Multidrug resistant bacteria to antibiotics: a global problem

Pratiwi P. Sudarmono
Dept of Microbiology, Faculty of Medicine, University of Indonesia

Presented at "Seminar Nasional dan Diskusi Interaktif CIVAS : Ancaman Global Resistensi Antimikroba, Bagaimana Kita Harus Bertindak" , Jakarta 22 Maret 2014

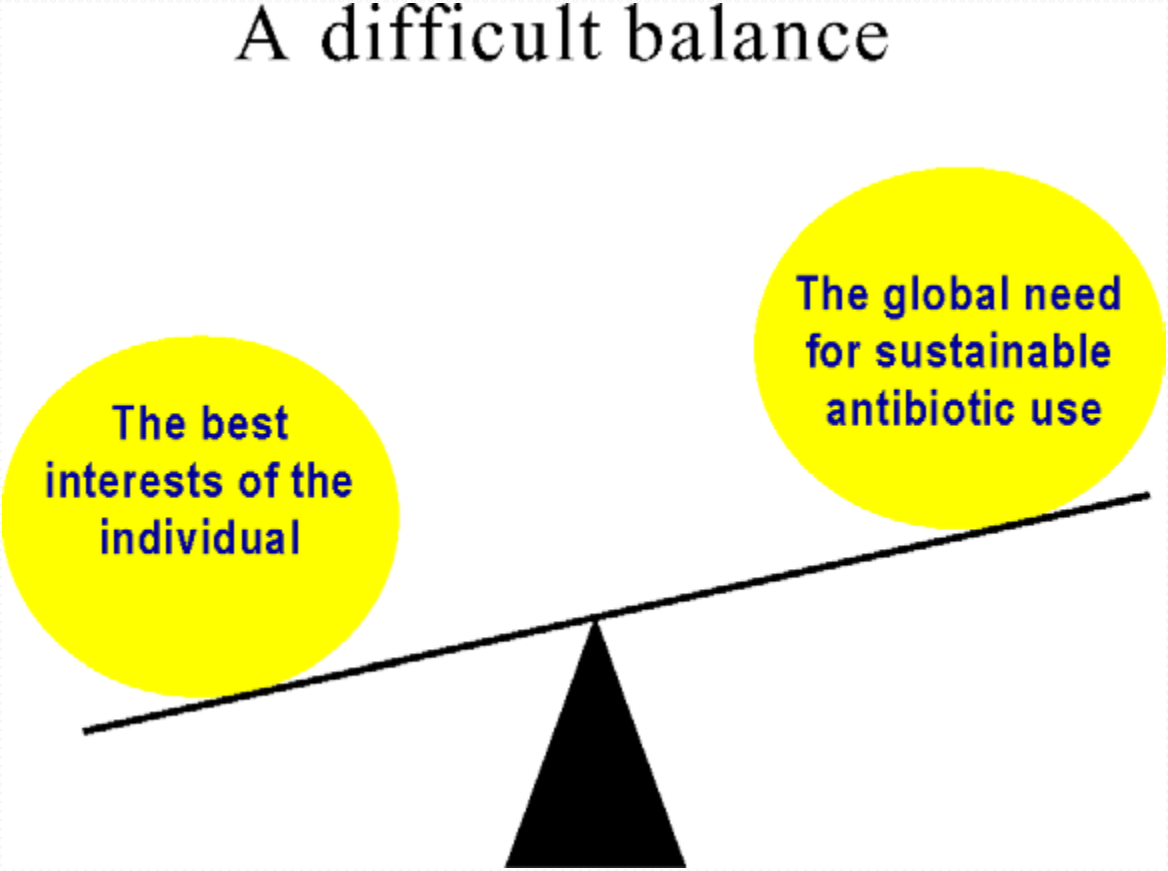
Introduction

- The introduction of antibacterial agents (commonly referred to as antibiotics) led to a revolution in the management of bacterial infections.
- Today, emerging and increasing resistance to antibiotics has become a threat to public health in Europe and globally.
- Only 70 years after their introduction, we are now facing the possibility of a future without effective antibiotics for several types of bacteria that cause infections in humans.

Reasons

- Inadequate control on over-the-counter sale and availability of antimicrobials.
- No national program for antimicrobial resistant surveillance as yet.
- Paucity of quality assuring laboratories for antimicrobial sensitivity test (AST).
- Insufficient AST data analysis and dissemination.
- Absence of national guidelines on antimicrobial use.

A difficult balance



Antibiotic resistance in the European Union

- The data presented in this section were collected by the European Antimicrobial Resistance Surveillance Network (EARS-Net) which is coordinated by the European Centre for Disease Prevention and Control (ECDC). The maps presented in this summary show the occurrence of antibiotic resistance in selected bacteria causing invasive infections and are based on laboratory results reported by countries participating in EARS-Net.

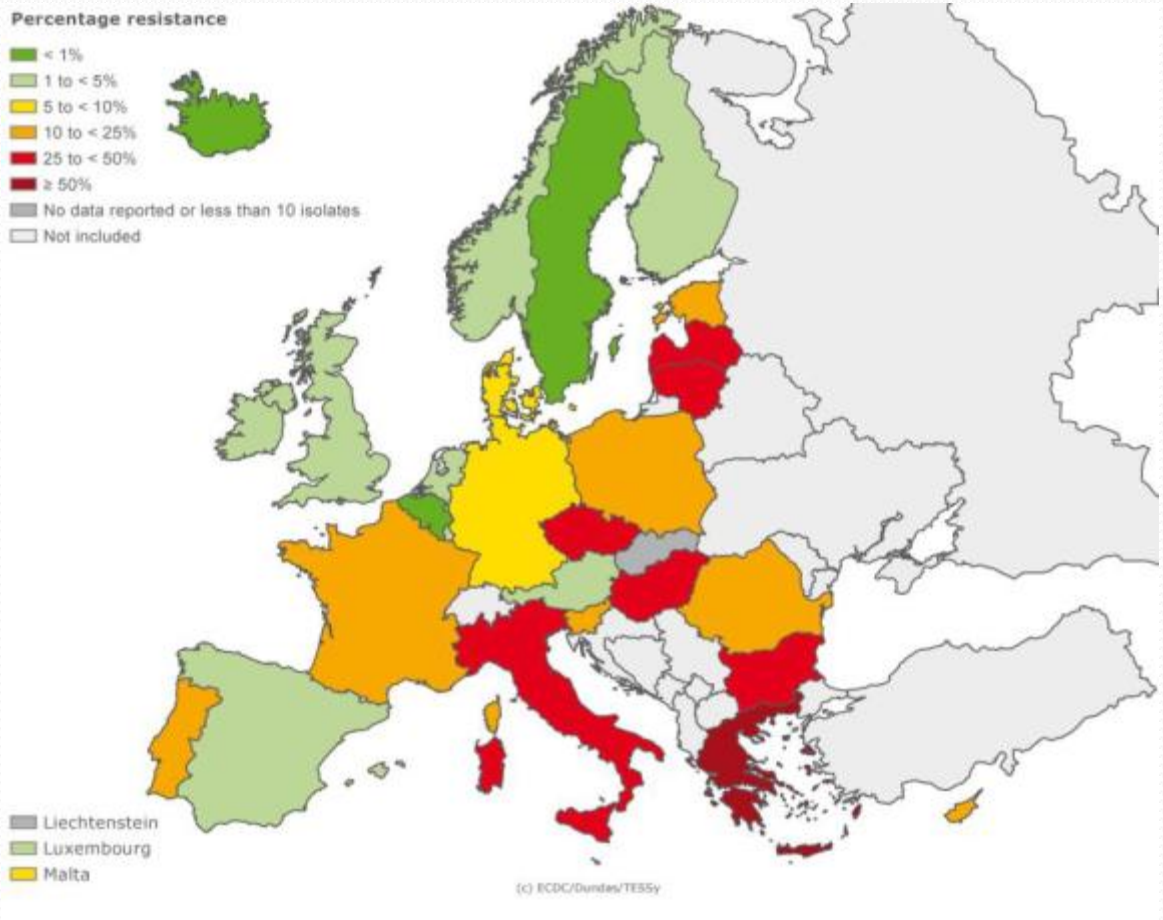
- Overall, it was estimated that in 2007 approximately 25 000 patients died from an infection due to any of the selected five antibiotic-resistant bacteria in the European Union, Iceland and Norway.

- In addition, infections due to any of the selected antibiotic-resistant bacteria resulted in approximately 2.5 million extra hospital days and extra in-hospital costs of more than EUR 900 million.

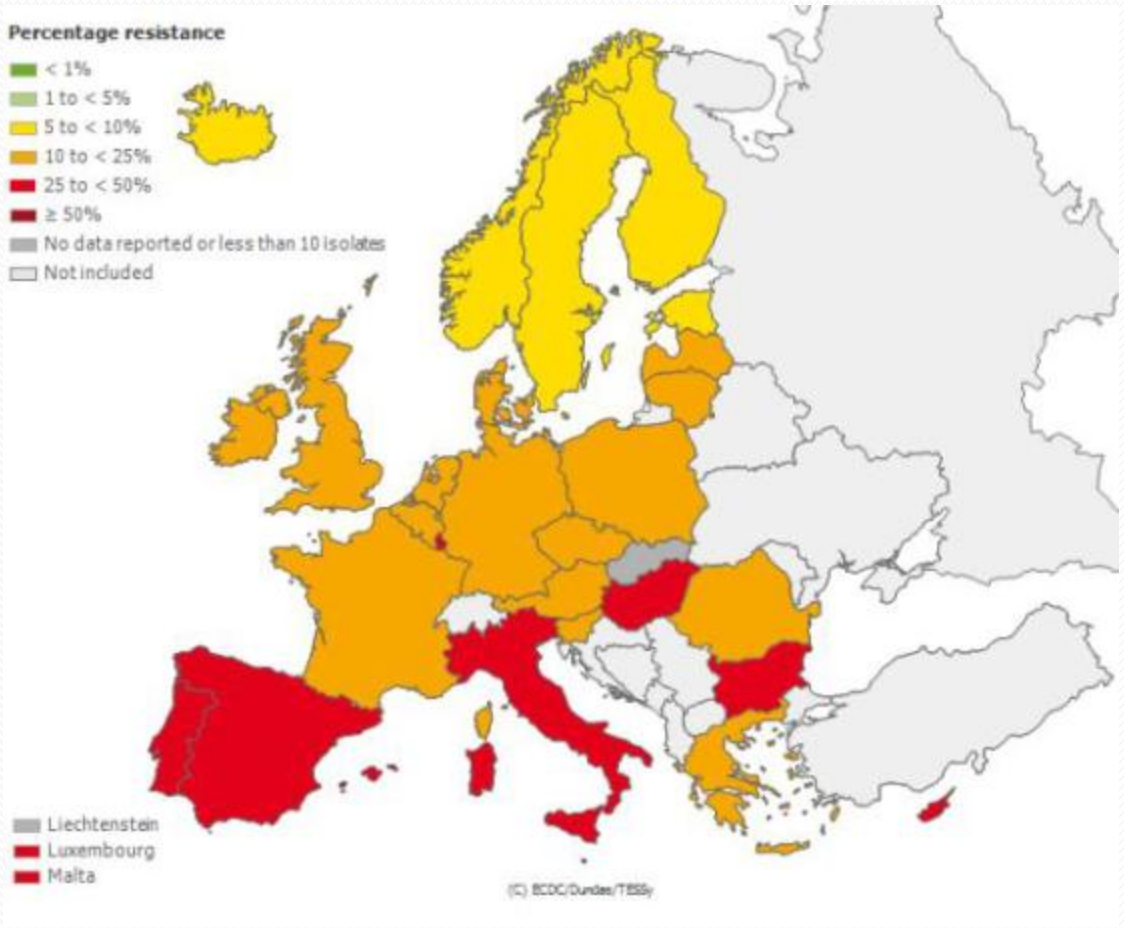
The most important MDR bacteria SUPER BUG

- *Staphylococcus aureus*, methicillin resistance (MRSA);
- *S. aureus*, vancomycin intermediate resistance and vancomycin resistance (VISA/VRSA);
- Enterococcus spp. (e.g. Enterococcus faecium), vancomycin resistance (VRE);
- Streptococcus pneumoniae, penicillin resistance (PRSP);
- Enterobacteriaceae (e.g. Escherichia coli, Klebsiella pneumoniae), third-generation cephalosporin resistance;
- Enterobacteriaceae (e.g. K. pneumoniae), carbapenem resistance; and
- Non-fermentative Gram-negative bacteria (e.g. Pseudomonas aeruginosa), carbapenem resistance.

***Klebsiella pneumoniae*: percentage of multidrug-resistant K. pneumoniae (third-generation cephalosporins, fluoroquinolones and aminoglycosides) in 2010 (Data source: EARS-Net)**



Percentage of *E. coli* resistant to fluoroquinolones in 2009



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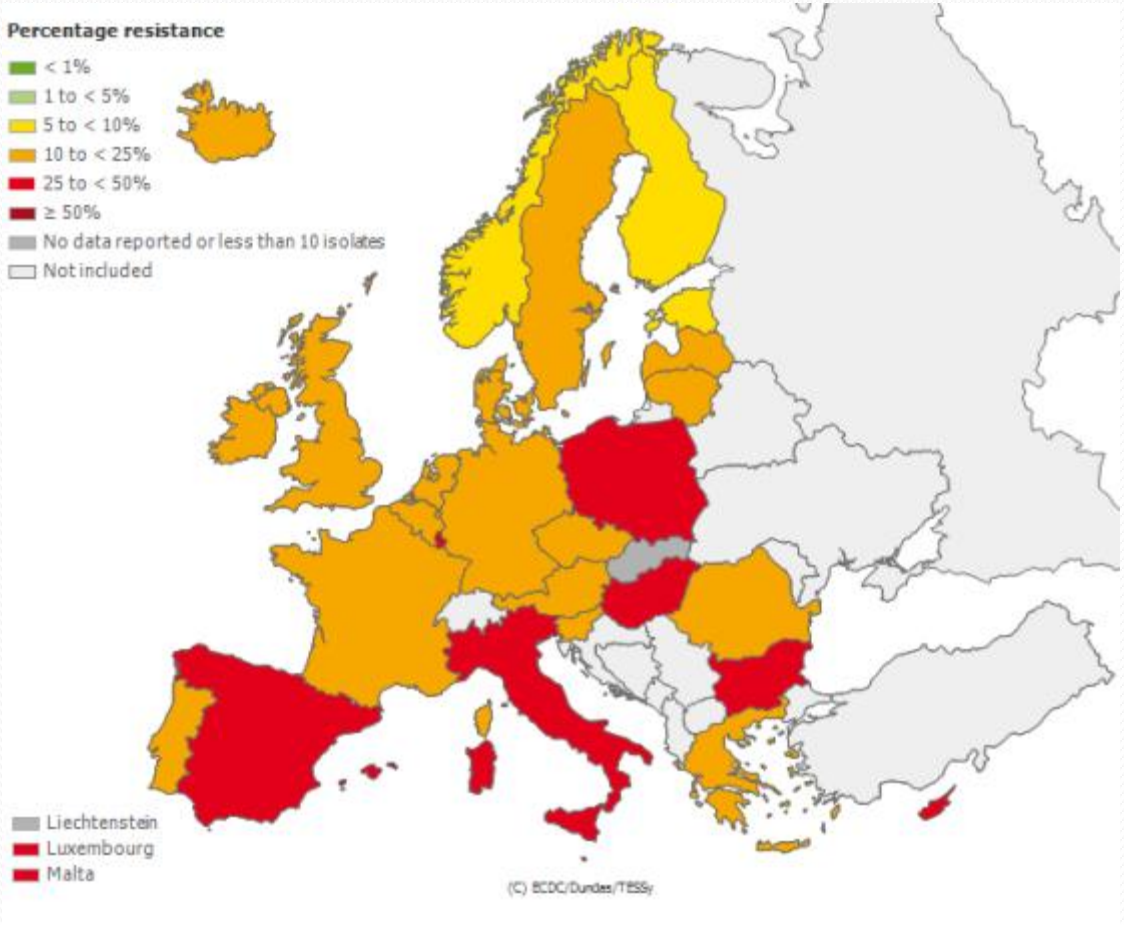
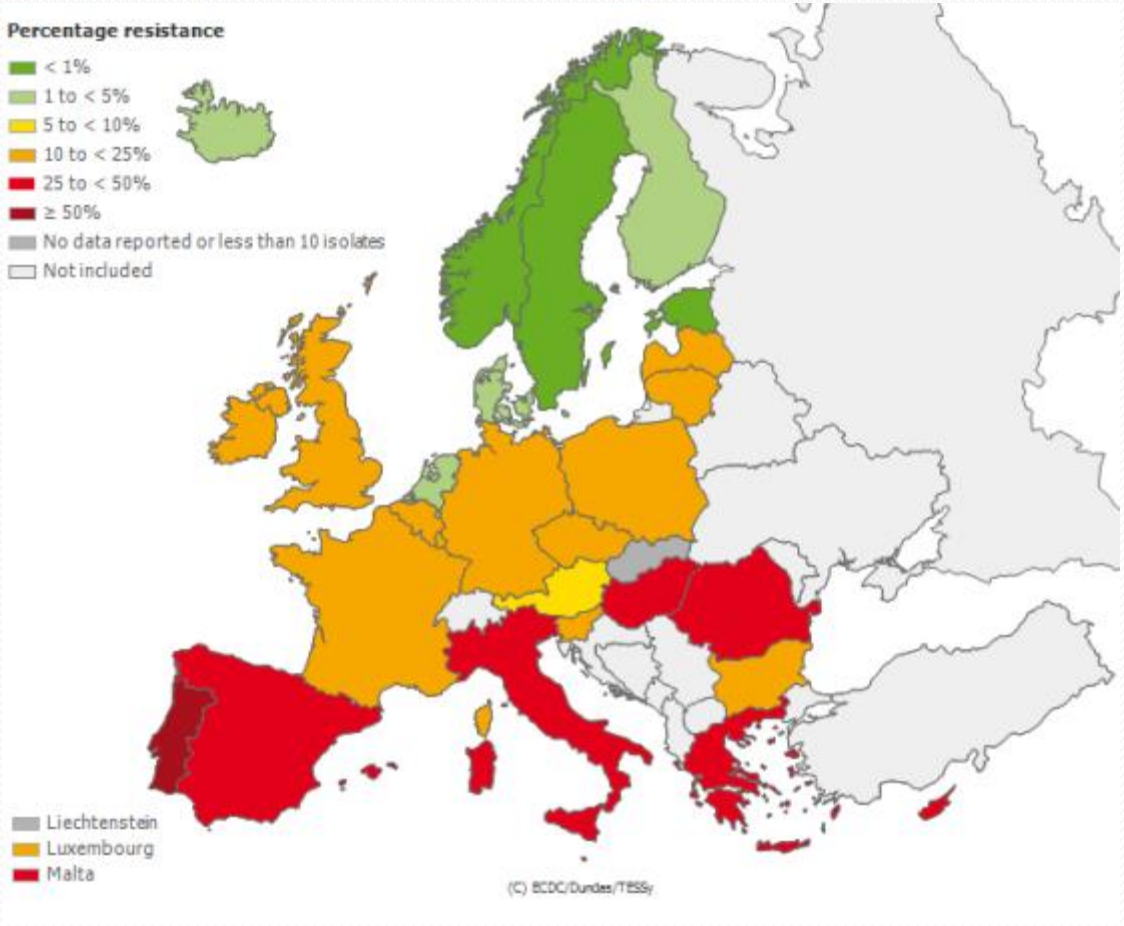
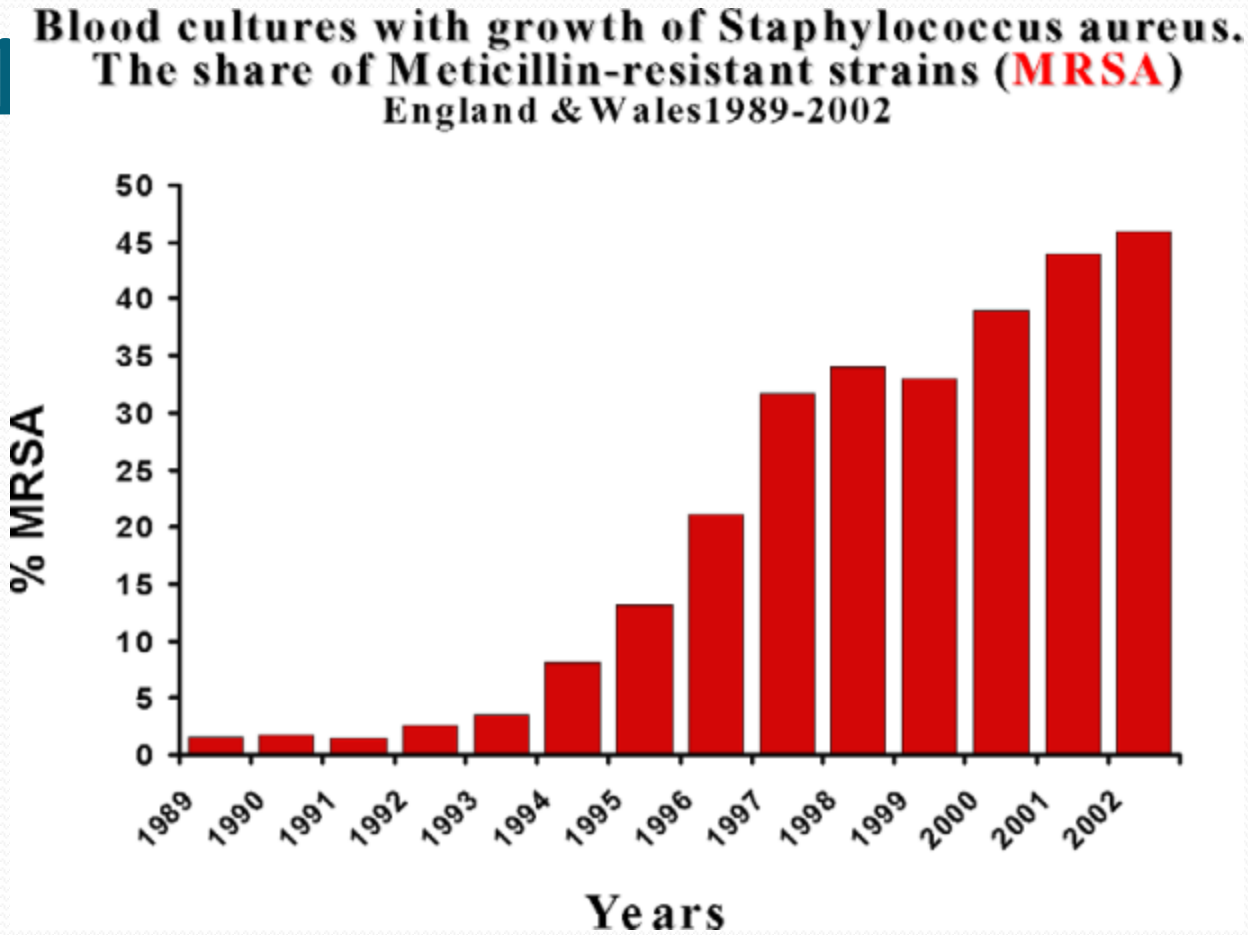


Staphylococcus aureus: percentage of invasive isolates resistant to meticillin (MRSA) and in 2010 (Data source: EARS – Net)



International Journal of Risk & Safety in Medicine 17 (2005) 103–110 1



MRSA

- first discovered in London in 1961, two years after Methicillin was first introduced to the world
- Methicillin-resistant *S. aureus produces a unique type of PBP, termed PBP2'. This protein has an extremely low affinity to beta-lactam antibiotics, allowing MRSA to continue cell-wall synthesis*
- It is known that MRSA acquired its resistance by acquisition of the mecA gene, which resides on Staphylococcal Cassette Chromosome mec (SCCmec), a mobile genetic element

- For many years, MRSA was an infection only associated to a hospital setting, invasive procedures such as urinary catheters, intra-arterial lines, or central venous lines, recent antibiotic use, or contact with health care workers. Hence, it became known as hospital-acquired MRSA or HA-MRSA.
- In recent years, its prevalence has spread to the community. We no longer have to worry only about MRSA in hospital-related settings, we now have to deal with a widespread presence of community-acquired MRSA (CA-MRSA).
- First reported in the U.S. in the 1980s, CA-MRSA carries its own set of risk factors: participation in contact sports, close contact with athletic equipment, immunosuppression, crowded or low-hygiene living conditions

- Additionally, patients are considered to not have CA-MRSA unless they have a diagnosis of MRSA made in an outpatient setting or by a culture positive for MRSA within 48 hours after admission to the hospital, and do not have a medical history of MRSA infection or colonization, admission to a hospital or hospital-like facility, on dialysis, have undergone recent surgery, or have permanent medical devices.
- CA-MRSA is different from HA-MRSA in other ways. It is believed to be more virulent

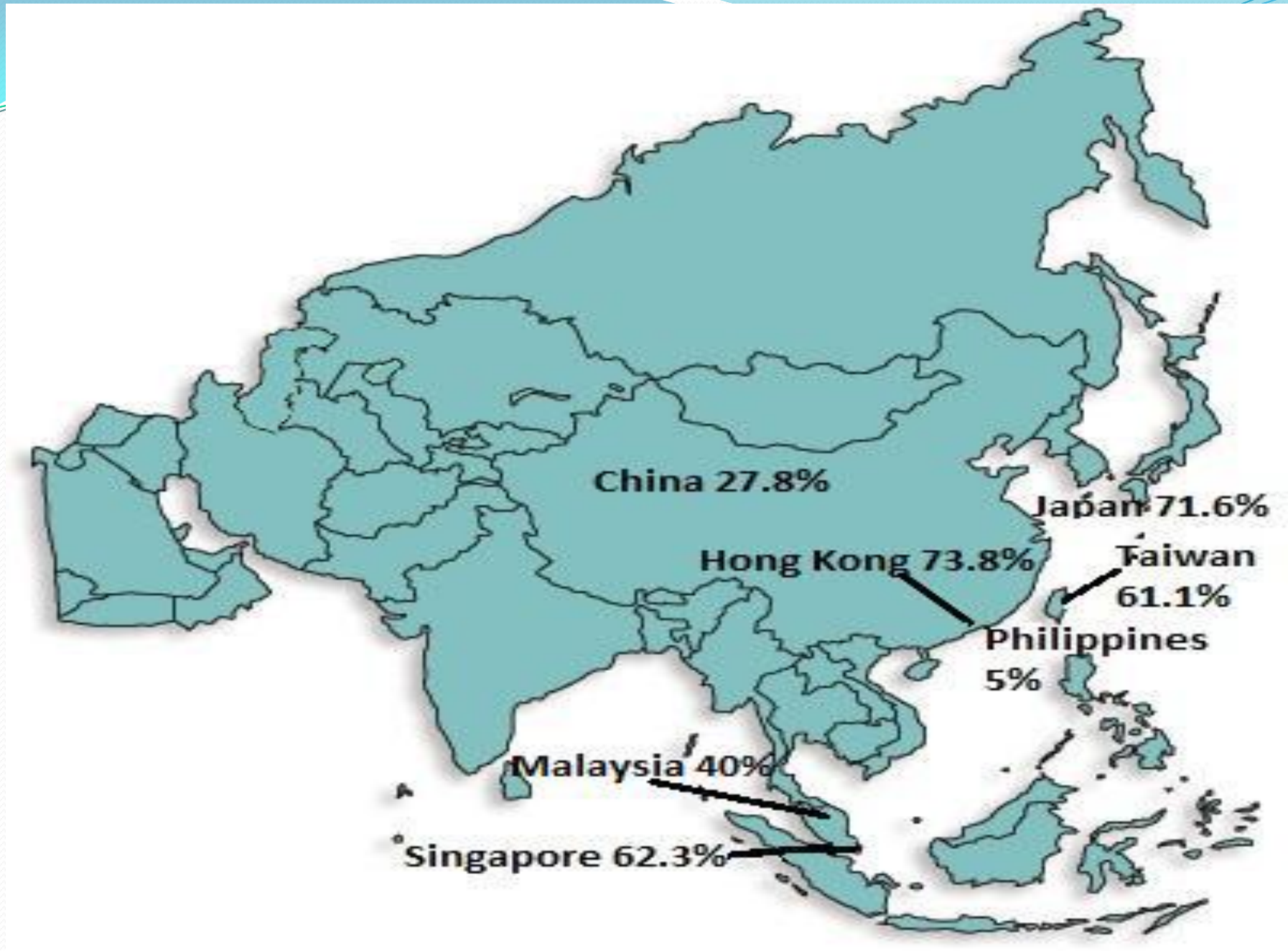
- It is believed to be more virulent due to the exotoxin Panton-Valentine leukocidin (PVL), allowing it to create pores in leukocytes. Although its relationship with PVL has been debated by some, this exotoxin is thought to be the reason why CA-MRSA is more often associated with sepsis, necrotizing pneumonia, soft tissue, and skin infections.

- It is actually estimated that 80-95% of CA-MRSA infections involve the skin and soft tissues; versus HA-MRSA, which is also linked to respiratory tract, urinary tract, and bloodstream infections.
- Furthermore, studies show the majority of CA-MRSA strains contain the SCCmec IV and SCCmec V phenotypes. They are PVL positive; while HA-MRSA are more often comprised of SCCmec I-III

Variation in rates of methicillin resistance among *Staphylococcus aureus* isolates, by nation, at European SENTRY centers, 1997—1998.

Nation[a]	No. of centers	No. of isolates (% resistant to methicillin)
Austria	1	117 (9.4)
Belgium	1	82 (25.6)
England	1	131 (27.6)
France	4	718 (21.4)
Germany	2	347 (4.9)
Greece	1	128 (34.4)
Italy	2	297 (60.5)
The Netherlands	1	147 (2.0)
Poland	2	159 (25.8)
Portugal	1	318 (54.4)
Spain	3	352 (19.3)
Switzerland	1	114 (1.8)
Turkey	1	104 (37.6)

[a] Only nations submitting ≥50 isolates are included.


China 27.8%
Japan 71.6%
Hong Kong 73.8%
Taiwan
61.1%
Philippines
5%
Malaysia 40%
Singapore 62.3%

Molecular epidemiology surveillance

- Multilocus sequence typing (MLST) is a technique in molecular biology used to characterize bacterial species using DNA sequences of internal fragments of multiple housekeeping genes.
- Pulsed-field gel electrophoresis (PFGE) is considered the gold-standard; but this technique is often not used due to its time commitment and required experience.
- Although MLST is expensive and has a lesser discriminatory power than PFGE, its clear protocols and ability to be highly reproducible make it a favorite of researchers working on population genetics.
- The majority of the studies used MLST and SCCmec phenotyping as parameters to identify MRSA clones, using the five major SCCmec phenotypes.
- SSCmec VI and VII have been recently discovered.

- The first MRSA strain (NCTC 10442), isolated during 1961 in the UK, harboured SCCmec type I, and this so-called archaic clone spread around theworld during the 1960s.
- In 1982, an MRSA strain (N315) with SCCmec type II was discovered in Japan, and this New York/Japan clone also

  spread worldwide;
- this was followed by the discovery in 1985 of an MRSA strain (85/2082) harbouring SCCmec type III in New Zealand.
- MRSA strains harbouring SCCmec IV spread round the world during the 1990s,
- beginning of the 21st century, the first MRSA strain (WIS) with SCCmec type V was described in Australia

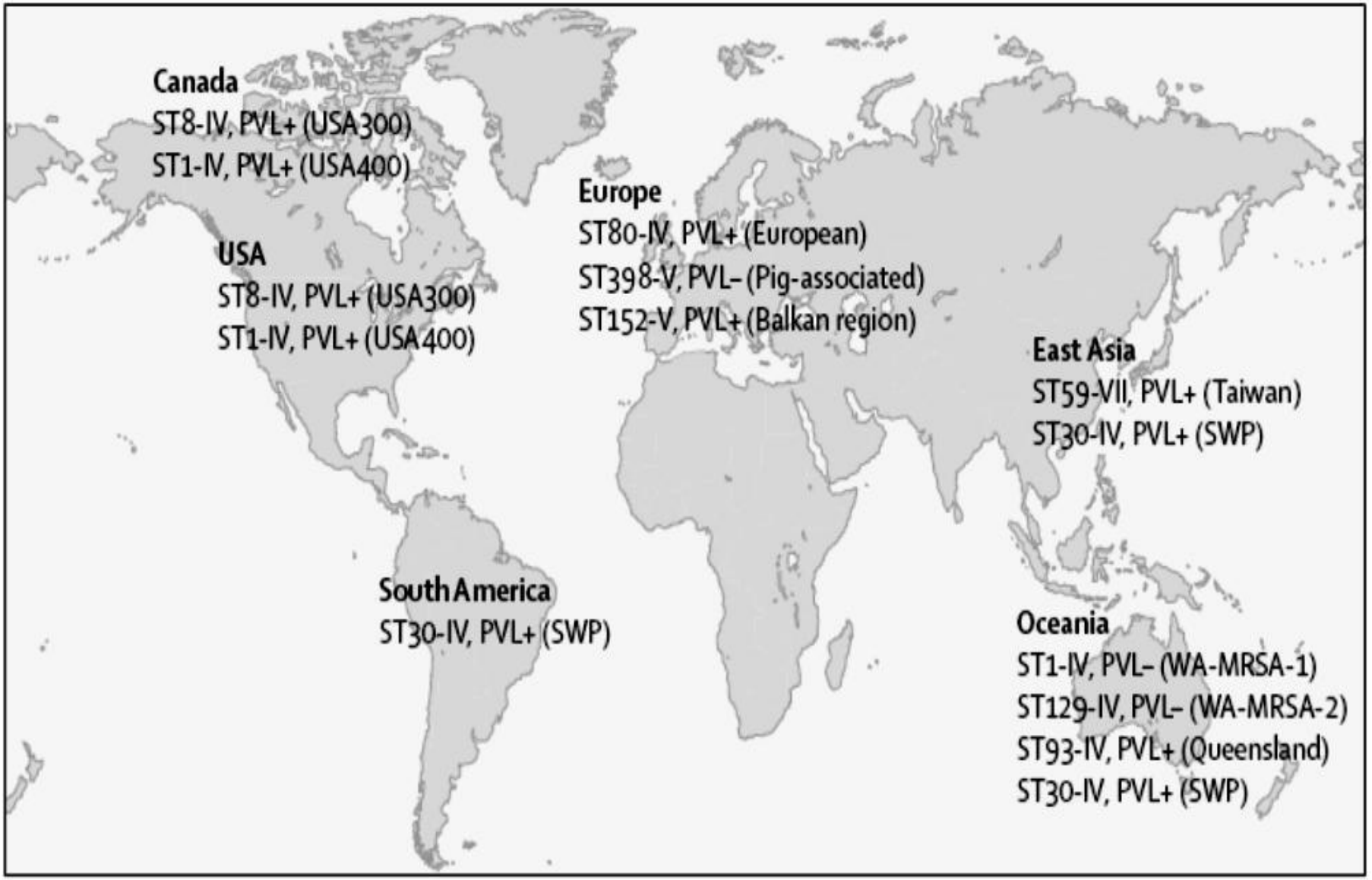


Figure: **Global distribution of predominant successful clones of community-associated meticillin-resistant *Staphylococcus aureus***

PVL+=Panton-Valentine leukocidin positive. PVL–=PVL negative. SWP=southwest Pacific. WA=western Australia.

Panel: **Five predominant health-care-associated MRSA MLST clonal complexes[14]**

The most frequent examples of clones within each complex are shown

CC5
ST5 SCC*mec* type II (New York/Japan)
ST5-IV (paediatric)
ST228-I (southern German)

CC8
ST250-I (Archaic clone)
ST8-IV (EMRSA -2,-6)
ST8-II (Irish-1)
ST239-III (Brazilian/Portuguese)
ST247-I (Iberian)

CC22
ST22-IV (EMRSA-15)

CC30
ST36-II (EMRSA-16)

CC45
ST45-IV (Berlin)

ST=multilocus sequence type.

- In an international study, which included 615 isolates from 11 Asian counties, it was observed that the majority of the strains belonged to ST239-III (in Saudi Arabia, India, Sri Lanka, Singapore, Indonesia, Thailand, Vietnam, Philippine, and China) and ST5-II (in Japan and Korea), both being known HA-MRSA clones

MRSA in Indonesia (U.C.Warsa et al , Journal of Infection and Chemotherapy March 1996, Volume 2, Issue 1, pp 29-33

- A total of 814 strains of *Staphylococcus aureus* isolated from clinical specimens in Jakarta from 1986 through 1993 were examined for their susceptibility to 18 antimicrobial agents. Strains with multiple resistance against sulfanilamide, penicillin, tetracycline, and chloramphenicol predominated. Strains resistant against new broad-spectrum antimicrobial agents, such as β-lactams, macrolides, aminoglycosides, and quinolones, increased rapidly after 1990.
- The incidence of methicillin-resistant*S. aureus* (MRSA), which increased from 2.5% in 1986 to 9.6% in 1990, partly accounted for the increased frequency of strains in *S. aureus* resistant to multiple drugs.
- All MRSA strains were coagulase type IV.
- On phage typing, 58.6% of methicillin-susceptible strains (MSSA) and 66.7% of MRSA strains were nontypable by routine test dilution (RTD).
- The predominant phage groups in MSSA and MRSA were group II (21.5%) and group III (19.0%), respectively.

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Antibiotic resistance as a global threat: Evidence from China, Kuwait and the United States

Ruifang Zhang[1], Karen Eggleston*[2], Vincent Rotimi[3] and Richard J Zeckhauser[4]

Address: [1]Goldman Sachs International, Global Investment Research, London, UK, [2]Tufts University Economics Department, Medford, MA 02155, USA, [3]Department of Microbiology, Faculty of Medicine, Kuwait University, Kuwait and [4]Harvard University Kennedy School of Government, Cambridge, MA, USA

Email: Ruifang Zhang - ruifang.zhang@gs.com; Karen Eggleston* - karen.eggleston@tufts.edu; Vincent Rotimi - vincent@HSC.EDU.KW; Richard J Zeckhauser - richard_zeckhauser@harvard.edu

* Corresponding author

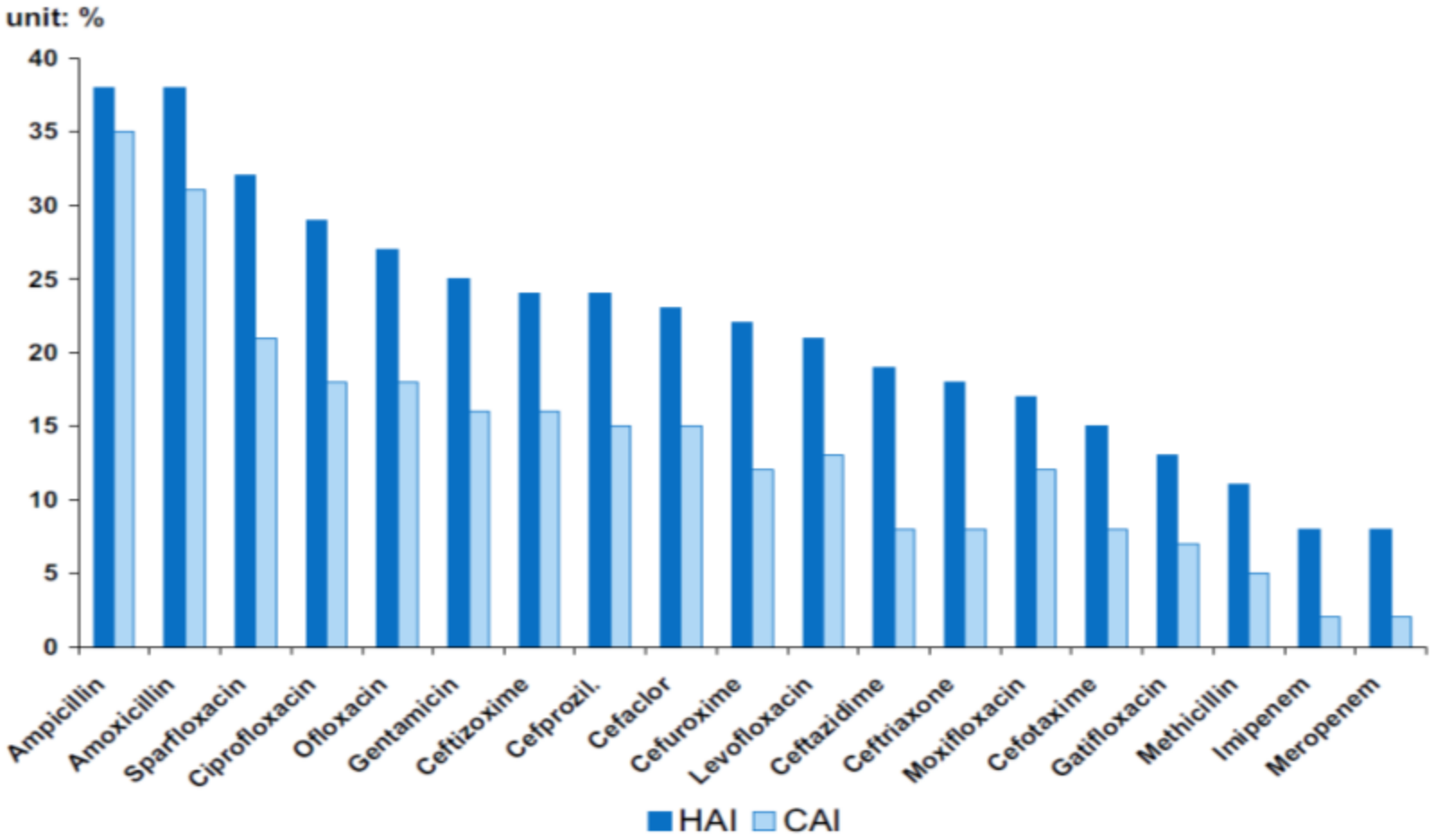

Figure 2
Hospital-acquired infections (HAI) are more resistant than community-acquired infections (CAI) to a wide range of antibiotics in China.

Table 5: Resistance prevalence of eight common bacteria, U.S. (all patients pooled), 1999–2002

unit: %

Bacterium	Resistant to antibiotic(s)	1999	2000	2001	2002	*Average Resistance*	*Average Growth Rate*
PAE	Ciprofloxacin /ofloxacin	23	25	28	29	***26***	***8***
	Levofloxacin	29	30	31	30	***30***	***1***
	Imipenem	12	12	15	13	***13***	***4***
	Ceftazidime	8	8	9	9	***9***	***4***
	Piperacillin	10	10	11	12	***11***	***6***
SAU (MRSA)	Methicillin	32	35	38	39	***36***	***7***
Enterococcus spp	Vancomycin	11	8	10	10	***10***	***-1***
ECO	Cef3	1	1	1	1	***1***	***0***
	Quinolone	2	3	4	5	***4***	***36***
KPN	Cef3	4	4	4	5	***4***	***8***
Enterobacter spp	Cef3	19	19	18	19	***19***	***0***
	Carbapenum	1	1	1	1	***1***	***0***
CNS	Methicillin	60	61	62	63	***62***	***2***
Pneumococcus spp	Penicillin	14	16	19	19	***17***	***11***
	Cef3	5	8	7	7	***7***	***16***
	Mean:					***17***	***7***

Table 1: Resistance prevalence of ten common bacteria to Ciprofloxacin in China, 1994–2000

unit: %

Rank	Bacter.		1994	1995	1996	1997	1998	1999	2000	*Average Resistance**	*Average Growth Rate**
1	Escherichia coli (ECO)		53	49	60	61	60	63	62	***59***	***3***
2	Pseudomonas aeruginosa (PAE)		9	10	7	18	13	17	18	***13***	***17***
3	Klebsiella pneumoniae (KPN)		2	4	7	8	14	17	18	***10***	***40***
4	Staphylococci epidermidis (SEP)		22	33	34	35	41	40	46	***36***	***9***
5	Staphylococci aureus (SAU)	MRSA**	47	65	74	88	83	78	76	***76***	***7***
		MSSA**	8	18	10	5	8	20	14	***11***	***8***
6	Enterococcus faecalis (EFA)		25	34	28	34	32	45	45	***34***	***9***
7	Enterobacter cloacae (ECL)		12	9	13	14	22	31	30	***18***	***26***
8	Acinetobacter baumannii (ABA)		7	7	19	20	23	31	37	***20***	***29***
9	Citrobacter freundii (CFR)		10	21	20	17	22	26	26	***20***	***10***
10	Proteus mirabilis (PMI)		8	2	13	2	5	14	12	***7***	***10***
		Mean								***28***	***15***
		Median								***20***	***10***

* Based on three-year running averages.

** Staphylococci aureus (SAU) is further grouped as methicillin susceptible staphylococci aureus (MSSA) and methicillin resistant staphylococci aureus (MRSA).

Table 9: Percentage of *Staphylococcus aureus* resistant to often-tested antibiotics over 5 years in Kuwait

Antibiotic	Percentage (%) of resistant isolates in:				
	1999 (n = 648)	2000 (n = 595)	2001 (n = 484)	2002 (n = 420)	2003 (n = 286)
Ampicillin	96	100	98	96	98
Amoxicillin-clavulanic acid	6	33	27	22	29
Cephalexin	33	30	25	36	34
Ciprofloxacin	10	35	30	45	50
Clindamycin	18	24	20	20	27
Cloxacillin	23	24	9	22	17
Erythromycin	38	34	26	28	27
Fusidic acid	NA	20	19	64	27
Gentamicin	25	21	16	24	27
Methicillin	23	24	9	22	17
Penicillin	95	95	99	96	99
Teicoplanin	0	0	0	0	0
TMP/SMX	24	27	31	18	94
Vancomycin	0	0	0	0	0

ESBL in Indonesia

- **Prevalensi Kuman ESBL *(Extended Spectrum Beta Lactamase)* dari Material Darah di RSUP Dr. Kariadi Tahun 2004-2005**
- Winarto *
- *M Med Indones,* **Volume 43, 5, 2009**

- *Four thousand three hundred and fifty blood samples were examined during 2 years periode with culture positive rate*
- *34.76% consist of gram negative bacteria 59.6% in which ESBL bacteria was 50.6%.*
- *ESBL bacteria significantly high recovered from intensive wards. Predominance bacteria were Ps. aeruginosa (50.9%), E. aerogenes (37.5%) and E. coli (8.7%).*

Sensitivity patterns to

meropenem >82.2%,

quinolone >65.6% except Ps. aeruginosa 52.5%,

fosfomisin >74% except Ps. aeruginosa 15.5%,

amikacin >82% except Ps. aeruginosa 20.6%.

conclusion

- MDR in pathogenic bacteria is becoming a global health problem, give a very big disease burden
- Special attention is necessary to find better strategy for disease management, mainly in MRSA, ESBL, increased resistant in acute infection as well as hospital acquired infection

Thank you