Antibiotic Resistance: Effectiveness of Strategies to Prevent Transmission and Control Antibiotic Utilization

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First Lesson in Infection Control: Be Careful What You Say

As an infectious-disease specialist, Dr. Donald Goldmann knows all about the dizzying selection of antibacterial soaps on the market that claim to fight everything from strep throat to athlete's foot.

What does he use at home to wash his hands?

"Whatever I can steal from a hotel," said Goldmann, an epidemiologist at Children's Hospital in Boston

Boston Sunday Globe – February 23, 1997

Modes of Transmission

- Direct contact
- Indirect contract
  - Fomites (surfaces, pagers, PDAs, ties)
  - Hands
- Endogenous (autoinfection)
- Droplet
- Airborne
  - Droplet nuclei (cloud baby of Eichenwald, cloud adult of Sheretz)
  - Shedding
- Common vehicle/common source
- Vector

Direct Contact

Not always so obvious

Colonized/Infected Personnel Can Cause Commons Source Outbreaks

- Classically, *S. aureus*
- Increasing recognition of outbreaks due to other pathogens
  - Candida (e.g., traced to nail infection)
  - Gram-negative bacilli

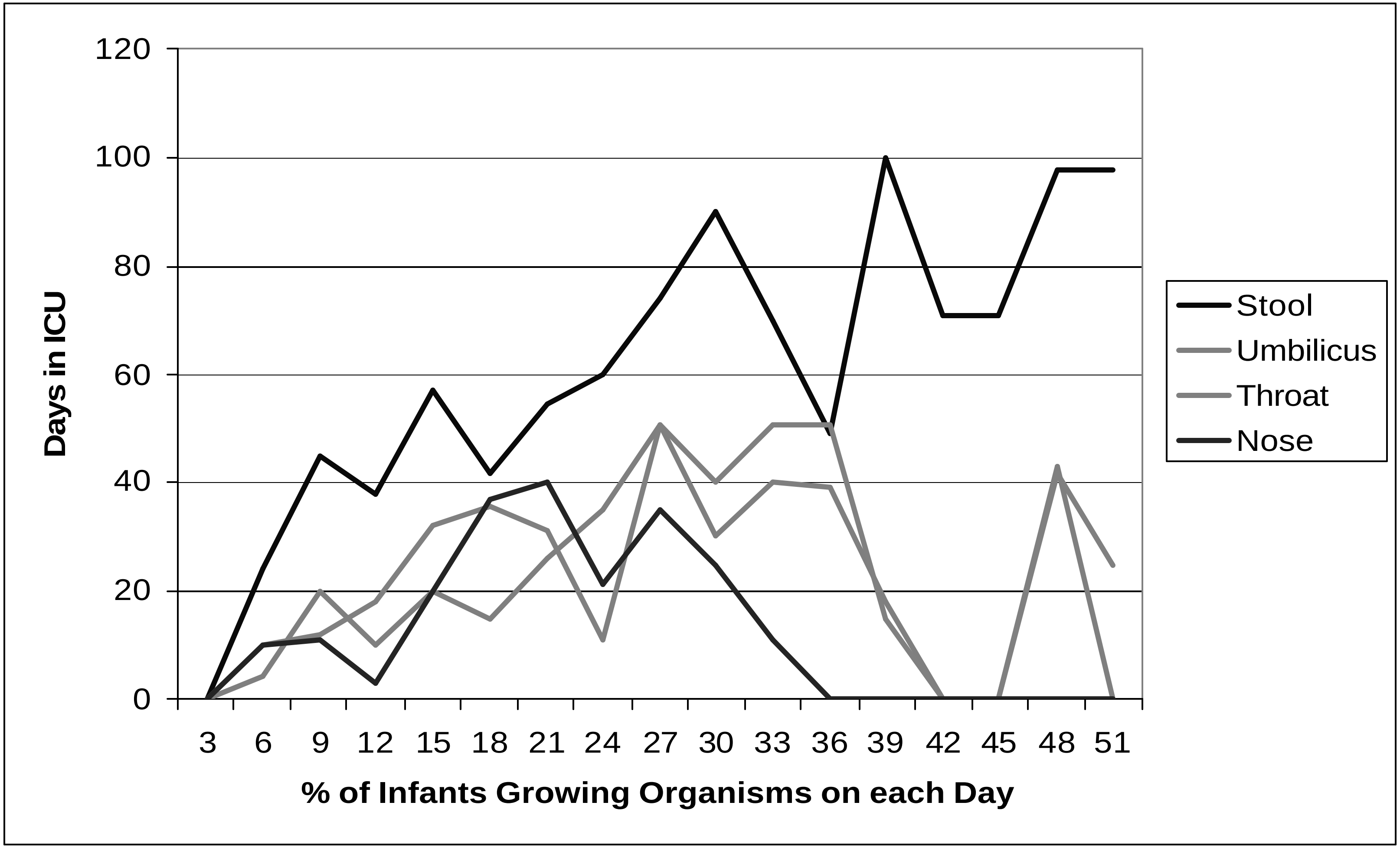
Indirect Contact

- Fomites
  - Important for certain bacteria: MRSA, VRE, *C. difficile*, probably Acinetobacter
  - Plays a role in spread of some viruses: RSV, coronavirus (e.g., SARS), norovirus
- Hands

Endogenous Infection

A Special Form of Indirect Contact Spread

Percent of infants growing *Klebsiella, Enterobacter*, or *Citrobacter*



Well known to Katherine Sprunt

of *S.epidermidis* Bacteremia Strains with Same Genotypes, 1982-91

Pattern	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991
A	_	1	5	4	1	5	1	2	3	_
B	_	3	5	3	5	3	2	1	_	2

Common Source/Common Vehicle Outbreaks

- Generally caused by Gram-negative pathogens
  - Gram-negative bacilli thrive wherever there is moisture
  - “Water bugs” survive in distilled water with penicillin as the only carbon source for more than a decade
    - Contaminated disinfectants
    - Enterobacter-associated IV fluid outbreaks (fix atmospheric nitrogen)
    - Contaminated fentanyl-associated outbreaks associated with drug abuse by hospital staff

Antibiotic Resistance

Antibiotics: Wonder Drugs of the 20th Century

- Curative
- Fast acting
- Few side effects
- Minimal serious risks
- When in doubt...

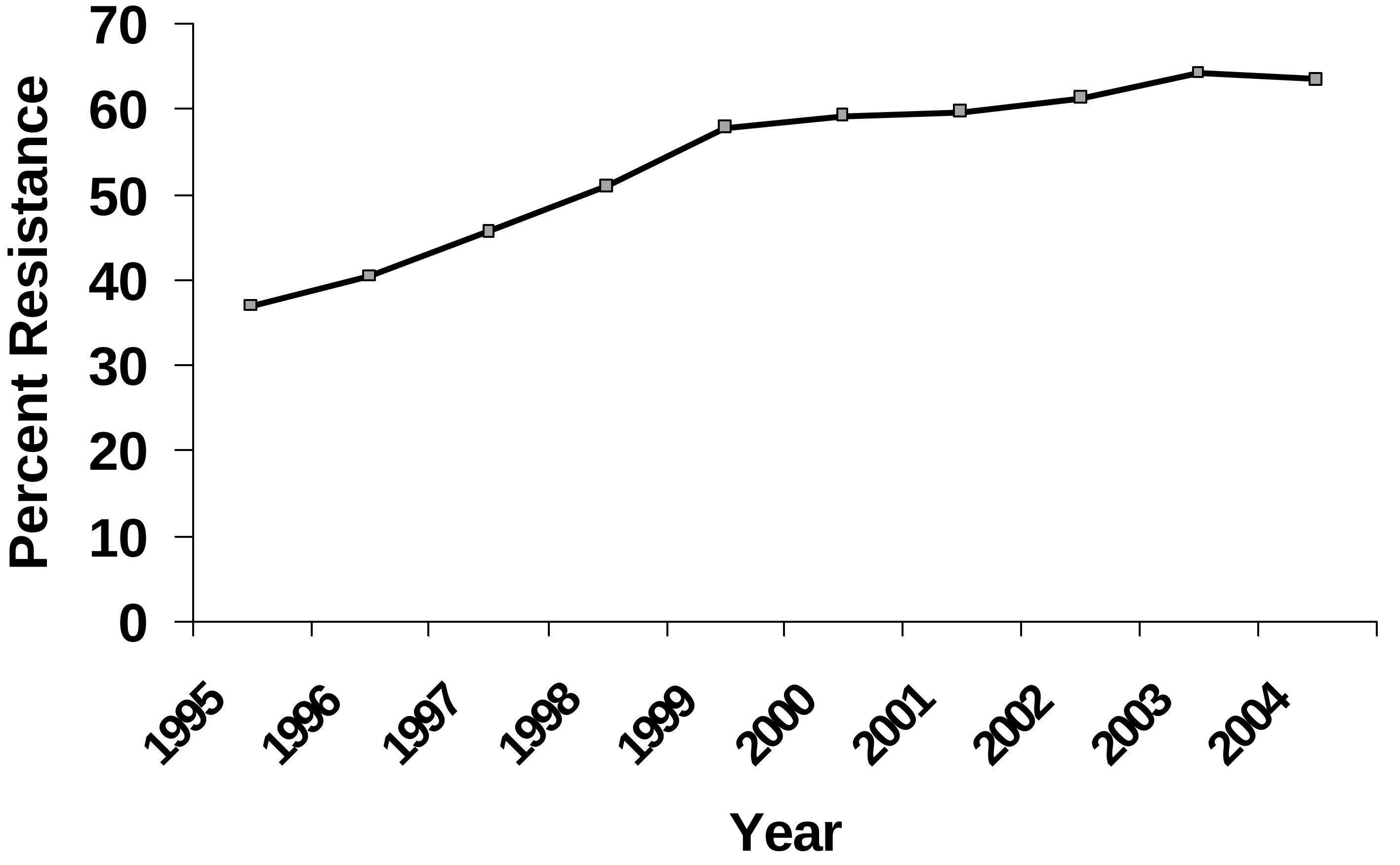
Resistance in the Community…

- Pneumococcus: > 50% non-susceptible to penicillin in some areas; increasing multi-drug resistance
- *E. Coli*: increasing resistance to ampicillin, TMP/SMX, even quinolones
- Salmonella (including typhoid)
- Gonococcus: multi-drug resistance, now including quinolones
- Group A strep: resistant to erythromycin in countries with overuse
  - In Boston 8.2% R to erythromycin, 1.5% clindamycin
- MRSA

Resistance Problems are not Confined to Bacteria…

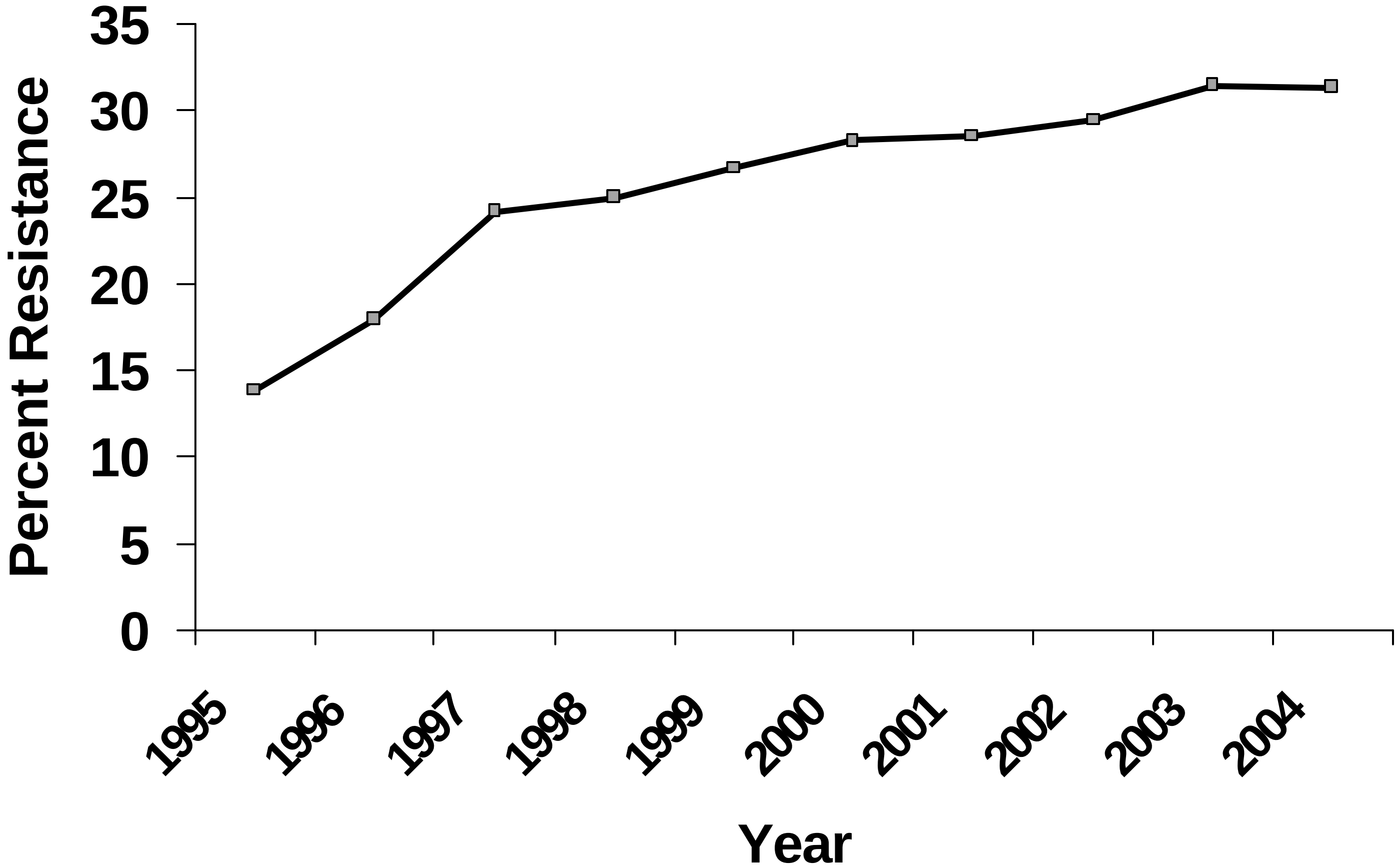
- Viruses (yes, even avian flu, not just HIV)
- TB
- Malaria
- Yeasts
- Disinfectants and Antiseptics
  - Quaternary ammonium compounds (“quats”)
  - Chlorhexidine
  - Triclosan
  - Mupirocin

Methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) Among ICU Patients, 1995-2004



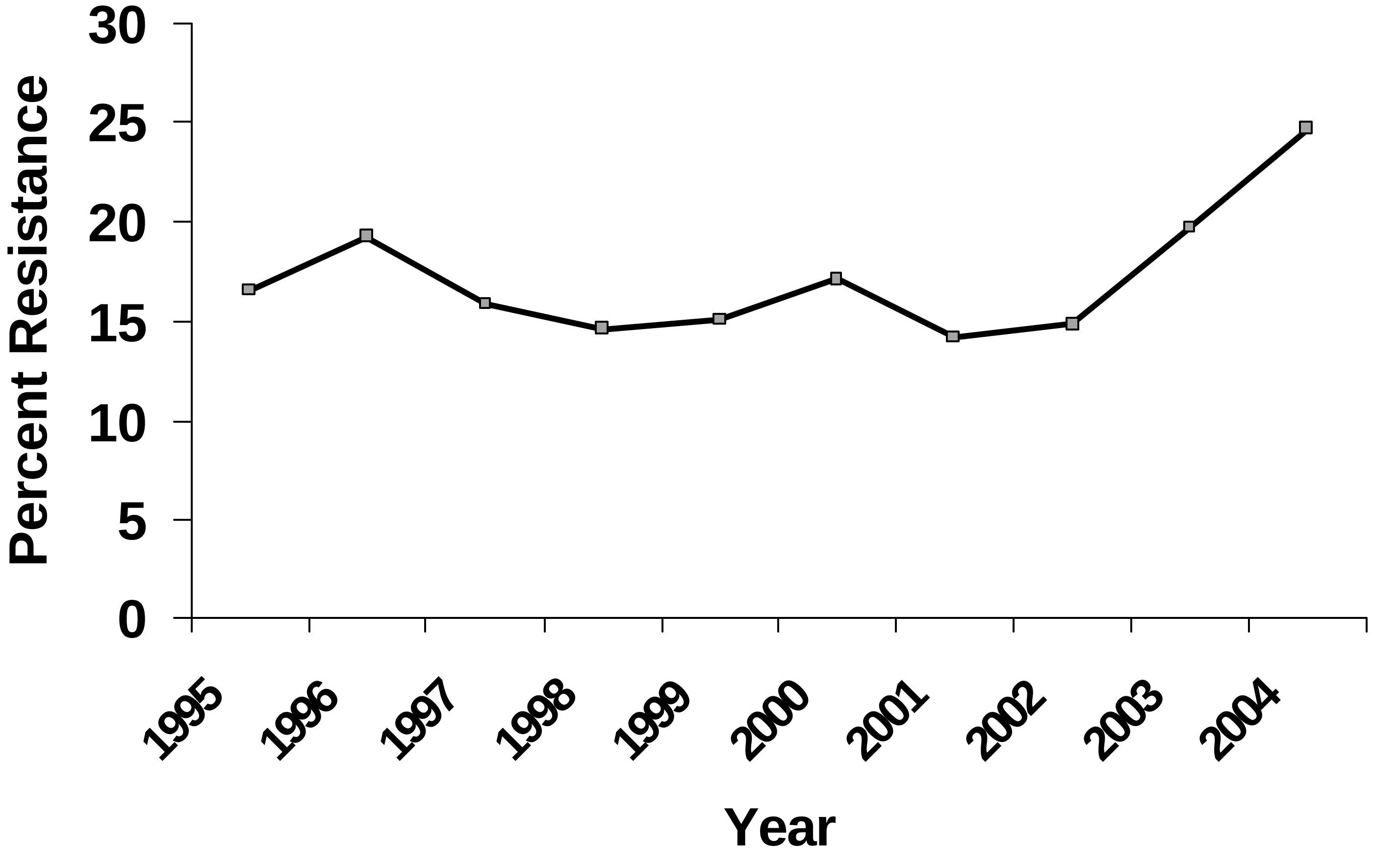
Source: National Nosocomial Infections Surveillance (NNIS) System

Vancomycin-resistant *Enterococci* Among ICU Patients, 1995-2004



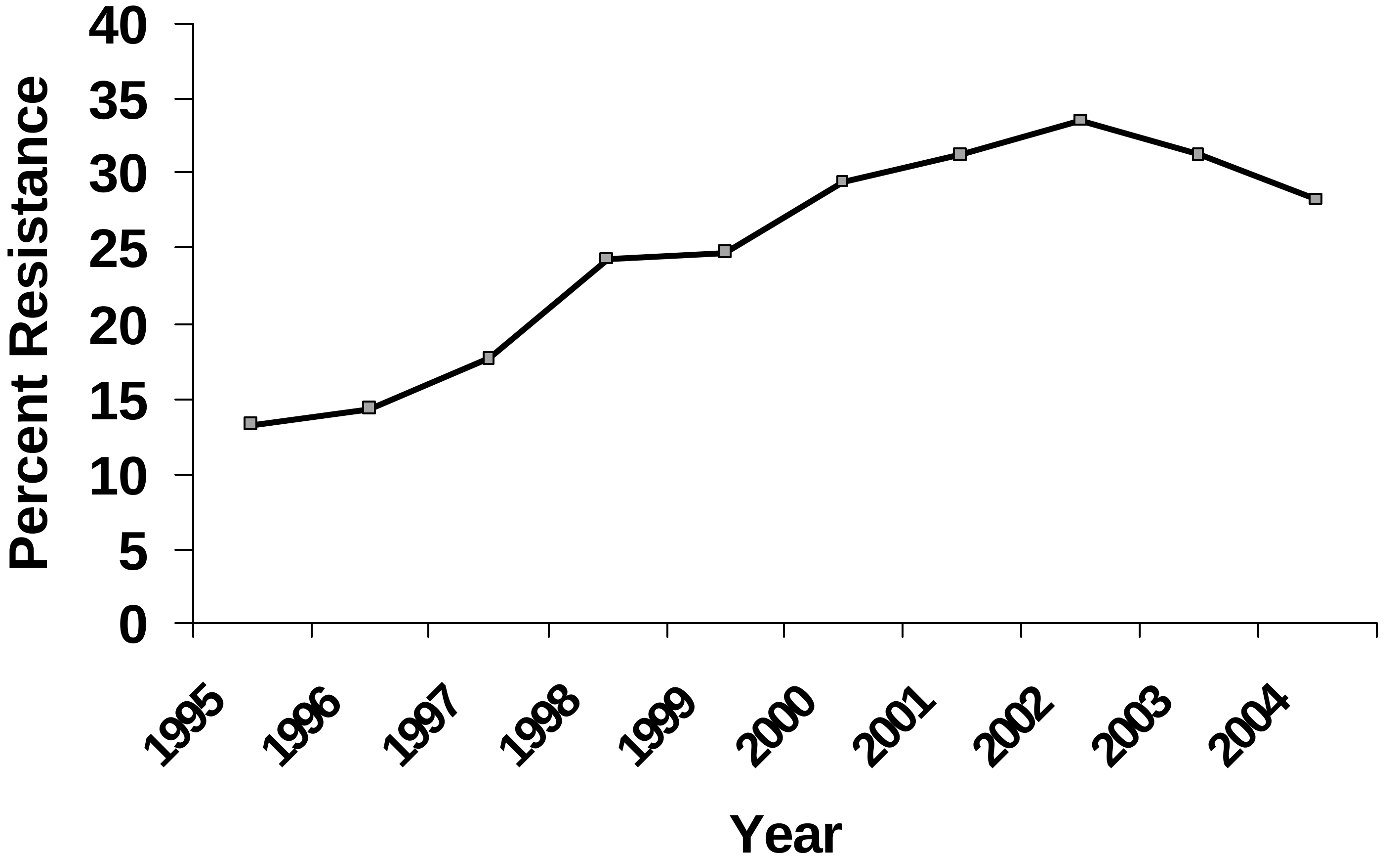
Source: National Nosocomial Infections Surveillance (NNIS) System

3rd generation cephalosporin-resistant *Kliebsiella pneumoniae* Among ICU Patients,1995-2004



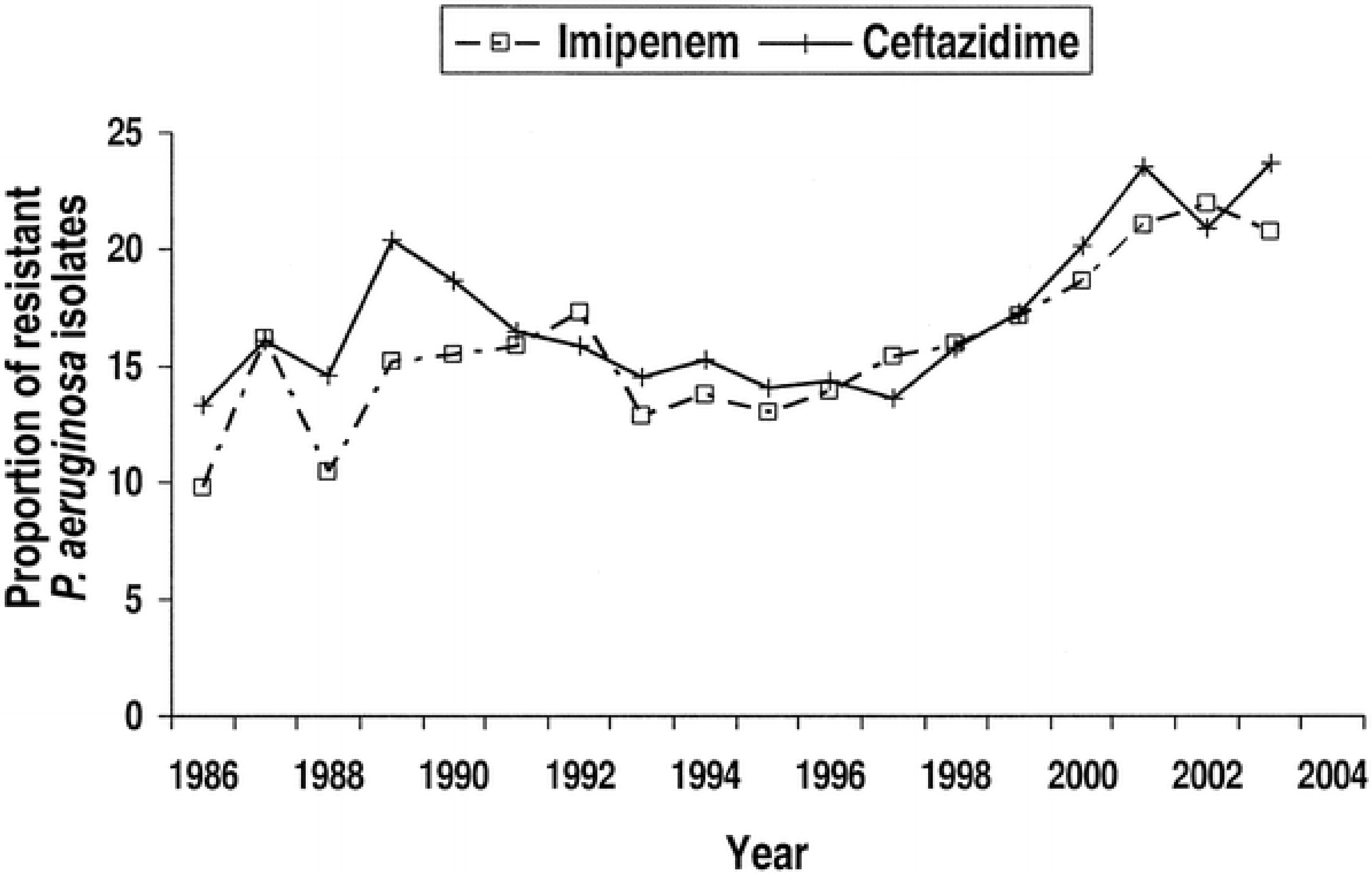
Source: National Nosocomial Infections Surveillance (NNIS) System

Fluoroquinolone-resistant *Pseudomonas aeruginosa* Among ICU Patients, 1995-2004

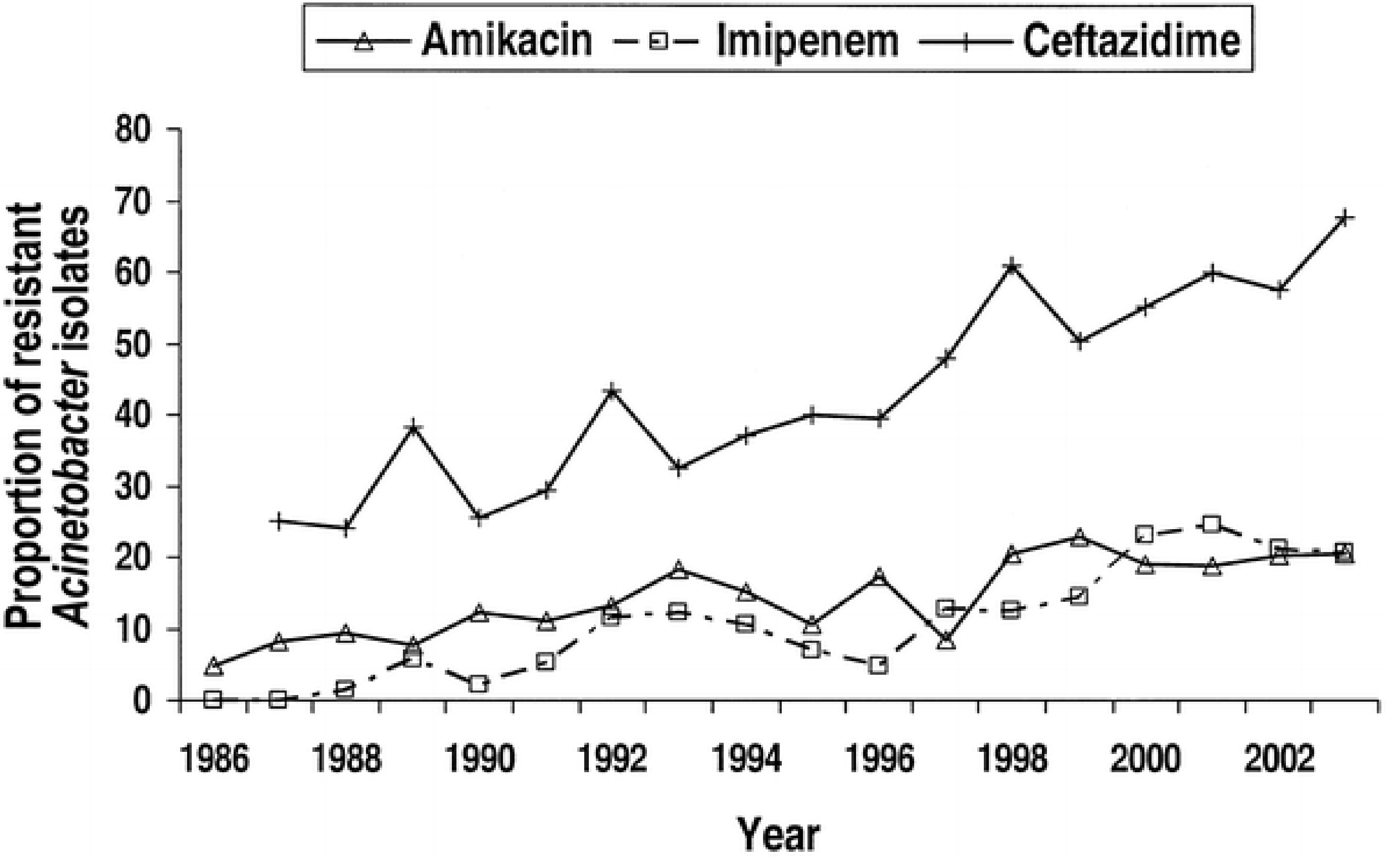


Source: National Nosocomial Infections Surveillance (NNIS) System

Pseudomonas ICU Resistance - CDC



Acinetobacter ICU Resistance -- CDC



Other Increasingly Problematic Gram-Negative Bacilli

- Stenotrophomonas
- Burkholderia
- Ralstonia
- Alkaligenes
- …And many other “water bugs”

5 Stages in the Evolution of Antimicrobial Resistance

- “Natural” resistance
- Mutation/Acquisition of resistance genes
- Selection
- Amplification
- Dissemination

“Natural” Resistance

Mutation and Acquisition of Resistance Genes

- Plasmids, transposons, integrons, pathogenicity islands, cassettes, and other mobile genetic elements
  - Some transferable elements appear to easily jump genera and species (TEM-1 beta-lactamase)
  - Some are surprisingly mobile (staphylococcal chromosomal cassette (SCC))
  - Tranformation with capsular switching (meningococcus and pneumococcus)

Selection

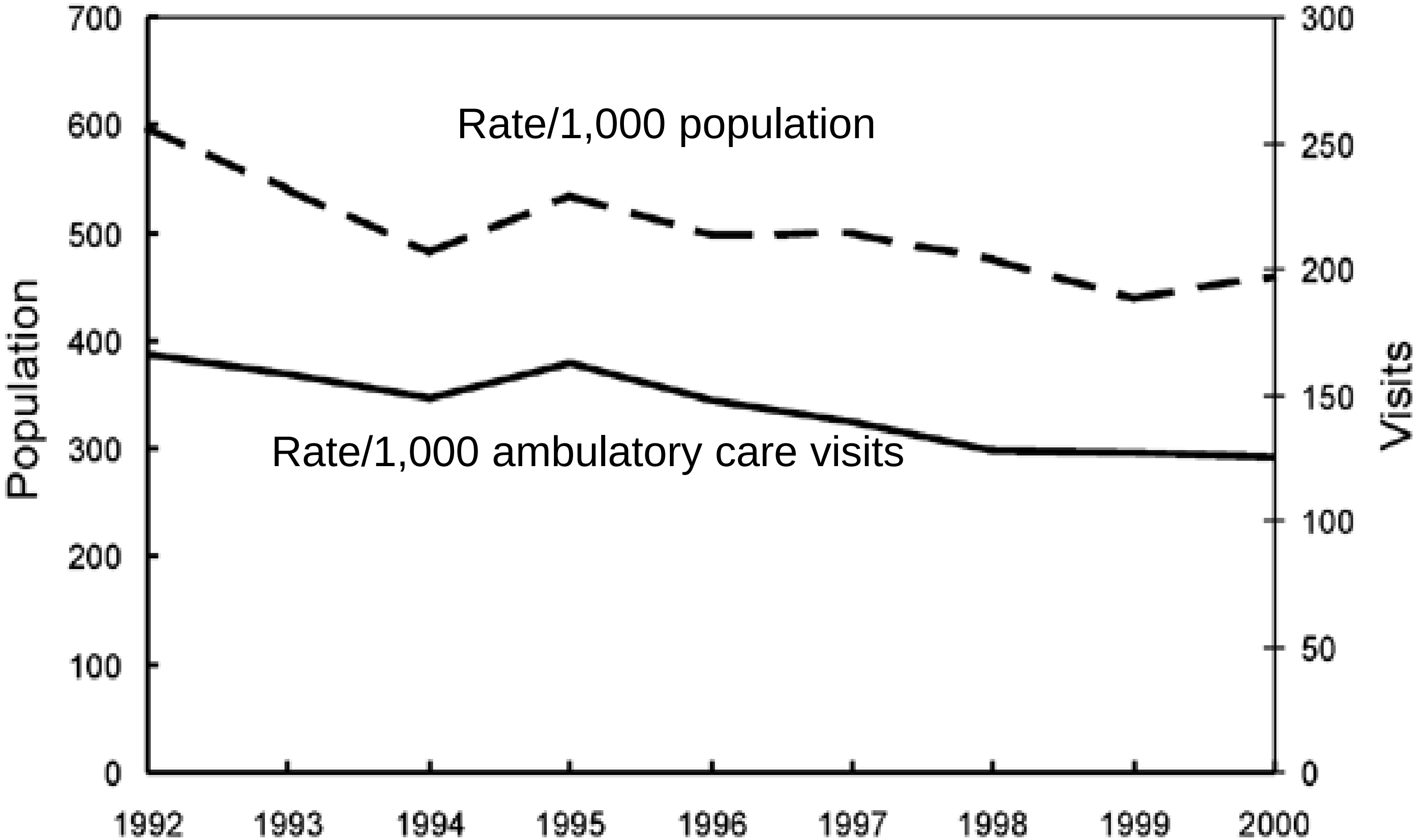
Increasing Selective Pressures

- Agricultural and other uses
  – animal feed, mainly for growth promotion
    - Avoparcin, virgniamycin, ceftiofur, quinolones)
    - EU, FDA and McDonalds finally do something right to improve agricultural practice
  – fish farming
  – uses in plants
  – biocides
  – tetracycline in battleship paint

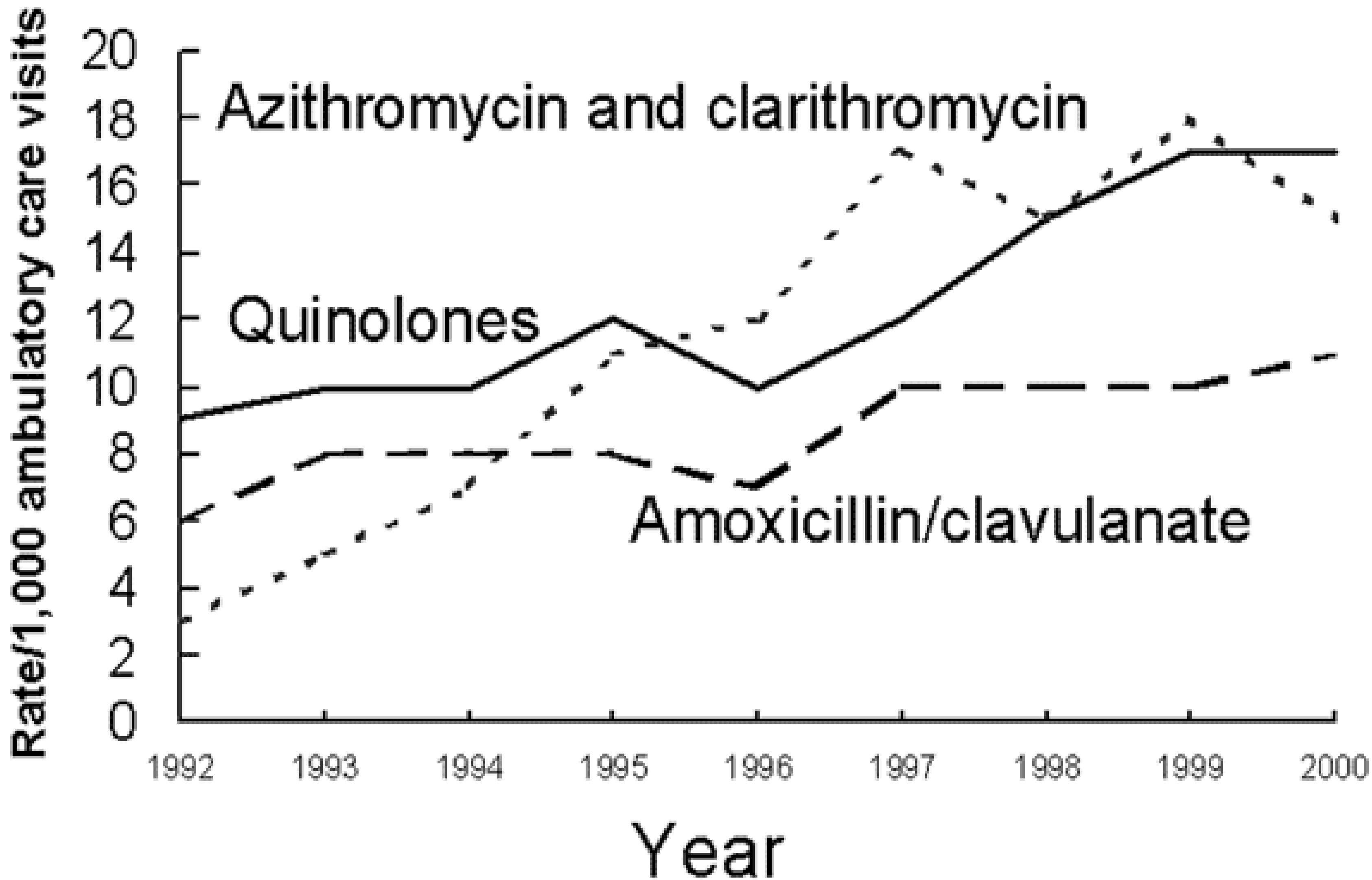
Increasing Selective Pressures

- Human use
  - Over-the-counter use
    - Non-physician dispensing
    - Local markets
    - “Indiginized” and folk use
  - Availability of unregulated multi-drug combinations; local production of patent and off-patent drugs
  - Self-medication of prescribed drugs
    - Potential for Internet abuse
  - Physician overuse, misuse (community and hospital)
    - Demand-side pressure

Trends in Antimicrobial Prescribing, United States National Ambulatory Medical Care Surveys



McCraig, EID 2003;9:432



Rate/1,000 ambulatory care visits
20
18
16
14
12
10
8
6
4
2
0
Azithromycin and clarithromycin
Quinolones
Amoxicillin/clavulanate
1992
1993
1994
1995
1996
1997
1998
1999
2000
Year

Amplification

- Daycare centers
  - Benighted policies for excluding febrile infants
- Hospital wards, especially ICUs
  - Sub-standard infection control practices
- Long term care facilities
  - Insufficient staffing to implement infection control practices
- Prisons
- Sports teams

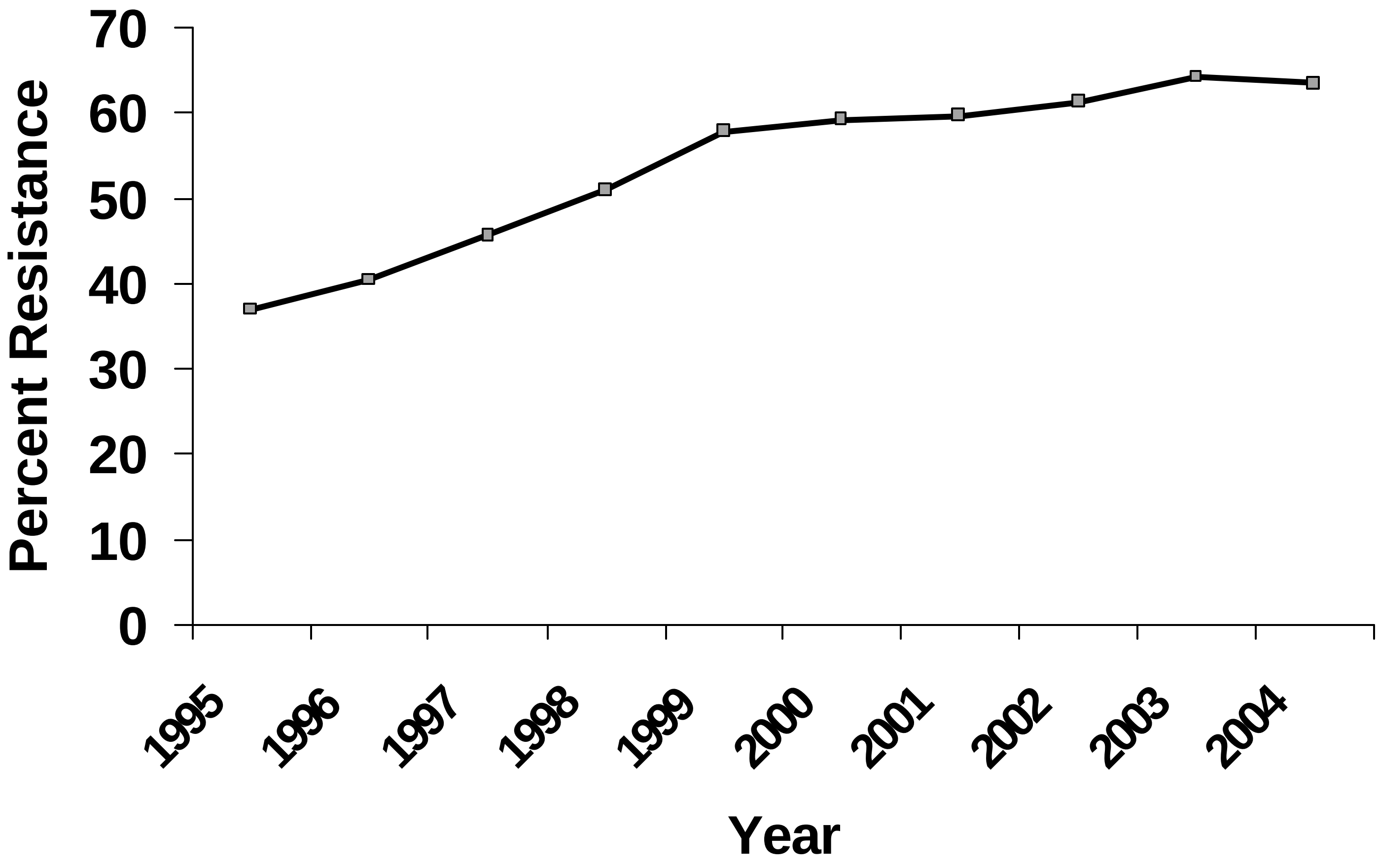
Dissemination

- Community to hospital (Pneumococci)
- Hospital to community (Salmonella)
- Among healthcare facilities
  - Acute and chronic (MRSA, VRE)
- Regional, national and international spread of resistant organisms and clonal resistance determinants
  - MRSA
  - Burkholeria

CDC's12 Steps to Prevent Antimicrobial Resistance

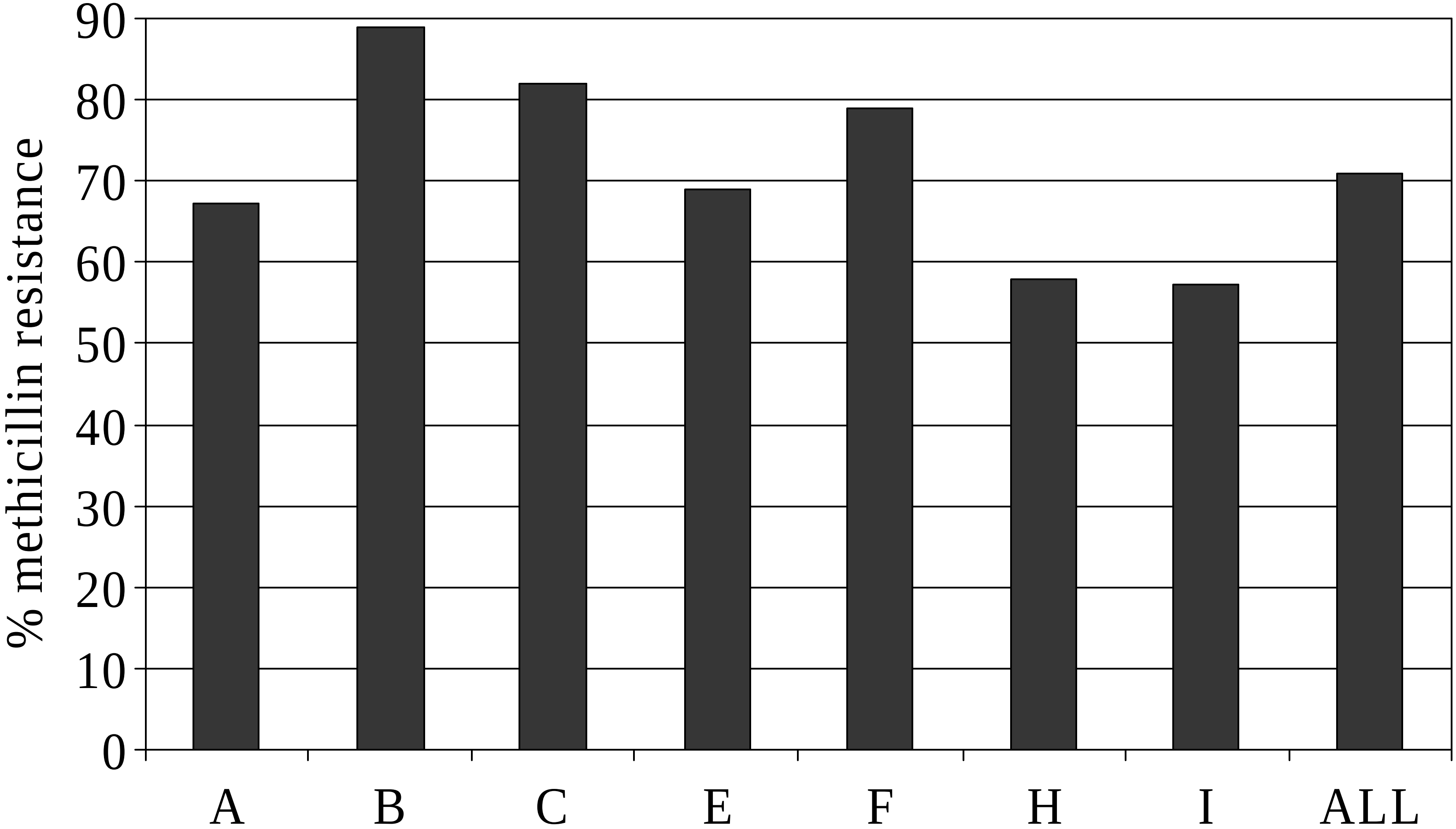
Methicillin-Resistant *Staphylococcus aureus* – Now A New Enemy at the Gates

Methicillin (oxacillin)-resistant *Staphylococcus aureus* (MRSA) Among ICU Patients, 1995-2004



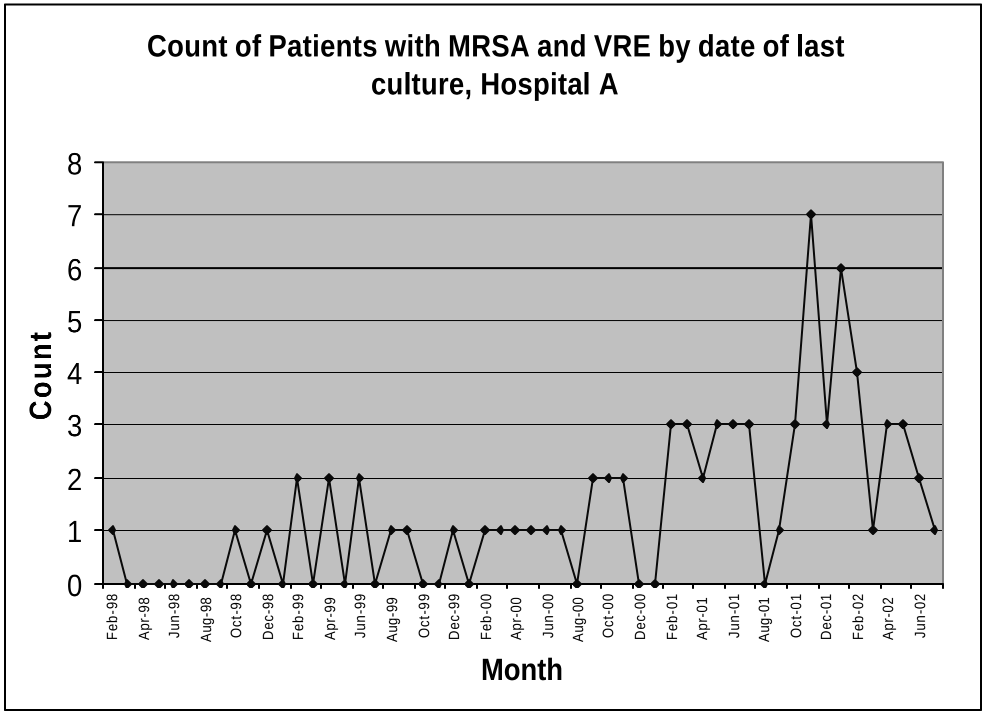
Source: National Nosocomial Infections Surveillance (NNIS) System

MRSA in US Long Term Care Facilities
The OMEGA Study



Beekmann SE, Doern GV, et al. Unpublished data.

USA: First VRSA



June 2002: 40 yo female with diabetes, chronic renal failure, co-colonized with MRSA & VRE Acquired a catheter exit site infection with VRSA after treatment with vancomycin

Vancomycin MIC, >128
Carried *vanA* resistance gene on a *S. aureus* plasmid

Now 4 cases

MMWR 2002;51:565-566.

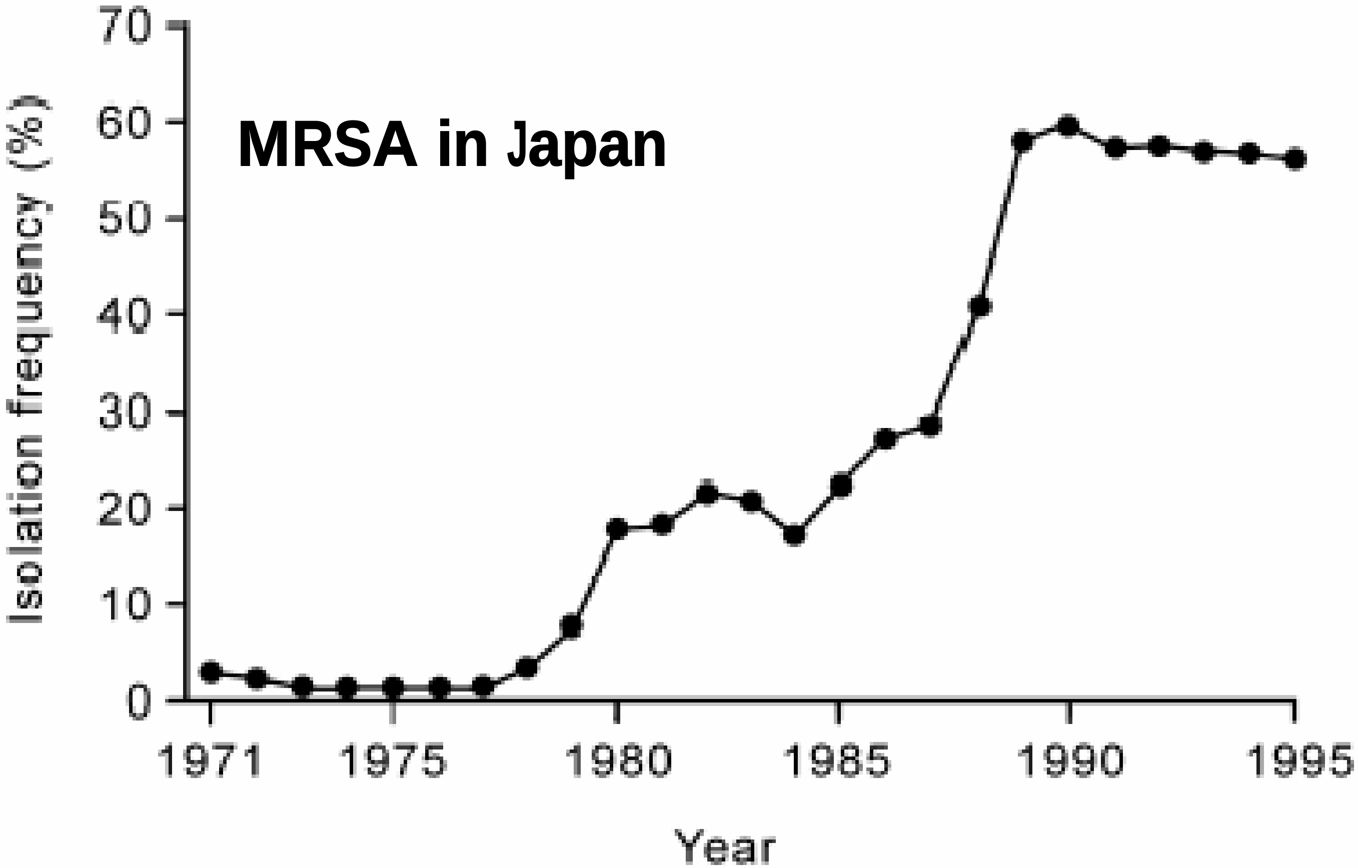
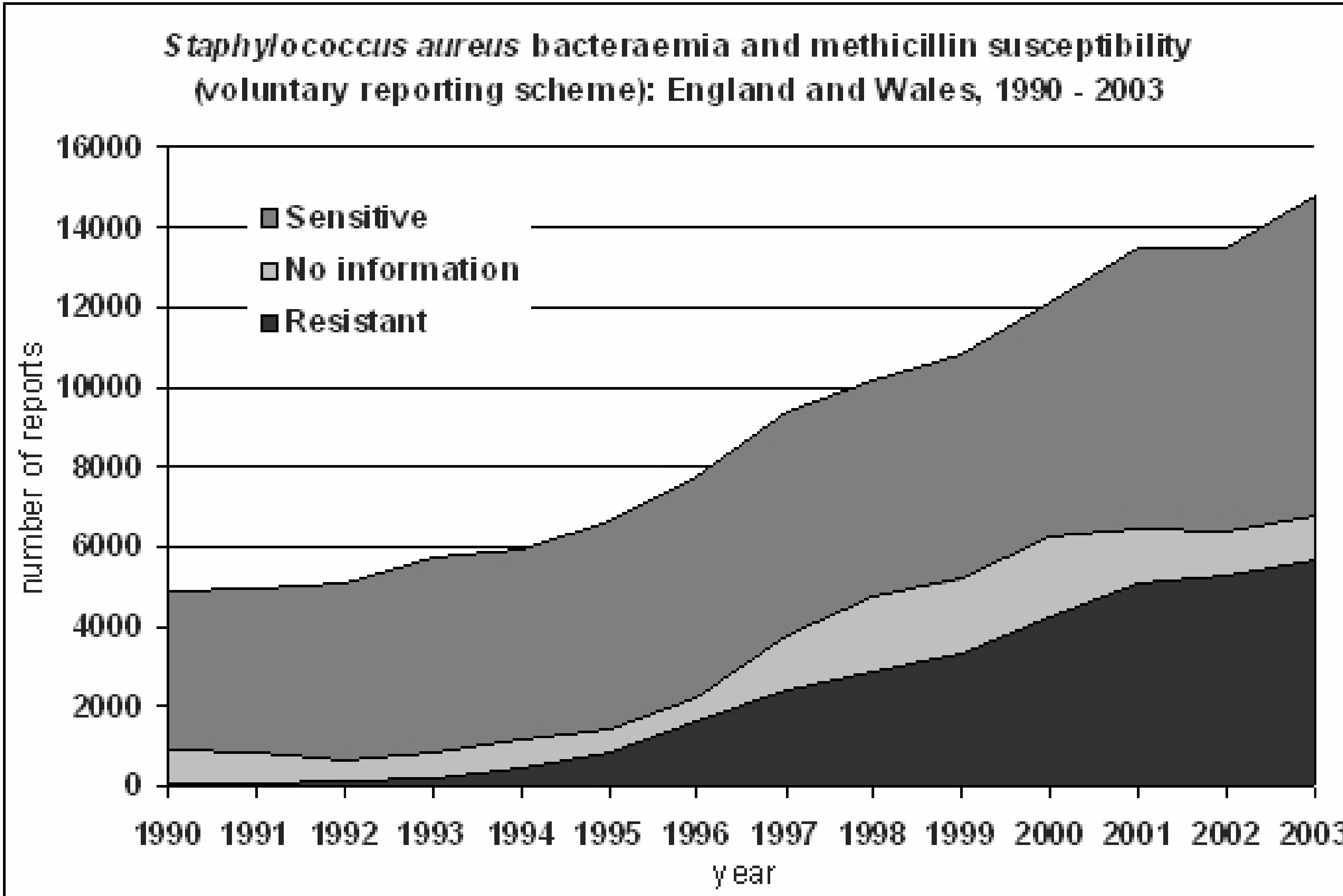


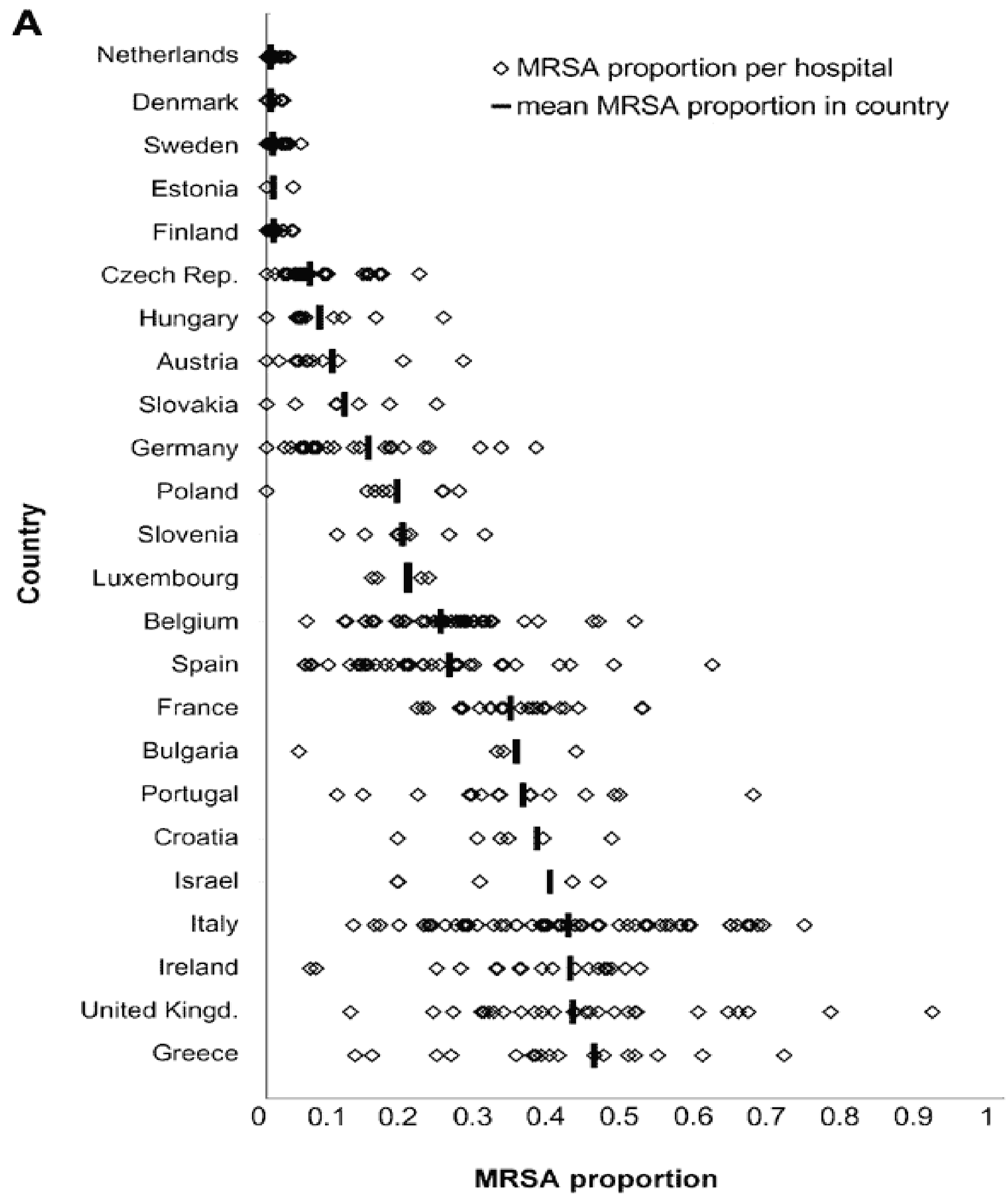
Fig. 1 Annual changes in the proportion of Methicillin-resistant *Staphylococcus aureus* (MRSA) in all *Staphylococcus aureus* isolates from most general hospitals in Japan. A rapid increase in MRSA has been observed since the early 1980s, reaching a rate of about 60%.

H. KITAJIMA; Peds Intern 2003; 45: 238-45

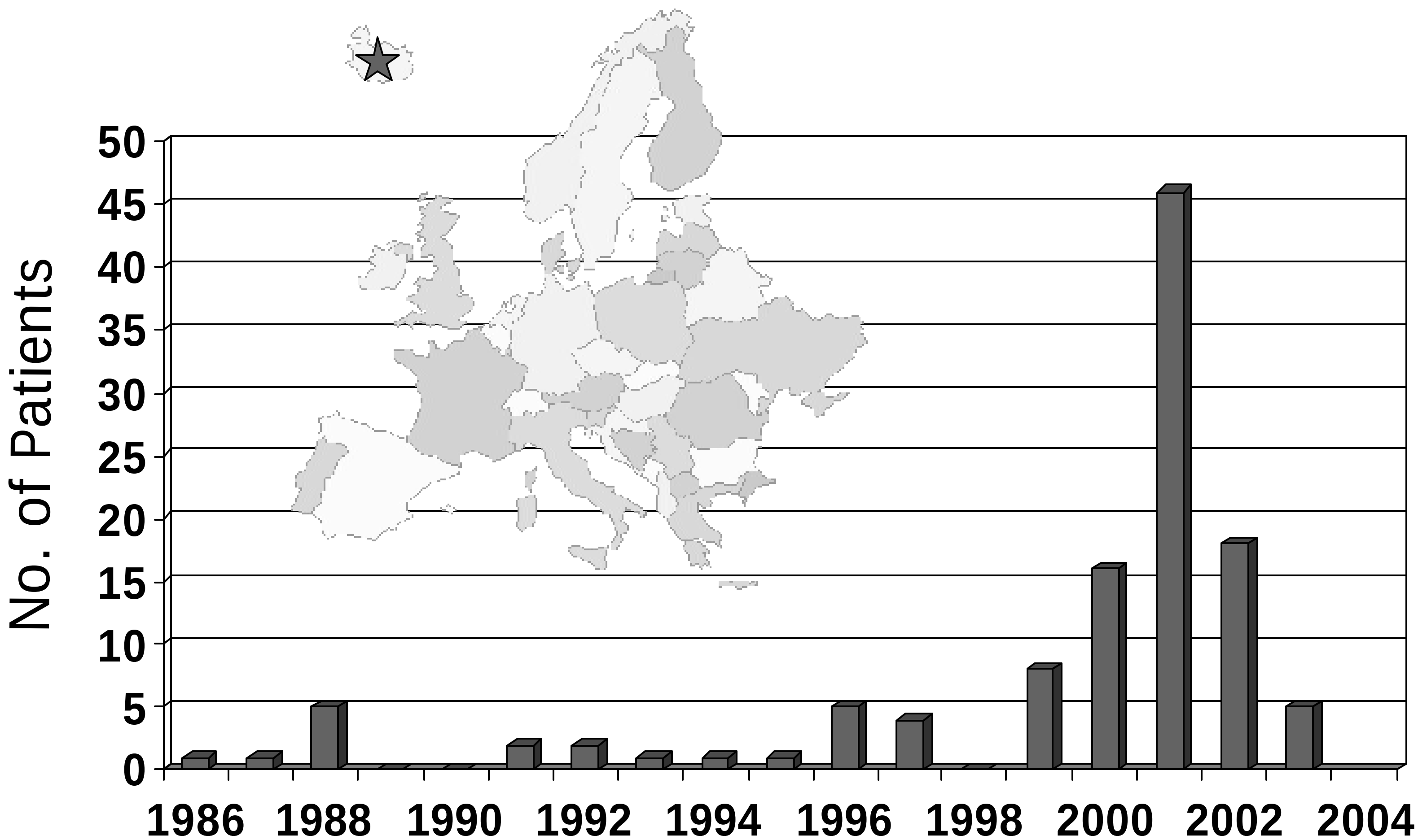


Staphylococcus aureus bacteraemia and methicillin susceptibility (voluntary reporting scheme): England and Wales, 1990 - 2003
Sensitive
No information
Resistant
number of reports
16000
14000
12000
10000
8000
6000
4000
2000
0
1990
1991
1992
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
2003
year

Methicillin-resistant *Staphylococcus aureus* in Europe, 1999–2002

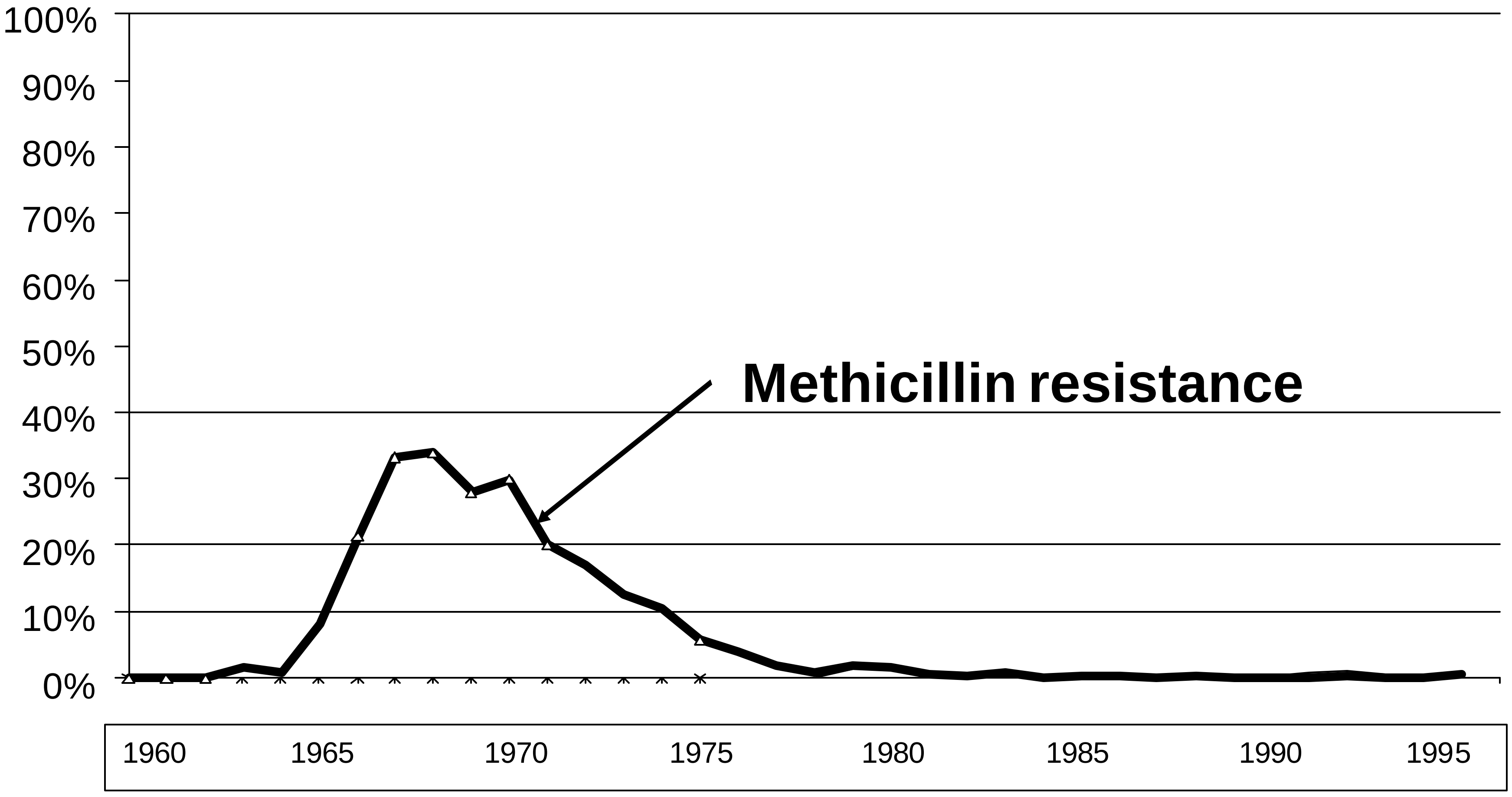


MRSA in Iceland 1986-2004



O. Gudlaugsson, H. Hardardottir, unpublished data

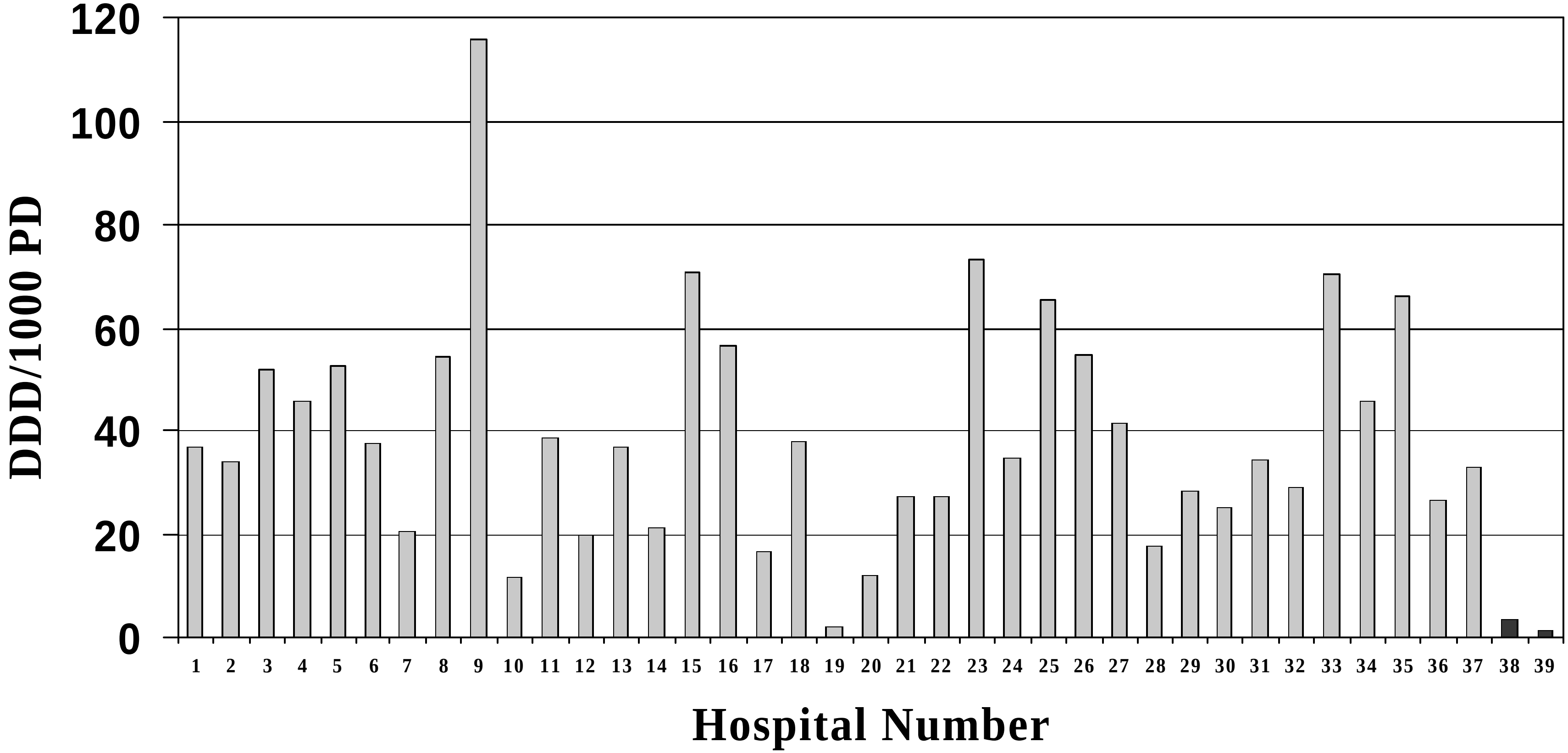
Antimicrobial Resistance in *Staphylococcus aureus* Blood Isolates, Denmark 1960-1995



DANMAP Report, 1997.
Rosdahl VT et al. Infect Control Hosp Epidemiol 1991;12:83-88.

Vancomycin Use

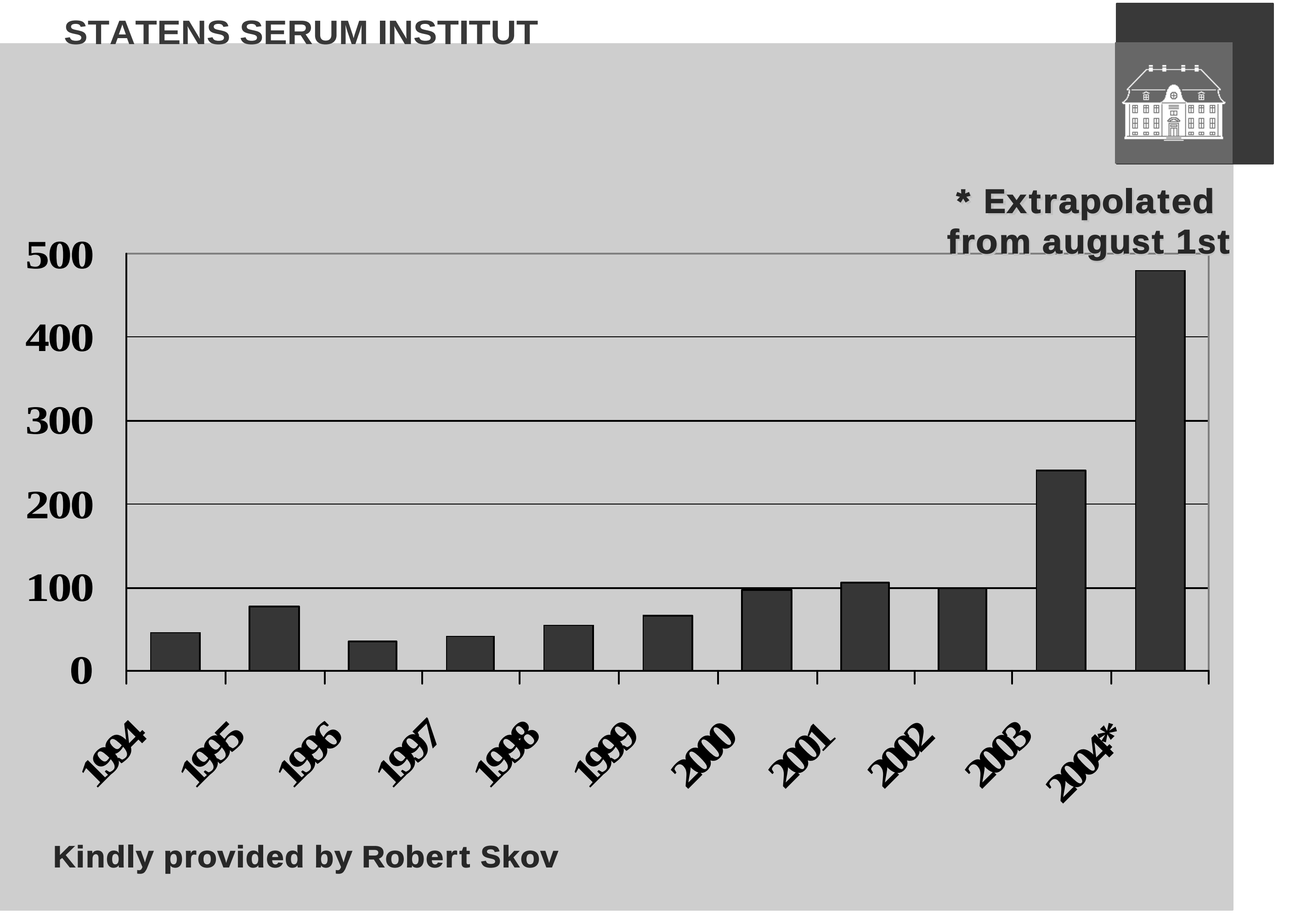
SCOPE MMIT Network vs. 2 Danish Hospitals



Courtesy: R. Polk

Jensen, Intern J Antimicrob Agents 1999

Vigilance is Important



Is this remarkable variation due to:

- Transmissibility and virulence of distinct genotypes?
- Size, design, or type of hospital?
- Case mix?
- Practice variation?
  - Compliance with known, measurable evidence based practices?
  - Less tangible features, such as culture and organization of an intensive care unit?
    - Are nosocomial infections an “expected” consequences of caring for very sick, complex patients, or intolerable, potentially preventable adverse events
      - Vermont Oxford NICQ visits to “best of breed” NICUs

Nosocomial vs. Community-Acquired MRSA

MW 2	**N 315, Mu50**
Faster growth in vitro	
18 toxins on allelic forms of genomic islands (Panton-Valentine Leukocidin) 16 superantigen genes; more potent lymphocyte proliferation	
Bacteriocin	

CA-MRSA
Reemergence of an Old Menace?

- Genotypic similarity to phage type 80/81a
  - Pandemic in the 1950s
  - Severe nursery outbreaks
- Strains of 80/81a from the 1950s/60s and contemporary CA-MRSA generally have Panton-Valentine Leukocidin (PVL)

CA-MRSA Now Worldwide and Encroaching on Hospitals

- Reports of outbreaks in hospitals seeded from the community
  - Saiman et al., Clin Infect Dis 2003;37:1313 (NY Presbyterian Hospital, post-partum infections)
  - Carleton et al., J Infect Dis 2004;190:1730 (San Francisco General Hospital, ST8:S)
- Many community outbreaks

CA-MRSA Community Outbreaks

- First detected as clusters of abscesses
- Various settings
  - Sports participants: Football, wrestlers, fencers, rugby players
  - Prisons
  - Men who have sex with men
  - Military recruits
  - Daycare centers

Risk Factors, College Football Team Outbreak

- Contact positions (cornerbacks, wide receivers)
- Artificial turf burns
- Body shaving
- Whirlpool use (inadequate disinfection)
- Playing with open wounds
- Towels washed in 44.4C water, not 71C
- No soap in showers

Begner et al., Clin Infect Dis 2004:39:1446

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What Can We Learn from the Experience of Other Countries?

- Dutch (Northern European) “search and destroy”
  - All patients with MRSA isolated in private rooms
  - Patients from foreign hospitals, suspected MRSA carriers screened (nose, throat, perineum, sputum, urine, wound); quarantined until –
  - If patient +, healthcare workers and roommates screened
  - Positive patients, healthcare workers decolonized with mupirocin and cholorhexidine (90% success, but 25-50% recolonized 3-6 months)
    - New agents being developed
  - 1 patient or healthcare worker colonized with same strain as index patient, ward closed, + healthcare workers sent home, patients isolated/cohorted
  - Advance warning if colonized patient transferred to another hospital
- How applicable is this approach once MRSA is highly endemic?

American "search and destroy" SHEA Guideline

- Screening on admission for "high risk" patients (principally nose)
  - Real-time PCR tests quite promising
- Weekly screening for "high risk" patients (specific wards, long-term antibiotics, long stay, underlying diseases)
- Facility-wide screening if "high" rates of MRSA
- Isolate/cohort colonized patients (contact +/- masks)
  - But be careful – these patients tend to be colonized with other resistant organisms!
- "Consider" eradication of colonization, but not if endemic
- Flag colonized patients
- Antibiotic stewardship

American "search and destroy" SHEA Guideline

- – Is this approach supported by the highest level of evidence?
  - Many longitudinal studies showing reduction in colonization
  - Many examples of staph outbreak control
  - At least 1 study with no spread despite continuous introductions of MRSA but no search and destroy (Nijjsen, CID 2005;40:405)
- – Can results of outbreak investigation and control be extrapolated to endemic MRSA?
- – Is this approach cost-effective?
- – US cluster randomized ICU trial

Olga’s Story

- What if we had known?
  - Would screening have permitted decolonization prior to surgery?
  - Would detection and decolonization have prevented infection
  - Would alternative prophylaxis changed the outcome?

Antimicrobial Prophylaxis: Can Eradication of Nasal Carriage Reduce SSI Risk?

- Early studies showed no benefit, but agents used were relatively ineffective in eliminating nasal carriage

Mupirocin Prophylaxis

- Evidence of efficacy in hemodialysis and peritoneal dialysis
  - Mupirocin resistance a concern

Randomized Trial of Mupirocin + Chorhexidine Shower

Nasal carriage eliminated in 83.4% mupirocin v. 27.4 placebo (p<0.001)

- Surgical site infection 7.9% v. 8.5% (n.s.)
- *S. aureus* surgical site 2.3% v. 2.4% (n.s.)
- In nasal carriers:
  - Any nosocomial staph infection (mainly SSI) 4.0% v. 7.7% (OR 0.49, 95% ci 0.25-0.92)
  - 84.6% PFGE match between nose and SSI staph strains
  - Trivial mupirocin resistance
- Foiled by low infection rate, 'wrong' primary outcome, large number of infections from nosocomial strains

Perl, NEJM 2002;346:1871

Randomized trial of Mupirocin in Non-surgical patients

- Mupirocin *S. aureus* nosocomial infection rate 2.6%, placebo 2.8%
- 77% of infections due to endogenous strains

Weinstein, Ann Intern Med 2004;140:419

Key Strategies

- Know the MRSA burden in each hospital (colonization, not just infection)
  - Knowledge is a pre-requisite for informed discussion
  - This requires screening cultures
  - The problem often is greater than it seems

Clean hospitals are important but not sufficient!

Lack of isolation beds or space for cohorting is no excuse!

Key Strategies

- Improve reliability of basic procedures
  - “Defect rates” of 60-80% are not tolerable
    - Screening cultures
    - Isolation Procedures
    - Hand hygiene

Tip

- A large portion of the CDC and NHS goals to reduce MRSA bloodstream infections by 50% can be achieved by reducing central venous catheter infections
  - VAP reduction would be a plus

New Approaches to Prevention -- Vaccines/Immunoglobulins

MSCRAMM polyclonal, monoclonal antibodies (Inhibitex)

- microbial surface components recognizing adhesive matrix molecules

- Anti-lipoteichoic acid (LTA) (Biosynexis)
- Anti-poly-*N*-acetyl glucosamine, PIA
  - Adhesin, capsular polysaccharide
  - Common to *S. aureus* and *S. epidermidis*
- C5, C8 capsular polysaccharide vaccine (NABI)
  - Just failed and studies discontinued

Vancomycin-Resistant Enterococci (VRE)

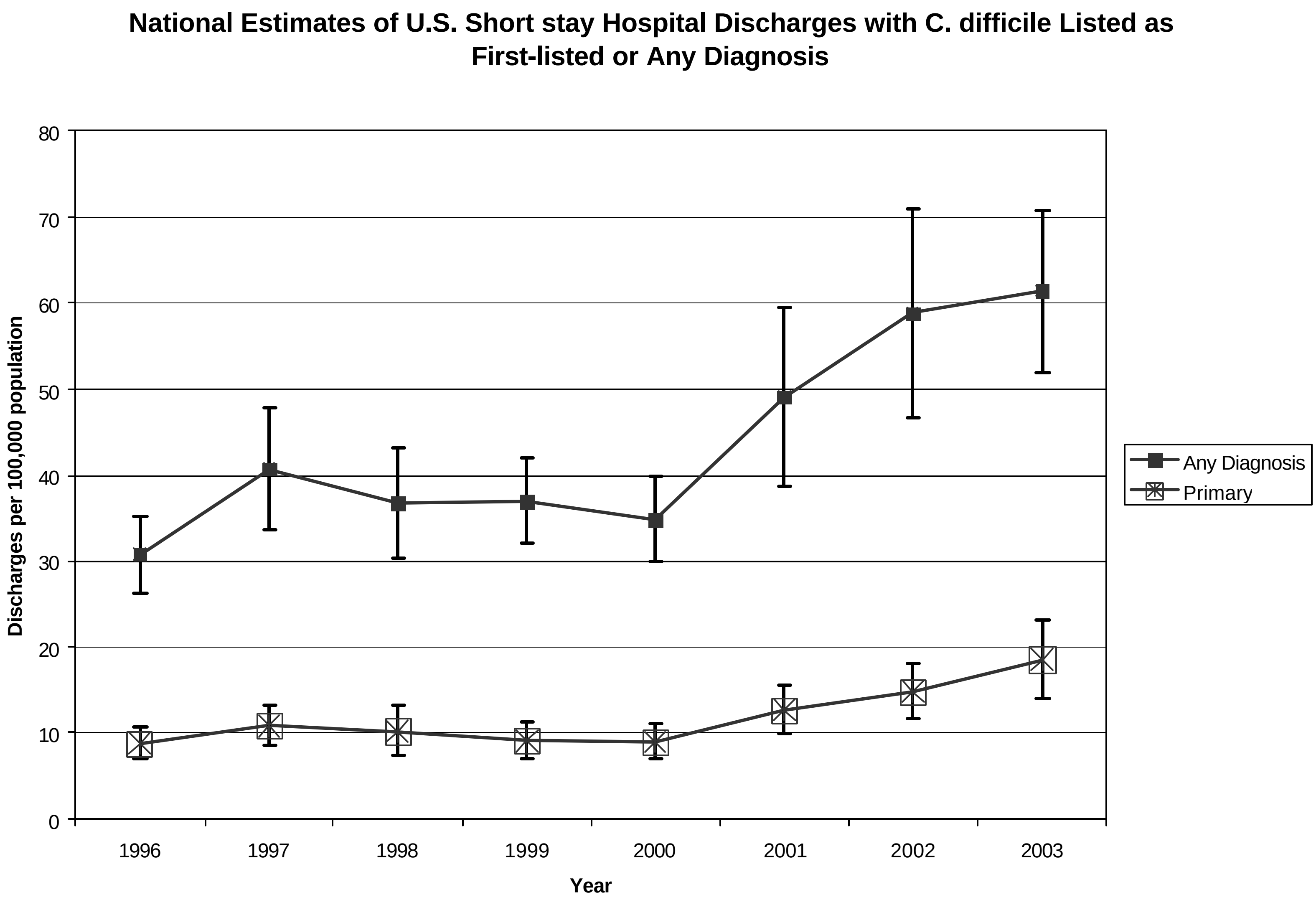
- The promiscuous vanA gene
  - Transposons
  - The fertile soil of the GI tract
- Environmental survival
- Aminogycoside and beta-lactam resistance compounds the problem…
- Multiple selective pressures
  - Vancomycin
  - Cephalosporins
  - Metronidazole
- Mathematical models suggest infection control is key

Mathematical Models of Transmission of Antibiotic Resistant Bacteria Tell a Clear Tale for MRSA and VRE

- Transmission is related to the rate of introduction of patients colonized with resistant strains
  - Screen for colonization
- Transmission is related to the number of clinician-patient encounters
  - Have adequate nurse:patient ratio
- Antibiotic control has little value if barrier technique and hand hygiene compliance is not very high
  - Improve compliance dramatically

Clostridium difficile

- Virtually any antibiotic can be a risk factor
- Hardy in the environment
  - Broadly disseminated by patients with diarrhea or incontinence
- Diagnostic tests are quite sensitive
  - But “negative” patients can turn positive with re-introduction of antibiotics
- Alcohol is not ideal!


National Estimates of U.S. Short stay Hospital Discharges with C. difficile Listed as First-listed or Any Diagnosis
Discharges per 100,000 population
80
70
60
50
40
30
20
10
0
1996
1997
1998
1999
2000
2001
2002
2003
Year
Any Diagnosis
Primary

Multivariable Model of Risk Factors for C. diff in Cases (n=59) versus Controls (n=118)

Risk Factor	mOR*	P value	Confidence Interval
Gastric acid suppressors	8.2	0.004	1.9 – 35.2
Cephalosporins	5.8	0.002	1.8 – 17.9
Fluoroquinolones	4.6	0.025	1.2 – 17.6
Length of stay (days)	1.2	<0.01	1.1 – 1.3

* Matched odds ratios are based on multivariate conditional logistic regression - PHREG.

New “Super” Strains of C. *diff.*

- Clonal spread in Canada and other countries
- Genes for toxin production de-repressed
  - 10-fold higher rates of toxin production
  - Increased virulence
- Soaring use of (expensive) oral vancomycin ($800 per course!)
- ?? Correlation with alcohol hand rub use (probably not valid)

C. diff in Low-Risk Populations

- Community-acquired
  - Pregnancy and childhood
- Limited, remote, or no exposure to antibiotics
- Contact transmission
- High rate of recurrence
- Binary toxin-positive (2 strains)

MMWR, December 2, 2005 / 54(47);1201-1205

Hand Hygiene Agents

- Soap and water
- Water plus
  - Chlorhexidine gluconate
  - Povidone iodine
  - PCMX
  - Triclosan
- Alcohol-based waterless rubs, gels and rinses

Hazard Analysis and Critical Control Point (HACCP)
aka Failure Modes and Effects Analysis

- A system that identifies and monitors specific foodborne hazards that can adversely effect the safety of a food product
- Pioneered by Pillsbury in cooperation with NASA, US Army, and US Air Force Space Laboratory
- In early 1960s, created food for astronauts that approached 100% assurance against contamination

Hazard Analysis Process

For each step in the flow diagram, ask a series of questions appropriate to that step, such as:

- Are practice parameters clear?
- Are necessary supplies readily available?
- Is the system (both facility and equipment) designed so that correct actions are feasible?
- Are personnel adequately trained?
- Are personnel verified as competent in the procedure?
- Do personnel have the time to perform the task correctly?
- Can correct performance of the task be verified?

Then….

- Develop preventive measures at each critical control point
- Determine critical limit for each control point and develop routine monitoring plan
- Use QI methods to design corrective action when critical limit has been exceeded

Critical Control Points in Hand Hygiene and Barrier Technique

- Precautions followed when patient on isolation?
- Hand hygiene prior to initial patient contact?
- Gloves donned as per "standard" precautions?
- Hand hygiene before inserting/manipulating invasive device (e.g., IV catheter connection)?
  - Hand hygiene performed when going from contaminated to clear body site?
- Hand hygiene after gloves removed?
- Hand hygiene when leaving bedside?
  - Including after touching potentially contaminated objects or surfaces?

A Hand Hygiene "Bundle"?

- Staff knowledge
- Staff competency
- Alcohol and gloves available at the point of care
  - Operational, full dispensers providing correct volume of rub
  - At least 2 sizes of non-latex gloves
- Correct performance of hand hygiene
- Gloves worn for standard precautions

The behavioral change literature suggests that multi-faceted approaches have the best chance of succeeding…

Antibiotic Stewardship

Strategies to Change Antibiotic Utilization Practice

- Education
- Clinical practice guidelines
- Formulary restriction
- Selective antibiotic reporting (dangerous?)
- Standardized order sets
  - Order sets with pre-approved indications (best if part of computerized physician order entry)
- Pharmacy substitution/switch; protocol-driven IV/PO switch
- Academic detailing, opinion leaders (tool kits)
- Provider/unit specific utilization feedback (“audit and feedback”)

Strategies to Change Antibiotic Utilization Practice

- Multi-disciplinary antibiotic stewardship (*Gross et al, Clin Infect Dis 2001:33:289*)
  - Multi-disciplinary drug utilization evaluation
- Therapeutic de-escalation
- Computer-assisted antibiotic management + CPOE
  - LDS experience (*Mullett et al, Pediatrics 2001;108:E75; Glowacki et al., Clin Infect Dis. 2003;37:59)*
- Antibiotic cycling
  - Best data with aminoglycosides
  - Pip-tazo/ceftaz did not work (*Toltzis et al, Pediatrics 2002;110:707*)

Antibiotic Stewardship?

- Important, but….
  - Evidence of impact on resistance is still weak
    - Evidence that resistance will disappear even with drastic reduction of use is mixed
      - Good news with Group A strep/macrolides; VRE in animals
  - Not well supported by mathematical models in the absence of pristine infection control (VRE, MRSA)
  - Choices are limited, especially when bacteria have multiple resistance determinants
    - “Squeezing the balloon”
    - Hard to design antibiotic cycling regimens
  - Clinicians are afraid to scrimp -- justifiably

High Quality Studies Supporting Antibiotic Stewardship – Few and Far Between

- Systematic review using Cochrane Criteria
  - 1980 to present
- 91/306 (30%) papers met minimum inclusion criteria
- Reasons for exclusion:
  - Uncontrolled before/after design (141)
  - Interrupted time series analysis (74)
    - Not enough data points
    - No statistical analysis
    - Incorrect statistical analysis

Ramsay et al., J Antimicrob Chemother 2003;52:764)

Sobering Conclusions

- High quality studies are sparse
- Data are insufficient to know what strategies really work
- Impact on the major outcomes of interest – rate of antibiotic resistance and antibiotic-resistant infections – is unclear

Therapeutic De-escalation

- Rationale
  - Initial therapy must not miss resistant pathogens because inappropriate empiric therapy is associated with increased mortality
  - Modern blood culture methods generally yield results in 48 hours, permitting early d/c of antibiotic if no pathogen is isolated
    - Or change of antibiotic to appropriate agent if isolate is resistant
    - Most labs can give a preliminary same-day result
  - De-escalation only is possible if initial diagnostic work up is optimal

Adequate vs Inadequate Antimicrobial Therapy in the ICU

	Inadequate Tx* (n = 169)	Adequate Tx* (n= 486)	*P*
Organ systems fail	2.5 ± 1.5	1.9 ± 1.4†	<.001
Hospital length of stay	22.8 ± 25.7	20.0 ± 25.8	.221
ICU length of stay	10.2 ± 10.2	7.1 ± 8.2†	<.001
Duration of mechanical ventilation	11.1 ± 10.6	7.6 ± 9.2†	<.001
Mortality rate, infection related	42.0%	17.7%	<.001

* Values are given as mean ± SD days
†*P*<.05

Kollef, et al. *Chest.* 1999;115:462–475.

Implications

- Start aggressively
  - Lessons/perils of the “sepsis bundle”
    - Reduced mortality by prompt institution of Rx covering potential pathogens
    - Potential overuse of drugs like vancomycin
- De-escalate promptly when negative culture results available

  and/or

- Change regimen to appropriate antibiotics according to susceptibility results
- Consider shorter courses in general (e.g., pneumonia)

When Treating, Know the Drug's Pharmacokinetics and Pharmacodynamics

- You only get one chance! Failure to hit the mark costs lives
- Beta-lactams and vancomycin are time-dependent drugs
- Aminoglocosides are concentration dependant
- Quinolones: AUC/MIC

Collaboration with the Micro Lab is Critical

- Ward-specific resistance data should be provided at least quarterly
  - Culture site and organism-specific
- Establish “critical values” for immediate notification so isolation and further investigation will be prompt
  - MRSA, VRE, 3rd generation GNB cephalosporin and aminoglycocide resistance
- Jointly watch for outbreaks
  - Even a few cases of Pseudomonas, Stenotrophomonas, Burkholderia, Serratia, Enterobacter, etc are cause for alarm

Clinical Cultures are the Tip of the Iceberg

- Routine screening can provide early detection of colonized patients, permitting targeted empiric antibiotic therapy
- Examples of patients to screen:
  - transfers from other institutions (they may have a resistance problem you do not have)
  - transfers from chronic care facilities
  - previous hospitalizations (flag charts)
  - complex medical conditions or medical devices
  - other risk factors (healthcare worked in home, antibiotic exposure)
- Weekly screening of patients in high risk wards for >48 hours
    - Antibiotic resistance screening should be guided by local resistance patterns

Accurate Diagnosis is the Key to Confident De-escalation

Improve Culture Procedures and Response to Culture Results

- Contaminated blood cultures
- Inappropriate volume of blood
- Sole through-the-line cultures
  - Include a second culture from a peripheral site whenever possible
- Poor quality sputum
  - Consider mini-bronch BAL
- Underutilization and misunderstanding of adjunctive tests (e.g., CRP, procalcitonin)
  - Importance of prior probability
- Failure to change antibiotics immediately based on reports of antibiotic resistance

Improve Laboratory Reporting

- Reporting not timely
- Reporting to individuals who are not responsible for prescribing
- Inappropriate reporting (30% of blood cultures *Diekema et al. J Clin Micro 2004;42:2258-60)*
  - Inclusion of inappropriate drugs
  - Misleading susceptibility interpretations
- Confusing, user unfriendly computer reporting formats

Impact of Antibiotic Order Form on Surgical Prophylaxis

Paradoxical Effect of Antibiotic Order Form with Pre-Approved Indications

- Standardized antibiotic order form with pre-approved indications
- Vancomycin pre-approved indications based on HICPAC slightly modified for pediatrics
  - Check boxes for pre-approved indications
  - Infectious Disease fellow approval required for other indications

Bolon et al, PIDJ

Antibiotic Order Form with Pre-Approved Indications

- 145 (63%) had indication for use checked
- 13 handwritten note stating ID approval
- 18 handwritten notes that vancomycin was for febrile neutropenia, not a pre-approved indication

Appropriateness of Vancomycin Use

65% pre-intervention period

61% post-intervention period

49% improved intervention period ($p<0.01$)

- Increased use of vancomycin in post-intervention period ($p<0.01$); no change in improved intervention period
  - Mirrored by increase in use of piperacillin-tazobactam, which also had pre-approved indications
- Very frequent prolonged courses of vancomycin without justification (no de-escalation)
  - No automated stop order in place)

Root Cause Analysis

- HICPAC guidelines not revised in a decade
  - Oncology and stem cell protocols encourage vancomycin for viridans strep coverage
  - SCCM sepsis protocols stress broad coverage
  - Increasing MRSA
  - Increasing concern about coag-neg staph foreign body infections
- Underestimation of resources required to achieve good compliance and appropriate use of form
- Replacement of “antiquated” and labor intensive system of ID fellow approval and faculty review
  - Circumvention of infectious diseases expertise

Manipulation of Antibiotic Order Form

Pseudo-Outbreak of Nosocomial Pneumonia in Virginia

Computerized Antimicrobial Decision Support

	1988	1994
Medicare case-mix index	1.7481	2.0520
Hospital mortality	3.65%	2.65%
Antimicrobial cost per treated patient	$122.66	$51.90
Properly timed preop. antimicrobial	40%	99.1%

- Stable antimicrobial resistance
- Adverse drug events decreased by 30%

Source: Pestotnik SL, et al: Ann Intern Med 1996;124:884-90

Computerized antibiotic assistant: LDS hospital

- Significant reductions in:
  - Orders for drugs with reported allergies (35 vs. 146)
  - Excess drug dosages (87 vs.405)
  - Antibiotic-susceptibility mismatches (12 vs. 206)
  - Mean number of days of excessive dosages (2.7 vs. 5.9)
  - Adverse events (4 vs. 28)

Evans et al. N Engl J Med 1998; 338:232-8

Detection of Prescribing Errors: Regimens with Redundant Antimicrobial Spectra

- 1189 inpatients receiving two or more antibiotics
- Computer-assisted screening identified 192 potentially redundancy (16%; range 9-31% per observation day)
- 137/192 (71%) were considered inappropriate (11.5% of total)
- MD over prescribing error found in 77 (55%) episodes (mostly gram-positive and anaerobic) and hospital drug distribution errors equally prevalent
- Interventions accepted in 100/104 cases
- Potential annualized cost saving of $48,000

Glowacki RC, et al. CID 2003;37:59-64.

Antimicrobial Management/Stewardship Programs and Improved Patient Care

- Randomized trial at University of Pennsylvania where patients got antibiotics with input from the antimicrobial management program or “usual practice” (whatever the prescriber asked for)

Antimicrobial Management Program (AMP) vs Usual Practice

Outcome	AMP	Non-AMP	RR (95%CI)
Agent appropriate	90%	32%	2.8 (2.1-3.8)
Cure	91%	55%	1.7 (1.3-2.1)
Failure*	5%	31%	0.2 (0.1-0.4)

Failures: clinical, microbiologic, superinfection, antibiotic change, ADR, recurrence