The Global Problem of Antimicrobial Resistance

Dr. Elaine Larson, Columbia University School of Nursing

A Webber Training Teleclass

Center for Interdisciplinary Research to Reduce Antimicrobial Resistance

Antimicrobial Resistance:
An Overview

Dr. Elaine Larson
Columbia University School of Nursing

Hosted by Paul Webber
paul@webbertraining.com

www.webbertraining.com

Microbes/Humans

- **Microbes: 5 X 10^{31}**
(50,000,0000,000,000,0000,000,0000,000,000)
- **Humans: 6 X 10^{9}**
(6,000,000,000)

- **Microbiology in the 21st century, ASM, 2004**

Microbial Adaptability (Blaser)

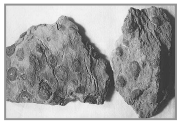
Without 0_2

Boiling water

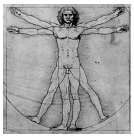
Ice

Crushing Pressure & No Sun

Rocks



Us



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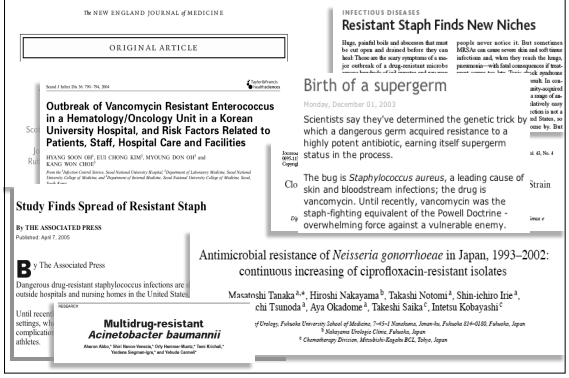
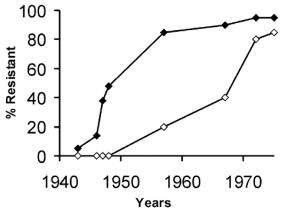
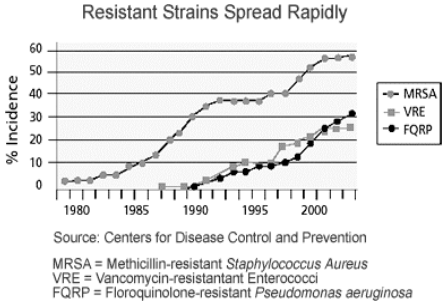
Bad Bugs!! (Blaser)





Secular trends of approximate prevalence rates for penicillinase-producing, methicillin-susceptible strains of Staphylococcus aureus in hospitals (closed symbols) and the community (open symbols), United States

The scientific problem being addressed



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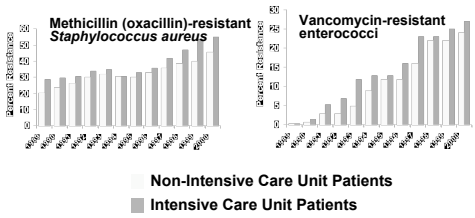
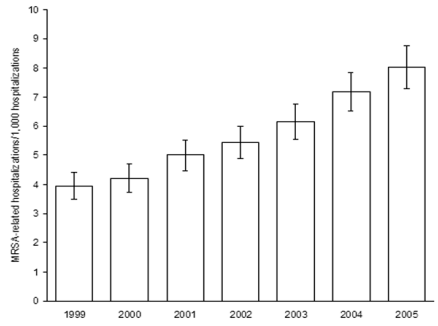
Antimicrobial Resistance among Pathogens Causing Hospital Infections



Non-Intensive Care Unit Patients

Intensive Care Unit Patients

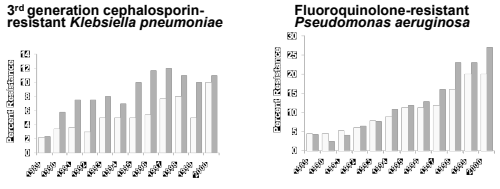
Source: National Nosocomial Infections Surveillance (NNIS) System



MRSA–related hospitalization rates, US, 1999–2005

Klein, et al. Emerg Infec Dis 2007; 13:1840-6

Antimicrobial Resistance among Pathogens Causing Hospital Infections



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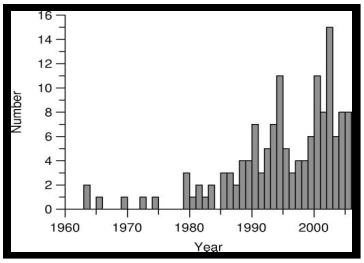
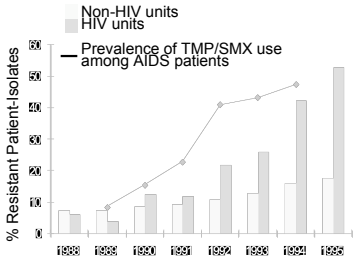
New β-lactamases Reported Per Year

(responsible for resistance to penicillins, cephalosporins, carbepenems, etc)



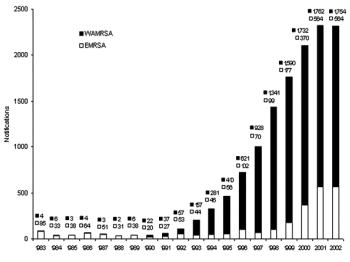
Jacoby GA, β-Lactamase Nomenclature, *Antimicrob Agents Chemother* 2006; 50:1123-9.

Trimethoprim/sulfamethoxazole (TMP/SMX) Resistance Among Bacterial Patient-Isolates*



**** 30,886 patient-isolates***
Staphylococcus aureus
Escherichia coli
Enterobacter spp.
Klebsiella pneumoniae
Morganella spp.
Proteus spp.
Serratia spp.
Citrobacter spp.

San Francisco General Hospital
Martin JN, et al: J Infect Dis 1999;180:1809-18



Notifications of methicillin-resistant *Staphylococcus aureus* (MRSA) in Western Australia, 1983–2002, community-acquired (WAMRSA) versus epidemic (EMRSA) strains

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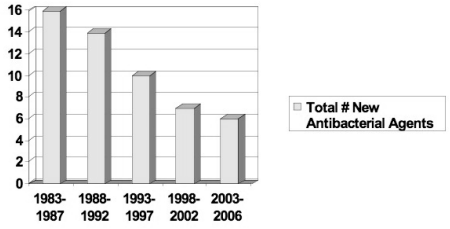
Prevalence of Antimicrobial-Resistant (R) Pathogens Causing Hospital-Onset Intensive Care Unit Infections: 5 years

Organism	%Increase*
Fluoroquinolone-R *Pseudomonas* spp. 2657	49%
3rd generation cephalosporin-R *E. coli* 1551	48%
Methicillin-R *Staphylococcus aureus* 2546	40%
Vancomycin-R enterococci 4744	40%
Imipenem-R *Pseudomonas* spp. 1839	20%

*** Percent increase in proportion of pathogens resistant to indicated antimicrobial**
Source: National Nosocomial Infections Surveillance (NNIS) System

Total Approved Antibacterials: US



Spellberg, et. al., CID May 1 2004, Modified

Drug-resistant pathogens are a growing threat

- **Each year ~2 million patients get an infection in US hospitals, about 90,000 of these die**
- **More than 70% of bacteria causing hospital-associated infections are resistant to ≥1 drug most commonly used to treat them**
- **Persons infected with drug-resistant organisms are more likely to have longer hospital stays and require treatment with less effective, more toxic, and/or more expensive drugs**

http://www.cdc.gov/drugresistance/healthcare/problem.htm

Resistance Expanding in the Community: S. aureus

- **25-30% of healthy people are colonized with *Staphylococcus aureus***
- **Generally this poses little risk, considered 'normal flora'**
- **In past 5 years, there are increasing cases, outbreaks and deaths among healthy persons with a new community strain of antibiotic-resistant *S. aureus***

The Human Face of MRSA: Carlos

- **1/07 Carlos Don, 12 years old, returned from a school trip with flulike symptoms. Started antibiotics, hospitalized on a ventilator, died**

The Human Face of MRSA: Simon

- **Healthy Simon, aged 14 months, mother with doctorate in public health, died within 24 hrs of MRSA sepsis**

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The Human Face of MRSA: Brandon

- **Washington Redskins defensive tackle Brandon Noble after knee surgery. "This infection has had a huge impact on my life and will continue to impact me and my family in the near future. Hopefully, I am not a carrier and will not have to worry about this forever. "**

The Human Face of MRSA: Bryce

- **A healthy 14-month old who contracted MRSA and spent weeks ICU. Survived.**
- **Medical bills to date: ~$1 million**

Bryce in the ICU

One Typical Day: 11/12/07

- Chicago Tribune: Superbugs Spur FDA, Drug Firms To Action
- Associated Press: Staph Germ Undermines Body's Defenses
- LA Times:'Superbug's' Killer Cousin; An Antibiotic-Resistant Staph Strain
- TriCities.com (TN):Staph Infections Aren't New
- The Courier News (IL):Staph Myth Debugged
- Wash Post:FDA Approves Products That Reduce Spread Of Dangerous Bacteria
- Wash Post:Are Antimicrobial Soaps Breeding Tougher Bugs?
- Rochester Democrat and Chronicle (NY):MRSA Increase Is Warning To Use Antibiotics Wisely
- Business Wire: Tommy G. Thompson Speaks Out Against Misinformation Regarding MRSA ``Superbug''
- The Columbus Dispatch (OH):Deadly Threat; Infections Are Reminder That Antibiotics Need Protection
- Chicago Tribune:Garlic vs. 'Superbug'
- Akron Beacon Journal (OH): Officials Seek To End Staph Misinformation
- Associated Press: Gregoire Asks Dept Of Health To Convene MRSA Panel
- US Fed News: Sen. Brown Introduces Strategies To Address Antimicrobial Resistance Act
- States News Service: With Lethal MRSA Infection Continuing To Pop Up In Schools Across NYS, Schumer Bill Will Provide Tax Credit For Research And Development Of Products To Combat Infectious Diseases
- Tallahassee Democrat (FL): Know The Facts About MRSA Infections

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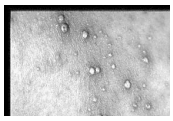
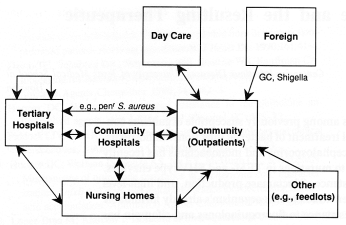


Many 'faces' of MRSA

Epidemiology of the Transmission of Antibiotic-Resistant Bacteria



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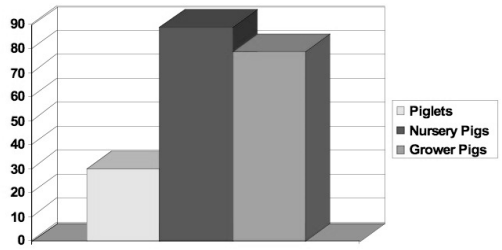
Antibiotics in Agriculture

- Antimicrobials are routinely added to animal feed and water to promote animal growth
  - Rationale is to promote more rapid growth reducing farming expenses
  - Mechanisms are debated although most commonly invoked is the reduction of infections, especially in unsanitary conditions
- Many of the antibiotics used in this setting are of the same class as those used to treat human infections
  - Macrolides, tetracyclines, glycopeptides

Percentage U.S. swine receiving antibiotics in their feed (2005-6)



US DOA, 2007 cited in NY Times, 12/16/07

Chronology/History: 1940s-50s

- 1940: Pathologist Florey discovers killing properties of penicillin, which was first widely available antibiotic and used in WWII for soldiers
- 1943: Drug companies mass produced
- 1958: Nobel Prize for discovery of bacteria's ability to exchange genetic material

Chronology/History: 1960s

- Fast-developing resistance, but large number of new antibiotics enter market
- 1960: Methicillin introduced
- 1961: MRSA turns up in UK hospital
- 1963: MRSA appears in Denmark
- 1967: Penicillin-resistant streptococcal pneumonia in New Guinea

Chronology/History: 1970s-80s

- Antibiotics routinely prescribed for viral infections (e.g. colds), strong antibiotics used for transplants, cancer
- 1977: Strep pneumonia bacterium resistant to every available drug (S.Afr)
- 1983: 18 people hospitalized for Ab-resistant salmonella from beef fed Abs
- 1986: Sweden bans Abs for animal food

Chronology/History: 1990s

- Drug firms reduce Ab R&D
- 1992: Ab-resistant infections kill 13,000 hospital patients
- 1998: Denmark taxes Abs used as animal growth promoters. EU bans use of human Abs for animals feed
- 1999: US Fed Interagency Task Force on AM Resistance launched

Chronology/History: 2000s

- **2000: Congressional Act to take strong steps to reduce resistance is not funded. Public health efforts lag**
- **2001: Anthrax scare results in stockpiling cipro**
- **2003: Drug resistant *Acinetobacter* infection Iraqi War soldiers, leading to many amputations**

Inappropriate use?

Chronology/History: 2000s

- **2005: France bans 12 sore-throat medications containing antibiotics**
- **2006: EU bans using any antibiotic to promote animal growth**
- **US STILL has made minimal similar efforts**

Chronology/History: 2007

- Cases of MDR-TB quadruple in S. Afr
- WHO launches plan to fight MDR-TB
- Avian flu virus is evolving to be resistant to current vaccine strains
- 10 times as many cases of MRSA in hospitals than previously thought
- FDA still considering approval for a new Ab for cows that could increase resistance in Abs used in humans
- CQ Researcher 2007; 17:683

MDR-TB

- Kills ~2 million worldwide annually
- MDR-TB has doubled in past few years in many countries (WHO)
- Summer 2007: Andrew Speaker: Healthy US newlywed on honeymoon had MDR-TB. Where did he get it?
- Only 30-50% of those with extensively resistant strains recover

- Now we have XDR (extensively resistant) TB

(Music courtesy of R. Weinstein)

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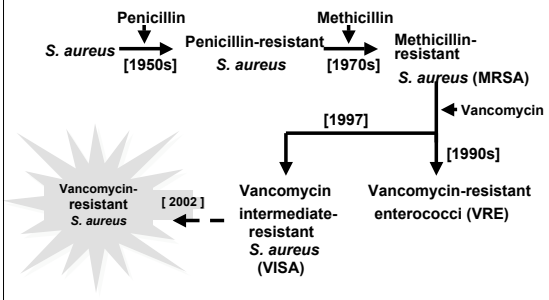
Evolution of Drug Resistance in S. aureus



Attributable Costs of Resistance

- MRSA (vs MSSA)
  - Bacteremia[1]
    - Median hospital stay increased by 2 days
    - Median hospital charges increased $6916
  - Surgical site infection[2]
    - Median hospital stay increased by 5 days
    - Median hospital charges increased $13,901

FOR MORE INFO...

1. Cosgrove SE et al. Infect Control Hosp Epidemiol 2003
2. Engemann JJ et al. Clin Infect Dis 2003

MRSA Prevalence Survey: NYS Prisons

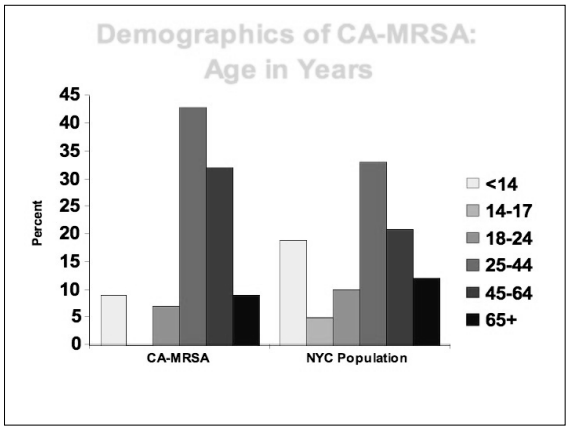
	Sing Sing	Bedford Hills
Number of inmates	1741	792
Ethnic status (%)		
African American	55	50
Hispanic	31	22
White	11	27
Average length of incarceration (months)	21	38
No prior arrest	17	37
No prior conviction	6.5	7.5
Prior jail term	17.5	21
Violent felony	80	65
Drug felony	12	10

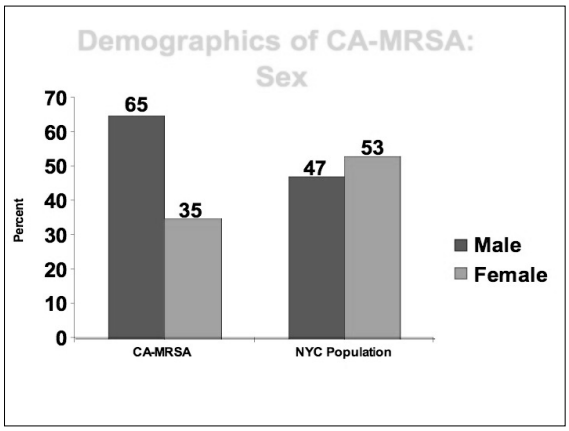
Results: Feb-May 2006

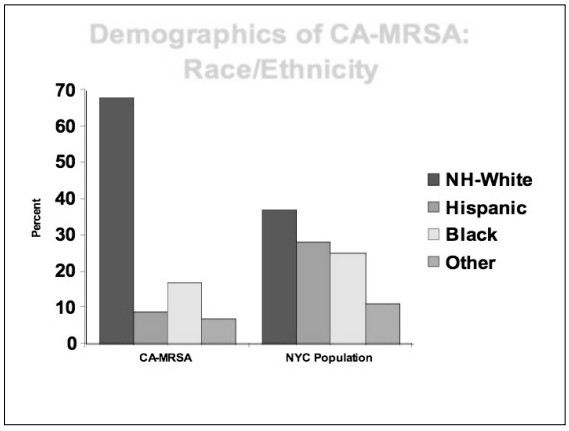
- ***S. aureus* positive** • **25.5 (124/487)**
- **MRSA** • **10.5 (13/124)**
- **SCC*mec* type IV** • **100 (13/13)**
- **PVL + MSSA** • **21.6 (24/111)**
- **PVL + MRSA** • **61.5 (8/13)**

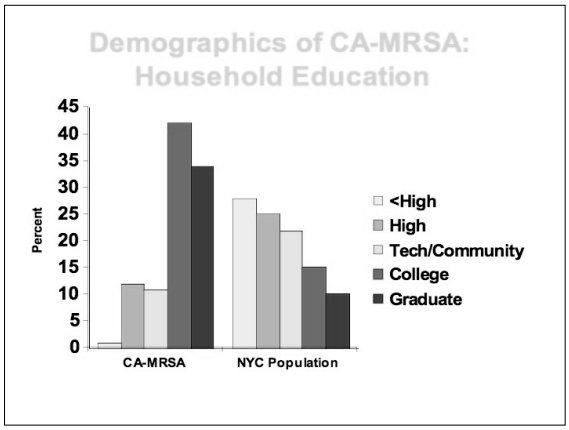
Staphylococcus aureus Reports Lab A: April – October 2005 Manhattan

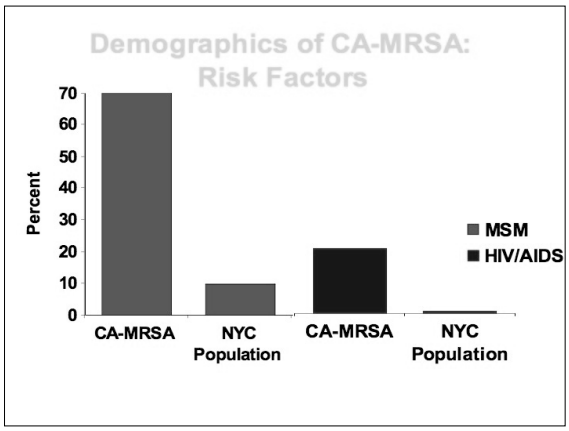
- **MSSA 58% (446)**
- **MRSA 35% (270)**


Demographics of CA-MRSA:
Age in Years
Percent
45
40
35
30
25
20
15
10
5
0
CA-MRSA
NYC Population
<14
14-17
18-24
25-44
45-64
65+


Demographics of CA-MRSA:
Sex
Percent
70
60
50
40
30
20
10
0
65
35
47
53
CA-MRSA
NYC Population
Male
Female


Demographics of CA-MRSA:
Race/Ethnicity
Percent
70
60
50
40
30
20
10
0
CA-MRSA
NYC Population
NH-White
Hispanic
Black
Other





Summary: CA-MRSA cases differ significantly from NYC population

- **Predominantly male**
- **White, non-Hispanic**
- **Higher proportion 24-64 y-o**
- **Affluent**
- **Highly educated**
- **Concentrated in Manhattan**

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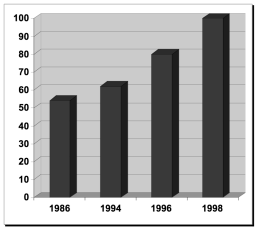
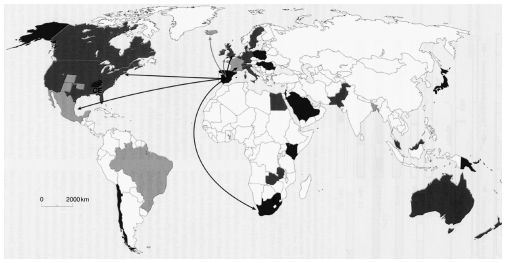
"At the beginning of the 21st century, antimicrobial resistance is common, has developed against every class of antimicrobial drug, and appears to be spreading into new niches."

http://www.cdc.gov/ncidod/EID/vol11no06/05-0167.htm



Proportion of resistance to ≥3 antimicrobial agents among isolates of *E. coli* in Nigeria

International Spread of Resistant Clones of Pneumococcus



Dowson, Trends Microbiol

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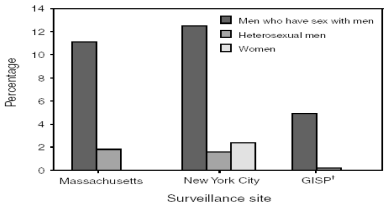
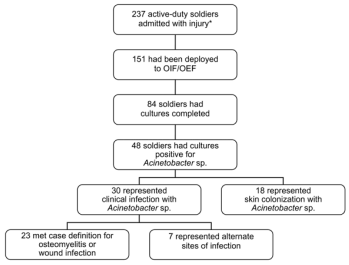
Resistant N. gonorrhoeae

FIGURE. Prevalence of fluoroquinolone-resistant *Neisseria gonorrhoeae* infection, by sex, sexual behavior, and surveillance site — United States, 2003*



* Data from Massachusetts and New York City are from sexually transmitted disease clinics. In the Gonococcal Isolate Surveillance Project (GISP), data are presented for all areas, excluding Hawaii and California; no women are surveyed in GISP. All data are preliminary.
† Gonococcal Isolate Surveillance Project.

Resistant Acinetobacter Infections: Military



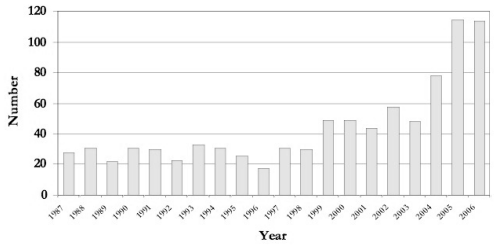
http://www.cdc.gov/ncidod/EID/vol11no08/05-0103-G.htm

Antibiotic Resistance Genes in Multidrug-Resistant* Acinetobacter *sp. Isolates from Patients Treated at the Walter Reed

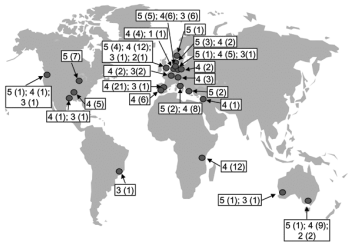
- **Sixteen unique resistance genes and four mobile genetic elements detected in 75 unique patient isolates**
- **89% resistant to at least 3 antibiotic classes; 15% resistant to all antibiotics tested**
- **Eight major clonal types, very complex genetic background**

Hujer et al, *Antimicrob Agents Chemother* 2006; 50:4114-23.

PubMed Citations for Antibiotic Resistant Acinetobacter, 1987-2006



Global Spread of Distinct Genetic Hospital Strain of VRE



http://www.cdc.gov/ncidod/EID/vol11no06/04-1204-G4.htm

Mechanisms of Resistance

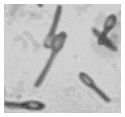
- ***Emergence, which occurs because of microbial evolution***
- ***Dissemination of resistant organisms***
  - ***at the microbial level (e.g. clonal spread, plasmids, transposons)***
  - ***at the population level (e.g. hospital or community spread)***

Courvalin P. Emerg Infec Dis
http://www.cdc.gov/ncidod/EID/vol11no10/05-1014.htm

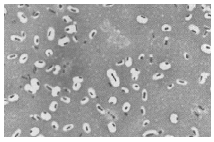
Characteristics that Enhance Resistance

- **Speed. Bacterial populations can double ~ every 20 mins**
- **Exchangeability. Bacteria can exchange genetic material**
- **Mutation. Under antibiotic pressure, resistant mutants emerge**

Some species are intrinsically more resistant



Spores



Capsules

Three Fundamental Mechanisms

- **Enzymatic degradation of antibacterial drugs**
- **Alteration of bacterial proteins that are antimicrobial targets, and**
- **Changes in membrane permeability to antibiotics.**

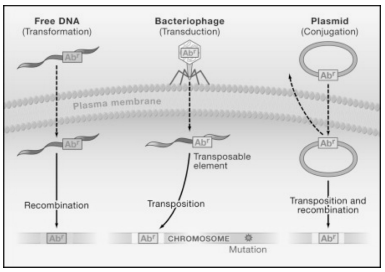
Transfer of Resistance

Mutation (no transfer required)

Transformation

Transduction

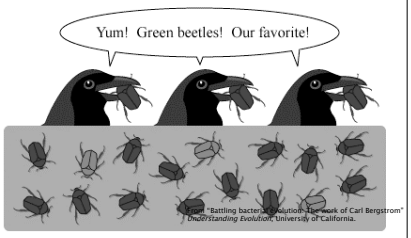
Conjugation



How does natural selection work?

Variation
Inheritance
Selection
Time
Adaptation

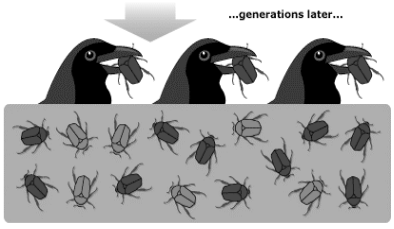
Natural selection, in a nutshell:



From "Battling bacteria, Evolution 101: The work of Carl Bergstrom" *Understanding Evolution*, University of California.

How does natural selection work?

Variation
Inheritance
Selection
Time
Adaptation



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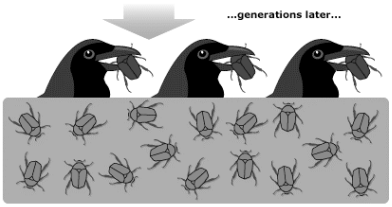
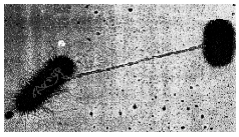


Green beetles have been selected against, and brown beetles have flourished.

Antibiotic resistance can be either plasmid mediated or maintained on the bacterial chromosome



Discussion

- **Determine at least 2-3 actions that could be taken to reduce resistance by**
  - **The public**
  - **The healthcare community**
  - **The government**
- **Develop a plan of action for making this happen**
- **Describe how you would evaluate the effectiveness of this plan**

Avoiding Resistance: What the Public Can Do

- Careful hygiene, particularly in moist, busy environments such as gyms
- Don't share towels, clothes
- Avoid antibacterial soaps with triclosan; consider using alcohol rubs
- Don't demand Abs for viral infections
- Don't save or take anybody else's Abs
- Find out about hospital infection rates

Public Knowledge/Attitudes

- 453 Wash Heights households interviewed (2,386 people)
- 88% thought colds were caused by bacteria
- Only 29.8% agreed that most colds and flu would improve without medication
- 89.9% stated that antibiotics are usually or sometimes needed to treat viral throat infections
- 27.6% stated that Abs were usually or sometimes indicated for asthma attacks.

Antibiotics without Prescription

- Availability of antibiotics without prescription in New York City
- 42nd Annual Meeting of the Infectious Diseases Society of America (IDSA), Boston, 10/04.

Larson & Figueroa, J Urban Health 2004; 81:498-504

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Methods

Survey of all independent pharmacies, grocery stores, delicatessens, bodegas and botanical or health food stores in 30 blocks of the major commercial areas of three neighborhoods were surveyed:

Predominantly Hispanic neighborhood (Washington Heights)
Predominantly Black neighborhood (Central Harlem)
Predominantly Caucasian neighborhood (Upper West Side)

Procedure

- **A trained surveyor of same ethnicity as the neighborhood residents entered each store and ascertained whether antibiotics were available on the shelf or upon request to the store attendant.**

Results

- **101 stores were surveyed**
- **No antibiotics were available in the predominantly Black or Caucasian neighborhoods**
- **In 7/34 (20.6%) of stores in the Hispanic neighborhood, antibiotics were available on the shelves, and were also available upon request in all other stores**

What Types?

- **Antibiotics offered included ampicillin, amoxicillin, tetracycline, erythromycin**
- **Antibiotics were offered as single doses individually wrapped and in larger quantities.**

Educational Materials: Hands

Clinician Prescribing Patterns: Community

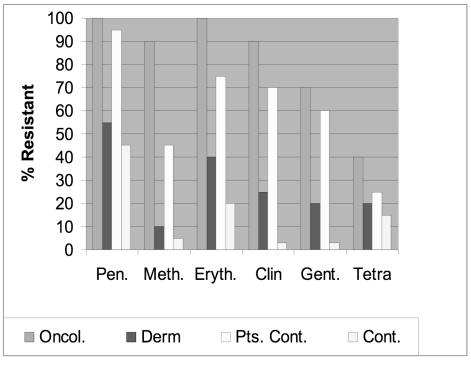
- **Rates of prescribing antibiotics for viral URI range from 25-56%**
- **When presented with clinical scenarios of viral pharyngitis, 81% of 948 clinician respondents used an inappropriate treatment strategy**
- **22% of 1,363 ED visitors reported that their physician routinely prescribed Abs for a cold**
- **>800 physicians rated the issue of resistance as the lowest of seven determinants of their choice regarding antibiotic prescribing**

Nurse Practitioners (NP)

- **Survey of 149 (48%) educational programs**
- **45.3% reported <4 hours of lecture on antimicrobial therapy, but 51.9% did not offer a microbiology course** (Sym, et.al. J Am Acad Nurse Pract 2007; 19:477-485).
- **National NP guidelines do not include competencies regarding antimicrobial resistance and/or proper antibiotic prescribing**
- **NPs misuse and overuse antimicrobial agents in a similar fashion to physicians.**

Avoiding Resistance: What Healthcare Systems Can Do

- **Control antibiotic use**
- **Prevent cross-transmission between patients and from healthcare worker to patient**
  - **Appropriate barrier techniques (cohorting, isolation)**
  - **Appropriate hygiene, particularly hands**
- **Identify and act on infections rapidly**



Current Status in Hospitals

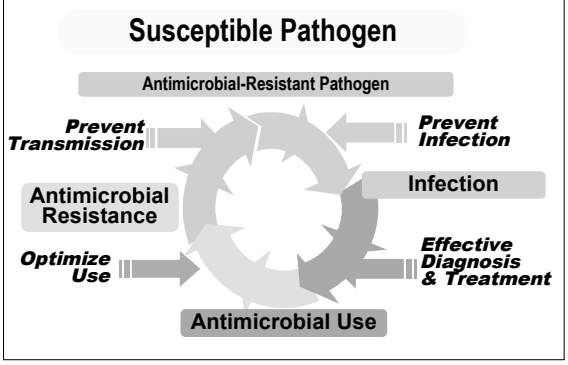
- 34/1000 patients have active HA-MRSA infections and 12/1000 additional are colonized
- About 1.2 million patients infected annually
- Resistance increasing similarly in other organisms

Antimicrobial drug use: 130 U.S. Hospitals

- 59.8% of patients received one of 50 antibacterial agents (1,074,174/1,795,504)
- 776/1000 patient days
- 792 doses/100 patient days

Polk et al. CID 2007; 44:664-70

CDC's Key Prevention Strategies



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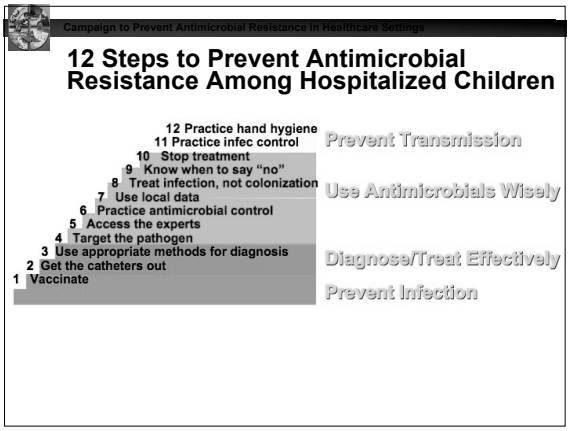

Potential Barriers to Adherence to Guidelines

Knowledge

Lack of awareness **– No knowledge of CDC 12 Steps**

Lack of familiarity **– Unfamiliar with 12 Steps in general or with specific component(s)**

Potential Barriers to Adherence to Guidelines

Attitude

Lack of agreement **– Disagreement with CDC 12 steps or with specific component(s)**

Lack of self efficacy **- Perceived lack of confidence or lack of preparation to perform specific guideline(s)**

Lack of outcome expectancy **– Lack of belief that guideline(s) will lead to an important patient outcome**

Potential Barriers to Adherence to Guidelines

Practice

Frequency (Adherence) - **How often guideline(s) are followed**

External factors - **Lack of time, support staff, administrative support, and/or financial reimbursement**

Cabana MD, et al. Why Don't Physicians Follow Clinical Practice Guidelines? A Framework for improvement. JAMA 1999; 282:1458-1465

Survey

- **Neonatology fellows and faculty attending a conference *"Infection and Immunity in the Preterm Infant"* at the 70th Annual Perinatal Development Symposium on June 1, 2007**

- **Used with permission from Patel S, Saiman L. Columbia University Department of Pediatrics.**

Knowledge

Lack of Awareness

- **Awareness of 12 Step Campaign**
  - **59% not aware of the campaign**
  - **25% somewhat aware**
  - **16% very aware**
  - **28% received educational materials**
    - **(including 4 unaware of 12 Steps)**

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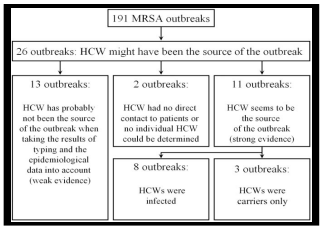
Outbreak of Multidrug-Resistant* Acinetobacter *in the US Military Health Care System Associated with Military Operations in Iraq

- **Evaluated 3 potential sources: patient skin, soil, healthcare environment**
- **Prevalence**
  - **Skin: 1/160 patients (0.6%)**
  - **Soil: 1/49 samples (2%)**
  - **Environment: 7/7 hospitals (100%)**
- **Environmental contamination played a major role**

Scott et al, *Clin Infect Dis* 2007; 44:1577–84

How Often Do Asymptomatic Healthcare Workers Cause Methicillin-Resistant* Staphylococcus aureus *Outbreaks? A Systematic Evaluation

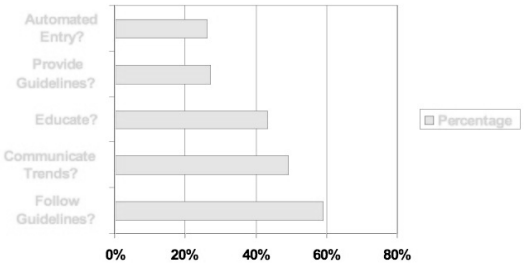


Distribution of MRSA outbreaks with a strong epidemiological association with healthcare workers.

Vonberg et al, *Infect Control Hosp Epidemiol* 2006; 27:1123-7.

Fighting Resistance in Hospitals

(Zillich, Infect Contr Hosp Epidemiol 2006; 27:1088)



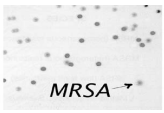
Hosted by Paul Webber paul@webbertraining.com

www.webbertraining.com

Proven Control Measures

– "Barrier precautions"
- Gowns
- Gloves
- Hand hygiene
- Control of solid waste disposal

- Admission culturing for MRSA?



Avoiding Resistance: What Can Government Do?

- Good surveillance: National Antibiotic Resistance Monitoring System (NARMS) is run on a shoestring
- Stricter tabs and regulations regarding Ab use in humans and animals
- Private sector has been unwilling on its own
- Better support of development of new Abs
- Funds for social marketing campaigns

IDSA recommendations

- "Wild-card patent extension."
- A company could extend the market exclusivity period of another FDA-approved drug as long as the company commits to invest a portion of the profits derived during the extension period back into antibiotic R&D.
- Restoration of all patent time lost during FDA's review of priority antibiotics
- Extended market exclusivity similar to what has been successfully implemented for pediatric and orphan drugs
- Other potential statutory incentives:
- Tax incentives for R&D of priority antibiotics Measured liability protections
- Additional statutory flexibility at FDA regarding approval of antibiotics, as needed
- Antitrust exemptions for certain company communications
- A guaranteed market

http://www.idsociety.org/temp.aspx?RefURL=http%3a%2f%2fold.idsociety.org%3a80%2fTemplate.cfm%3fSection%3dAntimicrobials%26Template%3d%2fContentManagement%2fContentDisplay.cfm%26ContentID%3d9770

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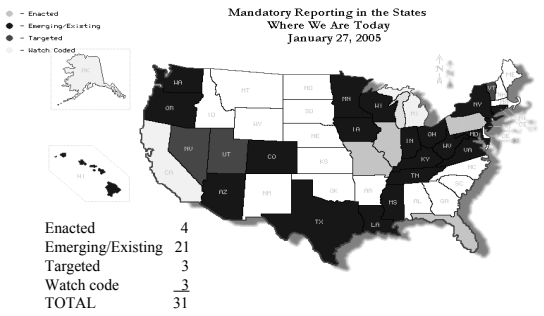
STARR Act

- **On 9/27/07, Reps. Jim Matheson (D-UT), Michael Ferguson (R-NJ) and other members of Congress introduced the Strategies to Address Antimicrobial Resistance (STAAR) Act, H.R. 3697. The STAAR Act provides necessary and critical solutions to prevent and control the spread of antimicrobial-resistant "bad bugs."**
- **http://www.idsociety.org/STAARAct.htm**

State Laws Requiring Outcome Measurement



Enacted	4
Emerging/Existing	21
Targeted	3
Watch code	3
TOTAL	31

Will It Work?

- **In European countries (e.g. Netherlands, Denmark) where hospital stringent policies regarding are in place, rates of MDRO have dropped precipitously**
- **No mechanism in US to mandate such policies; must be done on an individual system or institution basis.**

Thanks to…

- **M. Blaser, F. Lowy, R. Weinstein, M. Marx, A. Ratner, S. Patel from whom slides were obtained with permission**