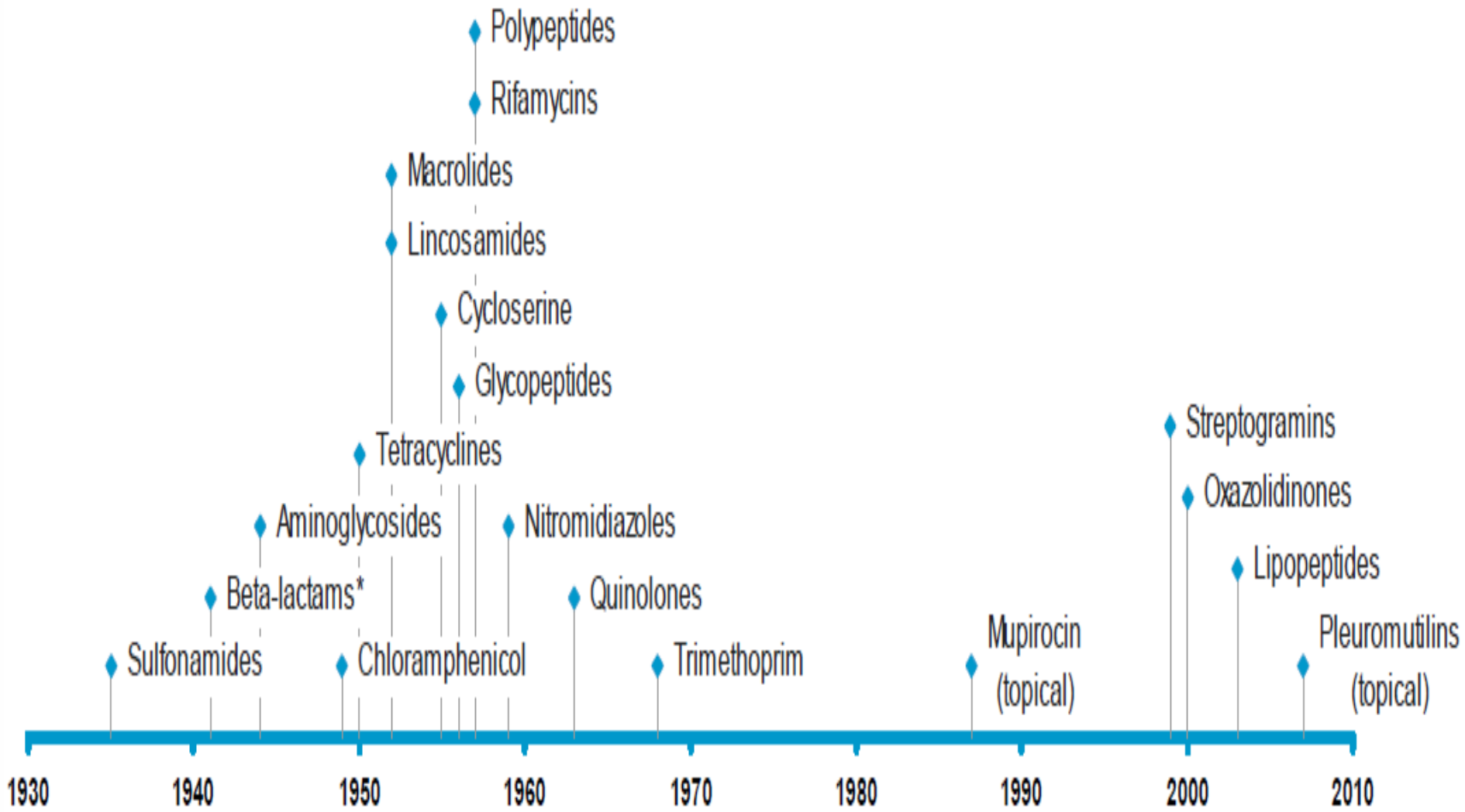
Antibiotics: Rethinking the Old

Jonathan G. Lim, MD, DPPS, DPIDSP

Objectives

- Do old antibiotics still work?
- What are the newer indications for the old antibiotics?

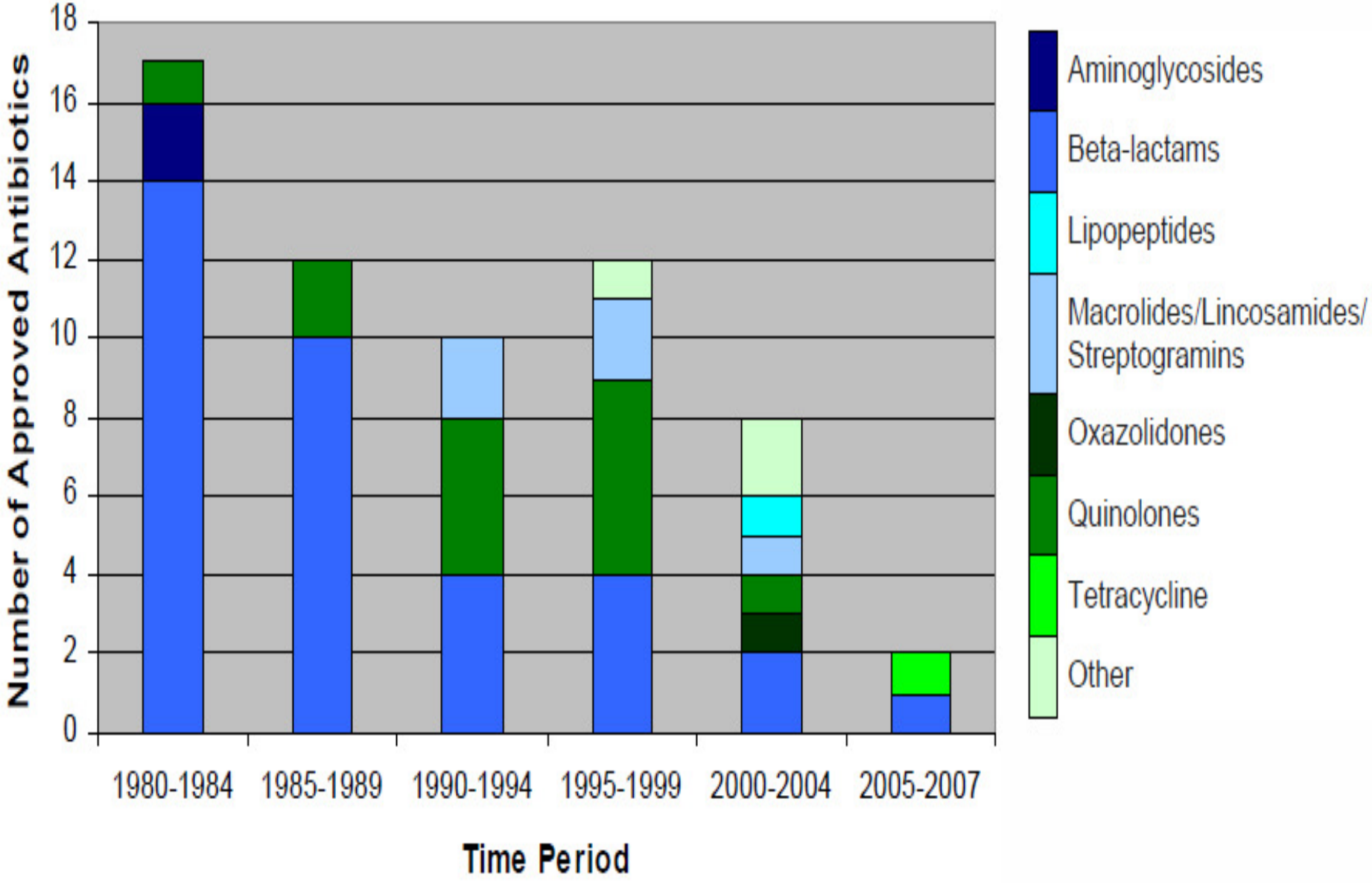
Figure 1: 14 classes of antibiotics were introduced for human use between 1935 and 1968; since then, 5 have been introduced.



* Beta-lactams include three groups sometimes identified as separate classes: penicillins, cephalosporins, and carbapenems.

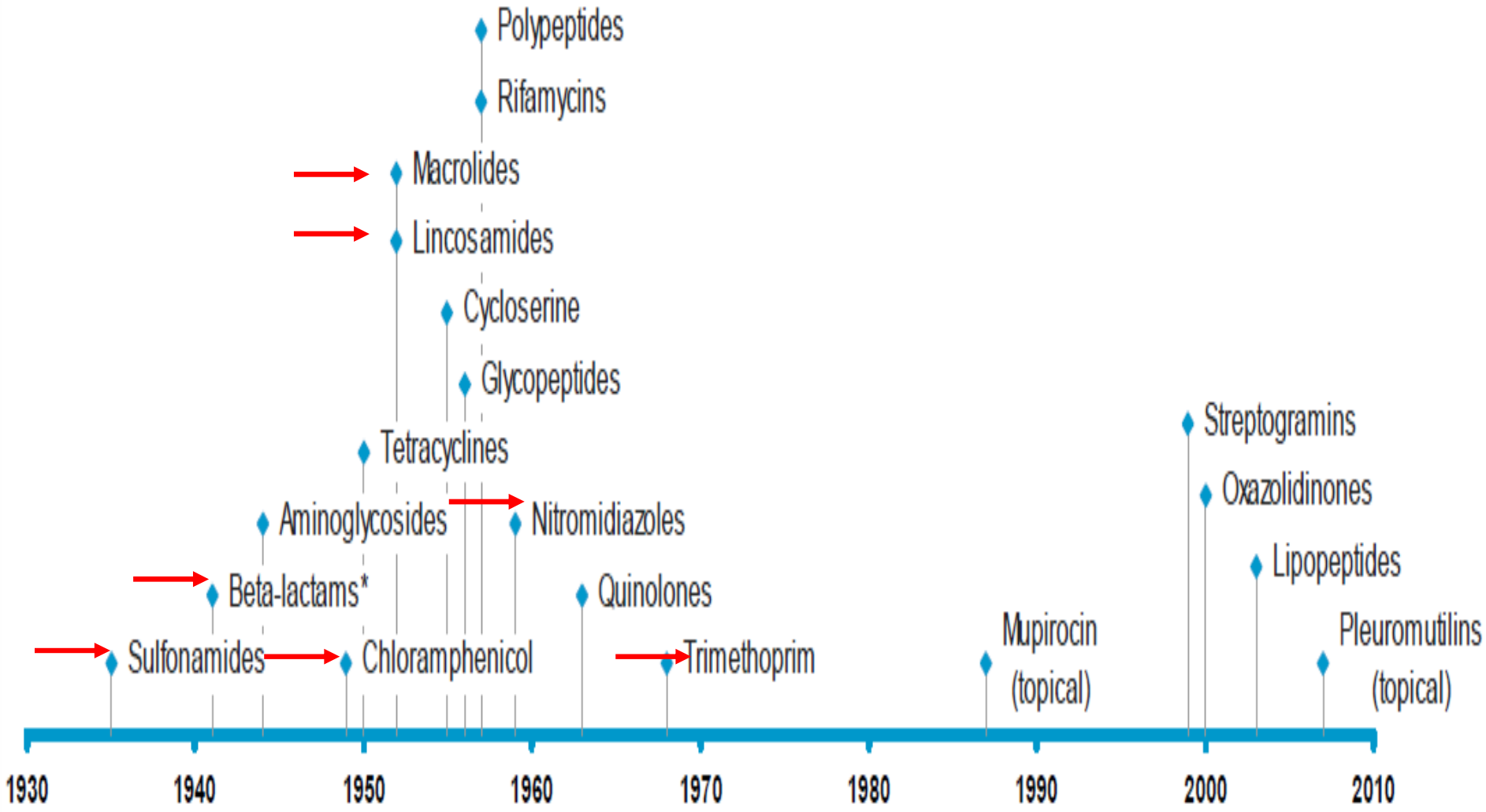
www.extendingthecure.org

Figure 2: The number of new systemic antibiotic agents has declined since 1980, and most (75%) of these drugs are in two classes, beta-lactams and quinolones.



www.extendingthecure.org

Figure 1: 14 classes of antibiotics were introduced for human use between 1935 and 1968; since then, 5 have been introduced.



* Beta-lactams include three groups sometimes identified as separate classes: penicillins, cephalosporins, and carbapenems.

www.extendingthecure.org

Current Uses of “Old” Antibiotics

- Penicillin
- Amoxicillin
- Chloramphenicol
- Trimethoprim/sulfamethoxazole

Current Uses: Penicillin (Drug of choice)

- Actinomyces
- Bacillus anthracis
- Clostridium species
- Corynebacterium diphtheriae
- Leptospira
- Neisseria gonorrheae
- Neisseria meningitidis
- Spirillum
- Streptococcus sp.
- Treponema pallidum

Feigin, et. al., Textbook of Pediatric Infectious Diseases, 5th ed.

S. pneumoniae Resistance Rate

1048 isolates out of 3028 children (NPS/blood/CSF)

- 22 (2.1%) Penicillin
- 4 (0.2%) Chloramphenicol,
- 3 (0.2%) Erythromycin,
- 39 (3.7%) Tetracycline
- 4 (0.2%) to trime/sulfamethoxazole

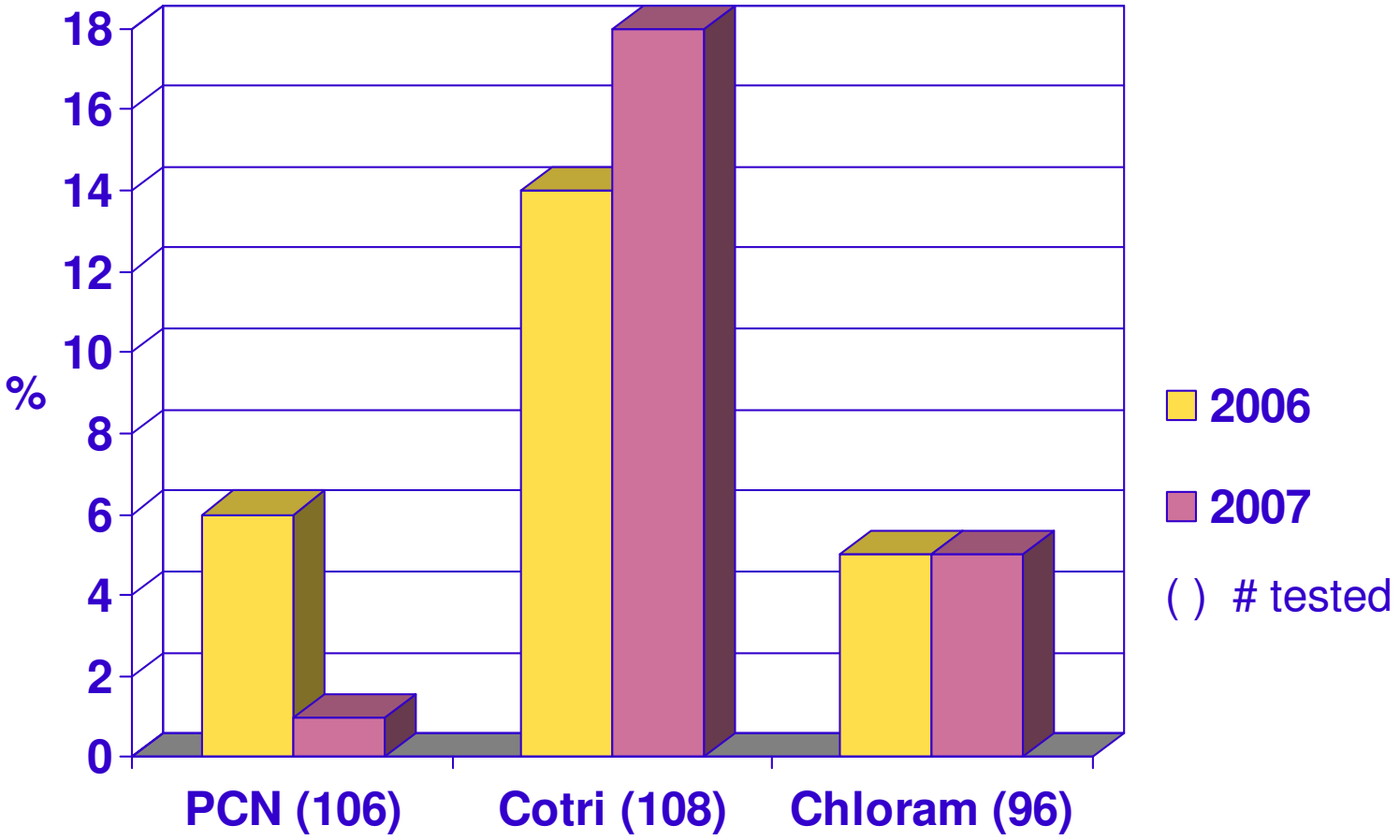
Sombrero, et. al., Low incidence of antibiotic resistance among invasive and nasopharyngeal isolates of *Streptococcus pneumoniae* from children in rural Philippines between 1994 and 2000. Eur J Clin Microbiol Infect Dis. 2008 Oct;27(10):929-35.

S. pneumoniae Resistance Rate

- 54 isolates
  - PCN 3.7%
  - Tetracycline 3.7%
  - Trime-sulfa 22.2%

Capeding, et. al., Pneumococcal Serotypes Among Filipino Children Admitted to a Tertiary Care Center for Infectious Diseases in 2000-2005 PIDSPJ 2007 vol 11 No. 1 pp1-3

S. pneumoniae Resistance Rate



Carlos, C. The 2007 Antibiotic Resistance Surveillance Data. Phil J Microl Infect Dse vol37(1);Jan-Jun2008

Current Uses: Amoxicillin

Current Uses: Amoxicillin

- Lower respiratory tract infections
- Acute otitis media
- Shigellosis/salmonellosis
- Infections of the GUT
- Animal bites/skin infections

Feigin, et. al., Textbook of Pediatric Infectious Diseases, 5th ed.

AHA Infective Endocarditis Guidelines 2007

Antibiotic Regimens

Situation	Agent	Regimen: one dose 30-60 min. prior to procedure Adults	Children
Oral	Amoxicillin	2g	50mg/kg
Oral Allergic to Penicillin	Cephalexin** Clindamycin Azith/Clarithromycin	2g 600mg 500mg	50mg/kg 20mg/kg 15mg/kg
Unable to take oral medication	Ampicillin Cefazolin (Ancef/Kefzol) Ceftriaxone(Rocephin)	2g IM or IV 1g IM or IV 1g IM or IV	50mg/kg IM or IV 50mg/kg IM or IV 50mg/kg IM or IV
Unable to take oral medication Allergic to Penicillin	Cefazolin or Ceftriaxone Clindamycin	1g IM or IV 600mg IM or IV	50mg/kg IM or IV 20mg/kg

AHA Infective Endocarditis Guidelines 2007

Cardiac conditions where prophylaxis is recommended:

1. Prosthetic cardiac valve
2. Previous IE
3. Cardiac transplant with acquired valvulopathy

AHA Infective Endocarditis Guidelines 2007

Cardiac conditions where prophylaxis is recommended:

4. CHD
   - Unrepaired cyanotic CHD
   - Completely repaired CHD with prosthetic device
   - Repaired CHD with residual defects at/near the patch or device which inhibits endothelialization

AHA Infective Endocarditis Guidelines 2007

Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of Congenital Heart Disease(!)

S. typhi Resistance Rate

- Ampicillin 2.3%
- Cotrimoxazole 1.7%
- Chloramphenicol 0%
- Ceftriaxone 0%
- Ciprofloxacin 0%

Carlos, C. The 2007 Antibiotic Resistance Surveillance Data. Phil J Microl Infect Dse vol37(1);Jan-Jun2008

S. typhi Resistance Rate

" Therefore, empiric therapy for suspected uncomplicated typhoid fever should still consist of CHLORAMPHENICOL, COTRIMOXAZOLE or AMOXICILLIN."

Carlos, C. The 2007 Antibiotic Resistance Surveillance Data. Phil J Microl Infect Dse vol37(1);Jan-Jun2008

Current Uses:
Trimethoprim/sulfamethoxazole

Current Uses: Trimethoprim/sulfamethoxazole

- Shigella
- Otitis media
- UTI
- P. jirovecii (PCP)
- Chronic bronchitis (adults)

Feigin, et. al., Textbook of Pediatric Infectious Diseases, 5th ed.

Current Uses: Trimethoprim/sulfamethoxazole

- Otitis media, UTI
  - 8 mg/kg/day trimethoprim in two divided doses for 10 days
- Shigella
  - Same dose for 5 days

Feigin, et. al., Textbook of Pediatric Infectious Diseases, 5th ed.

PCP Prophylaxis

- Eleven trials = 1155 patients (520 children), between the 1974 and 1997
- 91% reduction in PCP in patients receiving prophylaxis with trime/sulfa, RR 0.09 (95% CI 0.02 to 0.32), eight trials, 821 patients.
- PCP-related mortality was significantly reduced, RR 0.17 (95% CI 0.03 to 0.94), seven trials, 701 patients.

Green H, et. al., Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients.
Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD005590

PCP Prophylaxis

- Conclusion:
  - This review of randomised controlled trials (RCTS) found that prophylaxis with trimethoprim/sulfamethoxazole, significantly reduced the occurrence of PCP by > 90%.

Green H, et. al., Prophylaxis for Pneumocystis pneumonia (PCP) in non-HIV immunocompromised patients.
Cochrane Database of Systematic Reviews 2007, Issue 3. Art. No.: CD005590

Current Uses: Trimethoprim/sulfamethoxazole

"….Cotrimoxazole is cheap and effective against a wide range of organisms, including Pneumocystis jirovecii pneumonia (PCP), which is an important cause of death and illness in the first year of life."

Grimwade K, Swingler GH. Cotrimoxazole prophylaxis for opportunistic infections in children with HIV infection. *Cochrane Database of Systematic Reviews* 2006, Issue 1. Art. No.: CD003508.

Trimethoprim/sulfamethoxazole in PCP

- Prophylaxis:
  - TMP 150mg/m2 in 2 divided doses on 3 consecutive days per week
- Treatment:
  - TMP 15 mg/kg/day in 3-4 doses for 14-21 days

2006 AAP Red Book, 27th ed.

Newer indications

- Trimethoprim/sulfamethoxazole
- Clindamycin
- Tetracycline
- Metronidazole
- Macrolides

MRSA

- first described in 1961 in UK
- thought to have appeared because of the selection pressure of antibiotic use within hospitals
- The first community-acquired MRSA (CA-MRSA) infections occurred in 1980 and were associated with spread from hospitals into the community

Crum, et.al. Fifteen-Year Study of the Changing Epidemiology of Methicillin-Resistant *Staphylococcus aureus.* JAMA 2006; 119:943-951

Trimethoprim/sulfamethoxazole

	Resistance Rate	
	CA-MRSA	N-MRSA
clindamycin	19%	81%
erythromycin	80%	98%
trime/sulfa	2%	8%

Crum, et.al. Fifteen-Year Study of the Changing Epidemiology of Methicillin-Resistant *Staphylococcus aureus.* JAMA 2006; 119:943-951

Resistance rate: S. aureus

- BenzylPCN 95% (1200)
- Oxacillin 30.6% (1173)
- Vancomycin 0 (1228)
- Trime/sulfa 4.3% (1054)

Carlos, C. The 2007 Antibiotic Resistance Surveillance Data. Phil J Microl Infect Dse vol37(1);Jan-Jun2008

Trimethoprim/sulfamethoxsazole

"Sulfonamides remain as a valuable agent for most CA-MRSA infections…."

Elston, Methicillin-Sensitive and Methicillin-Resistant Staphylococcus aureus: Management Principles and Selection of Antibiotic Therapy.
Dermatol Clin 25 (2007):157–164

Clindamycin

Clindamycin treatment of invasive infections caused by community-acquired, methicillin-resistant and methicillin-susceptible Staphylococcus aureus in children

MARTÍNEZ-AGUILAR, GERARDO MD; HAMMERMAN, WENDY A. RN; MASON, EDWARD O. JR. PhD; KAPLAN, SHELDON L. MD

Pediatric Infectious Disease Journal:Volume 22(7)July 2003 pp 593-599

Clindamycin

- CA-MRSA and CA-MSSA caused invasive infections in 46 and 53 children, respectively

- median ages (range) of the children were: MRSA, 3.5 years (2 months to 18.6 years); MSSA, 4.8 years (3 months to 19.8 years).

Martinez-Aguilar, et. al., Pediatr Infect Dis J 22(7);July 2003:593-599

Clindamycin

- Among MRSA patients, 39 (20 received clindamycin, 18 had vancomycin initially and 8 had a ß-lactam initially) received clindamycin and 6 received vancomycin as primary therapy

- Among MSSA patients, clindamycin, nafcillin or other beta-lactam antibiotics were used in 24, 18 and 9, respectively

Martinez-Aguilar, et. al., Pediatr Infect Dis J 22(7);July 2003:593-599

Clindamycin

- The median number of febrile days was 3 (0 to 14) and 2 (0 to 6) for MRSA and MSSA patients, respectively.

- The median number of days with positive blood cultures was 2 for the MRSA (**n** = 16) and 1 for the MSSA (**n** = 18) patients.

Martinez-Aguilar, et. al., Pediatr Infect Dis J 22(7);July 2003:593-599

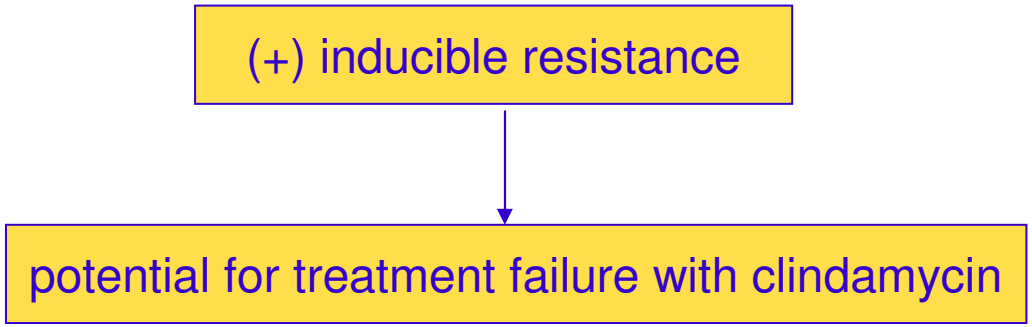
Clindamycin

- sulfonamide resistance in areas with large HIV-positive populations????

- the erm gene≈ inducible macrolide-lincosamide streptogramin B phenotype

Elston, Methicillin-Sensitive and Methicillin-Resistant Staphylococcus aureus: Management Principles and Selection of Antibiotic Therapy.
Dermatol Clin 25 (2007):157–164

Clindamycin



"….macrolide resistance may be a marker for inducible lincosamide resistance."

Elston, Methicillin-Sensitive and Methicillin-Resistant Staphylococcus aureus: Management Principles and Selection of Antibiotic Therapy. Dermatol Clin 25 (2007):157–164

DOH Revised Guidelines for the Diagnosis and Treatment of Malaria

Uncomplicated Falciparum Malaria in Adults and Older Children

Second line of treatment

Quinine sulfate + Doxycycline
OR Tetracycline **OR**
Clindamycin

DOH Revised Guidelines for the Diagnosis and Treatment of Malaria

Uncomplicated Falciparum Malaria in Adults and Older Children

Dosing Schedule for Quinine sulfate+ Doxycycline OR Tetracycline OR Clindamycin

Medicine	Dosing Schedule
Quinine	10 mg/kg oral every 8 hours for 7 days
Doxycycline	3 mg/kg every 24 hours OR Tetracycline 250 mg QID for 7 days OR Clindamycin 10 mg/kg BID for 7 days

DOH Revised Guidelines for the Diagnosis and Treatment of Malaria

Uncomplicated Falciparum Malaria in Adults and Older Children

Dosing Schedule for Quinine sulfate+ Doxycycline OR Tetracycline OR Clindamycin

Medicine	Dosing Schedule
Quinine	10 mg/kg oral every 8 hours for 7 days
Doxycycline	3 mg/kg every 24 hours OR Tetracycline 250 mg QID for 7 days OR Clindamycin 10 mg/kg BID for 7 days

Tetanus

- Penicillin G
  - 100,000 u/kg/day q 6hrs x 10 days
  - Agonist to tetanospasmin by inhibiting the release of GABA
- Metronidazole
  - 30 mg/kg/day q 6hrs

Macrolides

- 14-member (clarithromycin, erythromycin, roxithromycin)
- 15-member (azithromycin)

Macrolides

- Immunomodulatory effects
- Decreases length of stay and mortality

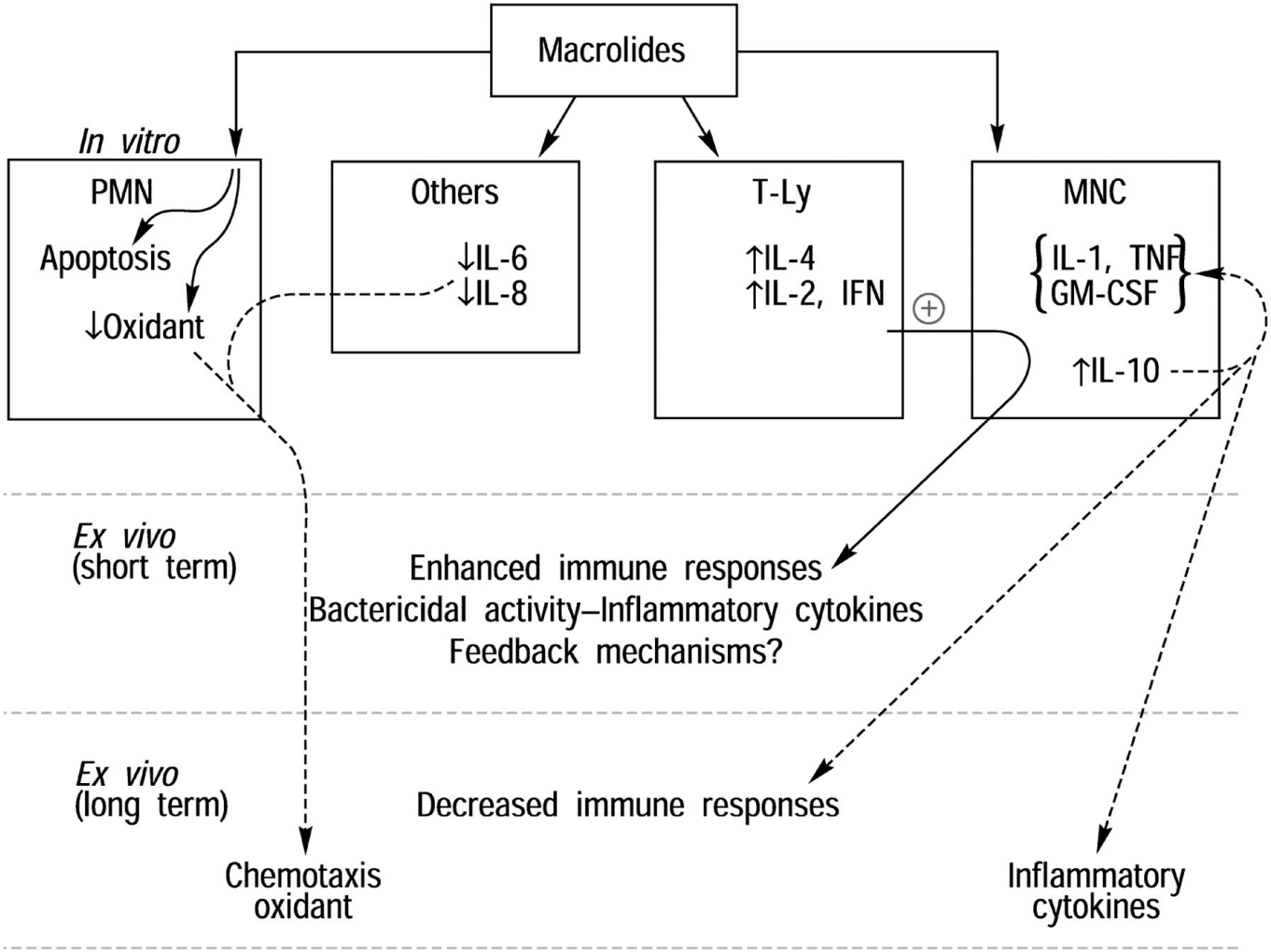
G. W. Amsden. Anti-inflammatory effects of macrolides—an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? J Antimicrob Chemother 2005 55(1):10-21

Macrolides

- Decrease sputum/mucus production
- suppress the overabundance of neutrophils (PMNs)
- eosinopenic effect
- break down and prevent further development of biofilms of *P. aeruginosa*

G. W. Amsden. Anti-inflammatory effects of macrolides—an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? J Antimicrob Chemother 2005 55(1):10-21

Macrolides and inflammation. Proposed immunomodulatory activities induced by macrolides



Tamaoki J. Chest 2004;125:41S-51S


Thank you!