Emerging Infections, Prevention & Control

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Introduction of MRSA

- 1961 : Barber, Europe
- Mid 1970 : Boyce J.M , USA
- 1978 : Scragg J.N , South Africa
- 1982 : Mc Donald P.J , Australia

Methicillin Resistant *Staphylococcus aureus*

- **Transfer**
- **Community**
- **Nosocomial**

F.Moreno et al , Clinical Infectious Diseases 1995 ; 21 : 1308 - 1312

Incidence of MRSA : 170 patients*
(0,2 per 1.000 patients - days)

- ***Community 99 (58%)***
- ***Nosocomial 48 (28.5%)***
- ***Transfers 23 (13.5%)***

**** During a 21-month period***

F.Moreno et al,Clinical Infectious Diseases 1995 ; 21 : 1308 - 1312

Mechanism of Methicillin Resistance

1. **Intrinsic Methicillin Resistance (MRSA)**

   - **Due to production of PBP 2' (low affinity for various β-lactams)**
   - **Chromosomally mediated and encoded by the *mec* gene**
   - **Multiple resistance to antimicrobials of several classes**

2. **Acquired or Borderline Resistance (BORSA)**

   - **Due to hyperproduction of penicillinase**
   - **MIC oxacillin : 1 – 2 µg/ml**
   - **Not multi-resistant**

3. **Methicillin Intermediate *S.aureus* (MODSA)**

   - **MIC oxacillin : 1 – 2 µg/ml**
   - **Due to production of PBP 1 , 2 & 4**

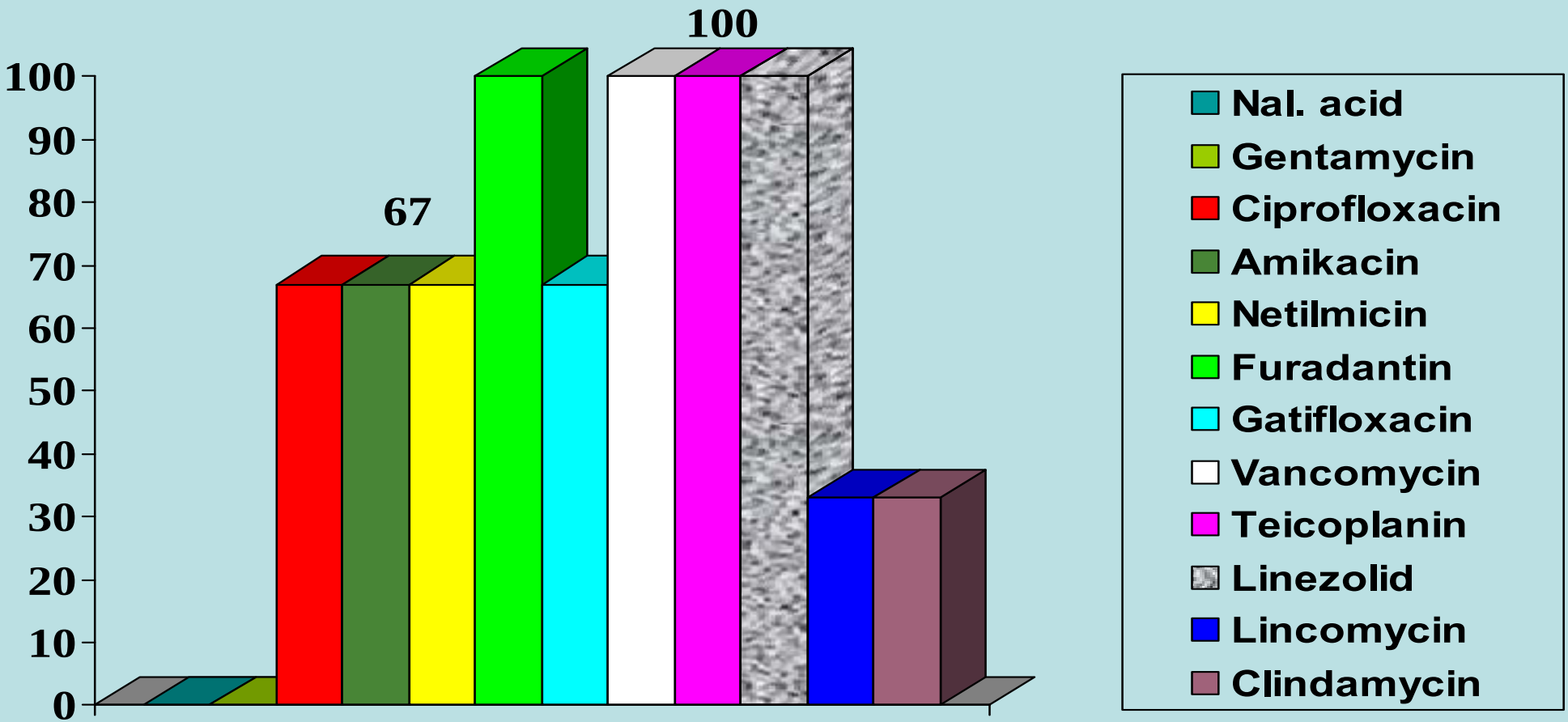
Distribution of MRSA in services units at Children's and Maternity " Harapan Kita " Hospital, January - December 2004

WARDS	POSITIVE
• Third class pediatric ward	31 (37.4%)
• PICU	9 (10.8%)
• First class pediatric ward	7 (8.4%)
• NICU/ LEVEL II	7 (8.4%)
• Second class pediatric ward	7 (8.4%)
• VIP class pediatric ward	2 (2.4%)
• Transitional neonatal ward	2 (2.4%)
• Surgical pediatric ward	1 (1,2%)
• In patients	• 66 (79,5%)
•Out patients	• 17 (20,5%)

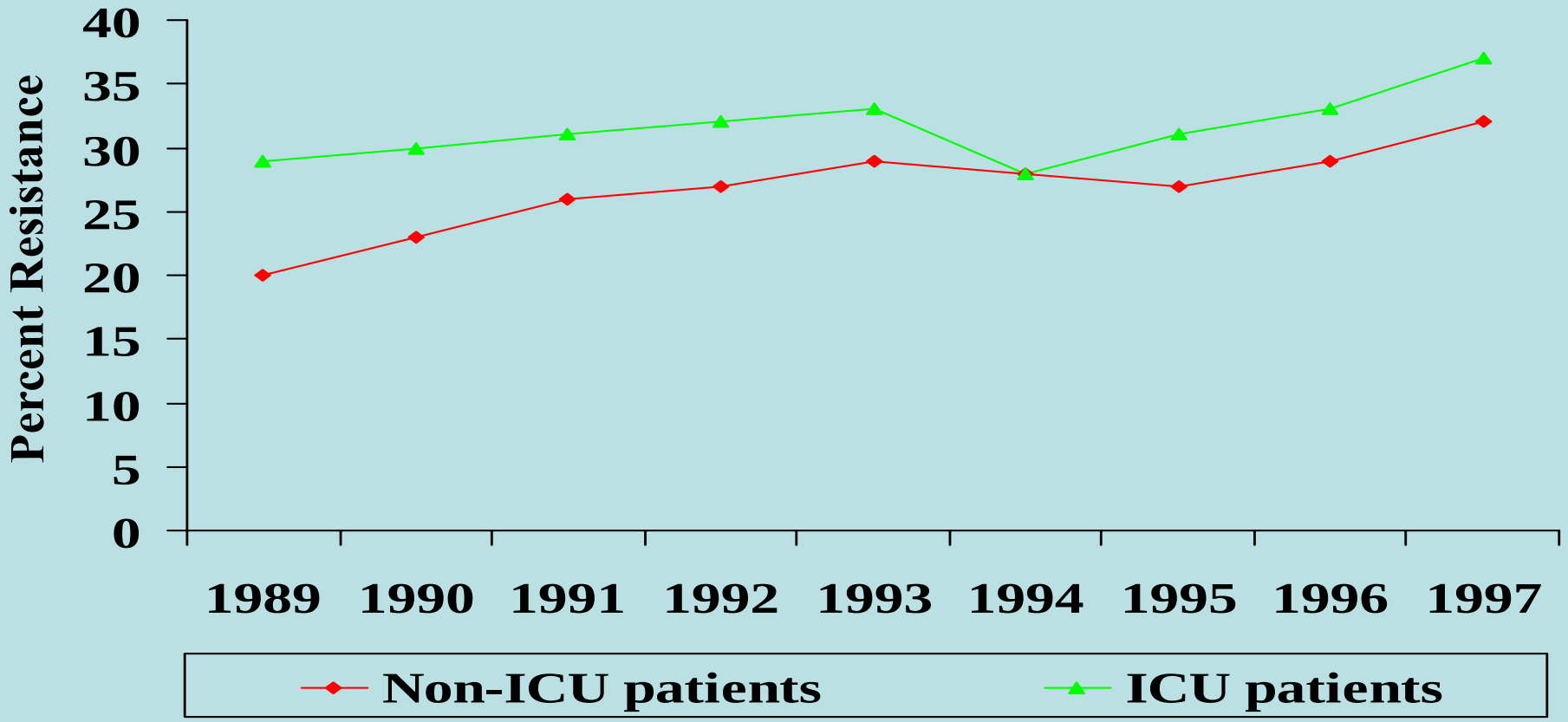
MRSA isolates from 83 various clinical specimens at Children's and Maternity " Harapan Kita " Hospital January - December 2004

Specimens	Positive
• Stools	40 (48.2%)
• Urines	24 (29%)
• Blood	9 (10.8%)
• Throat swab	4 (4.8%)
• Endotracheal tubes	2 (2.4%)
• Bronchial discharge	2 (2.4%)
• Peritoneal lavage	1 (1.2%)
• Neck abcess	1 (1.2%)
• Total	83 (100 %)

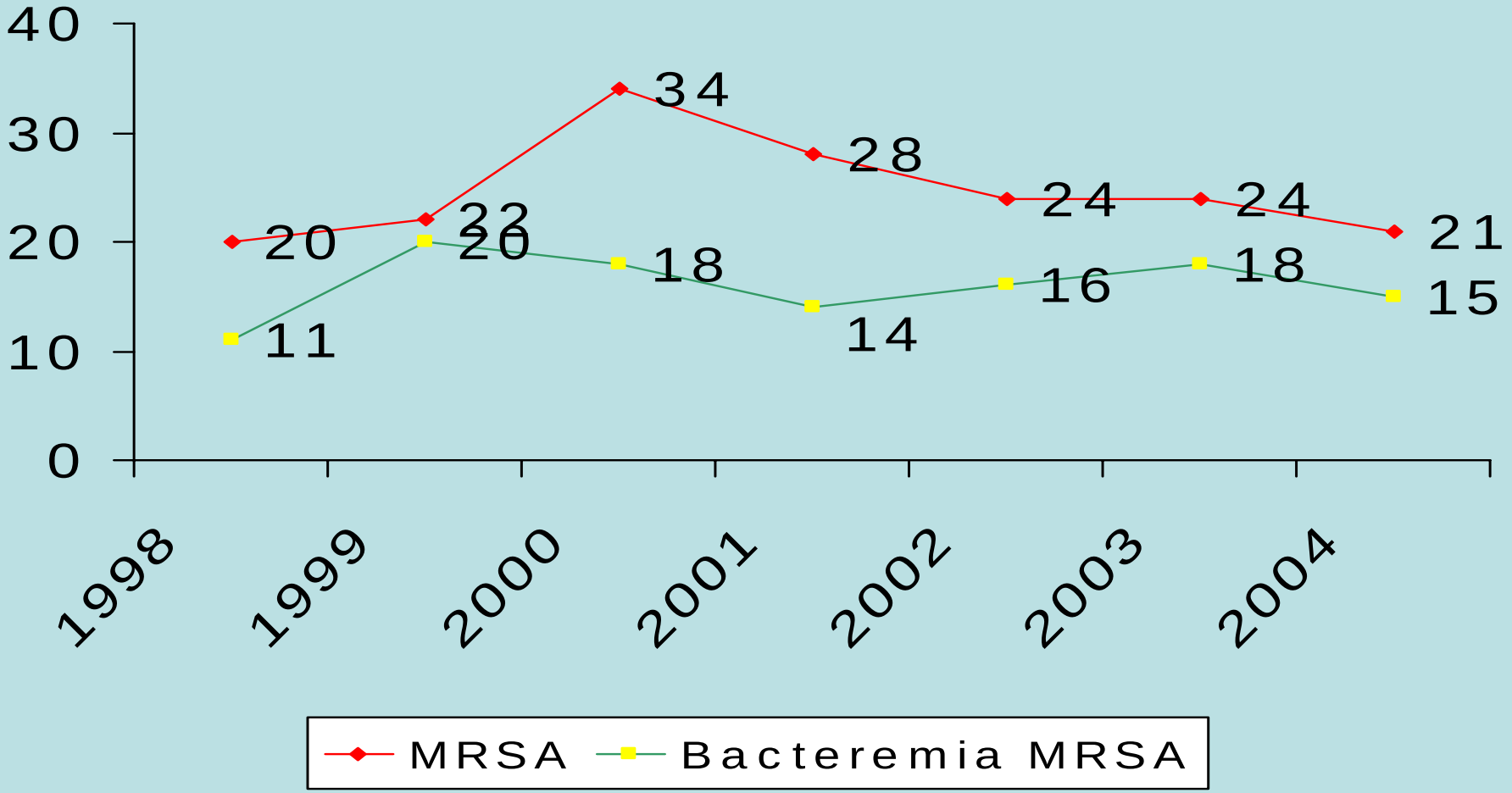
Susceptibility Pattern of MRSA (21 %) to Non-Beta-Lactam Agents in PICU/NICU Children's and Maternity " Harapan Kita " Hospital, January – December 2004



Proportion of isolates associated with a nosocomial infection among ICU or non-ICU patients who were MRSA



Trends of MRSA and bacteremia MRSA in Children's and Maternity " Harapan Kita " Hospital



MRSA

- Spread between hospital by movement of colonised or infected patients and staff
- Often multiple resistant
- Vancomycin or Teicoplanin - “drug of choice”
- Sepsis occurs in 5 -60% of this colonised ---> more frequently in ICU or surgical patients (David Wilkis)

Risk factors for acquiring MRSA

- Prolonged hospitalisation
- Prior antimicrobial therapy
- Severe underlying disease
- Exposure to other infected or colonised individuals
- Old age
- Invasive procedures

CDC recommendation for isolation of patients with MRSA infection or colonization

- **Use of contact precautions, include :**
  - **Handwashing**
  - **Routine use of non-sterile gloves**
  - **Non-sterile gowns are recommended if contamination of clothing with body fluids is likely to occur**
  - **Patients care equipment and the environment need to be appropriately cleaned**
  - **A single room (or a system of cohorting) and limited transport of the patient from the room**

Measures to monitor the frequency of MRSA infection

1. Collecting nasal (or nasal and rectal) cultures prior to admission from any patient previously documented to have had MRSA infection or colonization or who is being transferred from an institution where MRSA is prevalent

2. Reviewing microbiology records to identify new cases of MRSA infection or colonization

3. Maintaining a list of infected or colonized patients

4. Marking these patients medical records to indicate that they are infected or colonized

In outbreak situations

- Culture the nares of health care workers who have been contact with MRSA infected or colonized patients
- Use of mupirocin to eliminate carriage in HCW's and patients is also done in selected situations
- Increasing emphasis has recently been placed on the environment as a potential source for contamination of a HCW's hands
- Limitation on the use of broad spectrum antimicrobials

Screening for MRSA

- **Since MRSA is endemic, there is no necessity to conduct routine screening for MRSA carriage except for patients undergoing renal dialysis program**
- **A patient is deemed non infectious upon completion of adequate appropriate antimicrobial therapy**

Criteria for isolation

- MRSA pneumonia patients who have not completed appropriate antimicrobial therapy
- MRSA wounds that can not be adequately covered with sealed dressing
- Exfoliative dermatitis patients with MRSA isolated on skin

VISA or VRSA

- **VISA :**
  - **MIC Vancomycin : 8 µg/ml**
  - **First reported in Japan, 1996**
  - **Due to prolonged intermittent use of vancomycin in the treatment of MRSA**
- **Prevention :**
  - **Prudent use of vancomycin**
  - **Contact precautions to prevent transmission of organisms from person to person**

VRE (Vancomycin Resistant Enterococcus)

- *Enterococcus spp.* :
  - Normal flora of gastro-intestinal & genito-urinary tracts
- First reported in France, 1986 → USA : 1989
- Most of the isolates → USA : *E.faecium* & Europe : *E.faecalis*
- Spread of VRE in hospitals involves :
  - Patient-patient transfer
  - Contaminated equipment
  - Transmission through the food chain

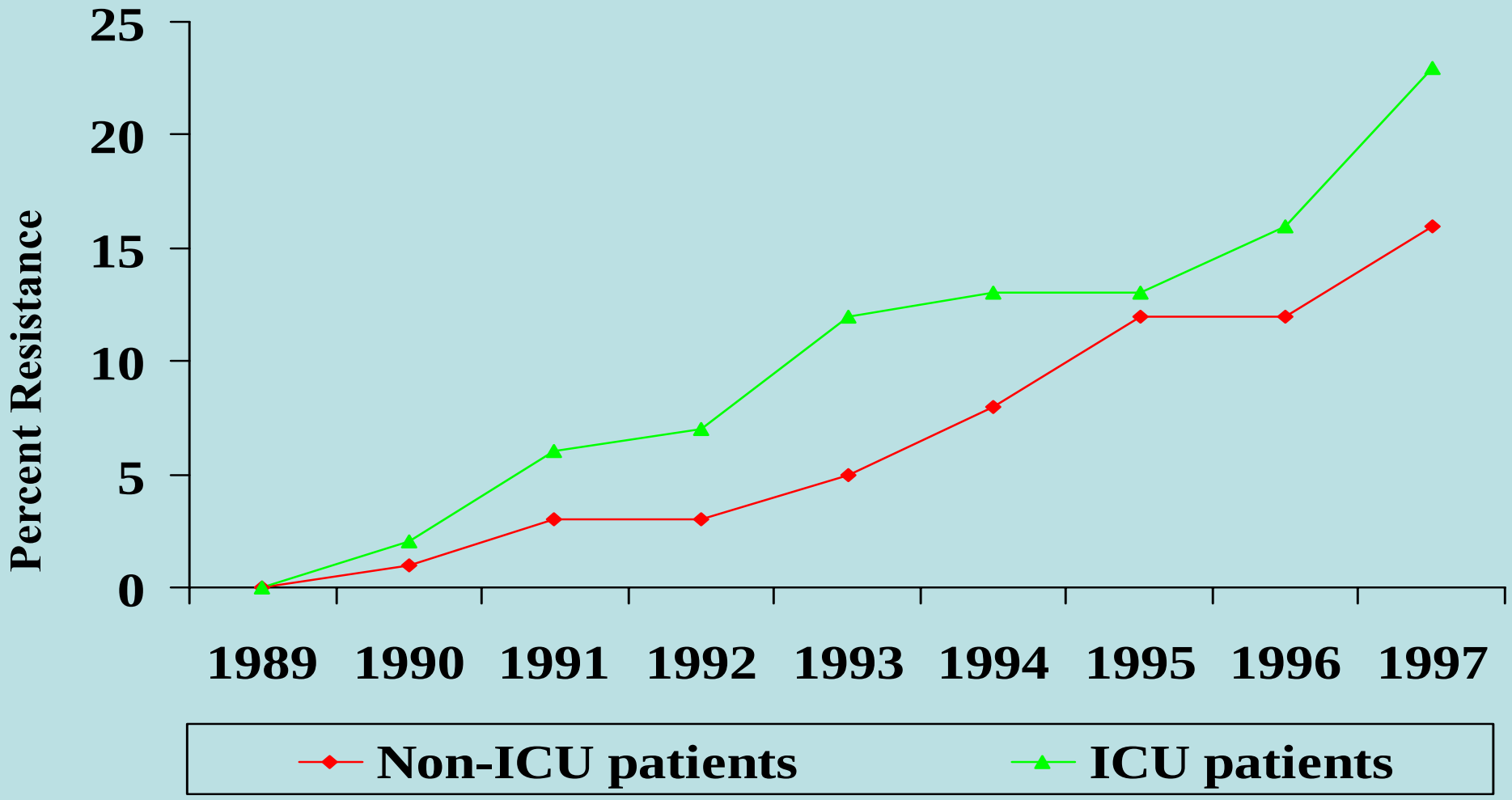
Mechanism Resistance of VRE

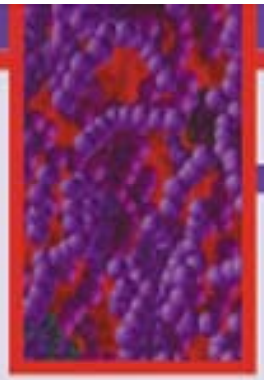
- **Acquisition of a series novel genes (*vanA, vanB, vanC, vanD*) → enable the bacterium to build a new cell that no longer contains the binding site for vancomycin**
- **In Europe, due to of administration of avoparcin as a feed additive in animal husbandry (pig & chicken)**
- **In North America, due to the heavy use of vancomycin**
- **The genetic transfer of resistance due to plasmids and transposons**

Treatment Options of VRE

- **Teicoplanin : *vanB* strains**
- **Combination of glycopeptide + aminoglycoside**
- **Chloramphenicol : *vanA E.faecium***
- **Quinupristin/dalfopristin : not active against *E.faecalis***
- **UTI : nitrofurantoin or quinolones**

Proportion of isolates associated with a nosocomial infection among ICU or non-ICU patients who were VRE





GLYCOPEPTIDE RESISTANCE IN ENTEROCOCCI

PATIENT RISK FACTORS FOR VRE

- Prior antibiotic use, especially vancomycin.
- Length of hospital stay.
- Prior nosocomial infection.
- Number of unisolated ICU days.
- Proximity to case or RN for case.
- Severity of illness.
- Neutropenia.

Prevention & Control of VRE

1. Prudent vancomycin use

2. Educational programmes → epidemiology of VRE & its impact on patient outcome and cost

3. Laboratory surveillance → antibiotic susceptibility on enterococci from all specimen sources (especially from ICUs, oncology or transplant wards)

4. Policy

Prevention & Control of VRE (cont.)

4. Policy :

- Notify appropriate staff promptly
- Isolate or cohort colonized / infected patients, institute Contact Precautions and reinforce handwashing practices
- Screen patients (rectal swab or stool culture) who share a room with colonized / infected patients
- Remove patients from Isolation Precautions after at least 3 consecutive negative cultures from multiple body sites taken at least 1 week apart
- Flag records of colonized / infected

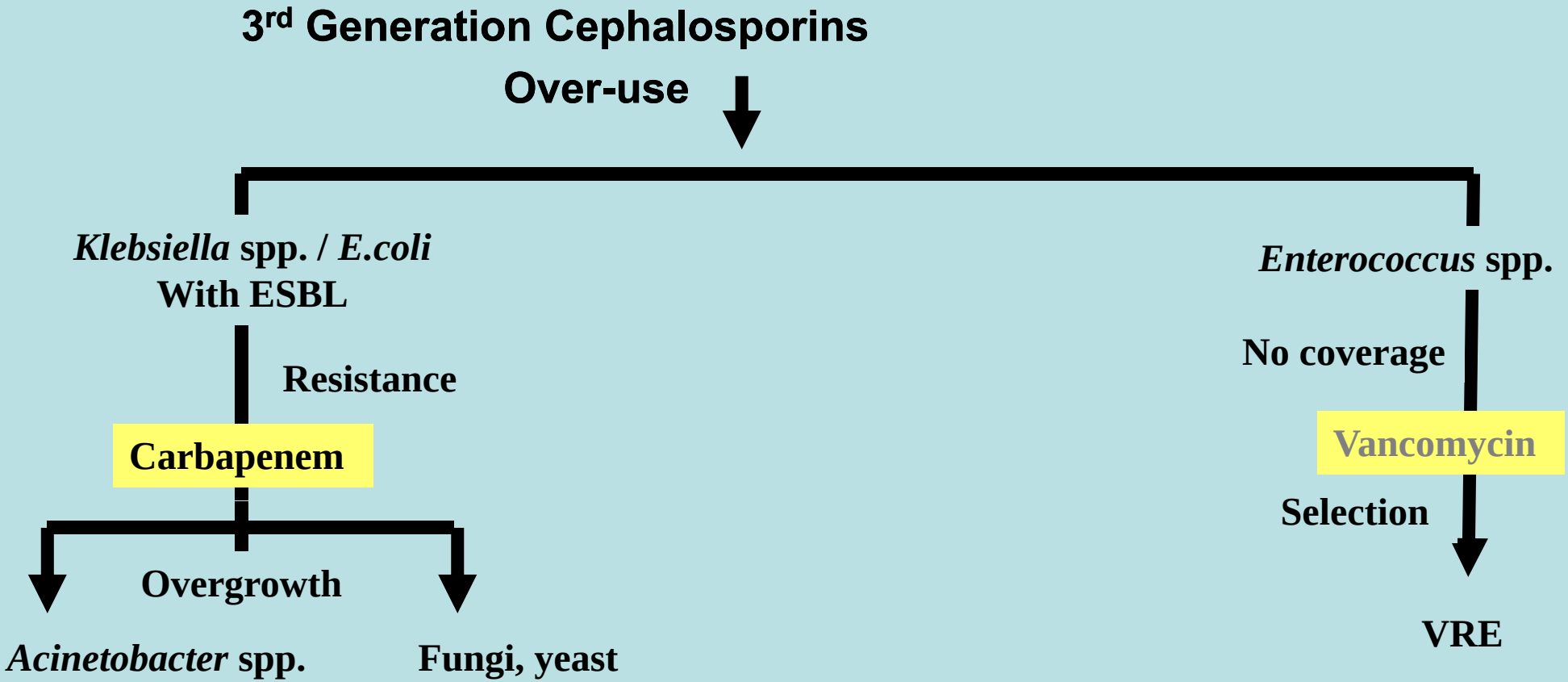
ESBL
(Extended Spectrum Beta-Lactamase)

- **Plasmid-mediated β-lactamases derived from TEM -1 or TEM -2 and SHV -1 enzymes**
- **Produced by Enterobacteriaceae, predominantly *Klebsiella* species and *E.coli***
- **Inactivated by β-lactamases inhibitors such as clavulanic acid, sulbactam, or tazobactam**

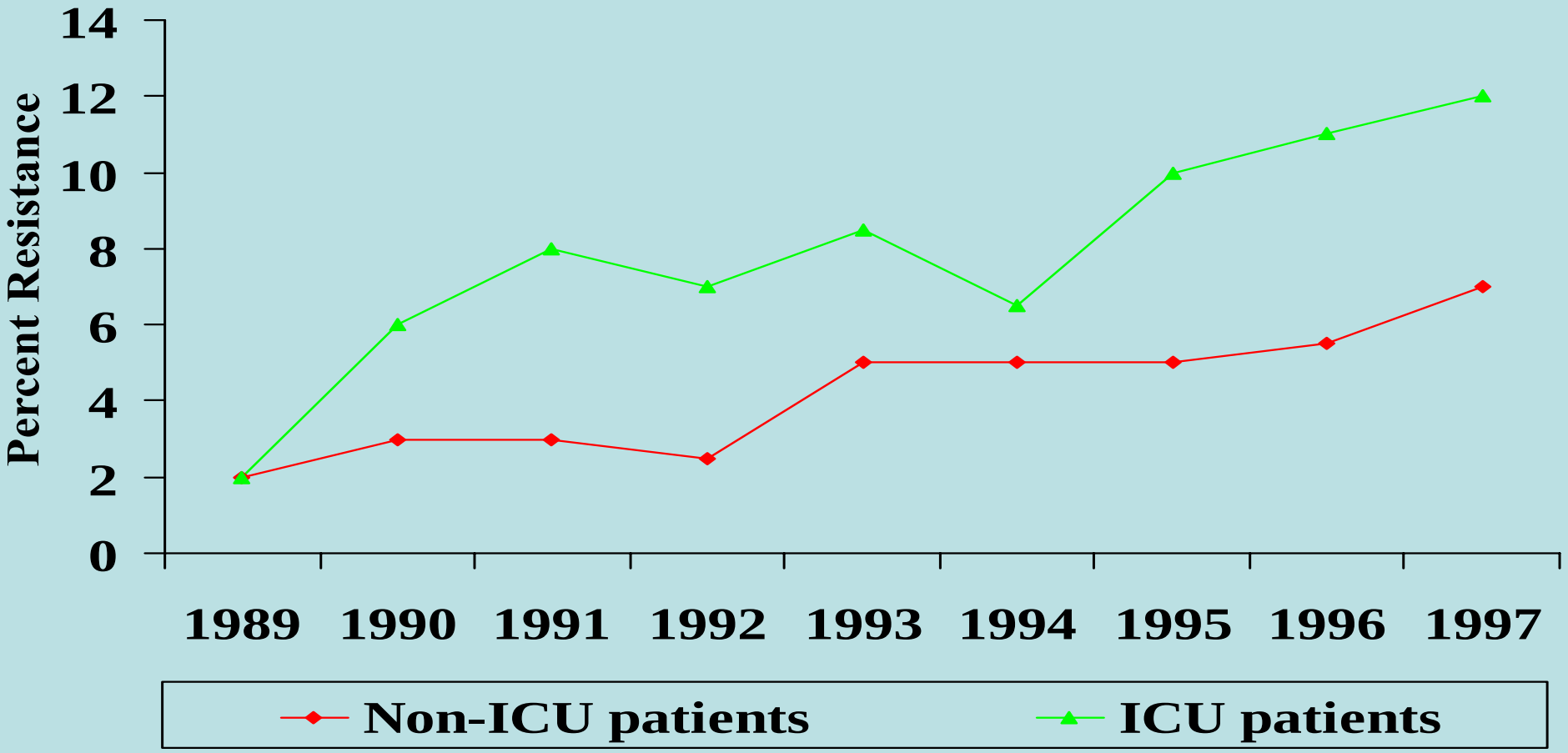
ESBL (cont.)

- Arise from mutations of a single amino acid substitution in an existing enzyme → due to selected pressure of 3rd gen. cephs.
- First reported in Germany, 1983 → now endemic worldwide
- Drug of choice : carbapenem

Consequences of resistance to third-generation cephalosporins



Proportion of isolates associated with a nosocomial infection among ICU or non-ICU patients who were ESBLP*K.pneumoniae*

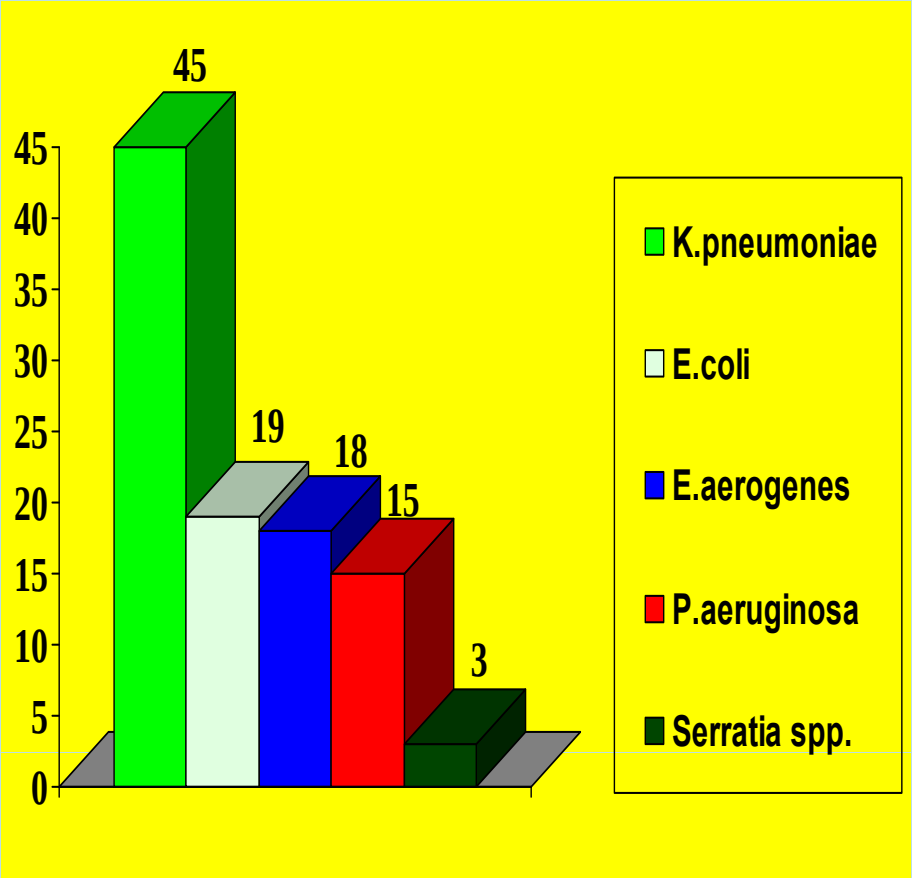


Risk Factors of Colonization or Infection With ESBLPE

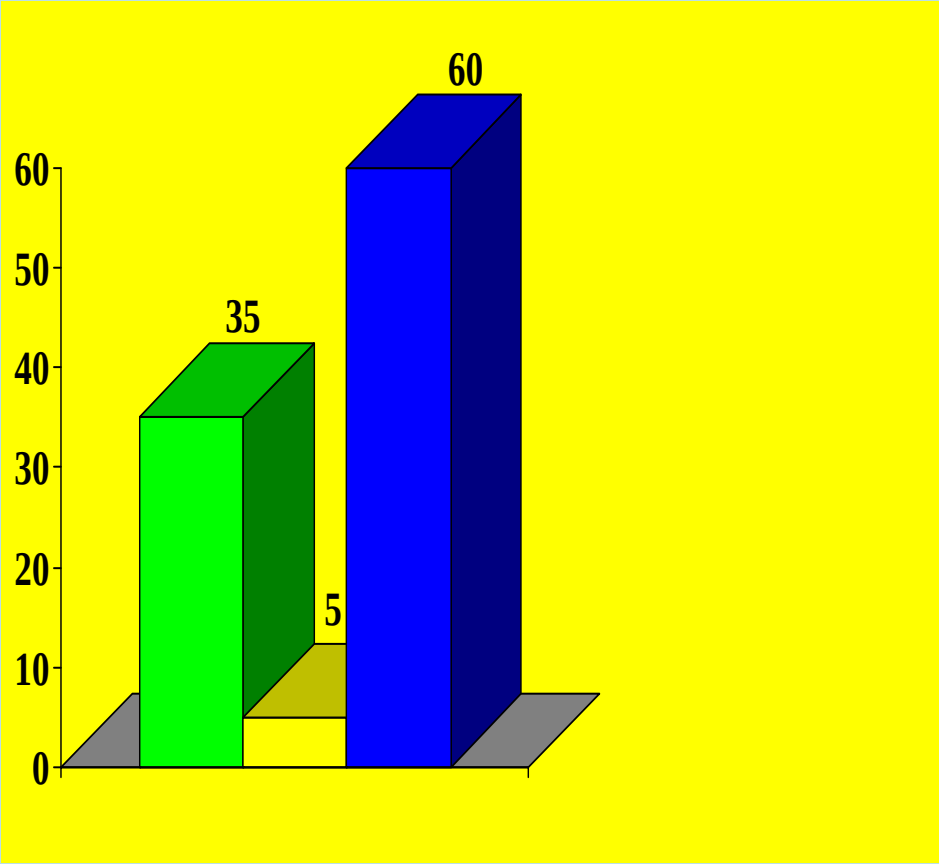
- Placement of intravascular catheters (central venous catheter, arterial catheter) or a urinary catheter
- Emergency intra-abdominal surgery
- Gastrostomy or jejunostomy tube placement
- Gastrointestinal colonization
- Length of hospital or intensive care unit stay
- Previous antibiotics (including third-generation cephalosporins)
- Severity of illness
- Ventilator assistance

Pattern of ESBLPE (16%) from Clinical Specimens in PICU/NICU Children's and Maternity " Harapan Kita " Hospital, July – December 2002

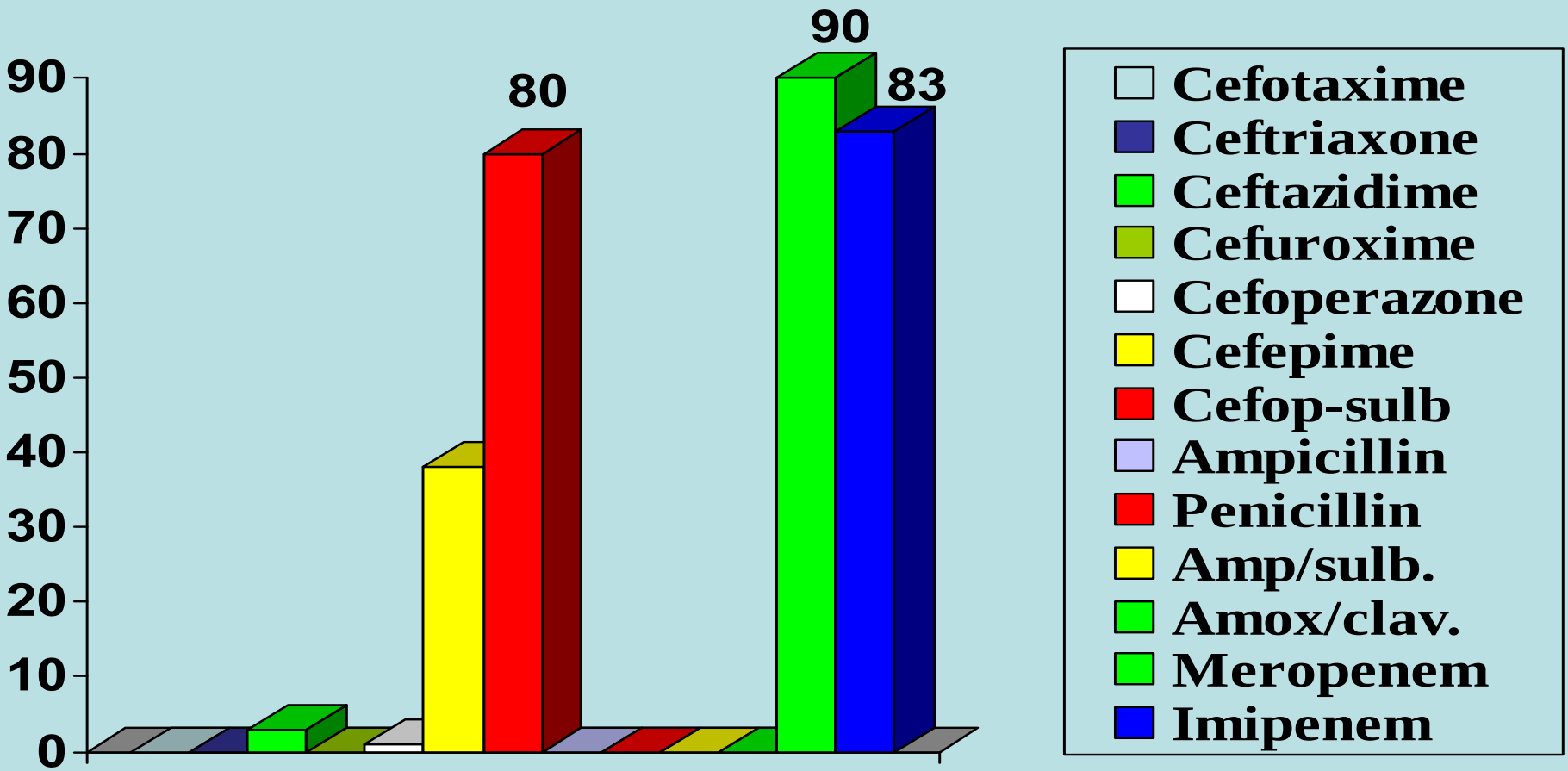
PICU



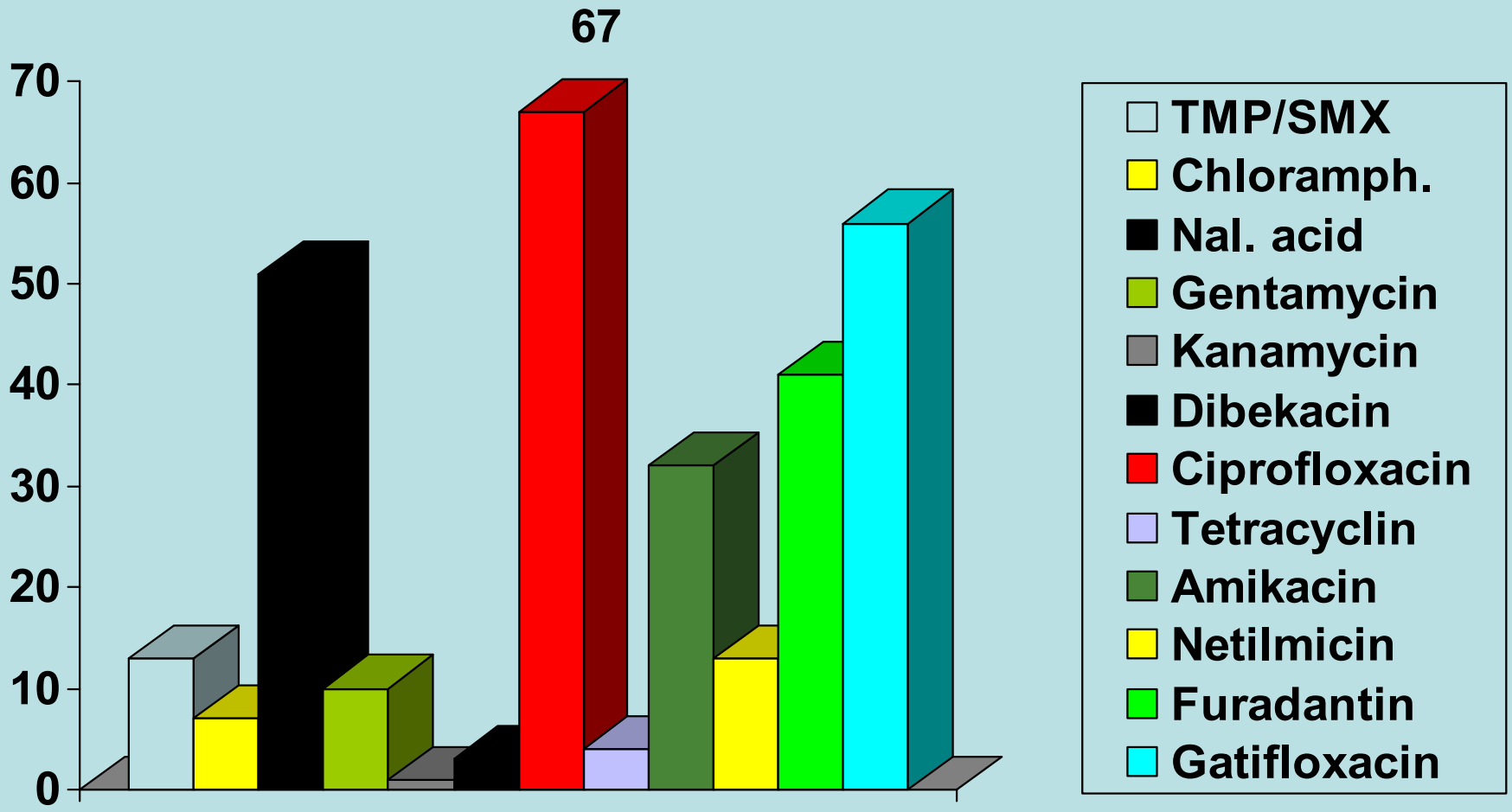
NICU



Susceptibility Pattern of ESBLPE (%) to Beta-Lactam Agents in PICU Children's and Maternity " Harapan Kita " Hospital, July – December 2002



Susceptibility Pattern of ESBLPE (%) to Non-Beta-Lactam Agents in PICU Children's and Maternity " Harapan Kita " Hospital, July – December 2002



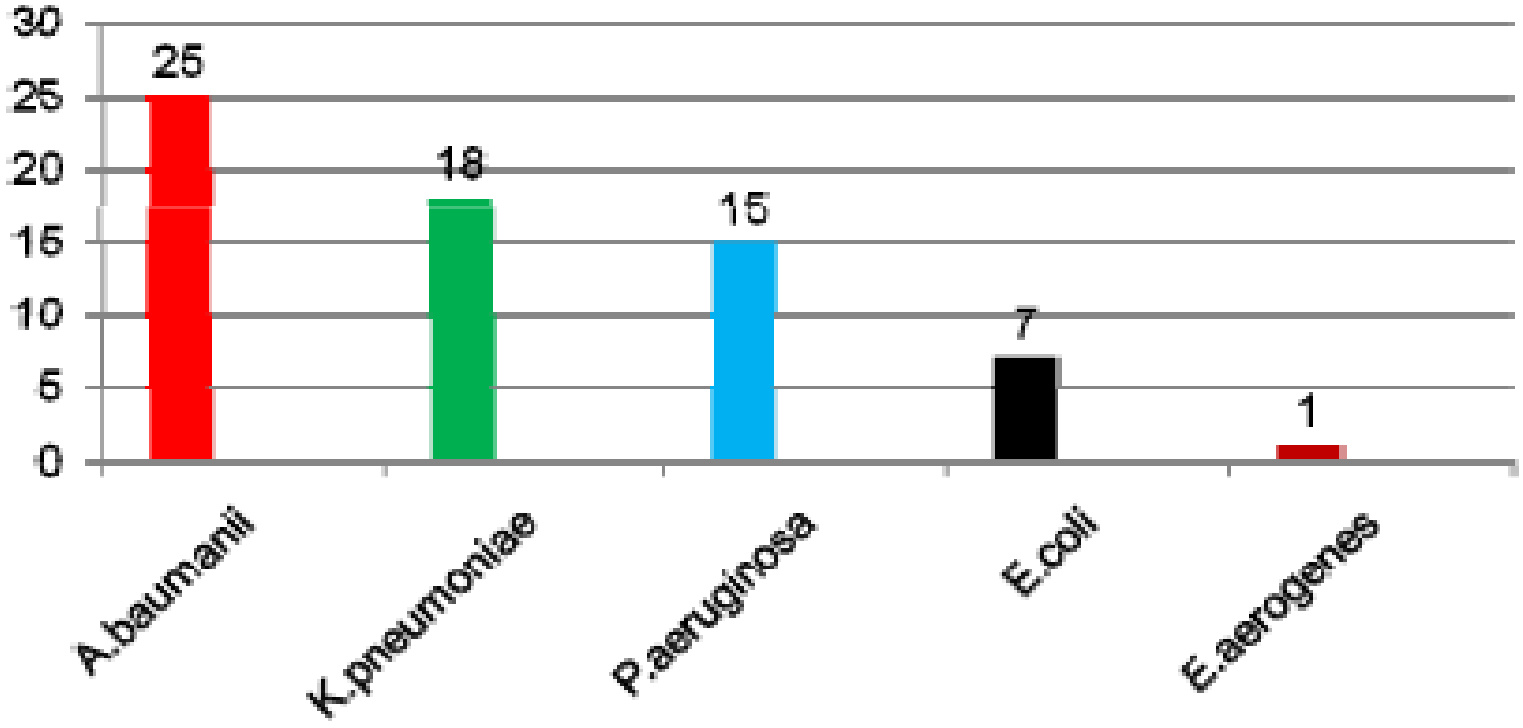
Characteristic of ESBLPE in PICU/NICU Children's and Maternity " Harapan Kita " Hospital, July – December 2002

- **Wards :**
  - **PICU : 64 %**
  - **NICU : 36 %**
- **Mortality : 24 %**

Prevention and Control of ESBL

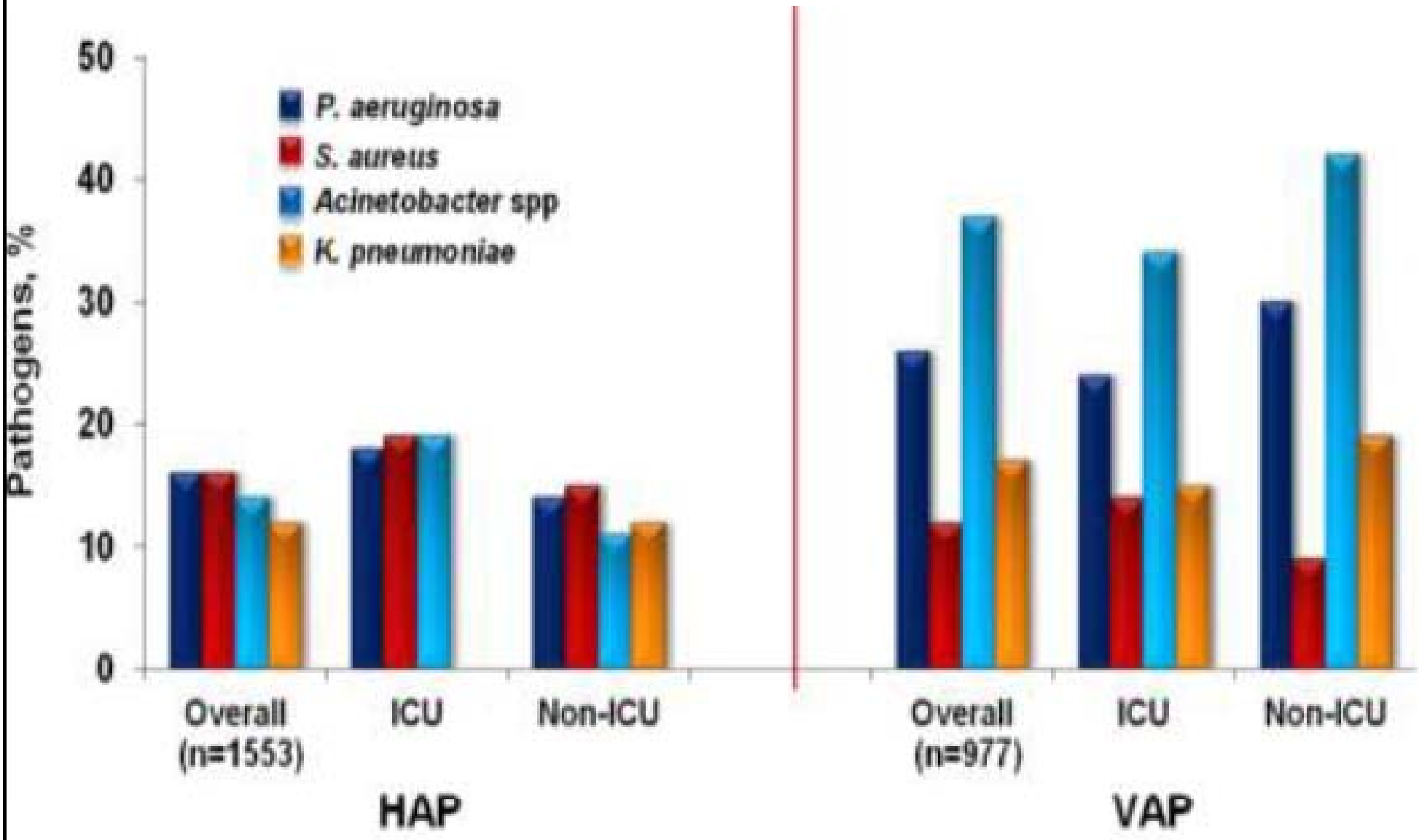
- Once ESBLPE invade a hospital, it is difficult to eradicate them
- Restriction of 3rd gen. cephs. monotherapy (antibiotic cycling)
- Contact Precautions
- Antibiotic Policy (including De-escalation Therapy)

Pola Mikroba Gram Negative (n = 418) di CVC RSJPHK 2008 (%)

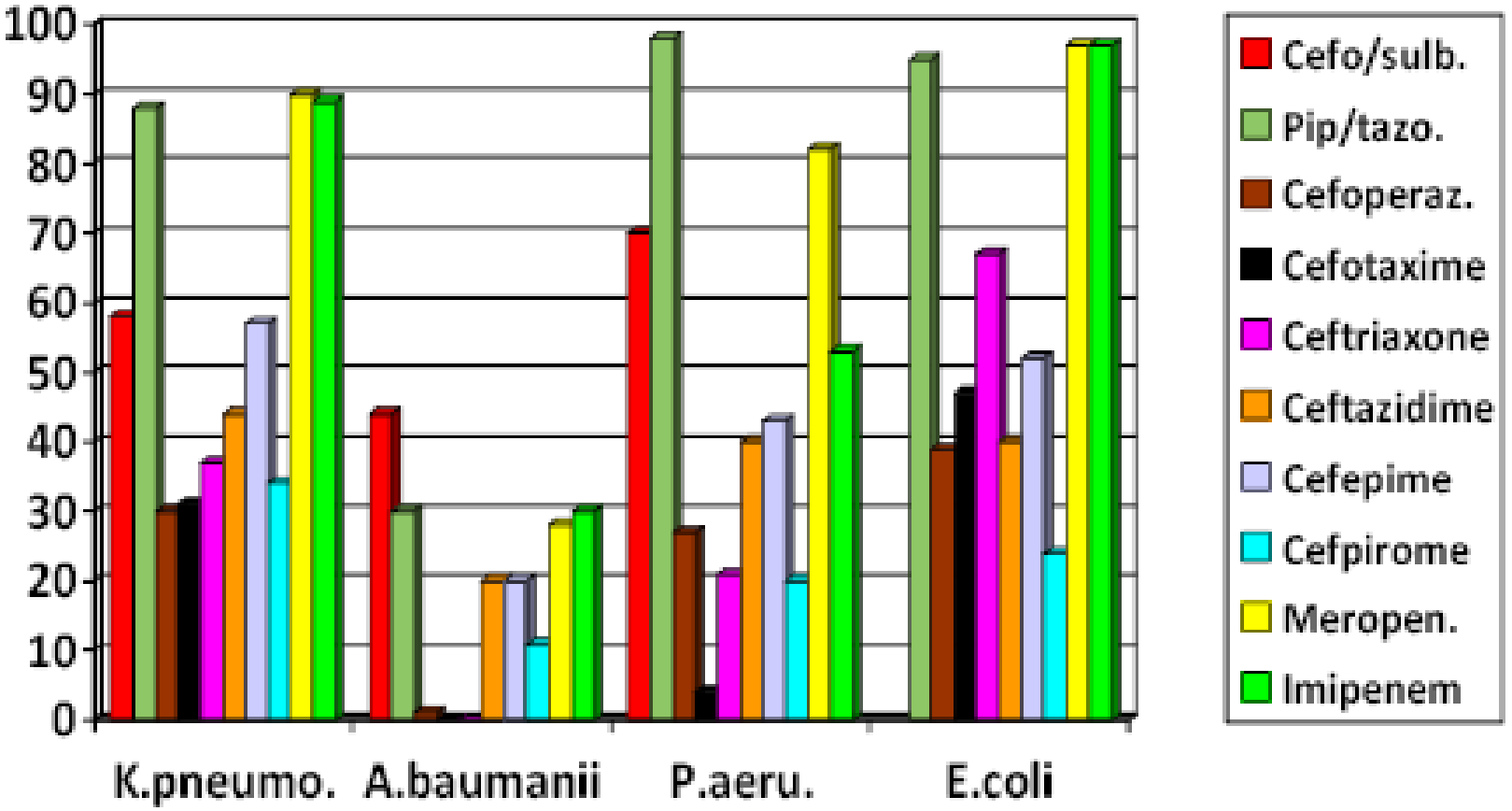


Latre , 2008

Prevalence of Bacteria in NP in ICUs vs. Non-ICUs



Sensitivitas Bakteri Gram Negative terhadap Antibiotik Gol. Beta-Laktam (%) di CVC-RSJPHK 2008



Latre , 2008

Antimicrobial resistance in nosocomial pathogens
Major issues in Asia

Infection	Major pathogen	Major resistance
Urinary tract infection	*E. coli, K. pneumoniae* *Enterococci*	ESBL VRE
Pneumonia	*P. aeruginosa* *A. baumanni*	MDR/PDR/XDR
Surgical site infection	*S. aureus*	MRSA
Bloodstream infection	*Coagulase(-) Staphylococci* *S. aureus*	MR-CNS, MRSA

Key Pathogens VAP vs HAP : Indonesia

KEY PATHOGEN	Number of cases	
	VAP (% of 20 cases)	**HAP** (% of 21 cases)
Klebsiella pneumoniae	7 (35 %)	7 (33.3 %)
Pseudomonas aeruginosa	5 (25 %)	1 (4.8 %)
Enterobacter aerogenes	7 (35 %)	4 (19 %)
Acinetobacter spp	5 (25 %)	4 (19 %)
E coli	0	3 (14.3 %)
Staph aureus	2 (10 %)	0 (%)
Steril	0	5 (23.8 %)

Note: Some cases have polymicrobial pathogens

Latre , 2009

Major causative pathogens of HAP/VAP in Asia

	Korea (n=219)	China (n=348)	Hongkong (n=275)	India (n=26)**	Indonesia (n=53)	Malaysia (n=45)**	Philippines (n=28)	Singapore (n=9)	Taiwan (n=25)**	Thailand (n=105)
1	S. au (41.6%)	S. au (21.8%)	P. aeru (21.5%)	P. aeru (38.5%)	K. pn (24.5 %)	A. baum (31.1%)	P. aeru (28.6%)	P. aeru (33.3%)	K. pn (28 %)	A. baum (35.0%)
2	P. aeru (15.5%)	P. aeru (21.0%)	S. au (16.4%)	A. baum (34.6%)	E. aero (20.8%)	K. pn (22.2 %)	K. pn (28.6 %)	K. pn (22.2 %)	P. aeru (20%)	P. aeru (22.3%)
3	K. pn (11.0%)	A. baum (20.1%)	K. pn (12.7 %)	K. pn (7.7 %)	A. baum (17.0%)	P. aeru (11.1%)	A. baum (7.1%)	S. malto (22.2%)	A. baum (16%)	K. pn (15.0 %)
4	A. baum (9.1%)	K. pn (8.3 %)	H. inf (10.2%)	S. malto (10.2%)	P. aeru (13.2%)	S. au (11.1%)	E. aero (7.1%)	E. cloa (11.1%)	S. malto (12%)	S. au (13.5%)

ANSORP Nosocomial Pneumonia Study

Antimicrobial Resistance of Major Bacterial Isolates

- *S.aureus* (N=303) — MRSA = 82.1%
- *K.pneumoniae* (N=275) — ESBL+ve = 41.4%; Carbapenem R = 2.2%
- *P.aeruginosa* (N=411) — Ceftazidime R = 34.7%; Carbapenem R = 27.2%
- *Acinetobacter* sp. (N=479) — Carbapenem R = 67.3%; Colistin R = 0.8%

ANSORP Nosocomial Pneumonia Study

30-Day All-Cause Mortality

- ✓ VAP 45.7%
- ✓ HAP 34.4%

($p<0.001$)

30-Day Pneumonia-Related Mortality

- ✓ VAP 31.1%
- ✓ HAP 22.4%

($p<0.001$)

ANSORP Nosocomial Pneumonia Study

All-Cause Mortality of NP by Country

✓ Singapore	12.5%
✓ China	24.2%
✓ Korea	26.8%
✓ Taiwan	33.9%
✓ Hong Kong	38.6%
✓ Philippines	42.3%
✓ Thailand	51.7%
✓ Malaysia	55.4%
✓ Indonesia	61.4%

ANSORP Nosocomial Pneumonia Study

- Mortality rate (MR) due to type of pathogens

	All-cause MR	Pneumonia-related MR
✓ *Acinetobacter* sp.	48.8%	35.1%
✓ *K.pneumoniae*	37.7%	22.7%
✓ *P.aeruginosa*	31.0%	22.4%
✓ *S.aureus*	30.7%	18.9%

Classification of Microorganism Producing Carbapenemases

Ambler class	Enzyme	Function	Known organisms
A	KPC[1]	Hydrolyzes all β-lactam antibiotics; inhibited by clavulanate	*K pneumoniae*, Enterobacteriaceae
B	MBLs[2] (NDM, IMP, VIM, GIM, SPM)	Hydrolyze all β-lactams except aztreonam; may be inhibited by clavulanate; require zinc for enzymatic activity; inhibited by EDTA	*P aeruginosa*, *Acinetobacter* spp, Enterobacteriaceae
D	OXA	Oxacillin hydrolyzing; less able to hydrolyze carbapenems	*P aeruginosa*, *A baumannii*, Enterobacteriaceae

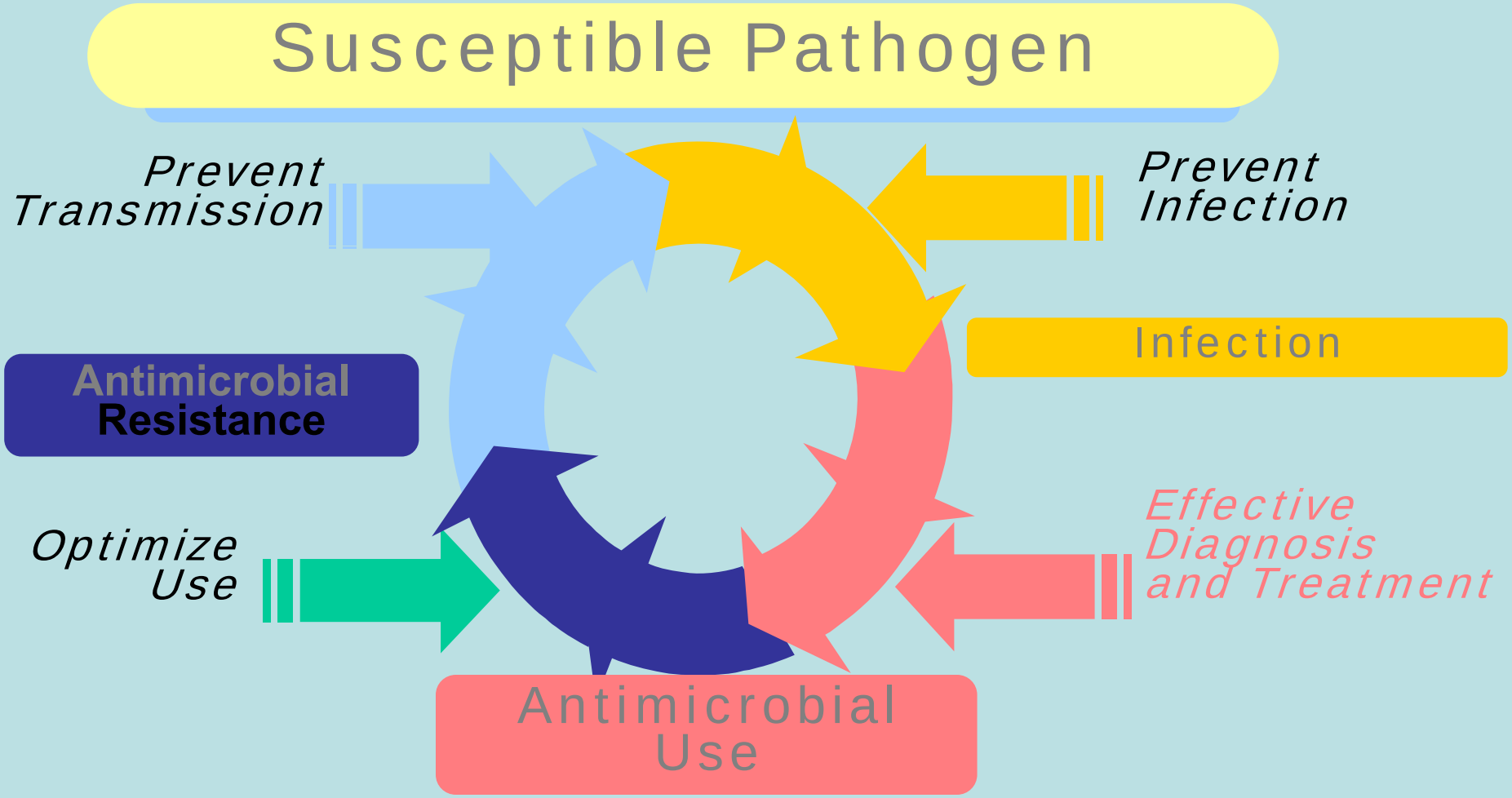
Schofeild CB, The Anarchy of Antibiotic Resistance : Mechanism of Bacterial Resistance,2010

Classification of beta-lactamases by Bush, Jacoby, and Medeiros (BJM)

Class	Representative bacteria	Beta-lactams affected	Beta-lactams not affected
I	*Pseudomonas aeruginosa*, *Enterobacter cloacae*, *Acinetobacter baumannii*	Penicillins, cephalosporins, aztreonam	Carbapenems
IIa	*Staphylococcus aureus*	Penicillins	Cephalosporins, carbapenems
IIb	*Escherichia coli*, *Klebsiella pneumoniae*, many gram-negative bacteria	Penicillins	Cephalosporins, carbapenems, aztreonam
IIbe (ESBLs)	*Escherichia coli*, *Klebsiella pneumoniae*, many gram-negative bacteria	Penicillins, cephalosporins, aztreonam	Carbapenems
IIf (KPCs)	*Klebsiella pneumoniae*	Penicillins, cephalosporins, aztreonam, carbapenems	
III (MBLs)	*Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*	Penicillins, cephalosporins, carbapenems	Aztreonam (clinical utility unknown)

Management of Antimicrobials in Infectious Disease: Impact of Antibiotic Resistance 2010

Antimicrobial Resistance: Key Prevention Strategies




Thank You