2001-2016 15 YEARS TELECLASS EDUCATION

Epidemiology, Prevention and Control of Gram Negative Antibiotic Resistant Rods

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Hosted by Paul Webber
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Outline

- General National Trends in Prevalence/Incidence
  - *E. coli*
  - *A. baumannii*
  - *K. pneumoniae*
  - *P. aeruginosa*
- Focus on hospitals, pediatrics, nursing homes
- What next?

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National Trends

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Percent (Rank) of GNB Causing HAI (2009-10)

Organism	CLABSI	CAUTI	VAP	SSI	Total
A. baumannii	2.1% (13)	0.9%	6.6% (5)	0.6%	1.8% (14)
E. coli	4.0% (9)	26.8% (1)	5.9% (6)	9.4% (3)	11.5% (2)
K. pneumoniae	7.9% (5)	11.2% (3)	10.1% (3)	4.0% (7)	8.0% (4)
P. aeruginosa	3.8% (10)	11.3% (2)	16.6% (2)	5.5% (5)	7.5% (5)

Sievert, et al. Infect Contr Hosp Epidemiol 2013; 34:7

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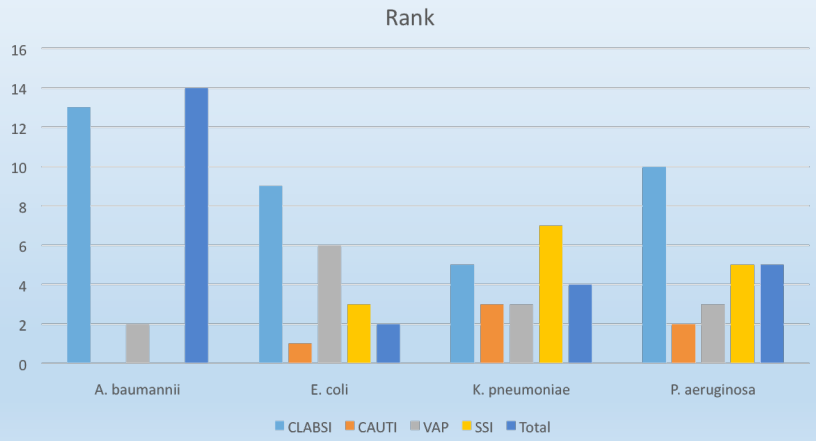
Rank of total HAIs caused by selected GNBs



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Top Contenders (in alphabetical order)

- *Acinetobacter baumannii* (carbapenem/colistin resistant)
- *Carbapenem resistant Enterobacteriaceae*
- *Escherichia coli* (ESBL producing)
- *Klebsiella pneumoniae* (ESBL producing, carbapenem resistant)
- *Extended spectrum β-lactamase (ESBL) producing Enterobacteriaceae*

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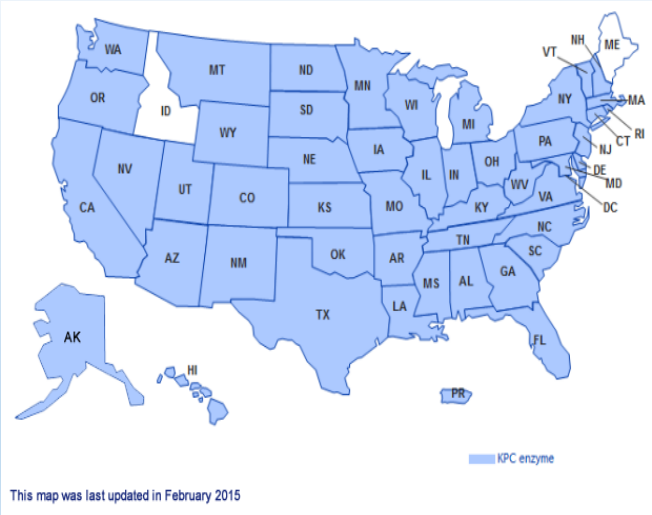
Carbpenemase-Resistant Enterobacteriaceae:
US, 1915



http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html

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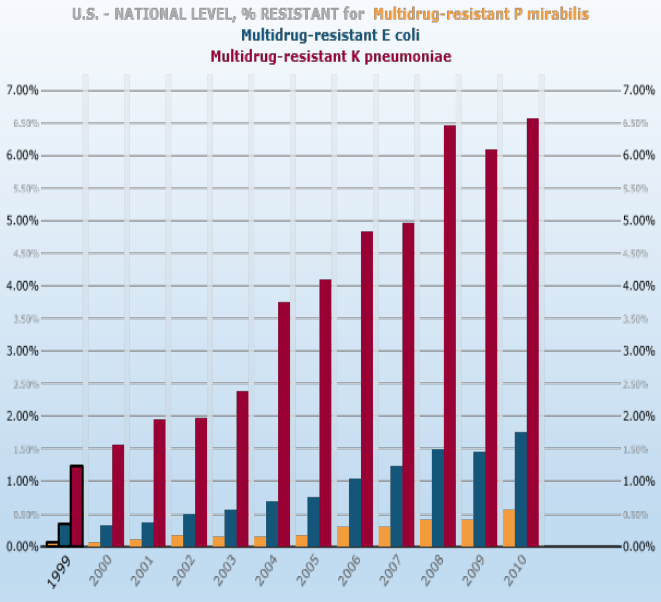

http://www.cddep.org/projects/resistance_map/resistance_overview_0

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Intra-abdominal isolates (2002-12)

- Decreased activity of amikacin, ceftazidime, ceftriaxone, ciprofloxacin, levofloxacin, imipenem-cilastatin against all Enterobacteriaceae from ICUs
- Reduced susceptibility of *A. baumannii*
- ESBL-positive isolates between 2007-8 and 2010-12
  - *E. coli* increased from 4.6% to 6.8% (2007 to 2012)
  - *K. pneumoniae* decreased from 17.5% to 12.7%
- ESBL rates in pediatric ICU isolates, 2010
  - *E. coli*: 4%
  - *K. pneumoniae:* 25%

Hackel, et al. Surg Infect 2015; 16: epub ahead of print

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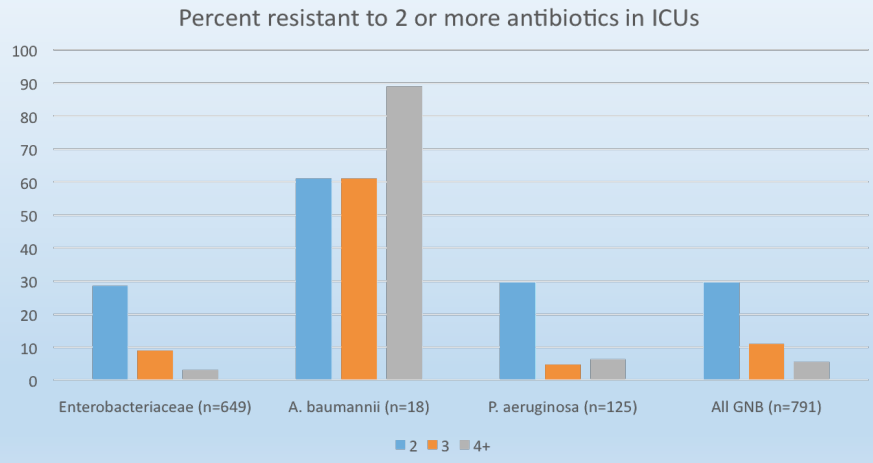
Intra-abdominal isolates: US 2010-12



Hackel, et al. Surg Infect 2015; 16: epub ahead of print

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MMWR Morb Mortal Wkly Rep.
2013
Mar 8;62(9):165-70.

- In 2012, 4.6% of acute-care hospitals reported at least one **CRE** HAI (short-stay hospitals, 3.9%; long-term acute-care hospitals, 17.8%)
- The proportion of *Enterobacteriaceae* that were **CRE** increased from 1.2% in 2001 to 4.2% in 2011
- Most of the increase was observed in *Klebsiella* species (from 1.6% to 10.4% in NNIS/NHSN)
- 92% of **CRE** episodes occurred in patients with substantial health-care exposures.

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CRE in US military system

- 75 million person-years and 1,969,315 cultures from all 266 hospitals US military health system (2005-2012)
- Incidence remained under 1 case per 100,000 person-years
- Incidence increased relative to 2005 baseline levels in 3 of 7 subsequent years, then decreased in 2012 ($P<0.05$)
- Inpatient consumption of fluoroquinolones was significantly correlated ($P=0.0007$) with CR in *E. coli*

  - Lesho EP, et.al. Diagn Microbiol Infect Dis 2015; 81:119-25.

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Multi-Site Gram-Negative Bacilli Surveillance Initiative (MuGSI)

- Established in 2012 as part of Emerging Infections Program of CDC
- Objectives:
  - Determine the extent of CRE and MDR *Acinetobacter* disease in the United States
  - Identify people most at risk for illness from these organisms
  - Measure trends of disease over time
- As of 2014, surveillance in 8 states, population of 13,725,041

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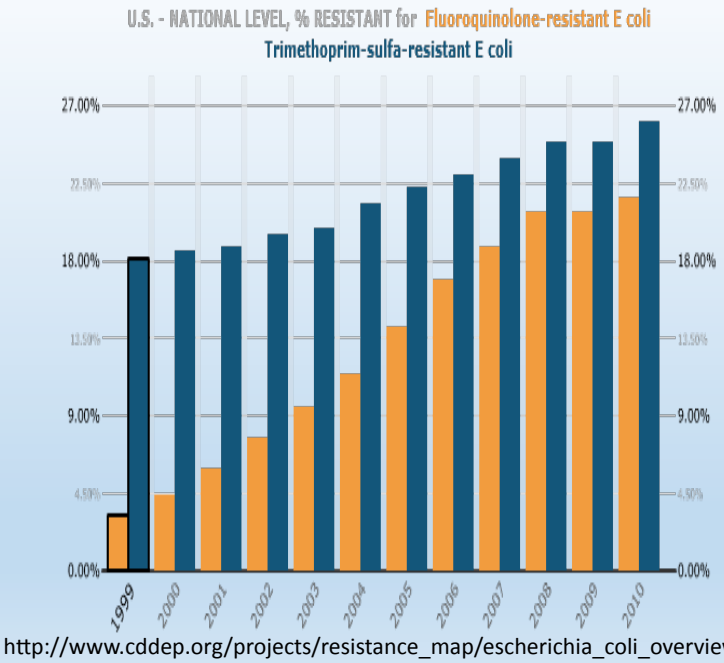

http://www.cddep.org/projects/resistance_map/escherichia_coli_overview_0

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Status: *E. coli*

- Resistance to trimethoprim-sulfamethoxazole (TMP-SMZ) and fluoroquinolones has been climbing at a steady pace over the last decade.
- Since the 1990s, fluoroquionolones like ciprofloxacin have been prescribed in place of the older therapies, particularly in communities where TMP resistance exceeds 20%.
- National-level *E. coli* multidrug resistance (simultaneous resistance to third-generation cephalosporin, aminoglycoside and fluoroquinolone) increased yearly from 0.37% in 1999 to 1.76% in 2010.
- Growing resistance spread uniformly throughout the country, starting from East North Central states.

http://www.cddep.org/projects/resistance_map/multidrug_resistant_escherichia_coli

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Status: *Acinetobacter baumannii*

- Drug-resistant *A.baumannii* frequently dwells on IV and catheter lines of ICU patients.
- Because of *Acinetobacter's* low virulence, few colonized patients develop a disease. However, when an infection does occur, it often results in hospital-wide outbreaks and relatively high rates of mortality.
- In the outpatient setting, the pathogen has been associated with wound infections among soldiers, earning it the name "Iraqibacter."

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Antibiotic Resistance Genes in Multidrug-Resistant Acinetobacter sp. Isolates from Patients Treated at Army Hospital

- 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.

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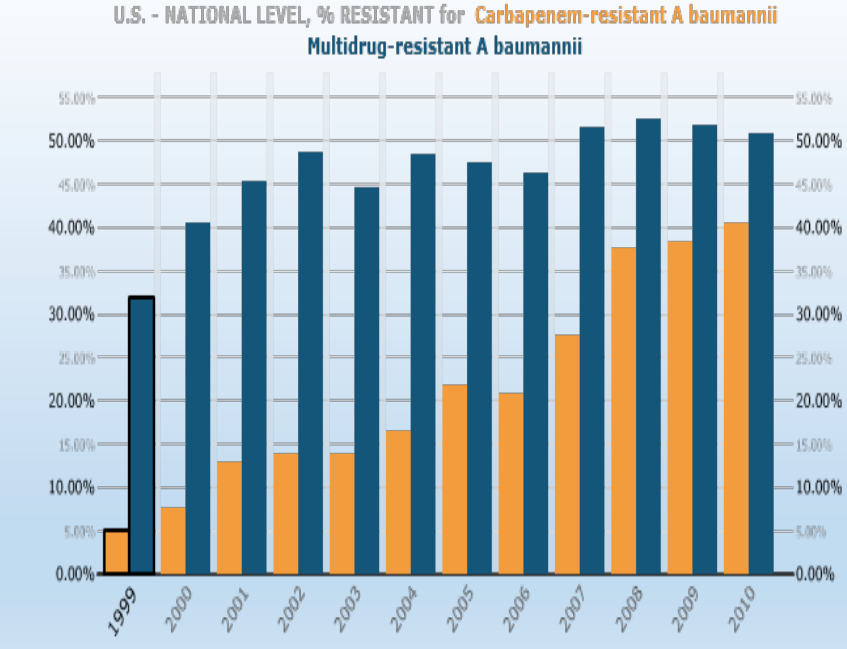

http://www.cddep.org/projects/resistance_map/acinetobacter_baumannii_overview

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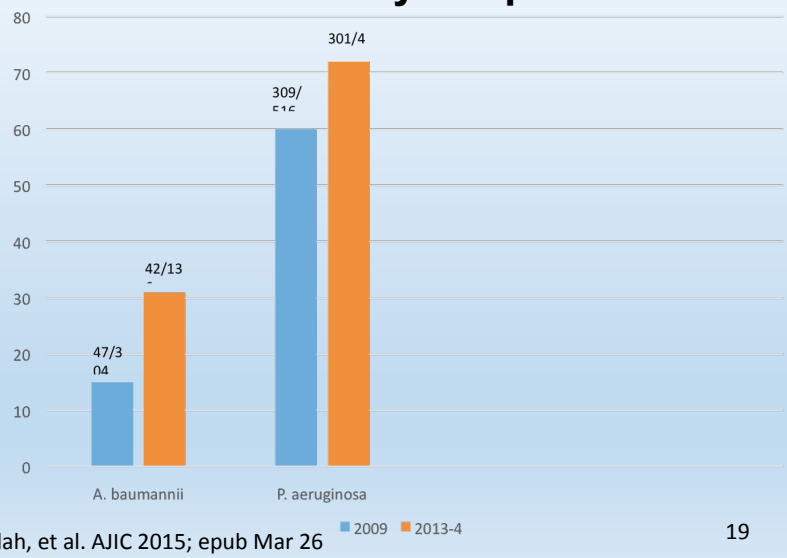
Meropenem susceptible isolates of *A. baumannii* and *P. aeruginosa:* 10 New York City hospitals



Abdallah, et al. AJIC 2015; epub Mar 26

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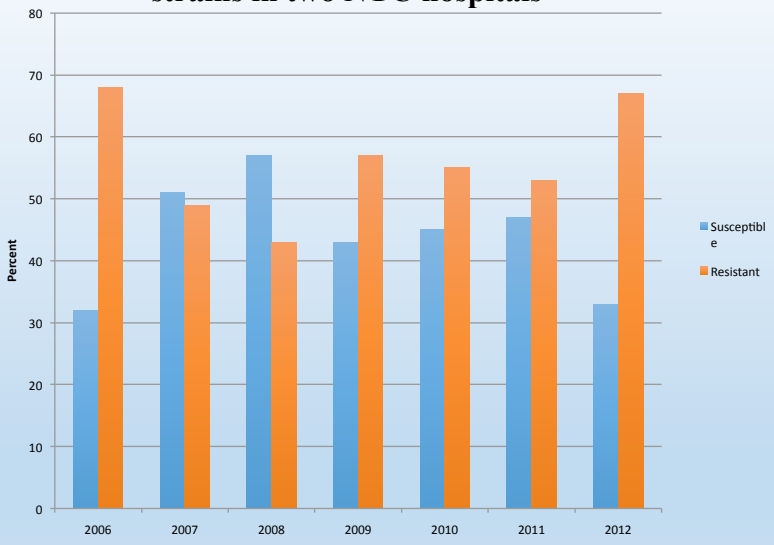
Healthcare-associated resistant vs. susceptible *A. baumannii* strains in two NYC hospitals



Two-sided Cochran-Armitage trend test, p-value=0.73

Ellis, Cohen, Liu, Larson, in press

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Factors associated with HAIs caused by antimicrobial resistant vs. susceptible *A. baumannii*

Covariates	Odds ratio
Length of Stay Prior to Infection	1.03 (1.01, 1.04)
Hospital A vs. B	0.35 (0.13, 0.93)
Respiratory Infection	2.96 (1.04, 8.44)
Antibiotic Use Prior to Infection	2.88 (1.02, 8.13

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Fatal Outbreak of Emerging Clone of Extensively Resistant *A. baumannii*

- Six immunocompetent patient deaths, 2011
- Mean: 60 years (28-81), none traveled outside U.S.
- Two unrelated clades were associated
- Clade B was distinct from other international clonal complexes and more virulent than comparator strains

- Jones, et.al. Clinical Infectious Diseases 2015;61(2):145

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Features of the *A. baumannii* Strain in Jones et al Compared With "Typical" Healthcare-Associated Strains Reported Around the World

Feature	Jones et al	Typical strains
Geographic locale	Northwestern United States	Worldwide
Belongs to international clonal complex	No (ST10)	Typically
Carbapenem resistant	Sometimes	Frequently
Mechanism of carbapenem resistance	Porin loss; no carbapenemase	Carbapenemase (typically)
Virulence	Highly virulent	Low virulence

Jones, et.al. Clinical Infectious Diseases 2015;61(2):145;
Peterson DL, Harris PNA. Clin Infect Dis 2015; 61(2):155-6

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Conclusions

- Clade B isolates resist early innate effectors, leading to sustained bacteremia
- …"these findings support the contention that the first dose of antibiotic is the most crucial and so should be rationally dosed for greatest impact."
- "Clinicians and infection preventionists should remain vigilant for XDR and highly virulent clade B"

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Colistin-resistant *A. baumannii:* Beyond carbapenem resistance

- 20 patients at U Pittsburgh Med Center
- 19/20 had received colistin for carbapenem resistant *A. baumannii*
- 30% mortality rate

- Qureshi, et al. Clin Infect Dis 2015; 60 (1 May): 1295-1304

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Status: *K. pneumoniae*

- Carbapenem-resistant *K. pneumoniae* (KPC) originated in North Carolina in 1996. Within two years, KPC was reported in every census division with national levels of resistance growing every year.
- Major outbreaks in New York City (2000s) and spread internationally
- Parallel to KPC, rates of multidrug-resistant *K. pneumoniae* (simultaneously resistant to third-generation cephalosporins, fluoroquinolones in blue and aminoglycosides in orange) have been increasing each year and now exceed 6% nationally.
- Of note is the rise and overlapping trend in resistance to fluoroquinolones and third-generation cephalosporins, likely due to the spread of ESBL-producing strains from cities on the East Coast into other parts of the country.
  - http://www.cddep.org/projects/resistance_map/klebsiella_pneumoniae_overview
  - Hawkey PM, J Hosp Infect 2015; 89:241-7.

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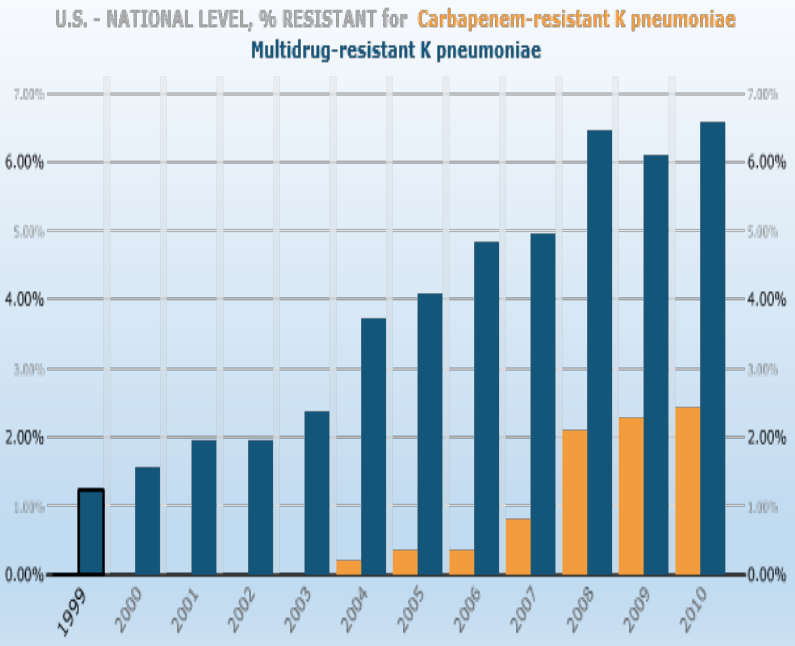

http://www.cddep.org/projects/resistance_map/klebsiella_pneumoniae_overview

CRE *K. pneumoniae* outbreak

- At US NIH Clinical Center, 2011
- 18 patients, 11 died
- Patient 1 known to be colonized with CRE-KP admitted to ICU
- Immediately placed on contact precautions in private room
- No spread noted during her hospitalization
- Patient 2, 3 weeks later, positive tracheal aspirate
- In following weeks, about 1 new case/week for the next 6 months was detected

- Snitkin ES, et.al. Science Translational Medicine 2012; 4(148):116

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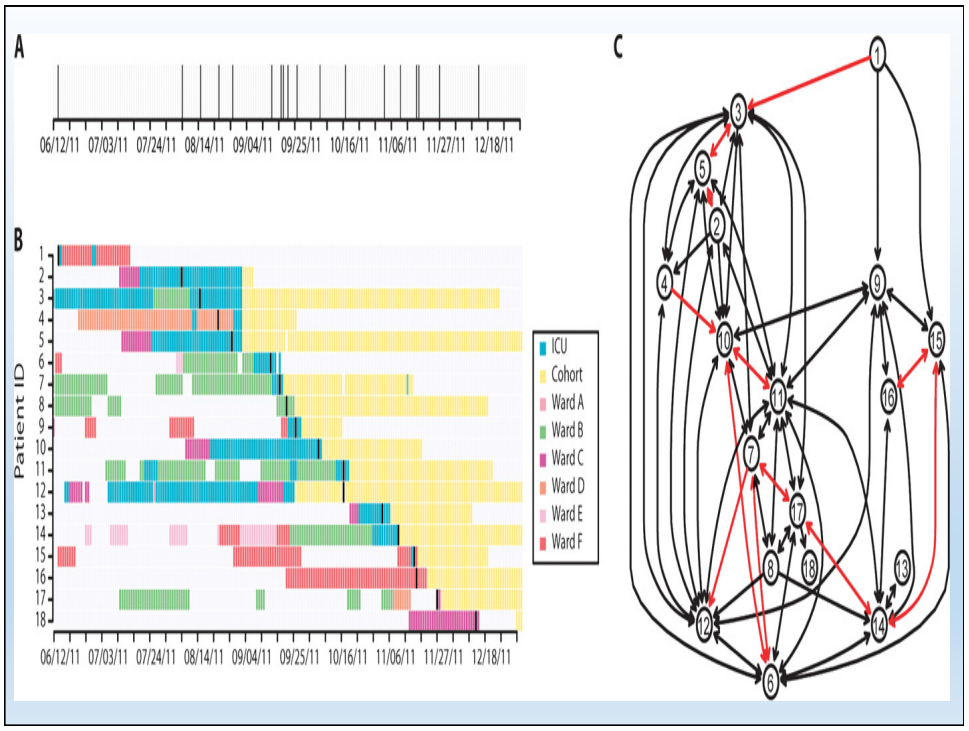
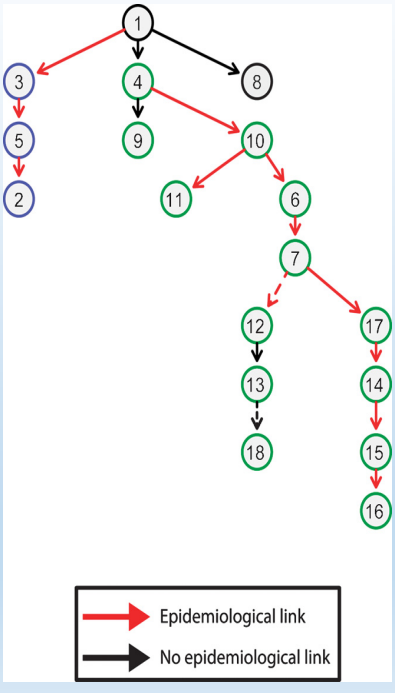


Transmission Map

Blue, cluster I;
Green, cluster II.
Red arrows, opportunity for direct transmission from patients overlapping in the same ward;
Black arrows, transmission events that cannot be explained by patient overlap (may result from a more complicated transmission route or an intermediate patient or environmental source);
Dashed lines, at least one other transmission link exists leading to the given patient.



Conclusions (based on genomic and epidemiologic analyses)

- All cases likely originated from at least two different body sites in the index patient
- There were at least three different initial transmission events
- One of the infections could be linked to contamination of a ventilator
- ***Traditional contact precautions and patient isolation were insufficient to stop transmission***

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In the Hospital Environment

- 119 samples from 15 rooms (8 surfaces) that housed CRE-positive patients
- Infrequent environmental surface contamination (8.4%) and at low levels (average, 5.1 colony-forming units [CFU]/120 cm^2 per contaminated surface)
- Three species of **CRE** (*Klebsiella, Enterobacter*, and *Escherichia*) survived poorly (>85% die-off in 24 hours) with ~2 log10 CFU inoculated onto 5 different environmental surfaces

  - Weber, et.al. Infect Contr Hosp Epidemiol 2015; 36:590

CRE *Klebsiella*

- Carbapenem-resistant *Klebsiella* in US hospitals: < 1% in 2000, 8% in 2006–2007, 12% in 2009–2010
- Initial outbreaks of KPC-producing *Klebsiella* occurred in NYC hospitals in 2003-2004
- We examined all data from all patient discharges, 2006-12 from 4 NYC hospital, n=761,426

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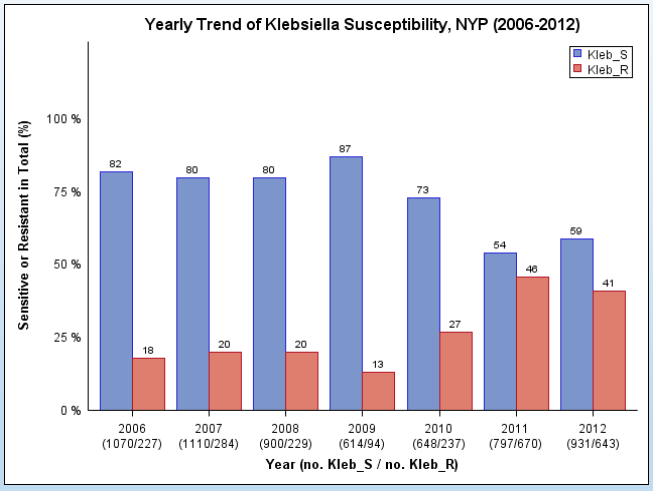
Carbapenem-resistant *Klebsiella*, 2006-2012



- **Dramatic increase in 2010-2012**
- **18-20% in 2006-2007 (8% national rate)**
- **13-27% in 2009-2010 (12% national rate)**

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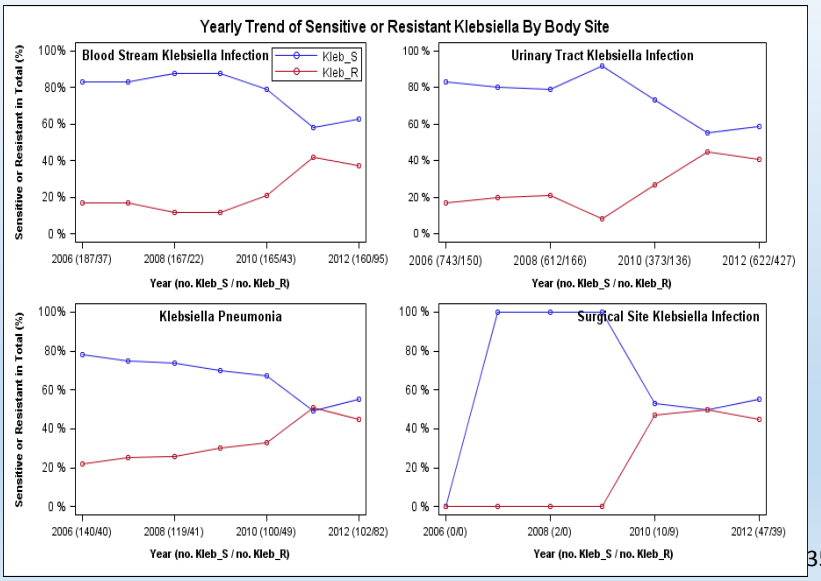
Carbapenem-resistant *Klebsiella* by body site, 2006-2012



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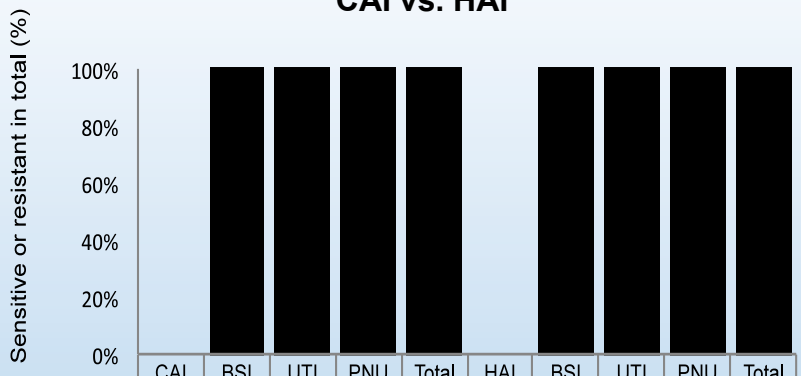
Sensitive and resistant *Klebsiella* infections by body site: CAI vs. HAI



	CAI	BSI	UTI	PNU	Total	HAI	BSI	UTI	PNU	Total
Kleb_R		142	900	97	1139		207	649	295	1151
Kleb_S		618	2459	200	3277		528	1564	594	2686

- Blood stream infection resistance (18.7% vs. 28.2%)
- UTI resistance (26.8% vs. 29.3%)
- Pneumonia resistance (23.7% vs.33.2%)

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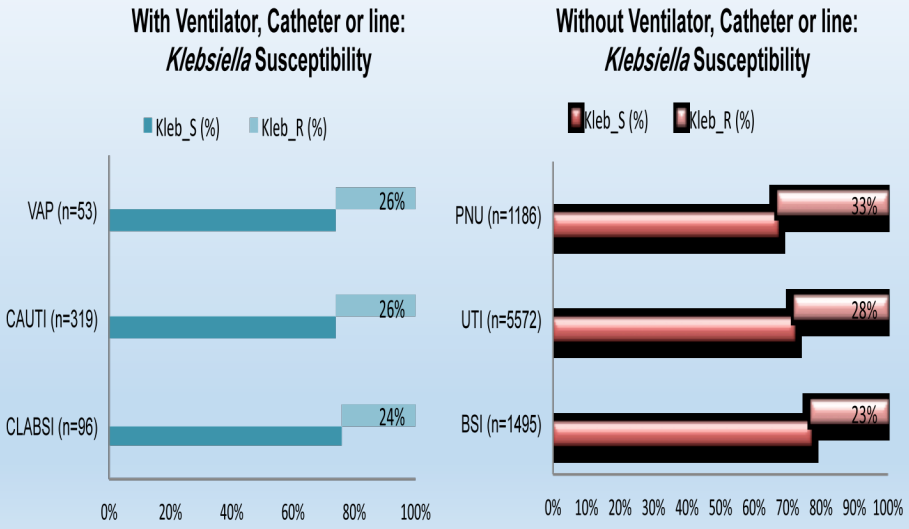
Device-associated *Klebsiella* resistance, 2006-2012



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In Pediatrics

- 347-bedpediatric tertiary care center in Los Angeles, CA
- Eleven CRE isolates recovered from 10 patients between April 2011 and May 2013
- Sporadic cases with no molecular or epidemiologic links to one another
- CRE in pediatric patients still rare
  - Pia, et.al. Pediatr Infect Dis J 2015; 34:11

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Genomically informed surveillance

- 41 carbapenem-resistant *K. pneumoniae* and *E. cloacae* isolates collected over 3 years underwent whole genome sequencing
- Limited outbreaks; rather sporadic detection of identical plasmids up to more than a year apart
- No common hospital reservoir could be identified
- Still much to learn!

- Pecora, et al. mBio 2015; Jul 28;6(4). pii: e01030-15. doi: 10.1128/mBio.01030-15

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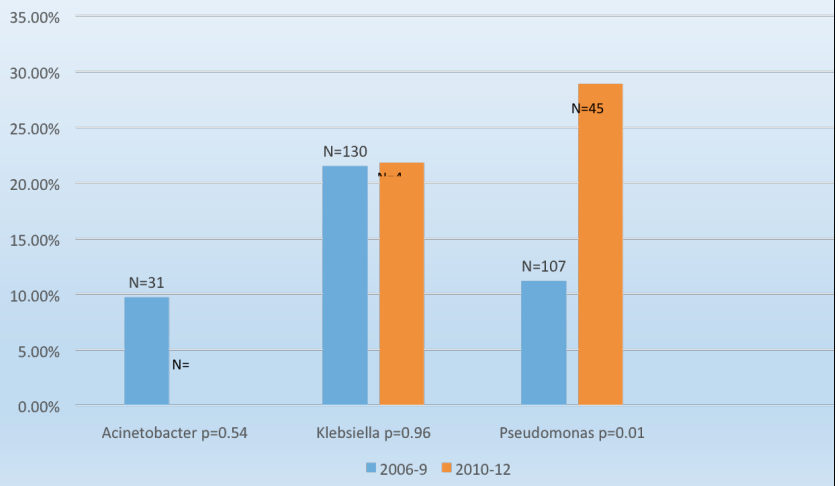
MDRO GNB infections: Tertiary Care Pediatric Hospital NYC (n=87,132 discharges)



Ellis, Cohen, Liu, Larson, in press

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In Nursing Homes

- 22 nursing homes, Boston, 2009-14
- Among residents with advanced dementia
- 57.9% (110/190) of samples tested grew MDR-GNB resistant to ≥3 of the following: ciprofloxacin, extended-spectrum penicillins, meropenem, gentamicin, third-generation cephalosporins
- Percent clonally related: 0-36% (mean: 36%)
- >50% strains clonally related in 3 nursing homes
- Co-colonization with several MDR-GNB in 18.4% of residents

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KPC-Producing Bacteria in 4 Longterm Care Hospitals: Chicago, 2012-13

- Interventions ongoing
  - Screening for KPC rectal carriage, daily chlorhexidine bathing, medical staff education
  - Cohorting: (1) all KPC-positive patients on 1 floor), (2) single rooms for KPC-positive patients, and (3)all KPC-positive patients on 1 floor, supplemented with KPC-negative patients
- 95,982 patient days and 3,257 admissions of 2,575 unique patients
- KPC colonization was 29.3%; 18% on admission
- Conclusion: Cohorting or single rooms for KPC-positive patients seemed to limit transmission
- Haverkate, et.al. *Infec Contr Hosp Epidemiol* 2015; 36(10): 1148-1154

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Nursing Homes and MDR *A. baumannii*

- Four nursing homes in Michigan
- 15% (25/168) colonized with MDR *A. baumannii*
- 88% were colonized with multiple antibiotic-resistant organisms and 64% were co-colonized with at least one other resistant gram-negative bacteria.
- Compared with controls, cases were significantly more disabled, colonized with *Proteus mirabilis*, and diabetic.

- Mody, et al. *Infec Contr Hosp Epidemiol* 2015; 36(10): 1155-1162

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Fluoroquinolone (FQ)-resistant *E. coli* in nursing homes

- 50% of NH residents with FQ-susceptible *E. coli* acquire FQ-resistance within a year
- Risk factors: fecal incontinence, urinary catheter, amoxicillin-clavulanate
  - Han, et al. J Infect Dis 2014; 209:420
- In a case-control study, 12% (11/94) NH residents colonized rectally with FQ-resistant *E. coli* became clinically infected within 1 year.
- Risk factors for infection: urinary catheter or tracheostomy, diabetes, SMZ-TMP
  - Manning, et al. Infect Contr Hosp Epidemiol 2015; 36:575
- Conclusion: FQ-resistant *E. coli* is highly prevalent in nursing homes

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In the food supply

- 2012, Arizona
- 241/508 (47%) meat samples from 9 food store chains positive
- 174/1728 (10%) urine samples positive
- 32% of meat isolates and 8% of clinical isolates were multi-resistant (p=0.01)
- Third generation cephalosporin resistance and ESBL production was only in meat samples
- Close genetic relationship between meat and clinical isolates
- In same time period, >5.9 million kg of tetracyclines and >270,000 kg of aminoglycosides were sold for food animal production

  - Davis, et.al., Clin Infect Dis 2015; 61(6):892-900.

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Antibiotics in Agriculture

- In 2011, 30 million pounds of antibiotics were sold for use in beef, pork and poultry production. That's four times the amount sold to humans who were sick

  (NY Times, Jul 10, 2013)

- Many of the antibiotics used in this setting are of the same class as those used to treat human infections
  - Macrolides, tetracyclines, glycopeptides

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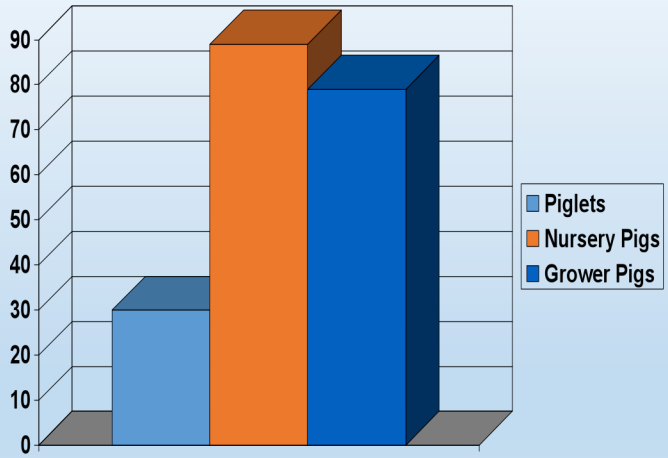
Percentage U.S. swine receiving antibiotics in their feed



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

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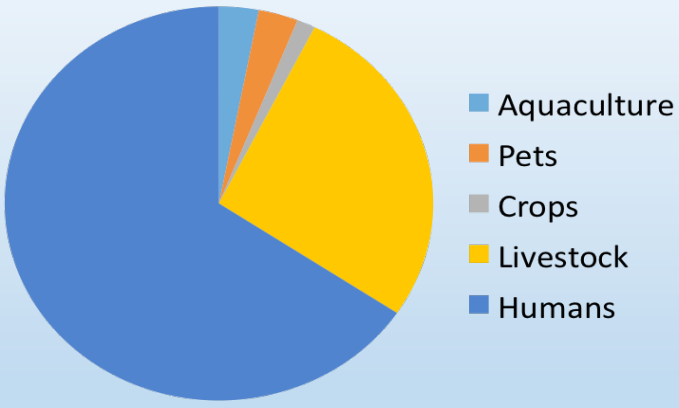
Estimated Annual Antibiotic Use in the United States (kg/year



NEJM 2013; 369:2474

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Science, 1/27/14

- "A federal analysis of 30 antibiotics used in animal feed found that the majority of them were likely to be contributing to the growing problem of bacterial infections that are resistant to treatment in people"

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"More than 30 years ago when I was commissioner of FDA we proposed eliminating the use of penicillin and two other antibiotics to promote growth in animals raised for food. When agribusiness interests persuaded Congress not to approve that regulation, we saw first-hand how strong politics can grump wise policy and good science."

Donald Kennedy, NY Times, 4/18/10

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Nov 10,2011

- FDA denied a pair of long-pending petitions from consumer and other groups to limit the use of several antibiotics in farm animals, saying a voluntary approach the agency proposed last year will lead to more "judicious use" of the drugs in agriculture.

Center for Infectious Disease Research and Policy (http://www.cidrap.umn.edu/cidrap/content/fs/food-disease/news/nov1011petitions.html, accessed 11/11/11)

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Progress?

"The FDA released a policy document stating that agricultural uses of antibiotics should be limited to assuring animal health, and that veterinarians should be involved in the drugs' uses.

While doing nothing to change the present oversight of antibiotics, the document is the first signal in years that the agency intends to rejoin the battle to crack down on agricultural uses of antibiotics that many infectious disease experts oppose. "

NY Times, Jun 29, 2010S

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April 10, 2012

- New FDA ruling after trying for more than 35 years to stop feeding antibiotics to cattle, pigs, chickens and other animals as growth promoters
- Farmers and ranchers for the first time need a prescription from a veterinarian before using antibiotics in farm animals

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CDC Report: Antibiotic Resistance Threats in the United States, 2013

- **Four core actions to fight antibiotic resistance**:
- Preventing infections, preventing the spread of resistance
- Tracking resistance patterns
- Improving use of antibiotics
- Developing new antibiotics and diagnostic tests
- http://www.cdc.gov/narms/resources/threats.html

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Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria

- First meeting Sept 25, 2015
- http://www.hhs.gov/ash/carb/index.html
- Provides advice, information, and recommendations regarding programs and policies intended to support and evaluate the National Strategy for Combating Antibiotic-Resistant Bacteria (Strategy) and the National Action Plan for Combating Antibiotic-Resistant Bacteria (Action Plan).

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Can CRE be eradicated?

- 276 prior **CRE** carriers declared **CRE**-free
- 36 (13%) had recurrence of **CRE** carriage within a year
- Factors significantly associated with **CRE** recurrence:
  - time in months between the last positive **CRE** sample and presumed eradication (odds ratio, 0.94 [95% CI, 0.89-0.99] per month),
  - presence of foreign bodies at the time of presumed eradication (4.6 [1.64-12.85]),
  - recurrent admissions to healthcare facilities during follow-up (3.15 [1.05-9.47]).
- Recurrence rate: 25% when carrier status was presumed to be eradicated 6 months after the last known **CRE**-positive sample, compared with 7.5% if presumed to be eradicated after 1 year.

- Bart Y, et.al., Infect Contr Hosp Epidemiol 2015; 36(8):936-41.

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Perhaps much relates to behavior and systems

- 420 health care workers from 1 acute care and 1 long-term care facility (Israel)
- Organizational culture/staff engagement positively correlated with infection prevention attitudes and compliance with contact precaution protocols and negatively correlated with **CRE** acquisition rate

- Fedorowsky R. AJIC 2015 Jun 23 (epub ahead of print)

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Contact precautions significantly reduced the proportion of hospital acquired MDR *A. baumannii*

	Standard Precautions: All positive	Contact Precautions/ Cohort: All positive	Contact Precautions/ Cohort:Only MDR positive	P value
Patient Days	18,074	10,604	13,853	
MDR *A. baumannii*	19% (4/21)	14% (2/14)	8% (1/13)	NS
Hosp-acquired	95% (20/21)	64% (9/14)	69% (9/13)	0.03

Tawney, et al. Infec Contr Hosp Epidemiol 2015; 36(9): 1108-10

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What Next?

- Rethink barrier/isolation precautions
- Rethink impact of organization systems and culture
- Maintain carrier status for at least 1 year following 'eradication'
- Consider enhanced environmental cleaning
- Enhance antibiotic stewardship program

- "Yet, at the present time, our best defense against (MDRO)…remains old-fashioned, stringent infection control measures combined with the application of effective antimicrobial stewardship."
  - Peterson and Harris. Clin Infect Dis 2015; 61(2):156

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Happy Reading

- Report to the President on Combating Antibiotic Resistance, 2014: https://www.whitehouse.gov/sites/default/files/microsites/ostp/PCAST/pcast_carb_report_sept2014.pdf
- Antibiotic Resistance Threats in the US, 2013: http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf#page=6
- CDC Antibiotic Resistance Website: http://www.cdc.gov/drugresistance/index.html

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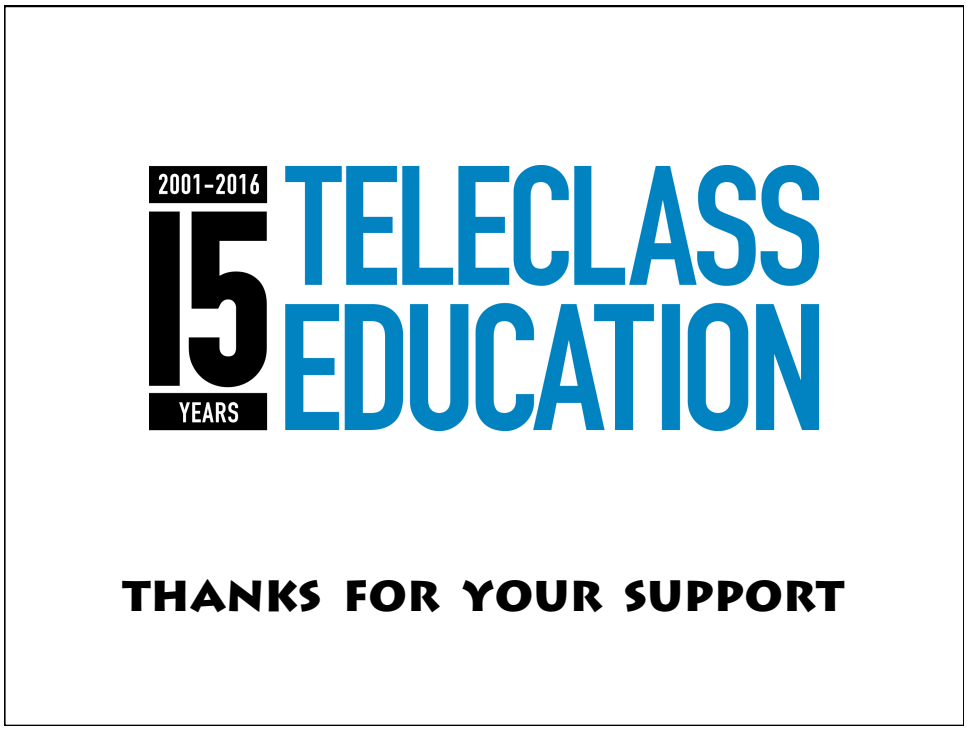
Coming Soon
January 28 MRSA IN THE HOSPITAL AND THE COMMUNITY
Dr. Geoffrey Taylor, University of Alberta
February 17 (Free WHO Teleclass ... North America)
SUCCESSFUL IMPLEMENTATION STRATEGY FOR THE PREVENTION OF SURGICAL SITE INFECTIONS
Prof. Sean Berenholtz, Johns Hopkins Schools of Medicine, Baltimore
February 24 (South Pacific Teleclass)
PATIENT EMPOWERMENT AS PART OF AN ASIAN HAND HYGIENE PROGRAMME
Prof. Yee Chun Chen, National Taiwan University Hospital and College of Medicine
March 3 MERS-COV: IMPLICATIONS FOR HEALTHCARE FACILITIES
Prof. Sotirios Tsiodras, University of Athens Medical School, Greece
March 10 (FREE Teleclass)
BARRIERS TO TB INFECTION CONTROL IN DEVELOPING COUNTRIES
www.webbertraining.com/schedulep1.php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