Beyond MRSA

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May 26, 2012

Disclosures

- Nothing to disclose

Outline

- Antibiotic Resistance
  - What? Where? Why?
- Three Illustrative Cases
  - The Bad
  - The Worse
  - The Very Ugly
- Fighting back
  - Infection Control
  - Antimicrobial Stewardship

Antimicrobial Resistance

Malaria

Gonorrhea

Tuberculosis

Salmonella

VRE

Influenza

Candida

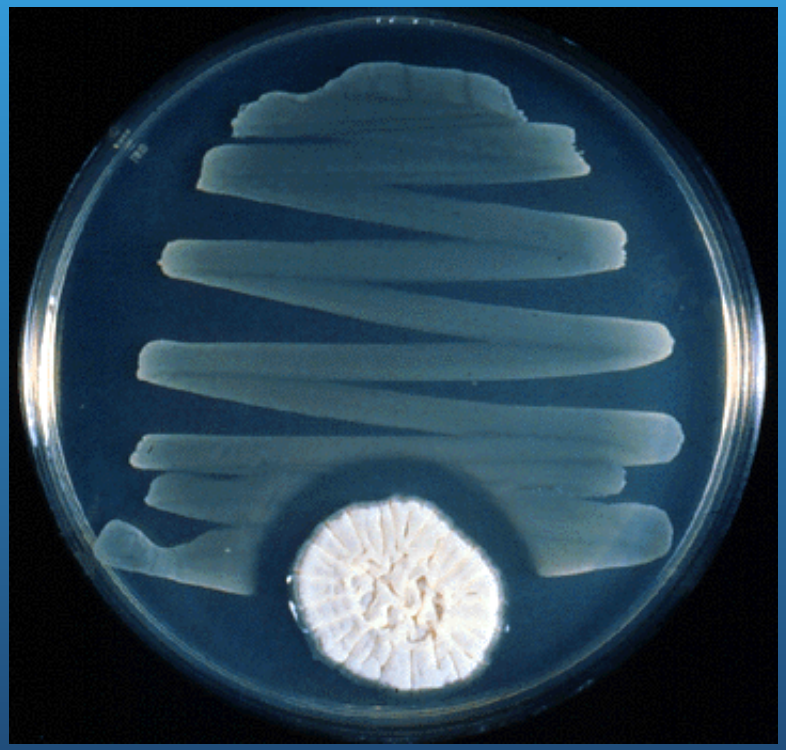
HIV

E. coli

MRSA

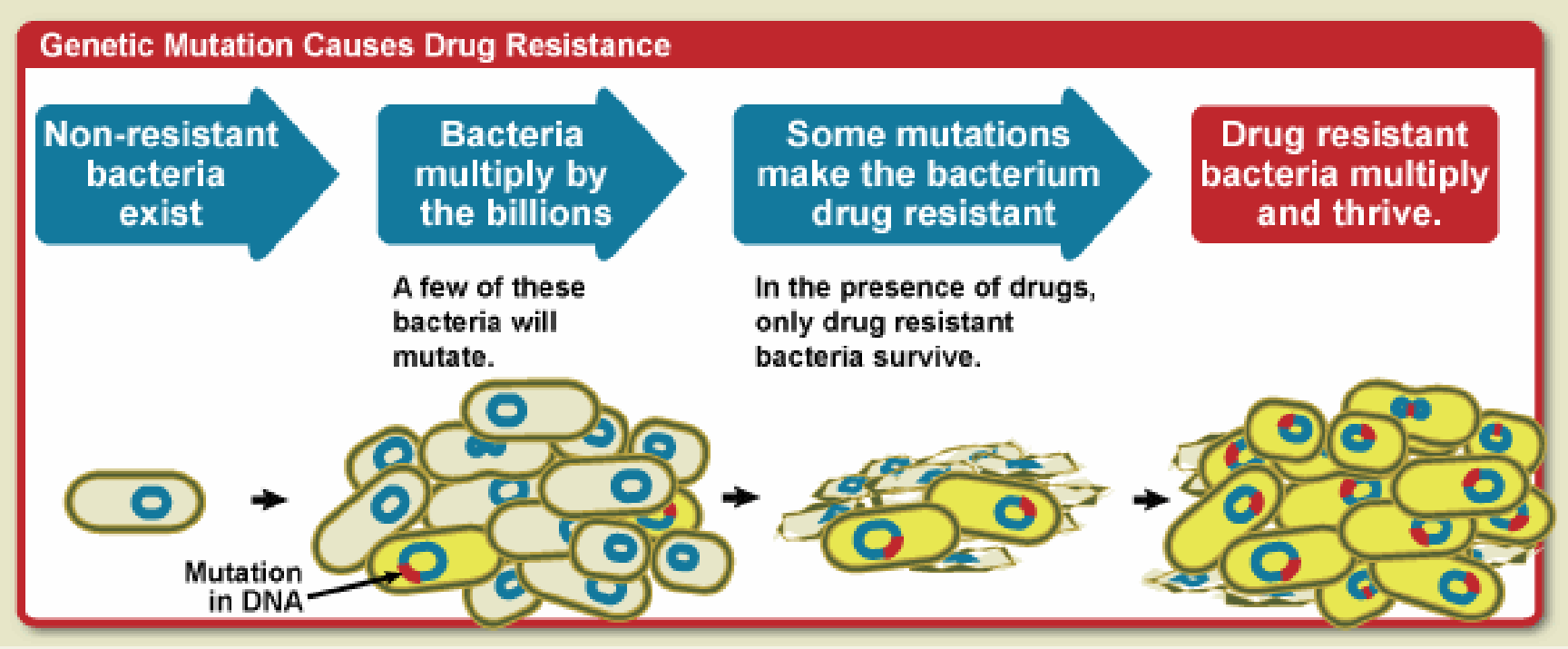
Strep pneumoNiae

Antibiotic Resistance



- Alexander Fleming
  - Penicillium mould (1928)
- Penicillin usage
  - 1941- 1943
- Resistance
  - 1944
- 1950s widespread resistance

Creation of Resistance

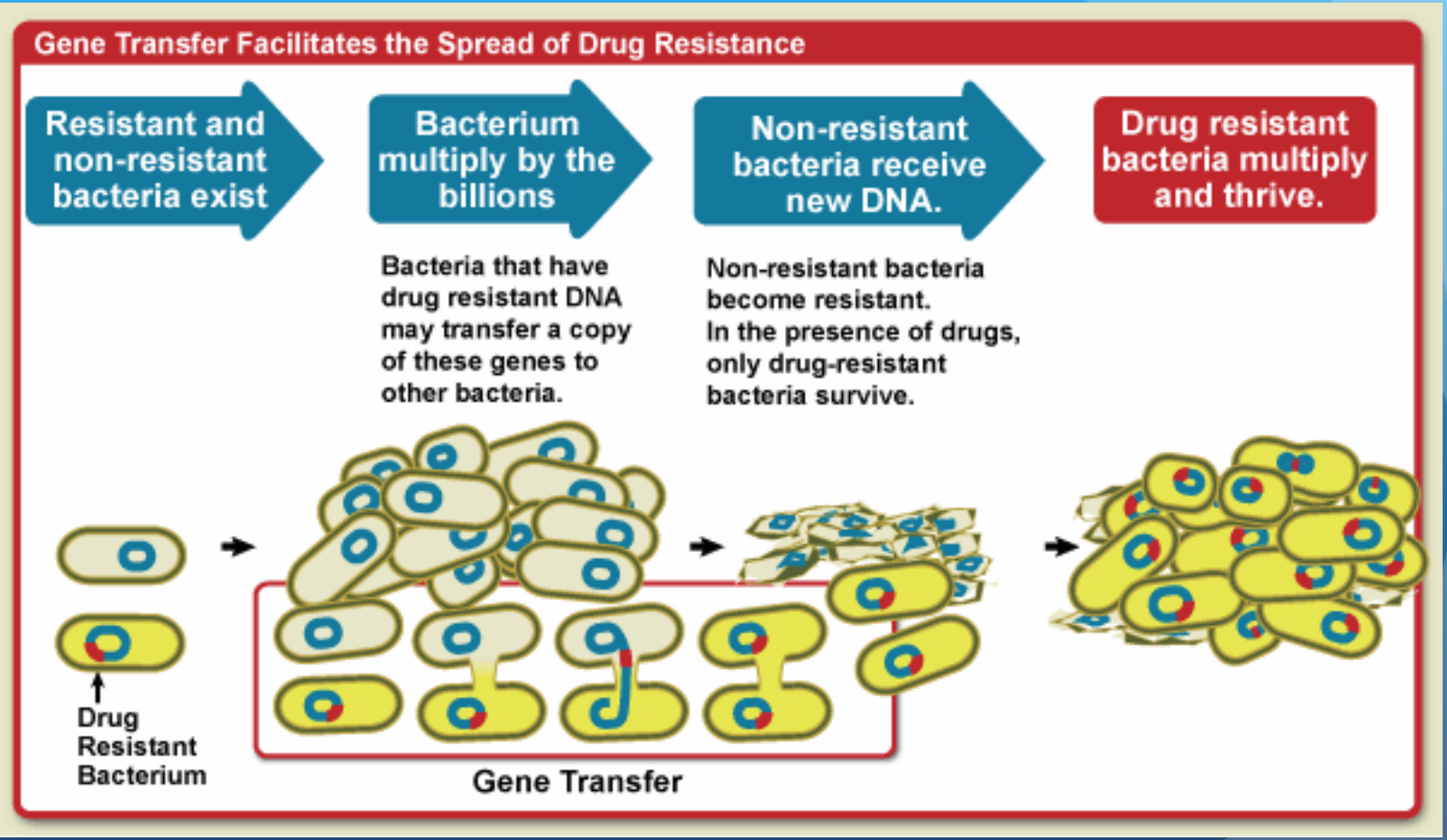


Manufacturing of Clones

→ all identically resistant to antibiotic(s)

Souce: NIAID Website
http://www.niaid.nih.gov/TOPICS/ANTIMICROBIALRESISTANCE/UNDERSTANDING/Pages/causes.aspx

Spread of Antibiotic Resistance



Souce: NIAID Website
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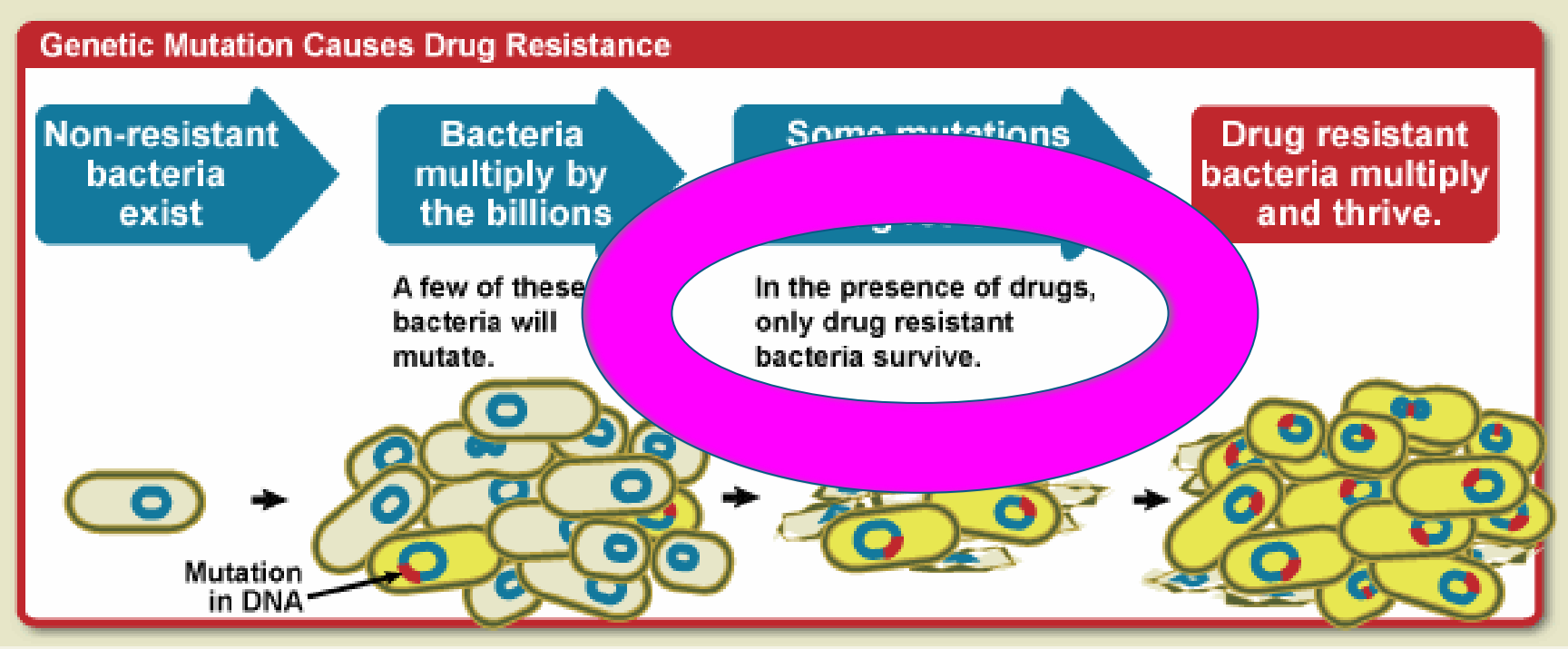
Creation of Resistance



Manufacturing of Clones

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“Presence of Antimicrobials”

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Antibiotic are misused in a variety of ways

- Given when they are not needed
  - Non-infectious process or contamination/colonization
- Continued when they are no longer necessary
- Given at the wrong dose
- Broad spectrum agents are used to treat very susceptible bacteria
- The wrong antibiotic is given to treat an infection
- Prolonged prophylactic therapy
- Excessive use of certain antimicrobial agents

Antibiotics are misused in hospitals

- **"Approximately 60% of adult patients admitted to US hospitals receive at least 1 dose of antibiotic during their stay"**
- **"It has been recognized for several decades that up to 50% of antimicrobial use is inappropriate"**
  - **IDSA/SHEA Guidelines for Antimicrobial Stewardship Programs (http://www.journals.uchicago.edu/doi/pdf/10.1086/510393)**

Ohl *et al.* J Hosp Med 2011;6:S4-15

Consequences of Antibiotic Misuse

- Consequence can be seen at patient level or as an undesired outcome measure at level of healthcare institution
- May include:
  - Increased morbidity & mortality
  - Adverse drug reactions
  - Increased length of hospital stay & cost
  - Predisposition to secondary infections
  - Emergence or selection of antibiotic resistant organisms

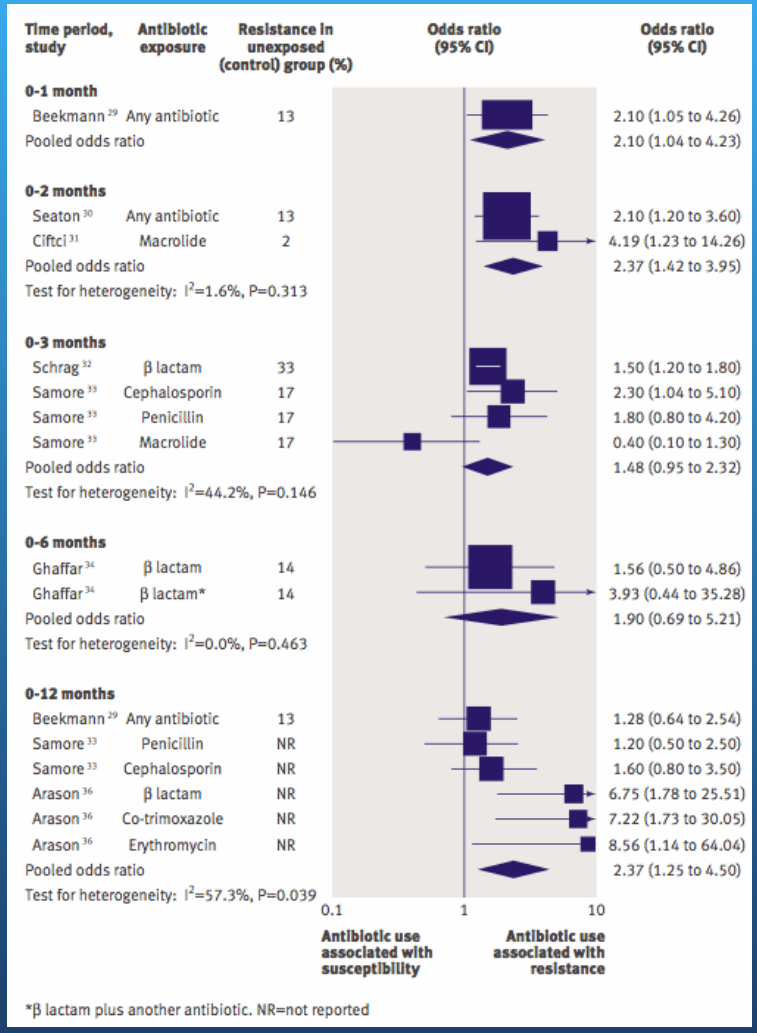
Ohl *et al.* J Hosp Med 2011;6:S4-15

Mortality of resistant (MRSA) vs. susceptible (MSSA) *S. aureus*

- **Mortality risk associated with MRSA bacteremia, relative to MSSA bacteremia: OR: 1.93; $p < 0.001$.[1]**
- **Mortality of MRSA infections was higher than MSSA: relative risk [RR]: 1.7; 95% confidence interval: 1.3–2.4).[2]**

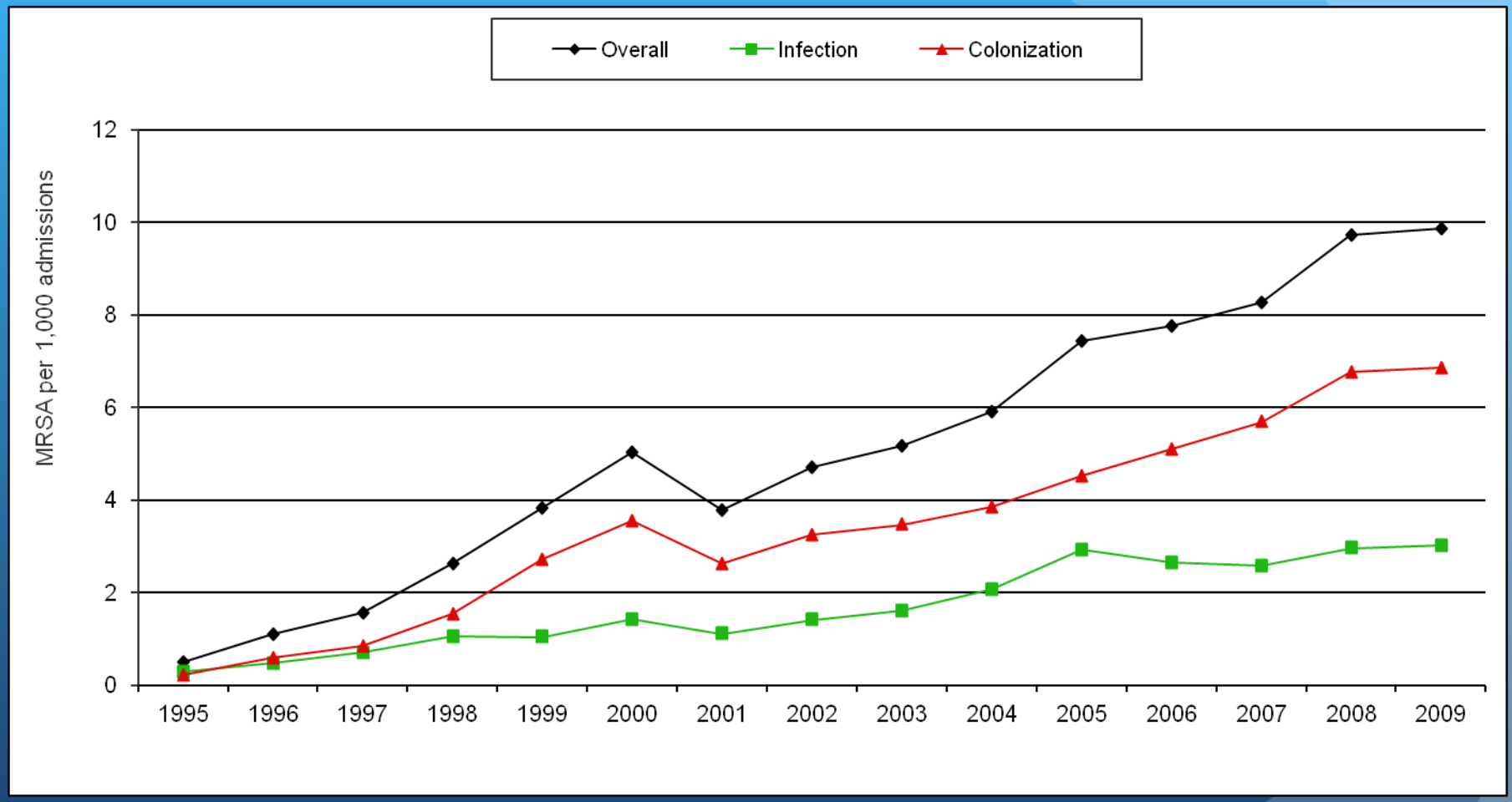
1. *Clin. Infect. Dis.*36(1),53–59 (2003).
2. Infect. Control Hosp. Epidemiol.28(3),273–279 (2007).

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



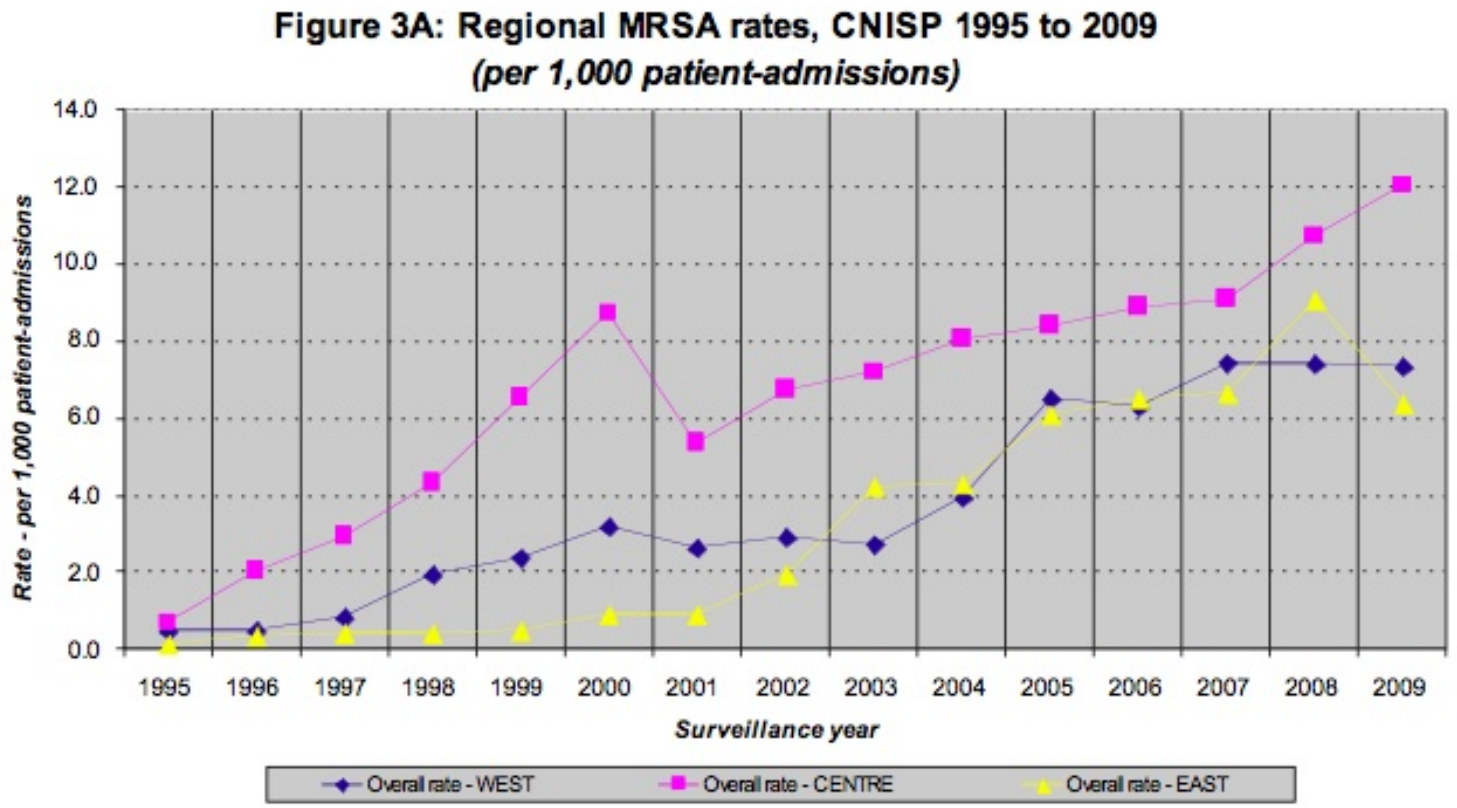
Costelloe C. BMJ. 2010.

MRSA in Canada, 1995-2009



Simor, Infect Control Hosp Epidemiol 2010; Canadian Nosocomial Infection Surveillance Program

Regional MRSA rates



Public Health Agency of Canada, RESULTS of the SURVEILLANCE of METHICILLIN RESISTANT STAPHYLOCOCCUS AUREUS — FROM 1995 TO 2009 — A PROJECT of the CANADIAN NOSOCOMIAL INFECTION SURVEILLANCE PROGRAM (CNISP)

It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

Could things get worse???

Well, yes, they might actually…

Case 1 – Bad enough

- 58 year old Female
- Renal transplant (diabetic nephropathy)
- Prolonged stay tertiary care post-transplant
  - Acute rejection
  - Multiple courses of antimicrobials
- Urinary urgency & frequency, dysuria
- Urine culture sent, started on Ciprofloxacin

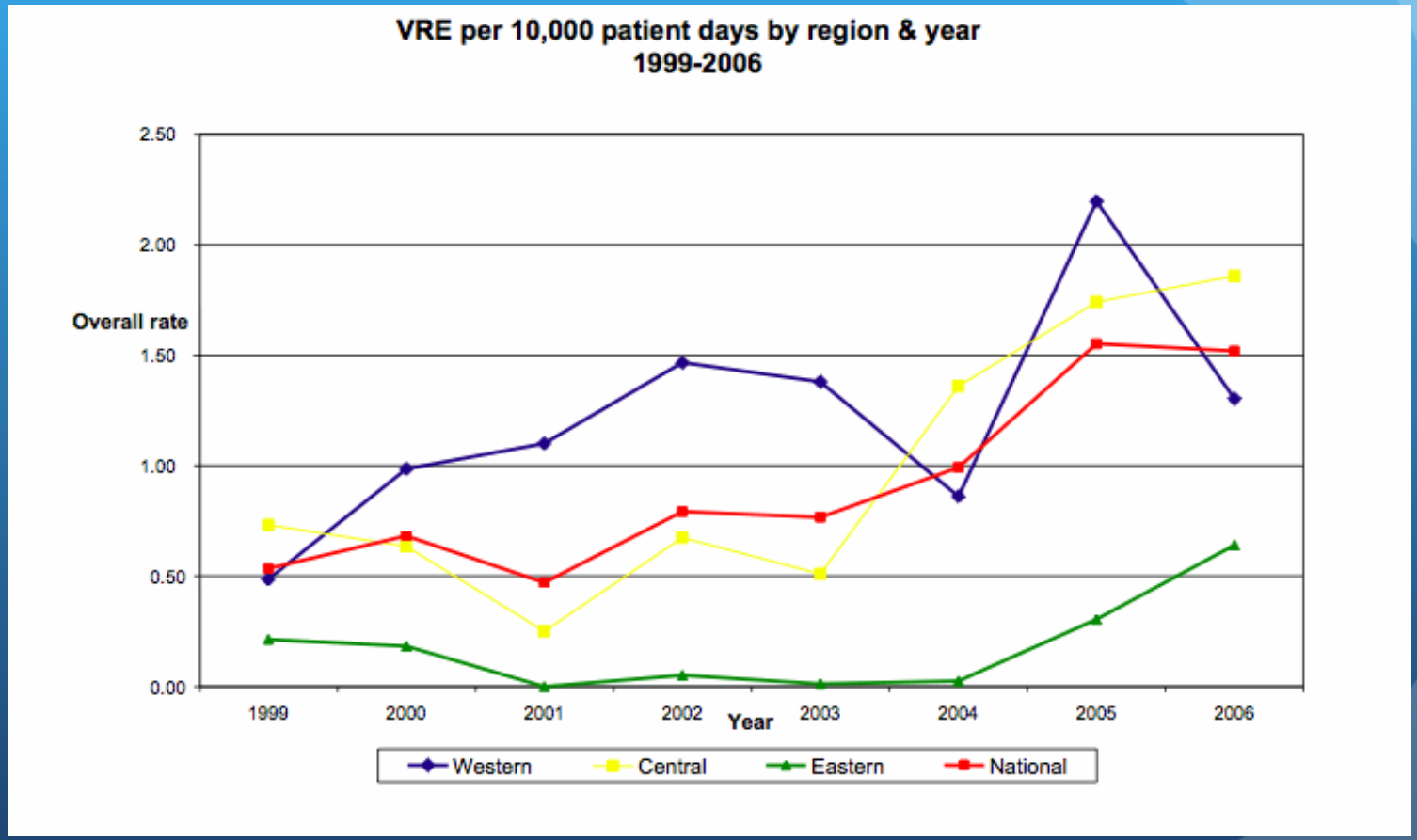
Case 1 – Bad enough

- Urine Cutures
  - Gram positive cocci likely Enterococcus
  - Next day Enterococcus
- A couple days later VRE!!!!
- Hmm, what now?

Vancomycin Resistant Enterococcus

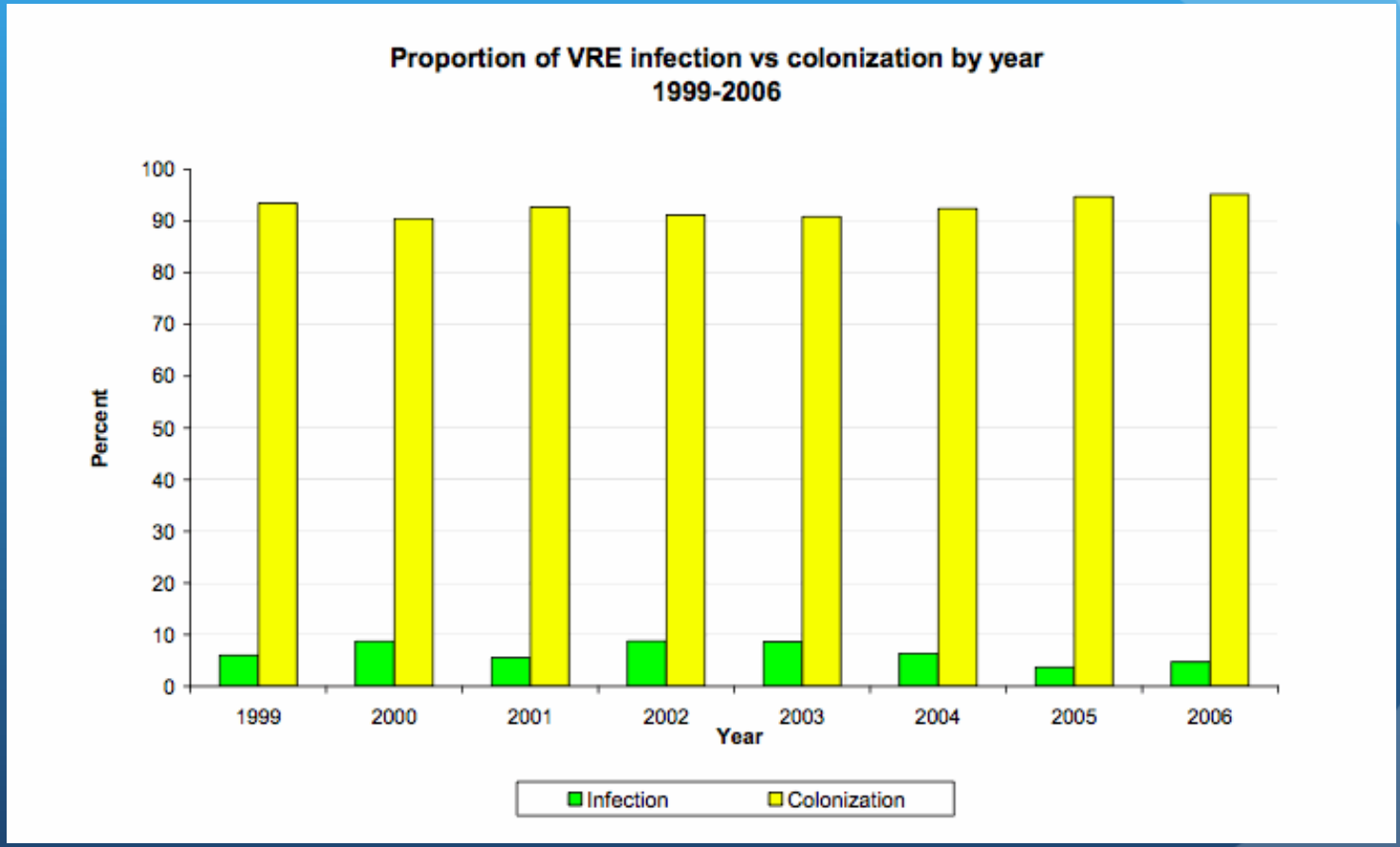
- Enterococcus that have some how gained a mobile gene encoding resistance
  - *Enterococcus faecium*
- Risk factors:
  - Immunosuppression
  - Long hospital stay
  - ICU stays
  - Previous antibiotic, especially Vanco, Cephs, AGs

Vancomycin Resistant Enterococci



CNISP (Canadian Nosocomial Infection Surveillance Program) data

VRE



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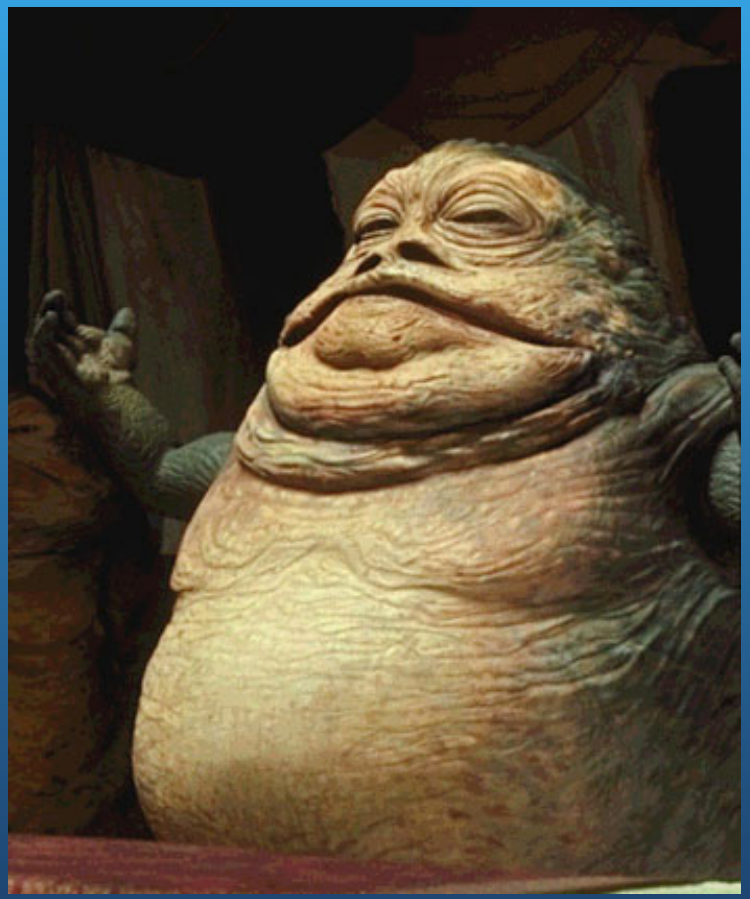


- Colonization more than infection
- On the rise
- Very difficult to treat
  - Linezolid
  - Daptomycin
  - Quinupristin-dalfopristin

Case 2 – Even Worse

- 72 year old male
- Recently returned from USA
  - Hospitalized with acute coronary syndrome
- Now presents with delerium, fever, low BP
- Cultures sent (Blood, urine)
- Broad spectrum antimicrobials started

Case 2 – Even Worse

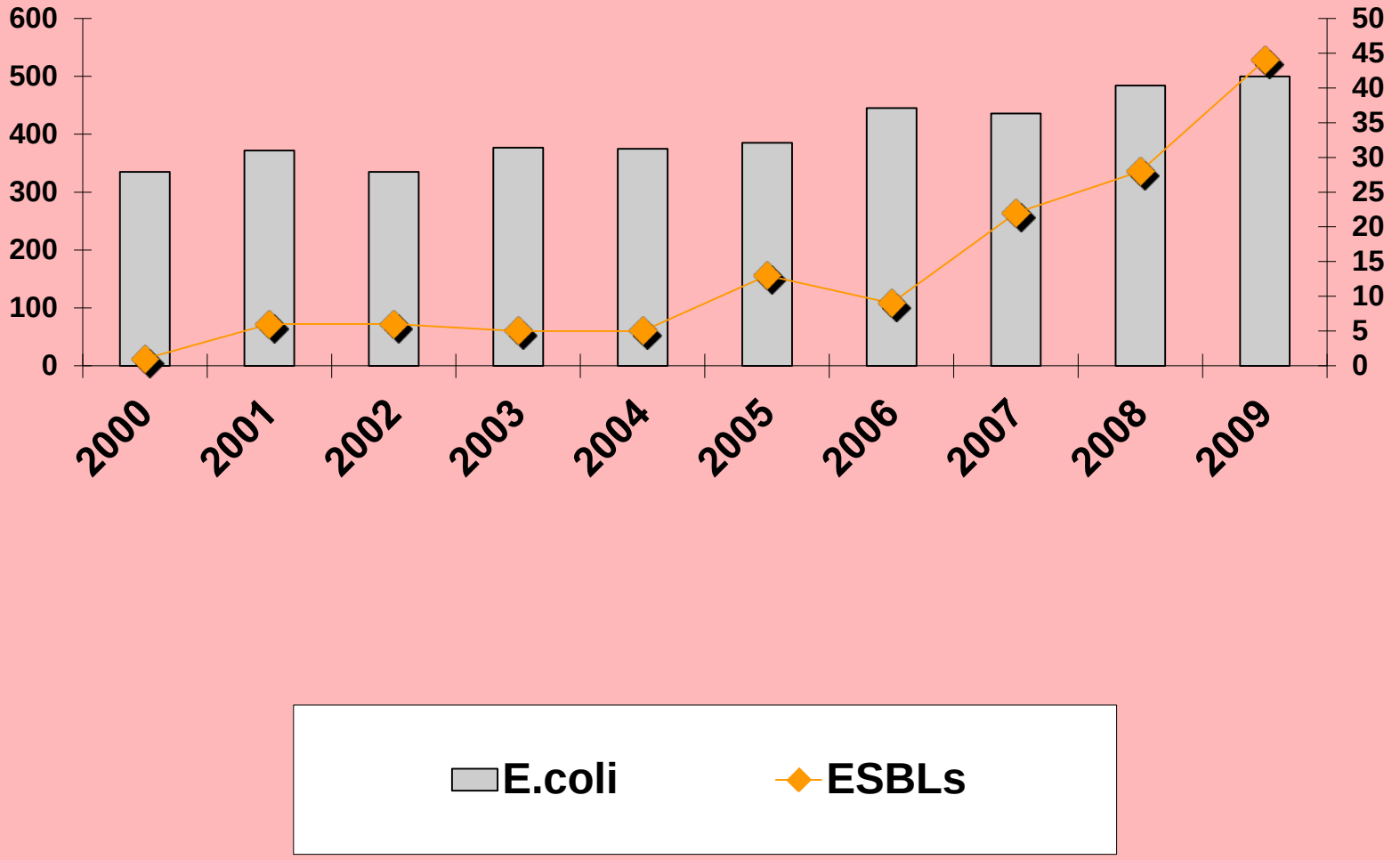
- Blood cultures positive at 9 hours
  - Gram negative
  - Likely *E. coli*
  - ESBL!!!

- ES…EB…E-What?

Extended Spectrum Beta-Lactamase

- ESBL producers (clones)
  - *E. coli*
  - *Klebsiella*
  - (other)
- Hydrolyze
  - Penicillins, Cephalosporins
- More likely to have other antibiotic resistance

ESBL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E.coli
ESBLs

Case 3 – The Very Ugly

- 48 year old male, PHx Diabetes mellitus
- Visiting relatives in Dhaka, Bangladesh
  - On 3rd day motor vehicle collision, ORIF L tibia #
  - Given cefazolin for UTI
- Upon return to Canada reassessed
  - Loosening of hardware (likely infection)
  - Revision with intraoperative cultures

Case 3 – The Very Ugly

- *Klebsiella pneumoniae* resistant to:
  - Fluoroquinolones, aminoglycosides
  - ALL beta-lactams tested including carbapenems

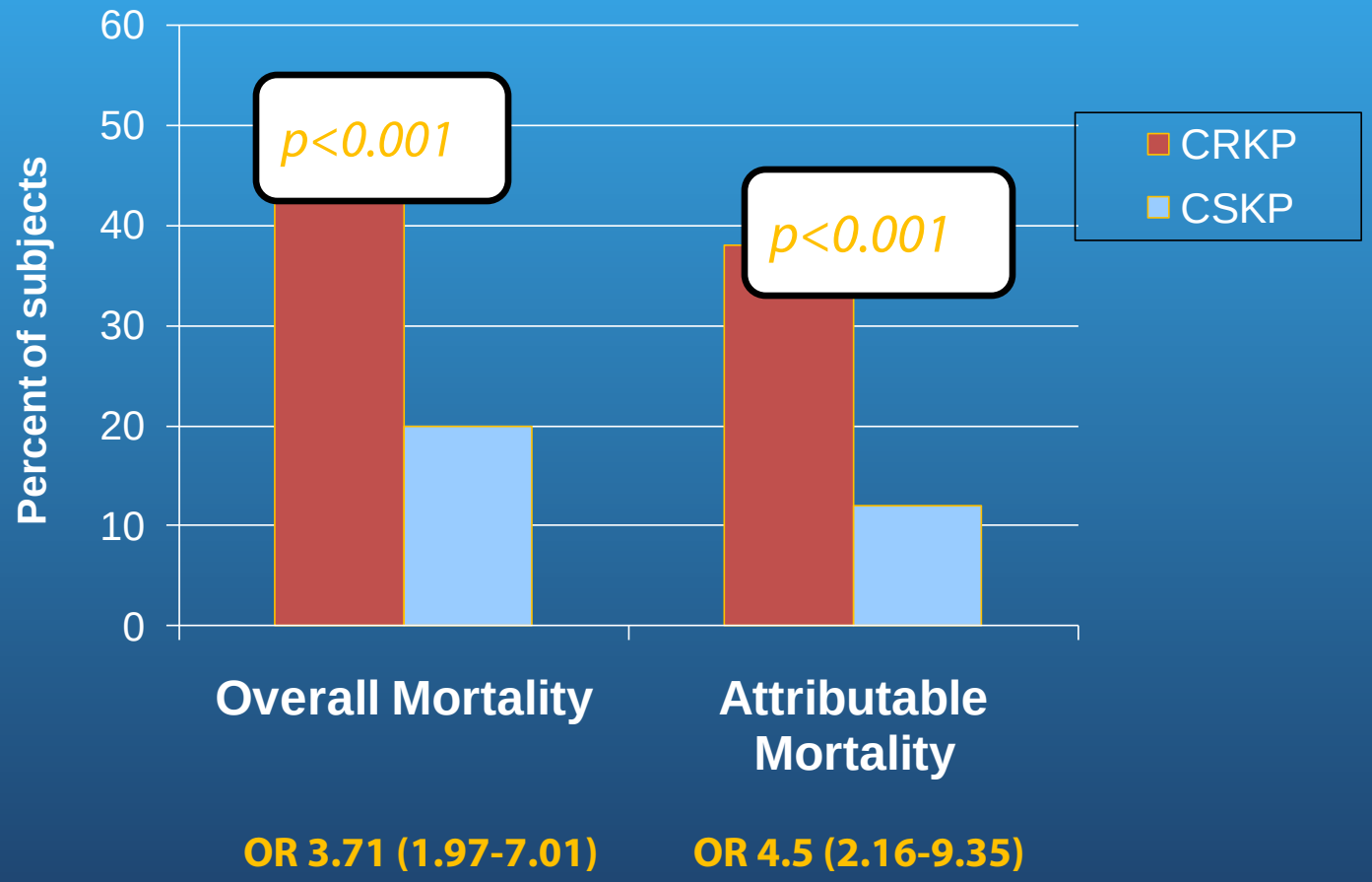
- Subsequently confirmed:
  - NDM-1 (New Delhi metallo-beta-lactamase-1)

Carbapenemase

- High mortality rates
  - 50% (bacteremia)
- Broadly resistant
  - Colistin
  - Tigecycline
- Seems easily spread
- Limited data

Pillai DR et al. CMAJ. 2011.

Mortality associated with carbapenem resistant (CR) vs susceptible (CS) Klebsiella pneumoniae (KP)



Patel G et al. *Infect Control Hosp Epidemiol* 2008;29:1099-1106

NDM -1 Carbapenemase

- Identified in Ontario, British Columbia, Alberta
- And now… New Brunswick
- Risk Factor
  - Hospitalization/Health care Indian Subcontinent
  - ?Medical Tourism

Fighting back

What's to be done?

- Changing Veterinary practice
  - Optimize use
  - Formulary restriction
- Global measures
  - Drug quality controls, surveillance systems, training programs
- Local level measures

New Antimicrobials

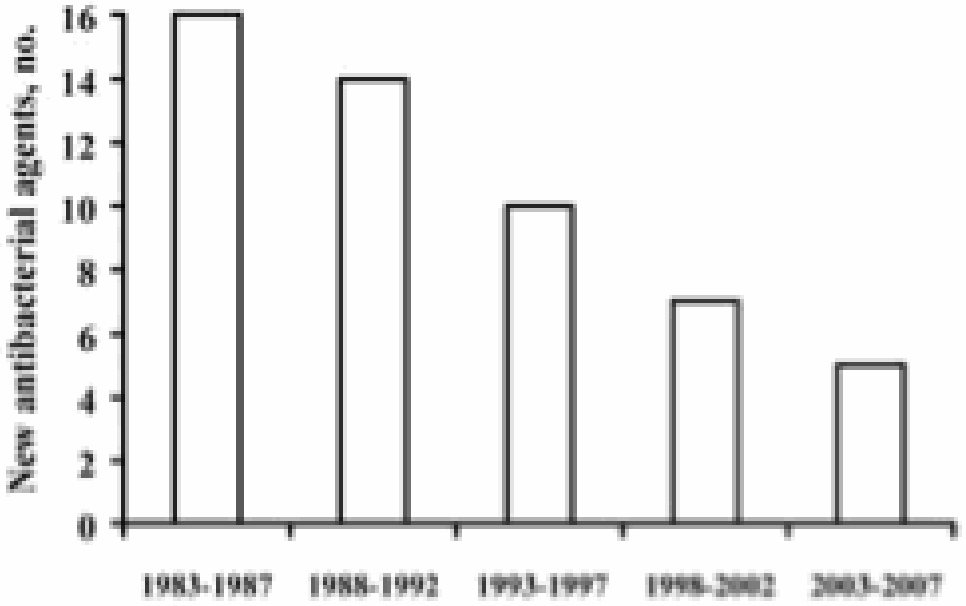


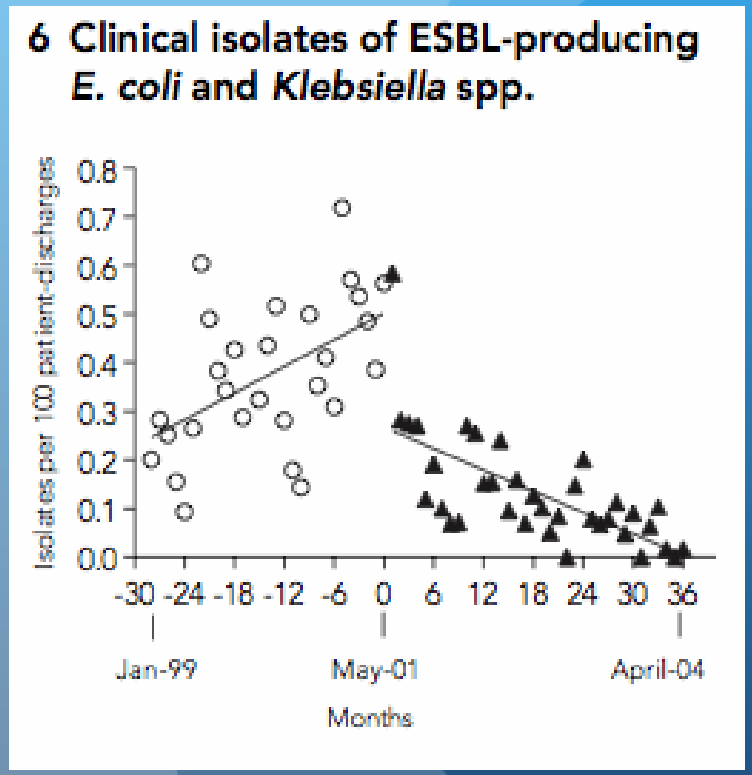
Figure 1. New antibacterial agents approved in the United States, 1983–2007, per 5-year period [2, 3].

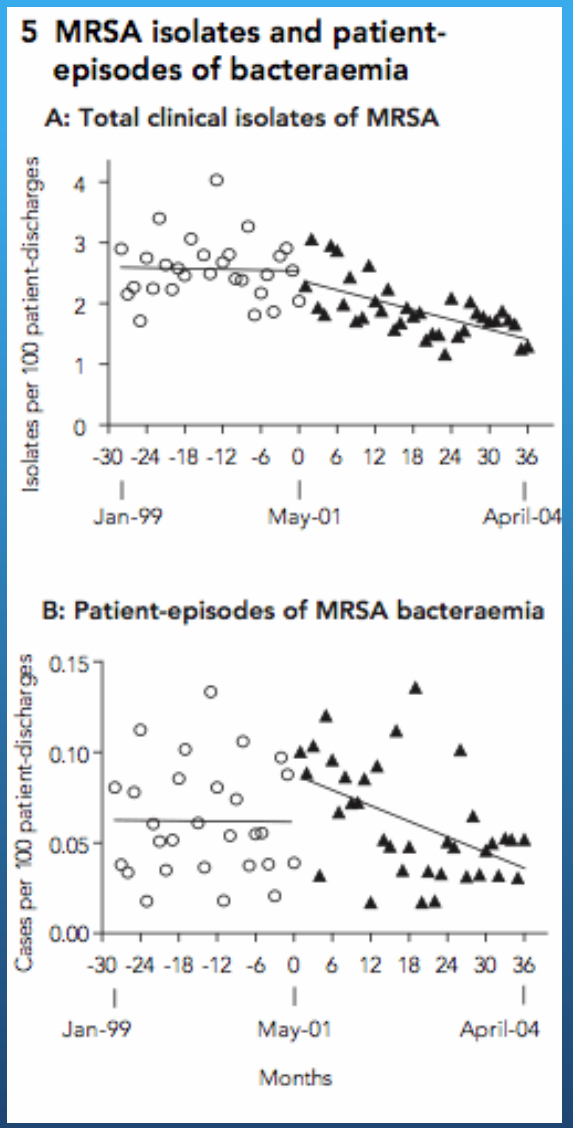
Boucher et al. CID. 2009.

Infection Control

- Education
- Hand washing
- Source Control
  - Isolation measures
  - Decontamination procedures

Infection Control – Hand Washing!!





Johnson PDR et al. Australian Med J. 2005.

What is Antimicrobial Stewardship?

- "…a coordinated effort to promote the judicious and effective use of antimicrobial agents that includes but is not limited to the appropriate selection, dosing, route of administration and duration of antimicrobial therapy…"
- "An effective antimicrobial stewardship program will limit inappropriate and excessive antimicrobial use, but more importantly improve and optimize therapy for the individual patient."

Ohl *et al*. J Hosp Med 2011;6:S4-15
www.LeadStewardship.org

Goals of Antimicrobial Stewardship: IDSA/SHEA Guidelines

- Primary Goal:
  - "optimize clinical outcomes while minimizing unintended consequences of antimicrobial use, including toxicity, the selection of pathogenic organisms (such as *Clostridium difficile*) and the emergence of resistance"

- Secondary Goal:
  - "reduce health care costs without adversely impacting quality of care"

Dellit *et al*. CID 2007;44:159-77

Core Strategies

- IDSA/SHEA guidelines call for 2 proactive core strategies as the foundation of an Antimicrobial Stewardship Program:
  - Formulary Restriction &/or Preauthorization
  - Prospective Audit with Intervention and Feedback

Formulary Restriction or Preauthorization

- Involves not including an antimicrobial agent on formulary or limiting use:
  - Through preauthorization for certain indications or patient populations
  - To certain prescribers or physician services
- Take into account antimicrobial resistance patterns & patient safety
- Often uses pager or phone call
- Important for individual granting authorization to have clinical experience & respect of medical staff as it may be considered a “mini-consult”
- Consider for antimicrobials used in complex infections or patients, not “work horse” antimicrobials

Formulary Restriction or Preauthorization

- Pros:
  - Provides immediate reduction in use & cost
- Cons:
  - May increase use & resistance to an alternative antimicrobial agent
  - Increased staffing requirements
  - Loss prescriber autonomy
  - Delays in initial therapy (apply restriction to subsequent doses, not first dose)
  - Hard to say “no”

Prospective Audit & Feedback

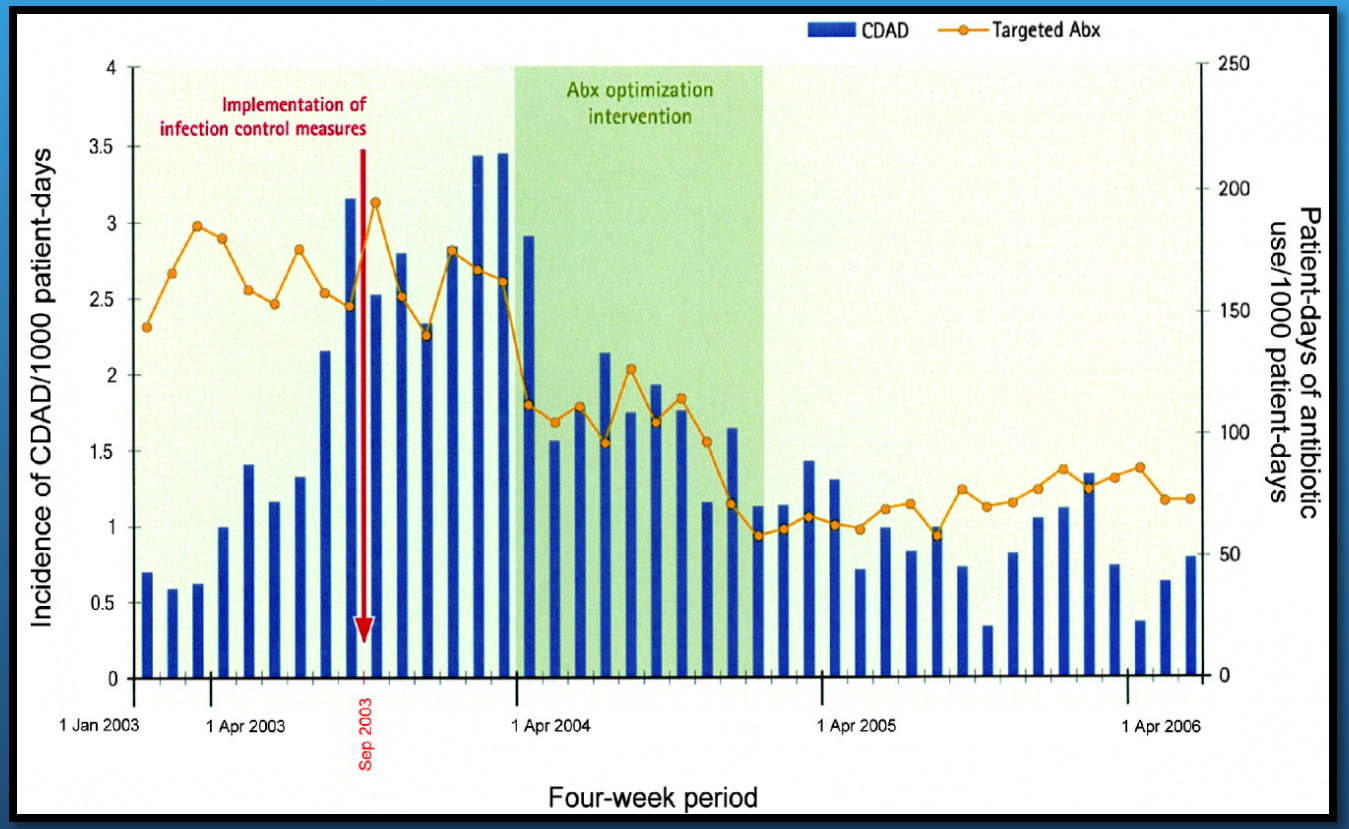
- Process of reviewing the appropriateness of antimicrobial regimens & then intervening to provide feedback & recommendations to the prescriber to improve or streamline therapy
- Reduces inappropriate antimicrobial use & provides an educational opportunity to change future prescribing
- Usually focuses on problem antimicrobials or usage
- Infectious Disease Physician &/or Clinical Pharmacist
- Pros:
  - Prescribers maintain autonomy
- Cons:
  - Difficult to identify patients with inappropriate therapy & communicating recommendations
  - Compliance is voluntary
  - Resource intense
  - Legal concerns

Supplementary Strategies

- Education
  - Should be given in conjunction with active intervention
  - Education alone is only marginally effective
- Guidelines & Pathways
  - Should be evidence based, consider local resistance patterns & have multidisciplinary input
  - Compliance is voluntary
  - “Cookbook” medicine
- Computerized Methods
  - CPOE & decision support
- Streamlining & De-escalation
- Dose Optimization
- Parenteral-to-oral conversion
- Microbiology Interventions

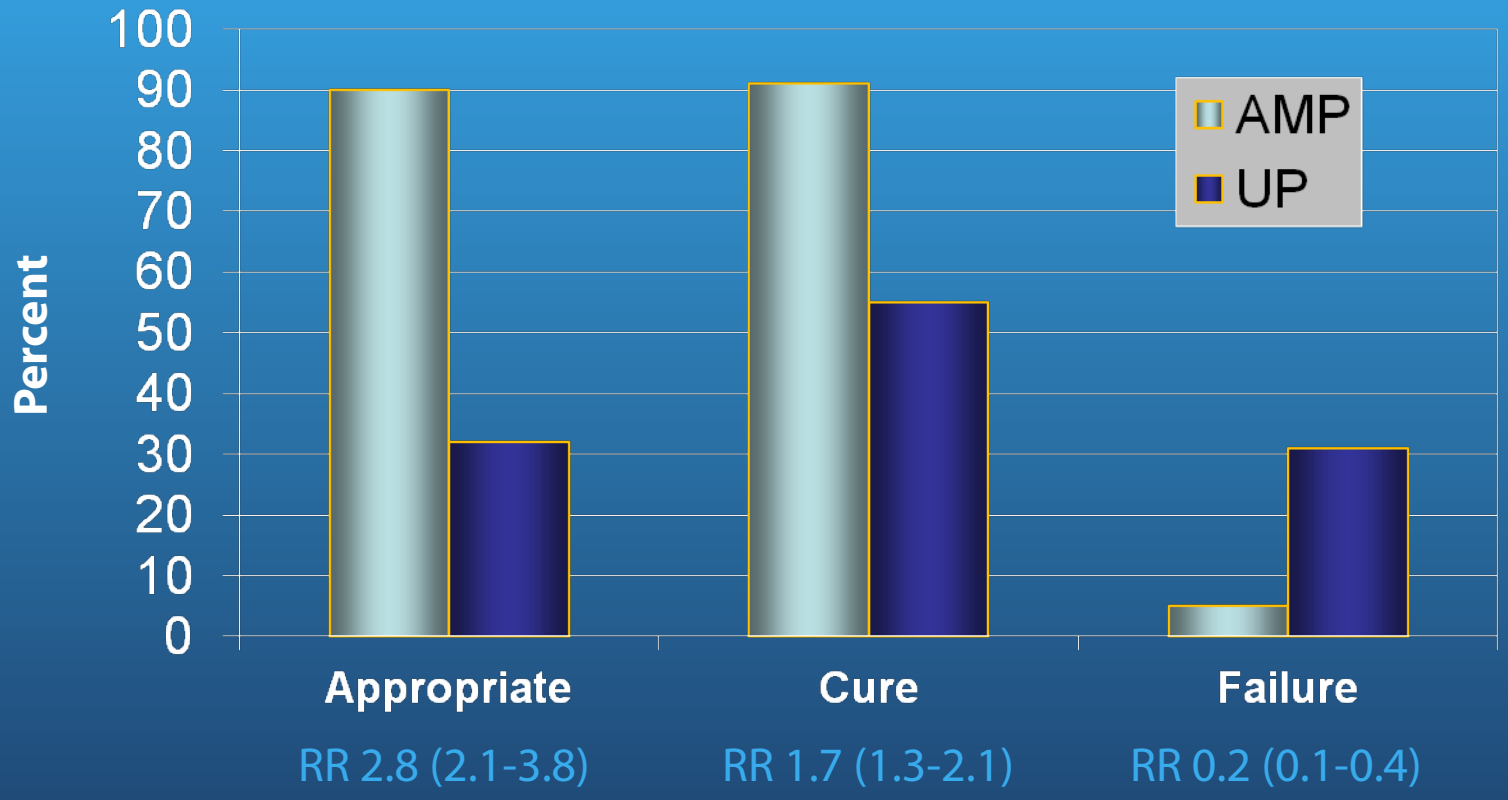
Targeted antibiotic consumption and nosocomial *C. difficile* disease

Tertiary care hospital; Quebec, 2003-2006



Valiquette, et al. *Clin Infect Dis* 2007;45:S112.

Clinical outcomes better with antimicrobial management program



Fishman N. *Am J Med.* 2006;119:S53.

AMP = Antibiotic Management Program
UP = Usual Practice

[Intervention Review]

Interventions to improve antibiotic prescribing practices for hospital inpatients

Peter Davey[1], Erwin Brown[2], Lynda Fenelon[3], Roger Finch[4], Ian Gould[5], Giles Hartman[6], Alison Holmes[7], Craig Ramsay[8], Eric Taylor[9], Mark Wilcox[10], Philip J Wiffen[11]

Main results

Sixty-six studies were included and 51 (77%) showed a significant improvement in at least one outcome. Six interventions only aimed to increase treatment, 57 interventions aimed to decrease treatment and three interventions aimed to both increase and decrease treatment. The intervention target was the decision to prescribe antibiotics (one study), timing of first dose (six studies), the regimen (drug, dosing interval etc, 61 studies) or the duration of treatment (10 studies); 12 studies had more than one target. Of the six interventions that aimed to increase treatment, five reported a significant improvement in drug outcomes and one a significant improvement in clinical outcome. Of the 60 interventions that aimed to decrease treatment, 47 reported drug outcomes of which 38 (81%) significantly improved, 16 reported microbiological outcomes of which 12 (75%) significantly improved and nine reported clinical outcomes of which two (22%) significantly deteriorated and 3 (33%) significantly improved. Five studies aimed to reduce CDAD. Three showed a significant reduction in CDAD. Due to differences in study design and duration of follow up, it was only possible to perform meta-regression on a few studies.

Authors' conclusions

The results show that interventions to improve antibiotic prescribing to hospital inpatients are successful, and can reduce antimicrobial resistance or hospital acquired infections.

THE COCHRANE COLLABORATION®

Does Antimicrobial Stewardship Work?

- Studies have shown:
  - Decreased antimicrobial usage & cost
  - Decreased rates of inappropriate antimicrobial use
  - Decreased *C. difficile* infection rates
  - Decreased adverse drug reactions
  - Decreased length of stay
  - Decreased antimicrobial resistance

- See also:
  - CDC's Getsmart: Evidence to Support Stewardship (www.cdc.gov/getsmart/healthcare/support-efforts/index.html)
  - Patel *et al.* Antimicrobial Stewardship Programs: Interventions and Associated Outcomes. Expert Rev. Anti Infect. Ther. 2008:6(2);209-222

Local Initiative

- Pilot and evaluation of an active intervention program of antimicrobial stewardship
  - Team: ID physician, ICU clinical pharmacist, Medical Microbiologist
  - Daily review of all patients on antimicrobials in the Medical and Surgical ICUs
  - Recommendations for improved antimicrobial management communicated via ICU pharmacist
    - Streamline, de-escalation/discontinuation, dose optimization, IV to PO, duration change, further testing

Outcomes

- Primary
  - Implementation rate of outcomes
  - Type of suggestions
- Secondary
  - Adverse Drug Reactions
  - CDAD (*Clostridium difficile*-associated disease)
  - Qualitative opinions of intensivists
  - Time spent on project by study team members

Follow up study

- Retrospective, matched cohort comparison
- All patients in our cohort with diagnosis of pneumonia (of any kind) matched with patients admitted to medical-surgical ICU within same time period a year ago
  - Matching criteria: age, COPD status, pneumonia diagnosis (CAP, VAP, HAP), weight

Follow up study

- Outcomes:
  - Antimicrobial utilization costs
  - Length of stay in ICU
  - Adverse Drug Reactions
  - CDAD (*Clostridium difficile*-associated disease)

Preliminary results

- 67 patients included in the study
  - CV surgery patients excluded
  - November 1, 2011 – January 13, 2012
  - Used Intention-To-Treat
    - If transferred out of ICU before suggestions implemented, considered rejection

Preliminary results

Diagnosis:	
Pneumonia	33
CAP HAP/VAP Aspiration	19 10 4
Post-op prophylaxis	17
Intra-abdominal sepsis	6
Sepsis/Bacteremia (?source)	5
Clostridium difficile infections	4
Urosepsis	3
Graft infection	2
Other	4

Preliminary results

Recommendations:	Number	Number accepted (%)
Total	78	72(92)
Streamline/De-escalate/Discontinue	39	37(95)
Dose optimization	6	6(100)
IV to PO stepdown	0	N/A
Duration Change	10	8(80)
Further Testing	23	21(91)

Preliminary Results

- Secondary Outcomes
  - No Adverse Drug Reactions
    - ?one questionable rash
  - No NEW *C. difficile* associated disease
  - Time:
    - Total pharmacist time: 22 hours
      - Average 22 minutes/day
      - **Already rounding with team
    - Total ID physician time: 12.25 hours
      - Average 12 minutes/day

Preliminary Results (from Follow-up Study)

- Groups from both years fairly similar
  - Can do analysis
- Trend towards lower antimicrobial costs
- Trend towards shorted ICU stays

Up and coming projects

- Big question:
  Where are the big problems???
- Other questions:
  - What about other hospitals?
  - Limited resources – can we focus on high needs areas?
  - What are we going to do now that antimicrobial stewardship is part of hospital accreditation?

Up and coming projects

- Fundamental issues
  - Antimicrobial usage in New Brunswick
  - APPROPRIATENESS of antimicrobial usage in New Brunswick
- Let’s study this!!

Province-wide Study

- Point prevalence study
  - All antimicrobial use on one specific day
  - Data collected on demographics, diagnostics, therapeutics by independent survey team
  - Review of data by the study investigators to assess (based on pre-defined criteria):
    - Appropriateness of therapy
    - Opportunities for de-escalation, IV to PO conversion and dose optimization

Horizon Health Region

- Questions to be answered:
  1. What are the current patterns of antimicrobial usage within Horizon Health Network with respect to patient characteristics, indication, prescribed daily dose, route and prescriber?
  2. Based on antimicrobial usage patterns, where do opportunities exist to improve patient outcome and safety through implementation of targeted antimicrobial stewardship interventions within hospitals of Horizon Health Network?
  3. Is antimicrobial usage within Horizon Health Network appropriate based on some specific pre-defined criteria?

Province-wide Study

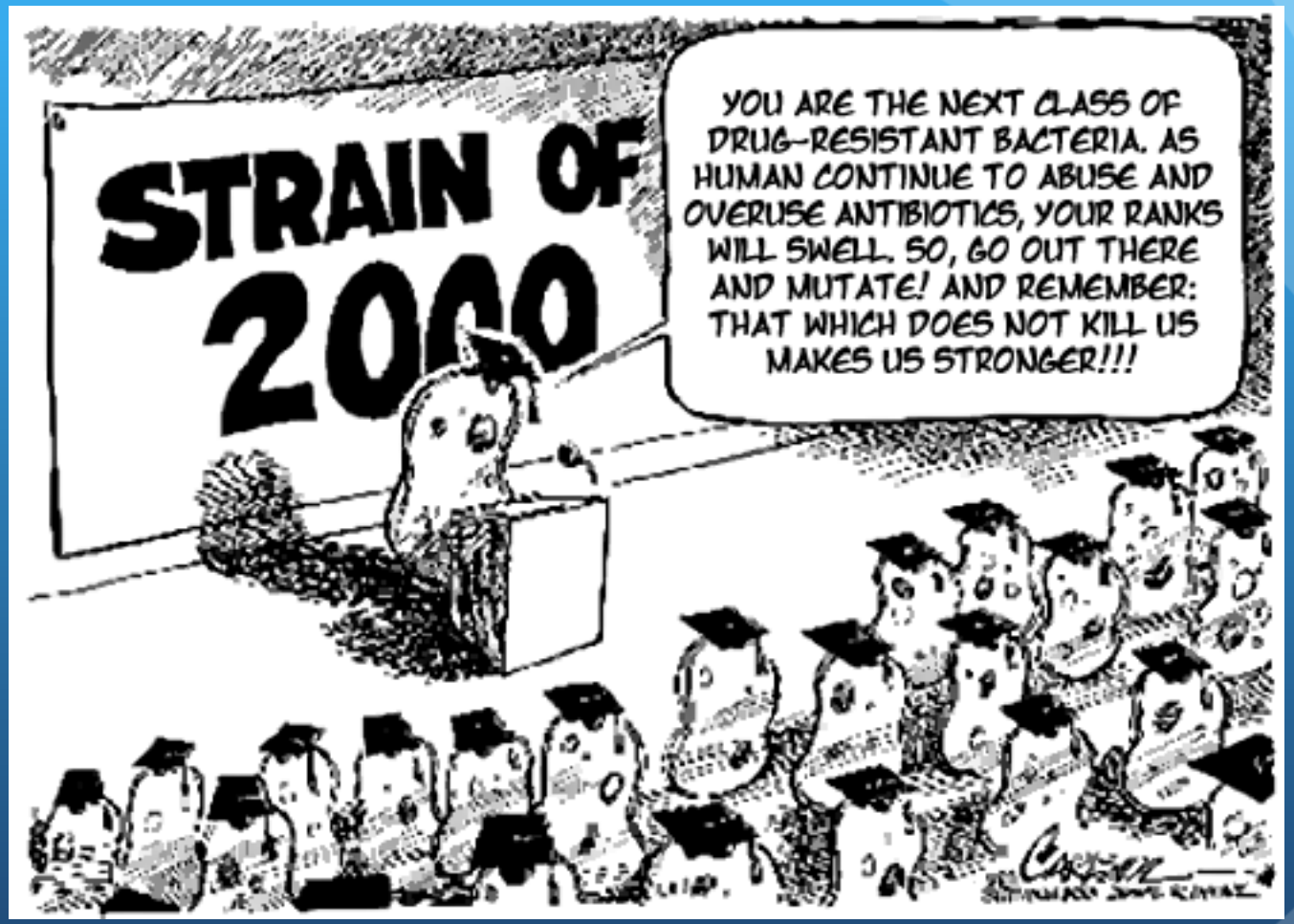
- Point prevalence study
  - Small grant application in
  - REB application pending
  - Working with partners in Vitalité to expand to the entire province

Conclusion/Take Home Points:

- Antimicrobial Resistance is a natural process selected for by overuse of antimicrobials
- Antimicrobial Resistance is on the rise, even in Atlantic Canada and is starting to cause significant clinical issues
  - Pretty bad, even worse and totally ugly!!
- The solutions to the issues of antimicrobial resistance are not simple but there is more data to support infection control and antimicrobial stewardship interventions
- Changes are coming to how we use antimicrobials in the hospital setting

Thanks to:

- Lindsay Creamer
- Glenn Myers
- Sameh El-Bailey
- Tim Maclaggan


STRAIN OF
2000
YOU ARE THE NEXT CLASS OF DRUG-RESISTANT BACTERIA. AS HUMAN CONTINUE TO ABUSE AND OVERUSE ANTIBIOTICS, YOUR RANKS WILL SWELL. SO, GO OUT THERE AND MUTATE! AND REMEMBER: THAT WHICH DOES NOT KILL US MAKES US STRONGER!!!