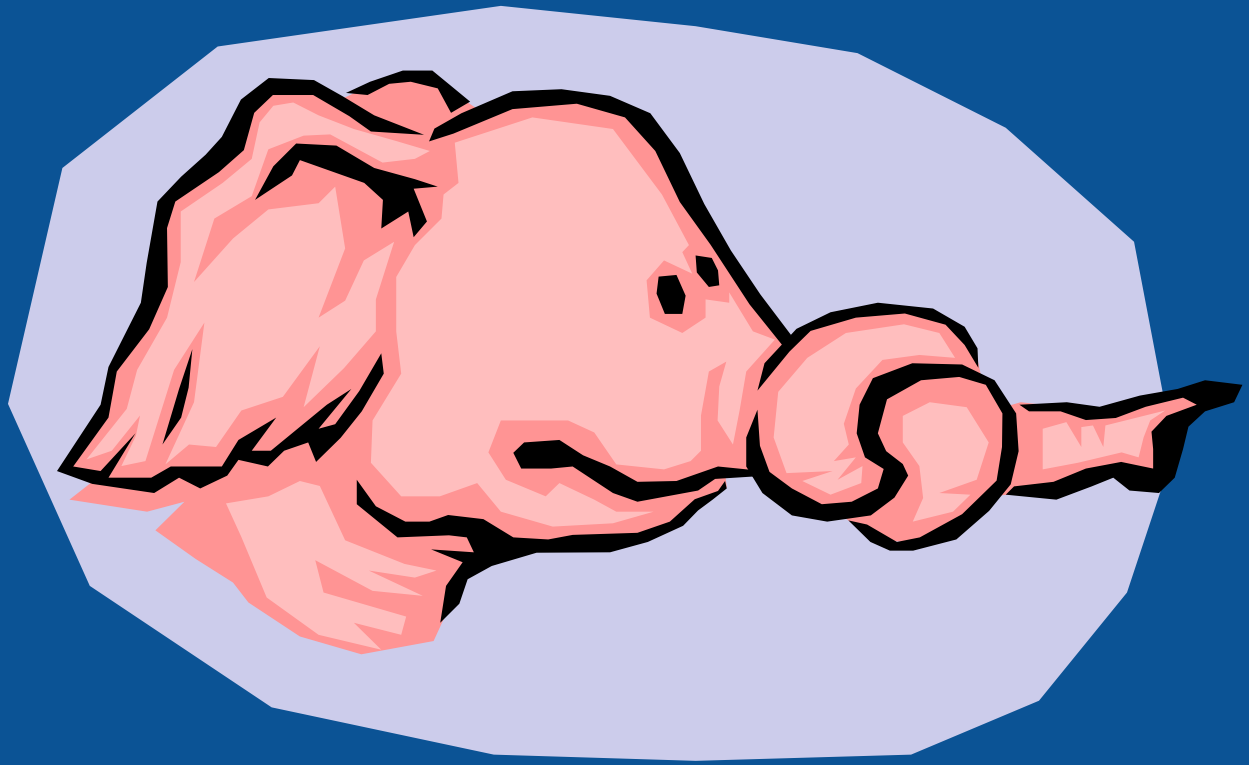
‘Tis the Season



Connie Basch, MD

Family Medicine of Southwest Washington

FAMILY MEDICINE RESPIRATORY JEOPARDY

Better than a Pound of Cure	This too Shall Pass	It's Complicated	Cold Comfort	The Nose Knows
100	100	100	100	100
200	200	200	200	200
300	300	300	300	300
400	400	400	400	400
500	500	500	500	500

HOME

Upper Respiratory Infections

- Common Cold
  - 2nd most common diagnosis during FP visits in US: 1995-1998 National Ambulatory Medical Care Survey Ann Fam Med 2004 Sep-Oct;2(5):411
  - Average adult has 2-4 colds/year
  - Average schoolchild has 6-10 colds/year
    - J Allergy Clin Immunol 1995 May;95(5 Pt 2):1133
- Virology
  - >50% Rhinovirus – fall and spring
  - 10-20% Coronaviruses – winter, early spring
  - 10 – 15% Influenza
  - 5% Adenoviruses

Risk Factors

- Exposure

- Susceptibility – only 70 – 80% exposed develop symptoms

Risk Factors

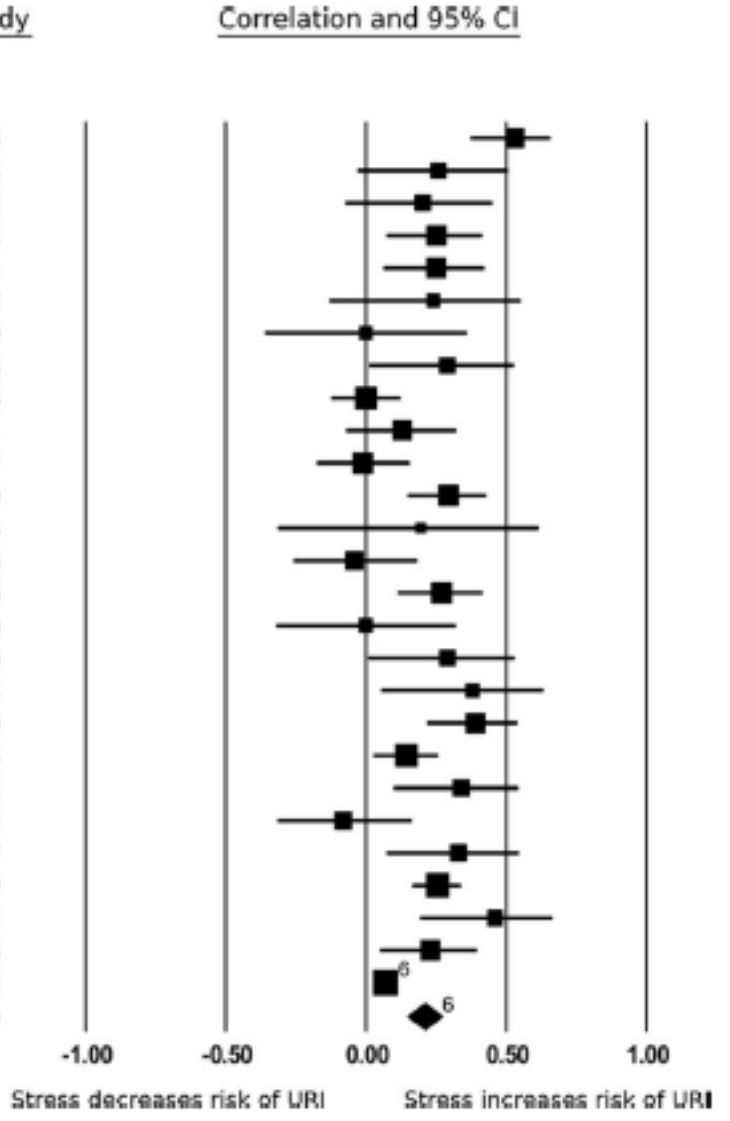
- Exposure
  - Droplets
  - Surface
    - Rhinovirus can survive 2 hours to 7 days BMC Infect Dis 2006 6:130
  - Recent airplane travel JAMA 2002 Jul 24/31;288(4):483,
- Susceptibility - only 70 – 80% exposed develop symptoms

Risk Factors

- Exposure
- Susceptibility
  - Tobacco – contradictory, data on incidence, but duration definitely increased Arch Intern Med 2004 Nov 8;164(20):2206, Ann Epidemiol 2001 May;11(4):225
  - Allergies
  - Stress
  - Sleep
  - Nutrition

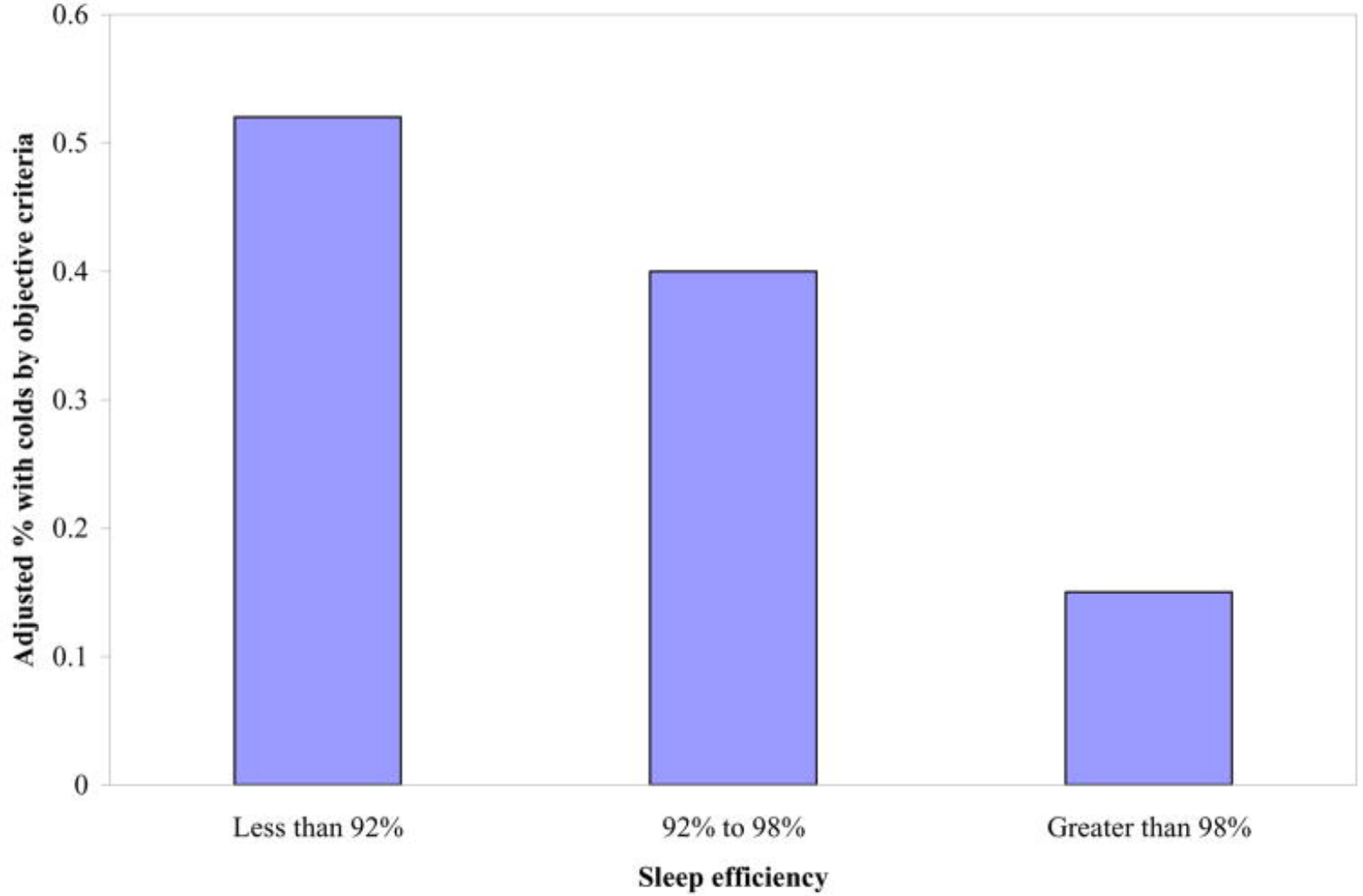
Stress and URI

Study	Stress type	URI measure	Correlation	Lower limit	Upper limit
Meyer & Haggerty, 1962	Chronic	Biological	0.530	0.372	0.658
Totman et al. 1977	Experiment	Combined[4]	0.258	-0.031	0.508
Totman et al. 1980	Major	Combined[4]	0.204	-0.073	0.452
Graham et al. 1986	Major	Combined[5]	0.250	0.071	0.414
Linville, 1987	Major	Self-report	0.250	0.062	0.421
Stone et al. 1987	Minor	Self-report	0.240	-0.132	0.552
Evans et al. 1988	Minor	Self-report	0.000	-0.360	0.360
Chapar et al. 1988	Major	Self-report	0.290	0.010	0.528
Clover et al. 1989	Major	Biological	0.000	-0.125	0.125
Evans & Edgarton, 1991	Minor	Self-report	0.130	-0.071	0.321
Kiecolt-Glaser et al. 1991	Natural	Self-report	-0.010	-0.177	0.157
Cohen et al. 1991	Index	Combined[4]	0.295	0.147	0.429
Stone et al. 1992	Combined[2]	Clinical	0.195	-0.315	0.618
Stone et al. 1993	Minor	Self-report	-0.040	-0.259	0.183
Lyons & Chamberlain, 1994	Minor	Self-report	0.270	0.111	0.415
Lee et al. 1995	Perceived	Self-report	0.000	-0.320	0.320
Sheffield et al. 1996	Major	Self-report	0.290	0.006	0.530
Evans et al. 1996	Major	Self-report	0.380	0.054	0.633
Cobb & Steptoe, 1996	Combined[3]	Clinical	0.390	0.216	0.540
Cohen et al. 1998	Major	Biological	0.144	0.026	0.258
Cobb & Steptoe, 1998	Minor	Clinical	0.340	0.099	0.544
Deinzer & Schüller, 1998	Perceived	Self-report	-0.080	-0.316	0.165
Cohen et al. 1999	Perceived	Clinical	0.330	0.071	0.547
Takkouche et al. 2001	Combined[2]	Self-report	0.255	0.166	0.340
Lutgendorf et al. 2001	Natural	Self-report	0.460	0.192	0.664
Cohen et al. & Hamrick et al. 2002[1]	Combined[2]	Combined[5]	0.230	0.049	0.396
Smolderen et al. 2007	Perceived	Self-report	0.070	0.043	0.096
Overall mean effect size correlation			0.209	0.146	0.270



Psychosomatic Medicine 72:823–832 (2010)

Sleep



Poorer sleep efficiency and shorter sleep duration are associated with increased susceptibility Arch Intern Med. 2009 January 12; 169(1): 62–67.

Nutrition

- Fruits and vegetables

Three-month risk of upper respiratory infection by fruit and vegetable intake in pregnant women (N = 1034), 1996-2002

Food Group	Crude HR	95% CI	Adjusted HR*	95% CI*	Test for trend *P*
Fruits and vegetables					
1st Quartile	1.00		1.00		
2nd Quartile	0.77	0.52-1.12	0.76	0.52-1.13	0.03
3rd Quartile	0.68	0.46-1.01	0.68	0.44-1.03	
4th Quartile	0.62	0.41-0.93	0.61	0.39-0.97	

Public Health Nutr. 2010 February; 13(2): 276–282

- IRR 0.66 (0.48-0.90) for vitamin C from food > 150 mg vs < 50 mg
  - *J Am Coll Nutr August 2011 vol. 30 no. 4 248-258*

URI- once you have one

- Sore throat, malaise, low-grade fever
- Nasal congestion, rhinorrhea, cough within 24-48 hours
- Median duration 11 days

Antibiotics are indicated for/I

 Text a **CODE** to **37607**

 Submit a **CODE**

A. URI	**559572**
B. URI with history of recurrent sinusitis	**559575**
C. Sinusitis	**559576**

Antibiotics are indicated for /I prescribe for:

- URI
- URI with history of recurrent sinusitis
  - Not indicated J Fam Pract 2001 Jan;50(1):26)
- Sinusitis
- Bronchitis
- Both C and D

What Was Happening

- 1992
  - 12 million antibiotic prescriptions for URTI in adults
    - Antibiotics were given to:
      - 51 % of patients with colds
      - 52% of patients with URTI
      - 66% of patients with bronchitis *JAMA*. 1997;278(11):901-904.
  - 6.5 million in kids <18 yo
    - Abx for:
      - 44% of kids with colds
      - 46% with URI's
      - 75% with bronchitis *JAMA*. 1998;279(11):875-877

What Is Happening

- National Ambulatory Medical Care Survey (1995-2006)
  - Antibiotics for 58% of ARTI *JAMA*. 2009:302:758-766.
- Mayo Clinic Family Medicine offices
  - 69% of ARTI received antibiotics
  - Macrolides most commonly prescribed

    J Fam Pract 2012 Jun;61(6):330-5
- Sinusitis
  - 76% in 2005 (83% in 1999) J Fam Pract. 2008 July; 57(7): 464–468

Q: Are antibiotics effective in URI?

A: How do you define effective?

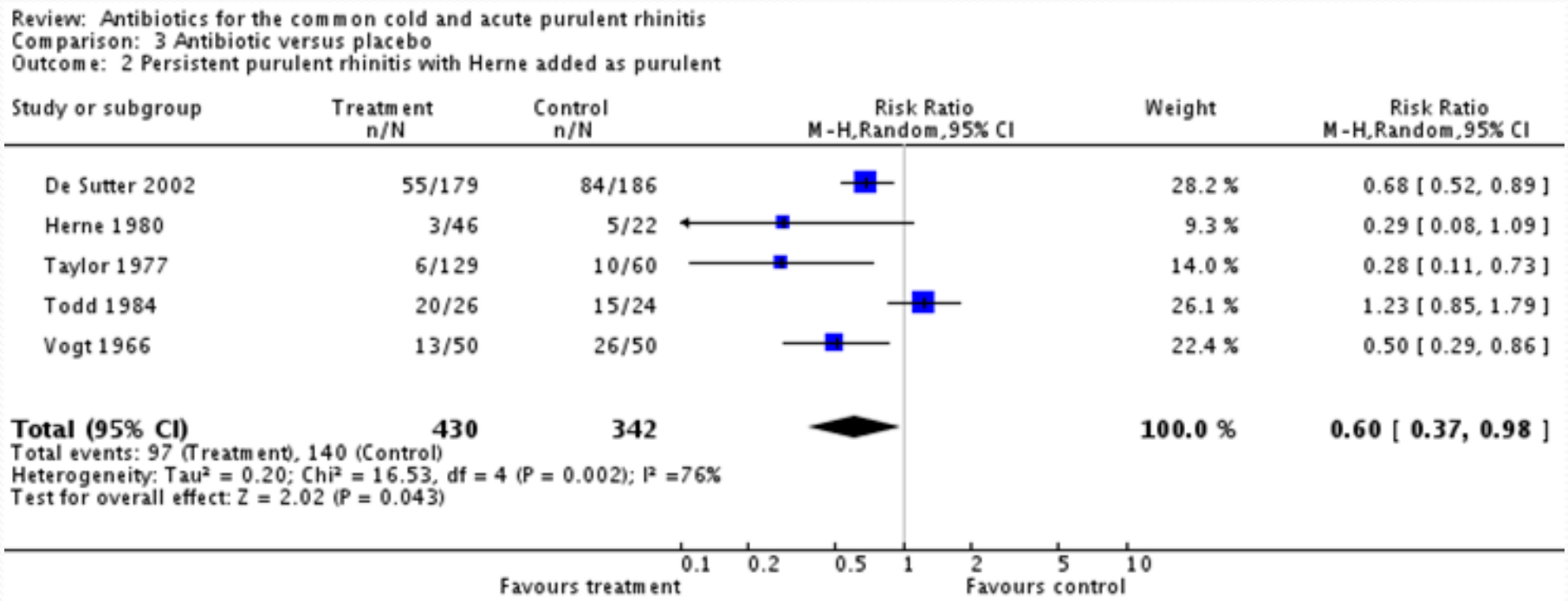
From: **Amoxicillin for Acute Rhinosinusitis: A Randomized Controlled Trial**

JAMA. 2012;307(7):685-692

Table 4. Treatment Use, Outcomes, and Adverse Effects

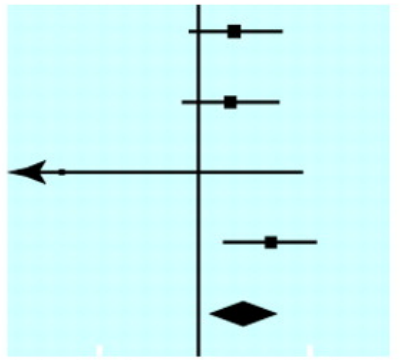
	Amoxicillin Group (n = 85)	Control Group (n = 81)	*P* Value[a]
Treatment Use			
Treatment duration, d			
Mean (SD)	6.89 (4.55)	6.47 (4.75)	.56
Median (IQR)	10 (0-10)	10 (0-10)	
Adherent with 10-d treatment dosing regimen (self-report), No./total (%)	55/81 (68)	51/71 (72)	.58
Treatment Outcomes			
Change in SNOT-16 scores from day 0, mean (95% CI)[b]			
Day 3	0.59 (0.47-0.71)	0.54 (0.41-0.67)	.69
Day 7	1.06 (0.93-1.20)	0.86 (0.71-1.02)	.02
Day 10	1.23 (1.08-1.37)	1.20 (1.07-1.32)	.85
Self-reported significant improvement in symptoms since day 0, % (95% CI)			
Day 3	37 (27-48)	34 (23-45)	.67
Day 7	74 (64-83)	56 (45-67)	.02
Day 10	78 (69-87)	80 (71-90)	.71
Period missed from work, mean (95% CI), d	0.55 (0.28-0.82)	0.55 (0.22-0.87)	.99

Persistent Purulent Rhinitis Day 8



Meta-analysis of studies of outcomes of purulent rhinitis at five to eight days, antibiotic versus placebo

Study or subcategory	Antibiotic (n/N)	Placebo (n/N)	Relative risk (random) (95% CI)	Weight (%)	Relative risk (random) (95% CI)
Taylor 1977a sulfa	72/75	25/30		33.43	1.15 (0.98 to 1.36)
Taylor 1977b amox	51/54	25/30		31.85	1.13 (0.95 to 1.35)
Todd 1984 Cefalexin	6/26	9/24		1.79	0.62 (0.26 to 1.47)
De Sutter 2002 amox	125/180	95/179		32.93	1.31 (1.11 to 1.55)
Total (95% CI)	335	263		100.00	1.18 (1.05 to 1.33)



Total events: 254 (antibiotic), 154 (placebo)

Test for heterogeneity: χ^2=3.98, df=3, P=0.26, I^2=24.6%

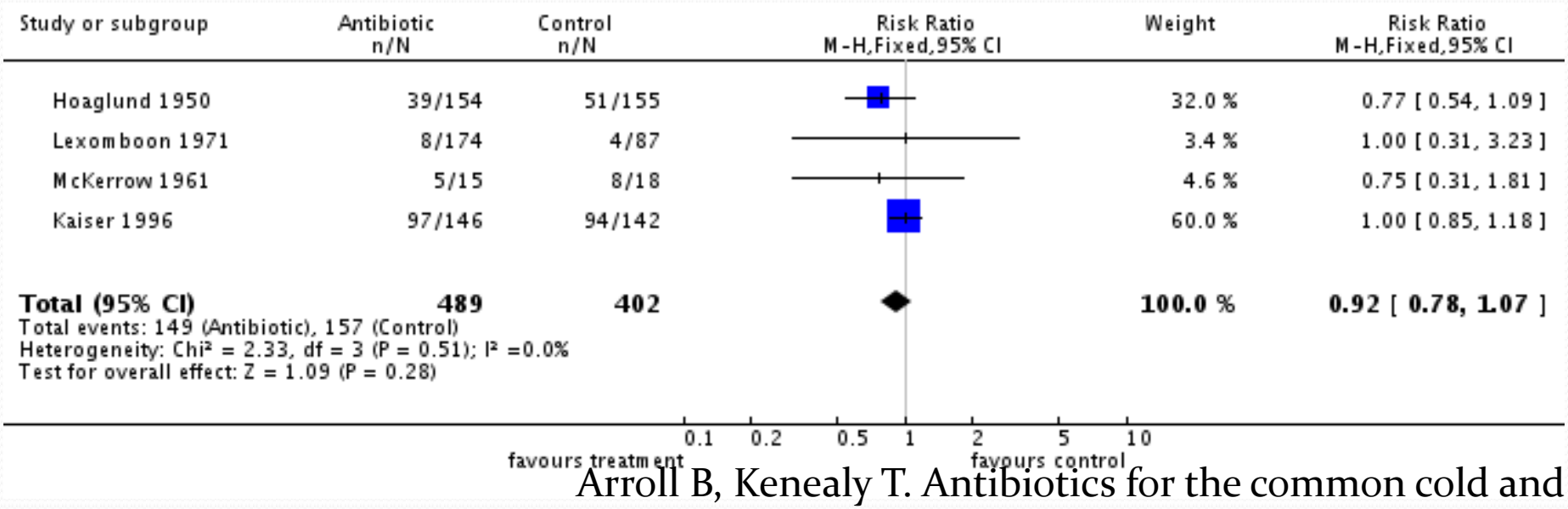
Test for overall effect: z=2.78, P=0.005

NNT 7-15 for improvement at 5-8 days
NNH 12-78 for side effects
No serious events occurred in placebo groups

Arroll B , Kenealy T BMJ 2006;333:279

Abx vs. Placebo in Cold/Purulent Rhinitis

- RR for lack of cure or persistence of symptoms is 0.95, 95% CI 0.59 to 1.51
- RR adverse effects for antibiotics given to participants with the common cold is 1.8



Persisting symptoms days 1-7

Arroll B, Kenealy T. Antibiotics for the common cold and acute purulent rhinitis. Cochrane Database of Systematic Reviews 2005, Issue 3. Art. No.: CD000247.

Azithromycin in Acute Rhinosinusitis

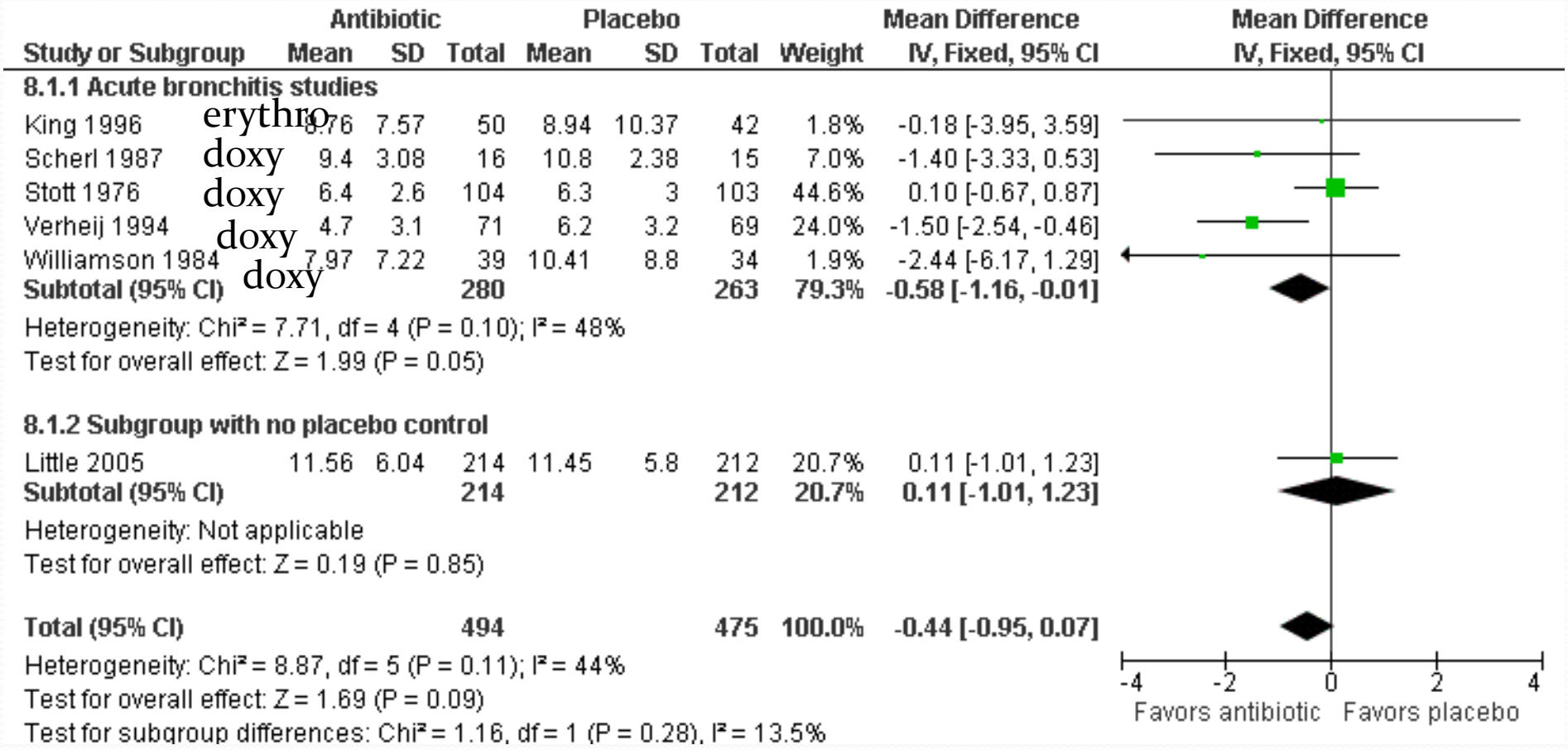
Duration/Outcome	Percent of Patients	
	Azithromycin	Placebo
3-5 days Cure	14.3	8.6
3-5 days Improvement	79.7	79.0
10-12 days Cure	58.1*	31.7
10-12 days Improvement	34.9	56.1
23-27 days Cure	79.3	67.1
23-27 days Improvement + Cure	90	88

*P=0.001

Patients with clinical signs of sinusitis but no radiological signs

Eur J Clin Microbiol Infect Dis (1998) 17 :309–312

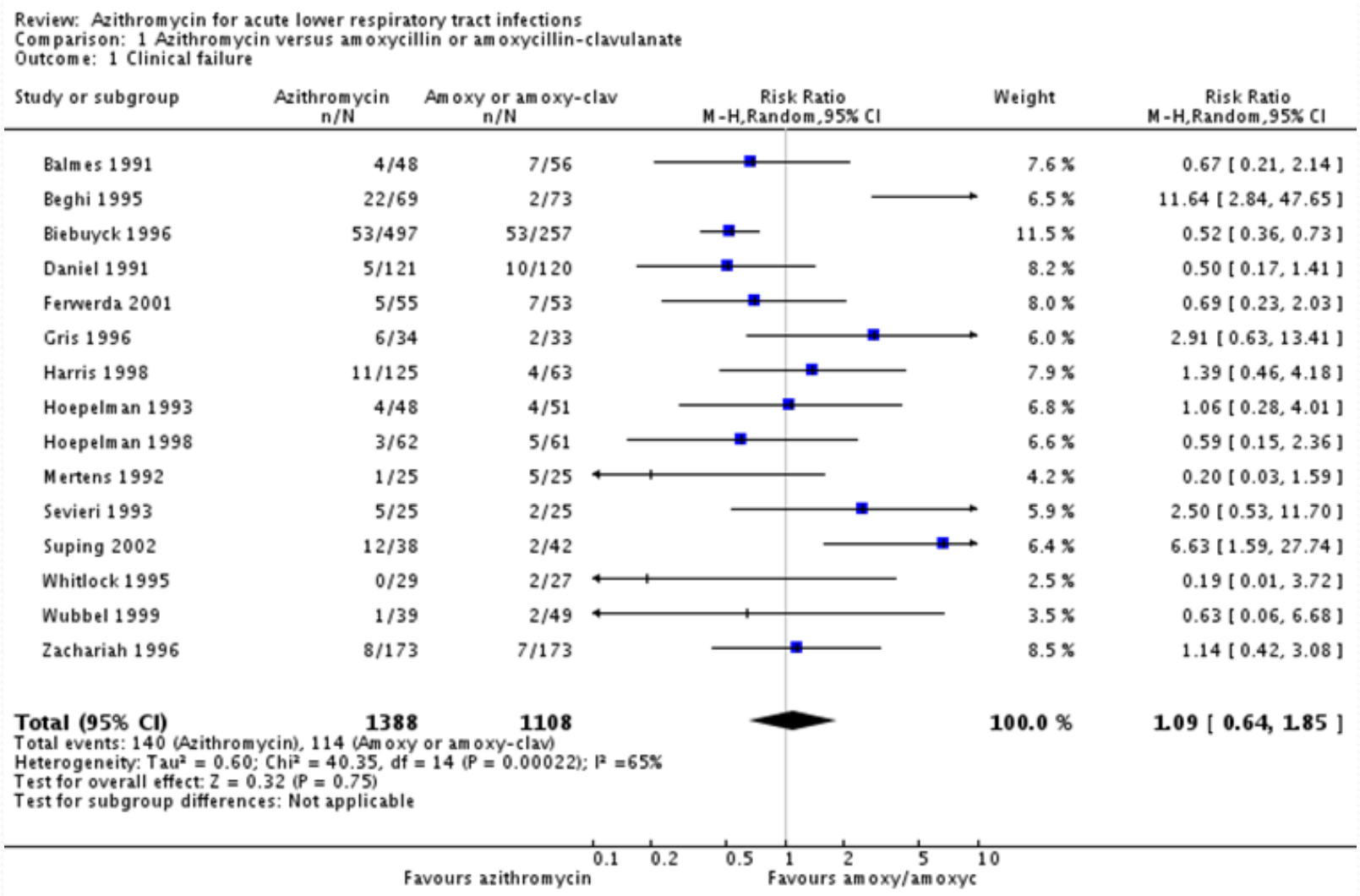
Acute Bronchitis



-0.64 days of feeling ill (95% CI -1.16 to -0.13)

Cochrane Database Syst Rev. 2004 Oct 18;(4):CD000245

Azithromycin vs Amox or Amox/Clav in Acute LRTI



Laopaiboon M, Panpanich R, Lerttrakarnnon P. Azithromycin for acute lower respiratory tract infections. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD001954

Why not give antibiotics?

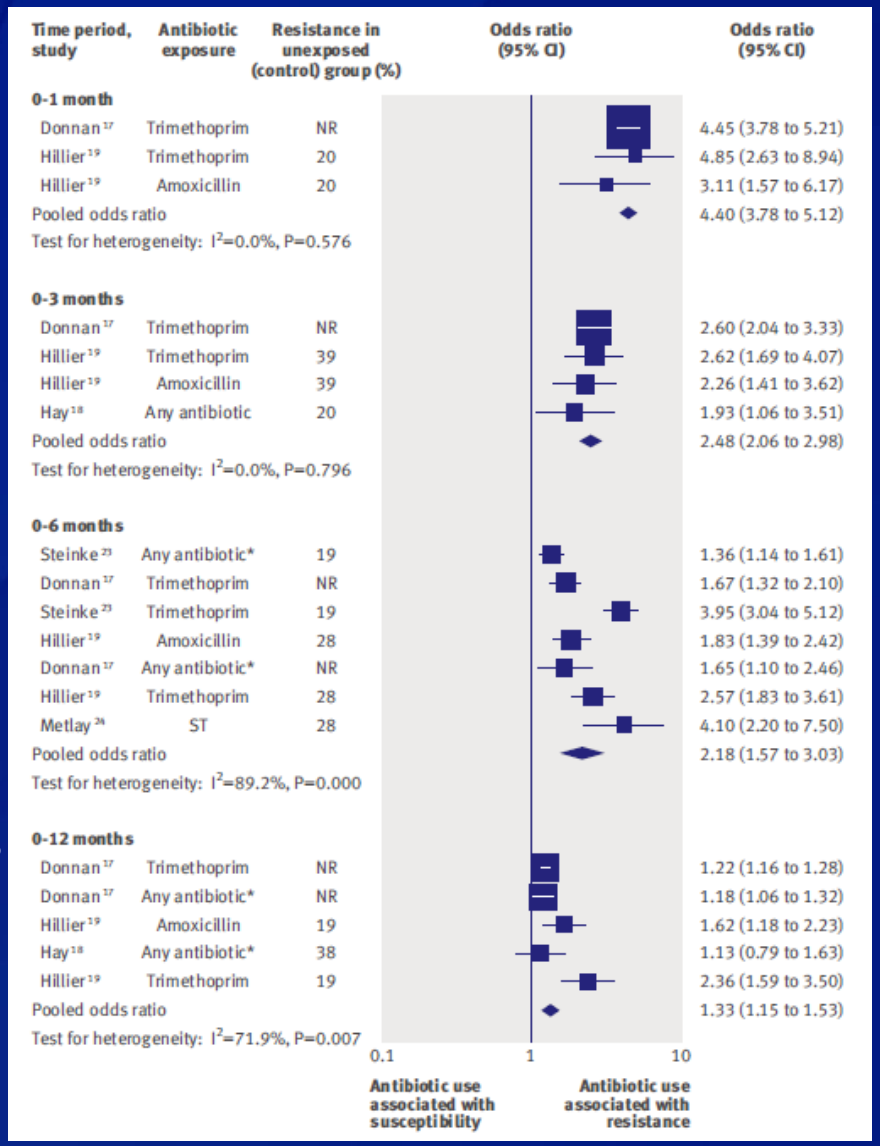
Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis

0-1 month

0-3 months

0-6 months

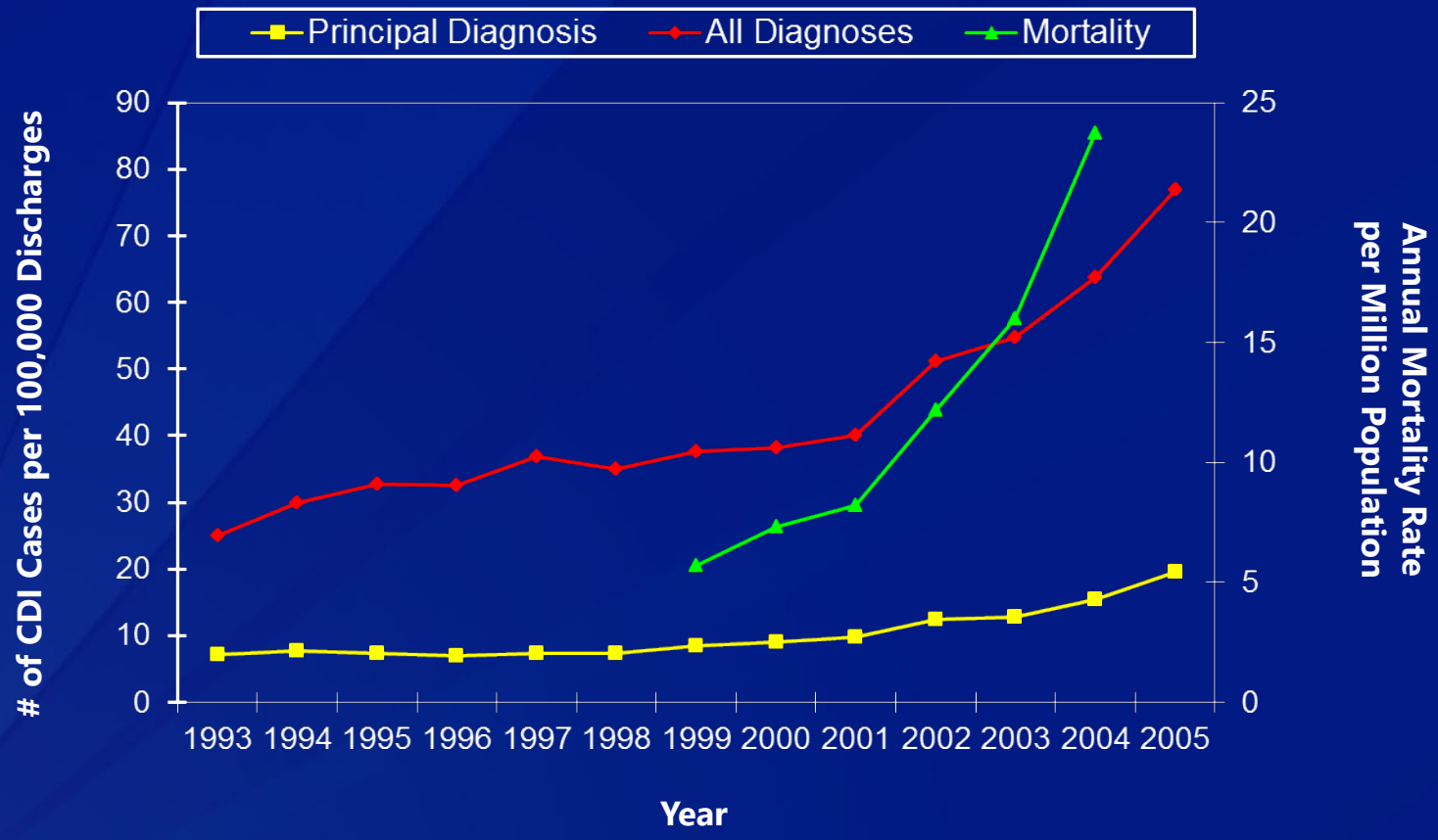
0-12 months



Longer duration and multiple courses were associated with higher rates of resistance.

Costelloe C et al. *BMJ.* 2010;340:c2096.

C. diff Incidence and mortality are increasing in US



Elixhauser A, et al. Healthcare Cost and Utilization Project: Statistical Brief #50. April 2008. Available at: http://www.hcup-us.ahrq.gov/reports/statbriefs/sb50.pdf. Accessed March 10, 2010.

Redelings MD, et al. Emerg Infect Dis. 2007;13:1417-1419.

Impact of fluoroquinolone restriction on rates of *C. difficile* infection

Infect Control Hosp Epidemiol. 2009 Mar;30(3):264-72.

Current Guidelines

- Common cold is caused by viral pathogens
- Symptoms may last up to 14 days, average is 7-11 days
  - (J Clin Micro 1997;35:2864; JAMA 1967;202:158)
- Purulent secretions neither predict bacterial infection nor benefit from antibiotic treatment

- http://www.cdc.gov/getsmart/campaign-materials/adult-treatment.html

Current Guidelines

- Dx/Tx for bacterial rhinosinusitis should be reserved for sx > 7 days and maxillary tenderness/purulent secretions
  - Even then, treat with antibiotics only if moderate to severe, use narrow-spectrum agent for S. pneumoniae and H. flu
- Bronchitis should not be treated with antibiotics unless pertussis is suspected (and then confirmatory testing should be ordered)
- http://www.cdc.gov/getsmart/campaign-materials/adult-treatment.html

How can we prescribe fewer antibiotics?

What about the delayed antibiotic prescription?

- 44.4% consumed the antibiotic course
- 29.6% started their "delayed" course on the day of prescription
  - Br J Gen Pract. 2012 Sep;62(602):639-46
- Postdating this is no better Can Fam Physician. 2010 Oct;56(10):1032-6
- With patient handout:
  - use of antibiotics within 2 weeks in 46.2% vs. 59.4%
    - BMJ 2002 Jan 12;324(7329):91
    - Handout available at http://www.bmj.com//content/324/7329/91.1?variant=full-text

Access to Rapid PCR for Respiratory Viruses Can Reduce Antibiotic Prescriptions

- 4.5% antibiotics at initial visit vs. 12.3% controls (P=0.005)
- Later: 13.9% rapid result group vs. 17.2% delayed
  - BMC Med. 2011 Apr 26;9:44
- Cost in our lab: $783

Monitoring of Prescribing

- May not be helpful
  - Hedis quality measure for avoiding antibiotics in 466.0 Acute Bronchitis
  - Increase in use of dx code 490 (Bronchitis NOS) Am J Manag Care. 2012 Jun 1;18(6):e217-24.

Educate Patients to Decrease Demand

- Only multifaceted interventions aimed at
  - Providers
  - Patients
  - General public

have sufficient effect size to impact antibiotic resistance

Decrease in macrolide resistance : 16.5% (1992) to 8.6% (1996)

Cochrane Database Syst Rev. 2005 Oct 19;(4):CD003539

But until they stop asking. . . . .

What about offering something else that does work?

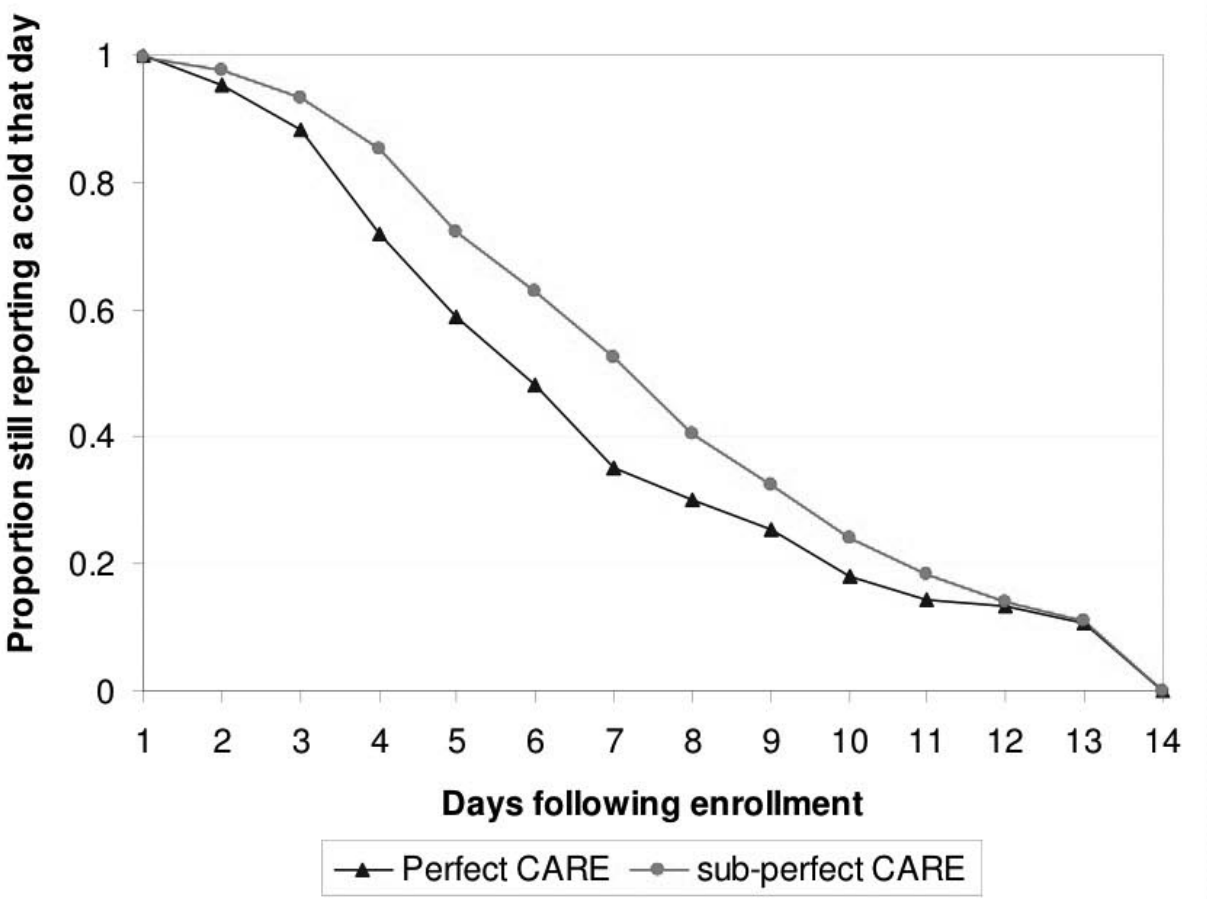
Effective Alternatives

- Shorten Course
- Treat Symptoms

Effective Alternatives

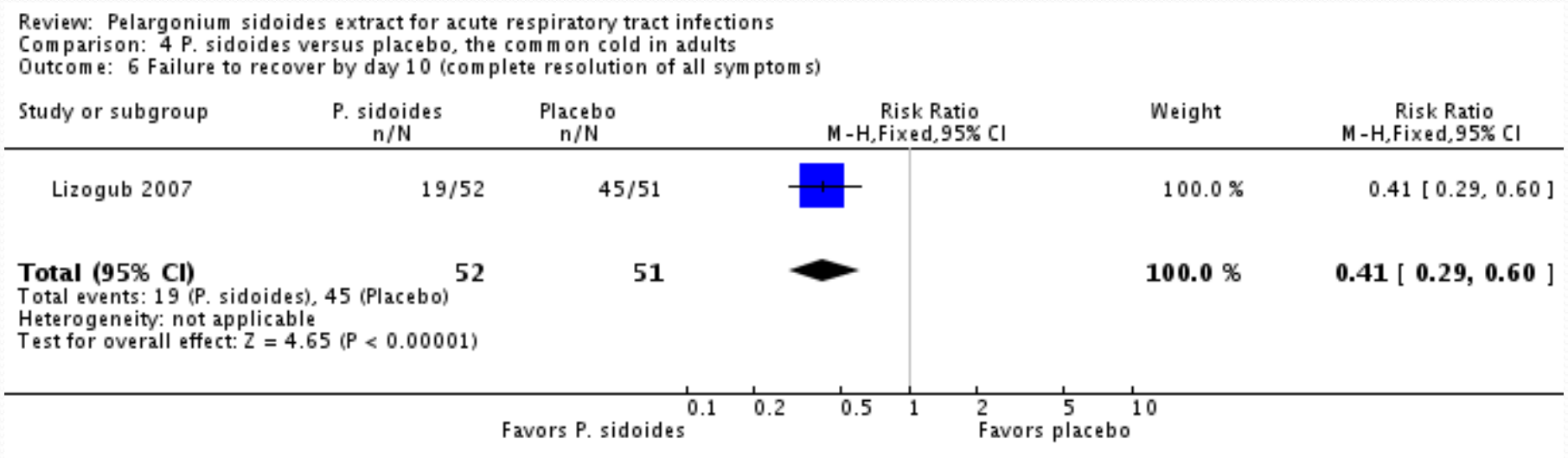
- Shorten Course
  - Display Empathy
  - Pelargonium Sidoides
  - Andrographis paniculata
  - +/- Echinacea – contradictory trials, inc rashes in kids
  - Zinc
- Treat Symptoms

Practitioner empathy (perceived) and the course of the common cold



Fam Med 2009;41(7):494-501

Pelargonium Sidoides - Common Cold

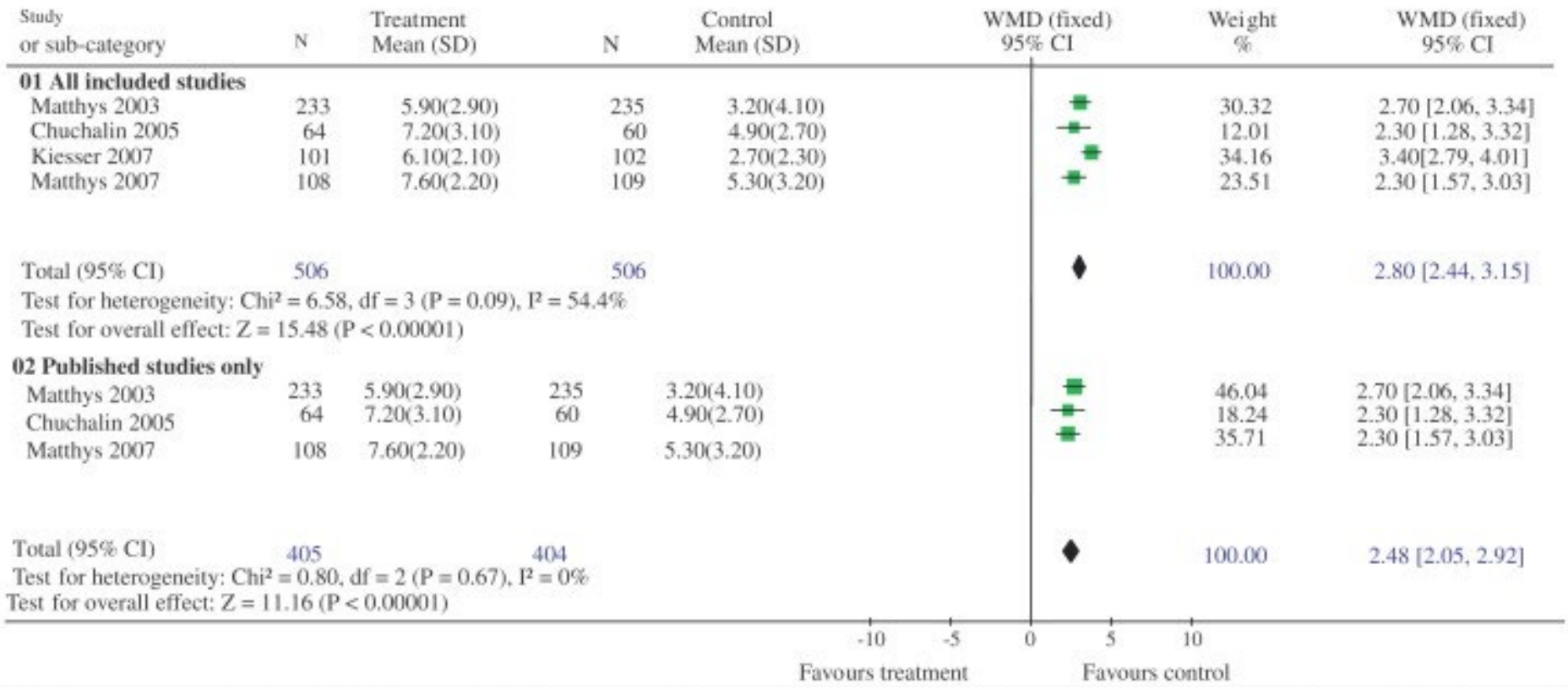


- Symptom resolution by 10 days
  - Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD006323.

Pelargonium Sidoides in Bronchitis

Review: Pelargonium sidoides for the treatment of acute bronchitis
Comparison: 01 EPs7630 vs. placebo
Outcome: 01 BSS score

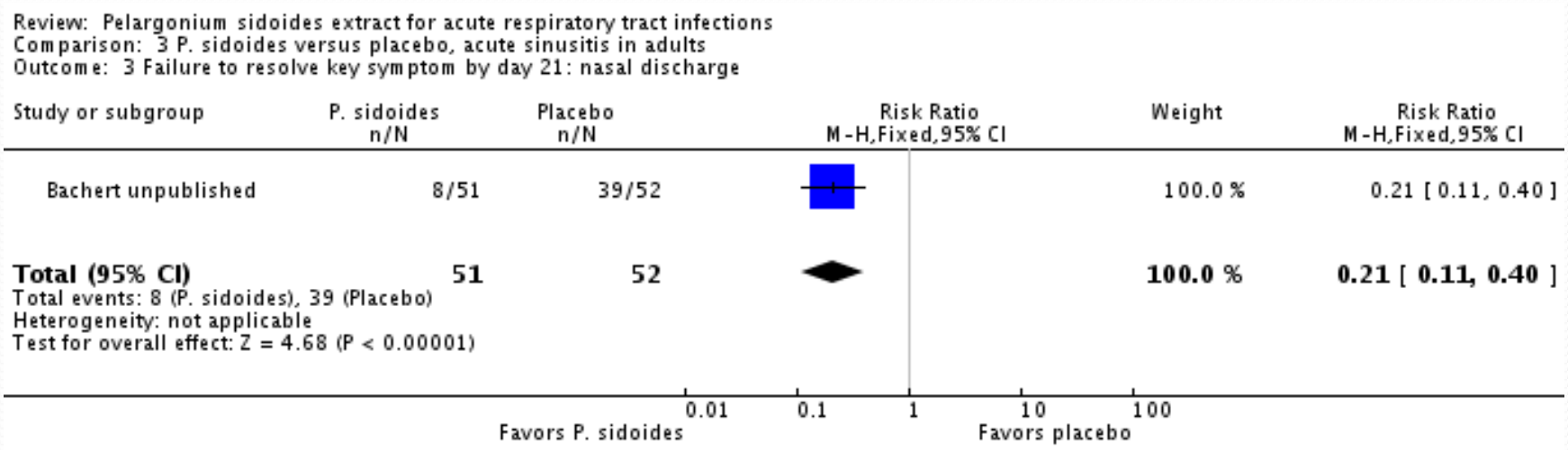
Study or sub-category	N	Treatment Mean (SD)	N	Control Mean (SD)	WMD (fixed) 95% CI	Weight %	WMD (fixed) 95% CI
01 All included studies							
Matthys 2003	233	5.90(2.90)	235	3.20(4.10)		30.32	2.70 [2.06, 3.34]
Chuchalin 2005	64	7.20(3.10)	60	4.90(2.70)		12.01	2.30 [1.28, 3.32]
Kiesser 2007	101	6.10(2.10)	102	2.70(2.30)		34.16	3.40[2.79, 4.01]
Matthys 2007	108	7.60(2.20)	109	5.30(3.20)		23.51	2.30 [1.57, 3.03]
Total (95% CI)	506		506			100.00	2.80 [2.44, 3.15]
Test for heterogeneity: $Chi^2 = 6.58$, df = 3 (P = 0.09), $I^2 = 54.4\%$							
Test for overall effect: Z = 15.48 (P < 0.00001)							
02 Published studies only							
Matthys 2003	233	5.90(2.90)	235	3.20(4.10)		46.04	2.70 [2.06, 3.34]
Chuchalin 2005	64	7.20(3.10)	60	4.90(2.70)		18.24	2.30 [1.28, 3.32]
Matthys 2007	108	7.60(2.20)	109	5.30(3.20)		35.71	2.30 [1.57, 3.03]
Total (95% CI)	405		404			100.00	2.48 [2.05, 2.92]
Test for heterogeneity: $Chi^2 = 0.80$, df = 2 (P = 0.67), $I^2 = 0\%$							
Test for overall effect: Z = 11.16 (P < 0.00001)							



Phytomedicine Volume 15, Issue 5 2008 378 – 385

Bronchitis Symptom Score higher in placebo than treated

Pelargonium Sidoides Acute Sinusitis



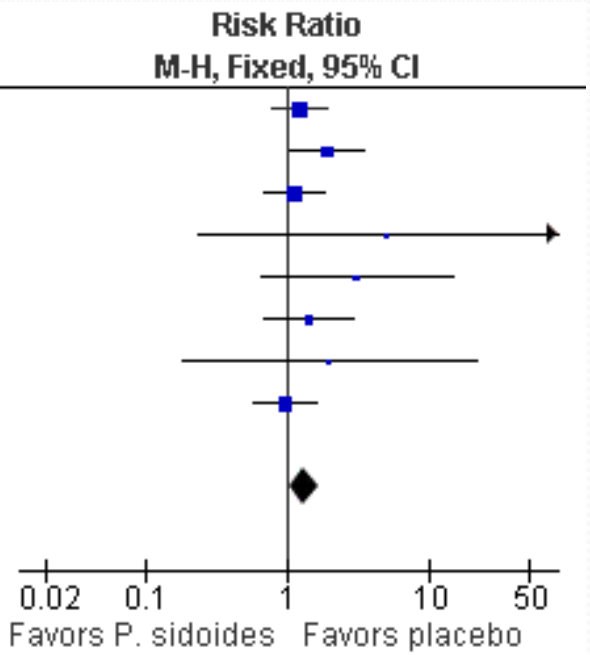
Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD006323.

Pelargonium Sidoides Adverse Events

Study or Subgroup	P. sidoides Events	P. sidoides Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Anonymous 001	31	103	24	97	23.4%	1.22 [0.77, 1.92]
Anonymous 002	62	303	11	102	15.6%	1.90 [1.04, 3.46]
Anonymous 003	59	298	18	101	25.4%	1.11 [0.69, 1.79]
Anonymous 004	2	111	0	109	0.5%	4.91 [0.24, 101.13]
Bachert unpublished	6	51	2	52	1.9%	3.06 [0.65, 14.45]
Chuchalin 2005	15	64	10	60	9.8%	1.41 [0.69, 2.88]
Lizogub 2007	2	52	1	51	1.0%	1.96 [0.18, 20.97]
Matthys 2007a	23	108	24	109	22.6%	0.97 [0.58, 1.60]
Total (95% CI)		**1090**		**681**	**100.0%**	**1.32 [1.04, 1.66]**
Total events	200		90			

Heterogeneity: Chi² = 5.45, df = 7 (P = 0.60); I² = 0%

Test for overall effect: Z = 2.33 (P = 0.02)



Cochrane Database of Systematic Reviews 2008, Issue 3. Art. No.: CD006323.

Pelargonium Mechanism

- Cytoprotective effect against virus-induced cell destruction
- Increases release of antimicrobial peptides (also known as defensins) from neutrophilic granulocytes
- Increase release of tumor-necrosis factor (TNF-α)
- Stimulate synthesis of nitric oxide and interferon-b
- Increase NK Cell activity
- Increase phagocytosis
    - Natural Medicine Journal 1(4), December 2009

Andrographis paniculata

Symptoms	Treatments	Day 1	Day 3	Day 5	Effect (Day 1-5)
Cough	Placebo	55.1	36.6	35.9	19.2
	KalmCold	57.9	39.2	23.3	34.6*
Nasal discharge	Placebo	44.9	29.5	26.7	19.0
	KalmCold	42.8	25.7	11.5	32.5*
Malaise/Fatigue	Placebo	39.5	28.0	24.3	18.9
	KalmCold	44.8	23.9	10.3	34.4*

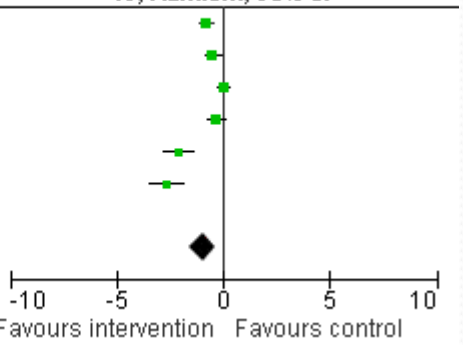
$P < 0.05$

- Anti-inflammatory, immunostimulant and anti-pyretic properties Phytomedicine 17(3/4)March 2010, Pages 178–185
- Systematic review found 3 previous studies of high quality design with similar results Explore(NY)2006 Jan;2(1):25-9.

Zinc for treatment – lozenges or syrup

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kurugol 2006a	4.7	0.8	97	5.3	0.7	97	18.0%	-0.80 [-1.09, -0.50]
Kurugol 2007	5.5	1.97	60	6.5	1.97	60	17.5%	-0.50 [-0.87, -0.14]
Macknin 1998	8.5	2.85	125	8.5	2.85	124	18.2%	0.00 [-0.25, 0.25]
Petrus 1998	4.4	1.4	52	5.1	2.8	49	17.4%	-0.32 [-0.71, 0.08]
Prasad 2000	4.5	1.6	25	8.1	1.8	23	14.7%	-2.08 [-2.80, -1.37]
Prasad 2008	4	1.04	25	7.12	1.26	25	14.2%	-2.66 [-3.43, -1.88]
Total (95% CI)			**384**			**378**	**100.0%**	**-0.97 [-1.56, -0.38]**

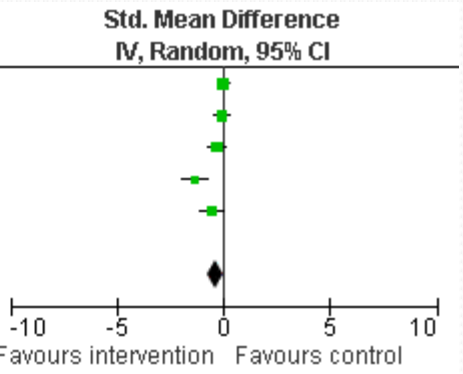
Heterogeneity: Tau² = 0.48; Chi² = 68.88, df = 5 (P < 0.00001); I² = 93%
Test for overall effect: Z = 3.22 (P = 0.001)



Duration

Study or Subgroup	Intervention Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kurugol 2006a	0.2	4.92	97	0.4	5.9	97	24.0%	-0.04 [-0.32, 0.24]
Kurugol 2007	0.3	4.64	60	0.7	6.97	60	22.2%	-0.07 [-0.43, 0.29]
Petrus 1998	1.41	0.29	52	1.5	0.28	49	21.3%	-0.31 [-0.71, 0.08]
Prasad 2000	2.7	2	25	5.4	1.9	23	15.5%	-1.36 [-1.99, -0.73]
Prasad 2008	3.45	5	25	5.61	2.5	25	17.0%	-0.54 [-1.10, 0.03]
Total (95% CI)			**259**			**254**	**100.0%**	**-0.39 [-0.77, -0.02]**

Heterogeneity: Tau² = 0.13; Chi² = 16.10, df = 4 (P = 0.003); I² = 75%
Test for overall effect: Z = 2.05 (P = 0.04)



Severity

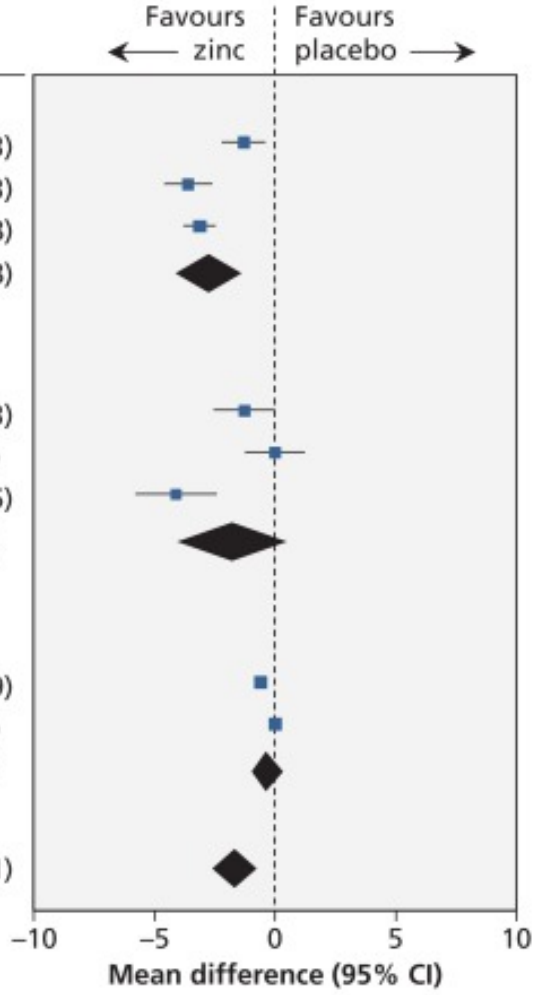
Cochrane Database Syst Rev. 2011 Feb 16;2:CD001364

Note significant bad taste, nausea

Form of Zinc - Acetate

Study	Duration of symptoms, d, mean (SD) Zinc	*n*	Placebo	*n*	Mean difference (95% CI)
Zinc acetate					
Petrus et al.[35]	3.8 (1.4)	52	5.1 (2.8)	49	−1.30 (−2.17 to −0.43)
Prasad et al.[36]	4.5 (1.6)	25	8.1 (1.8)	23	−3.60 (−4.57 to −2.63)
Prasad et al.[37]	4 (1.04)	25	7.12 (1.26)	25	−3.12 (−3.76 to −2.48)
Subtotal		102		97	−2.67 (−3.96 to −1.38)
Heterogeneity: $I^2 = 87\%$					
Zinc gluconate					
Godfrey et al.[30]	4.86 (2.69)	35	6.13 (2.69)	38	−1.27 (−2.51 to −0.03)
Macknin et al.[33]	9 (5.2)	125	9 (4.4)	124	0.00 (−1.20 to 1.20)
Mossad et al.[34]	5.2 (2.9)	49	9.3 (5.2)	50	−4.10 (−5.75 to −2.45)
Subtotal		209		212	−1.72 (−3.89 to 0.44)
Heterogeneity: $I^2 = 87\%$					
Zinc sulfate					
Kurugöl et al.[31]	4.7 (0.8)	97	5.3 (0.7)	97	−0.60 (−0.81 to −0.39)
Kurugöl et al.[32]	6 (0.74)	60	6 (0.74)	60	0.00 (−0.26 to 0.26)
Subtotal		157		157	−0.31 (−0.89 to 0.28)
Heterogeneity: $I^2 = 92\%$					
Overall		468		466	−1.65 (−2.50 to −0.81)
Heterogeneity: $I^2 = 95\%$					

Test for subgroup differences: $\chi^2 = 11.51$, df = 2 ($p = 0.003$), $I^2 = 82.6\%$

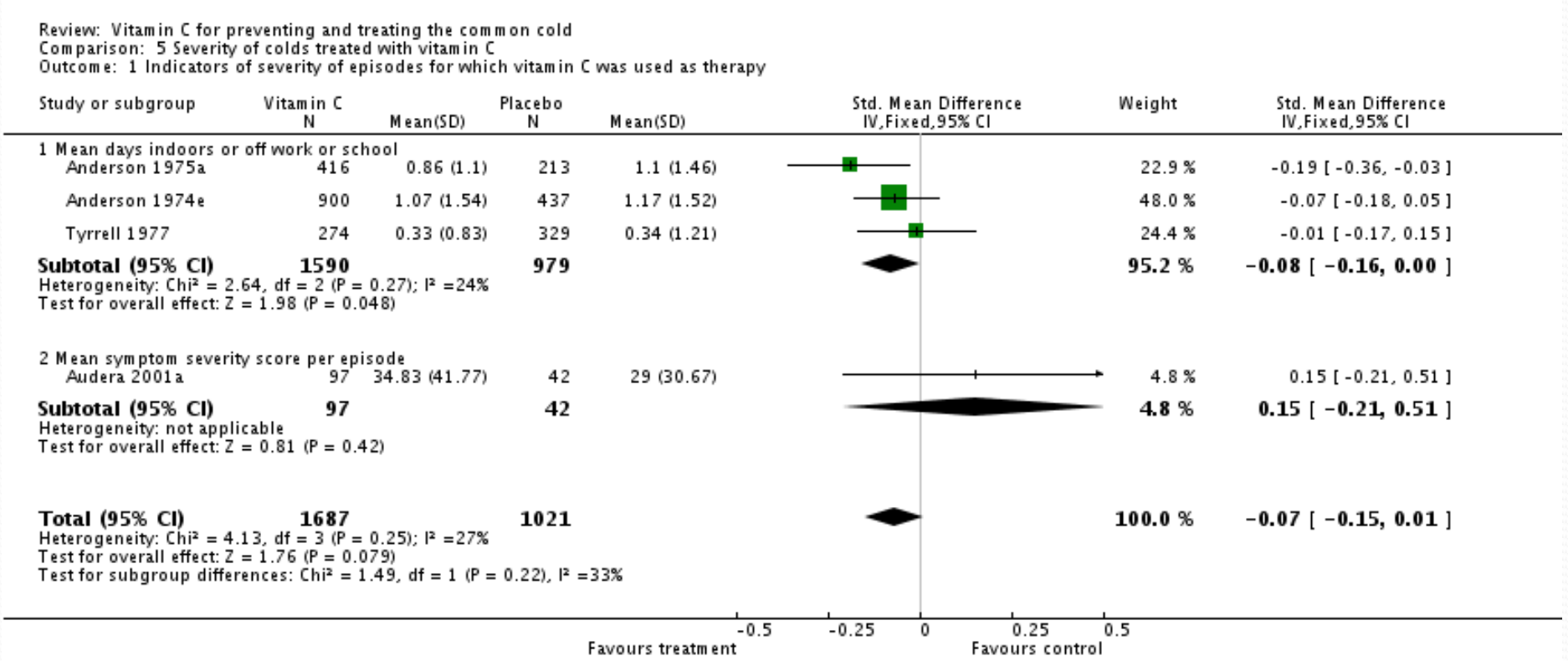


CMAJ. 2012 July 10; 184(10): E551-E561

Effective Alternatives

- Shorten Course
- Treat Symptoms
  - Vitamin C
    - Decrease severity, Cochrane 2007, 3: CD000980
    - 9% - 37 % reduction in symptom days in multiple clinical trials with ≥1 gram per day *Cochrane Dbase Syst Rev* 2000; 2:CD000980
  - Pain
  - Cough
  - Nasal Symptoms

Vitamin C and Symptom Severity



- Audera used only 1 g x 3 days
  - Cochrane 2007, Issue 3. Art. No.: CD000980

Effective Alternatives

- Shorten Course
- Treat Symptoms
  - Vitamin C
  - Pain
    - Analgesics – acetaminophen, NSAIDs
    - But some possible reasons for caution?
      - ASA, acetaminophen: ↑nasal symptoms, ↓Ab response (P<0.05) J Infect Dis. 1990 Dec;162(6):1277-82.
      - ASA: increased viral shedding *JAMA* 231:1248-1251, 1975
      - And mortality? 34% increase in animal RCTs w/aspirin, paracetamol and diclofenac J R Soc Med. 2010 103(10): 403–411
  - Cough
  - Nasal Symptoms

Treat Symptoms

- Vitamin C
- Pain
- Cough
  - Dextromethorphan - decrease cough scores 19-36% [1]
  - Guaifenesin [2] –
    - decrease cough frequency /intensity in 75% vs 31% controls
  - Honey [3] (in kids) – more effective than DM
- Nasal Symptoms

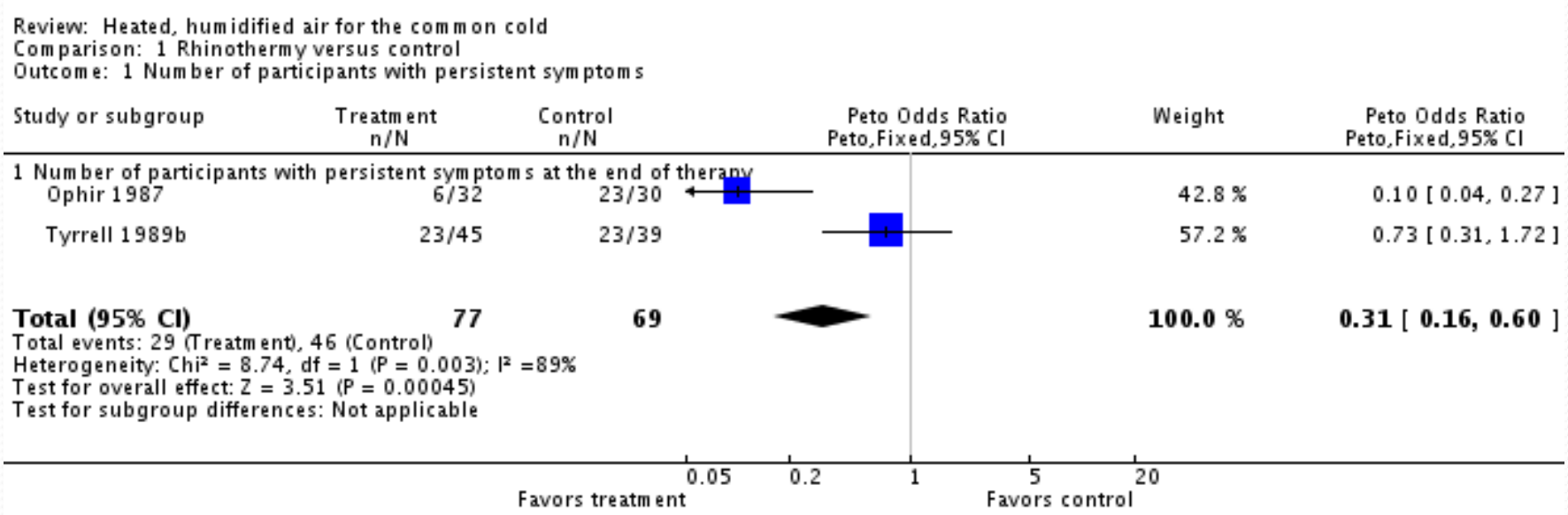
1, 2: Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD001831.

3: Pediatrics. 2012 Sep;130(3):465-71.

Treat Symptoms

- Pain
- Cough
- **Nasal Symptoms** – data to follow
  - Steam Cochrane 2011, Issue 5. Art. No.: CD001728
  - Essential oils – vapor rub or steam inhalation Pediatrics 2010;126(6):1092
  - Decongestants – nasal or oral JAMA 1993 May 5;269(17):2258-63
  - Ipratopium nasal – imp rhinorrhea but not congestion "
  - Isotonic saline nasal wash Am Fam Physician. 2009 80(10): 1117–1119
  - Bromelain in Sinusitis Otolaryngology - Head &Neck Surgery 135(4):496, 2006
  - Hot drink Rhinology. 2008 Dec;46(4):271-5
  - Chicken Soup – increased nasal mucus velocity Chest. 1978 Oct;74(4):408-10.
  - Decongestants – topical or oral *Cochrane* 2007;(1):CD001953.

Steam



- #patients with persistent symptoms
  - Cochrane Database of Systematic Reviews 2011, Issue 5. Art. No.: CD001728

+/- Essential Oils

- Vapor rub studied in kids Pediatrics 2010 Dec;126(6):1092
- In vitro broad-spectrum antimicrobial activity
- Also anti-inflammatory, mucolytic
- Improve mucus clearance in COPD J Altern Complement Med. 2003 Apr;9(2):243-9
- Case report in O2-dependent RSV EXPLORE July/Aug 2008, 4(4)
- Interventional trial in acute sinusitis – more effective than placebo Laryngorhinootologie 1997 Jan;76(1):23-7
- Articles in German and Russian

Treat Symptoms

- Pain
- Cough
- **Nasal Symptoms** – data to follow
  - Steam Cochrane 2011, Issue 5. Art. No.: CD001728
  - Essential oils – vapor rub or steam inhalation Pediatrics 2010;126(6):1092
  - Decongestants – nasal or oral JAMA 1993 May 5;269(17):2258-63
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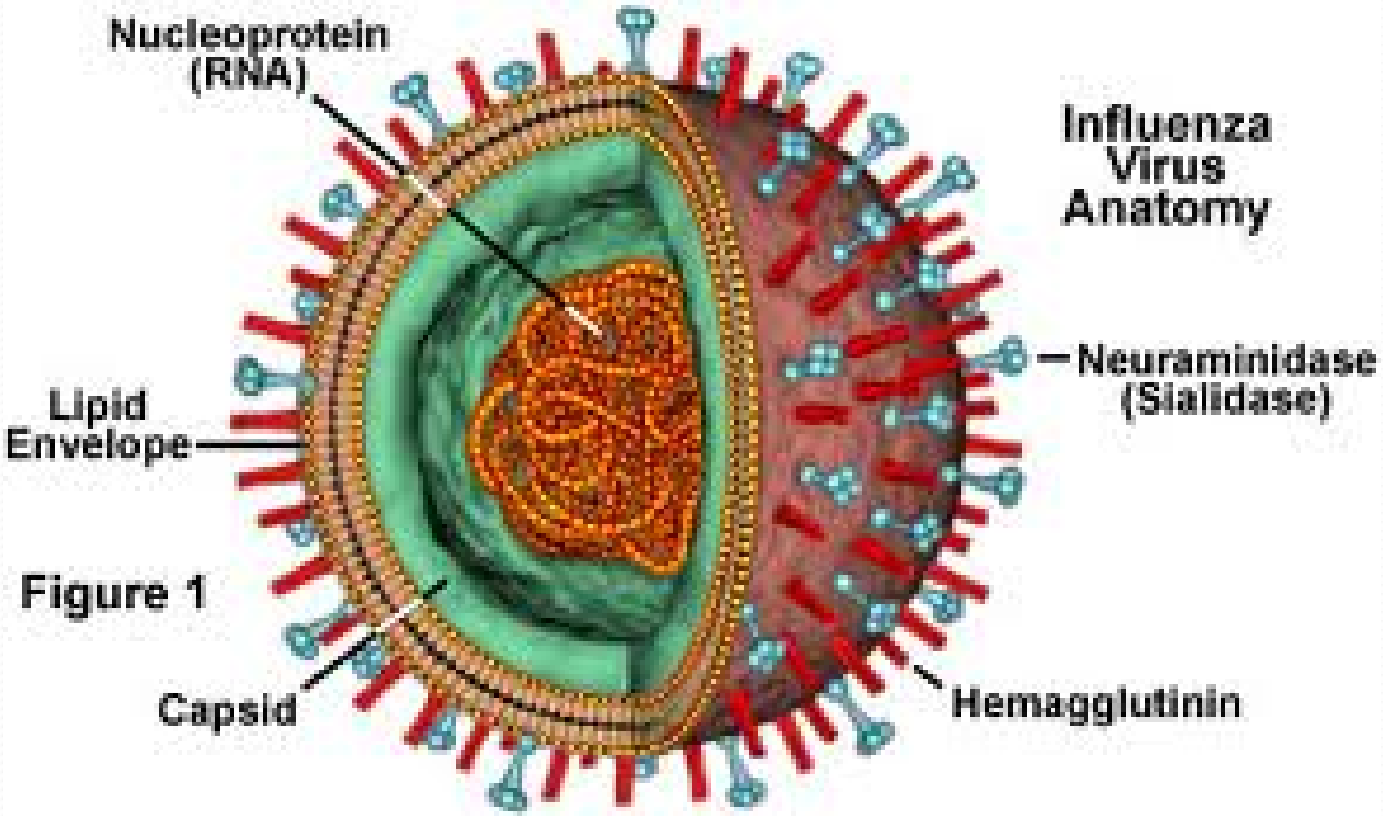
  - Hot drink Rhinology. 2008 Dec;46(4):271-5
  - Chicken Soup – increased nasal mucus velocity Chest. 1978 Oct;74(4):408-10.
  - Decongestants – topical or oral *Cochrane* 2007;(1):CD001953.

Not Recommended

- Airborne – not studied
- Nasal Zinc –may be associated with anosmia
- Cough
  - Beta-2 agonists Cochrane Database of Syst Reviews 2011, Issue 7. Art. No.: CD001726
  - Codeine Cochrane Database of Syst Reviews 2008, Issue 1. Art. No.: CD001831.
  - Antihistamine/decongestants – minimal decrease in one study, no change in another, with significant side effects

    Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD001831.
- Nasal Symptoms
  - Nasal steroids not effective J Allergy Clin Immunol 2000 Sep;106(3):467

Influenza


Nucleoprotein
(RNA)
Influenza
Virus
Anatomy
Neuraminidase
(Sialidase)
Lipid
Envelope
Figure 1
Capsid
Hemagglutinin

Common Cold	Influenza
Gradual onset of symptoms	Abrupt onset
Low-grade fever	Significant fever, usually >100 degrees F
	Chills sweats, fatigue
Less achiness	Muscle aches
Sore, itchy throat, stuffy and/or runny nose	Sore, itchy throat, runny nose
Sneezing	Photophobia (pain with bright light)
Very Annoying	Potentially Life-threatening

Influenza

- Average 23,600 deaths per year
- Mortality higher in
  - Pregnancy
  - Adults > 65 yo
  - Patients with comorbid conditions

  - MMWR Morb Mortal Wkly Rep 2010 Aug 27;59(33):1057

Diagnosis

- Clinical
  - fever, cough, acute onset sufficient during an outbreak
- Laboratory testing indicated if:
  - No recent cases locally
  - Hospitalized patient with suspected influenza
  - Results would change management

Laboratory Testing

- Point-of-care testing only indicated when virus is prevalent in community
- Rapid tests
  - Sensitivity 62.3% (95% CI 57.9%–66.6%)
    - Worse for influenza B
  - Specificity 98.2% (95% CI 97.5%–98.7%)
    - Ann Intern Med 2012 Apr 3;156(7):500

Treatment - Pharmaceutical

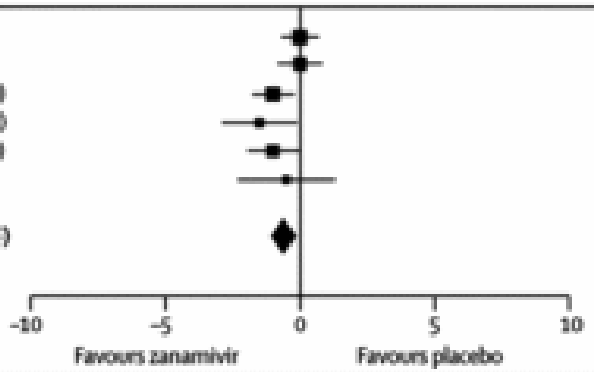
- Adamantines – amantadine, rimantadine
  - Only effective against influenza A
  - Not recommended in recent outbreaks based on antiviral resistance patterns
- Neuraminidase inhibitors
  - Oseltamivir 75 mg po bid (qd for Ccr 10 – 30 mL/min)x5d
  - Zanamivir 10 mg (2 inhalations) bid x 5 d
    - Not recommended in patients with airways disease
  - Resistance relatively low
    - 0.3 – 3% of Pandemic H1N1 in 2009
    - 0.2% in seasonal A(H3N2)

Efficacy - Duration

- Effective if started within 48 hours
  - Reduce symptom duration by 0.55 days
  - In higher-risk patients, reduce symptom duration by 0.74 days (oseltamivir) or 0.98 days (zanamivir)

Study or subgroup	Zanamivir		Total	Placebo		Total	Weight (%)	Median difference (95% CI)
	Median	SD		Median	SD			
Boivin 2000[9]	5	3·67	363	5	5·14	305	24·3	0·00 (−0·69 to 0·69)
GlaxoSmithKline NAI30011[5]	4·5	5·21	229	4·5	3·88	237	20·0	0·00 (−0·84 to 0·84)
Hayden 1997[11]	3·5	3·22	132	4·5	3·36	144	21·6	−1·00 (−1·78 to −0·22)
Makela 2000[12]	5	4·44	161	6·5	7·79	163	10·2	−1·50 (−2·88 to −0·12)
MIST 1998[14]	5	4·82	190	6	4·54	189	17·3	−1·00 (−1·94 to −0·06)
Puhakka 2003[10]	2·2	15·23	293	2·7	4·02	295	6·5	−0·50 (−2·30 to 1·30)
Total (95% CI)			**1368**			**1333**	**100·0%**	**−0·57 (−1·07 to −0·08)**

Heterogeneity: τ^2=0·14; χ^2=8·08, df=5 (p=0·15); I^2=38%
Test for overall effect: Z=2·26 (p=0·02)



Lancet Infect Dis. 2009 Sep;9(9):537-45. Epub 2009 Aug 7

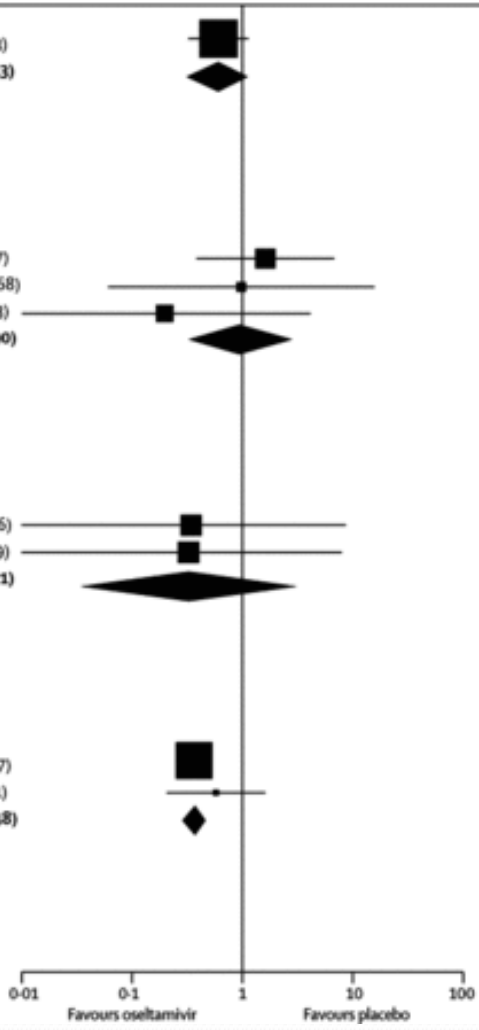
Efficacy - Complications

Complications Requiring Hospitalization

Pneumonia

Antibiotic use

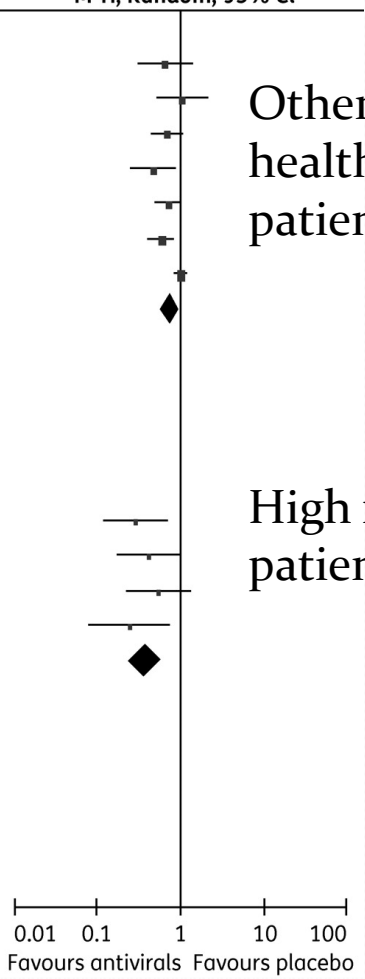
Study or subgroup	Oseltamivir Events	Oseltamivir Total	Placebo Events	Placebo Total	Weight (%)	Odds ratios (95% CI)
Overall complications						
Treanor 2000[29]	18	210	28	209	100·0	0·61 (0·32 to 1·13)
Subtotal (95% CI)		**210**		**209**	**100·0**	**0·61 (0·32 to 1·13)**
Total events	**18**		**28**			
Heterogeneity: Not applicable						
Test for overall effect: Z=1·57 (p=0·12)						
Complications requiring hospitalisation						
Deng 2004[33]	5	599	3	577	46·3	1·61 (0·38 to 6·77)
Nicholson 2000[27]	1	241	1	235	15·4	0·97 (0·06 to 15·68)
Treanor 2000[29]	0	210	2	209	38·2	0·20 (0·01 to 4·13)
Subtotal (95% CI)		**1050**		**1021**	**100·0**	**0·97 (0·33 to 2·90)**
Total events	**6**		**6**			
Heterogeneity: χ^2=1·53, df=2 (p=0·47); I^2=0%						
Test for overall effect: Z=0·05 (p=0·96)						
Pneumonia						
Kashiwagi 2000[32]	0	154	1	159	49·3	0·34 (0·01 to 8·46)
Nicholson 2000[27]	0	241	1	235	50·7	0·32 (0·01 to 7·99)
Subtotal (95% CI)		**395**		**394**	**100·0**	**0·33 (0·03 to 3·21)**
Total events	**0**		**2**			
Heterogeneity: χ^2=0·00, df=1 (p=0·98); I^2=0%						
Test for overall effect: Z=0·95 (p=0·34)						
Antibiotic use						
Deng 2004[33]	129	599	248	577	95·3	0·36 (0·28 to 0·47)
Nicholson 2000[27]	6	241	10	235	4·7	0·57 (0·21 to 1·61)
Subtotal (95% CI)		**840**		**812**	**100·0**	**0·37 (0·29 to 0·48)**
Total events	**135**		**258**			
Heterogeneity: χ^2=0·71, df=1 (p=0·40); I^2=0%						
Test for overall effect: Z=7·78 (p<0·00001)						



Lancet Infect Dis. 2009 Sep;9(9):537-45. Epub 2009 Aug 7

Complications of Influenza after Treatment with Neuraminidase Inhibitors vs. Placebo

Study or Subgroup	Antiviral group Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.11.1 Otherwise healthy patients with confirmed influenza infection						
Hayden 1997	14	173	11	89	7.3%	0.65 [0.31,1.38]
Nicholson 2000	21	314	10	161	7.5%	1.08 [0.52, 2.23]
Hedrick 2000	26	164	42	182	11.8%	0.69 [0.44,1.07]
Treanor 2000	17	245	19	129	8.9%	0.47 [0.25, 0.87]
Makela 2000	33	136	47	141	13.0%	0.73 [0.50, 1.06]
Whitley 2001	36	217	65	235	13.2%	0.60 [0.42,0.86]
Puhakka 2003	115	222	108	213	16.3%	1.02 [0.85, 1.23]
Subtotal (95% CI)		**1471**		**1150**	**78.0%**	**0.74 [0.58, 0.95]**
Total events	262		302			
Heterogeneity: $\tau^2=0.06$; $\chi^2=13.89$, df=6($P=0.03$); $I^2=57\%$						
Test for overall effect: $Z=2.38$ ($P=0.02$)						
1.11.2 High risk patients						
The MIST study group 1998	5	37	18	39	5.9%	0.29 [0.12, 0.71]
Murphy 2000	7	160	16	153	6.1%	0.42 [0.18, 0.99]
Makela 2000	4	12	11	18	5.9%	0.55 [0.23, 1.32]
Lin Jiang-tao 2006	3	27	13	29	41%	0.25 [0.08, 0.78]
Subtotal (95% CI)		**236**		**239**	**22.0%**	**0.37 [0.24, 0.59]**
Total events	19		58			
Heterogeneity: $\tau^2=0.00$; $\chi^2=1.59$, df=3($P=0.66$); $I^2=0\%$						
Test for overall effect: $Z=4.17$ ($P<0.0001$)						



Otherwise healthy patients

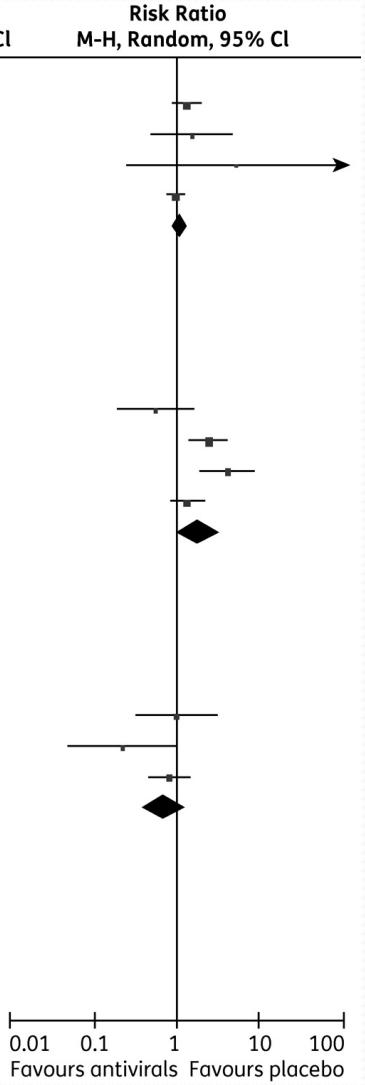
High risk patients

Falagas M E et al. J. Antimicrob. Chemother. 2010;65:1330-1346

Journal of Antimicrobial Chemotherapy

Adverse Events

Study or Subgroup	Antiviral group Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.10.1 Total adverse events						
Hayden 1997	66	273	26	144	13.9%	1.34 [0.89, 2.01]
Hedrick 2000	7	224	5	247	6.1%	1.54 [0.50, 4.79]
Lin Jiang-tao 2006	2	58	0	60	1.3%	5.17 [0.25, 105.42]
Puhakka 2003	77	293	80	295	15.6%	0.97 [0.74, 1.27]
Subtotal (95% CI)		**848**		**746**	**36.9%**	**1.10 [0.87, 1.40]**
Total events	152		111			
Heterogeneity: $\tau^2=0.00$; $\chi^2=3.14$, df=3 ($P=0.37$); $I^2=5\%$						
Test for overall effect: $Z=0.82$ ($P=0.41$)						
1.10.2 Nausea/vomiting						
The MIST study group 1998	5	227	9	228	6.5%	0.56 [0.19, 1.64]
Treanor 2000 (1)	74	411	15	204	12.3%	2.45 [1.44, 4.16]
Treanor 2000 (2)	58	411	7	204	9.4%	4.11 [1.91, 8.85]
Whitley 2001	31	217	25	235	12.8%	1.34 [0.82, 2.20]
Subtotal (95% CI)		**1266**		**871**	**41.0%**	**1.78 [0.91, 3.45]**
Total events	168		56			
Heterogeneity: $\tau^2=0.33$; $\chi^2=11.86$, df=3 ($P=0.008$); $I^2=75\%$						
Test for overall effect: $Z=1.69$ ($P=0.09$)						
1.10.3 Diarrhoea						
Puhakka 2003	6	293	6	295	6.2%	1.01 [0.33, 3.09]
The MIST study group 1998	2	227	9	228	4.1%	0.22 [0.05, 1.02]
Whitley 2001	19	217	25	235	11.8%	0.82 [0.47, 1.45]
Subtotal (95% CI)		**737**		**758**	**22.1%**	**0.70 [0.36, 1.37]**
Total events	27		40			
Heterogeneity: $\tau^2=0.12$; $\chi^2=2.85$, df=2 ($P=0.24$); $I^2=30\%$						
Test for overall effect: $Z=1.04$ ($P=0.30$)						



Total

Nausea/ Vomiting

Diarrhea

Falagas M E et al. J. Antimicrob. Chemother. 2010;65:1330-1346

Journal of Antimicrobial Chemotherapy

Treatment – Who?

- Severe, complicated or progressive illness
- Hospitalization Required
- At high risk for complications
  - chronic respiratory disease (including asthma and COPD)
  - chronic heart disease
  - chronic renal disease
  - chronic liver disease
  - chronic neurological conditions
  - diabetes mellitus
  - patients ≥ 65 years old
  - patients who are immunosuppressed

Elderberry

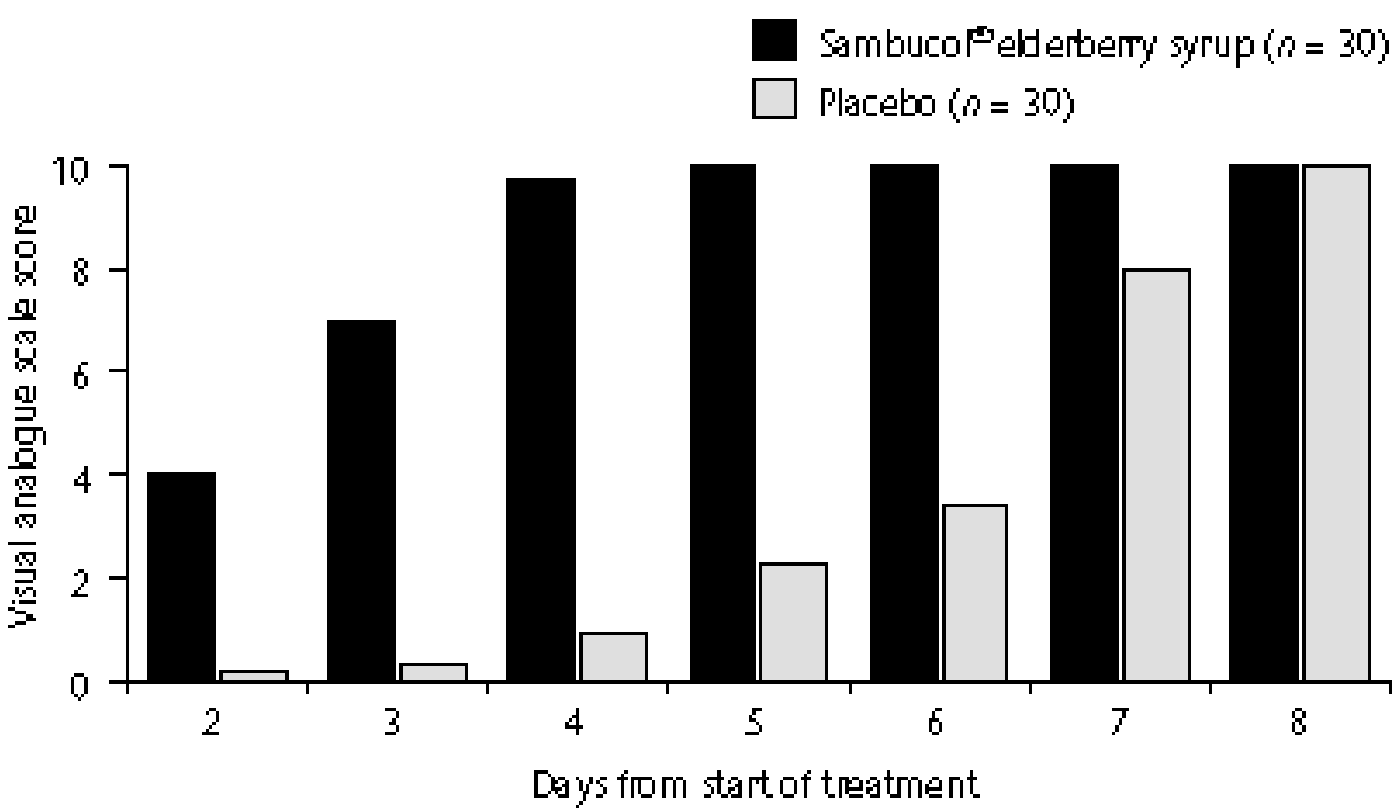


FIGURE 1: The development of self-evaluation scores in global well-being in the 60 patients with influenza who received either elderberry syrup or placebo (15 ml, four times daily with meals, for 5 days)

J Int Med Res 2;32 (2004):132-140

Elderberry

	Sambucus nigra	Placebo
Day "Improvement" Noted 1 day	20%	8.3%
2 days	73.3%	16.7%
3 days	6.7%	33.3%
Complete resolution 2 days	40%	16.7%
3 days	86.7	33.4%

Improvement before the 5th day OR 22.7 ($p<0.001$)
Complete cure before the 5th day OR 31.1 ($p<0.001$)

THE **JOURNAL** OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 1, Number 4, 1995. pp. 361-369

Oscillococcinum

- RR 1.5 for symptom resolution in 48 hours
- Shorten course by 0.3 days
  - The American Journal of Medicine – 120(11):923-929 (November 2007)

Better than a pound of cure. . . .

Handwashing/Hand Sanitizer and Absenteeism in Students

			Intervention		Control		
Trials		No. of students	No. of absences (no. of student-days)	Absenteeism rate per 100 student-days	No. of absences (no. of student-days)	Absenteeism rate per 100 student-days	Percent Relative Effect (95% CI)*
White et al. [41]		770	153 (9615)	1.59	222 (9459)	2.35	33 (17, 45)
Dyer et al. [27]	Phase 1	420	70 (4136)	1.69	105 (4120)	2.55	34 (10, 50)
	Phase 2	420	28 (4156)	0.674	63 (4140)	1.52	56 (31, 72)

BMC Public Health. 2004; 4: 50.

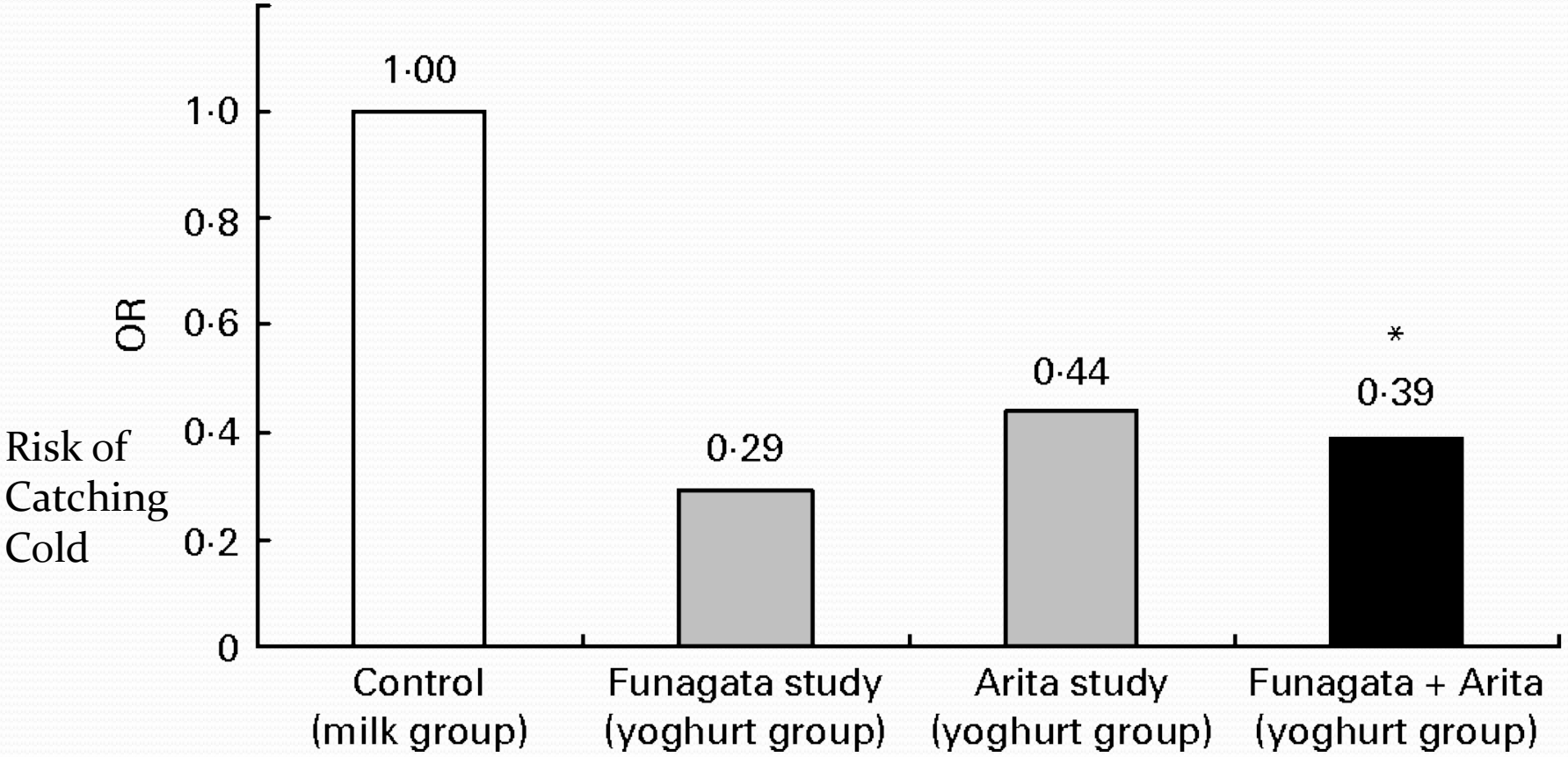
Garlic

- Allicin-containing supplement vs. placebo
- Colds:
  - 24 vs 65, P < .001
- Days of Sx:
  - 1.52 vs. 5.01, P<.001

Josling, P. (2001). Preventing the common cold with a garlic supplement: a double-blind, placebo-controlled survey. Advances in therapy, 18(4).

"Or maybe people just didn't get close enough to the garlic eaters to give them a virus."

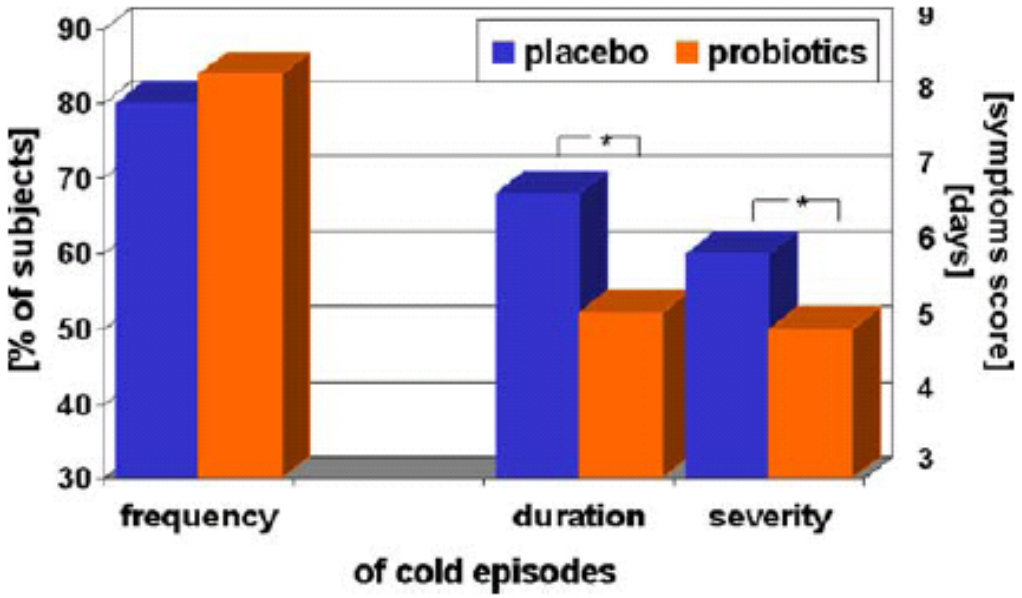
Probiotics in the Elderly



90 g yogurt vs. 100 mL milk in the elderly

British Journal of Nutrition / Volume 104 / Issue 07 / October 2010 , pp 998-1006

Probiotics and URI Prevention



Ages 18-67 No decrease in incidence, but decreased severity and duration

Clin Nutr 24:481–491; Lactobacillus gasseri PA 16/8, Bifidobacterium longum SP 07/3, B. bifidum MF 20/5

Same conclusion Vaccine. 2006 Nov 10;24(44-46):6670-4. Epub 2006 Jun 6

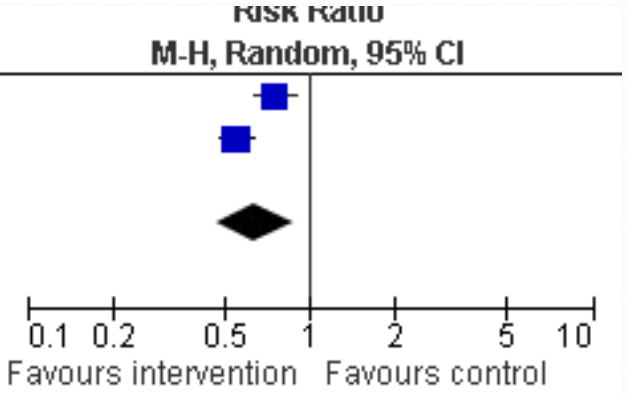
Also produce decreases in fever, clinic visits, child care absences, and antibiotic prescriptions in infants in daycare *Pediatrics*.2005; 115:5 -9.

Zinc for Prevention

Study or Subgroup	Intervention Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Kurugol 2006b	121	281	160	281	48.8%	0.76 [0.64, 0.90]
Vakili 2009	170	480	310	480	51.2%	0.55 [0.48, 0.63]
Total (95% CI)		**761**		**761**	**100.0%**	**0.64 [0.47, 0.88]**
Total events	291		470			

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 8.39$, df = 1 (P = 0.004); $I^2 = 88\%$

Test for overall effect: Z = 2.76 (P = 0.006)



15 mg daily in kids

Cochrane Database Syst Rev. 2011;(2):CD001364

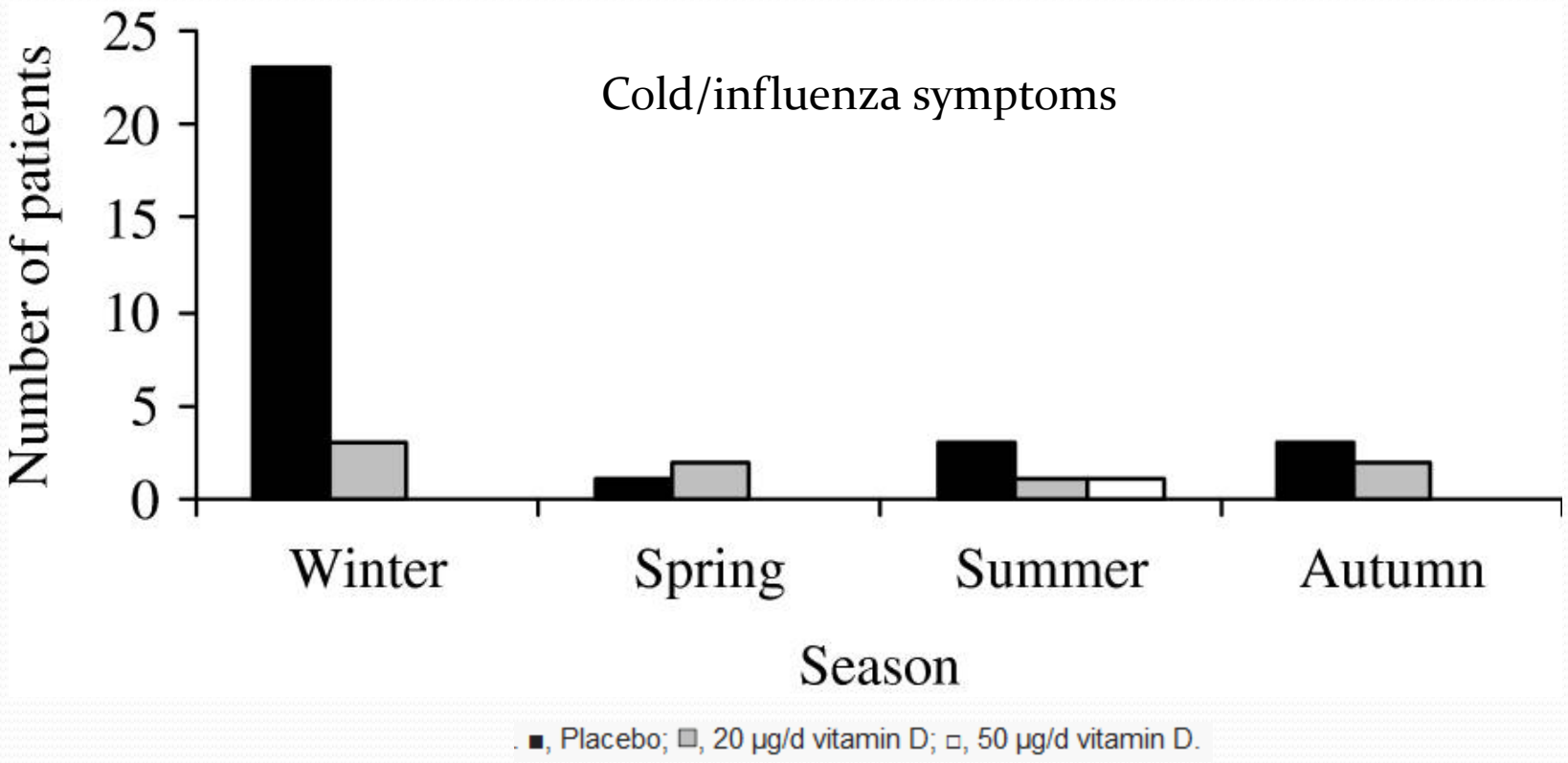
Vitamin D

- Schoolchildren 6-15 yo, 1200 IU D3/d Dec thru March

Subjects with influenza A			
D3 (%)	Placebo (%)	RR	P value
10.8	18.6	0.58	0.04

Am J Clin Nutr May 1, 2010 vol. 91 no. 5 1255-1260

Adults (African American postmenopausal women) treated with 800 IU vitamin D x 2 years then 2000 IU vitamin D x 1 year (vs. placebo)



Epidemiol Infect. 2007 October; 135(7): 1095–1098

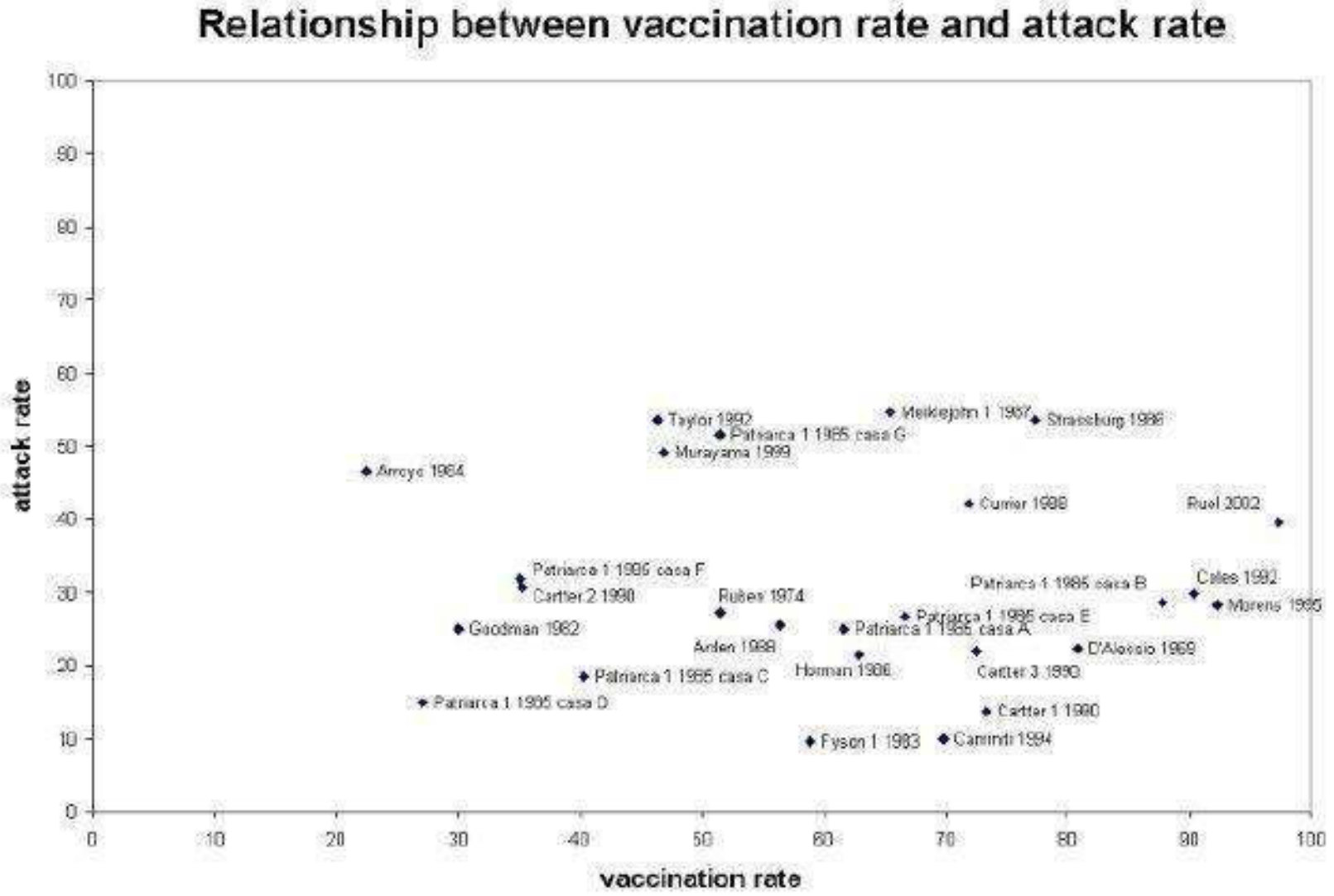
Military recruits 400 IU vitamin D: 51.3% remained healthy vs. 35.7% placebo; p=0.045
J Infect Dis. (2010) 202 (5): 809-814.

And finally. . . .

- Flu vaccine
- Prophylactic treatment of flu exposed patients with neuraminidase inhibitors – not adddressed

Overall Vaccine Efficacy

- Better when vaccine is well-matched to circulating strains
- Adults: reduce infection and slightly reduce absence from work; no evidence they reduce transmission, hospitalization, pneumonia, or death.
- Medical staff and patients: decrease mortality of patients in long-term care
- Little good-quality evidence for the older population in general, however. Clinical Evidence June 2008



- Cochrane Database of Systematic Reviews 2010 issue 2 Art No CD004876
- In the elderly

Flu shots in the elderly. . .

- Vaccinated vs. unvaccinated patients
  - Mean hospitalization rates per season 0.6% vs. 0.7%
  - Mean mortality per season 1% vs. 1.6% (NNT 166)
  - This was statistically significant after adjusting for other variables
    - N Engl J Med 2007 Oct 4;357(14):1373

Seasonal Flu Shot Increased Risk of H1N1 illness in 2009

- Based on cohort study and 3 case-control studies in Canada
- OR 1.4 – 2.5
  - PLoS Med 2010 Apr 6;7(4):e1000258
- Study in US suggested vaccine effectiveness -0.10%
  - MMWR Morb Mortal Wkly Rep. 2009 Nov 13;58(44):1241-5