



# Antimicrobial Stewardship:

**Arizona Partnerships Working to Improve the Use of Antibiotics in the Hospital and Community**

<http://www.azdhs.gov/phs/oids/hai/advisory-committee/antimicrobial-stewardship.htm>

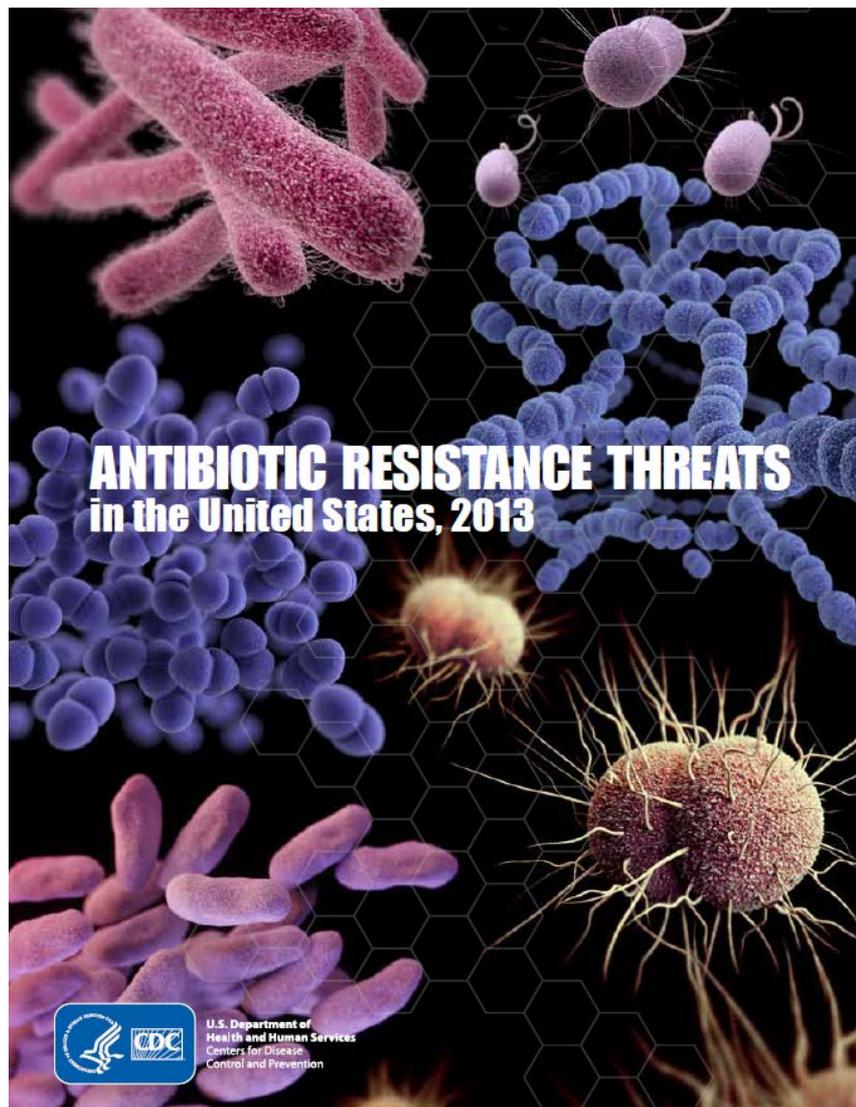
# ANTIBIOGRAMS

# Conflicts of Interest

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- Ortho-McNeil Pharmaceuticals (2000-2011)
  - Participated in research and development of new anti-infectives and dosage forms (levofloxacin, doripenem, ceftobiprole)
  - Own stock in Johnson and Johnson
- Optimer Pharmaceuticals (now Cubist Pharmaceuticals) (2011-2013)
  - Participated in research and development (fidaxomicin)
- Cubist Pharmaceuticals
  - Pursuing two publications on *C. difficile* infection and its treatment
- The Medicines Company (2014 to present)
  - Participate in research and development of several anti-infective products
  - Medical writing and publications

# Recent Report From The CDC



## NATIONAL SUMMARY DATA

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

At least  **2,049,442** illnesses,  
 **23,000** deaths

*\*bacteria and fungus included in this report*



Estimated minimum number of illnesses and death due to *Clostridium difficile* (*C. difficile*), a unique bacterial infection that, although not significantly resistant to the drugs used to treat it, is directly related to antibiotic use and resistance:

At least  **250,000** illnesses,  
 **14,000** deaths

### WHERE DO INFECTIONS HAPPEN?

Antibiotic-resistant infections can happen anywhere. Data show that most happen in the general community; however, most deaths related to antibiotic resistance happen in healthcare settings, such as hospitals and nursing homes.

CS230550

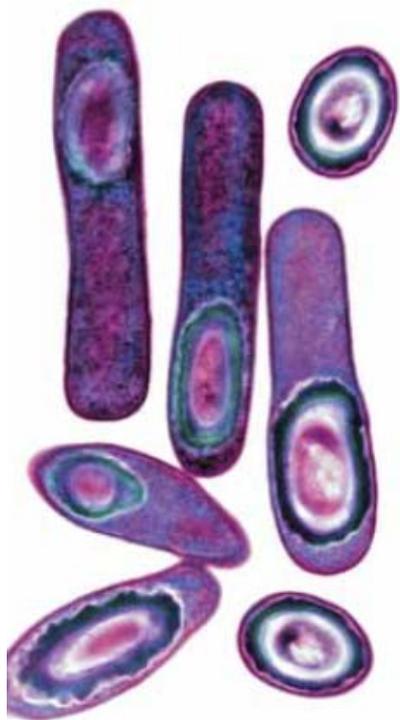


U.S. Department of Health and Human Services  
Centers for Disease Control and Prevention

# The Annual Cumulative Antibiogram

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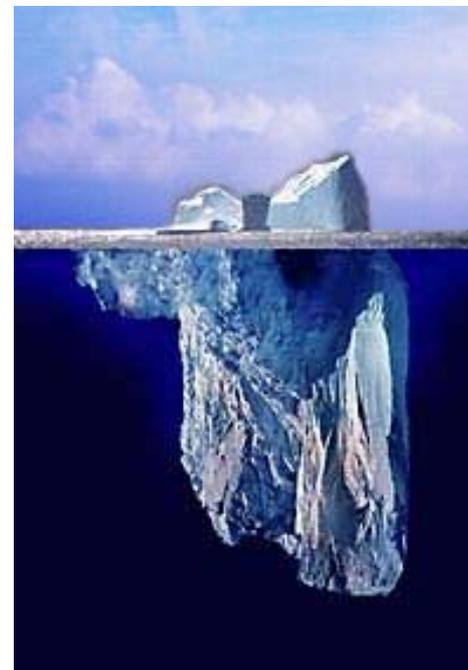
How does a CDC report on the threats of antibiotic resistance lead clinicians to see the value of an annual cumulative antibiogram?



*Clostridium difficile*

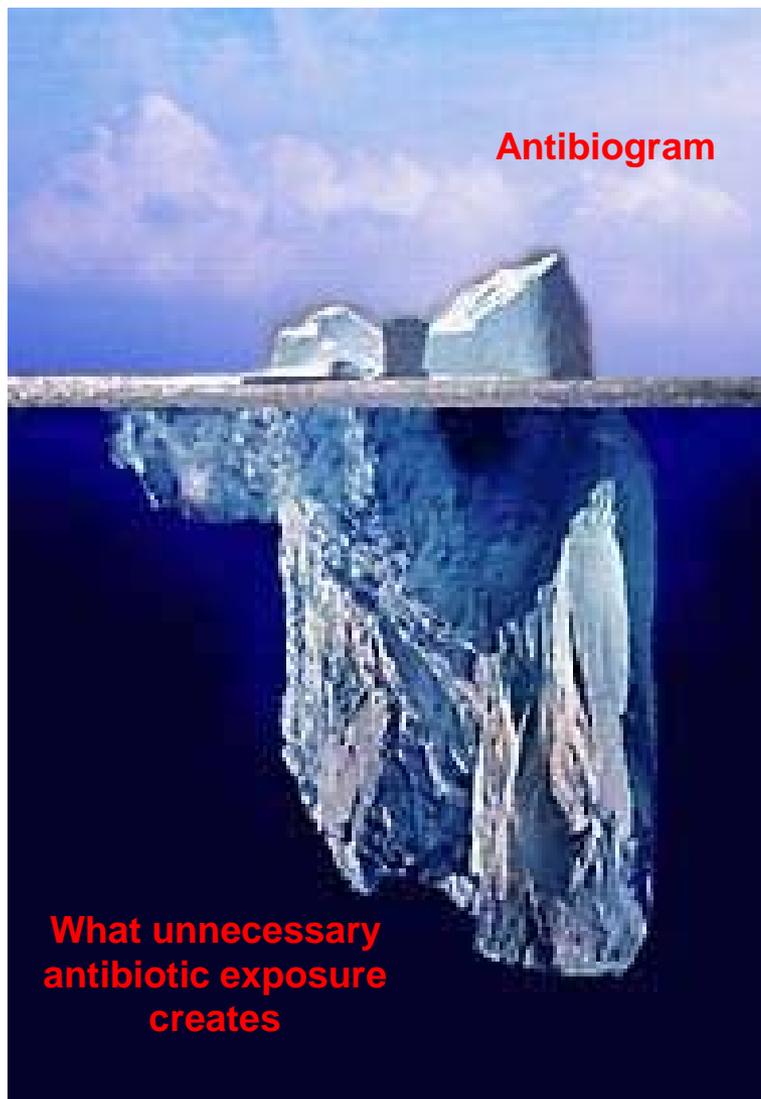


*Escherichia coli* on a spinach leaf



An iceberg

# The “Iceberg Effect”



The antibiogram represents:

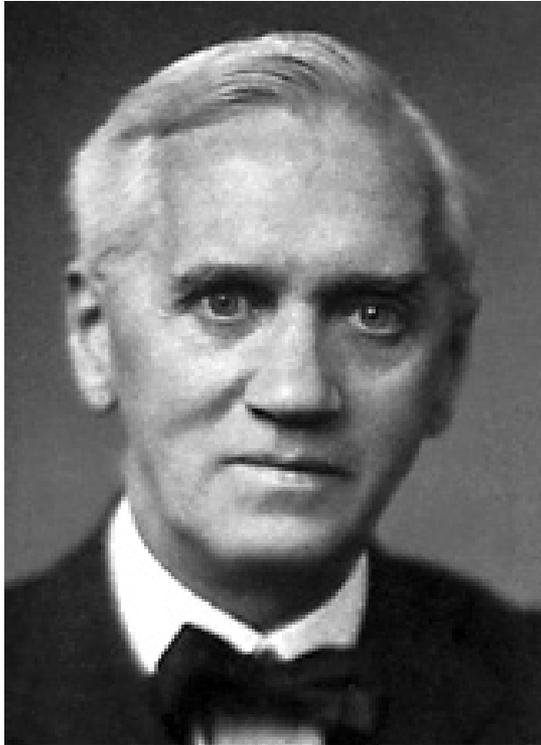
- Importation/exportation
- Weak or non-existent antimicrobial use policy
- Outbreaks
- Endemic resistance issues

When factors align:

- Poor hand hygiene
- Environmental (hospital) contamination
- Colonization of skin and mucosal surfaces (oropharynx, intestines, moist epithelium)
- Animals and food
- Human antimicrobial exposure
- Microbial evolution

## Words to Heed From Decades Past

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“The public will demand [the drug and]...then will begin an era...of abuses. The microbes are educated to resist penicillin and a host of penicillin-fast organisms is bred out which can be passed to other individuals and perhaps from there to others until they reach someone who gets a septicemia or a pneumonia which penicillin cannot save. In such a case the thoughtless person playing with penicillin treatment is morally responsible for the death of the man who finally succumbs to infection with the penicillin-resistant organism. I hope the evil can be averted.”

Sir Alexander Fleming. Penicillin's finder assays its future. New York Times 1945; 21.

# Antibiotics and Bacterial Resistance: “Tragedy of the Commons”

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- Antibiotics exist as a valuable resource for all
- Antibiotic therapy can cure an infection in a single person
- Overuse of the resource amongst a population leads to antibiotic resistance
- Antibiotic resistance restricts the value of the resource
- The resource becomes depleted as choices of antibiotics become limited
- No new novel antibiotics effective against MDROs
- Antibiotics exist no longer as a resource to treat infections

Centers for Disease Control and Prevention

**MMWR**

Morbidity and Mortality Weekly Report

Weekly / Vol. 59 / No. 37

September 24, 2010

**Update: Detection of a Verona Integron-Encoded  
Metallo-Beta-Lactamase in *Klebsiella pneumoniae* —  
United States, 2010**

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**MMWR**

Morbidity and Mortality Weekly Report

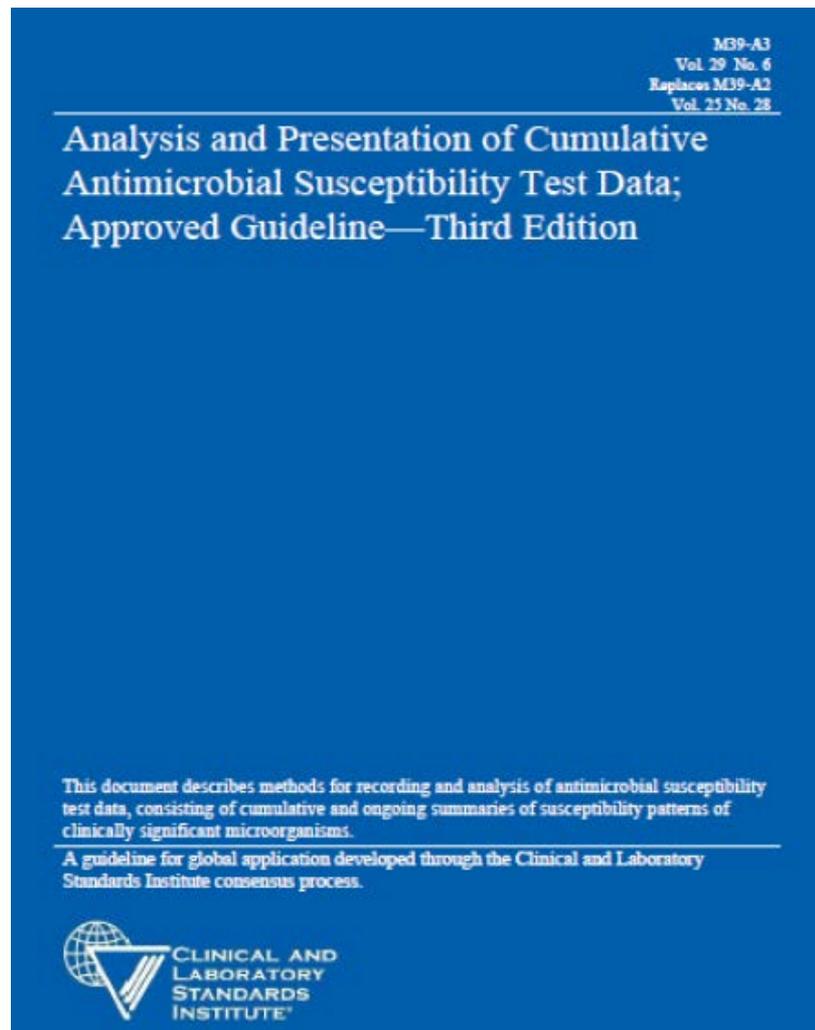
Weekly / Vol. 59 / No. 24

June 25, 2010

**Detection of *Enterobacteriaceae* Isolates Carrying Metallo-Beta-  
Lactamase — United States, 2010**

# Current Practice With Antibiograms

- Antibiograms are commonly constructed by microbiologists generally with minimal input from the antibiotic stewardship committee
- The antibiogram is frequently “left as is” without developing an approach for its utilization, expansion, or education
- The value of an antibiogram has considerable potential with numerous applications if certain rules are followed and additional analyses are undertaken
- CLSI’s M39-A3 is available in most laboratories (\$170, member) and provides excellent direction in construction
- However, the M39-A3 does not review the deficiencies of the antibiogram or provide direction on expanded analyses



# The Antibiogram Toolkit: Addressing Unmet Needs

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- “Nuts and bolts” of antibiograms
- Develop an expand analysis of “bacterial resistance demographics”
- Move away from the “single bug-single drug mentality”
- Work with multidisciplinary committees to develop programs which address the rise in bacterial resistance
- Assist multidisciplinary committees involved in antibiotic stewardship to consider additional analyses and antibiogram educational opportunities
- Address deficiencies of the cumulative antibiogram to produce more accurate empiric antibiotic selection tools
- “Go beyond the basics”

**The Antibiogram Toolkit has the potential to transform an institution’s antibiogram into the ultimate tool for use in empiric antibiotic prescribing, resistance trending, and antibiotic resistance education**

# Examples of Simple Pitfalls With Antibiograms

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- Institutional antibiogram shows *E. coli* susceptibility to ciprofloxacin has fallen to 64%
- New policy is instituted to restrict fluoroquinolones to community-acquired pneumonia only
- Ceftriaxone becomes preferred antimicrobial for treatment of UTIs and intra-abdominal infections
- ESBL rates have increased to 24%
- Formulary shift from ceftazidime to imipenem
- Ceftazidime is restricted to ID service
- Ceftazidime use drops to almost nothing over 2 years while imipenem use climbs above baseline ceftazidime use

**What is missing in these scenarios?**

# Questions Which Could Be Asked Prior To Formulary Decisions: Avoiding the “Knee-Jerk” Response

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- Who is represented in the other 36% (susceptible)
- What is current ceftriaxone usage (DDD/1000 pt-bed days)
- What is the ESBL rate?
- Were fluoroquinolones used inappropriately (asymptomatic bacteriuria)?
- Which patients had risk factors for ESBLs?
- How was ceftazidime used?
- What is the expected imipenem use in the ICU?
- Is there carbapenem resistance in *Pseudomonas aeruginosa*?
- Are there other drugs for treatment of ESBL infections besides carbapenems?

# Contents Of The Antibiogram Toolkit

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## **Antibiograms: Developing Cumulative Susceptibility Reports for Your Clinicians and Ensuring Their Appropriate Interpretation and Effective Use”**

- Key provisions of the antibiogram
  - Ten recommendations for preparation of a cumulative antibiogram
  - Ideas on educating prescribers on how to read and interpret the antibiogram
  - Antibiogram pitfalls and how to fix them
- References: essential readings on antibiogram development, validation, utilization, and projects

## **Antibiograms: Projects To Improve The Analytical Power Of The Antibiogram**

- Ten solutions to enhance the utility of antibiograms, education of prescribers, and identification of projects

## **Antibiogram Templates:**

- Not a reminder for antimicrobial costs, but a true source of education

# Ten Valuable Lessons

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## **Build on solutions to further enhance the utility of antibiograms, education of prescribers, and identification of projects**

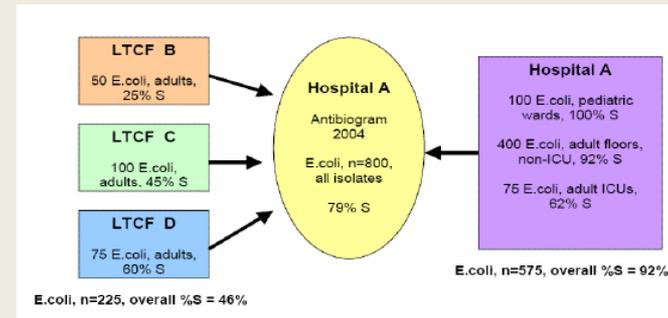
- Contributions to antibiotic resistance may be out of your control: the importance of patient location on susceptibilities
- The problem with antibiograms: numbers represent single-drug resistance
- Detecting excessive influence of repeat (duplicate) isolates
- Cascade (selective) testing and reporting: a pitfall
- When antibiogram data fails to provide direction to narrowing the antibiotic spectrum in select patient circumstances
- Presenting multi-institutional cumulative antibiogram data: local, regional, and national results
- Presenting trends in resistance as an educational section of the antibiogram
- Institutional antibiograms do not provide information on how antibiotic use is epidemiologically linked to resistance rates
- Assessing resistance trends: utilizing statistical analysis to evaluate changes in susceptibility rates
- Using the antibiogram as part of antimicrobial stewardship initiatives

# Example: Patient Demographics

- Where is resistance coming from?
- Drill down patient demographics
- Antibiograms are cumulative and reflect a variety of patient demographics: antibiotic exposures, risk for MDROs, environmental concerns, importation of resistance
- Antibiograms present the mean of bacterial species-single drug combinations

## Contributions to Antibiotic Resistance May Be Out of Your Control: The Importance of Patient Location on Antibiotic Susceptibilities

In the antibiogram pictured below, an institution (Hospital A) shows a % susceptible value of 79% for *E. coli* (n=800 isolates) to Drug B. However, various sources contribute to this overall value and the number of first isolates tested. The number of isolates contributed by inpatients at Hospital A consists of pediatric patients, adult inpatients (non-ICU), and adult inpatients (ICU). When the sources of inpatient isolates (n=575) are considered, the overall %S to Drug B is 92%, which contrasts sharply from the overall antibiogram results of 79% S. So where is the additional resistance coming from?



During a pilot project, it is noted that *E. coli* isolates in patients from 3 local long-term care facilities exhibited high resistance rates to Drug B. This came up during ICU rounds where 3 patients from LTCF B had been admitted for uresepsis and each grew out *E. coli* from the blood and urine resistant to Drug B. All three patients had been started by the ICU fellow on Drug B plus a single dose aminoglycoside (not Drug B).

The Antibiotic Stewardship Team (AST) approached the Microbiology laboratory to retrieve all test results from the current antibiogram year for patients admitted from these LTC facilities and who showed positive cultures for *E. coli*. The laboratory confirmed that all 225 isolates had contributed to the antibiogram. As a matter of expediency, the Pharmacist selected 50 patient isolates at random. The antibiotic susceptibilities were calculated and extrapolated according to the left-hand boxes above for LTCF B, C, and D.

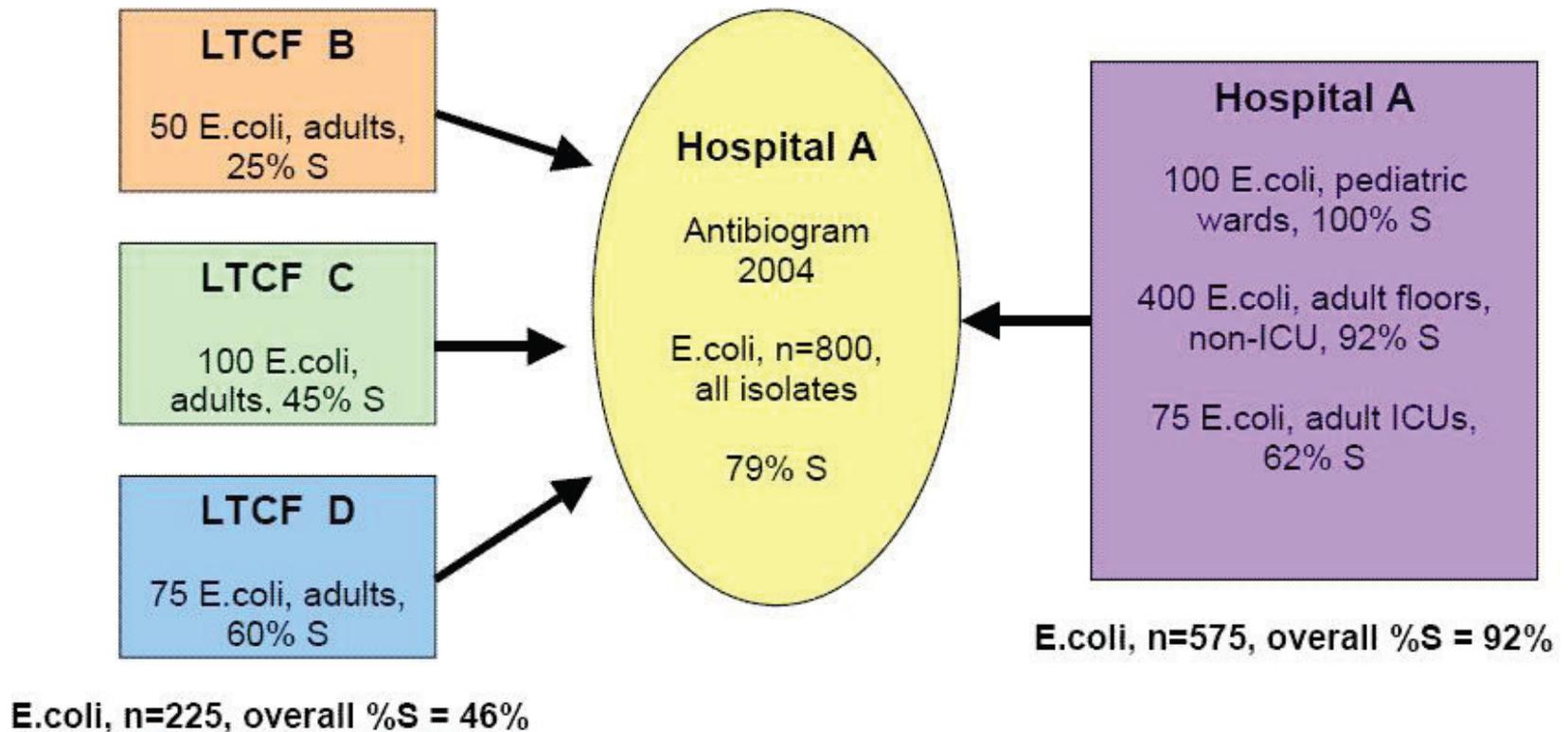
It became immediately apparent that the high resistance rate of *E. coli* to Drug B was largely determined by patient isolates from long-term care facilities but not from other inpatients within the hospital except for the adult ICU (62% S). LTCF B appeared to be the "worst offender".

As a quality improvement project, the AST approached the Medical Directors of all 3 LTCFs and asked if they could assist the hospital in determining why resistance to Drug B was high. The Medical Directors and the hospital AST assisted in developing appropriate recommendations for use of Drug B for the attending physicians, infection prevention, and nursing at all 3 LTC facilities. The AST tracked *E. coli* susceptibilities to Drug B and 3 other agents over the following year.

A word of caution: since many patients in long-term care transition back-and-forth between hospital and nursing home it may be difficult to determine the precise moment or location of acquisition of resistant pathogens. Not all resistance is "imported", but can be "exported" as well. A study such as that above should note this caveat.

# Example: Patient Demographics (cont'd)

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**Embrace patient differences!**

# Multiple Templates and Presentation Hints

## Key Notes on *Streptococcus pneumoniae* Antimicrobial Susceptibilities

[This section should be included in antibiograms to discuss important trends in resistance for this pathogen]

[For few other pathogens are susceptibilities and their reporting so confusing as with *Streptococcus pneumoniae*. This is often related to differing breakpoints depending on whether the pathogen is isolated from CSF as with bacterial meningitis or from blood as in pneumococcal pneumonia with bacteremia. Note that the number of strains is 100 but the same for non-meningitis and meningitis. Thus, this presentation expresses all isolates in terms of %susceptible applied to both breakpoints. It is important to note in this box the number of pneumococcal isolates from CSF and non-CSF specimens. Also, the antibiogram template may be expanded to additional rows to include adult and pediatric data separately]

[Dosing recommendations may be suggested in this box, especially when dealing with the beta-lactam agents and vancomycin for the treatment of meningitis]

## St. Elsewhere Medical Center

### 2012 Antibiogram

Isolates, Jan - Dec 2012

### % Susceptible

Organism	# Strains	Amoxicillin (PO)	Cefotaxime	Ceftriaxone	Clindamycin	Erythromycin	Levofloxacin	Moxifloxacin	Penicillin (IV)	Penicillin (PO)	Trimethoprim-sulfamethoxazole	Vancomycin
<i>S. pneumoniae</i> (ALL)	100		- <sup>a</sup>	- <sup>a</sup>					- <sup>a</sup>	64 <sup>§</sup>		100
Non-meningitis	100	-	94 <sup>†</sup>	95 <sup>†</sup>	-	-	-	-	84 <sup>†</sup>	-	-	-
Meningitis	100	-	85 <sup>†</sup>	84 <sup>†</sup>	-	-	-	-	64 <sup>†</sup>	-	-	-

Examples of footnotes for *Streptococcus pneumoniae* include the following examples:

<sup>a</sup> Breakpoints differ for cefotaxime, ceftriaxone, and penicillin based on diagnosis

<sup>†</sup> Susceptible breakpoint for *S.pneumoniae* in patients with meningitis is  $\leq 0.5$  mg/L for cefotaxime and ceftriaxone and  $\leq 0.06$  mg/L for penicillin

<sup>†</sup> Susceptible breakpoint for *S.pneumoniae* in patients with nonmeningitis infections is  $\leq 1$  mg/L for cefotaxime and ceftriaxone and  $\leq 2$  mg/L for penicillin

<sup>§</sup> Susceptible breakpoint for *S.pneumoniae* is  $\leq 0.06$  mg/L for penicillin when penicillin V is administered by the oral route



# Summary

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- The cumulative antibiogram lends itself to valid mathematical manipulations (a rarity in evidenced-based medicine!)
- There are plenty of pitfalls, and these can be averted, investigated, and solved
- A cooperative microbiology/pathology department is very important (bring them donuts regularly)
- Use the antibiogram for education; otherwise you may find the printed copy filed (in the trash bin)
- Use the antibiogram to validate empiric antibiotic choices and formulary recommendations, and prove its value to the medical staff
- Regularly review “antibiogram investigations” with infection prevention, microbiology, intensivists, and infectious diseases physicians

<http://www.azdhs.gov/phs/oids/hai/advisory-committee/antimicrobial-stewardship.htm>