrhalis</i>	10	2-15
<i>S. pyogenes</i>	3	0-11
<i>S. aureus</i>	2	0-16
others	0	0-24

ISOLATES IN 475 ITALIAN CHILDREN WITH AOM

Marchisio P et al. 8th International Symposium on Recent Advances in Otitis Media.
Fort Lauderdale; June 3-7, 2003

	tympanocentesis [n: 145]	otorrhea [n: 330]
 <i>Streptococcus pneumoniae</i>	28.3 %	13.6 %
 <i>Haemophilus influenzae</i>	22.8 %	32.7 %
 <i>Streptococcus pyogenes</i>	14.5 %	20.9 %
 <i>Staphylococcus aureus</i>	2.7 %	3.3 %
 <i>Moraxella catarrhalis</i>	2.7 %	1.2 %
 Others	3.4 %	5.1 %
 No growth	25.6 %	23.0 %

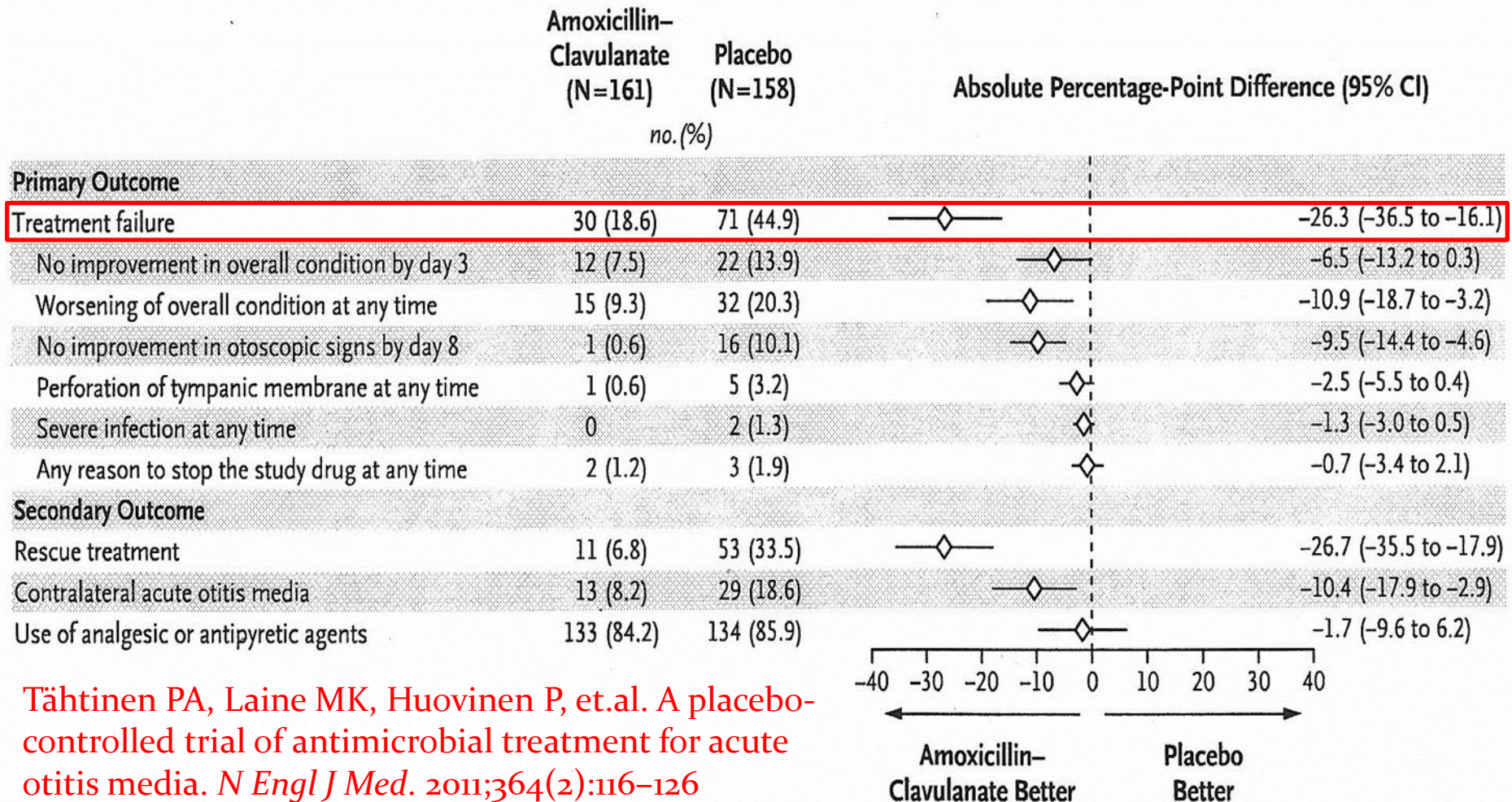
OMA e antibiotici fino agli anni '90

Considerando che:

- L'OMA era malattia di origine batterica nella maggioranza dei casi
- La differenziazione delle forme batteriche da quelle virali era sul piano clinico praticamente impossibile.
- Il mancato trattamento poteva associarsi all'insorgenza di complicanze gravi (mastoidite, infezioni intracraniche)

gli esperti consigliavano l'uso sistematico degli antibiotici sia per la terapia ,sia per la profilassi

Absolute Differences between the Amoxicillin-Clavulanate and Placebo Groups in Cumulative Rates of Primary and Secondary Outcomes



Tähtinen PA, Laine MK, Huovinen P, et.al. A placebo-controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med.* 2011;364(2):116-126

Natural history of AOM

(from Rosenfeld RM. Laryngoscope 2003)

Year and First Author	Country	Age Range	Diagnostic Certainty*	Symptomatic Relief of AOM, n (%)†			Clinical Resolution‡
				24 Hours	2-3 Days	4-7 Days	
1968 Halsted ³⁰	United States	2 m-6 y	Low (o)	—	20/27 (74)	—	21/21 (100)
1970 Laxdal ³¹	Canada	<14 y	Low (o)	—	—	30/48 (62)	22/48 (46)
1972 Howie ³²	United States	<2.5 y	High (o,n)	—	—	116/116 (100)	—
1981 Mygind ³³	Denmark	1 y-10 y	High (e,o)	—	48/77 (62)	53/77 (69)	53/77 (69)
1981 van Buchem ³⁴	Netherlands	2 y-12 y	High (e,o)	29/40 (73)	—	34/38 (89)	—
1986 Thalin ³⁵	Sweden	2 y-15 y	High (e,m)	96/158 (61)	133/158 (84)	156/158 (99)	146/158 (92)
1991 Appleman ³⁶	Netherlands	6 m-12 y	High (e,o)	—	44/54 (81)	—	—
1991 Burke ³⁷	England	3 y-10 y	Low (o)	61/117 (52)	—	85/114 (75)	101/118 (86)
1991 Kaleida ³⁸	United States	7 m-12 y	High (p,t)	—	454/492 (92)	—	—
2000 Damoiseaux ⁴⁰	Netherlands	6 m-2 y	Low (o)	—	—	34/123 (28)	36/120 (30)
2001 Jacobs ⁴¹	United States	18 m-6 y	Low (o)	—	—	26/38 (68)	—
Random effects meta-analysis							
Combined sample size				315	808	712	542
Estimate of combined rate, (95% CI)				.61 (.50, .72)	.80 (.69, .90)	.74 (.64, .85)	.70 (.49, .92)
Test for heterogeneity, Q statistic				6.1, df = 2	45.9, df = 4	417.3, df = 7	236.1, df = 5
Test for heterogeneity, P value				.048	<.001	<.001	<.001

*Studies with high certainty confirmed diagnosis of AOM with tympanometry (t), pneumatic otoscopy (p), otomicroscopy (m), needle aspiration (n), or referral to an ear, nose, and throat specialist (e); low-certainty studies relied on nonpneumatic otoscopy (o) and clinical symptoms.

†Symptomatic relief implies absence of fever and relief of otalgia; some authors^{34,35,37} did not mention fever or considered it a separate endpoint.

‡Absence of all presenting signs and symptoms of middle ear infection within 7 to 14 days after therapy started; some authors further required an improved appearance of the tympanic membrane.^{30,40}

Antibiotics for acute otitis media in children (Review)

Venekamp RP, Sanders S, Glasziou PP, Del Mar CB, Rovers MM



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This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in *The Cochrane Library* 2013, Issue 1

<http://www.thecochranelibrary.com>

- Antibiotic treatment led to a statistically significant reduction of children with AOM experiencing pain at 2 to 7 days compared with placebo but since most children (82%) settle spontaneously, about 20 children must be treated to prevent one suffering from ear pain at 2 to 7 days.
- Additionally, antibiotic treatment led to a statistically significant reduction of tympanic membrane perforations (NNTB 33) and contralateral AOM episodes (NNTB 11).
- These benefits must be weighed against the possible harms: for every 14 children treated with antibiotics, one child experienced an adverse event (such as vomiting, diarrhoea or rash) that would not have occurred if antibiotics had been withheld.
- Antibiotics appear to be most useful in children under two years of age with bilateral AOM, or with both AOM and otorrhoea.

Treatment strategies for uncomplicated AOM

(from Marchisio P, et al. Int J Pediatr Otolaryngol 2010)

Diagnosis	Certain			
	Bilateral ^b		Monolateral ^b	
	Severe ^c	Mild ^c	Severe ^c	Mild ^c
Age <6 months	Immediate antibiotics	Immediate antibiotics	Immediate antibiotics	Immediate antibiotics
Age 6–24 months	Immediate antibiotics	Immediate antibiotics	Immediate antibiotics	Watchful waiting
Age >24 months	Immediate antibiotics	Watchful waiting	Watchful waiting	Watchful waiting

^a Absence of otorrhea, intracranial complications or a history of recurrences.

^b Laterality.

^c Severity.

Antibiotic choices for AOM

(from Marchisio et al. Int J Pediatr Otolaryngol. 2010)

Episode characteristics	Recommended	Alternative
Mild symptoms No otorrhea No recent recurrences No risk factors ^a	Amoxicillin (50 mg/kg/day, 2-3 doses)	Cefaclor (40-50mg/kg/day, 2 doses)
Severe symptoms Otorrhea Recent recurrences Risk factors ^a	Amoxicillin + clavulanic acid (80-90 ^b mg/kg/day, 2-3 doses)	Cefpodoxime proxetil (8 mg/kg/day, 2 doses), cefuroxime axetil (30 mg/kg/day, 2 doses)

^a Risk factors for bacterial resistance: age <3 years, day-care attendance, older siblings, recent antibiotic therapy (<1 month), no PCV-7.

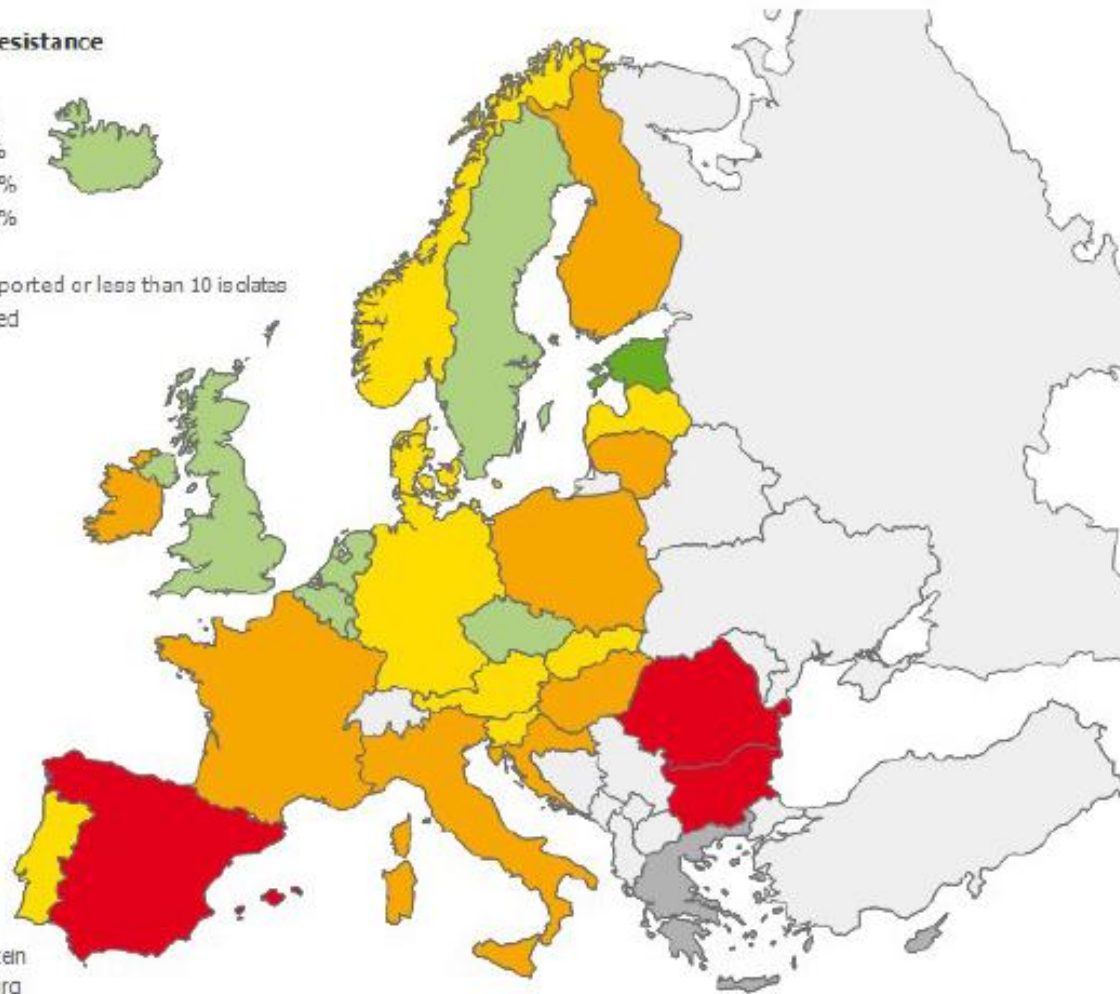
^b Amoxicillin referred dosage.

Proportion of Penicillins Resistant (R+I) *Streptococcus pneumoniae* Isolates in Participating Countries in 2012

Percentage resistance

- < 1%
- 1 to < 5%
- 5 to < 10%
- 10 to < 25%
- 25 to < 50%
- ≥ 50%
- No data reported or less than 10 isolates
- Not included

- Liechtenstein
- Luxembourg
- Malta



(C) ECDC/Durdee/TESSy

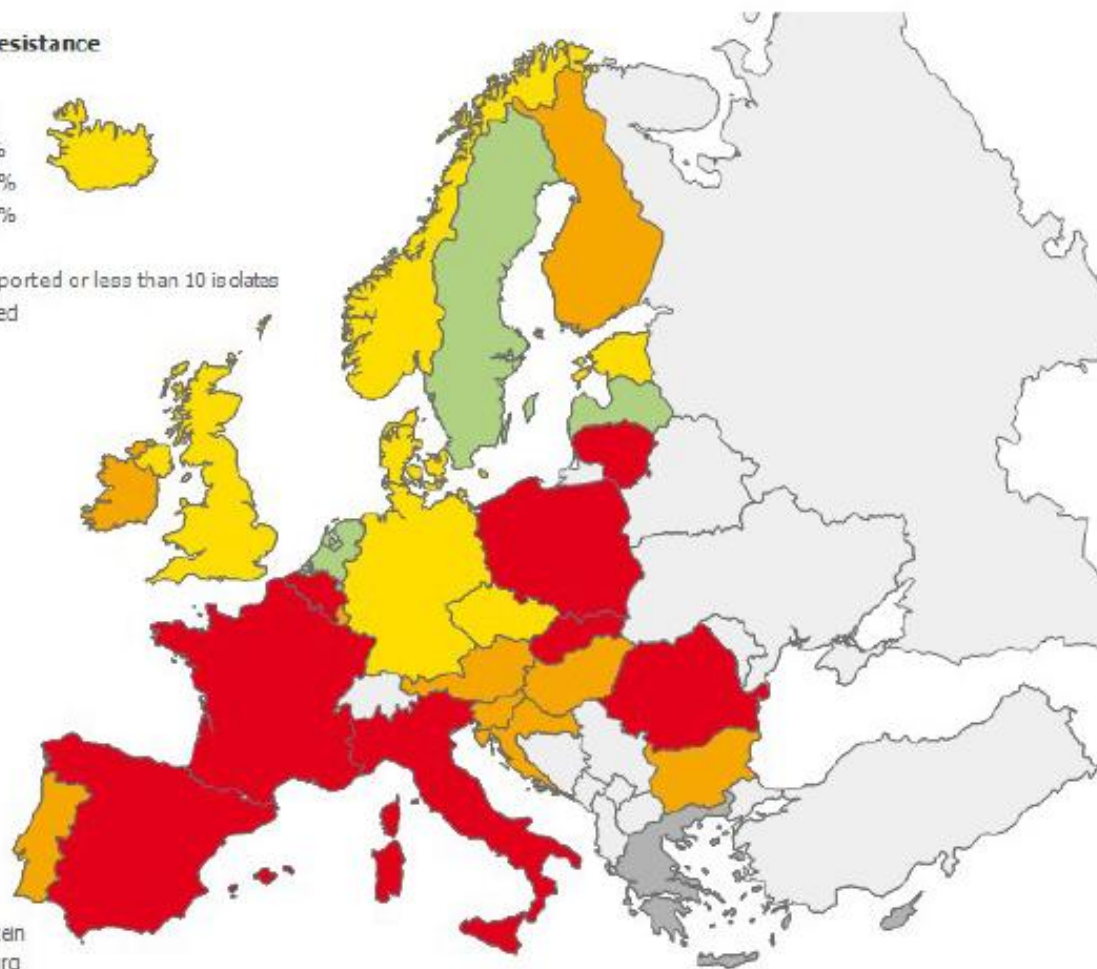
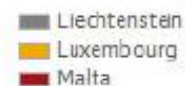
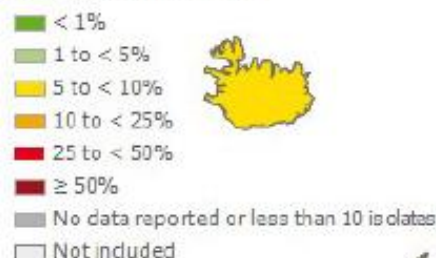
Organism	Antimicrobial agent	PK/PD breakpoint ($\mu\text{g/mL}$) ^b	No. tested	% S at PK/PD breakpoint
<i>S. pneumoniae</i>	Amoxicillin	≤ 2	8882	95.1
	Amoxicillin/ clavulanate	≤ 2	8882	95.5
	Cefprozil	≤ 1	8992	78.1
	Cefuroxime	≤ 1	8882	78.6
	Cefixime	≤ 1	8882	69.2
	Cefdinir	≤ 0.5	6512	76.5
	Cefditoren	≤ 0.25	207	66.7
	Cefpodoxime	≤ 0.5	207	63.3
	<i>H. influenzae</i>	Amoxicillin	≤ 2	8523
Amoxicillin/ clavulanate		≤ 2	8523	98.1
Cefprozil		≤ 1	8523	22.3
Cefuroxime		≤ 1	8523	83.6
Cefixime		≤ 1	8523	99.8
Cefdinir		≤ 0.5	5651	92.0
Cefditoren		≤ 0.25	100	100.0
Cefpodoxime		≤ 0.5	100	99.0
<i>M. catarrhalis</i>		Amoxicillin	≤ 2	874
	Amoxicillin/ clavulanate	≤ 2	874	100.0
	Cefprozil	≤ 1	874	16.0
	Cefuroxime	≤ 1	874	61.9
	Cefixime	≤ 1	874	100.0
	Cefdinir	≤ 0.5	421	100.0
	Cefditoren	≤ 0.25	49	96.0
	Cefpodoxime	≤ 0.5	49	94.0

Calcolo delle probabilità che una dose standard di antibiotico rimanga sopra la MIC del patogeno infettante per almeno il 40% del tempo compreso tra le dosi

(da Block S: et al. Clin Microbiol Infect Dis 2007)

Proportion of Macrolides Resistant (R+I) *Streptococcus pneumoniae* Isolates in Participating Countries in 2012

Percentage resistance

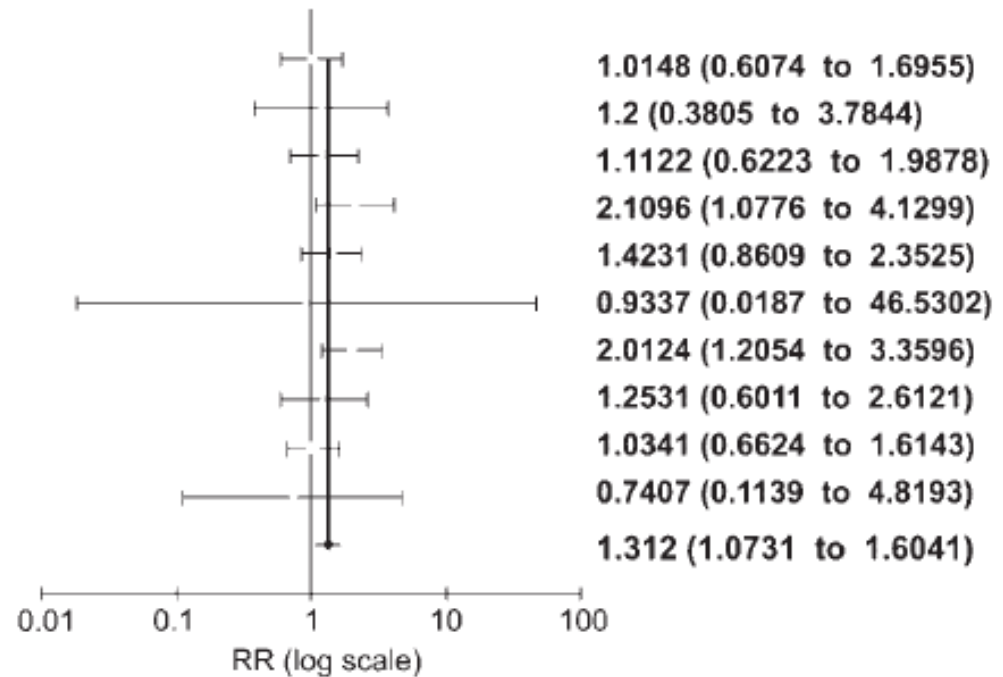


(C) ECDC/Durdes/TESSy

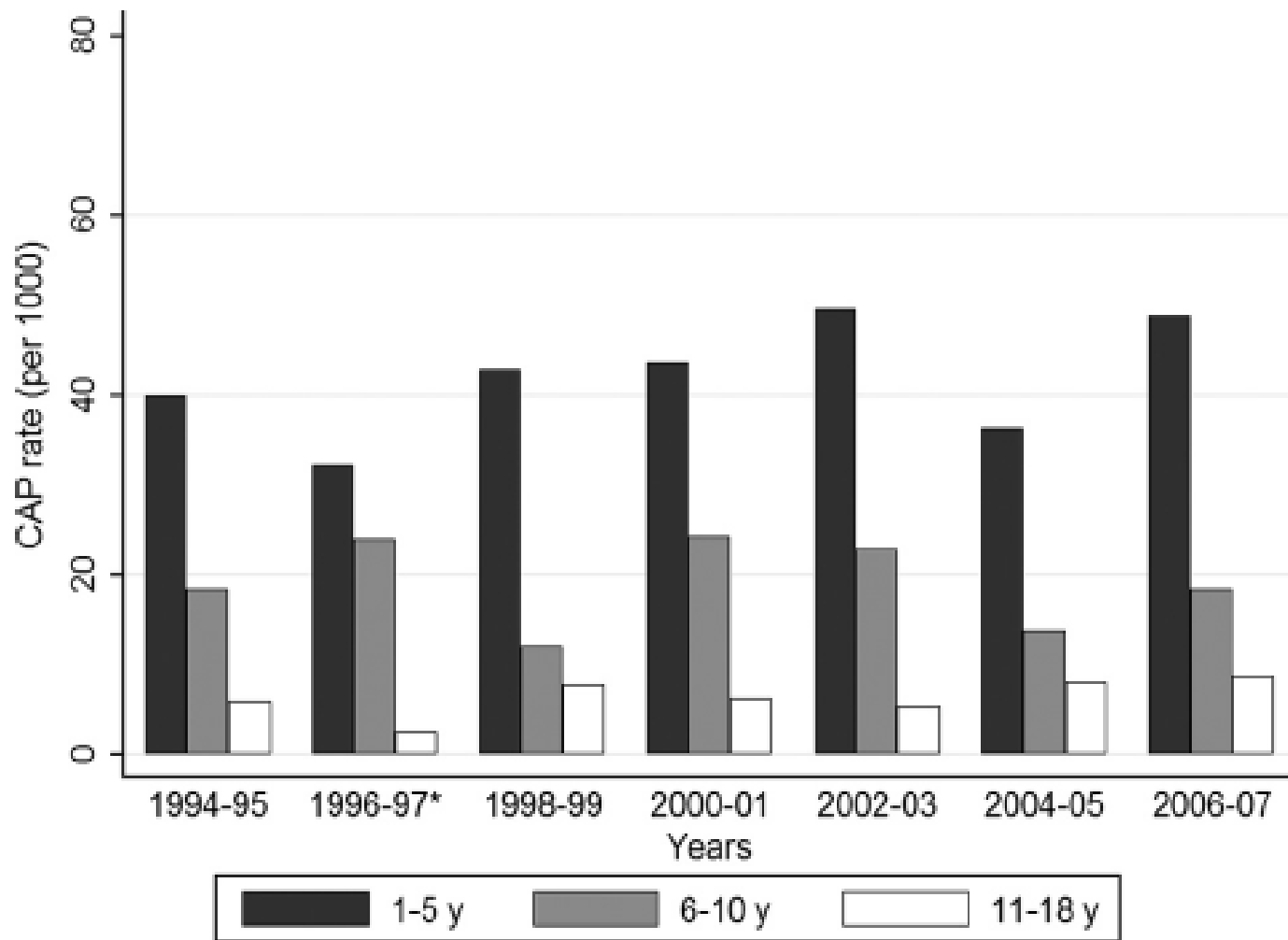
Studies comparing amoxicillin and macrolides in the treatment of AOM

(Courter JD, et al. Ann Pharmacother. 2010)

Arguedas et al	2005	25/155	24/151
Aspin et al	1994	6/86	5/86
Block et al	2003	21/160	19/161
Dagan et al	2000	22/73	10/70
Dunne et al	2003	32/185	22/181
Guyen et al	2006	0/90	0/84
Hoberman et al	2005	39/204	19/200
McCarthy et al	1993	14/135	12/145
McLinn et al	1996	35/280	33/273
Pukander et al	1993	2/27	2/20
META-ANALYSIS:		196/1395	146/1371



GLI ANTIBIOTICI E LA POLMONITE



Two-yearly community-acquired pneumonia rates by age group. *Estimate for the 11- to 18-year-old age group contains fewer than 30 unadjusted records.

ETIOLOGY OF COMMUNITY-ACQUIRED PNEUMONIA IN HOSPITALIZED CHILDREN

AGE (Years)	N°	VIRAL ETIOLOGY	BACTERIAL ETIOLOGY	MIXED ETIOLOGY	ALL*
<2	108	80	47	34	93
2-5	84	58	56	33	81
>5	62	37	58	19	76
TOTAL	254	62	53	30	85

*Total with detected etiology. Results expressed as percentages of patients. Adapted from Juven et al. *Pediatr Infect Dis J* 2000

Episodes of Rx-confirmed CAP with viruses in children aged 0-12 months

(Esposito S et al., Influenza Other Respir Viruses 2013)

VIRUS	2007-08		2008-09		2009-10		Total episodes	
	No. (%) *	Coinf. No. (%) ^	No. (%) *	Coinf. No. (%) ^	No. (%) *	Coinf. No. (%) ^	No. (%) *	Coinf. No. (%) ^
RSV	14 (33.3)	3 (21.4)	26 (44.8)	13 (50.0)	22 (22.2)	10 (45.4)	62 (36.8)	26 (41.9)
Rhinovirus	17 (40.4)	11 (64.7)	15 (25.8)	10 (66.6)	15 (15.1)	7 (87.5)	47 (28.1)	28 (59.5)
Bocavirus	7 (16.6)	6 (85.7)	2 (3,4)	2 (100)	5 (5,0)	5 (100)	14 (10.1)	13 (92.8)
Influenza	2 (4.7)	1 (50.0)	5 (8.6)	1 (20.0)	3 (3.0)	2 (66.6)	10 (7.2)	4 (40.0)
Metapneu.	10 (23.8)	3 (30.0)	5(8.6)	1 (20.0)	2 (2.0)	1 (50.0)	17 (12.2)	5 (29.4)
Coronavirus	2 (4.7)	2 (100)	0 (0.0)	0	5 (5.0)	5 (100)	7 (5.0)	7 (100)
Parainfluenza (1-4)	0 (0)	0	1 (1.7)	0 (0.0)	1 (1.0)	1 (100)	2 (1.4)	1 (50.0)
Adenovirus	0 (0)	0	0 (0.0)	0 (0.0)	1 (1.0)	1 (100)	1 (0.7)	1 (100)
Episodes with viruses	38/42 (90.4)	12/38 (31.5)	43/58 (74.1)	16/43 (37.2)	37/39 (94.8)	15/37 (40.5)	118/139 (84.9)	43/118 (36.4)

•% among the total number of CAP investigated;

•^ % of the total number of infections in which the virus was identified

Episodes of Rx-confirmed CAP with viruses in children aged 13-36 months

(Esposito S et al., Influenza Other Respir Viruses 2013)

VIRUS	2007-08		2008-09		2009-10		Total episodes	
	No. (%) *	Coinf. No.(%)^	No. (%)*	Coinf. No.(%)^	No. (%)*	Coinf. No.(%)^	No. (%)*	Coinf. No.(%)^
RSV	35 (41.1)	16	58 (38.6)	21	30 (30.3)	10	123 (36.8)	47
Rhinovirus	26 (30.5)	15	44 (29.3)	21	24 (24.2)	7	94 (28.1)	43
Bocavirus	12 (14.1)	9	15 (10.0)	11	12 (12.1)	6	39 (11.6)	26
Influenza	4 (4.7)	1	16 (10.6)	6	10 (10.1)	1	39 (11.6)	8
Metapneumo	12 (14.1)	5	13(8.6)	4	6 (6.1)	0	31 (9.2)	9
Coronavirus	3 (3.5)	2	7 (5.8)	3	5 (5.0)	4	15 (4.5)	9
Parainfluenza (1-4)	0 (0)	0	4 (2.6)	2	6 (6.1)	2	10 (3.0)	4
Adenovirus	1 (1.1)	0	4 (2.6)	3	2 (2.0)	1	7 (2.1)	4
Episodes with viruses	68/85 (80.0)	20/68 (29.4)	122/150 (81.3)	36/122 (29.5)	78/99 (78.8)	14/78 (17.9)	268/334 (80.2)	70/268 (26.1)

•% among the total number of CAP investigated;

•^ % of the total number of infections in which the single virus was identified

Principal bacteria causing childhood CAP by age

(from Principi N, Esposito S, Thorax 2011)

Bacteria	Age group			
	Birth to 1 month	1 to 3 months	3 months to 5 years	5 to 18 years
<i>Streptococcus pneumoniae</i>	+	+++	++++	+++
<i>Haemophilus influenzae</i> *	+	+	+	±
<i>Streptococcus pyogenes</i>		+	+	+
<i>Staphylococcus aureus</i>	++	++	+	+
<i>Streptococcus agalactiae</i>	+++	+		
<i>Escherichia coli</i>	++	+		
<i>Mycoplasma pneumoniae</i>		+	++	++++
<i>Chlamydia pneumoniae</i>		+	+	++
<i>Chlamydia trachomatis</i>	+	++		
<i>Bordetella pertussis</i>	±	++	+	+

BACTERIAL vs VIRAL PNEUMONIA

Virkki et al. Thorax 2002

N=215	Bacterial	Viral
	%	%
Alveolar infiltrates	71	29
Interstitial infiltrates	48	52
WBC >15 x 10⁹/l	63	37
ESR > 30 mm/h	64	36
CRP > 40 mg/l	70	30
CRP > 80 mg/l	75	25

Approccio terapeutico alla CAP

Considerate le difficoltà di differenziare le forme batteriche dalle virali, si considera accettabile il trattamento sistematico di ogni caso di CAP certa.

Eccezioni possono essere fatte per:

- i casi lievi che possono non essere ospedalizzati
- i casi che si manifestano in periodo con alta epidemiologia di virosi respiratorie

VALUTAZIONE DI GRAVITA' DELLA CAP DEL BAMBINO

- Temperatura corporea $> 39^{\circ}\text{C}$
- Frequenza respiratoria > 30 o > 50 atti/min nel bambino grande o nel lattante, rispettivamente
- Rientramenti intercostali di grado medio-alto o dispnea grave
- Alitamento delle pinne nasali
- Cianosi
- Apnea intermittente
- Difficolta' ad alimentarsi o segni di disidratazione
- Versamento pleurico esteso
- Segni di sepsi

HOW TO TREAT PEDIATRIC CAP

The choice of empirical antibiotic treatment for paediatric CAP should be based on **diagnostic algorithms that begin with age of the patient**, and then consider epidemiological and clinical factors (with particular attention on **severity of the disease**), vaccination status, PK/PD characteristics and finally the results of laboratory tests and chest radiography

Antibiotic treatment of CAP in neonates and younger children (I)

(from Esposito S, et al. *Pediatr Infect Dis J* 2012)

Age Group	Antibiotic of Choice	
	Recommended Treatment	Alternative Treatment
Birth to 1 month*	Ampicillin iv and aminoglycoside iv (ie, gentamicin) (dose depends on weight and gestational age)	Cefotaxime iv (dose depends on weight and gestational age)
1–3 months*	<p>Oral amoxicillin or ampicillin iv (50–90 mg/kg/d in 2–3 doses) for 7–10 days</p> <p>†Erythromycin (40 mg/kg/day in 3–4 divided doses) or oral or parenteral clarithromycin (4–8 mg/kg/d iv in 2 divided doses or 15 mg/kg/d orally in 2 divided doses) for 10–14 days or oral azithromycin (10 mg/kg/d in 1 dose for 3 days or 1 dose of 10 mg/kg/d and then 5 mg/kg/d for 4 days)*</p>	<p>†Erythromycin (40 mg/kg/d in 3–4 divided doses) oral or parenteral</p> <p>Oral amoxicillin/clavulanate (amoxicillin component: 50–90 mg/kg/d in 2 doses) for 7–10 days (5–7 days may be adequate)</p> <p>Benzympenicillin iv 200,000 units/kg/d in 4–6 doses Ceftriaxone iv (50 mg/kg once a day) or cefotaxime iv (100–150 mg/kg/d in 3 divided doses)</p>

*In infants aged <6 weeks, treatment with clarithromycin or azithromycin should be recommended because there have been reports of hypertrophic pyloric stenosis as well as torsade de pointe in infants receiving erythromycin.

† In cases of *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, *Chlamydia pneumoniae* or *Bordetella pertussis*.

Antibiotic treatment in older infants, toddlers and older children (II)

(from Esposito S, et al. *Pediatr Infect Dis J* 2012)

Age Group	Antibiotic of Choice	
	Recommended Treatment	Alternative Treatment
3 months to 5 years	Oral amoxicillin or ampicillin iv (50–90 mg/kg/d in 2–3 doses) for 7–10 days (5–7 days may be adequate)	Oral amoxicillin/clavulanate (amoxicillin component: 50–90 mg/kg/d in 2 doses) for 7–10 days (5–7 days may be adequate) Oral cefuroxime axetil (30 mg/kg/d in 2 divided doses) Benzylpenicillin iv 200,000 units/kg/d in 4–6 doses Ceftriaxone iv (50 mg/kg once a day) or cefotaxime iv (100–150 mg/kg/d in 3 divided doses) ‡Oral cephalaxine or iv cloxacillin, cephazoline or vancomycin†Erythromycin oral or parenteral (40 mg/kg/d in 3–4 divided doses), or oral or parenteral clarithromycin (4–8 mg/kg/d iv in 2 divided doses or 15 mg/kg/d orally in 2 divided doses) for 10–14 days, or oral azithromycin (10 mg/kg/d in 1 dose for 3 days or 1 dose of 10 mg/kg/d and then 5 mg/kg/d for 4 days)
5–18 years	Oral amoxicillin or ampicillin iv (50–90 mg/kg/d in 2–3 doses) for 7–10 days (5–7 days may be adequate) †Erythromycin oral or parenteral (40 mg/kg/d in 3–4 divided doses), or oral or parenteral clarithromycin (4–8 mg/kg/day iv in 2 divided doses or 15 mg/kg/d orally in 2 divided doses) for 10–14 days, or oral azithromycin (10 mg/kg/d in 1 dose for 3 days or 1 dose of 10 mg/kg/d and then 5 mg/kg/d for 4 days)	Benzylpenicillin iv 200,000 units/kg/d in 4–6 doses Ceftriaxone iv (50 mg/kg once a day) or cefotaxime iv (100–150 mg/kg/d in 3 divided doses)‡Oral cephalaxine or iv cloxacillin, cephazoline or vancomycin

† In cases of *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, *Chlamydia pneumoniae* or *Bordetella pertussis*.

‡ Staphylococcal pneumonia is unusual; however, if cultures of blood or pleural fluid grow *Staphylococcus aureus*, oxacillin or (in areas where methicillin-resistant *S. aureus* is a reasonable possibility) vancomycin should be added.

RUOLO DELLA RESISTENZA DI SP ALLA PENICILLINA SUL DECORSO DELLA CAP

(Da Cardoso MRA et al., Arch Dis Child 2008)

Treatment outcome	Susceptible	Intermediate	Resistant	Total	P
All children (n = 240)					0.75*
Success	94 (78)	49 (77)	46 (82)	189 (79)	
Failure	26 (22)	15 (23)	10 (18)	51 (21)	
Children without pleural effusion on admission (n = 111)					0.87*
Success	48 (86)	29 (91)	20 (87)	97 (87)	
Failure	8 (14)	3 (9)	3 (13)	14 (13)	
Children with pleural effusion on admission (n = 129)					0.37*
Success	46 (72)	20 (63)	26 (79)	92 (71)	
Failure	18 (28)	12 (37)	7 (21)	37 (29)	

*Fisher's exact test.

Major studies of the prevalence of ML-resistant *M. pneumoniae* in different countries and at different times

(from Principi N, Esposito S J Antimicrob Chemother 2013)

Authors	Country	Population	Main findings
Liu <i>et al.</i> ¹¹	China	paediatric patients with respiratory infection	from 2005 to 2008, 44/53 isolates (83%) were resistant to erythromycin, azithromycin and clarithromycin
Xin <i>et al.</i> ¹²	China	paediatric patients with respiratory infection	from 2003 to 2006, 46/50 strains (92%) were ML resistant
Morozumi <i>et al.</i> ¹³	Japan	paediatric patients with CAP	from 2002 to 2006, 50/380 strains (13.2%) were ML-resistant
Yamada <i>et al.</i> ¹⁷	USA	paediatric patients with <i>M. pneumoniae</i> infection	during the period 2007–10, ML resistance was 8.2%
Dumke <i>et al.</i> ¹⁹	Germany	adults with CAP	between 2003 and 2008, ML resistance was 3.0%
Peuchant <i>et al.</i> ²⁰	France	<i>M. pneumoniae</i> -positive specimens	before 2005, no resistance was found; among 51 samples collected between 2005 and 2007, 5 (9.8%) had a resistant genotype
Spuesens <i>et al.</i> ²¹	The Netherlands	<i>M. pneumoniae</i> -positive specimens	between 1997 and 2008, no ML-resistant strains out of 114
Chironna <i>et al.</i> ²²	Italy	paediatric patients with CAP	in 2010, 11/43 strains (25.6%) were ML resistant
Averbuch <i>et al.</i> ²³	Israel	adults and children with CAP	9/30 strains (30.0%) in 2010 had a resistant genotype; in 2011, 176/202 (87.1%) were ML resistant

CAP, community-acquired pneumonia; ML, macrolides.

Patient	Gender	Age	Date of sample collection	Macrolide susceptibility (mutation) ^a	Subtype	MPN528a ^b
1011	M	7 years	02/01/2010	S	1	A
1066	M	6 years	01/02/2010	S	1	A
1256	M	7 years	13/04/2010	S	1	A
1328	M	13 years	19/05/2010	R (A2064G)	1	A
1331	M	4 years	20/05/2010	S	1	A
1339	F	8 years	22/05/2010	S	1	A
1348	F	13 years	25/05/2010	S	2	C
1360	F	15 years	31/05/2010	S	1	A
1387	F	10 years	14/06/2010	S	2	C
1473	F	8 years	19/06/2010	R (A2063G)	1	A
1406	M	14 years	21/06/2010	S	1	A
1403	M	5 years	21/06/2010	S	1	A
1421	F	7 years	28/06/2010	S ^c	2	C
1421/II			05/07/2010	S ^c	—	—
1421/III			09/07/2010	R (A2063G) ^c	—	—
1425	F	6 years	28/06/2010	S	1	A
1435	F	5 years	01/07/2010	S	1	A
1444	F	5 years	03/07/2010	S	ND	ND
1445	F	4 years	03/07/2010	S	1	A
1454	F	16 years	06/07/2010	S	1	A
1458	M	18 months	07/07/2010	S	1	A
1462	M	7 years	09/07/2010	R (A2064G)	1	A
1464	M	7 years	10/07/2010	S	1	A
1466	M	8 years	12/07/2010	R (A2064G)	1	A
1480	F	4 years	14/07/2010	S	2	C
1481	M	2 years	15/07/2010	R (A2063G)	ND	ND
1489	M	10 years	16/07/2010	S	1	A
1487	F	7 years	16/07/2010	S	2	C
1488	F	16 years	16/07/2010	S ^c	1	A
1488/II			28/07/2010	S ^c	—	—
1488/III			06/09/2010	R (A2063G) ^c	—	—
1513	F	7 years	27/07/2010	S	1	A
1515	M	4 years	27/07/2010	S	1	A
1516	F	10 years	28/07/2010	S	1	A
1522	M	8 years	29/07/2010	S	1	A
1524	M	3 years	29/07/2010	R (A2063G)	1	A
1529	F	13 years	30/07/2010	S	1	A
1536	F	4 years	02/08/2010	S	2	C
1537	M	2 years	02/08/2010	R (A2063G)	1	A
1547	M	11 years	07/08/2010	S	1	A
1558	F	12 years	12/08/2010	S ^c	1	A
1558/II			14/09/2010	R (A2063G) ^c	—	—
1561	M	15 months	13/08/2010	R (A2064G)	ND	ND
1574	M	3 years	20/08/2010	S	1	A
1603	M	6 years	02/09/2010	S	1	A
1606	F	2 years	03/09/2010	S	2	C
1607	M	3 years	03/09/2010	S	1	A
1631	F	13 years	10/09/2010	S	1	A

Resistance of *M. pneumoniae* to macrolides: an Italian study

(from Chironna M, et al. J Antimicrob Chemother 2011)

Comparison of children with CAP and macrolide-resistant and macrolide-sensitive *M. pneumoniae* infection (III)

(from Cardinale F, et al. J Clin Microbiol 2013)

	Result		P value
	Macrolide-resistant <i>M. pneumoniae</i> (n = 8)	Macrolide-sensitive <i>M. pneumoniae</i> (n = 38)	
Demographic and finding			
Outcomes during macrolide treatment			
Total no. of febrile days, median (range)	7 (3–15)	4 (2–10)	0.36
No. of febrile days during macrolide administration, median (range)	4 (1–10)	1.5 (1–3)	0.03
No. of days with cough during macrolide administration, median (range)	5 (1–14)	2 (1–4)	0.04
No. of patients with a febrile period 48 h after macrolide administration (%)	7 (87.5)	2 (5.3)	<0.0001
No. (%) of patients with a change of prescription after macrolide administration	7 (87.5)	10 (26.3)	0.002
Median duration of hospitalization, days (range)	10 (2–32)	4 (2–20)	0.03
Median duration of antibiotic therapy, days (range)	28 (15–46)	14 (10–21)	0.02

Number and Cure Rate at the Test-of-Cure-Visit of Clinically Evaluable Children With Important Lower Respiratory Microorganisms Isolated From Specimens Obtained at Enrollment

Age Group	Pathogen	Source of Specimen	Levofloxacin		Comparator	
			N*	% Cured	N*	% Cured
Age, ≥0.5 to <5 yr						
	<i>Mycoplasma pneumoniae</i>	Serology	66	89	18	83
	<i>Chlamydophila pneumoniae</i>	Serology	1	100	3	67
	<i>Streptococcus pneumoniae</i>	Blood	2	100	2 [‡]	50
		Sputum	0	—	0	—
		Other	5 [†]	60	1 [‡]	0
	<i>Moraxella catarrhalis</i>	Sputum	2	0	0	—
	<i>Haemophilus influenzae</i>	Sputum	3	67	1	100
Age, ≥5 to 16 yr						
	<i>Mycoplasma pneumoniae</i>	Serology	63	100	21	95
	<i>Chlamydophila pneumoniae</i>	Serology	2	100	1	100
	<i>Streptococcus pneumoniae</i>	Blood	3	100	1	100
		Sputum	4	100	1	100
	<i>Streptococcus pyogenes</i>	Sputum	2	100	0	—
	<i>Klebsiella pneumoniae</i>	Sputum	1	100	0	—
	<i>Haemophilus spp</i>	Sputum	1	100	0	—
	<i>Haemophilus influenzae</i>	Sputum	0	—	2	100

*Includes children clinically evaluable at the test-of-cure visit as per protocol.

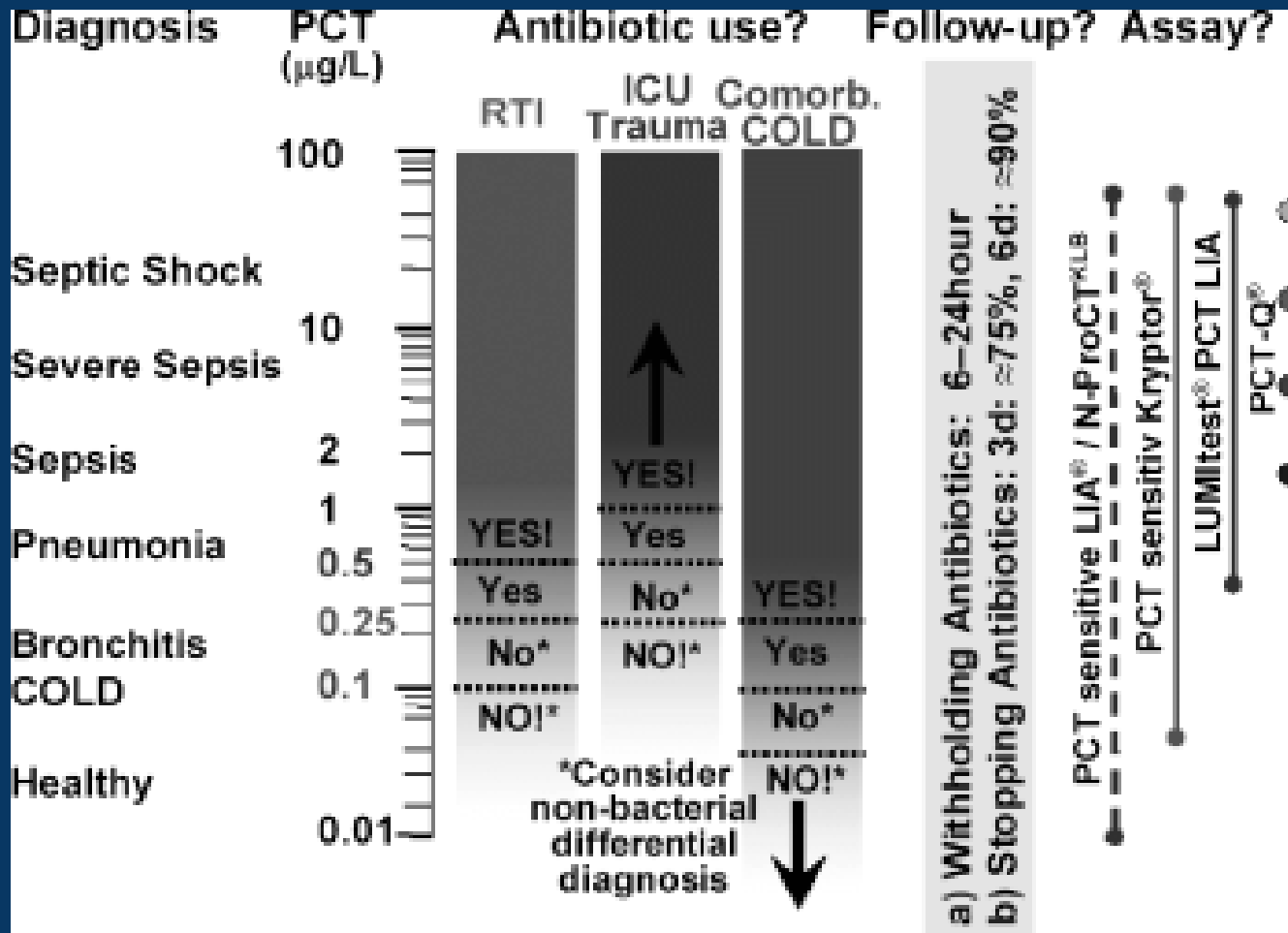
[†]Sputum was collected from infants through nasopharyngeal (2) or oropharyngeal (3) aspiration; see Table 4 for details.

[‡]Includes 1 infant who had a blood taken for culture and a sputum collected through nasopharyngeal aspiration.

From Bradley J, et al. *Pediatr Infect Dis J* 2007

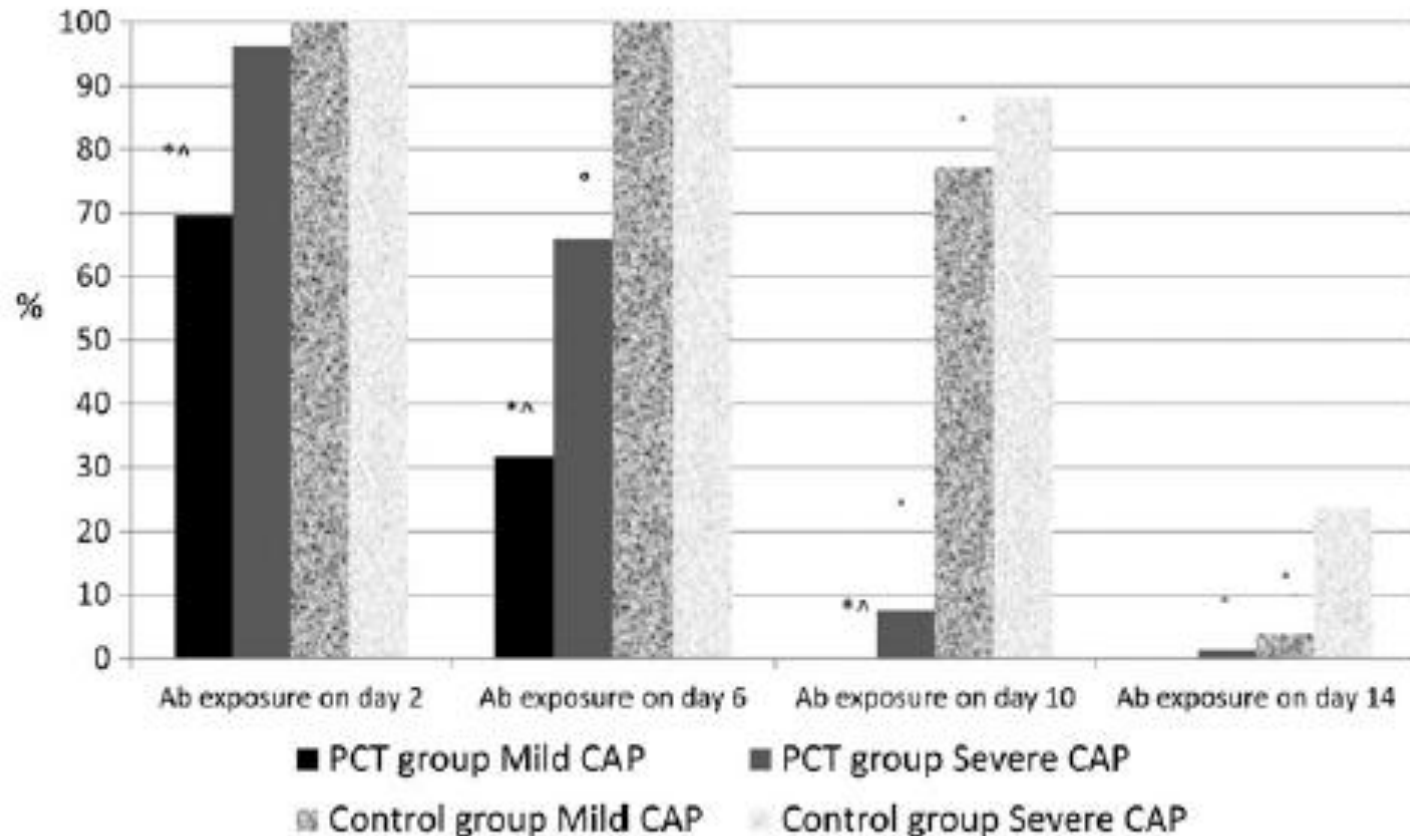
USO DELLA PROCALCITONINA NELLA GESTIONE DELLA POLMONITE (I)

(da Muller e Prat. Clin Microbiol Infect 2006)



Antibiotic exposure by treatment group and CAP severity

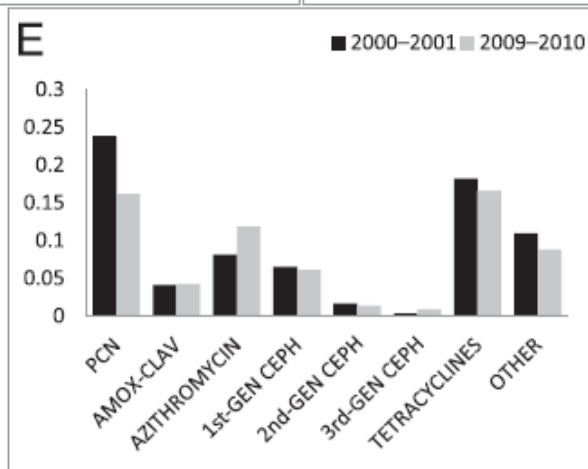
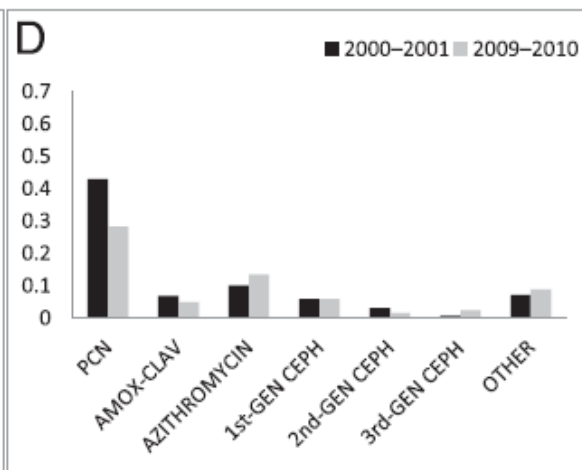
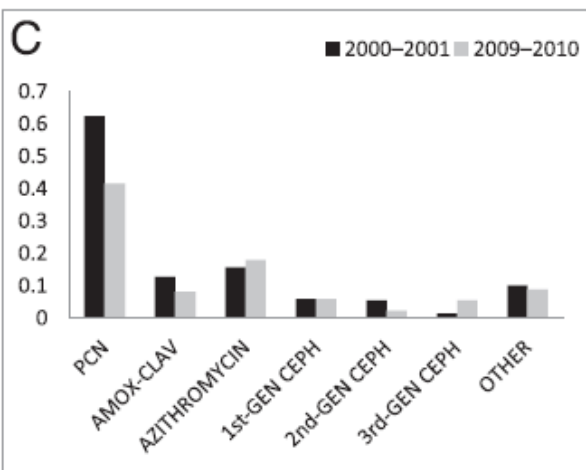
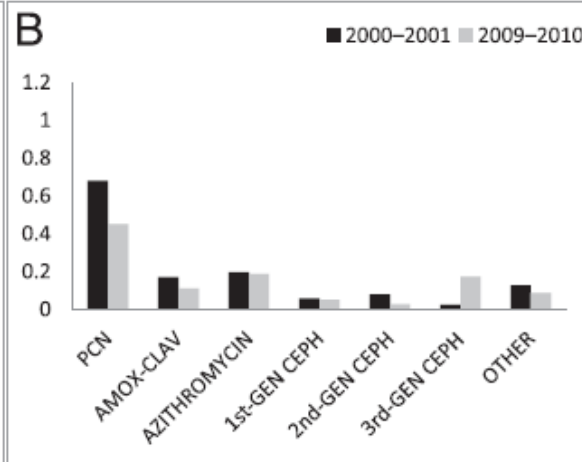
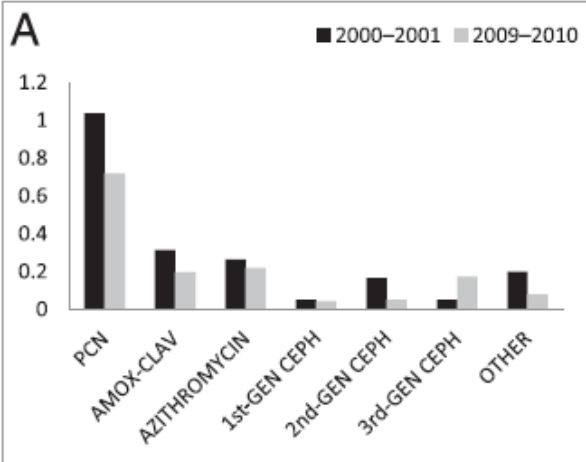
(from Esposito S, et al. Resp Med 2011)



*p<0.05 vs PCT group Severe CAP; ^p<0.05 vs Control group Mild CAP; *p<0.05 vs Control group Severe CAP

E' SEMPRE NECESSARIO ESEGUIRE LA RADIOGRAFIA DEL TORACE PER PORRE DIAGNOSI DI CAP?

- No nei casi di lieve o media gravità con sintomatologia clinica ben espressa
- Sì nei casi dubbi, per evitare inutili trattamenti antibiotici
- Sì nei casi gravi, per definire la situazione di partenza della malattia
- Sì nei casi inseriti in protocolli di ricerca per definire i rapporti esistenti tra le variabili in studio e i tipi di alterazione polmonare



Distribution of antibiotic classes among health plans, 2000-2001 and 2009-2010 for children:

A 3 to 24 months,
 B 2 to < 4 years,
 C 4 to < 6 years,
 D 6 to < 12 years,
 E 12 to < 18 years.

Changes were statistically significant for all the antibiotic classes ($P < 0.05$).

(from Vaz LE, et al. Pediatrics 2014)

Distribution of diagnosis linked with 3rd generation cephalosporins dispensing at each health plan in 2009-2010, (from Vaz LE, et al. Pediatrics 2014)

Age Group	Plan	OM (%)	Pneumonia (%)	Pharyngitis (%)	Sinusitis (%)	Other Bacterial Infections (%)	Presumed Viral RTI (%)	All Other (%) ^a
3 to <24 mo								
	A	76	2	1	3	3	1	13
	B	81	3	1	4	2	0 ^b	9
	C	70	6	1	4	1	3	14
2 to <4 y								
	A	60	4	5	7	4	3	16
	B	68	6	3	8	3	0 ^b	11
	C	57	7	5	8	3	4	16
4 to <6 y								
	A	47	5	11	11	8	2	15
	B	61	5	4	12	6	0 ^b	12
	C	46	7	10	12	3	5	16
6 to <12 y								
	A	33	4	16	15	8	2	20
	B	51	5	5	14	8	0 ^b	15
	C	31	7	15	16	5	4	21
12 to <18 y								
	A	14	4	14	25	12	3	27
	B ^c	27	NA ^b	6	20	9	0 ^b	29
	C	19	5	14	28	5	3	26

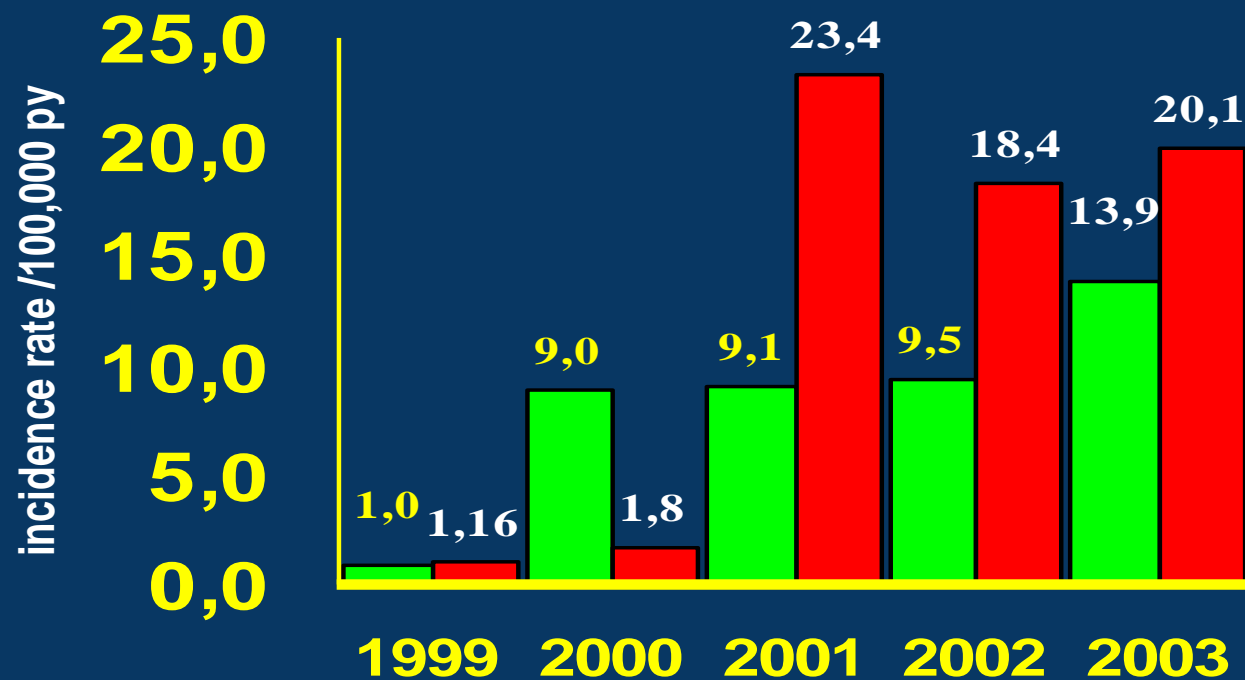
NA, not applicable.

^a Includes dispensings unlinked to diagnoses.

^b Less than 0.5%.

^c Due to an antibiotic rate <0.5% among multiple diagnoses in a combined category, total percentage may not add to 100%.

INCIDENCE RATES OF ACUTE MASTOIDITIS IN ITALIAN CHILDREN AGE 14 YEARS AND YOUNGER
LOMBARDIA (high antibiotic prescription rate)
vs FRIULI (low antibiotic prescription rate)



■ LOMBARDIA ■ FRIULI

Complications and adverse events of antibiotic treatment of AOM

Adverse Event	Amoxicillin–Clavulanate Group (N=144)			Placebo Group (N=147)		
	During Receipt of Amoxicillin–Clavulanate	During Receipt of Rescue Therapy	Total	During Receipt of Placebo	During Receipt of Rescue Therapy	Total
	<i>number of children (percent)</i>					
Mastoiditis†	0	0	0	1 (1)	0	1 (1)
Perforation of tympanic membrane	1 (1)	0	1 (1)	6 (4)	1 (1)	7 (5)
Protocol-defined diarrhea‡	34 (24)	2 (1)	36 (25)	11 (7)	11 (7)	22 (15)§
Diaper-area dermatitis	67 (47)	6 (4)	73 (51)	24 (16)	27 (18)	51 (35)¶
Oral thrush	7 (5)	0	7 (5)	0	1 (1)	1 (1)
Vomiting	12 (8)	0	12 (8)	11 (7)	1 (1)	12 (8)
Rash**	1 (1)	0	1 (1)	1 (1)	1 (1)	2 (1)

Mastoiditis occurred in an 11-month-old with unilateral AOM with an AOM-SOS score of 14. Culture grew *S. pneumoniae* 19A highly resistant to penicillin.

Hoberman A, Paradise JL, Rockette HE, et al. Treatment of acute otitis media in children under 2 years of age. *N Engl J Med.* 2011;364(2):105–115

Risk factors for antibiotic treatment failure in AOM

(from Rovers MM, et al . *Lancet*. 2006;368(9545):1429-1435)

	Number (%)	Group given antibiotics (n=819)	Control group (n=824)	RD (95% CI)	NNT	RR (95% CI)	p value for interaction*
Pain, fever, or both at 3-7 days							
Age							
<2 years	567 (35%)	91 (33%)	137 (48%)	-15% (-23 to -7)	7	0.77 (0.68-0.89)	0.83
≥2 years	1076 (65%)	107 (20%)	166 (31%)	-11% (-16 to -6)	10	0.86 (0.80-0.93)	
Bilateral AOM							
No	872 (66%)	104 (24%)	132 (30%)	-6% (-12 to 0)	17	0.92 (0.85-1.00)	0.021
Yes	456 (34%)	64 (27%)	104 (47%)	-20% (-28 to -11)	5	0.72 (0.62-0.84)	
Age and bilateral AOM							
<2 years+bilateral AOM	273 (20%)	42 (30%)	74 (55%)	-25% (-36 to -14)	4	0.64 (0.62-0.80)	0.022
<2 years+unilateral AOM	261 (20%)	45 (35%)	53 (40%)	-5% (-17 to 7)	20	0.92 (0.76-1.11)	
≥2 years+bilateral AOM	183 (14%)	20 (23%)	30 (35%)	-12% (-25 to 1)	9	0.84 (0.70-1.02)	
≥2 years+unilateral AOM	611 (46%)	59 (19%)	79 (26%)	-7% (-14 to 0)	15	0.92 (0.85-1.01)	
Otorrhea							
Yes	116 (21%)	12 (24%)	39 (60%)	-36% (-53 to -19%)	3	0.52 (0.37-0.73)	0.039
No	439 (89%)	61 (28%)	94 (42%)	-14% (-23 to -5%)	8	0.80 (0.70-0.92)	
Pain at 3-7 days							
Age, years							
< 2 years	567 (35%)	77 (28%)	115 (40%)	-12% (-20 to -4%)	9	0.83 (0.73-0.93)	0.76
≥ 2 years	1076 (65%)	86 (16%)	142 (26%)	-10% (-15 to -5%)	10	0.88 (0.82-0.93)	
Bilateral AOM							
No	872 (66%)	85 (20%)	102 (23%)	-3% (-8 to -2%)	34	0.96 (0.89-1.03)	0.005
Yes	456 (34%)	48 (20%)	88 (40%)	-20% (-28 to -12%)	5	0.75 (0.66-0.85)	
Age and bilateral AOM							