Judicious (Appropriate) Antibiotic Use in the Pediatric Office Setting

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Outline of today's presentation

- Antimicrobial Resistance
- Antibiotic Use
- Treatment of Common Infections
- Clinician and Parent Perceptions of Antibiotic Use
- The microbiome

Framing the Issue

- Although antibiotics have saved countless lives, their use is not benign
- Antibiotic resistance is occurring in populations and individual patients
- At least 5% of hospitalized patients experience an adverse reaction
  - Rash, nephrotoxicity, *C. difficile* infection
- 50% are prescribed for people who do not need them or are not prescribed appropriately
- Very few antibiotics are being developed

Antibiotic Resistance

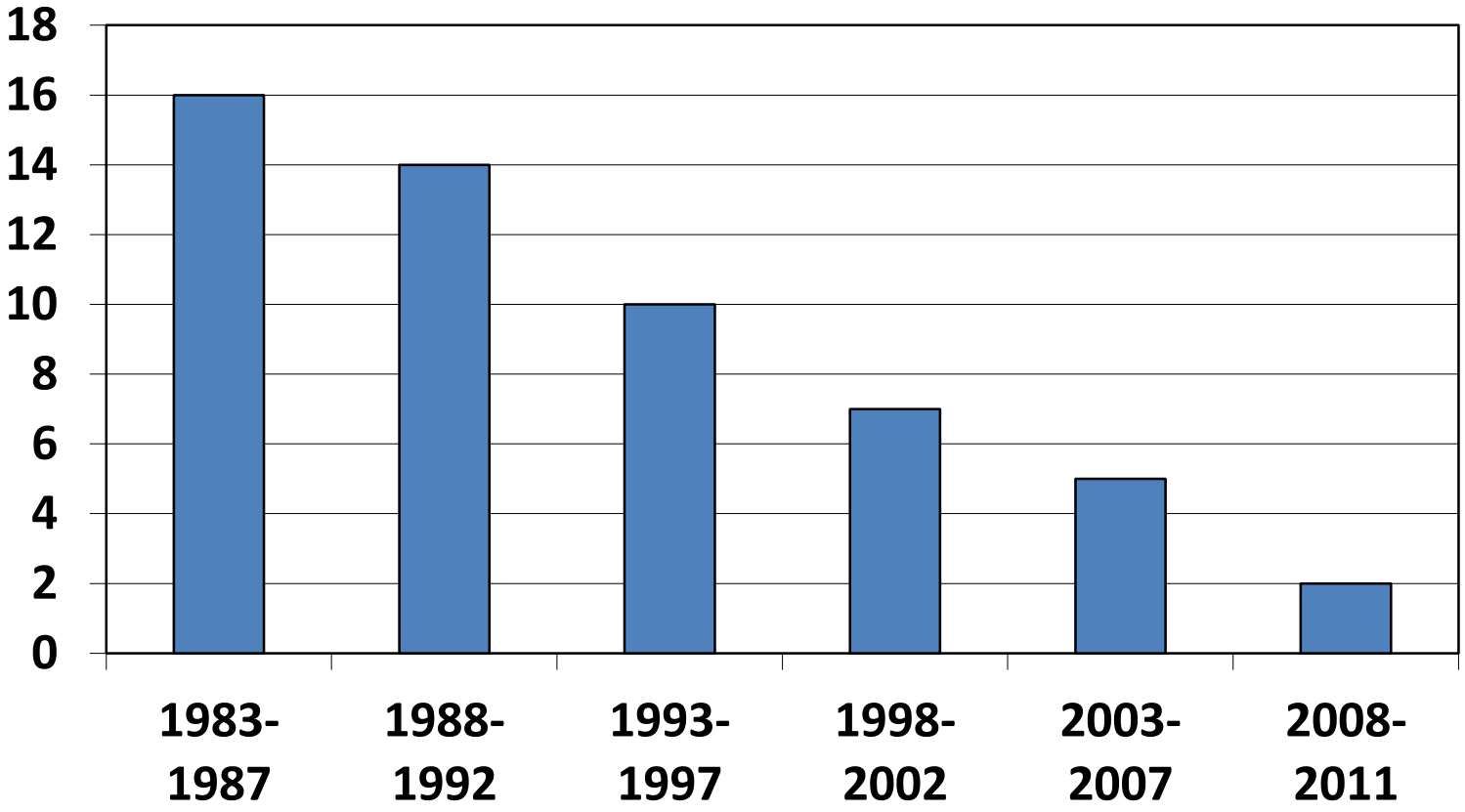
- CDC described antibiotic resistance as "one of the world's most pressing health problems”

- WHO has identified antibiotic resistance as "one of the three greatest threats to human health.”

Impact of Antibiotic Resistance

- Patients with resistant infections are at higher risk for disability and death
- $20 billion in excess direct healthcare costs with additional costs to society of $35 billion
- Loss of effective antibiotics
- Increased number of immunosuppressed patients
- Drug development is not sufficient to deal with this threat

New Antibacterial Agents Approved 1983-2011



Adapted from Spellberg B et al. Clin Infect Dis. 2004;38:1279-86.

Η Ελλάδα έχει ένα από τα *υψηλότερα* ποσοστά αντιμικροβιακής αντοχής στην Ευρώπη

Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net)

Estimated minimum number of illnesses and deaths caused annually by antibiotic resistance*:

At least **2,049,442** illnesses,

23,000 deaths

**bacteria and fungus included in this report*

INVITED ARTICLE ANTIMICROBIAL RESISTANCE

George M. Eliopoulos, Section Editor

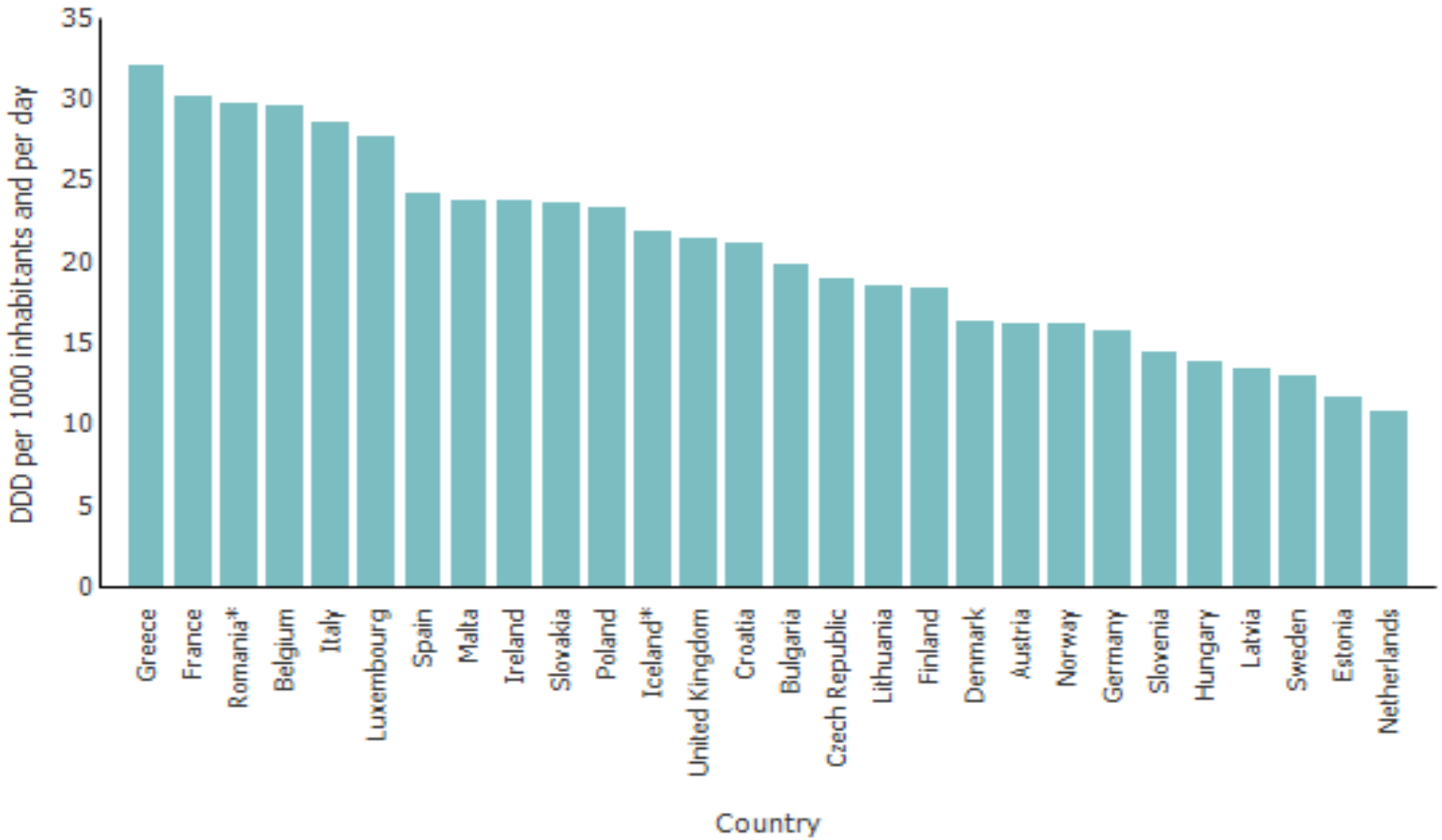
The Challenges of Antimicrobial Drug Resistance in Greece

Spiros Miyakis,[1] Angelos Pefanis,[2] and Athanassios Tsakris[3]

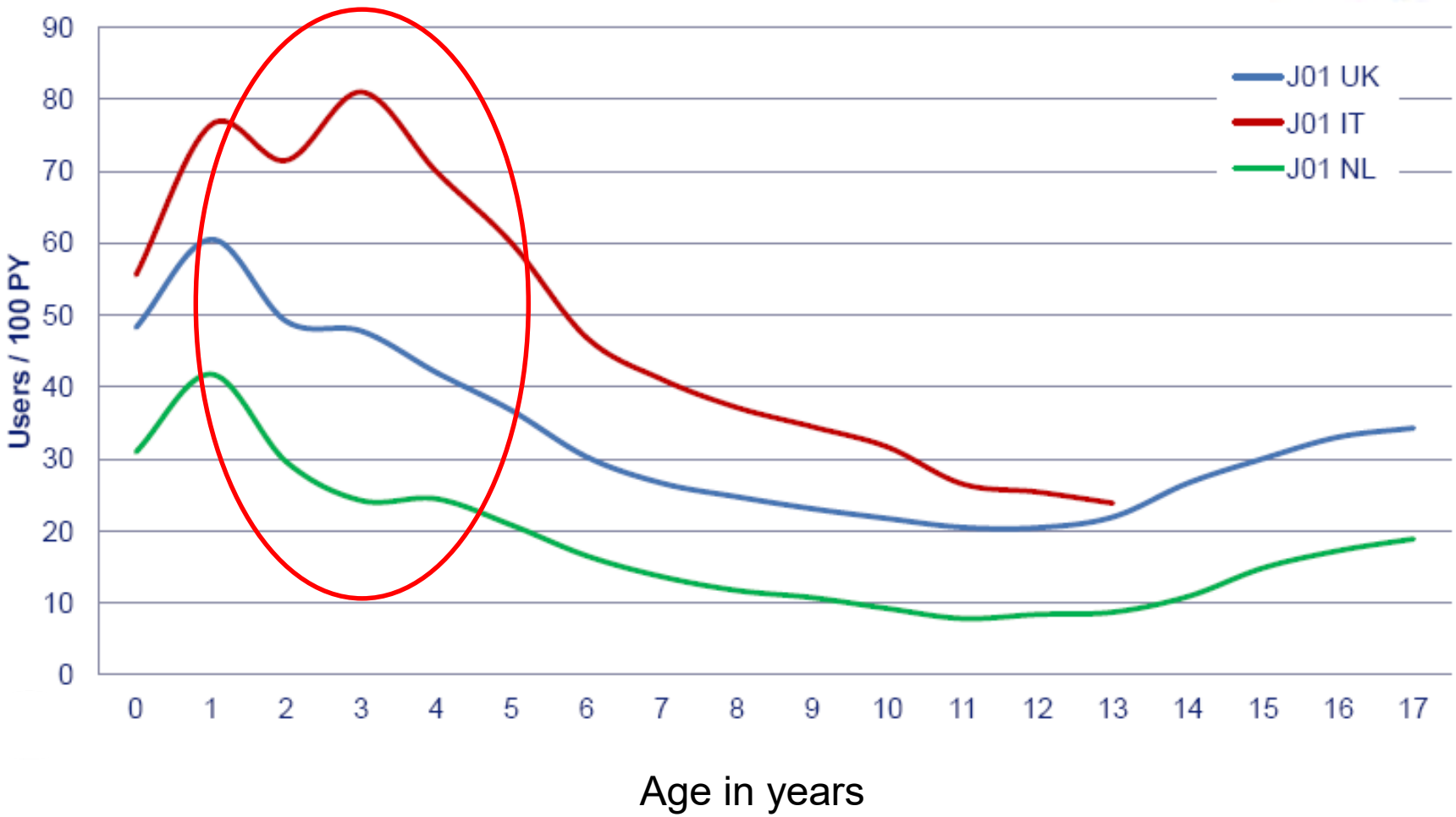
[1]Infectious Diseases Clinic, Third Department of Medicine, Aristotle University of Thessaloniki, "Papageorgiou" Hospital, Thessaloniki, Greece; [2]Department of Internal Medicine, "Sotiria" Chest Diseases and General Hospital of Athens, Athens, Greece; and [3]Department of Microbiology, Medical School, University of Athens, Athens, Greece

Clinical Infectious Diseases 2011;53(2):177–184

Consumption of antimicrobials of Antibacterials For Systemic Use (ATC group J01) in the community (primary care sector) in Europe, reporting year 2013



Antibacterial use by age in 2010 (ARPEC study)



Data provided by S. Debie and M. Sturkenboom

Antibiotic use for ARTIs

- acute respiratory infections (ARTIs) constitute about 10% of all ambulatory care visits in the United States and account for 44% all antibiotic prescriptions

- 21% of all ambulatory visits for children, 72% for ARTI

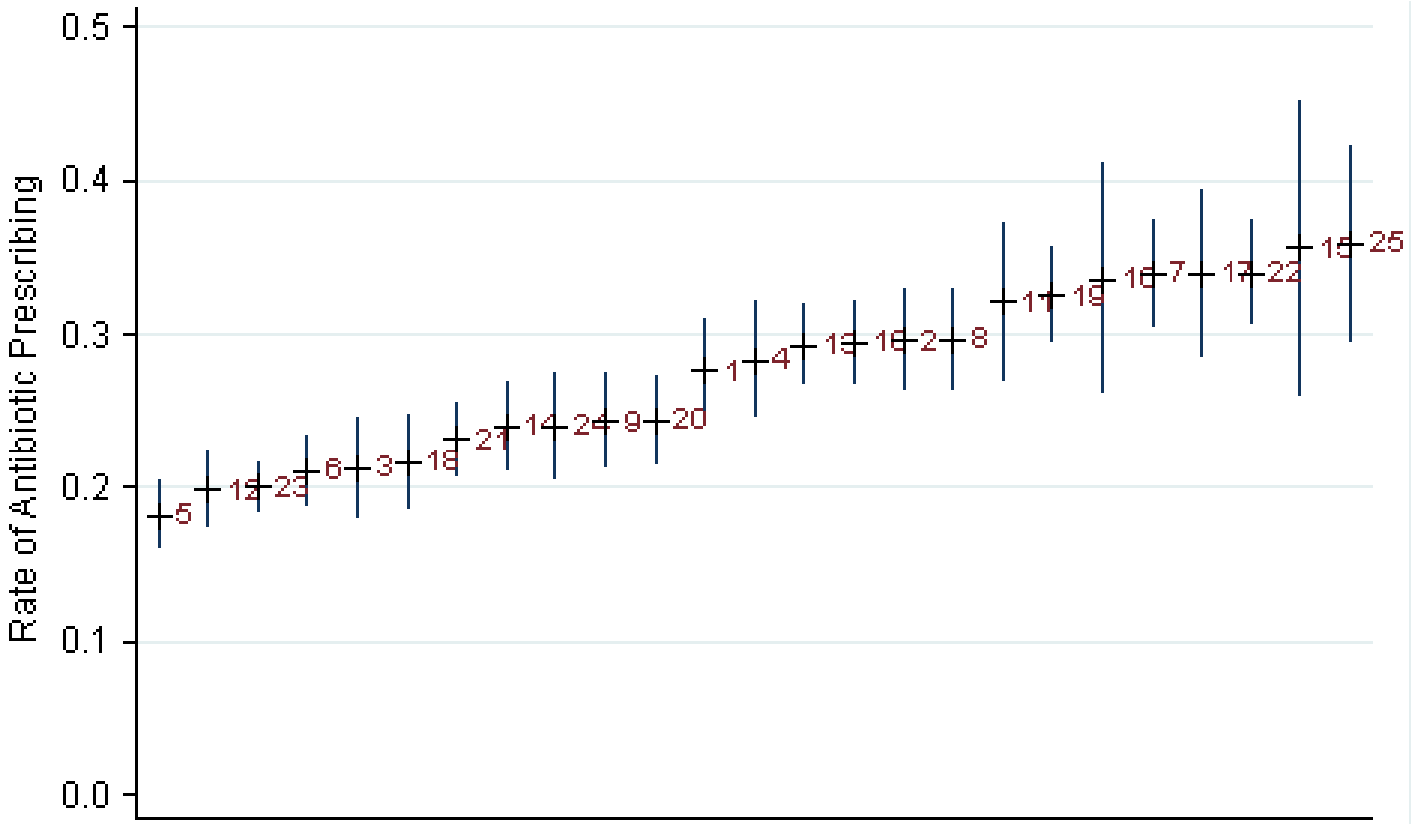
Grijalva *JAMA* 2009;302(7):758-766
Hersh *Pediatrics* 2011;128;1053

Antibiotics in Outpatient Pediatrics in Greece

- 2010 -2013, IMS database
- More than 7 million prescriptions 1100 antibiotics/1000 persons
- Acute respiratory tract infections accounted for 80% of prescriptions
  - Acute otitis media (22.3%)
  - Acute tonsillitis (19.5%)
  - Acute bronchitis/bronchiolitis (13.9%)
- Antibiotics
  - Cephalosporins (32.9%)
  - penicillins (32.3%)
  - macrolides (32.1%).
  - The majority (90.4%) of antibiotics were broad spectrum
  - Antibiotic expenditures totaled ~€50 million.

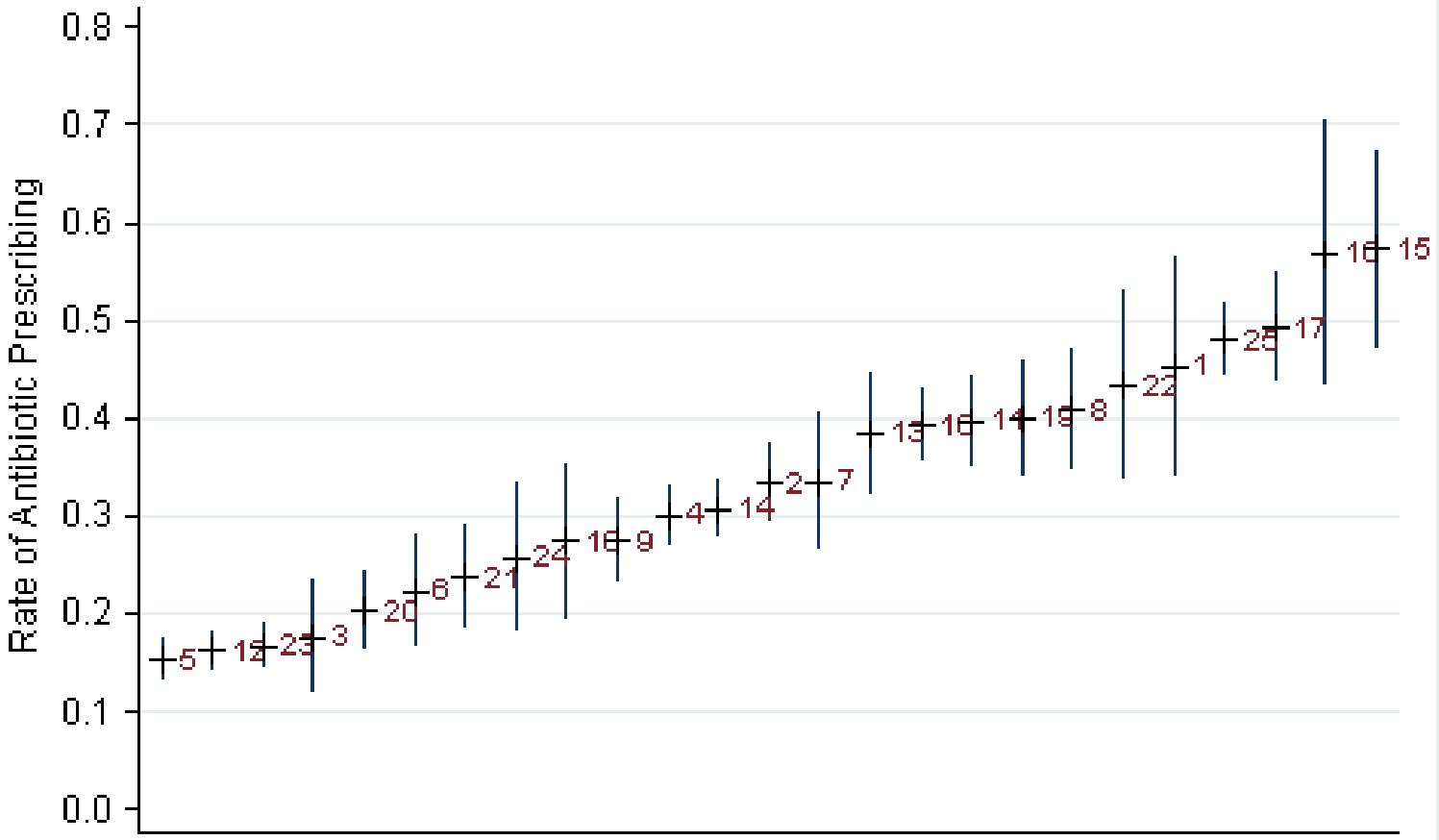
Kourlaba G, et al. J Antimicrob Chemother. 2015

Antibiotic Prescribing for Sick Visits in the Outpatient Setting



Gerber JS, et al. JPIDS in press

Broad Antibiotic Prescribing in the Outpatient Setting



Gerber JS, et al. JPIDS in press

Improving Antibiotic Use/Stewardship

- The use of antibiotics is the single most important factor leading to antibiotic resistance and the single most important action needed to greatly slow the development and spread of resistance
- Commitment to always use antibiotics appropriately and safely-only when they are needed to treat disease, and to chose the right antibiotics and to administer them in the right way in every case = antibiotic stewardship

Resistance Aside. . .

- 5%–25% diarrhea
- 1 in 1000 visit emergency department for adverse effect of antibiotic
  - comparable to insulin, warfarin, and digoxin
- 1 in 4000 chance that an antibiotic will prevent serious complication from ARTI

Shehab N. **CID 2008:47**; Linder JA. **CID 2008:47**

Non-Specific Upper Respiratory Tract Infection (URI)

- Symptoms of the common cold and bronchitis such as cough, congestion and sore throat account for 70% of prescriptions in US
- In absence of sinusitis, otitis media, pharyngitis antibiotics should not be prescribed
- Management should focus on symptomatic relief

Hersh A, et al. Pediatrics 2013

Table 3 | **Duration of common respiratory tract infections in children in current systematic review compared with current advice from UK National Institute for Health and Care Excellence (NICE) and the US Centers for Disease Control and Prevention (CDC)**

	Time (days, unless otherwise stated) for symptoms to resolve		Average illness duration (days)	
	In 50% of children	In 90% of children	NICE*	CDC
Croup	1	2*	—	—
Earache/otitis media	3	7-8	4	2-3†
Sore throat/tonsillitis	—	2-7‡	7	7-14§
Non-specific respiratory tract infection	7	16¶	—	—
Common cold	10	15**	10-11	14††
Acute cough	10	25	21	10-14‡‡
Bronchiolitis	13	21§§	—	—

*No of days to 80% resolution.

†Data from www.cdc.gov/getsmart/campaign-materials/info-sheets/child-otitismedia.pdf

‡Data not sufficient to calculate pooled proportions or time to 50% or 90% resolution; figures shown are ranges from included studies for days to complete resolution.

§Data from www.cdc.gov/getsmart/antibiotic-use/URI/sore-throat.html

¶Data from pooled proportions did not extend beyond time to 80% resolution (14 days), data presented is estimate for time to 90% resolution from fig 9.

**Data from pooled proportions did not extend beyond time to 60% resolution (10 days), figure shown is estimate for time to 90% resolution from fig 8.

††Data from www.cdc.gov/getsmart/campaign-materials/info-sheets/child-rhin-vs-sinus.pdf

‡‡Data from www.cdc.gov/getsmart/campaign-materials/info-sheets/child-cough-illness.pdf

§§No of days estimated from fig 7. Time to 60% resolution was 16 days.

Thompson M, Vodicka TA, Blair PS, Buckley DI, Heneghan C, Hay AD; TARGET Programme Team: Duration of symptoms of respiratory tract infections in children: systematic review. BMJ. 2013 Dec 11;347:f7027.

How to distinguish bacterial sinusitis from URI

- Symptoms that are either worsening, severe, or persistent
  - Worsening symptoms: worsening or new onset fever, daytime cough or nasal discharge after improvement of viral URI
  - Severe symptoms: fever > 39, purulent nasal discharge
  - Persistent symptoms without improvement: nasal discharge or daytime cough > 10 days

Bacteriology of Sinusitis and Acute Otitis Media

- *Streptococcus pneumoniae* *25-50%*
  - 15-30% are penicillin non-susceptible
- *Haemophilus influenzae* *15-30%*
  - 50% are beta-lactamase positive
- *Moraxella catarrhalis* 3-20%
  - 100% are beta-lactamase positive
- Viruses 40-75%

Time above the MIC (beta-lactams)

Drug	Susceptible	Intermediate	Resistant
Amoxicillin	100	59	46
Amox/clav	100	59	46
Cefaclor	44	0	0
Cefuroxime	73	33	0
Cefixime	48	0	0
Cefpodoxime	62	0	0
Cefprozil	78	28	0
Loracarbef	42	0	0

Amoxicillin as Initial Therapy

- Effective against most pneumococci
- *H.flu* and *M.cat* often resolve spontaneously
- Safety
- Low cost
- Acceptable taste
- Narrow spectrum

Why do we give antibiotics?

- To resolve clinical infection
- Pain
- To prevent complications

Evidence Assessment of Management of AOM

- Natural history of AOM
  - 78% of children would have experienced clinical resolution within 4 – 7 days of diagnosis in the absence of any antibiotic therapy
  - 1211 children without antibiotic treatment – estimate of incidence of mastoiditis 1 per 1000 (95% CI: 0-5)

Takata, et al Pediatrics 2001;108:239-247

Natural History of AOM

- Varies by organism
- Spontaneous resolution rates:
  - *S. pneumoniae* 20%
  - *H. influenzae* 50%
  - *Moraxella catarrhalis* 80%

Evidence Assessment of Management of AOM

- Antibiotic Versus No Antibiotic
  - Clinical failure at 2 to 7 days of those receiving either ampicillin or amoxicillin was 12%
  - In clinical terms, 8 children would have to be treated with amoxicillin or ampicillin to avoid clinical failure during this time frame
    - » Takata, et al Pediatrics 2001;108:239-247

Cochrane Acute Respiratory Infections Group

- Ten trials
- 2,287 children
- No reduction in pain at 24 hours
- 30% relative reduction (95% CI: 19-40) in pain at 2-7 days
- Absolute reduction of about 7% or about 15 children must be treated with antibiotics to prevent one child having pain after 2 days
  - » Glaziou, et al. Cochrane Database of Systematic Reviews. 2, 2004

Mastoiditis

- Antibacterial treatment often cited for decrease in rate of mastoiditis
- Pooled data from 6 clinical trials and 2 cohort studies
  - 0.59% in those that received initial antibiotics vs 0.17% in those who were observed (p=.212)
- Mastoiditis can occur without prior AOM
- 36-78% of patients with mastoiditis have received prior antimicrobial therapy

Mastoiditis

- Incidence rates of mastoiditis higher in the Netherlands, Norway, and Denmark than in US
- However, Norway and Denmark used antimicrobials twice as often than the Netherlands but no difference in incidence of mastoiditis

» Van Zuijlen, et al. Pediatr Infect Dis 2001;20:140-44

Bacteremia and Meningitis in Children with AOM

- Bacteremia may accompany AOM, esp. if temperature > 39 degrees Celsius
- 4860 children with AOM and no therapy – no cases of meningitis
- 240 children aged 6-24 months, one child with meningitis in placebo group
- Positive blood cultures as common in those receiving pre-admission antibiotics for AOM (77% vs. 78%)
  - » Van Buchem FL et al. Br Med J 1985;290:1033-37
  - » Damoiseaoux RA, et al. BMJ 2000;320:350-54
  - » Kilpi T, et al. Lancet 1991;338:406-9.

Pharyngitis

- Diagnosis of streptococcal pharyngitis requires culture
- Test if 2 of the following are present:
  - Fever
  - Tonsillar exudate/swelling
  - Swollen anterior cervical nodes
  - Absence of cough

Hersh et al. Pediatrics 2013

Causes of Exudative Pharyngitis

- Bacteria
- S. pyogenes
- A. haemolyticum
- Group C Streptococci
- N. gonorrheae
- C. diphtheriae
- Y. enterocolitica
- Atypicals

- Viruses
- Epstein Barr virus
- Enterovirus
- Adenovirus
- Influenza virus
- Herpes simplex virus

Group A streptococcal Pharyngitis

- Antibiotics shorten symptom duration
- Amoxicillin or penicillin
- Prevent rheumatic fever
- May limit secondary transmission
- Therapy may prevent suppurative complications – abscess
  - HOWEVER, number needed to treat is > 4000

Hersh et al. Pediatrics 2013

Viral Pneumonia

Common	Less Common
RSV	Varicella
Influenza A & B	Enteroviruses
Parainfluenza (1, 2, 3)	Cytomegalovirus
Adenovirus	Epstein-Barr virus
Human metapneumovirus	Herpes simplex virus
Coronavirus (NH)	Measles

Bacterial Pneumonia

Common	Less Common
S. pneumoniae	*S. pyogenes*
S. aureus	Anaerobes
*H. influenzae**	*B. pertussis*
	Gram-negative rods
	F. tularensis

Antibiotic Choice- Outpatient

Age of Child	Infant /Preschool Aged		School Aged	
Recommendation	**No antibiotics**	**Amoxicillin**	**Amoxicillin**	**Azithromycin**
Comments	Antibiotics NOT routinely required, because viral pathogens are most prevalent.	First-line therapy if previously healthy & immunized. Provides excellent coverage for *S. pneumoniae*	First-line therapy if previously healthy & immunizedP. Consider atypical bacterial pathogens.	For treatment of older children with findings compatible with CAP **caused by atypical pathogens.**
Strength	**Strong**	**Strong**	**Strong**	**Weak**
Evidence Quality	**High**	**Moderate**	**Moderate**	**Moderate**

What is the evidence for durations that we use?

- With few exceptions, the length of most courses of antibiotic therapy are arbitrary
- Historically, duration of therapy has not been a considered a problem because:
  - Plenty of available antibiotics
  - Extra antibiotic days were not considered to be harmful
  - Extra antibiotic days made of doctors feel better
  - Lots of clinical trials use long duration as a default

Duration of Community-acquired Pneumonia Therapy

- 1993 ATS Guidelines: 7-10 days
- 1998 IDSA Guidelines: 7-14 days
- 2007 ATS/IDSA Guidelines: minimum of 5 days
- PIDS/IDSA Guidelines:
  - Treatment courses of 10 days have been best studied, although shorter courses may be just as effective, particularly for more mild disease managed on an outpatient basis. ***(strong recommendation; level of evidence moderate)***

Shorter Works!

- Uncomplicated cellulitis
  - 5 days equal to 10 days in RCT
- Uncomplicated cystitis
  - 3 days with TMP/SMX or quinolone
  - 5 days with nitrofurantoin
  - 7 days with cephalosporins
- Pyelonephritis
  - 7 days if using ciprofloxacin; 5 days if using levofloxacin (750 mg)

Chastre et al. JAMA 2003; Warren JW, et al. Clin Infect Dis 1999; Hooten TM, et al. Clin Infect Dis; Talan DA et al. JAMA 2000; Peterson J et al. Urology 2008

What do clinicians think?

Qualitative Analyses

- most did not believe that their prescribing behavior contributed to antibiotic overuse
- reported frequently confronting parental pressure, sometimes acquiescing to:
  - appear competent
  - avoid losing patients to other practices that would “give them what they want”
  - provide comfort to anxious parents
  - help with upcoming travel, family celebrations, parent work schedules

Szymczak, *ICHE*, 2014, vol. 35, no. s3

“We have lots of parents who come in and they know what they want. They don’t care what we have to say. They want the antibiotic that they want because they know what is wrong with their child.”

Szymczak, *ICHE*, 2014, vol. 35, no. s3

Clinician Perceptions: Pediatrics

- interviewed 10 physicians, 306 parents
- physician perception of parental expectations for antimicrobials was the only predictor of prescribing antimicrobials for viral infections
  - when they thought parents wanted antimicrobial:
    - 62% vs. 7% prescribed antibiotic
- prescribing behavior was not associated with actual parental expectations for receiving antimicrobials

Mangione-Smith et al. *Pediatrics* 1999;103(4)

What do parents think?

Clinician Perceptions: Pediatrics

- direct parental request for antibiotics in 1% of cases
- parental expectations for antibiotics were not associated with physician-perceived expectations
- parents who expected antibiotics but did not receive them were more satisfied if the physician provided a contingency plan
- failure to meet parental expectations regarding communication events during the visit was the only significant predictor of parental satisfaction (NOT failure to provide expected antimicrobials)

Mangione-Smith et al. *Arch Pediatr Adolesc Med* 2001;155:800-806

Communication

- parent and clinician surveys after 1,285 pediatric ARTI visits to 28 pediatric providers from 10 practices in Seattle

- positive treatment recommendations (suggesting actions to reduce child's symptoms) were associated with decreased risk of antibiotic prescribing whether done alone or in combination with negative treatment recommendations (ruling out the need for antibiotics)

Mangione-Smith et al. *Ann Fam Med* 2015;13:221-227

Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial

Paul Little, Beth Stuart, Nick Francis, Elaine Douglas, Sarah Tonkin-Crine, Sibyl Anthierens, Jochen W L Cals, Hasse Melbye, Miriam Santer, Michael Moore, Samuel Coenen, Chris Butler, Kerenza Hood, Mark Kelly, Maciek Godycki-Cwirko, Artur Mierzecki, Antoni Torres, Carl Llor, Melanie Davies, Mark Mullee, Gilly O'Reilly, Alike van der Velden, Adam W A Geraghty, Herman Goossens, Theo Verheij, Lucy Yardley, on behalf of the GRACE consortium

- 246 practices, 4264 patients in 6 European countries
- training in enhanced communication skills – gathering information on patient concerns/expectations; exchange of information on symptoms, natural disease course, and treatments; agreement of a management plan
- communication training led to a >30% reduction in antibiotic prescribing for ARTI

www.thelancet.com **Vol 382 October 5, 2013**

Effect of an Outpatient Antimicrobial Stewardship Intervention on Broad-Spectrum Antibiotic Prescribing by Primary Care Pediatricians: A Randomized Trial

Gerber JS, Prasad PA, Fiks AG, Localio AR, Grundmeier RW, Bell LM, Wasserman RC, Keren R, Zaoutis TE:

JAMA. 2013 Jun 12;309(22):2345-52

From: **Effect of an Outpatient Antimicrobial Stewardship Intervention on Broad-Spectrum Antibiotic Prescribing by Primary Care Pediatricians: A Randomized Trial**

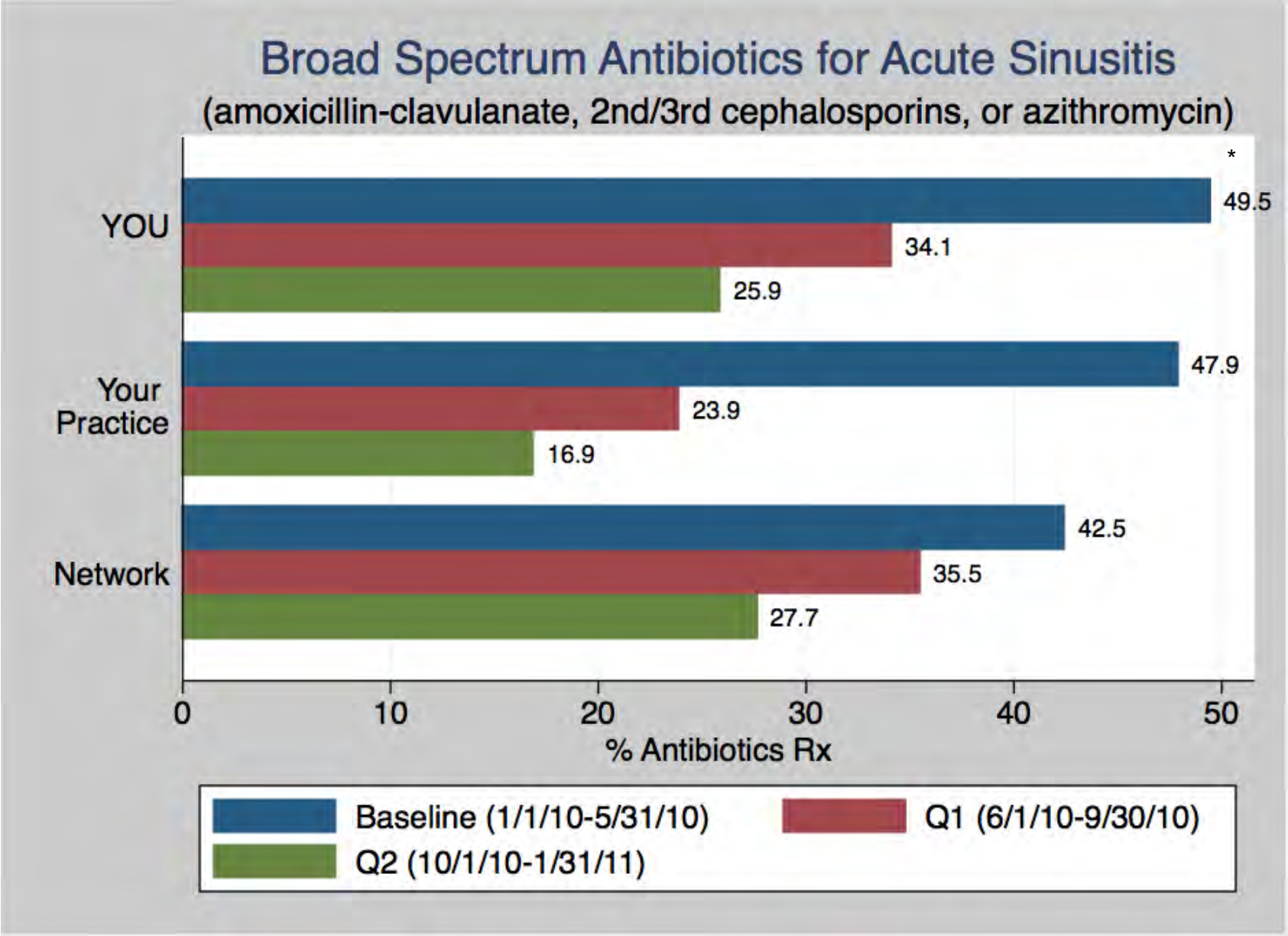
JAMA. 2013;309(22):2345-2352. doi:10.1001/jama.2013.6287

Figure Legend:

[a]Three clinicians in the intervention group and 5 in the control group did not attend acute-care encounters during the study period.

Antimicrobial Stewardship Intervention

- Guideline development
- Education
- **Prescribing Audit and Feedback**


Broad Spectrum Antibiotics for Acute Sinusitis
(amoxicillin-clavulanate, 2nd/3rd cephalosporins, or azithromycin)
YOU
Your Practice
Network
*
49.5
34.1
25.9
47.9
23.9
16.9
42.5
35.5
27.7
0
10
20
30
40
50
% Antibiotics Rx
Baseline (1/1/10-5/31/10)
Q1 (6/1/10-9/30/10)
Q2 (10/1/10-1/31/11)

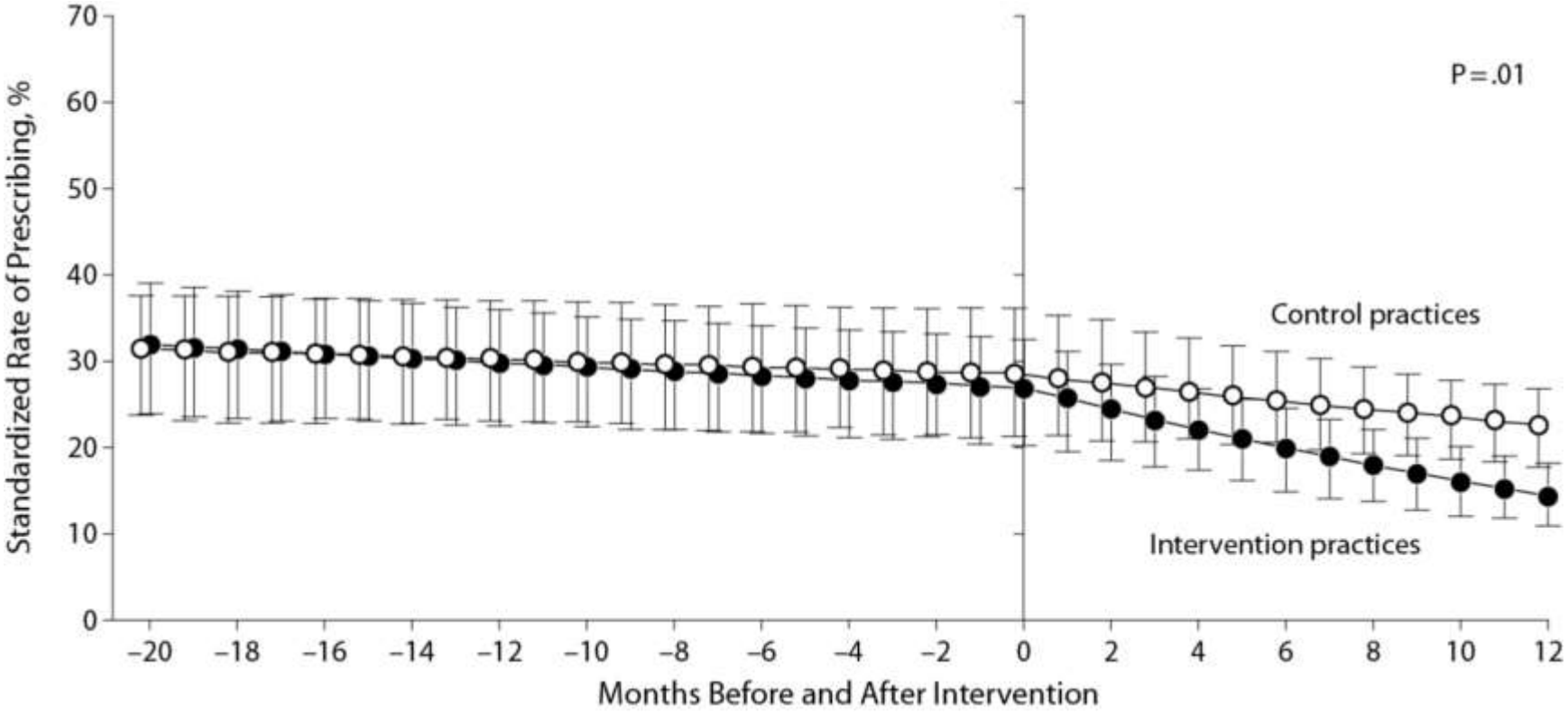


Figure Legend:

The estimate of interest (and associated P value) is the treatment × time interaction term, representing the relative changes in trajectories before and during the intervention. Error bars indicate 95% CIs.

Gerber JS, Prasad PA, Fiks AG, Localio AR, Grundmeier RW, Bell LM, Wasserman RC, Keren R, Zaoutis TE: Effect of an outpatient antimicrobial stewardship intervention on broad-spectrum antibiotic prescribing by primary care pediatricians: a randomized trial. JAMA. 2013 Jun 12;309(22):2345-52

From: **Durability of Benefits of an Outpatient Antimicrobial Stewardship Intervention After Discontinuation of Audit and Feedback**

JAMA. Published online October 10, 2014. doi:10.1001/jama.2014.14042

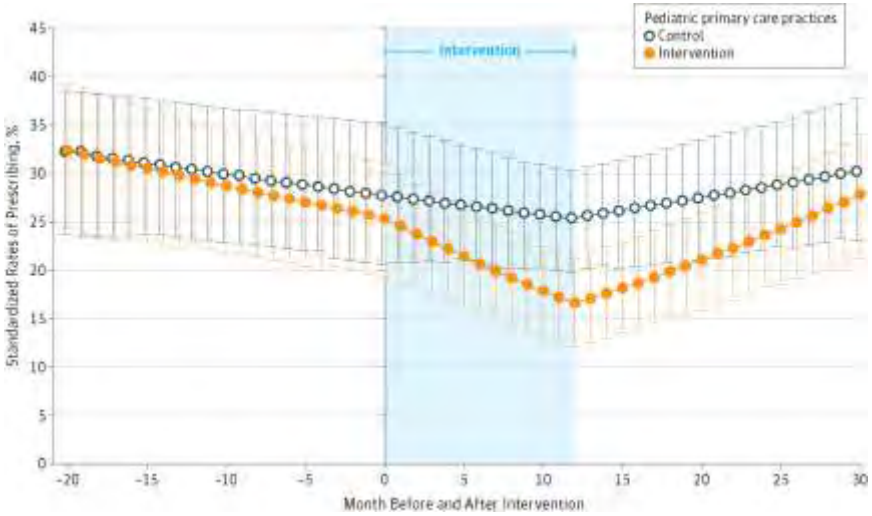


Figure Legend:

Standardized Rates of Broad-Spectrum Antibiotic Prescribing Before, During, and After Audit and FeedbackThe estimate of interest is the treatment × time interaction term, representing the relative changes in trajectories before and during the intervention. Error bars indicate 95% CIs.

COMMENT

HUMANS Did modern humans replace Neanderthals or co-exist with them? **p.385**

HISTORY Sigmund Freud and William Halstead on cocaine **p.397**

BIODIVERSITY DNA bank needed to conserve all species, not just plants **p.399**

OBITUARY Jonathan Widom, genomic map-maker, remembered **p.400**

Dosed up: could excessive prescription of antibiotics be hampering children's ability to fight disease?

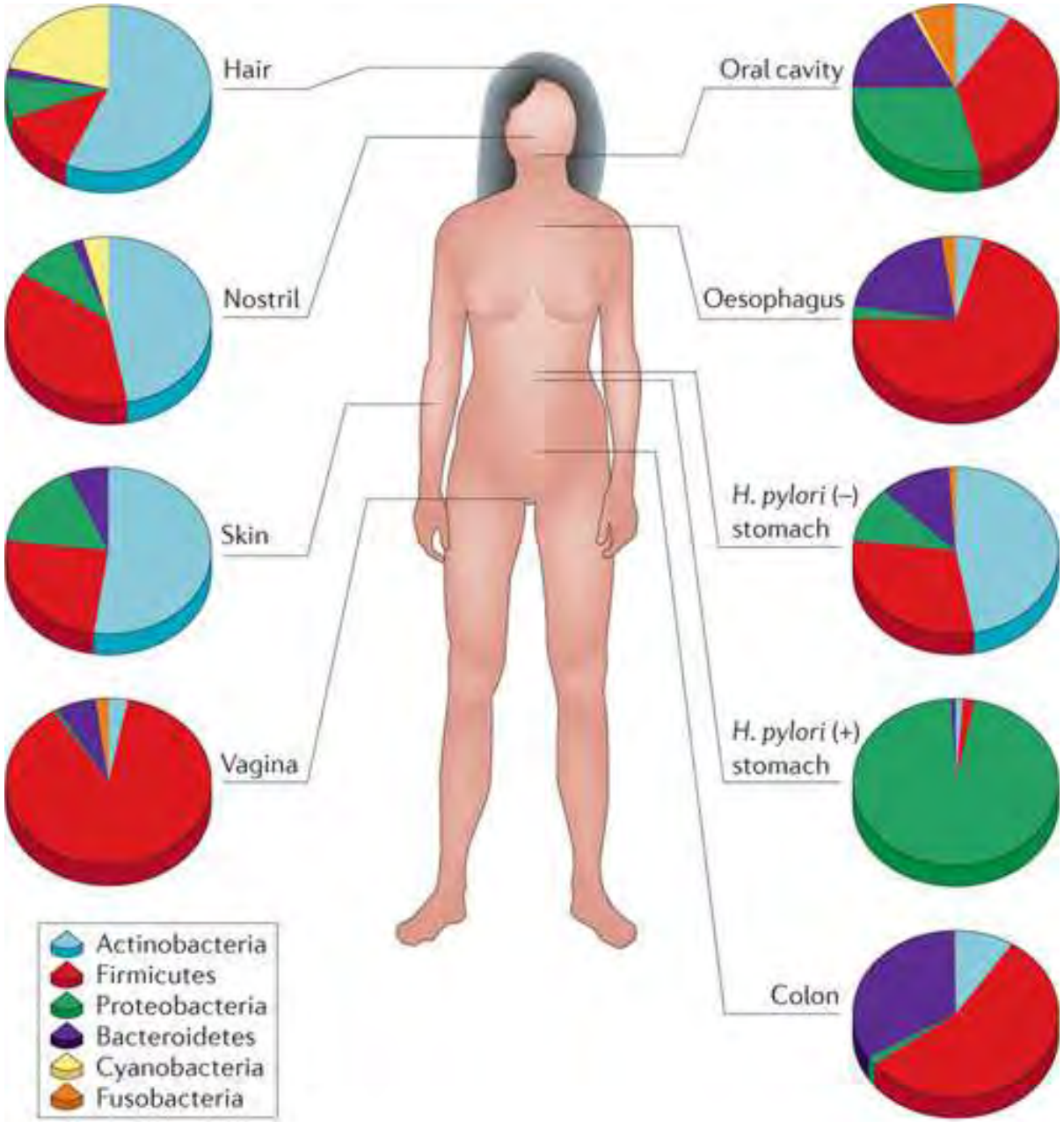
Stop the killing of beneficial bacteria

Concerns about antibiotics focus on bacterial resistance — but permanent changes to our protective flora could have more serious consequences, says **Martin Blaser**.

The average child in the United States and other developed countries has received 10–20 courses of antibiotics by the time he or she is 18 years old[1]. In many respects, this is a life-saving development. The average US citizen born in 1940 was expected to live to the age of 63; a baby born today should reach 78, in part because of antibiotics. But the assumption that antibiotics are generally safe has fostered overuse and led to an increase in bacterial resistance to treatments.

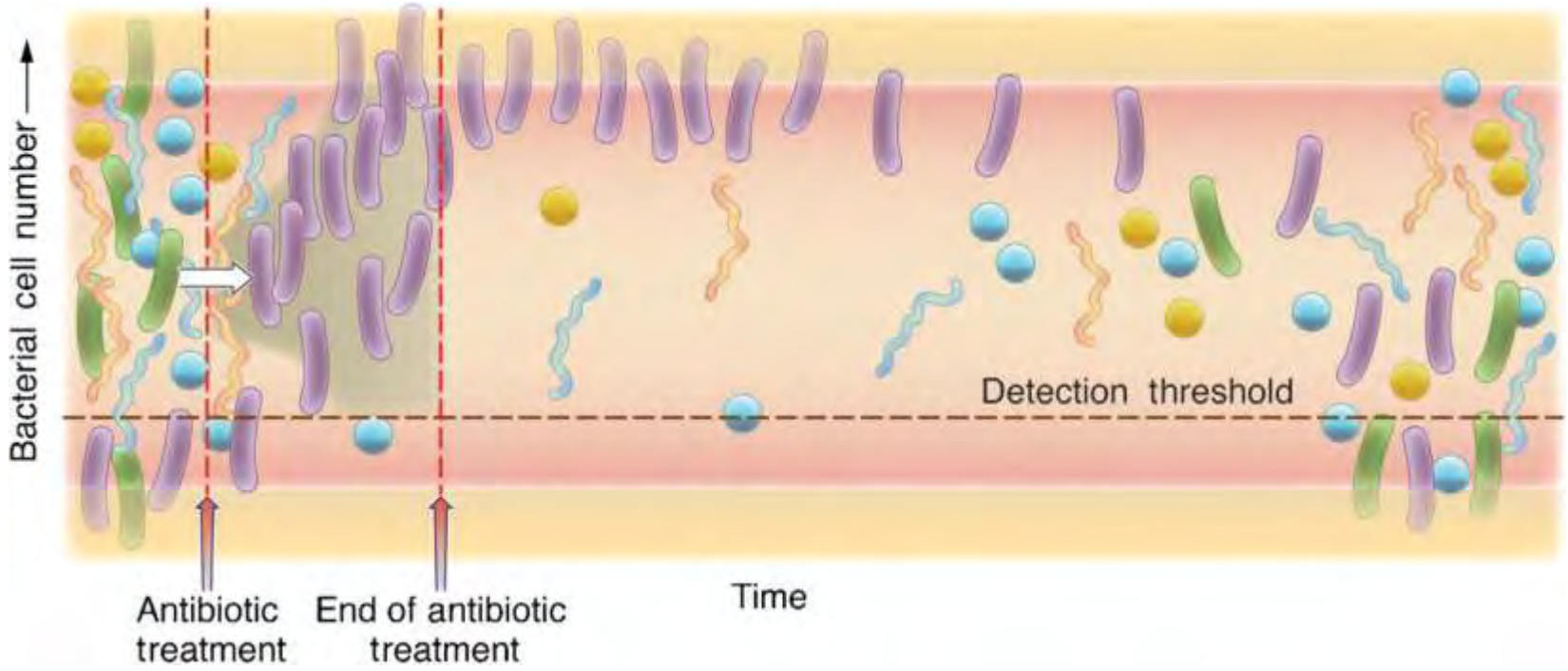
Other, equally serious, long-term consequences of our love of antibiotics have received far less attention. Antibiotics kill the bacteria we do want, as well as those we don't. Early evidence from my lab and others hints that, sometimes, our friendly flora never fully recover. These long-term changes to the beneficial bacteria within people's bodies may even increase our susceptibility to infections and disease. Overuse of antibiotics could be fuelling the dramatic increase in conditions such as obesity, type 1 diabetes, inflammatory bowel disease, allergies and asthma, which have more than doubled in many populations (see graph).

We urgently need to investigate this possibility. And, even before we understand the full scope, there is action we should take. ▶



Nature Reviews | Genetics

Fig. 1. Representation of the impact of antibiotic administration on the bacterial community of the colon.



Jernberg C et al. Microbiology 2010;156:3216-3223

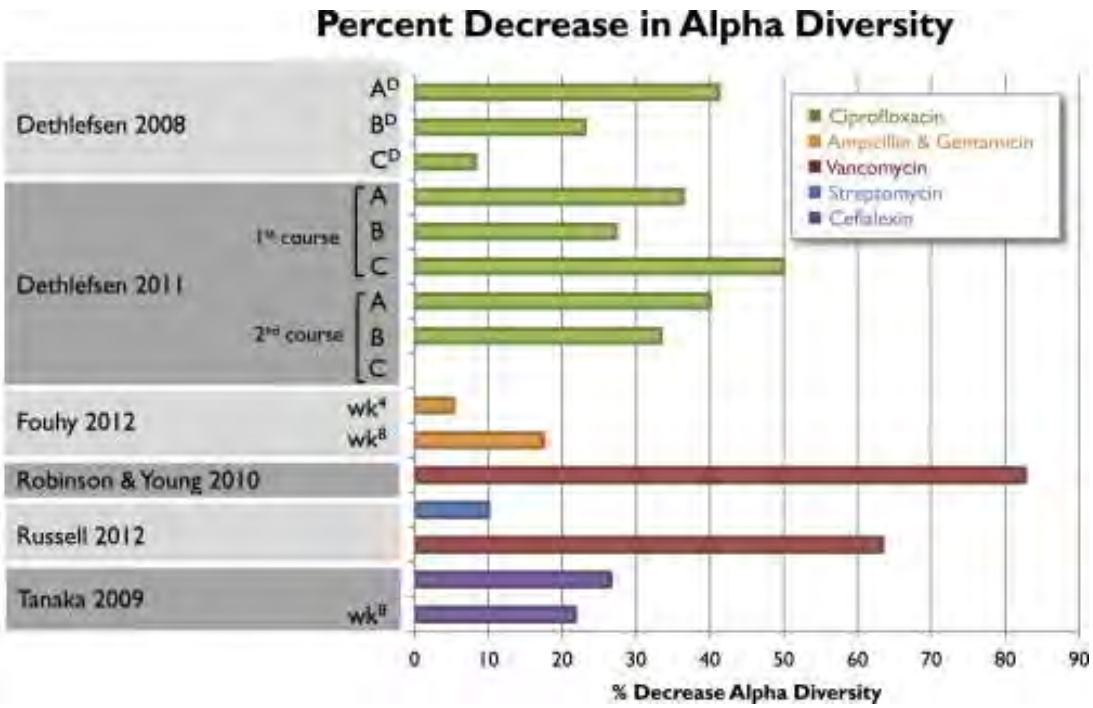


Figure 3 Percent Decrease in Gut Microbiome Biodiversity across Studies with Different Antibiotic Exposures All fecal samples were collected 1 week after antibiotic course was completed, except where noted by subscripts. The <ce:cross-ref refid="bib39" id...

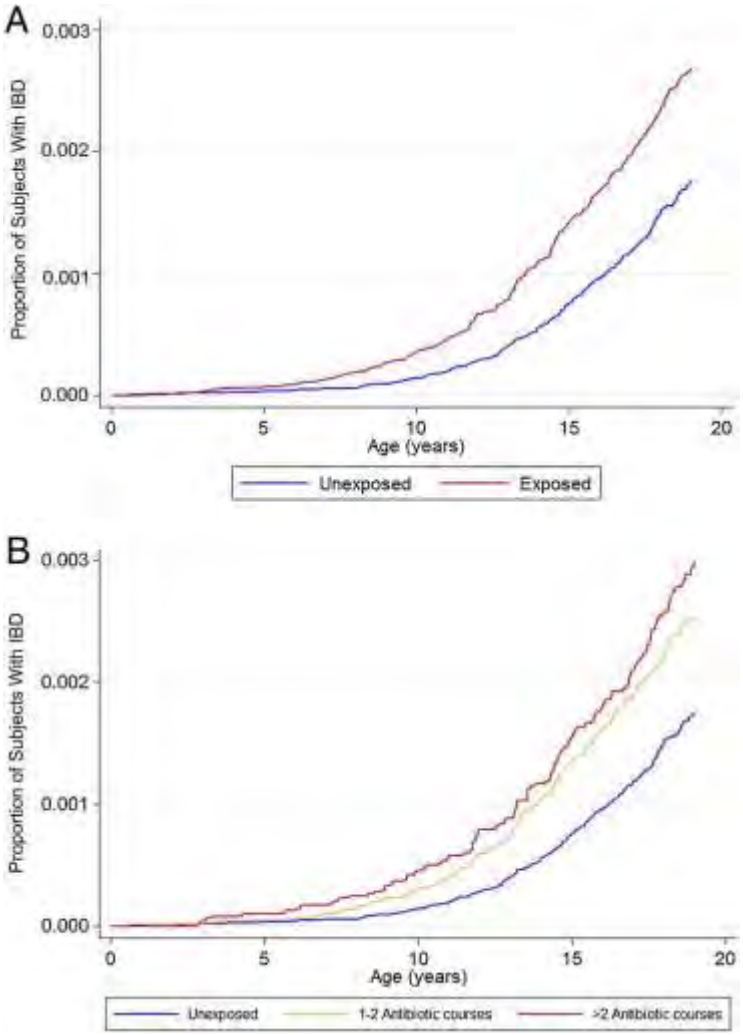
Pajau Vangay , Tonya Ward , Jeffrey S. Gerber , Dan Knights

Antibiotics, Pediatric Dysbiosis, and Disease

Cell Host & Microbe, Volume 17, Issue 5, 2015, 553 - 564

http://dx.doi.org/10.1016/j.chom.2015.04.006

A, Proportion of subjects developing IBD according to age and antianaerobic antibiotic exposure status.



Kronman M P et al. Pediatrics 2012;130:e794-e803

Antibiotics in early life alter the murine colonic microbiome and adiposity

- Mice fed subtherapeutic doses of antibiotics exhibited:
  - Increased adiposity
  - Increased hormone levels related to metabolism
  - Taxonomic changes of microbiome
  - Changes in copies of key genes involved in metabolism of carbohydrates to short-chain fatty acids
  - Alterations in hepatic metabolism of lipids and cholesterol
  - Increase in colonic levels of short chain fatty acids

Cho I et al. Nature 2012

Associations between the microbiome and disease

Disease	Relevant finding	Refs
Psoriasis	Increased ratio of Firmicutes to Actinobacteria	88
Reflux oesophagitis	Oesophageal microbiota dominated by gram-negative anaerobes; gastric microbiota with low or absent *Helicobacter pylori*	75,133
Obesity	Reduced ratio of Bacteroidetes to Firmicutes	17,31
Childhood-onset asthma	Absent gastric *H. pylori* (especially the cytotoxin-associated gene A (*cagA*) genotype)	96,134
Inflammatory bowel disease (colitis)	Larger populations of Enterobacteriaceae	113
Functional bowel diseases	Larger populations of *Veillonella* and *Lactobacillus*	135
Colorectal carcinoma	Larger populations of *Fusobacterium spp.*	101,102
Cardiovascular disease	Gut-microbiota-dependent metabolism of phosphatidylcholine	136

“The Island Where People Forget to Die”
Ikaria, Greece