Antimicrobial Resistance and the "Ying and Yang" of its Prevention

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Objectives

- Describe the roles of infection prevention in antimicrobial resistance
- Discuss the "dual" and symbiotic relationship between both strategies to combat antimicrobial resistance

Disclosures

- Medimmune (grant), Merck and Pfizer (advisory board), Pfizer (advisory board), Merck (grant)
- CIDRAP Advisory Board

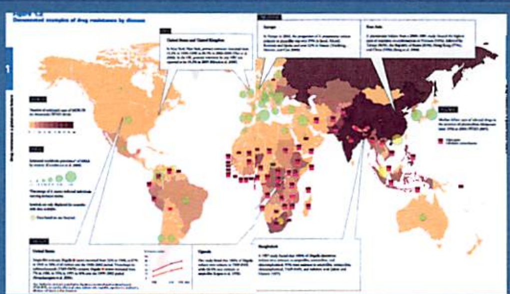
Why We Need to Do Something?

- Prevalence of multidrug-resistant gram-negative, Gram positive and other bacteria increasing worldwide
- Considerable morbidity and mortality from infections with MDR organisms
- Few antibiotics in development to treat these infections
  - use of older antibiotics previously discontinued because of toxicity
- Vulnerable patients at most risk
- Costly to patients and the healthcare system

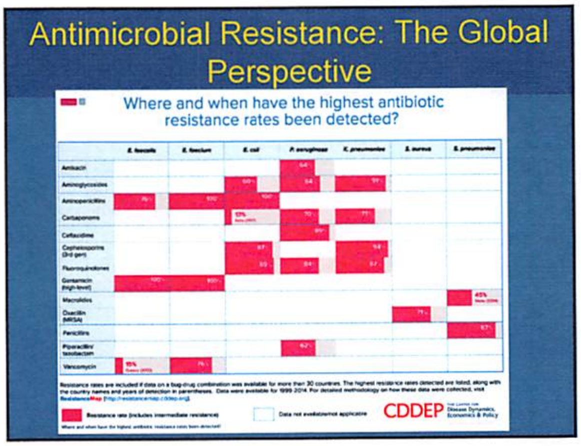
How Bad is Resistance and is it Increasing?

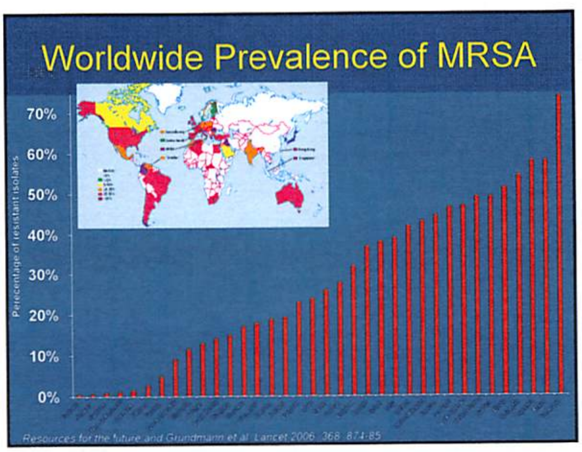
It was on a short-cut through the hospital kitchens that Albert was first approached by a member of the Antibiotic Resistance.

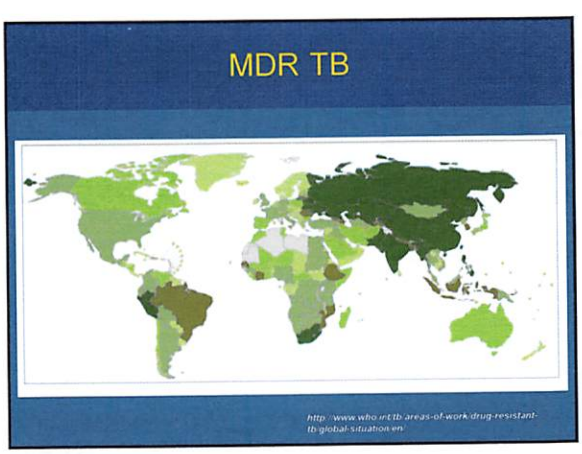
The World of Antimicrobial Resistance

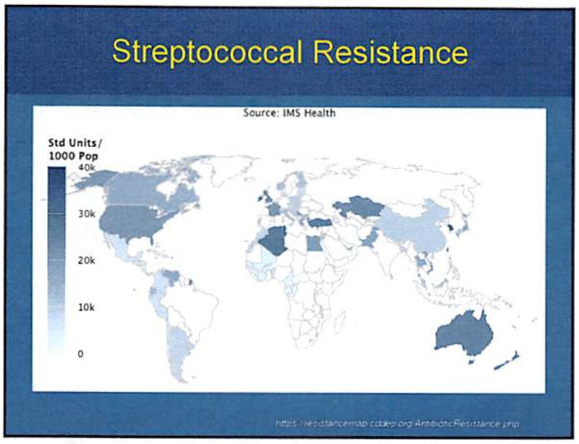


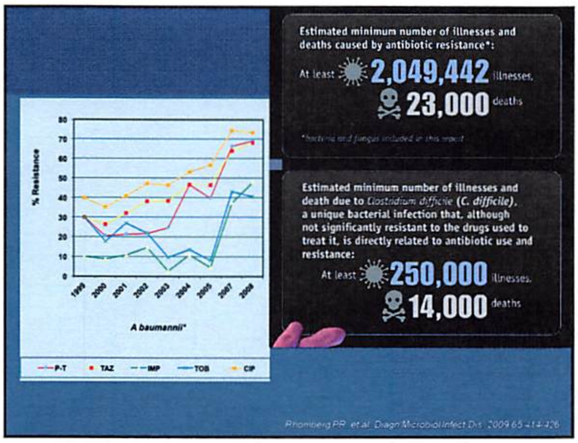
https://www.cgdev.org/files/1424207_file_CGD_DRWG_FINAL.pdf

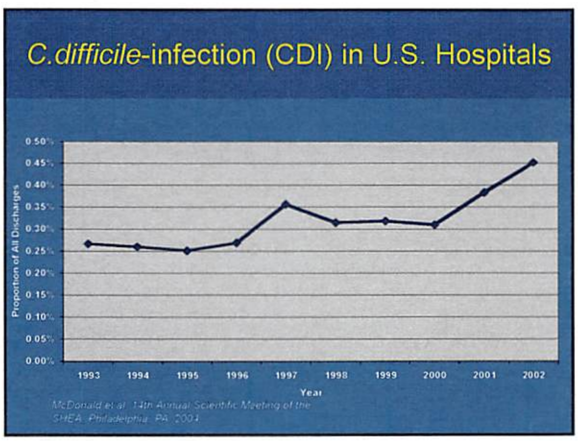

Antimicrobial Resistance: The Global Perspective
Where and when have the highest antibiotic resistance rates been detected?
E. faecalis
E. faecium
E. coli
P. aeruginosa
K. pneumoniae
S. aureus
S. pneumoniae
Amikacin
Aminoglycosides
Aminopenicillins
Carbapenems
Ceftazidime
Cephalosporins (3rd gen)
Fluoroquinolones
Gentamicin (high-level)
Macrolides
Oxacillin (MRSA)
Penicillins
Piperacillin/ tazobactam
Vancomycin
Resistance rate (includes intermediate resistance)
Data not available/not applicable
CDDEP
Disease Dynamics, Economics & Policy


Worldwide Prevalence of MRSA
70%
60%
50%
40%
30%
20%
10%
0%
Percentage of resistant isolates
Resources for the future and Grundmann et al. Lancet 2006 ; 368: 874-85


MDR TB
http://www.who.int/tb/areas-of-work/drug-resistant-tb/global-situation/en/


Streptococcal Resistance
Source: IMS Health
Std Units/
1000 Pop
40k
30k
20k
10k
0


% Resistance
80
70
60
50
40
30
20
10
0
1999
2000
2001
2002
2003
2004
2005
2007
2008
A baumannii*
P-T
TAZ
IMP
TOB
CIP
Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:
At least 2,049,442 illnesses,
23,000 deaths
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
Rhomberg PR et.al. Diagn Microbiol Infect Dis 2009 65 414-426


C.difficile-infection (CDI) in U.S. Hospitals
Proportion of All Discharges
0.50%
0.45%
0.40%
0.35%
0.30%
0.25%
0.20%
0.15%
0.10%
0.05%
0.00%
1993
1994
1995
1996
1997
1998
1999
2000
2001
2002
Year
McDonald et al. 14th Annual Scientific Meeting of the SHEA, Philadelphia, PA, 2004

Increasing Antimicrobial Resistance Among Gram Negative Organisms

- *Shigella spp.*
- *N. gonorrhea*
- Enterobacteraciae
- *Pseudomonas aeruginosa*
- *Acinetobacter baumannii*
- *Escherichia coli*
- *Berkholderia cepacia*
- *Ralstonia picketii*
- *Stenotrophomonas maltophilia.*
- *etc*

Worldwide Expansion

- France: 2005. KPC2 in a *K. pneumoniae* from a patient who has been in New York for medical treatment
- Colombia: 2006
- Israel: 2007
- China: 2007
- Greece: 2008
- France: 2009

Plasmid-Mediated Carbapenem-Hydrolyzing β-Lactamase KPC in a *Klebsiella pneumoniae* Isolate from France

First Detection of the Plasmid-Mediated Class A Carbapenemase KPC-2 in Clinical Isolates of *Klebsiella pneumoniae* from South America

Outbreak of carbapenem-resistant *Klebsiella pneumoniae* producing KPC-3 in a tertiary medical centre in Israel

Plasmid-Mediated KPC-2 in a *Klebsiella pneumoniae* Isolate from China[∇]

Plasmid-Mediated Carbapenem-Hydrolyzing β-Lactamase KPC-2 in *Klebsiella pneumoniae* Isolate from Greece[∇]

Infections with Extended-Spectrum beta-Lactamase-Producing Enterobacteriaceae

Pitout, Johann D.D. *Drugs.* 70(3):313-333, February 12, 2010. doi: 10.2165/11533040-000000000-00000

Fig. 1 Worldwide distribution of Escherichia coli that produce CTX-M-15 (grey shading).

The Resistance in *Enterobacteriaceae: β-lactamases*

T.R. Walsh / International Journal of Antimicrobial Agents 36S3 (2010) S8–S14

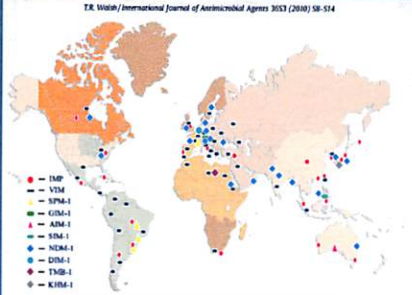
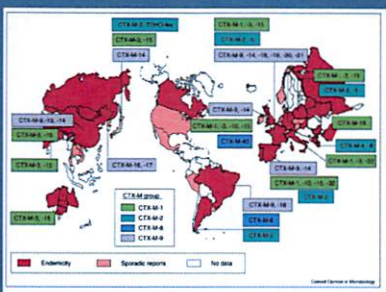


Fig. 3. Representation of the global distribution of mobile metallo-β-lactamases.

CTX β-lactamase Pandemic



Canton et al. Current Opinion Micro 2006 9 466-75

CTX β-lactamase Timeline

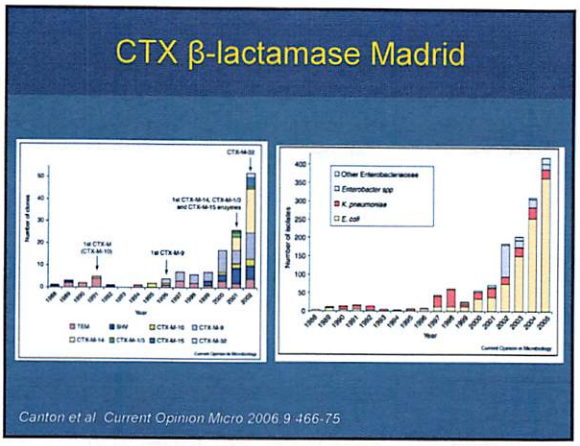
Table 1

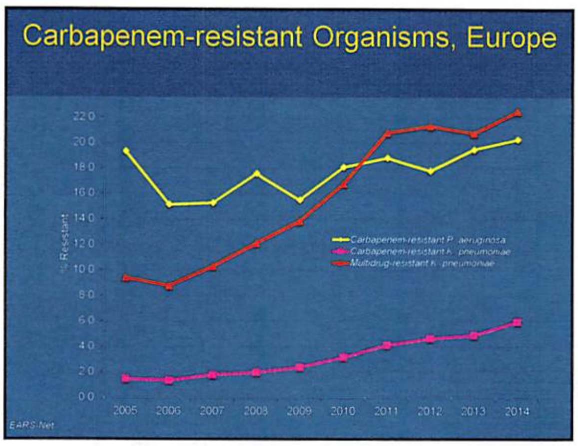
Different CTX-M clusters and origin of $bla_{CTX\text{-}M}$.

	CTX-M cluster				
	CTX-M-1	CTX-M-2	CTX-M-8	CTX-M-9	CTX-M-25
Year (enzyme, country)[a]	1989 (CTX-M-1, Germany)	1986 (FEC-1, Japan)	1996 (CTX-M-8, Brazil)	1994 (CTX-M-9, Spain)	2000 (CTX-M-25, Canada)
Enzymes	CTX-M-1, -3, -10, -11, -12, -15, -22, -23 -29, -30, -32, -33, -28, -36, -54, UOE-1	CTX-M-2, -4, -6, -7, -20, -31, -44 (previously TOHO-1), FEC-1	CTX-M-40	CTX-M-9, -13, -14, -16, -17, -18, -19, -24, -27, -45 (previously TOHO-2), -46, -47, -48, -49, -50,	CTX-M, -26, -25, -39, -41
Origin	*K. ascorbata*	*K. ascorbata*	*K. georgiana*	*K. georgiana*	ND

[a] Year of first isolation or description (first enzyme described and country of isolation); CTX-M-14 and CTX-M-18 are identical; ND: not defined.

Canton et al. Current Opinion Micro 2006 9 466-75


CTX β-lactamase Madrid
Other Enterobacteriaceae
Enterobacter spp
K. pneumoniae
E. coli
Canton et al Current Opinion Micro 2006 9 466-75


Carbapenem-resistant Organisms, Europe
22.0
20.0
18.0
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
% Resistant
Carbapenem-resistant P. aeruginosa
Carbapenem-resistant K. pneumoniae
Multidrug-resistant K. pneumoniae
2005 2006 2007 2008 2009 2010 2011 2012 2013 2014
EARS-Net

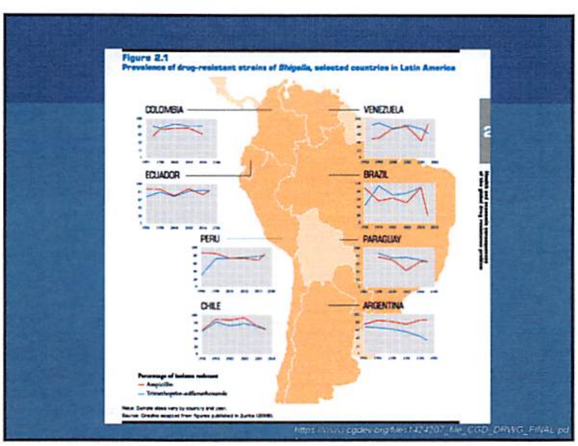
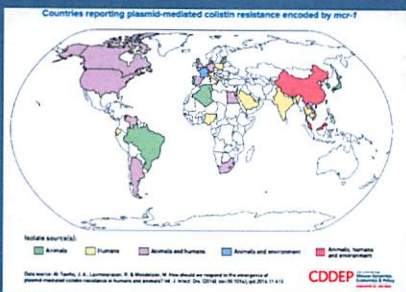


Figure 2.1
Prevalence of drug-resistant strains of Shigella, selected countries in Latin America
COLOMBIA
VENEZUELA
ECUADOR
BRAZIL
PERU
PARAGUAY
CHILE
ARGENTINA
Percentage of isolates resistant
Ampicillin
Trimethoprim-sulfamethoxazole

The New Kid on the Block



Deaths Due to Antimicrobial Resistance in Neonates

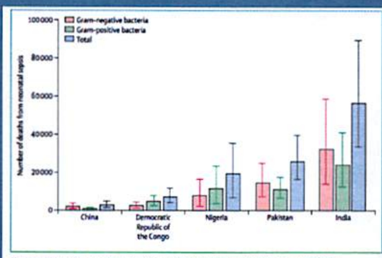


Figure 2: Estimated neonatal sepsis deaths caused by bacteria resistant to first-line antibiotics in five high-burden countries
Bars represent maximum and minimum values from Latin Hypercube Sampling model in appendix.

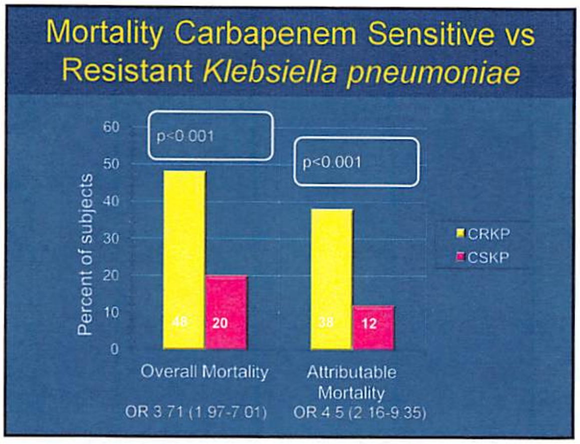
Laxminarayan Lancet 2015

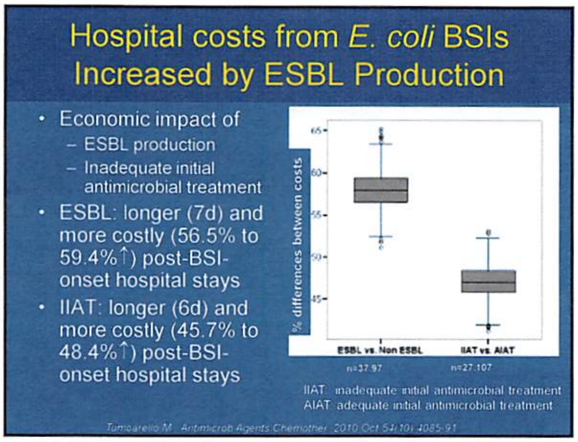
Adverse Outcomes Associated with Other Resistant Gram-Negative Organisms

Organism	Resistant to:	Mortality	Median LOS post culture
Enterobacter[1]	3rd-generation cephalosporins	5.02 (1.10–22.9)	1.47 (1.25–1.72)
P aeruginosa	imipenem	1.94 (1.22–3.10)	15.5 vs 9 days* (*P* = .02)
Acinetobacter[3]	MDR	2.6 (0.3–26.1)	2.5 (1.2–5.2)
All ESBL producers[4]	Beta lactams	1.85 (1.39-2.47)	

Multivariate RR or OR (95% CI) unless otherwise specified

1. Cosgrove SE, et al. Arch Intern Med. 2002;162:185-190. 2. Laudenbach E, et al. Infect Control Hosp Epidemiol. 2006;27:893-900. 3. Sunenshine RH, et al. Emerg Infect Dis. 2007;13:97-103. 4. Schwaber MJ, et al. J Antimicrob Chemother. 2007;60:913-920.





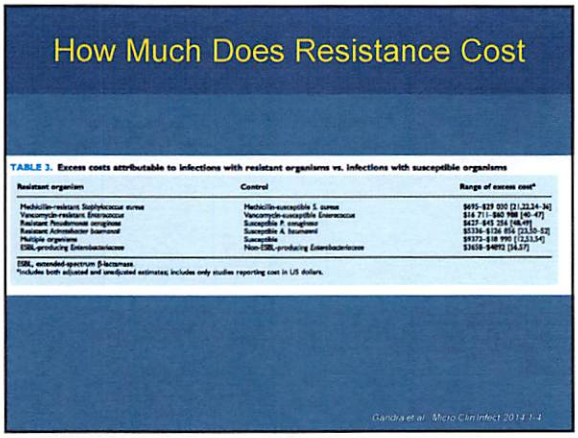


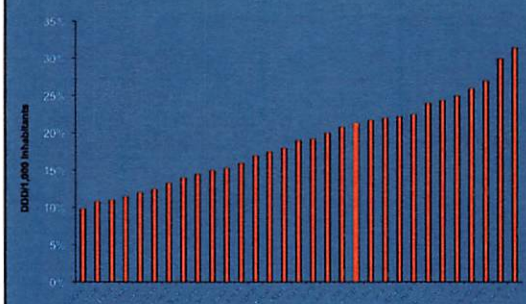
TABLE 3. Excess costs attributable to infections with resistant organisms vs. infections with susceptible organisms

Resistant organism	Control	Range of excess cost*
Methicillin-resistant *Staphylococcus aureus*	Methicillin-susceptible *S. aureus*	$695–$29 000 [21,22,24–36]
Vancomycin-resistant *Enterococcus*	Vancomycin-susceptible *Enterococcus*	$16 711–$60 988 [40–47]
Resistant *Pseudomonas aeruginosa*	Susceptible *P. aeruginosa*	$627–$45 256 [48,49]
Resistant *Acinetobacter baumannii*	Susceptible *A. baumannii*	$5336–$126 856 [23,50–52]
Multiple organisms	Susceptible	$9372–$18 990 [12,53,54]
ESBL-producing *Enterobacteriaceae*	Non-ESBL-producing *Enterobacteriaceae*	$3658–$4892 [56,57]

ESBL, extended-spectrum β-lactamase.
*Includes both adjusted and unadjusted estimates; includes only studies reporting cost in US dollars.

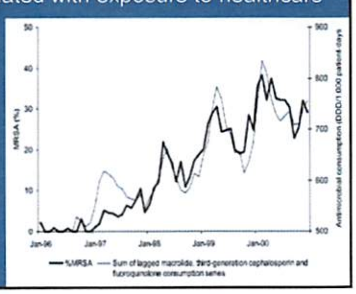
What Are the Drivers of Resistance?

Worldwide Antibiotic Use

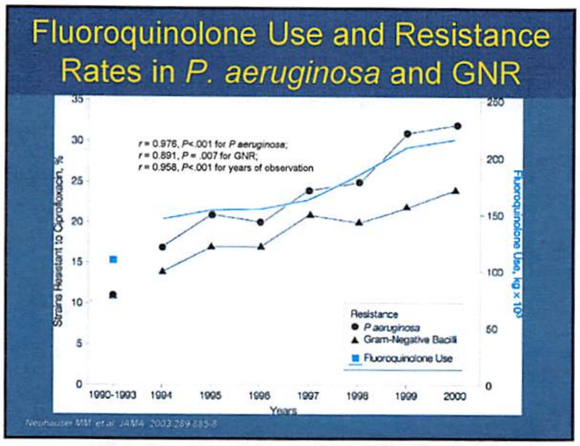


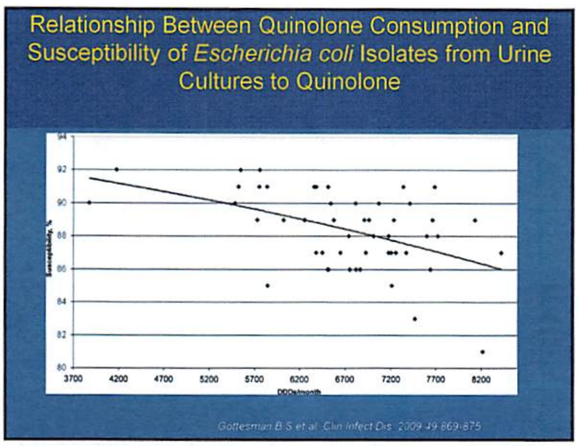
Does Antibiotic Use Increase MRSA

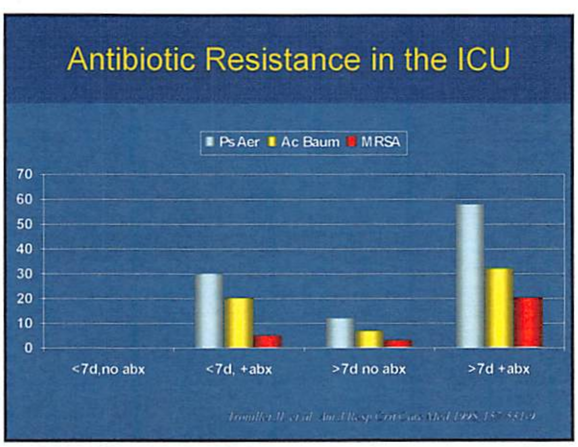
- MRSA is in addition to other *S. aureus* infections
- Traditionally associated with exposure to healthcare or antimicrobials
- In Europe, total ambulatory antibiotic use correlated with MRSA blood cultures (R=0.49, p=0.01)

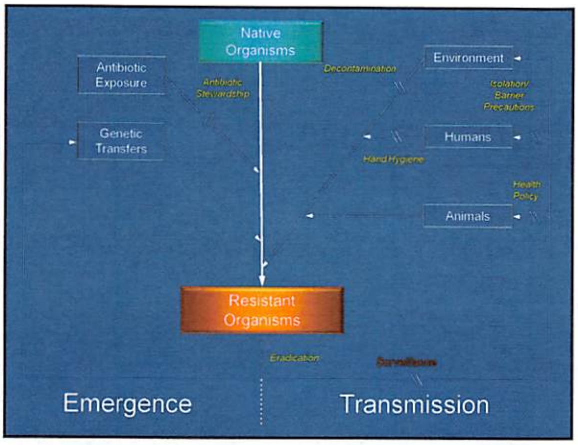


Monnet et al 2004 10: 1432
Wertheim et al 2006


Fluoroquinolone Use and Resistance Rates in *P. aeruginosa* and GNR
r = 0.976, P<.001 for P aeruginosa;
r = 0.891, P = .007 for GNR;
r = 0.958, P<.001 for years of observation
Strains Resistant to Ciprofloxacin, %
Fluoroquinolone Use, kg × 10³
Resistance
P aeruginosa
Gram-Negative Bacilli
Fluoroquinolone Use
1990-1993
1994
1995
1996
1997
1998
1999
2000
Years
Neuhauser MM et al. JAMA 2003 289 885-8


Relationship Between Quinolone Consumption and Susceptibility of *Escherichia coli* Isolates from Urine Cultures to Quinolone
Susceptibility, %
DDDs/month
Gottesman B S et al. Clin Infect Dis. 2009 49 869-875

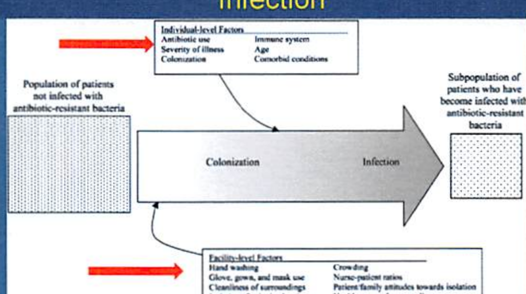

Antibiotic Resistance in the ICU
Ps Aer
Ac Baum
MRSA
<7d,no abx
<7d, +abx
>7d no abx
>7d +abx



Potential Prevention and Control Measures

- Infection Prevention/Control
  - Hand hygiene
  - Isolation and barrier precautions
  - Cohorting or separation of colonized/infected and non-colonized patients
  - Surveillance (active versus otherwise)
  - CHG bathing
  - Control of environmental or other potential sources
  - Vaccination
- Antibiotic stewardship/management

Factors that Influence Acquisition of a Nosocomial Antibiotic-Resistant Bacterial Infection



Harris et al Clin Infect Dis 2006 43 S57-61

Can We Identify These Cases?

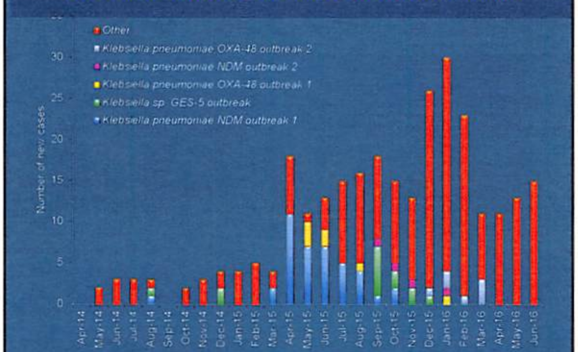
- Carriage of CTX-M found
  - 22% among patients with acute gastroenteritis
  - 7% among elderly Chinese

TABLE 1. Overview of the Different Colonization Patterns Detected in 133 Patients

Pattern	No. of patients (%)
1 colonization site	
Urine	32 (24.1)
Rectum	11 (8.3)
Groin	1 (0.7)
Throat	1 (0.7)
2 colonization sites	
Urine, rectum	38 (28.6)
Urine, groin	5 (3.8)
Urine, throat	1 (0.7)
Rectum, groin	6 (4.6)
Rectum, throat	1 (0.7)
Groin, throat	0 (0.0)
3 colonization sites	
Urine, rectum, groin	23 (17.3)
Urine, rectum, throat	2 (1.5)
Urine, groin, throat	1 (0.7)
Rectum, groin, throat	3 (2.3)
4 colonization sites	
Urine, rectum, groin, throat	8 (6.0)
Site totals	
Patients with colonization of the urine	110 (82.7)
Patients with colonization of the rectum	92 (69.2)
Patients with colonization of the groin	47 (35.3)
Patients with colonization of the throat	17 (12.8)

Tschudin Sutter et al ICHE 2012 33 1170-1 Muzaheed et al Indian J Med Res 2009 129 599-602 Tian et al Can J Microbiol 2008 54 781-85

Detection of new CPE cases at ICHT by month

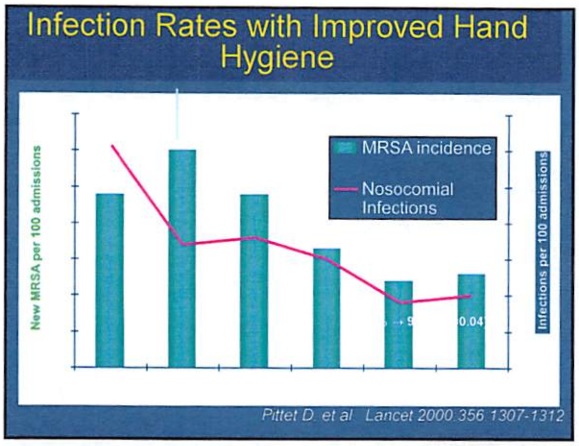


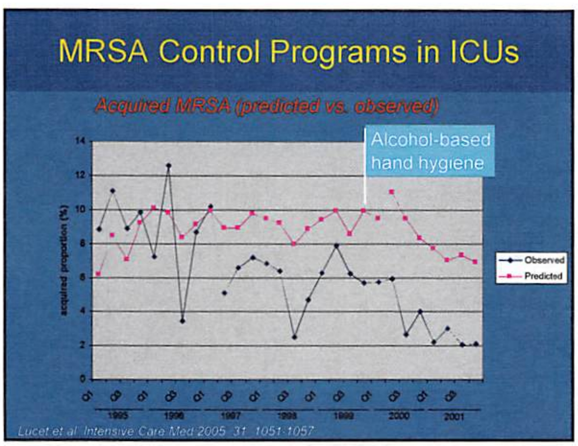
75% screens, 25% clinical cultures

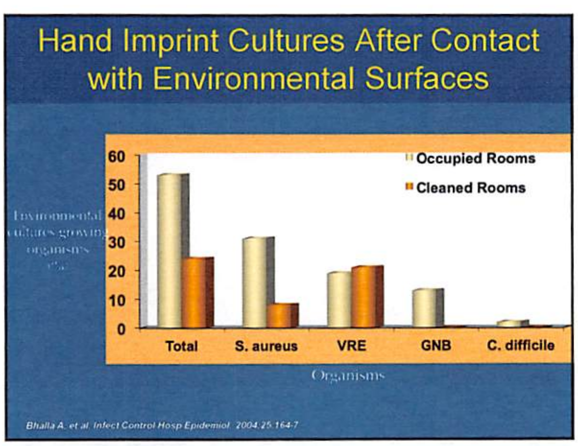
Monoclonal Transmission of HA-VRE Bacteremia

	HOSPITAL A	HOSPITAL B
Beds (ICU)/ Yearly Admissions	700(68)/35K	683(96)/34K
VRE bacteremia rate/100K pt days	17.1	8.2
Mean Vancomycin DDD/1000 pt days/yr (range)	70.3 (64-81)	65.5 (49-72)
% pts affected by largest clonal types	30%	14.5%
% pts affected by 4 most predominate clonal types	75%	37%
Active surveillance & isolation	NO	YES

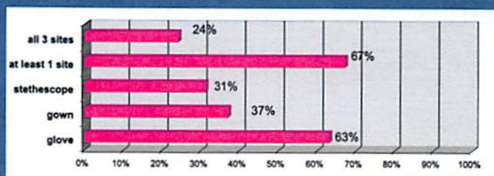
Price C. Clin Infect. Dis 2003. 37 921-8


Infection Rates with Improved Hand Hygiene
MRSA incidence
Nosocomial Infections
New MRSA per 100 admissions
Infections per 100 admissions
Pittet D. et al. Lancet 2000 356 1307-1312


MRSA Control Programs in ICUs
Acquired MRSA (predicted vs. observed)
Alcohol-based hand hygiene
acquired proportion (%)
Observed
Predicted
1995
1996
1997
1998
1999
2000
2001
Lucet et al. Intensive Care Med 2005 31 1051-1057


Hand Imprint Cultures After Contact with Environmental Surfaces
Occupied Rooms
Cleaned Rooms
Total
S. aureus
VRE
GNB
C. difficile
Organisms
Bhalla A. et al. Infect Control Hosp Epidemiol. 2004;25:164-7

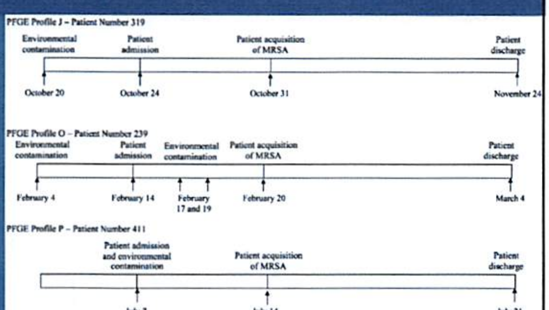
Contamination of Gowns, Gloves, and Stethoscopes with VRE During Routine Patient Examination (n=49)



Patients identified by rectal-swab culture alone were as likely to contaminate their examiners as were those identified by clinical specimens

Zachary Infect Control Hosp Epidemiol 2001 Sep 22(9) 560-4

Linking the Environment to Infection



Hardy et al. Infection Control and Hospital Epidemiology 2006 27 127-132

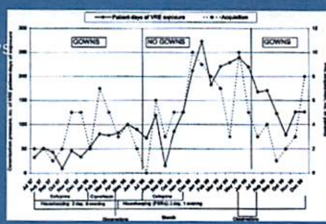
Does Contamination of a Prior Room Increase the Risk of Acquisition?

Study	Pathogen	Likelihood of patient acquiring HCAI based on prior room occupancy
Martinez 2003[1]	VRE – cultured w/in room	2.6x
Huang 2006[2]	VRE – prior room occupant	1.6x
	MRSA – prior room occupant	1.3x
Drees 2008[3]	VRE – cultured w/in room	1.9x
	VRE – prior room occupant	2.2x
	VRE – prior room occupant w/in previous 2 weeks	2.0x
Shaughnessy 2011[4]	*C. difficile* – prior room occupant	2.4x
Nseir 2010[5]	*A. baumannii* – prior room occupant	3.8x
	P. aeruginosa – prior room occupant	2.1x

Martinez et al. Arch Intern Med 2003; ... Huang et al. Arch Intern Med 2006; ... 1945-51. Drees et al. CID 2008; 46: 678-85. Shaughnessy ICHE 2011 32:201-206. Nseir et al. Clin Microbiol Infect 2010 (in press). Slide from J Otter

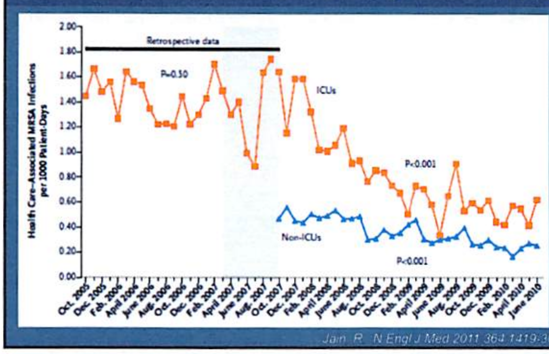
Preventing Transmission: Gowns + Gloves vs. Gloves Alone–2 Studies?

- JHH MICU-21% of patients at risk acquired VRE during the gown + glove period vs. 42% during the glove alone period (P=0.04)
  - VRE acquisition of 1.8 cases/100 days at risk with gowns + gloves compared to 3.78 cases with gloves alone (P=0.04, incidence rate ratio 0.48 (P=0.05, 95% CI 0.27-1.05)



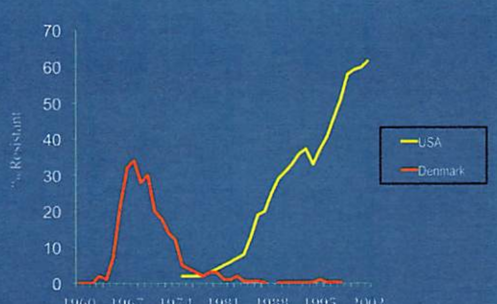
Srinivasan A, et al. Infect Control Hosp Epidemiol. 2002;23:424-8. Puzniak LA, et al. Clin Infect Dis. 2002;35:18-2

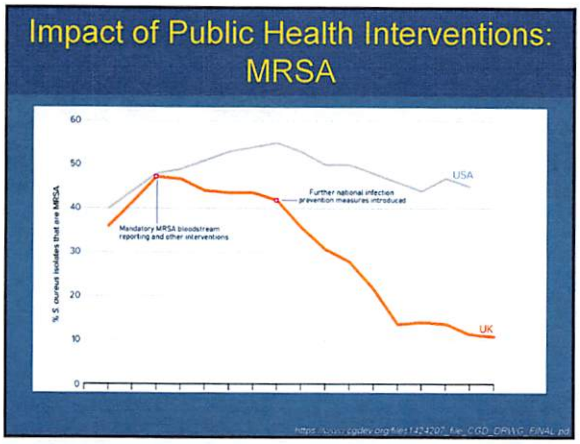
Rates of HAI with MRSA in Veterans Affairs (VA) Facilities in the United States, 2005-2010

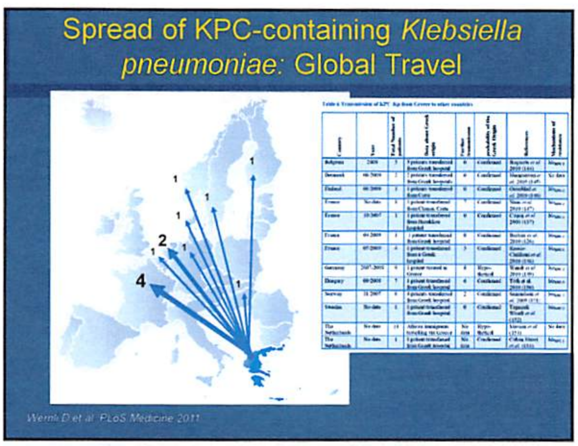


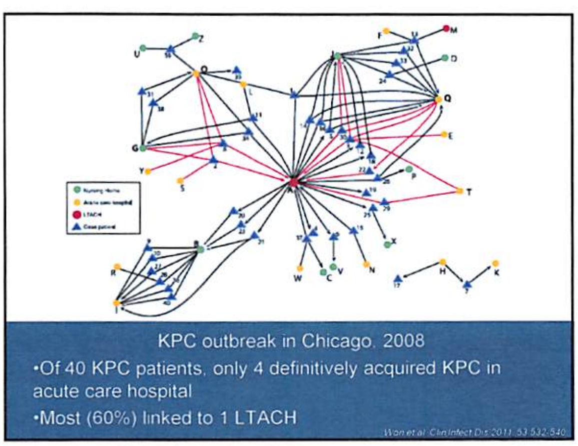
Jain R. N Engl J Med 2011;364:1419-30

Learning From Other Countries?




Impact of Public Health Interventions: MRSA
60
50
40
30
20
10
0
% S. aureus isolates that are MRSA
USA
UK
Mandatory MRSA bloodstream reporting and other interventions
Further national infection prevention measures introduced


Spread of KPC-containing *Klebsiella pneumoniae:* Global Travel
Werner D et al. PLoS Medicine 2011


KPC outbreak in Chicago, 2008
•Of 40 KPC patients, only 4 definitively acquired KPC in acute care hospital
•Most (60%) linked to 1 LTACH
Won et al. Clin Infect Dis 2011; 53:532-540

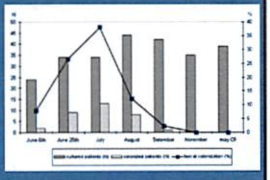
Other Considerations in 2017?

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

Unexpected Epidemiology

- Outbreak of ESBL *K. pneumoniae* in 2008 (clonal)
- 156 patients colonized
  - 22% infected
- 35% of the hospital kitchen–screened surfaces or foodstuff were colonized
- 6 (14%) of 44 food handlers found to be fecal carriers
- HCWs negative

Foodborne Nosocomial Outbreak of SHV1 and CTX-M-15–producing *Klebsiella pneumoniae*: Epidemiology and Control



Calbo et al. (2011) Clin Infect Dis 52:743-749

ESBL-producing Enterobacteriaceae in Retail Meat

- 262 fresh meat samples
- 30% of samples grew ESBL-producing Enterobacteriaceae
  - 80% of chicken samples
- Similarity between strains and ESBL enzymes in food and human samples

Overdevest et al. (2011) Emerg Infect Dis 17(7) 1216-22

Is the Source the Food Chain?

- 98 retail meat samples:
  - 94% contained ESBL-producing isolates
  - 39% of these belonged to *E. coli* genotypes also present in human samples

"

Leverstein-van Hall et al. (2011) Clin Microbiol Infect. (Epub 6 April)

Sources: More Unexpected Epidemiology

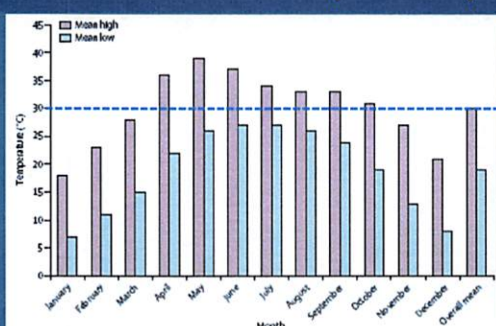
- Measure the prevalence of NDM-1 gene in drinking water and in pooled water from streets and small streams ("seepage") in New Delhi
- Sep 26-Oct 10, 2010
- Swabs of seepage water (n=171) and public tap water (n=50) collected from sites within 12 km radius of New Delhi
- Samples sent to UK and assessed for bla_{NDM-1} by PCR and DNA probing
- Compared to sewage effluent samples (n=70) from Cardiff, Wales (UK) as controls
- Performed susceptibility testing and typing
- Assessed plasmid transfer vs temperature

TR Walsh et al. Lancet Infect Dis 2011 11: 355–62

Results

- NDM-1 positive samples, New Delhi
  - Water 2/50 (4%)
  - Seepage 51/171 (30%)
- ALL seepage and water samples grew bacteria on cefotaxime containing media
- 94% seepage and 28% water samples grew bacteria on meropenem containing media

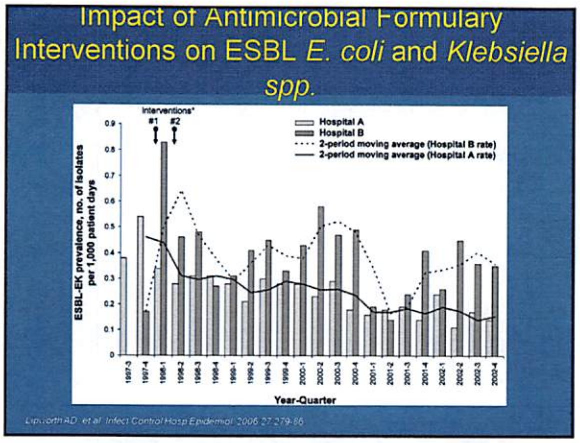
Mean Temperatures in New Delhi (Bar) vs Ideal Plasmid Transfer Temperatures (Line)

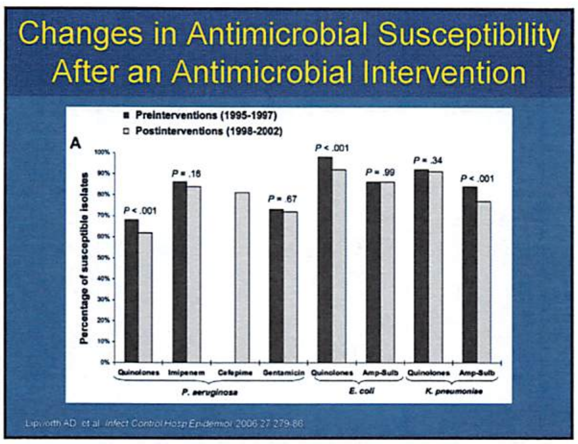


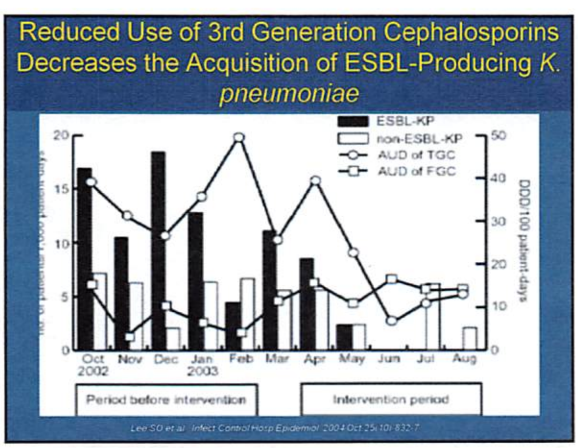
Impact of Antimicrobial Formulary Interventions on ESBL *E. coli* and *Klebsiella spp.*

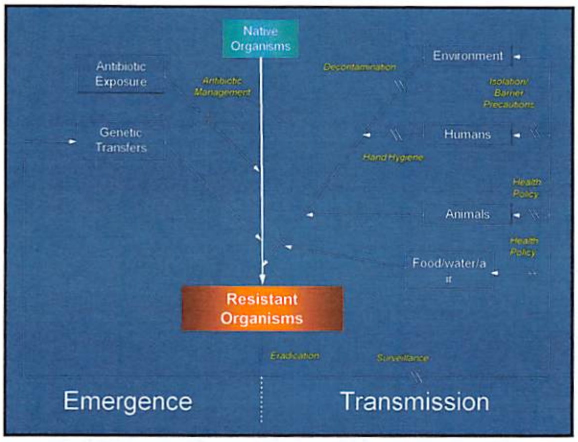
- Quasi-experimental design to evaluate the impact of antimicrobial interventions (ie. restriction of ceftazidime & ceftriaxone) to interrupt spread of ESBL in 2 hospitals (625 beds and 344 beds) over 5-years (7/1/1997 12/31/2002).
- Post-intervention: ceftriaxone use decreased 86% at Hospital A & 95% at Hosp B. Ceftazidime use decreased 95% at Hospital A & 97% at Hospital B
- ESBL prevalence decreased 45% at Hospital A ($P < .001$) & 22% at Hospital B ($P = .36$). ESBL-EK-infected patients at Hospital B were more likely to have resided in a LTCF (adjusted OR, 3.77 [95% CI, 1.70-8.37]), be older (adjusted OR, 1.04 [95% CI, 1.01-1.06]), and have a decubitus ulcer (adjusted OR, 4.13 [95% CI, 1.97-8.65]).

Lipworth AD, et al. Infect Control Hosp Epidemiol 2006;27:279-86


Impact of Antimicrobial Formulary Interventions on ESBL *E. coli* and *Klebsiella* spp.
Interventions*
#1 #2
Hospital A
Hospital B
2-period moving average (Hospital B rate)
2-period moving average (Hospital A rate)
ESBL-EK prevalence, no. of isolates per 1,000 patient days
Year-Quarter
Lipworth AD, et al. Infect Control Hosp Epidemiol 2006 27 279-86


Changes in Antimicrobial Susceptibility After an Antimicrobial Intervention
Preinterventions (1995-1997)
Postinterventions (1998-2002)
A
Percentage of susceptible isolates
P < .001
P = .18
P = .67
P < .001
P = .99
P = .34
P < .001
Quinolones
Imipenem
Cefepime
Gentamicin
Quinolones
Amp-Sulb
Quinolones
Amp-Sulb
P. aeruginosa
E. coli
K. pneumoniae
Lipworth AD, et al. Infect Control Hosp Epidemiol 2006 27 279-86


Reduced Use of 3rd Generation Cephalosporins Decreases the Acquisition of ESBL-Producing *K. pneumoniae*
ESBL-KP
non-ESBL-KP
AUD of TGC
AUD of FGC
DDD/100 patient-days
Oct 2002
Nov
Dec
Jan 2003
Feb
Mar
Apr
May
Jun
Jul
Aug
Period before intervention
Intervention period
Lee SO et al. Infect Control Hosp Epidemiol 2004 Oct 25(10) 832-7

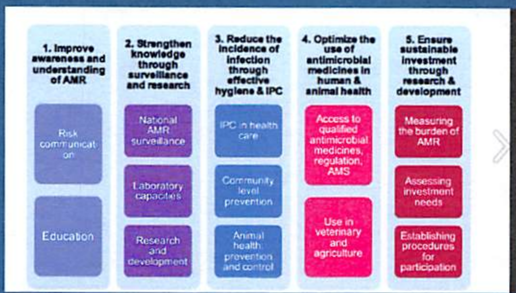


Potential Prevention and Control Measures

- Infection Prevention/Control
  - Hand hygiene
  - Isolation and barrier precautions
  - Cohorting or separation of colonized/infected and non-colonized patients
  - Control of environmental or other potential sources
- Antibiotic stewardship/management
- Vaccination
- Decreasing antimicrobial use in Animals/horticulture and agriculture

Is the Sky Falling?

WHO Plan For Action



Summary

- Antimicrobial resistance and its control is the challenge for the next decade if not longer
- Control measures are complicated and will likely require efforts that include
  - Infection prevention
  - Antimicrobial stewardship in humans, animals and agriculture
  - Public policy strategies
- To interrupt transmission and the emergence of resistance we will require a culture change
- Without additional research, the best and most effective interventions, the timing or implementation are not known