

Antibiotic Resistance Threats in the US

Contemporary Approach to Patient Care

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Objectives

1. Develop process to recognize new antibiotic threats and new drugs for treatment.
2. Educate patients regarding the importance of antibiotic resistance.
3. Develop evidence-based treatment strategies to select appropriate antibiotic treatments for common conditions.
4. Discuss current practice guidelines including CDC, AAFP, IDSA and WHO.

What is Antimicrobial Resistance?

- Natural

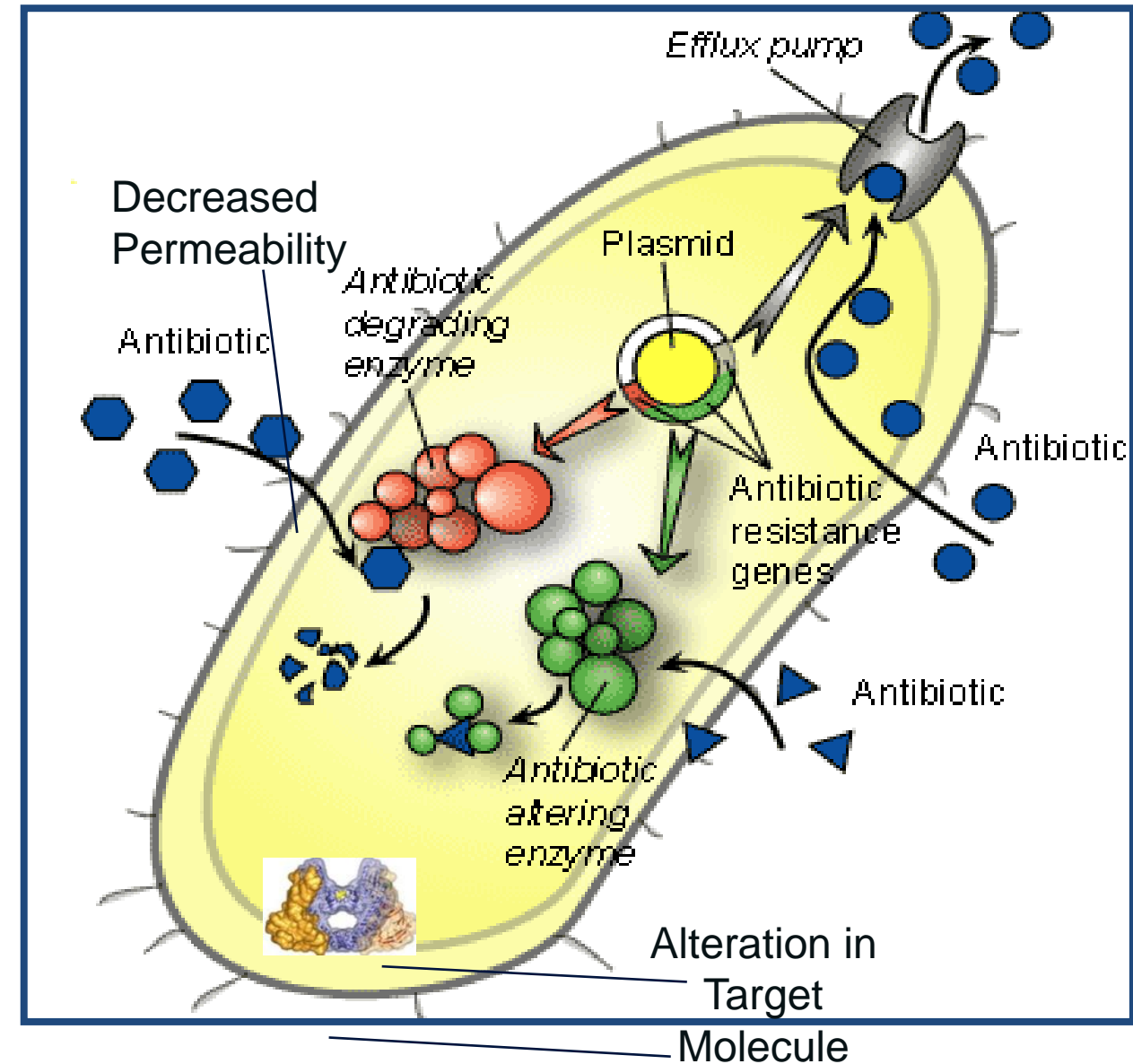
- Non-susceptible to a given antibiotic because the target for the antibiotic is not present in that bacteria species (Vancomycin for Gram negative bacteria)

- Acquired

- Susceptible but then develop resistance through various mechanisms (Beta-lactamase)

Mechanisms Of Antibiotic Resistance

- Bacteria are capable of becoming resistant through several mechanisms
- One or many mechanisms may exist in an organism
- Multidrug-resistant bacteria often have multiple mechanisms
- Genes encoding resistance may exist on plasmid or chromosome



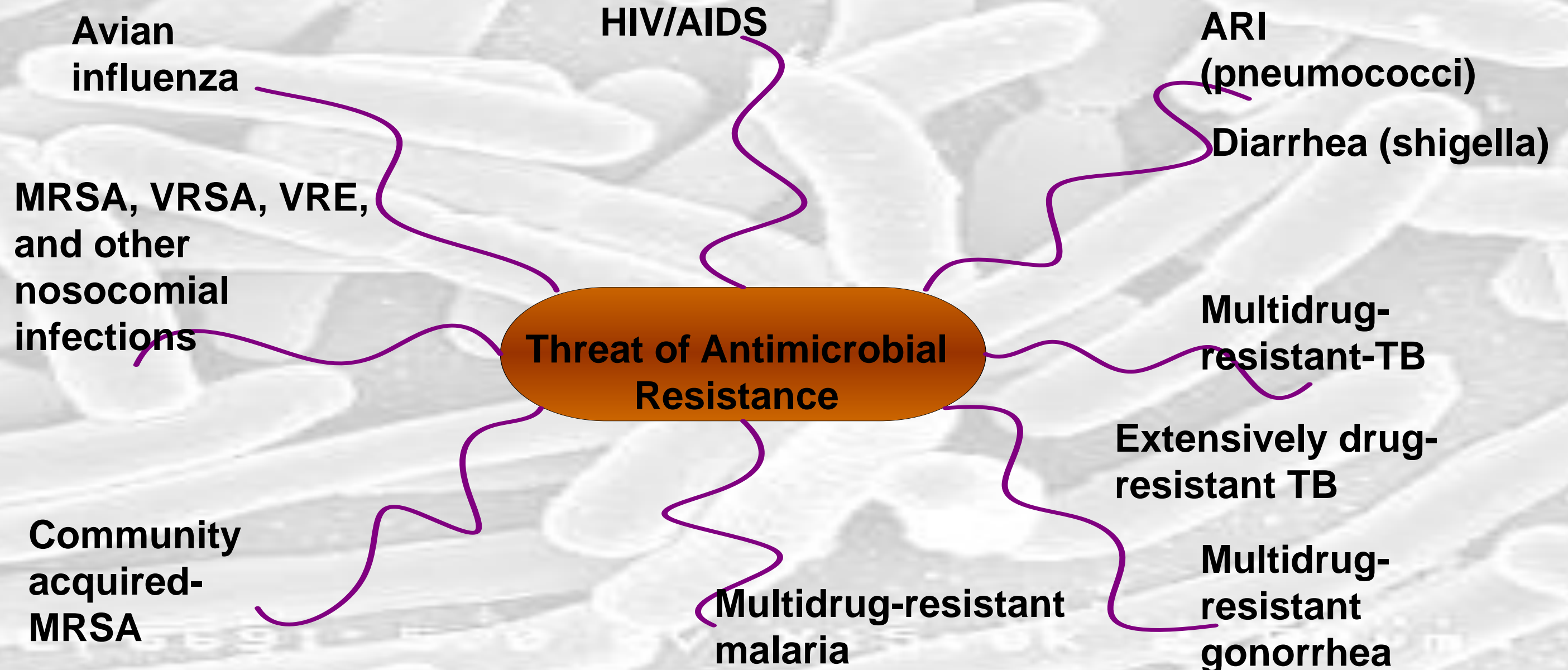
Mechanisms of Resistance: Current Concerns

- Enzymatic degradation of drug
 - Over 300 beta-lactamases (gr - > gr +)
- Chemical modification of drug
 - Aminoglycoside resistance
- Alteration to binding site
 - Strep Pneumo and Penicillins
 - MRSA and Vancomycin

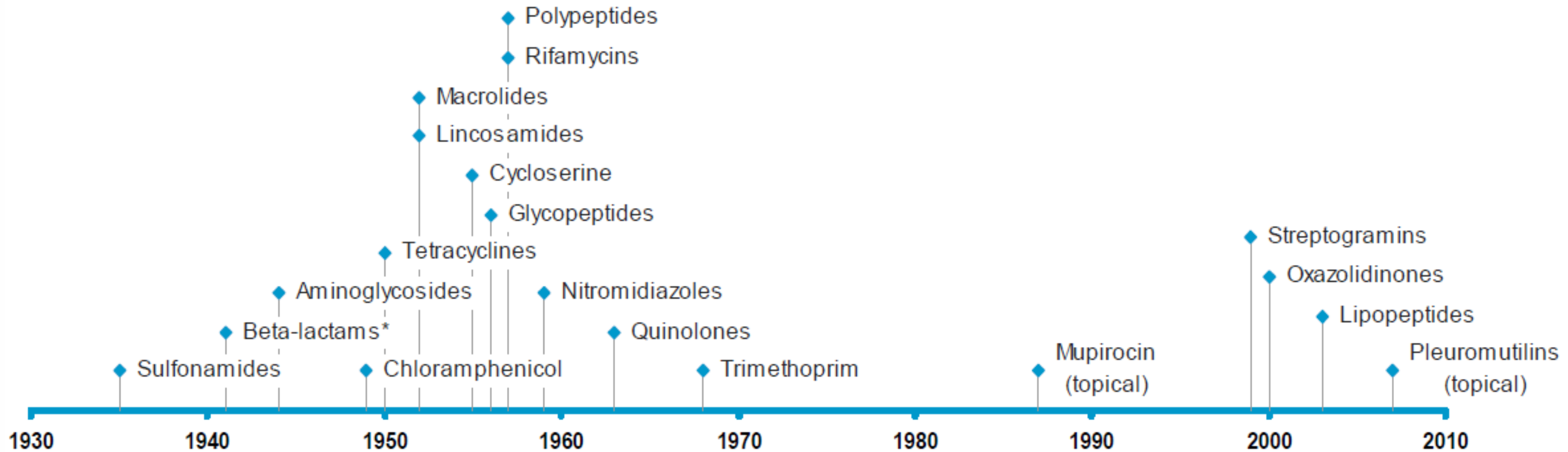
Mechanisms of Resistance: Current Concerns

- Inhibition of drug intake
 - Wise bacteria – Trojan Horse no longer working
- Increasing export / efflux of drug
 - Pseudomonas with Quinolones

Threat of Antimicrobial Resistance



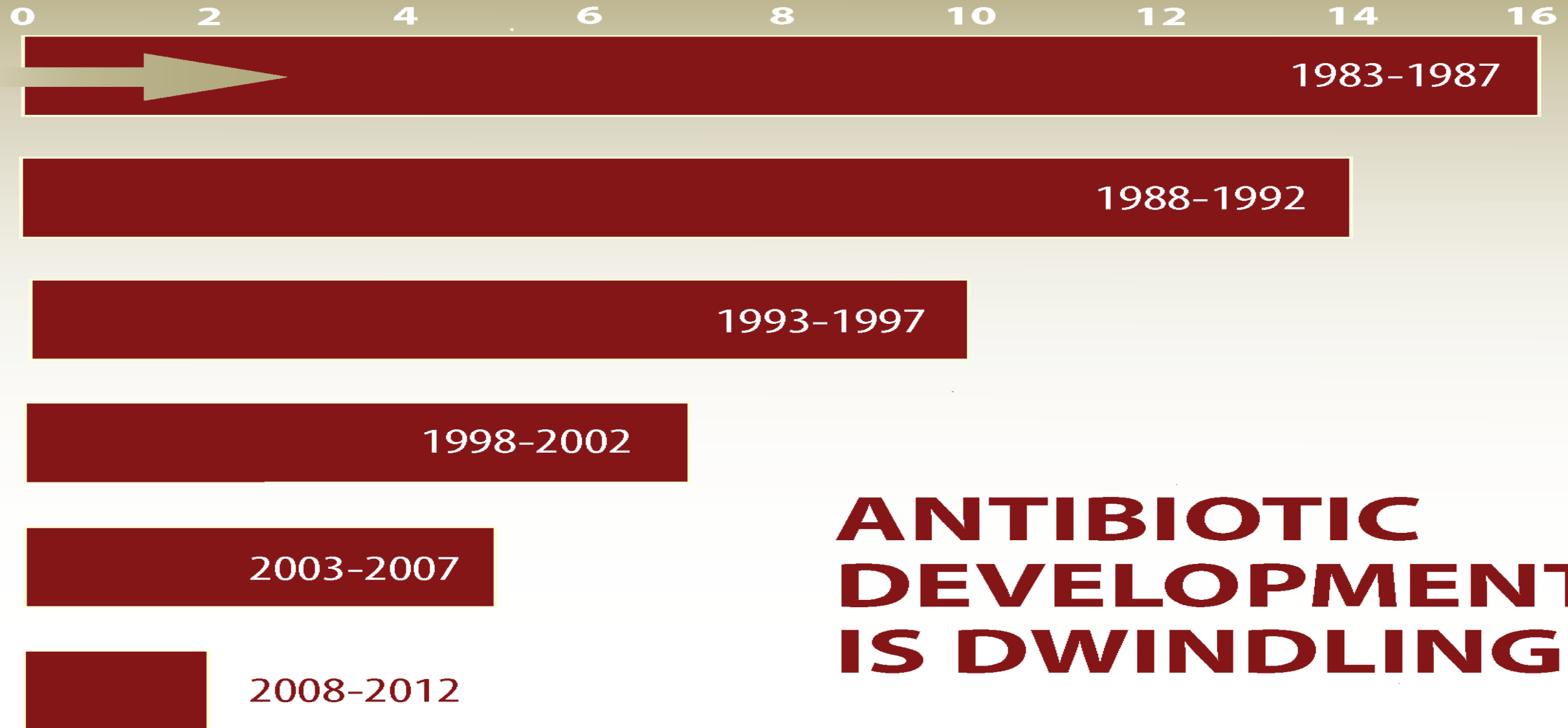
Antibiotic Pipeline



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

Pipeline is not Piping Hot

Total Number of New Antibacterial Agents



**ANTIBIOTIC
DEVELOPMENT
IS DWINDLING**

Source: *The Epidemic of Antibiotic-Resistant Infections*, CID 2008;46 (15 January)
Clin Infect Dis. (2011) May 52 (suppl 5): S397-S428. doi: 10.1093/cid/cir153

Which organization prioritizes and categorizes the resistance patterns of bacteria?

- A. FDA
- B. CDC
- C. IDSA
- D. ASHP

CDC: Resistance Report 2013

- Classified bacteria into three categories
 - Urgent Threats
 - ❖ High consequence threats because of significant impact
 - Serious Threats
 - ❖ Significant threats but have available therapeutic options
 - Concerning Threats
 - ❖ Require monitoring and fast action if breakout occurs to minimize resistance

The Truth Hurts

- The use of antibiotics is the single most important factor leading to antibiotic resistance
- Up to 50% of all antibiotics prescribed are not needed or are not optimally effective as prescribed

DK is a 32 yo WF who is 5 months pregnant. She presents today with 2 day h/o non-productive, dry cough and low grade fever. She c/o tenderness around her eyes and hasn't slept well over the past three nights. What is the appropriate treatment choice?

- A. Azithromycin x 5 days
- B. Doxycycline x 10 days
- C. Amoxicillin x 10 days
- D. Supportive Care

Reasons for Antibiotic Overuse

- Patient Concerns
 - Want clear explanation
 - Green nasal discharge
 - Need to return to work
- Physician Concerns
 - Patient expects antibiotic
 - Diagnostic uncertainty
 - Time pressure



Barden L.S. Clin
Pediatr 1998;37:665

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

Céire Costelloe, research associate,¹ Chris Metcalfe, senior lecturer in medical statistics,² Andrew Lovering, consultant clinical scientist,³ David Mant, professor of general practice,⁴ Alastair D Hay, consultant senior lecturer in primary health care¹

- Individuals prescribed an antibiotic in primary care for a respiratory or urinary infection develop resistance to that antibiotic
 - Greatest effect in the month immediately following treatment but may persist for up to 12 months

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

Which of the following is considered an urgent threat per the CDC?

- A. Neisseria gonorrhoeae*
- B. Vancomycin-Resistant Enterococcus*
- C. Streptococcus pneumoniae*
- D. Multi-drug resistant Candida*

CDC: Resistance Threat in US

CDC. Threat Report 2013. <http://www.cdc.gov/drugresistance/threat-report-2013/>

HAZARD LEVEL URGENT



These are high-consequence antibiotic-resistant threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so and require urgent public health attention to identify infections and to limit transmission.

Clostridium difficile (*C. difficile*), Carbapenem-resistant Enterobacteriaceae (CRE), Drug-resistant *Neisseria gonorrhoeae* (cephalosporin resistance)

HAZARD LEVEL SERIOUS



These are significant antibiotic-resistant threats. For varying reasons (e.g., low or declining domestic incidence or reasonable availability of therapeutic agents), they are not considered urgent, but these threats will worsen and may become urgent without ongoing public health monitoring and prevention activities.

Multidrug-resistant *Acinetobacter*, Drug-resistant *Campylobacter*, Fluconazole-resistant *Candida* (a fungus), Extended spectrum β -lactamase producing Enterobacteriaceae (ESBLs), Vancomycin-resistant *Enterococcus* (VRE), Multidrug-resistant *Pseudomonas aeruginosa*, Drug-resistant Non-typhoidal *Salmonella*, Drug-resistant *Salmonella* Typhi, Drug-resistant *Shigella*, Methicillin-resistant *Staphylococcus aureus* (MRSA), Drug-resistant *Streptococcus pneumoniae*, Drug-resistant tuberculosis (MDR and XDR)

HAZARD LEVEL CONCERNING



These are bacteria for which the threat of antibiotic resistance is low, and/or there are multiple therapeutic options for resistant infections. These bacterial pathogens cause severe illness. Threats in this category require monitoring and in some cases rapid incident or outbreak response.

Vancomycin-resistant *Staphylococcus aureus* (VRSA), Erythromycin-resistant *Streptococcus* Group A, Clindamycin-resistant *Streptococcus* Group B

Primary Care Threats: Just to Name a Few

- *Neisseria gonorrhoeae*
- CA-MRSA
- *Streptococcus pneumoniae*
- ESBL
- Group A Strep

Mechanisms of Resistance: Evolution of Bacteria

- **Persisters**

- Enter a physiologic state immune to antibiotics

- **Variable Gene Expression**

- Allows phenotypically drug resistant cells to arise
- Swarming away from antibiotic
- Sacrifice a few to save many

- **Collective Resistance**

- Biofilms-complex communities of bacterial cells that develop on a solid surface

Strategies to Combat Resistance: More We Know, More We Kill

- Quorum sensing inhibitors
- Biologics
 - Antimicrobial peptides
 - Bacteriophage
- Dual drug delivery approaches
 - Using various adjuvants/combinations
- Delivering antibiotics to site of infection
 - Polymers, nanoparticles, and liposomes....Oh My!

Strategies to Combat Resistance

- White House National Strategy with CDC
 - Prevention of infections
 - Tracking of bacteria
 - Improving stewardship
 - Develop new medications and dx testing

Strategies to Combat Resistance

- Current initiatives to reach these goals
 - CDC Checklist to create antibiotic stewardship programs
 - Initiative to slow development of resistance and prevent the spread of infections
 - Rapid response to hotspots
 - Support and track food safety
 - Data reporting expansion
 - Improve international collaboration
 - Leverage diagnostic testing for rapid identification and characterization of resistant bacteria
 - Increase financial incentives to hone lab testing
 - Use advanced molecular diagnostics

We Can Have an Impact

- Antibiotic overuse promotes resistance
 - 50% of the 258 million ATBs prescriptions are not needed
 - 2 million illnesses and 23,000 deaths annually from resistant bacteria
 - Goal – use most narrow spectrum agent for appropriate duration
- Increased resistant organisms are on the rise
- Inappropriate antibiotic dosing promotes resistance
- Antibiotic pipeline is diminishing
- Will take 5-10 yrs for new antibiotics to reach market
- What should you do?

Practice Recommendations

- Review current guidelines and use information to make empiric selections/recommendations (CDC and IDSA)
- Be prepared to defend “no antibiotic rule”
- Cycle antibiotic choices when appropriate
- Optimize anti-infective therapy
 - Drug- most specific choice possible
 - Dose - higher concentration
 - Duration - shorter course is better
 - Route – does it have to be systemic?

Application of What We Have Discussed

Case Studies

Continuing Medical Education



1. DK is a 32 yo WF who is 5 months pregnant. She presents today with 2 day h/o non-productive, dry cough and low grade fever. She c/o tenderness around her eyes and hasn't slept well over the past three nights. What is the appropriate treatment choice?
 - A. Azithromycin x 5 days
 - B. Doxycycline x 10 days
 - C. Amoxicillin x 10 days
 - D. Supportive Care
 - E. Antibiotic combination x 10 days

Management Decisions

No antibiotics - 0.5 - 2% transition to bacterial which means 98% are viral

Bacterial vs. Viral – 10 day rule

- Watchful waiting – even if bacterial without abx x 7d
- Can prescribe abx if >10d and opt not to do watchful waiting

Antibiotic Selection

Amoxicillin with or with clavulanic acid is first line x 5-10 days

High dose Augmentin (2g BID)

- PRSP pattern >10%
- Systemic toxicity
- Daycare
- Age <2yo or >65yo
- Recent hospitalization within 5 days
- Recent abx use in last month
- Immunocompromised/Co-morbidities

So if Viral now what?

Supportive Care

- Saline nasal irrigation is DOC
- IN steroids can be used
- Analgesics are an option
- Antihistamine NOT recommended
- Topical and systemic decongestants NOT recommended
- Antitussive could be used to help sleep
- Antipyretic if needed

2. A 21yo AAF presents with dysuria, burning, and a foul odor when she urinates. She is concerned since she is leaving town tomorrow for a Caribbean cruise. UA is grossly positive for UTI. Which of the following is considered first line treatment choice for this patient?
- A. Trimethoprim/sulfamethoxazole
 - B. Penicillin VK
 - C. Cephalexin
 - D. Moxifloxacin
 - E. Nitrofurantoin

Antibiotic Choices

Clinical Practice Guidelines 2011;52 (1 March)
by Gupta et al.

Choices listed by recommendation from IDSA

- Nitrofurantoin
 - CrCl >60ml/min needed
- Trimethoprim/sulfamethoxazole
 - Resistance patterns <20%
- Fosfomycin (remember coming off market)
- Quinolones
 - Resistance patterns <10%
- Extended spectrum β -lactams
- NO Amoxicillin or Ampicillin

“I think I have a yeast infection”

SW is a 64yo WF who presents today c/o malodorous vaginal discharge

PMH: HTN and RA

Social History: Widowed x 2 yrs, currently dating

Medications:

- Lisinopril 5mg daily
- MTX 7.5mg weekly + folic acid 5mg/week
- Etanercept (Enbrel) 50mg SC weekly

HPI and PE

Pt noticed burning with urination yesterday accompanied by vaginal discharge that she experienced after coming home from the Garden Club brunch.

PE reveals:

- + Mucopurulent discharge
- + bleeding with exam

Swabs and Cultures sent to lab

- Wet prep negative for BV
- KOH prep negative for yeast

SH:

- Sex with two partners over past year
- Does not use condoms since pregnancy is a non-issue

4. Which of the following is considered first line treatment for SW at this time?
- A. Levofloxacin 250mg x1 + Doxycycline 100mg BID x 7 days
 - B. Ceftriaxone 250mg IM x 1 + Doxycycline 100mg BID x 7 days
 - C. Ceftriaxone 125mg IM x 1 + Azithromycin 1g po x 1
 - D. Cefixime 400mg po x 1 + Azithromycin 500mg x 1 then 250mg daily x 4 days

GC Management

Ceftriaxone 250mg IM X 1

» or

Cefixime 400mg po X 1 (not recommended 2013)

» or

Single dose Cephalosporin Inj

» PLUS

Azithromycin 1 g po X 1

» or

Doxycycline 100mg BID X 7 days

If GC + also treat for Chlamydia

Rationale for Dose Increase of Ceftriaxone

- Decreased susceptibility to cephalosporins in vitro as noted with Cefixime resistance
- Reports of Ceftriaxone treatment failures
- Improved efficacy of 250mg dose for pharyngeal infections
- Utility of having a simple and consistent recommendation regardless of infected site

Chlamydia Management

Azithromycin 1g x 1

» or

Doxycycline 100mg bid x 7 days

» or

Ofloxacin 300mg bid x 7 days

» or

Levofloxacin 500mg daily x 7 days

If only Chlamydia + just treat for this infection

Abstain from sex until 7 days after treatment started

5. A 52 yo male with uncontrolled Type 2 DM presents with a “sore” on his upper LE near his groin. Upon examination the area is red with minimal streaking, however it does appear to be a fluctuate mass that has a pearly appearance. T=99F WBC 8,000 glucose 357. Which regimen is appropriate?

A. Clindamycin

B. I&D and

Trimethoprim/sulfamethoxazole

C. I&D alone

D. Doxycycline

E. Linezolid

Cellulitis and Abscess

CID 2011:52 (1 February) 1-37.

Estimated that >50% of current skin infections are due to CA-MRSA

- Athletes
- Military recruits
- Children
- Native Americans
- MSM
- Prisoners
- Close skin to skin contact
- Poor hygiene

Management of Abscess

I & D

- Simple abscesses and boils
- Adequate treatment

Add antibiotics if

- Extensive disease
- Aggressive wounds
- Immunosuppressed/Comorbidities
- Advanced age
- Area difficult to drain eg groin area
- Septic Phlebitis
- Lack of response to I&D

Management of Cellulitis

Purulent Cellulitis

- Empiric treatment for CA-MRSA
- Empiric treatment for strep not needed
- 5-10d of tx
- Bactrim Doxycycline, Clindamycin, Zyvox, Sivestro

Non-purulent Cellulitis

- B-hemolytic strep
- Consider CA-MRSA if do not respond to b-lactam
- 5-10 days of tx
- First Generation Cephalosporins are preferred

Thank you!