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Antimicrobial Resistance: An Overview
Dr. Elaine Larson
Columbia University School of Nursing

Microbes/Humans
- Microbes: $5 \times 10^{21}$
  $(50,000,000,000,000,000,000,000,000,000,000,000)$
- Humans: $6 \times 10^9$
  $(6,000,000,000)$

- Microbiology in the 21st century, ASM, 2004

Microbial Adaptability (Blaser)

- Without $O_2$
- Boiling water
- Ice
- Crushing Pressure & No Sun
- Rocks
- Us

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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
Resistant Strains Spread Rapidly

Source: Centers for Disease Control and Prevention
MSSA = Methicillin-sensitive Staphylococcus Aureus
VRE = Vancomycin-resistant Enterococci
PCRP = Pseudomonas aeruginosa

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Antimicrobial Resistance among Pathogens Causing Hospital Infections

- Methicillin (oxacillin)-resistant Staphylococcus aureus
- Vancomycin-resistant enterococci

Source: National Nosocomial Infections Surveillance (NNIS) System

Antimicrobial Resistance among Pathogens Causing Hospital Infections

- 3rd generation cephalosporin-resistant Klebsiella pneumoniae
- Fluoroquinolone-resistant Pseudomonas aeruginosa

Source: National Nosocomial Infections Surveillance (NNIS) System


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New $\beta$-lactamases Reported Per Year
(responsible for resistance to penicillins, cephalosporins, carbapenems, etc)


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

San Francisco General Hospital

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

<table>
<thead>
<tr>
<th>Organism</th>
<th>% Increase*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoroquinolone-R Pseudomonas spp. 2657</td>
<td>49%</td>
</tr>
<tr>
<td>3rd generation cephalosporin-R E. coli 1551</td>
<td>48%</td>
</tr>
<tr>
<td>Methicillin-R Staphylococcus aureus 2546</td>
<td>40%</td>
</tr>
<tr>
<td>Vancomycin-R enterococci 4744</td>
<td>40%</td>
</tr>
<tr>
<td>Imipenem-R Pseudomonas spp. 1839</td>
<td>20%</td>
</tr>
</tbody>
</table>

* 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

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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 flu-like 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

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': Killer Cousin; An Antibiotic-Resistant Staph Strain
- TriCities.com (TN): Staph Infections Aren't New
- The Courier News (IL): Staph Myth Debunked
- 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
- 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

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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

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**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

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**Inappropriate use?**

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**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

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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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>Resistance Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>1950s</td>
<td>S. aureus</td>
</tr>
<tr>
<td>Penicillin-resistant S. aureus</td>
<td>1970s</td>
<td></td>
</tr>
<tr>
<td>Methicillin</td>
<td>1997</td>
<td>S. aureus (MRSA)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1990s</td>
<td>Vancomycin-resistant enterococci (VRE)</td>
</tr>
<tr>
<td>Vancomycin-resistant intermediately-resistant S. aureus (VISA)</td>
<td>2002</td>
<td></td>
</tr>
</tbody>
</table>

Attributable Costs of Resistance

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

For more info...

MRSA Prevalence Survey:
NYS Prisons

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

Results: Feb-May 2006

- **S. aureus positive** 25.5 (124/487)
- **MRSA** 10.5 (13/124)
- **SCCmec 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)

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Demographics of CA-MRSA: Age in Years

Demographics of CA-MRSA: Sex

Demographics of CA-MRSA: Race/Ethnicity

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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

International Spread of Resistant Clones of Pneumococcus

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

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Resistant N. gonorrhoeae

![Graph showing prevalence of fluoroquinolone-resistant N. gonorrhoeae infection by sex, sexual behavior, and surveillance site—United States, 2007.]

- Endemic in Atlanta, Mobile, and New York City sites
- One site (the other New York City site) was not sexually transmitted

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


Resistant Acinetobacter Infections: Military

- 297 active-duty soldiers admitted with disease
- 1511 had received antibiotic therapy
- 84 patients had culture surveillance
- 25 had received therapy for unrelated illness
- 7 had received antibiotic therapy

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

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**PubMed Citations for Antibiotic Resistant Acinetobacter, 1987-2006**

![Graph showing PubMed citations for antibiotic-resistant Acinetobacter from 1987 to 2006.](graph.png)

**Global Spread of Distinct Genetic Hospital Strain of VRE**

![Map showing the global spread of a distinct genetic hospital strain of vancomycin-resistant enterococci (VRE).](map.png)


**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

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**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.

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Transfer of Resistance
- Mutation (no transfer required)
- Transformation
- Transduction
- Conjugation

How does natural selection work?
- Variation
- Inheritance
- Selection
- Time
- Adaptation

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How does natural selection work?

Variation
Inheritance
Selection
Time
Adaptation

| 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

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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

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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
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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

Susceptible Pathogen

Prevent Transmission
Antimicrobial-Resistant Pathogen
Prevent Infection
Antimicrobial Resistance
Optimize Use
Effective Diagnosis & Treatment
Antimicrobial Use

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12 Steps to Prevent Antimicrobial Resistance Among Hospitalized Children

1. Wash hands
2. Use appropriate methods for diagnosis
3. Target the pathogens
4. Access the experts
5. Practice antimicrobial control
6. Treat infection, not colonization
7. Use local data
8. Know when to say "no"
9. Practice hand hygiene
10. Stop treatment
11. Practice infus control
12. Prevent Transmission

Use Antimicrobial Wisely

Diagnose/Treat Effectively
Prevent Infection

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)

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

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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


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.

Fighting Resistance in Hospitals
(Zillich, Infect Contr Hosp Epidemiol 2006; 27:1088)

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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%3d9779

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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

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.

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Thanks to…

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