Antibiotic use, resistance and Hospital Acquired Infections with G- carbapenem resistant G- nosocomial infections

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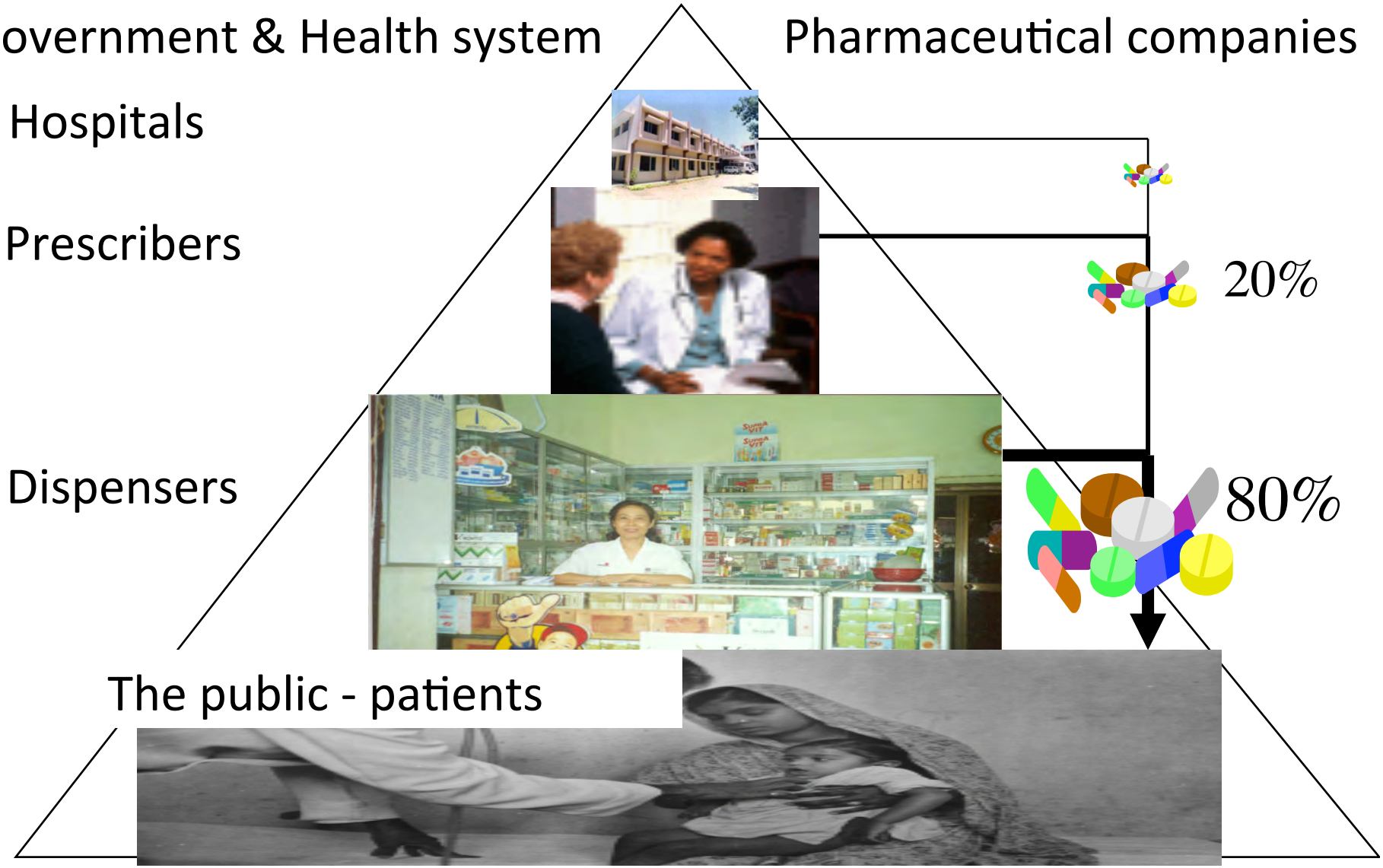
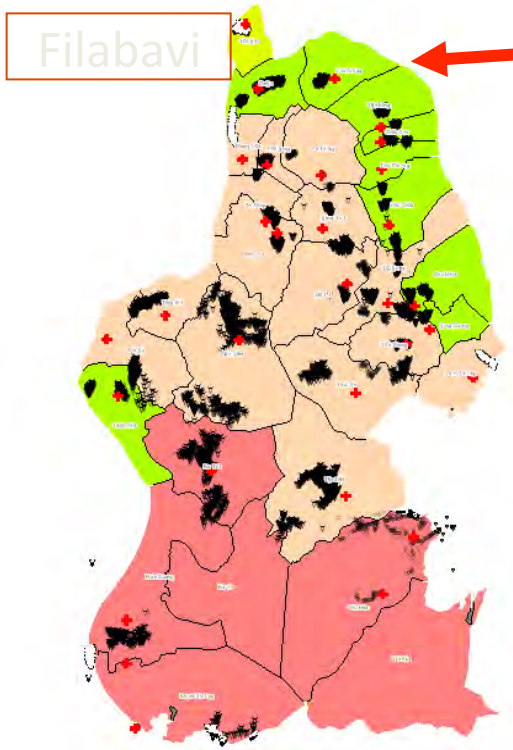
Training and Research Academic Collaboration (TRAC) Sweden – Vietnam

Linköping University, Karolinska Institutet and Vietnam National Childrens Hospital

Where does the antibiotrics come from?



Vietnam study sites



Bavi district

410 km2;

476 person/km2

247,000 persons

Descriptive study:
using quantitative and qualitative approaches

Hanoi city

920 km2;

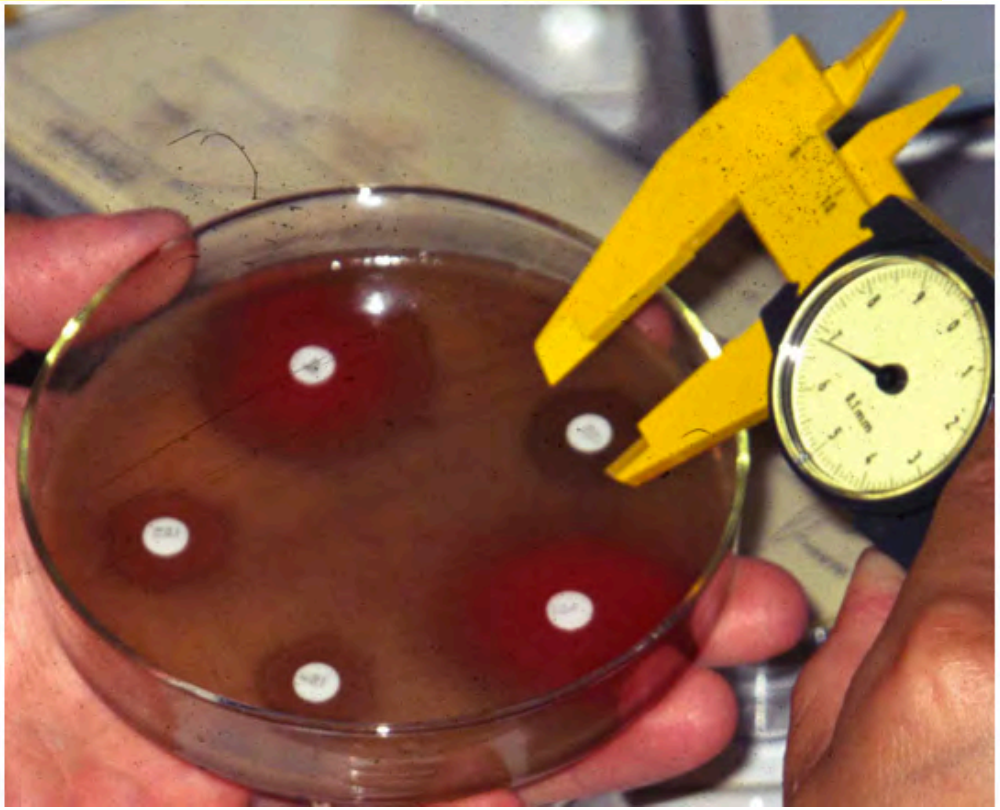
3,415 person/km2

4,5 million persons

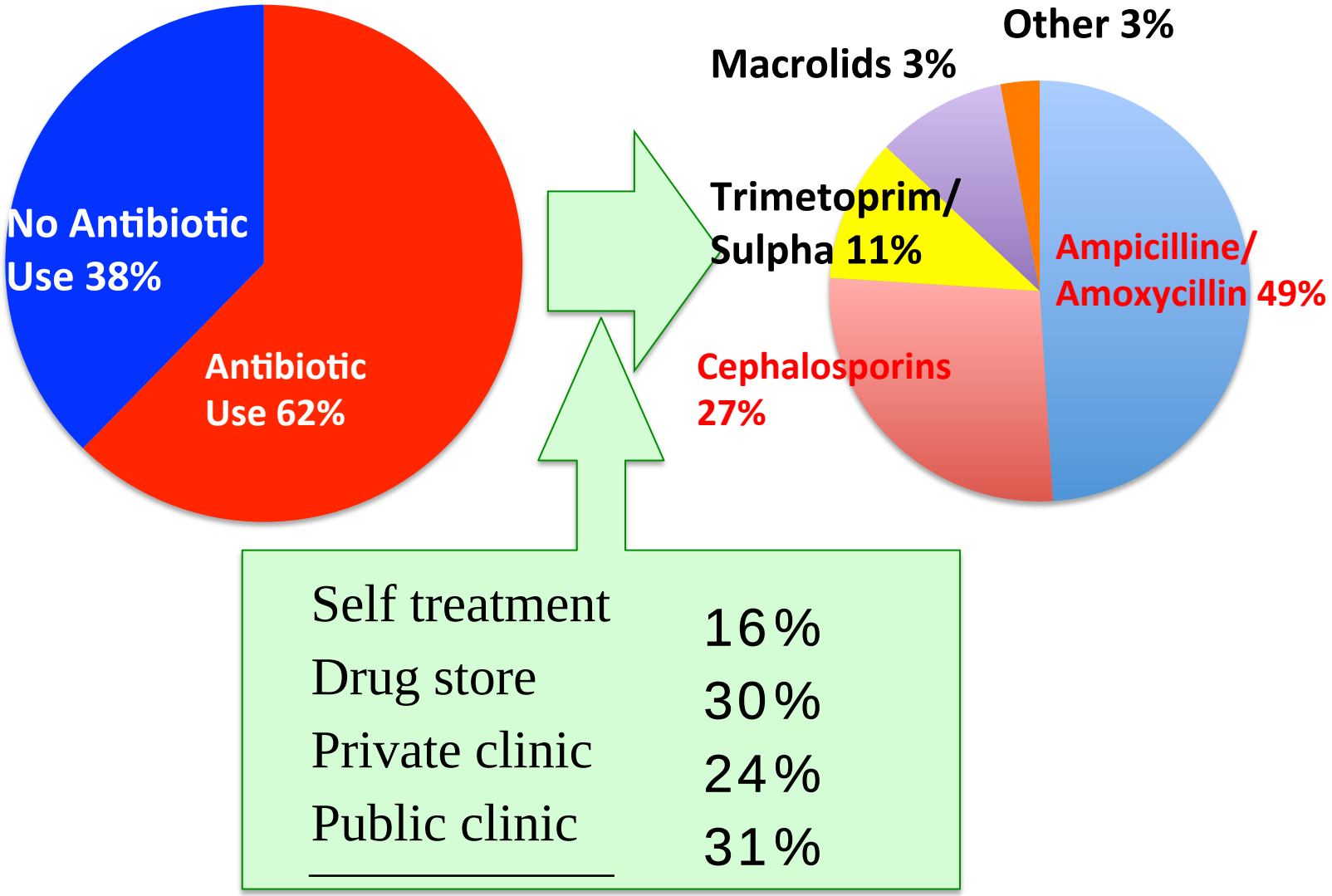
Antibiotic use and resistance community studies in Bavi 1999, 2007 and 2013

Method 1. Questionnaire assessing antibiotic use in the study population through interviews with the caretakers. Four trained interviewers conducted the interviews.

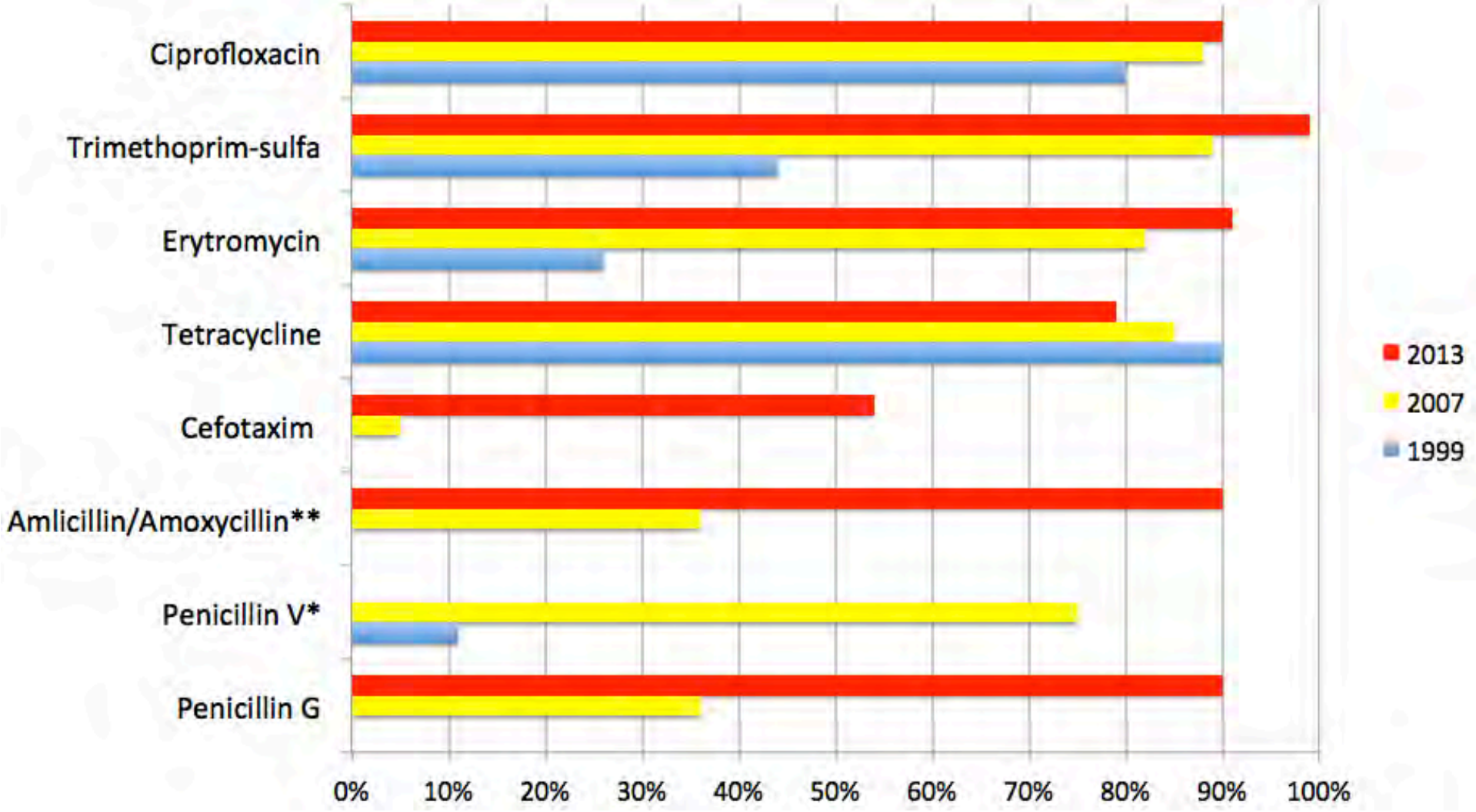
Method 2. Naso-pharynx and throat specimens were collected from the study population. Respiratory isolates were tested for antibiotic susceptibility according to the standard disk diffusion method.



Antibiotic use among 823 children during 28 days in Bavi 2007



S.pneumoniae resistance trends among children in Bavi community 1999, 2007and 2013



80% resistant to three or more antibiotics (2013)

Observational Study

VINA RES

Medicine

OPEN

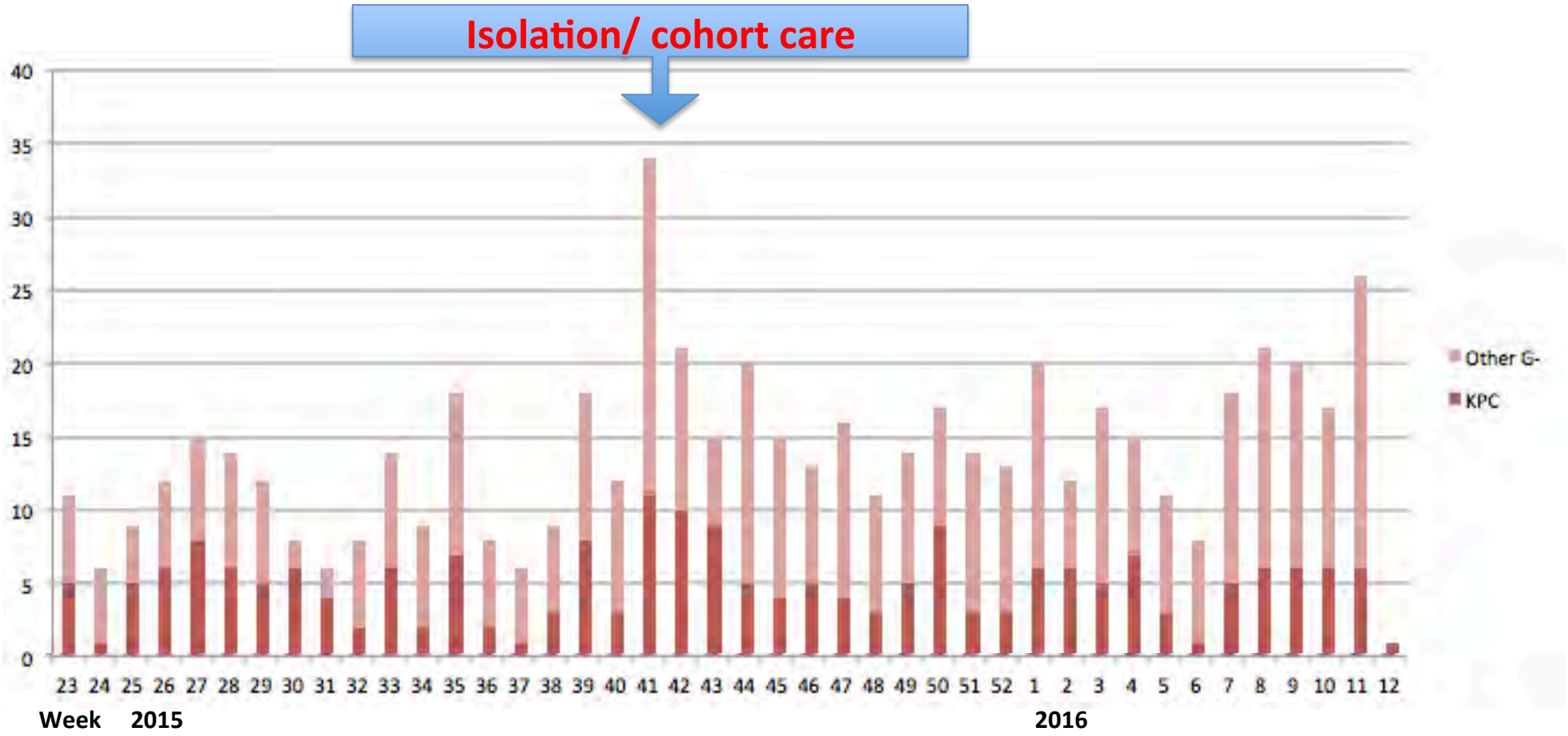
High prevalence of hospital-acquired infections caused by gram-negative carbapenem resistant strains in Vietnamese pediatric ICUs

A multi-centre point prevalence survey

Ngai Kien Le (MD, PhD)[a,*], Wertheim HF (MD, PhD)[b,c], Phu Dinh Vu (MD)[d], Dung Thi Khanh Khu (MD, PhD)[a], Hai Thanh Le (MD, PhD)[a], Bich Thi Ngoc Hoang (MD)[a], Vu Thanh Vo (MD, PhD)[e], Yen Minh Lam (MD)[f], Dung Tien Viet Vu (Master)[b], Thu Hoai Nguyen (MD)[a], Tung Quang Thai (MD)[e], Lennart E. Nilsson (PhD)[g], Ulf Rydell (MB, MSc (Pharm))[g], Kinh Van Nguyen (MD, PhD)[f], Behzad Nadjm (MBChB, MD)[b], Louise Clarkson (MD, MSc)[h], Håkan Hanberger (MD, PhD)[g], Mattias Larsson (MD, PhD)[b,h,]

- Point Prevalence Survey during 1 years (2013)
- 1363 cases (1143 children), 59.9% male, average age 11 months.
- Intubation 47.8%, CVC 29.4%, PVC 86.2%,
- HAI rate 33.1%. 276 isolates (43%): 50 Klebsiella pneumoniae Carbapenem resistance (CR) 55%, 46 Pseudomonas aeruginosa CR 71%, and 39 Acinetobacter baumannii CR 65%.
- Diagnosis: pneumonia (52.2%), septicemia (26.4%)
- Risk factors : age <7 months & intubation.
- Antibiotics 87.6%, 1.6 antibiotics per case.
- Colistin 96 patients (8%), CR in 49%.

Cases of Carbapenem Resistant G- per week
NHP weeks 23 2015 → 12 - 2016



- **12% blood culture → septicemia**
- **46% tracheal fluid, 34% nasopharynx → etiology/colonization?**

Material/methods

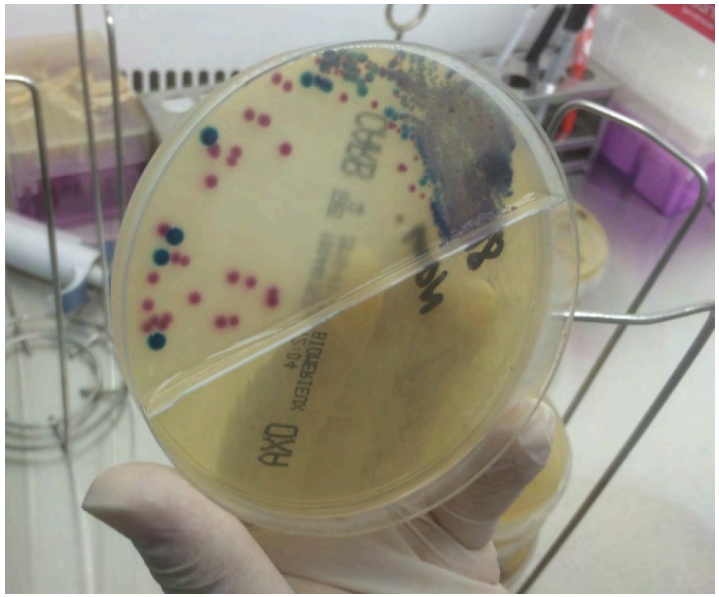
- De novo whole-genome sequencing (WGS) with the Illumina MiSeq platform
- 106 clinical isolates of KPC from 104 patients.
- Antimicrobial susceptibility testing with E-test.
- Sequence types **(**STs) and resistance genes.
- MDR = resistance to three or more antibiotics.
- Clinical data from the children was collected retrospectively from patient records.
- Cross sectional screening of 1046 patients at NHP February 2016 using chromogenic agar
- Continues data collection using on-line questionnaire

Results - clinical

- 104 children with culture confirmed Carbapenem Resistant *Klebsiella Pneumoniae* (106 specimen)
- Male 76 (74%)
- Average age: 6.9 months
- Department: Neonatal ICU 39, Pediatric ICU 22 and Surgical ICU 22.
- Origin: other hospitals 71, community 16.
- Diagnosis : pneumonia 32, respiratory failure 17 and septicaemia 12.
- Intubated 70, CVC 56
- Specimen : Tracheal Fluid 58, Naso-pharyx 29, Blood 9.
- Treatment outcome : Discharge 52, withdraw from treatment (Xin Ve) 32, death 7, in-treatment 6 and unknown 9 cases.

Cross sectional screening of 1046 patients

- NHP February 2016
- Faecal samples
- Chromogenic agar, selective for carbapenem resistant strains



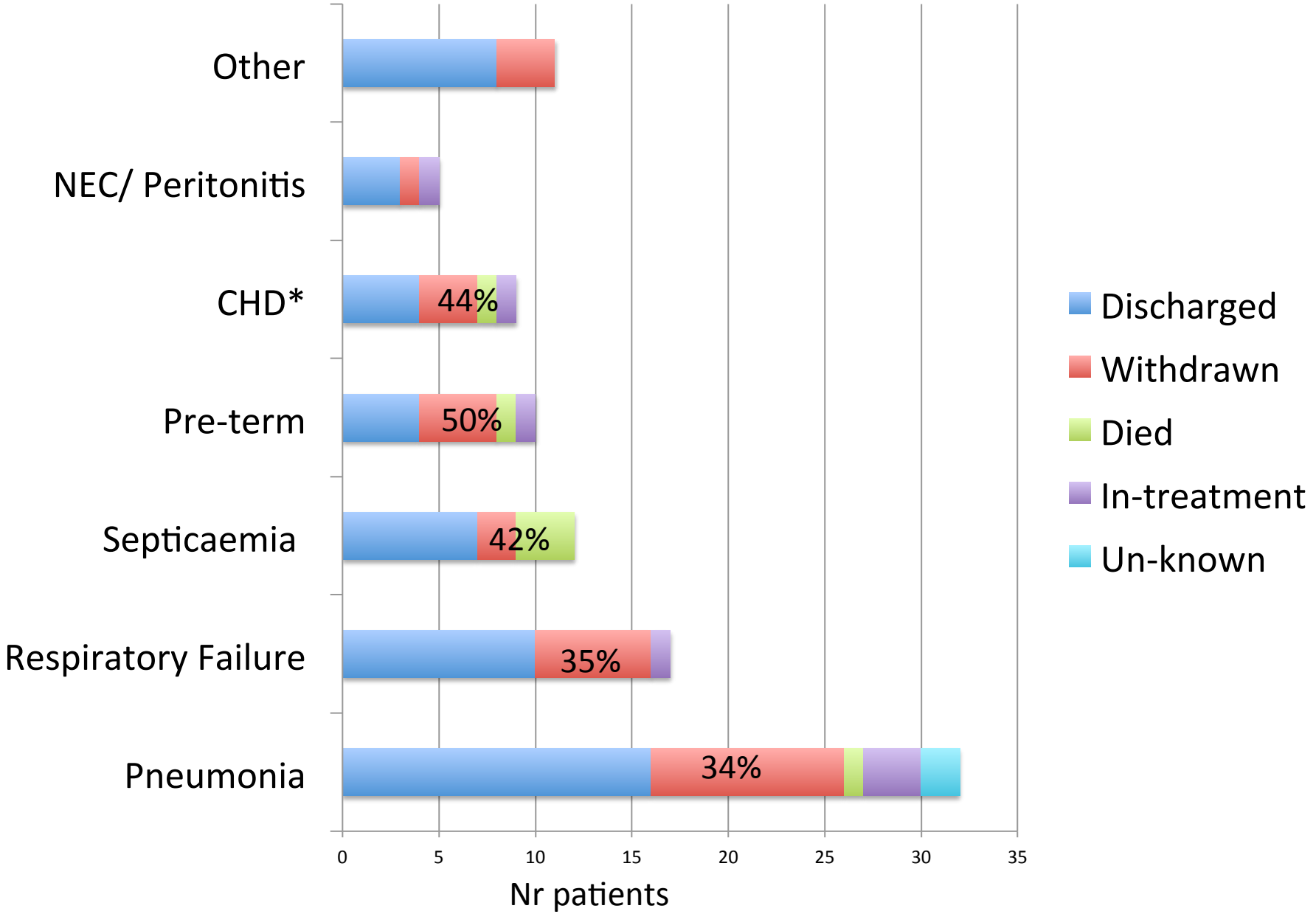
Colonization rate with carbapenem resistant G- bacteria

Whole hospital : 36%

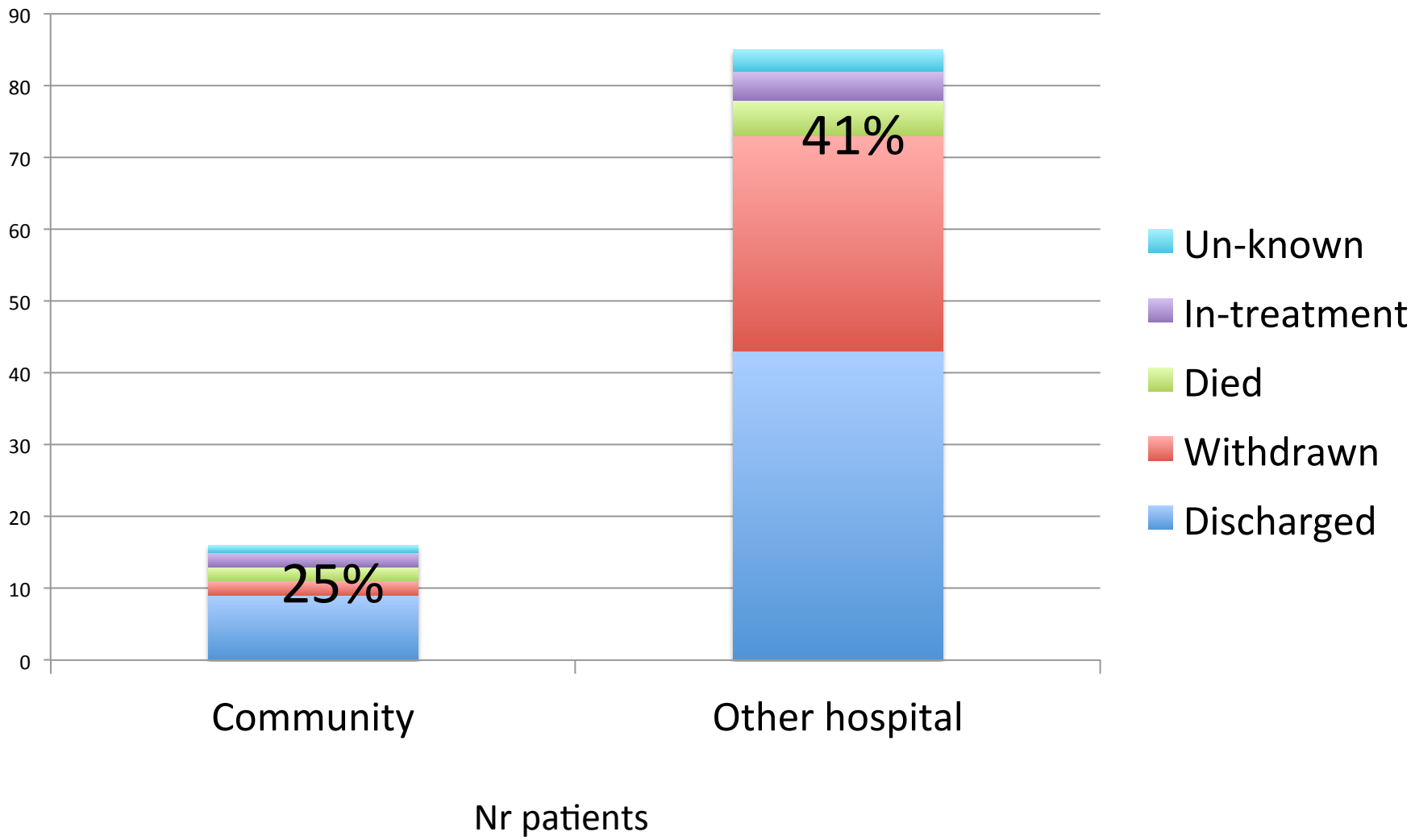
Medical and surgical ICU : 50%

Neonatal ICU : 63%

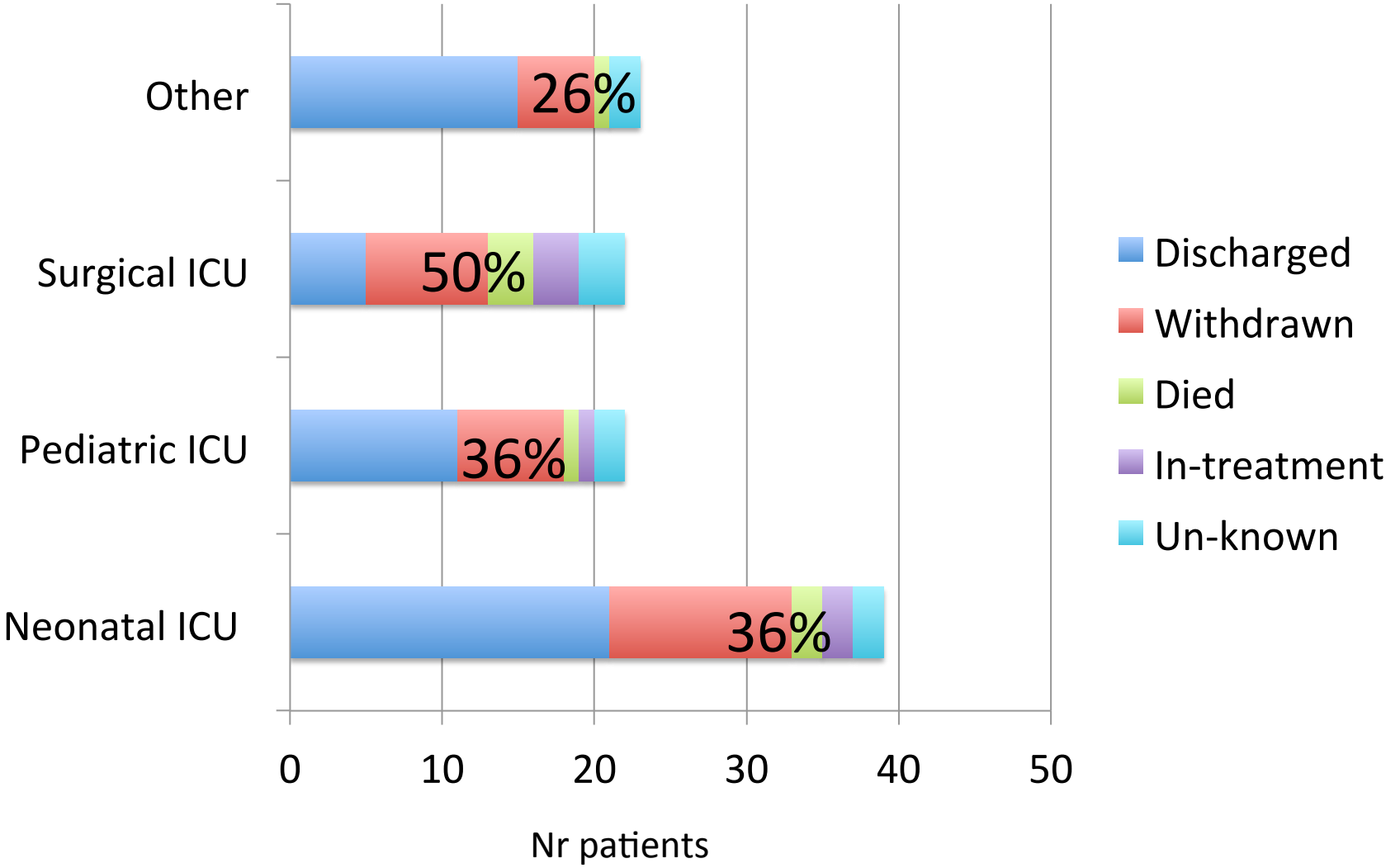
Diagnosis vs outcome



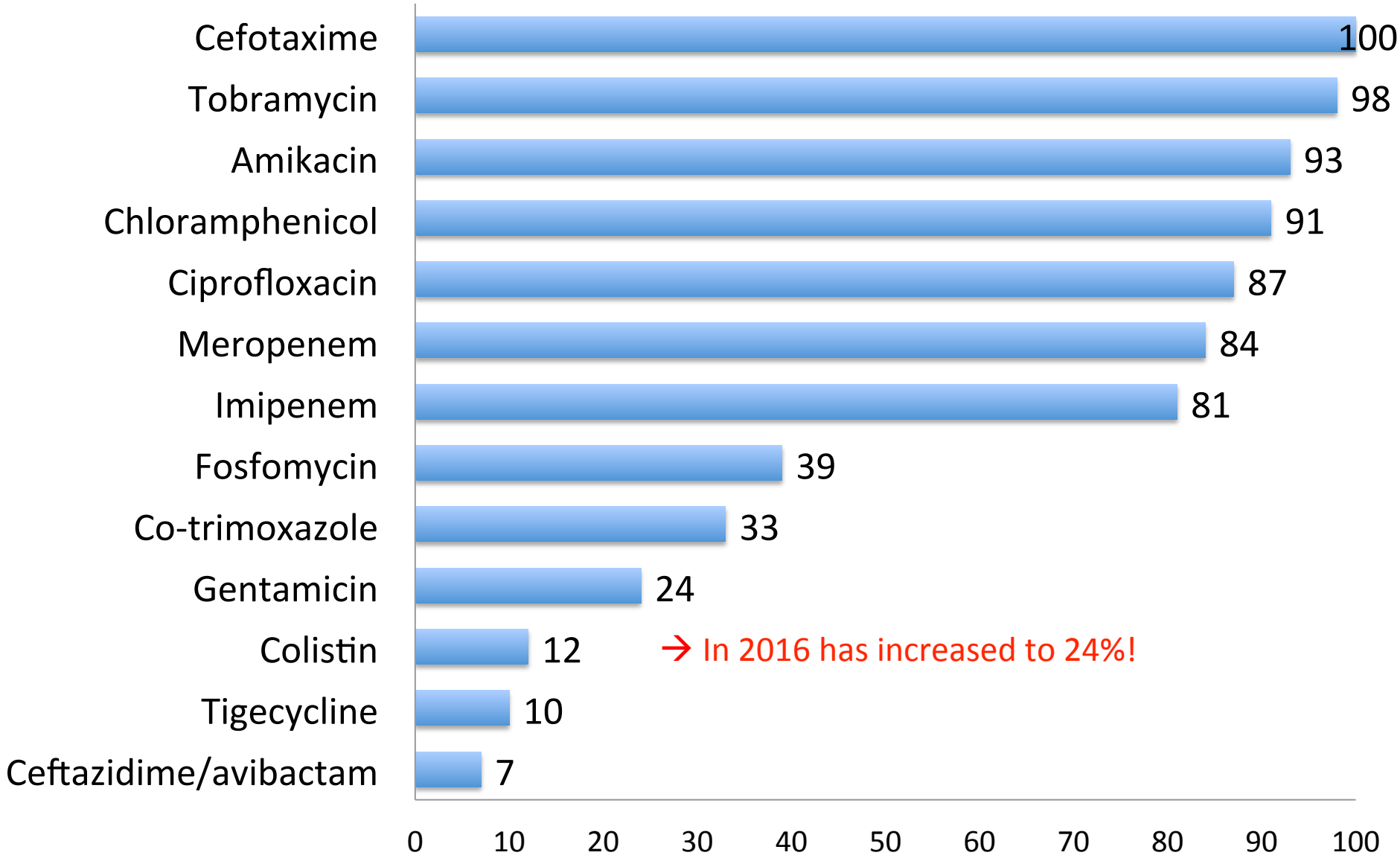
Origin of patients vs outcome



Department vs outcome

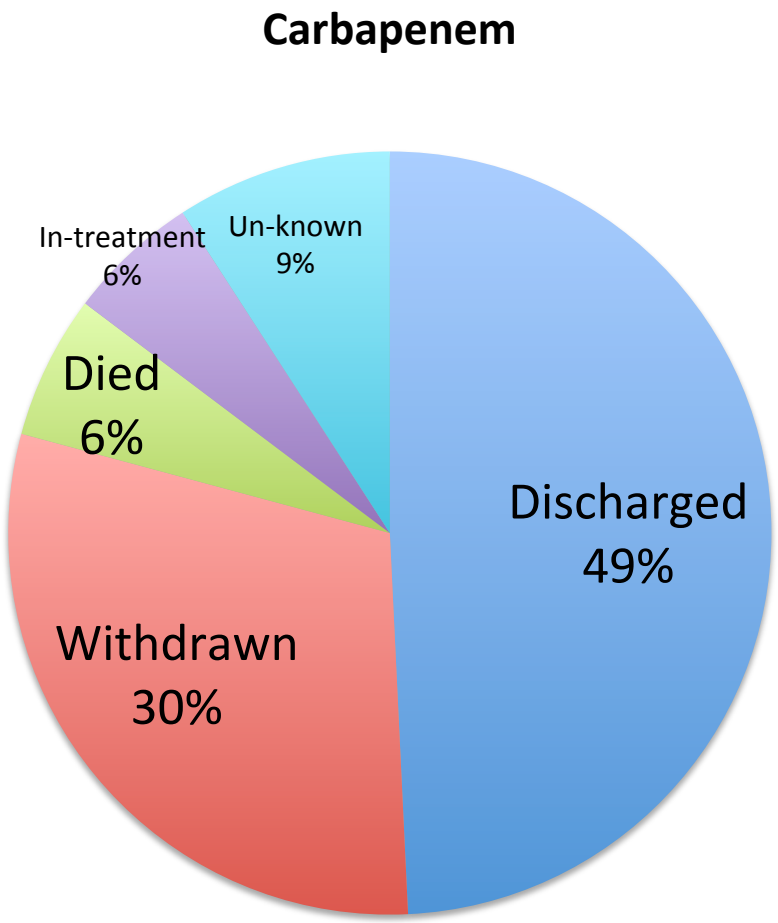


Resistance 106 Isolates *K. Pneumoniae*



Carbapenem resistance vs outcome

36%



Whole Genome Sequencing

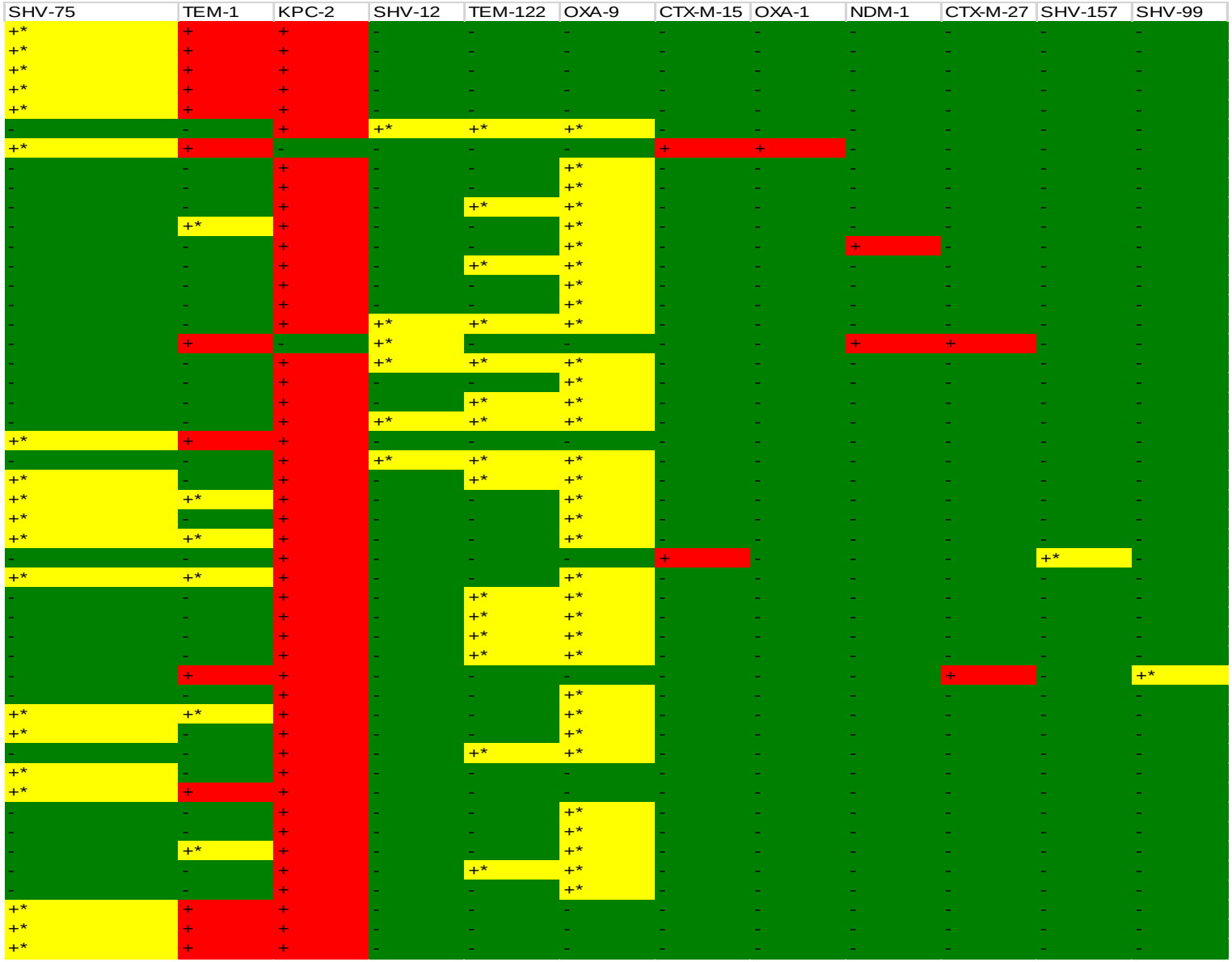
Isolation of bacteria

DNA extraction with pipetting robot

Next-generation sequencing with Illumina MiSeq

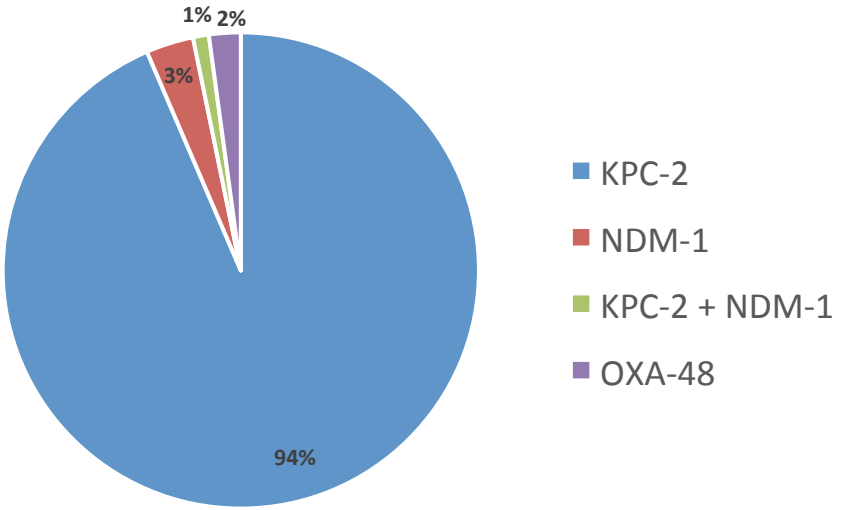
Genome assembly & data analysis

Resistance genes of carbapenem resistant K.pneumoniae isolates



Carbapenemases among 93 CRE isolates of *K. pneumoniae*

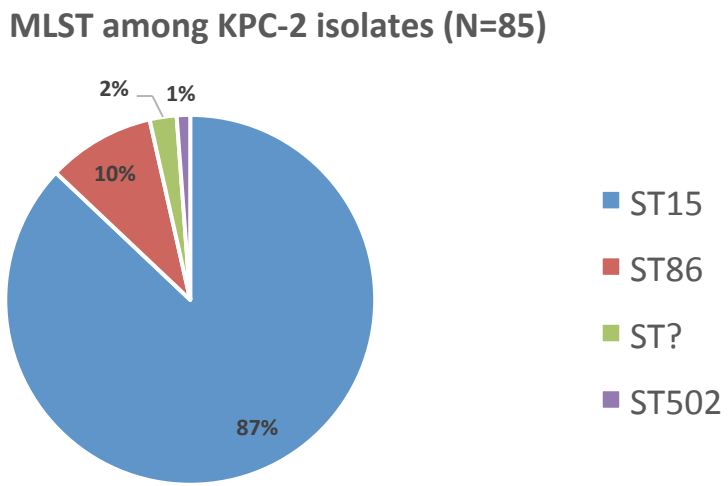
- 87 KPC-2
- 4 NDM-1
- 1 KPC-2 + NDM-1
- 2 OXA-48



MLST-types of 93 CRE isolates of K. pneumoniae

KPC-2 (N=85)

- 74 ST15
- 8 ST86
- 2 ST?
- 1 ST502



KPC-2 + NDM-1

- 3% ST15

NDM-1

- 1% each of ST1308, ST22, ST978,

OXA 48

- 2 % ST656

The *K. pneumoniae* outbreak strain

- **MLST-type ST15**
- Carbapenemase KPC-2
- Antibiotic susceptibility

  Ceftazidime-Avibactam 100% S

  Gentamicin 89% S

  Fosfomycin 84% S

  Colistin 79% S

  Trimethoprim-sulphamethoxazole 68% S

The *K. pneumoniae* outbreak strain

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Ceftazidime-Avibactam 100% S

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Fosfomycin 84% S

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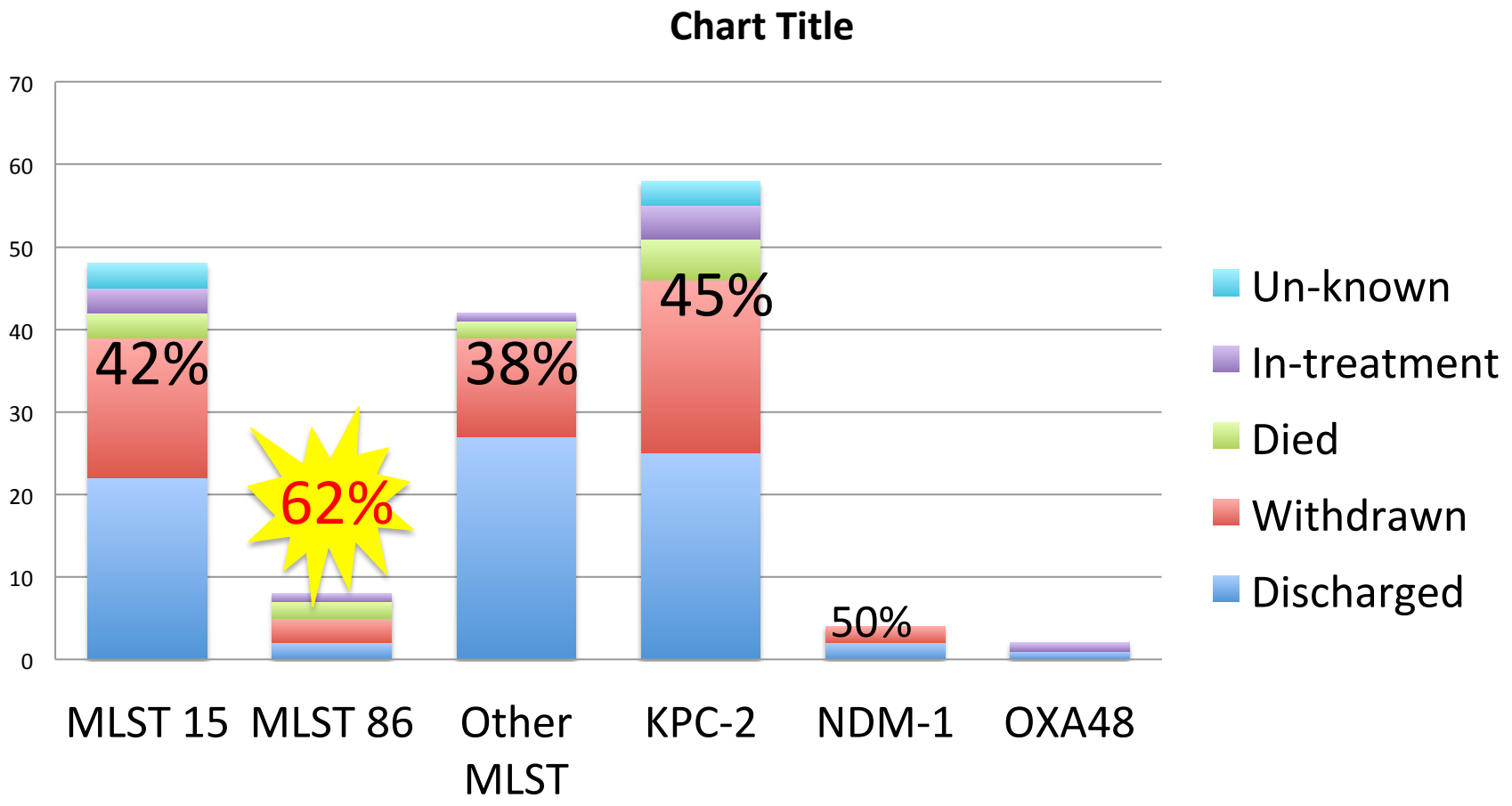
Trimethoprim-sulphamethoxazole 68% S

MLST type 86

Gentamicin 100% R

Fosfomycin 100% R

Resistance mechanism vs outcome



Hypervirulent *K. pneumoniae* MLST86 clone

- 13 MLST group ST86 hypervirulent *K. pneumoniae*
- Isolates taken April – August 2015 from different departments
  Blood isolates 5 of 13 (statistically overrepresented; $p<0.01$)
- 5 of 9 patients died/withdrawn
- Similar phenotype (antibiograms) and identical genotype of 8
- whole-genome sequenced isolates suggests a single clone***1st report: 9% of KPC2 isolates at NHP**
- WGS and ST – typing is important
- Extra resources to stop spread of hypervirulent strains!

Hypervirulent K. pneumoniae ST86 clone

Other clinical reports on ST86 K. pneumoniae include:

– **China** (Zhang Y, et al. Front Microbiol. 2015; 6:721),

– **Hong Kong, Singapore and Taiwan** (Lin JC, et al. Gut Pathogen. 2014; 6:21).

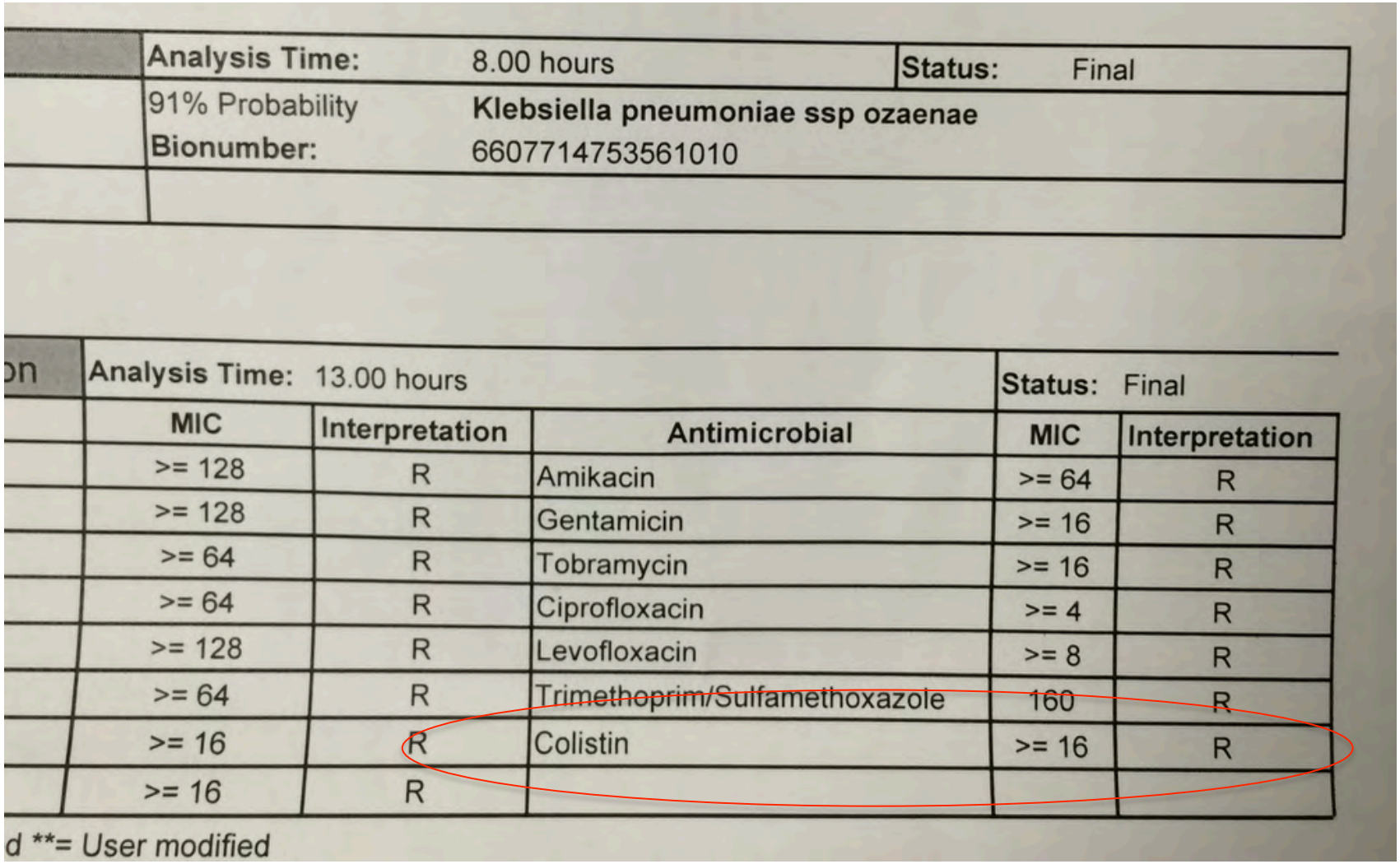
– **South Korea** (Jung SW, et al. Epidemiol Infect. 2013; 141(2):334-40.),

– **Spain** (Cubero M, et al. Clin Microbiol Infect. 2016; 22(2):154-60.

Cubero et al., 2016),

– **France** (Decré D, et al. J Clin Microbiol. 2011; 49(8): 3012-4.)

Colistin resistant Klebsiella Pneumoniae

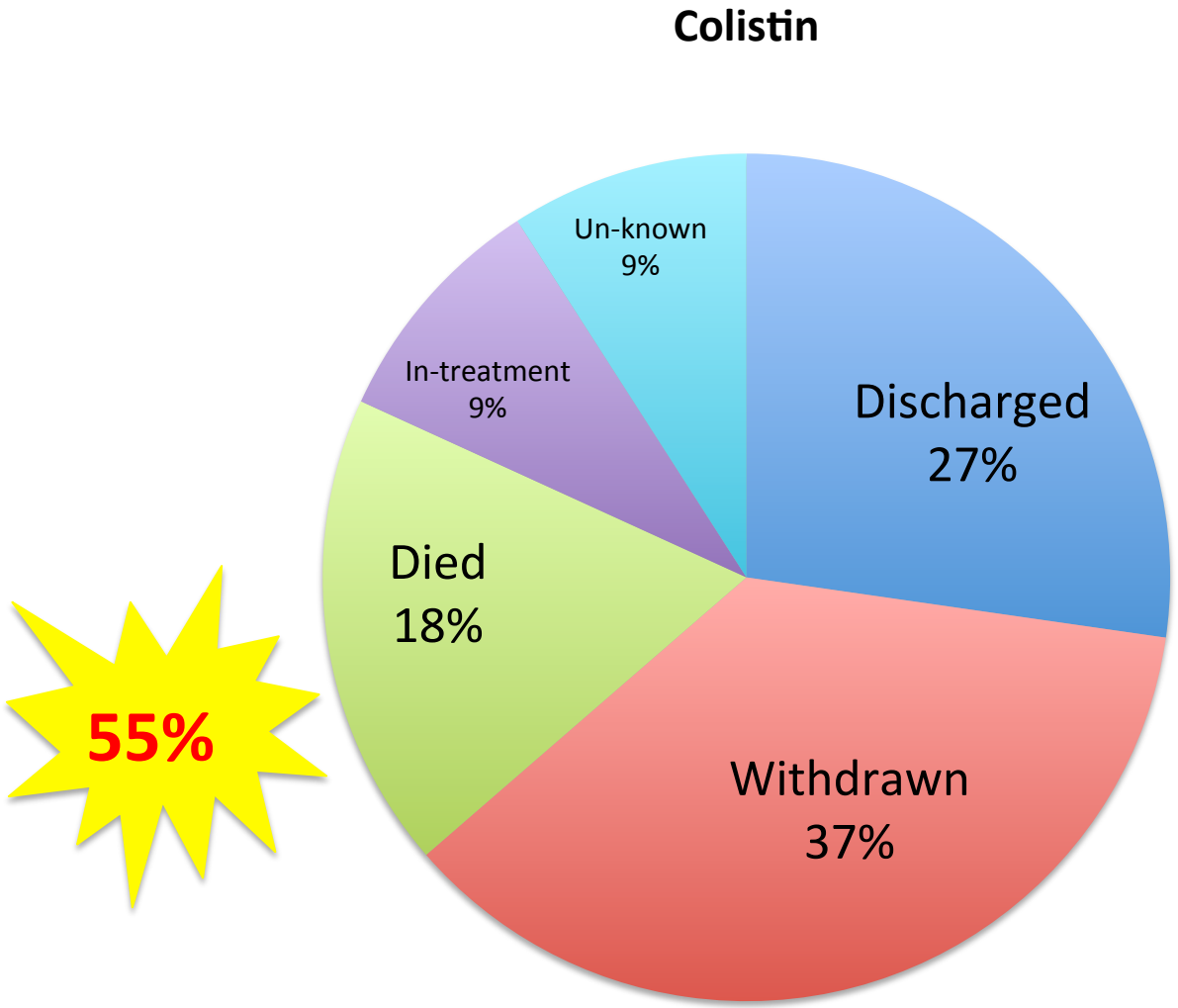


	Analysis Time:	8.00 hours	Status:	Final
	91% Probability	**Klebsiella pneumoniae ssp ozaenae**		
	Bionumber:	6607714753561010		

on	Analysis Time: 13.00 hours			Status: Final	
	MIC	**Interpretation**	**Antimicrobial**	**MIC**	**Interpretation**
	>= 128	R	Amikacin	>= 64	R
	>= 128	R	Gentamicin	>= 16	R
	>= 64	R	Tobramycin	>= 16	R
	>= 64	R	Ciprofloxacin	>= 4	R
	>= 128	R	Levofloxacin	>= 8	R
	>= 64	R	Trimethoprim/Sulfamethoxazole	160	R
	>= 16	R	Colistin	>= 16	R
	>= 16	R			

*d **= User modified*

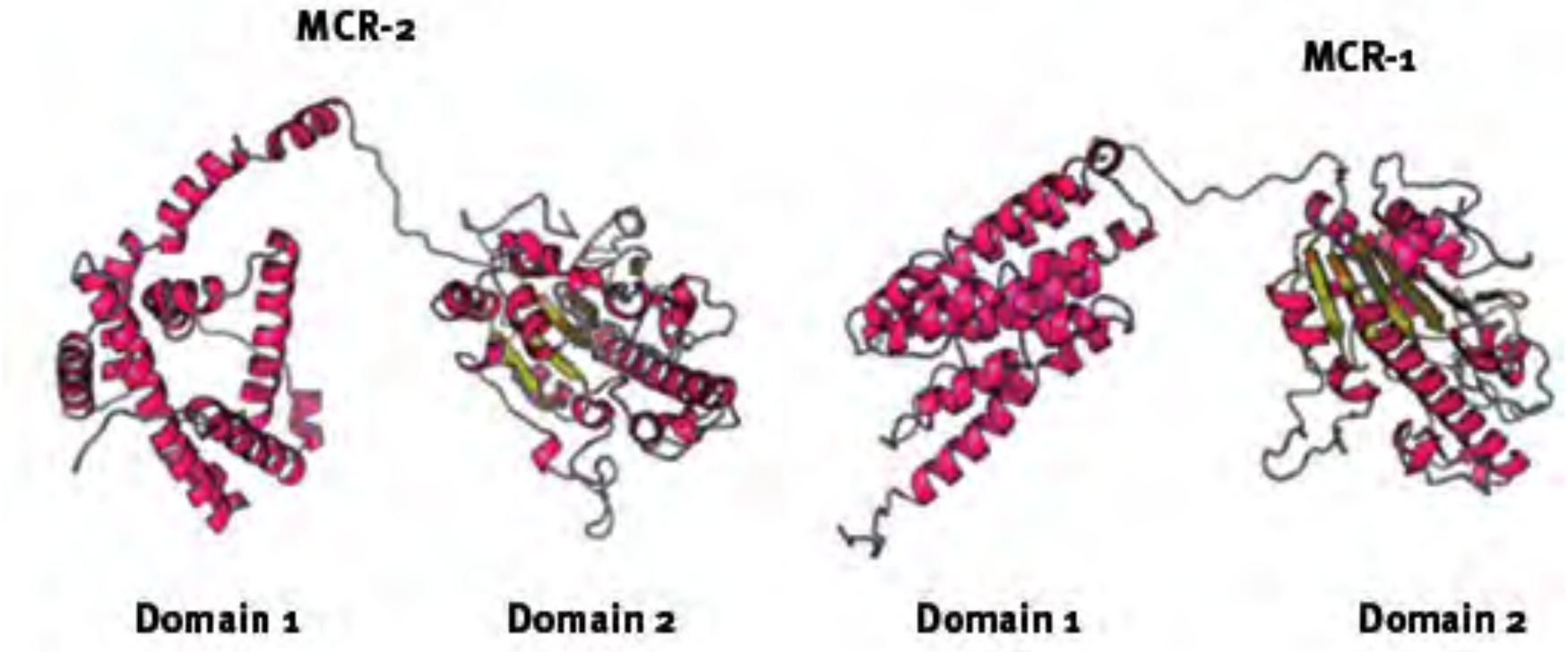
Colistin resistance vs outcome



55% mortality in patients infected with Colistin resistant *Klebsiella Pneumoniae*!!!

Colistin Resistance – Polymyxin E

Plasmid-mediated polymyxin resistance is with the mcr-1 gene. The mcr-1 gene encodes for a membrane-anchored phosphoethanolamine transferase that likely confers resistance to colistin by a modifying lipid A.



mcr-1-positive isolates at NHP

Isolate	Species	Department	Date of culture	Diagnosis	Specimen
VNX09	E. coli	General Pediatrics	2016-04-04	Bronchopneumonia	Nasopharynx
VE708	E. coli	Operating and anasthesia	2016-05-17	Sepsis	Pus
VE719	E. coli	General Pediatrics B	2016-05-28	Bronchopneumonia	Nasopharynx
VN806	K. pneumoniae	SS	2015-12-10	Respiratory failure	Tracheal fluid
VNX08	K. pneumoniae	Neonatal department	2016-04-05	Respiratory failure	Tracheal fluid
VN734	K. pneumoniae	ICU	2016-05-09	Bronchopneumonia	Blood

mcr-1-positive isolates at NHP

Whole-genome sequencing and phenotypic susceptibility testing has been performed on 2 isolates of K. pneumoniae (VN806 and VNX08).

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen*

Lancet Infect Dis 2015

Published Online

November 18, 2015

- mcr-1 gene – plasmid mediated Polymyxin resistance.
- *E coli, K pneumoniae* and *Pseudomonas aeruginosa*
- 15% of samples of raw meat sampled
- 21% of animals sampled
- 1% of inpatients with infection

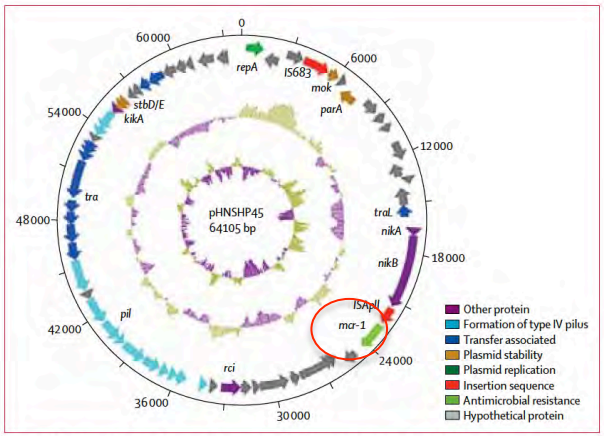
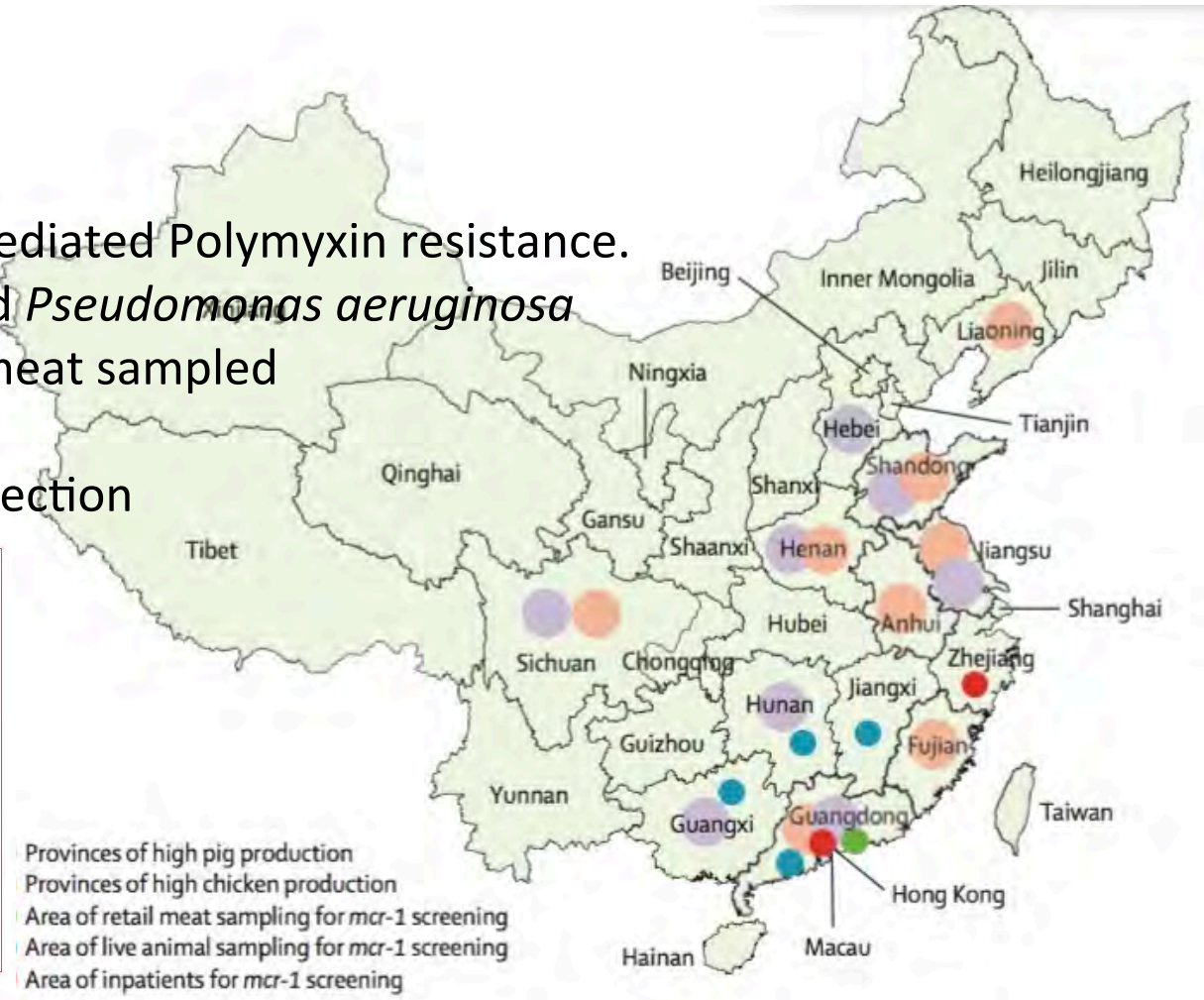


Figure 2: Structure of plasmid pHNSHP45 carrying *mcr-1* from *Escherichia coli* strain SHP45



32 countries reporting the mcr-1 gene present in bacteria of environmental, animal or human origin

Adapted from Xavier BB, Lammens C, Ruhal R, Kumar-Singh S, Butaye P, Goossens H, Malhotra-Kumar S. Identification of a novel plasmid-mediated colistin-resistance gene, mcr-2, in Escherichia coli, Belgium, June 2016. Euro Surveill. 2016;21(27):pii=30280. DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.27.30280.

Use of Colistin and Other Critical Antimicrobials on Pig and Chicken Farms in Southern Vietnam and Its Association with Resistance in Commensal *Escherichia coli* Bacteria

Nhung T. Nguyen,[a] Hoa M. Nguyen,[a] Cuong V. Nguyen,[a] Trung V. Nguyen,[a,b] Men T. Nguyen,[c] Hieu Q. Thai,[c] Mai H. Ho,[c] Guy Thwaites,[a,d] Hoa T. Ngo,[a,d] Stephen Baker,[a,d] and Juan Carrique-Mas[a,d]

Appl Environ Microbiol. 2016 Jul 1; 82(13): 3727–3735.

12 pig and chicken farms, Vietnam

Antimicrobials to produce 1 kg → Chicken : 94.7 mg/ Pig: 563.6 mg

E. Coli resistance : Ampicillin 97.8% / 94.4% (Chicken/ Pig)

Ciprofloxacin 73.3% /21.1% Gentamicin 42.2% / 35.6%

Colistin 22.2% / 24.4%

- *mcr-1* found in 19% / 22% (Chicken/ Pig)
- strong agreement with phenotypic colistin resistance.
- *mcr-1* gene-positive 54.0% of isolates in a plasmid consistent with one recently identified in China.

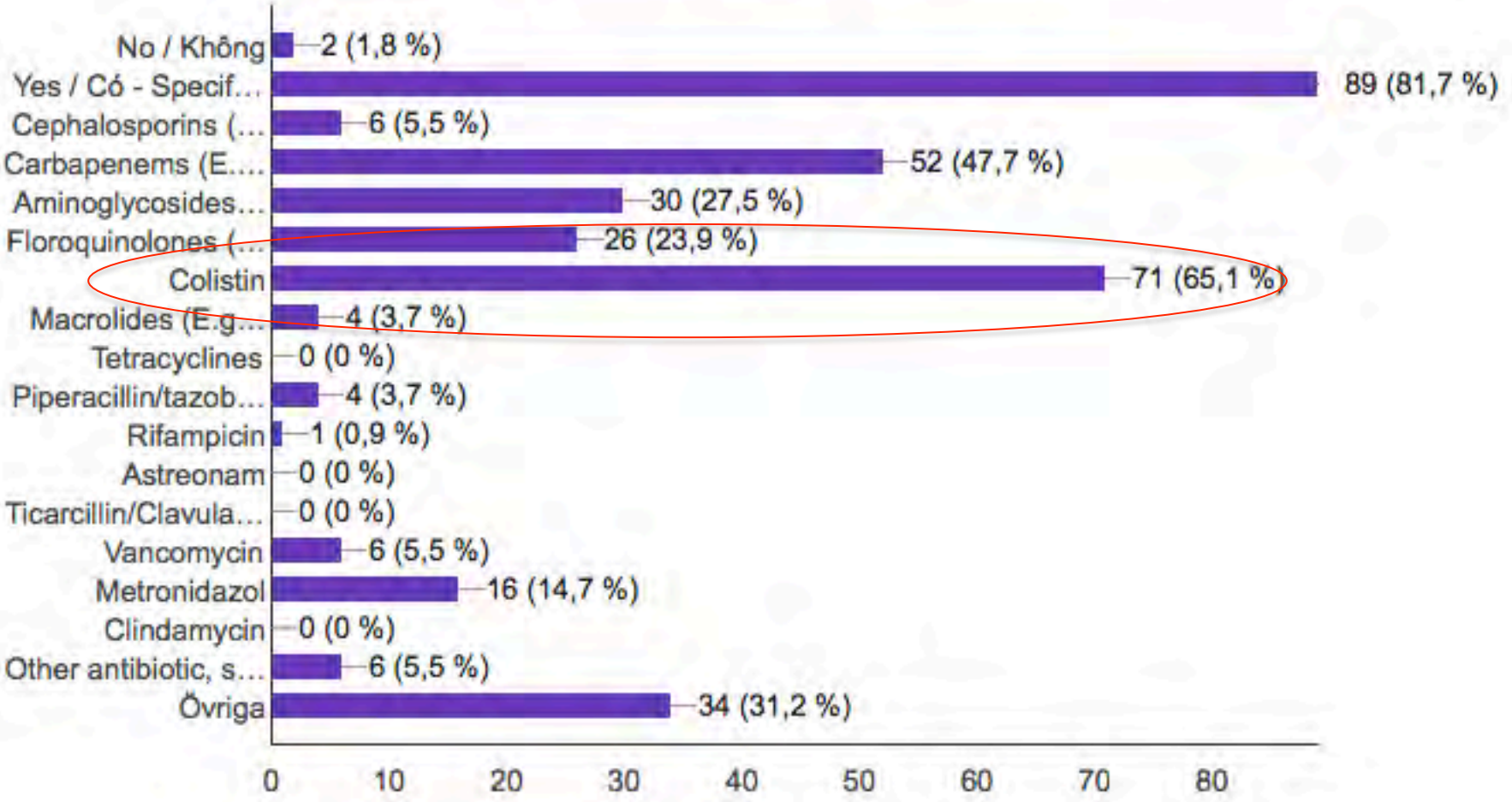
Patients treated with a carbapenem for a CPKP infection: Outcome according to MIC

MIC (µg/ml)	No of failures/No of patients	Failure rate (%)
≤ 1	5/17	29.4
2	3/12	33.3
4	2/7	28.6
8	2/6	33.3
>8[a]	**6/8**	**75**

[a] p=0.02; Data compiled from 15 studies published in English literature. *GL Daikos, CMR 2012*

All *K Pneumoniae* strains MIC >16, hence no synergistic effect of carabpenems!!!
= Colistin mono-therapy!

31. Current antibiotic use / sử dụng kháng sinh hiện tại (109 svar)

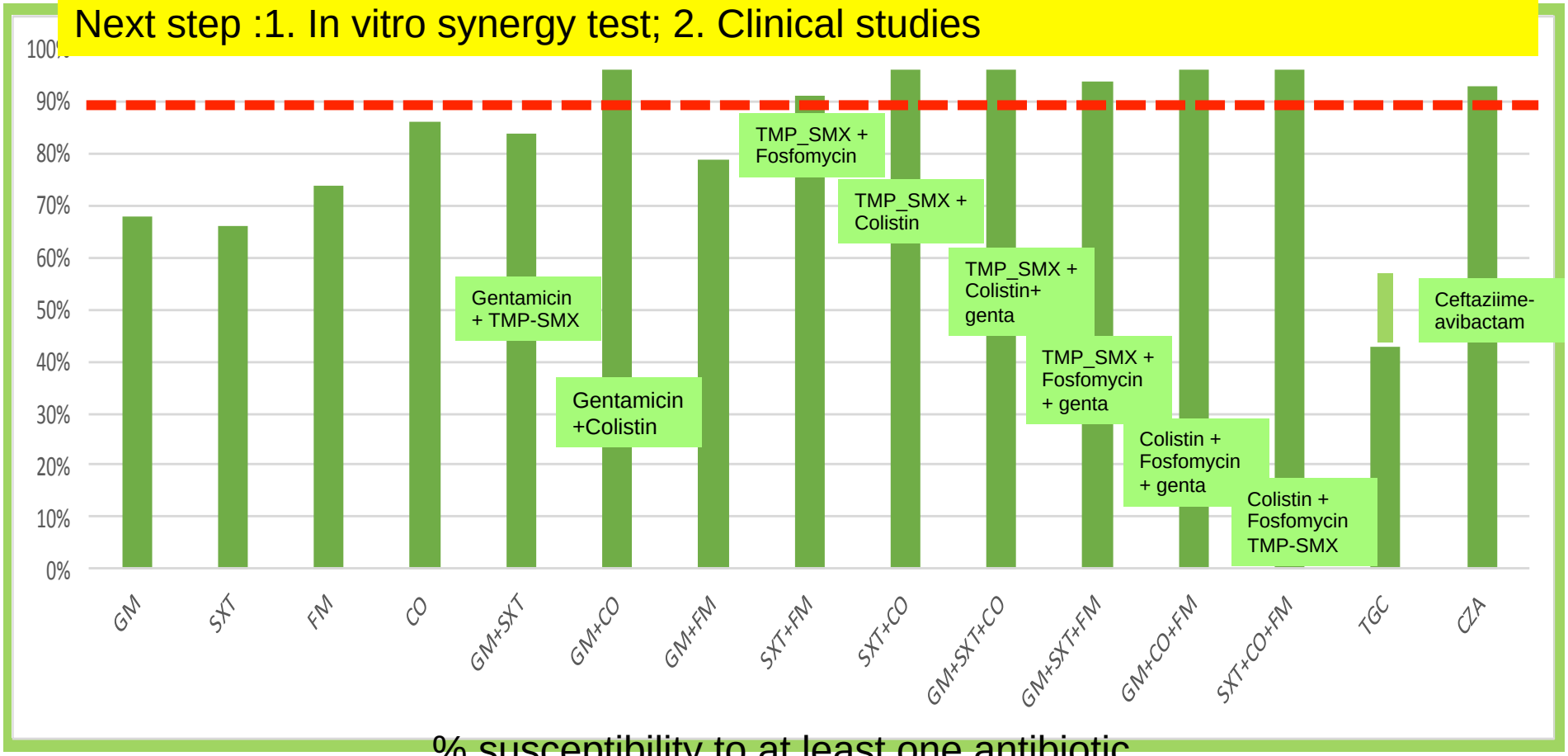


Antibiotic susceptibility

Carbapenem Resistant *K pneumonia* at NHP

Prel data, all data incl all MLST types, Total (n=90), CO, TGC n=28.

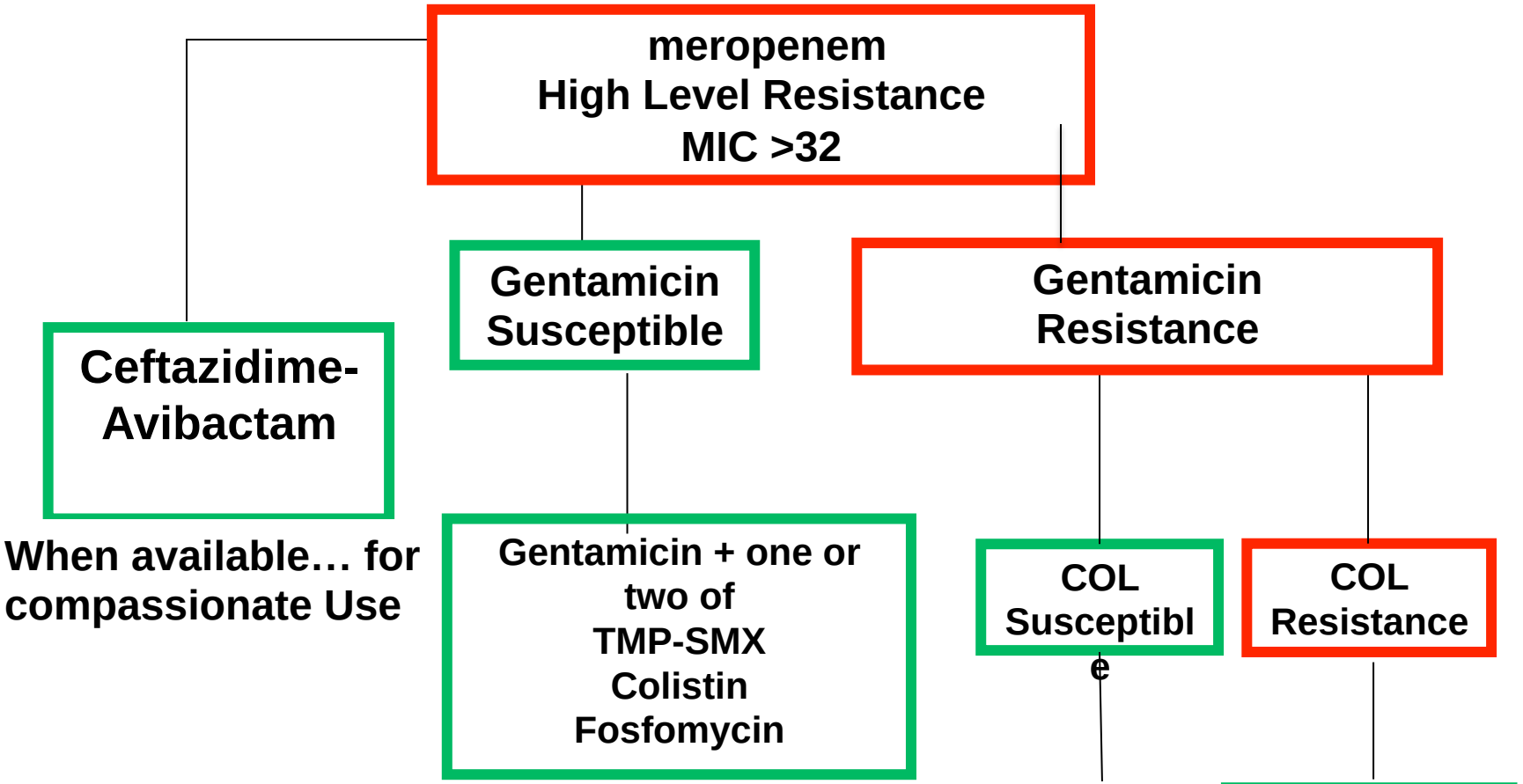
This shows S to at least one antibiotic
Next step :1. In vitro synergy test; 2. Clinical studies



% susceptibility to at least one antibiotic

Calculations by Dr Björn Berglund

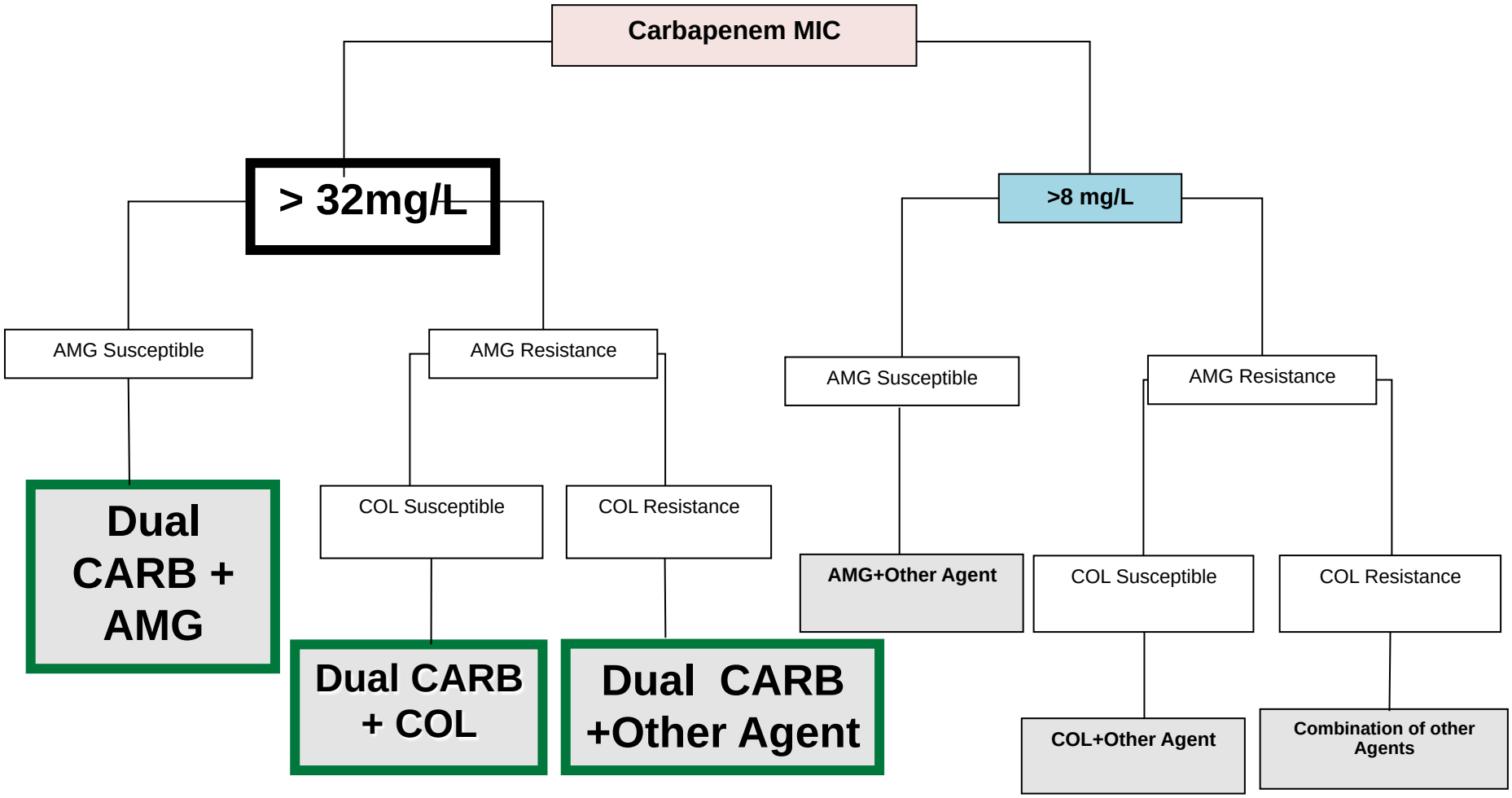
Severe sepsis/septic shock, Carbapenem saving treatment options of KPC at NHP



Site of infection!

modified based on E-test at LiU

Proposed Algorithm for Treatment of severe sepsis/septic shockCaused by Carbapenemase producing *K pneumonia*



Site of infection!

Daikos et al. Exp Rev Antiinfect Ther 2012, modified

The Burden of Antibiotic Resistance in Indian Neonates

1 million Indian children die in the **first 4 weeks** of life each year...

Of these deaths, **190,000** are caused by sepsis, a bacterial infection that overtakes the bloodstream.

58,319, or **just over 30%**, of neonatal sepsis deaths are attributable to antibiotic resistance.

CDDEP THE CENTER FOR Disease Dynamics, Economics & Policy

WASHINGTON DC • NEW DELHI

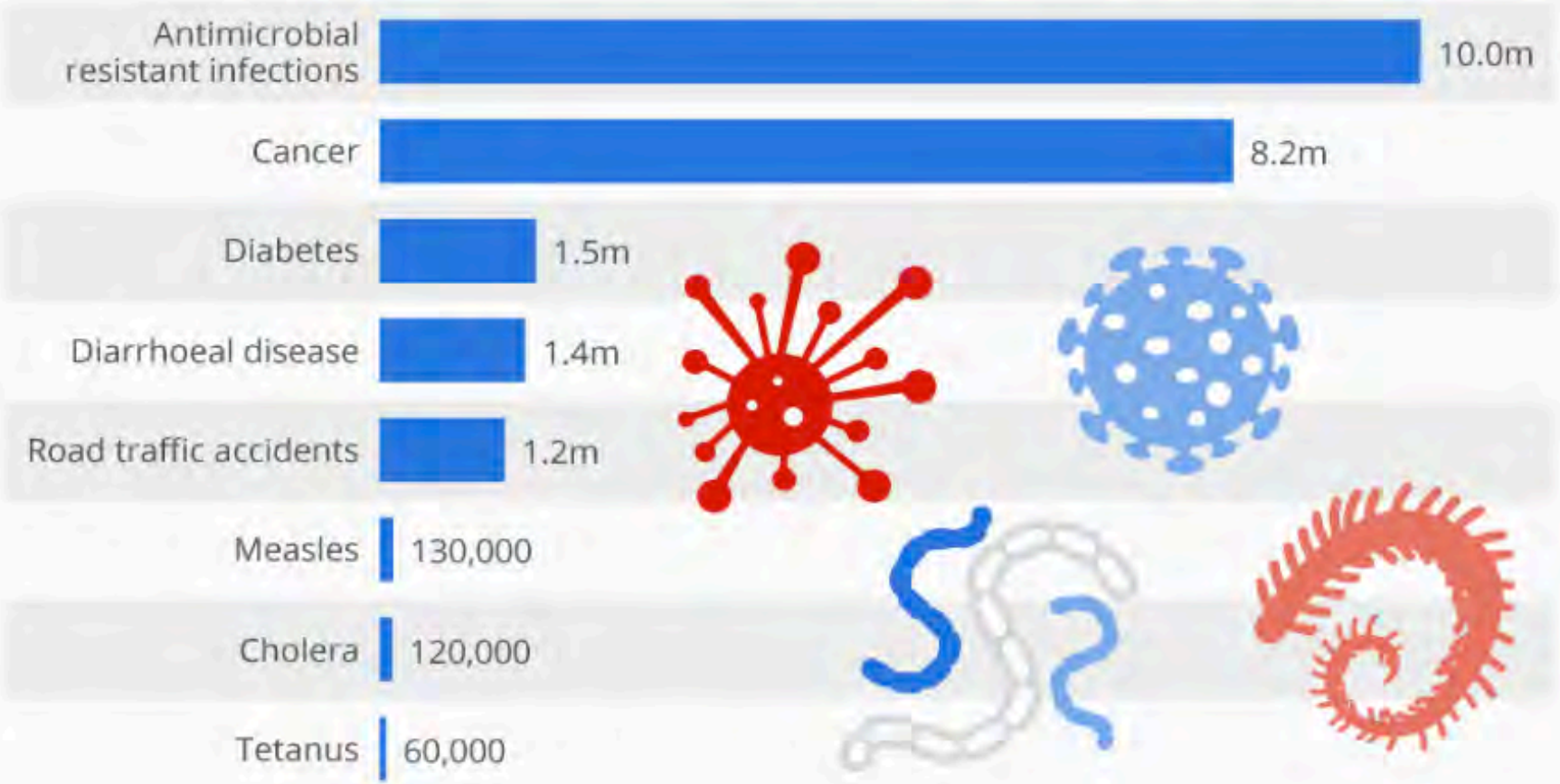
www.cddep.org

Sources: Sankar, Jeeva M., et al, 2008. Sepsis in the Newborn. AIIMS- NICU protocols. www.newbornwhocc.org.
Kayange, N., et al. 2010. Predictors of positive blood culture and deaths among neonates with suspected neonatal sepsis in a tertiary hospital, Mwanza- Tanzania. *BMC Pediatrics*. (10)39.

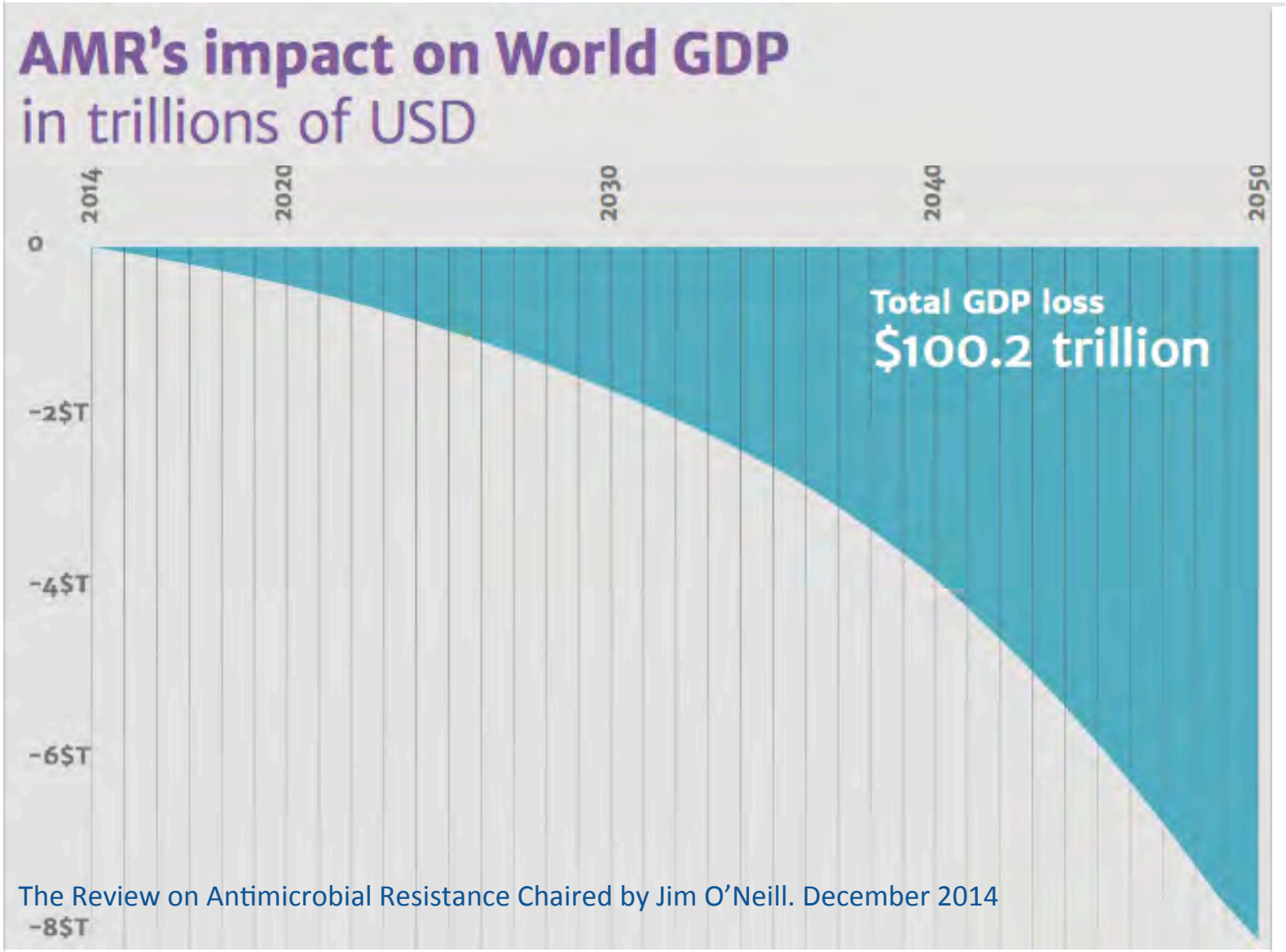
Images: iStock photo, Florida Center for Instructional Technology

Deaths From Drug-Resistant Infections Set To Skyrocket

Deaths from antimicrobial resistant infections and other causes in 2050



Source: Review on Antimicrobial Resistance



The Review on Antimicrobial Resistance Chaired by Jim O'Neill. December 2014

Conclusions

- There are several different resistance mechanisms including e-flux pumps and target modification
- Antibiotic resistance is selected by antibiotic pressure and transmitted vertically through genetic elements as plasmids
- Colistin is used in large amounts as growth promoter and profylactic treatment for animals
- MCR-1 has been found in enetrobactriasae from domesticated animals and humans
- Increasing colistin resistance in Hospital Aquired Infections with enterobactriasae
- High and increasing mortality due to colistin resistance

Gap of Knowledge

- Link between agricultural use of AB and selection of resistance mechanisms with impact on human health?
- What is the effect of Colistin used as growth promoter and profylactic treatment of animals on resistance?
- New last resort antibiotics for cases with carabapenem and colistin resistant G- infection?
- How to improve capacity international surveillance to detect and respond to urgent and emerging antibiotic resistance threats?
- How to improve antibiotic prescribing use in low and middle income countries?
- Can molecular detection technologies, to can identify antibitic resistance threats faster be more widely used?

Antibiotic Stewardship to preserve the effectiveness of last resort antibiotics

TRAC SWEDEN - VIETNAM

GÖTEBORG UNIVERSITY

LINKÖPING UNIVERSITY

Karolinska Institutet

UMEÅ UNIVERSITY

UPPSALA UNIVERSITY

UNIVERSITY OF MEDICINE AND PHARAMACY - HCMC

HANOI MEDICAL UNIVERSITY

RESEACH CENTER FOR CHILD HEALTH

TRAINING AND RESEARCH ACADEMIC CENTER

Main objective

To preserve the effectiveness of last resort antibiotics, colistin and polymixin B (India, Vietnam, Indonesia, Thailand) carbapenem (Malaysia)

Specific objectives

- To assess consumption of colistin and carbapenem in ICU
- To monitor prevalence of colistin / carbapenem resistant gram negative infections, and treatment duration and outcomes
- To implement antibiotic stewardship program to reduce unindicated use of colistin and carbapenem
- Assess implementation of Infection control measures including hand hygiene, isolation and surveillance cultures for colistin resistance.
- To assess the effect of intervention on colistin and carbapenem use and resistance
- To evaluate the antibiotic cost saving due to the intervention

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Thank you / Cảm Ơn