Global Antibiotic Research and Development (GARD) Partnership

Pasteur Institute – DNDi Meeting

February 29, 2016

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Antimicrobial Resistance (AMR) Threats in Thailand

AMR Bacteria with Urgent Threat

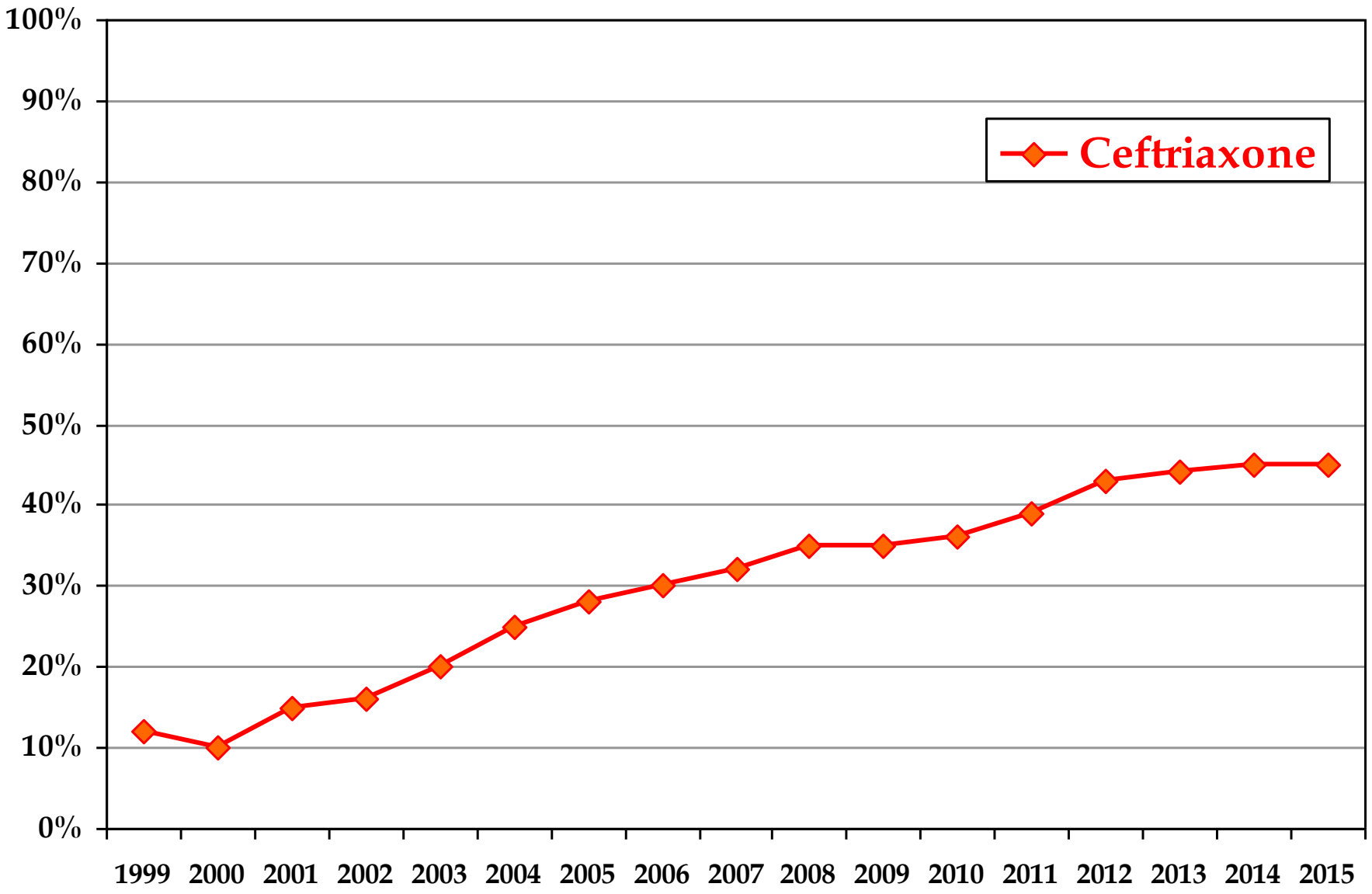
- Extended Spectrum β-Lactamase (ESBL) producing GNRs
- Carbapenem-Resistant *Acinetobacter* spp. & *P.aeruginosa*
- Carbapenem-Resistant Enterobacteriaceae (CRE)

AMR Bacteria with Serious Threat

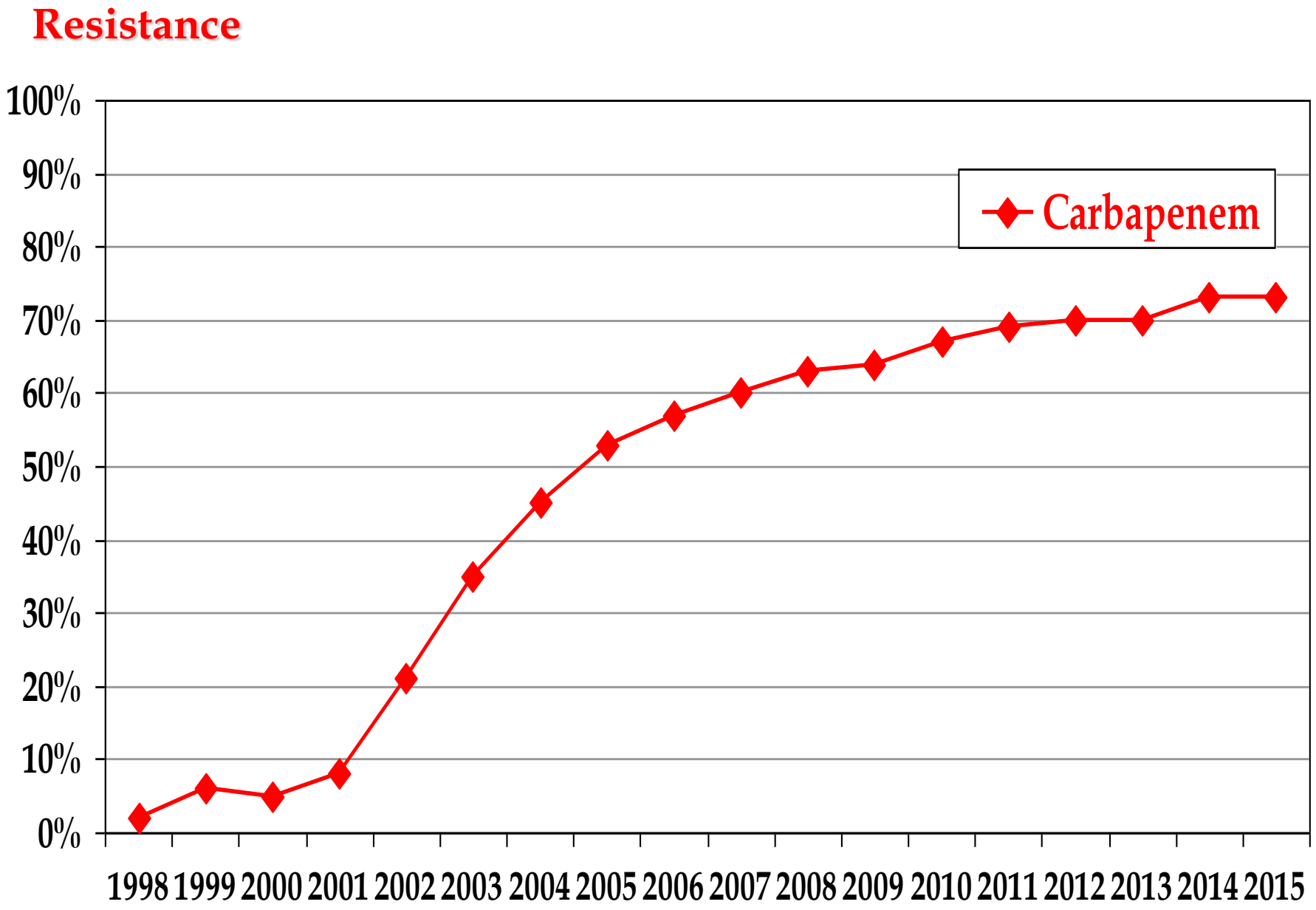
- Multidrug-Resistant *Neisseria gonorrhoeae*
- Multidrug-Resistant *Salmonella, Shigella, Campylobacter* spp.
- Methicillin-Resistant *Staphylococcus aureus* (MRSA)
- Multidrug-Resistant *Streptococcus pneumoniae*
- Vancomycin-Resistant Enterococci (VRE)
- *Clostridium difficile*

ESBL-producing *E.coli* in Thailand

Resistance

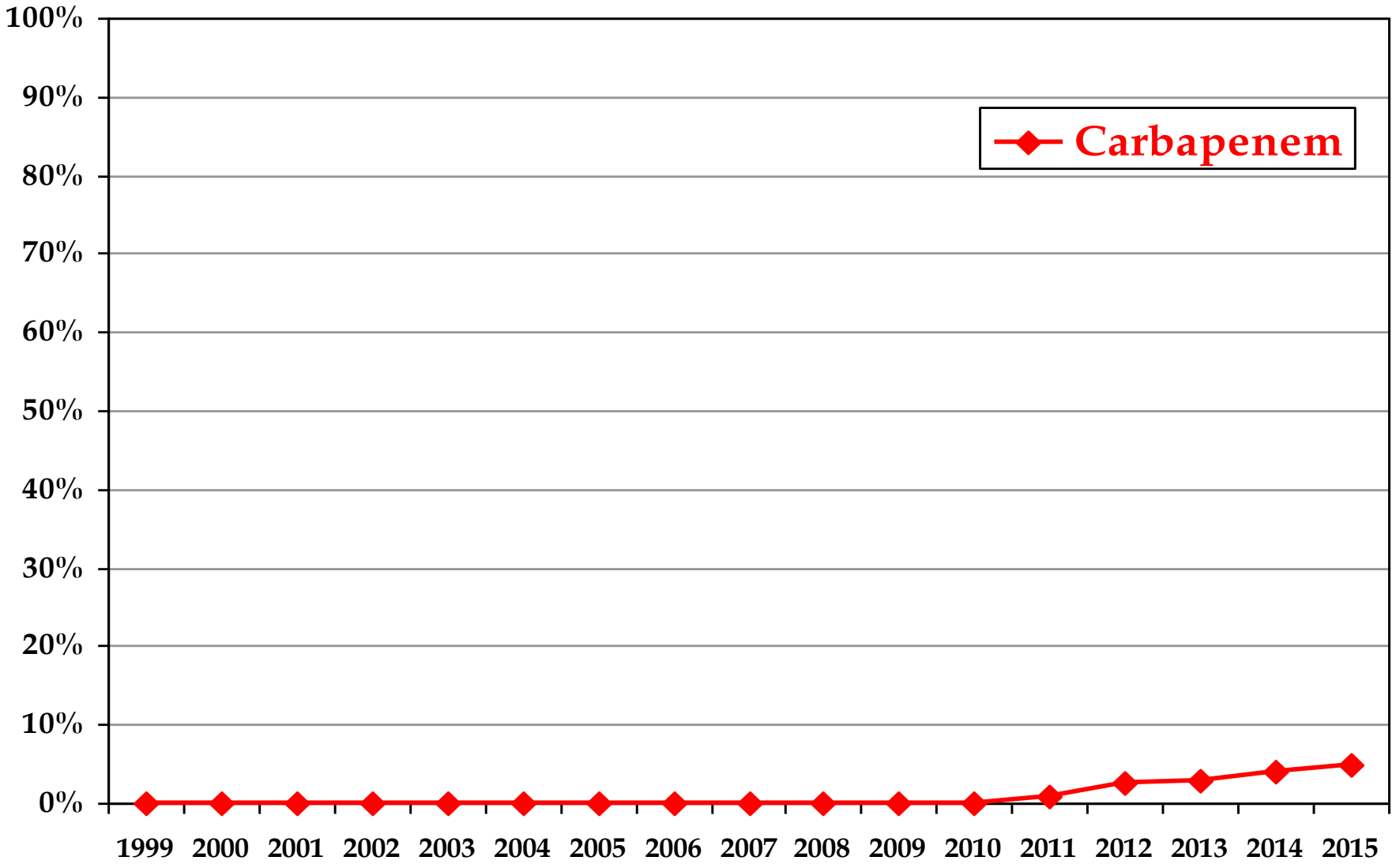


Carbapenem-Resistant *A.baumannii* in Thailand



Carbapenem-Resistant Enterobacteriaceae (CRE) in Thailand

Resistance



Thailand AMR Containment and Prevention Program 2012-2016

❖ ***10 Operational Actions***

1) Estimate national AMR burden
2) Establish dynamics of AMR chains
3) Develop national AMR containment & prevention governance
4) Develop laboratory & IT systems for AMR surveillance, antibiotic use and hospital-acquired infections
5) Regulate use & distribution of antibiotics in human & animals
6) Design AMR containment & prevention campaign
7) Generate local evidence for promoting responsible use of antibiotics and infection prevention & control practices
8) Create AMR containment & prevention package
9) Implement AMR containment & prevention package in selected pilot communities
10) Conduct research and development of diagnostics, therapy & prevention of AMR infections

R&D of Antimicrobials for Important AMR Bacteria in Thailand

- **Oral Tebipenem**

✓ Extended Spectrum β-Lactamase (ESBL) producing GNRs

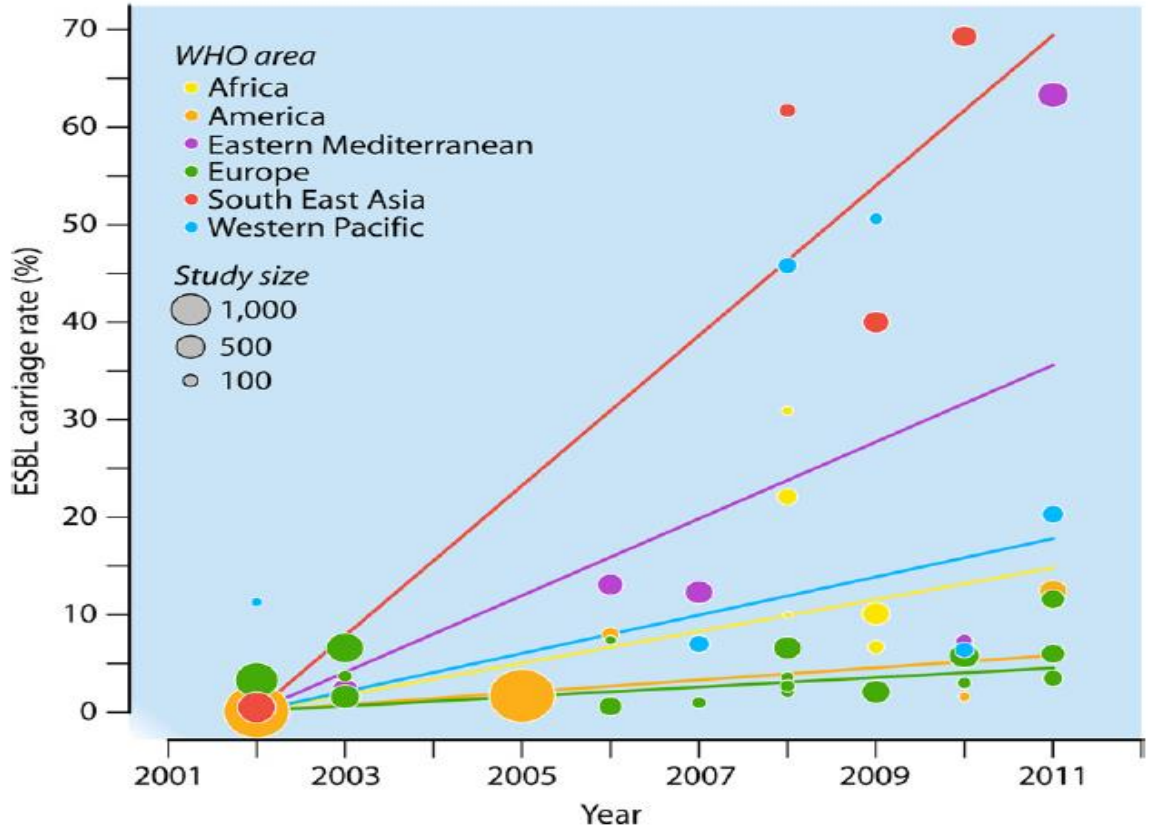
- **New Formulations of Parenteral Polymyxins**

✓ Carbapenem-Resistant *Acinetobacter* spp. & *P.aeruginosa*

✓ Carbapenem-Resistant Enterobacteriaceae (CRE)

ESBL-producing Gram-Negative Bacterial Infections

- Very common (30%-60%) in hospital-acquired infections
- Increasing in community-acquired infections (up to 30%)
- High prevalence of healthy carriers of ESBL+ve GNR due to consumption of antibiotics and/or consumption of foods contaminated with ESBL-producing GNR



CMR 2013;26:744

ESBL+ GNR carriage rates in community from 2002-2011

ESBL-producing Gram-Negative Infections

Antibiotic Treatment

- Severe infections in hospitalized patients

✓ Parenteral carbapenems e.g., ertapenem, imipenem, meropenem

✓ Other parenteral agents e.g., piperacillin/tazobactam, amikacin

- Mild to moderate infections in out-patients

✓ Parenteral etapenem OD

✓ Oral nitrofurantoin and fosfomycin trometanol - uncomplicated lower urinary tract infection (UTI), e.g., acute cystitis, but they are not indicated for upper UTI, e.g., acute pyelonephritis

✓ Oral amdinocillin (mecillinam) - active against ESBL-producing *E.coli*, but its efficacy for therapy of ESBL-producing *E.coli* infection is modest

✓ More effective oral antibiotics against infections due to ESBL-producing Enterobacteriaceae are needed

Tebipenem Pivoxil (Orapenem^{R})

- The first oral carbapenem antibiotic available for clinical use
- Broad-spectrum activity against Gram-positives & Gram-negatives
- Well absorbed and quickly converted to tebipenem
- Half life is 1 hour and it is mainly excreted by kidney
- Only available in Japan (Meiji Seika Kaisha, Ltd.) as fine granules for treatment of otitis media, sinusitis and pneumonia in children

fine granules in bottle

fine granules in sachet

Tebipenem Pivoxil (Orapenem^{R})

In Vitro & In Vivo Activity Studies in Thailand

• ESBL-producing	*E.coli*	*K.pneumoniae*
✓ MIC_{50}	$\leq$ 0.06	$\leq$ 0.06
✓ MC_{90}	$\leq$ 0.06	0.12
✓ MIC range	$\leq$ 0.06 - 0.25	$\leq$ 0.06 – 4

• In vivo study in healthy Thai subjects who received 300 mg tebipenem pivoxil PO 3 times a day for 2 consecutive days

✓ Very high inhibitory & bactericidal titers of serum and urine samples against ESBL-producing *E.coli*

✓ No side effects related to receiving tebipenem pivoxil

• Fluoroquinolone-resistant *Neisseria gonorrhoeae*

✓ Inhibition zone diameter of tebipenem (10-ug disk) 38-66 mm.

• *Burkholderia pseudomallei*

✓ MIC_{50} & MC_{90}	2 mg/L
✓ MIC range	1-2 mg/L

Tebipenem Pivoxil (Orapenem^{R})

R&D Gaps and Needs

- Formulate tebipenem pivoxil for use in adult
- Conduct clinical studies on efficacy & safety of tebipenem for

✓ therapy of mild to moderate infections due to ESBL+ve GNR in out-patient setting

✓ step down therapy for severe infection due to ESBL+ve GNR in hospitalized patient

✓ therapy of infection due to MDR *Neisseria gonorrhoeae*

✓ step down therapy and maintenance therapy of melioidosis

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  - ✓ therapy of infection due to MDR *Neisseria gonorrhoeae*
  - ✓ step down therapy and maintenance therapy of melioidosis

Concerns

- If tebipenem pivoxil which is a very effective oral antibiotic is widely available, it will induce carbapenem resistance in GNR
- Conservation measures for responsible use of tebipenem pivoxil are extremely important

R&D of Antimicrobials for Important AMR Bacteria in Thailand

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✓ Carbapenem-Resistant *Acinetobacter* spp. & *P.aeruginosa*

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Extensively Drug-Resistant (XDR) Gram-Negative Infections

- Extensively Drug-Resistant (XDR) Gram-Negative Bacteria
  - ✓ Carbapenem-Resistant *Acinetobacter* spp. & *P.aeruginosa*
  - ✓ Carbapenem-Resistant Enterobacteriaceae (CRE)
- XDR GNR are common causes of hospital-acquired infections
- Mortality of patients with XDR GNR infections is high

Extensively Drug-Resistant (XDR) Gram-Negative Infections

- Polymyxins are polypeptide antibiotics developed in the 1940s and they have been used for XDR GNR infections over past decade

✓ Parenteral polymyxin B is active form - polymyxin B sulphate

✓ Parenteral polymyxin E (colistin) is inactive pro-drug - colistimethate sodium (CMS)

Extensively Drug-Resistant (XDR) Gram-Negative Infections

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  - ✓ Parenteral polymyxin B is active form - polymyxin B sulphate
  - ✓ Parenteral polymyxin E (colistin) is inactive pro-drug - colistimethate sodium (CMS)
- Limitations of polymyxins for treatment of XDR GNR infections
  - ✓ Efficacy of polymyxins is moderate
  - ✓ Mortality of the patients is still high (20%-60%)
  - ✓ Doses of polymyxins are complicated and usually too low
  - ✓ Polymyxin-associated acute kidney injury is common (16%-60%)
  - ✓ Higher dose of polymyxin B sulphate and CMS to improve clinical outcomes should have more risk of polymyxin-associated adverse events than benefit
  - ✓ No solid evidence on more clinical benefit of polymyxin combination therapy that showed in vitro synergy

Polymyxins

R&D Gaps and Needs

- New antibiotics for XDR GNR (e.g. eravacycline, S-649266) will not be available over the next few years
- New formulations of polymyxins to increase dose of polymyxins that could have better clinical outcomes and decrease risk of AKI

✓ Parenteral colistin sulphate (an active form of polymyxin E)

➢ Preliminary results of therapy in patients with XDR GNR infections with parenteral colistin sulphate are available

Intravenous colistin sulfate: a rarely used form of polymyxin E for treatment of severe MDR Gram-negative bacterial infections *(Scand J Infect Dis 2010;42:260-5)*

- 15 patients with severe infections caused by MDR or pandrug-resistant GNR (13 *A.baumannii*, 4 *P.aeruginosa* & 2 *K.pneumoniae*) unresponsive to empirical regimens, 2006-2008
- Treated with colistin sulfate 1.28±0.25 mIU/d for 22.3±6.2 days

✓ Good clinical response	73.3%
✓ Microbiological clearance	60%
✓ Mortality	20%
✓ Possible nephrotoxicity	1 patient (7%)
✓ Neurotoxicity	None

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✓ Other polymyxin salt (in addition to colistin sulphate) or polymyxin analogue that is more active & safer than polymyxin B & colistin

Activity and Predicted Nephrotoxicity of Synthetic Antibiotics Based on Polymyxin B

(J Med Chem 2016 Feb 11;59:1068-77.)

- Systematic activity-toxicity study by varying 8 of 9 polymyxin amino acid free side chains, preparing over 30 analogues of polymyxin B using a novel solid-phase synthetic route

✓ Many new compounds possessed equal or better antimicrobial potency compared to polymyxin B

✓ Some were less toxic than polymyxin B and colistin against mammalian HepG2 cells and human primary kidney cells

- These initial structure-activity and structure-toxicity studies set stage for further improvements to polymyxin class of antibiotics

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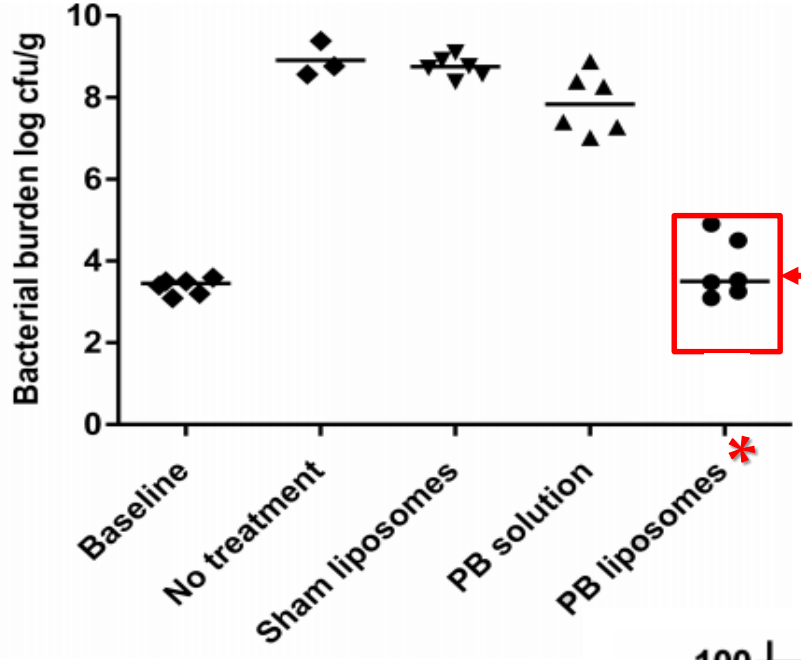
✓ Other polymyxin salt (in addition to colistin sulphate) or analogue that is more active & safer than polymyxin B & colistin

✓ Parenteral polymyxins (e.g., liposomal polymyxins) that can be given in higher doses to improve efficacy, enhance drug delivery, retain drug at site of infection, and decrease adverse effect

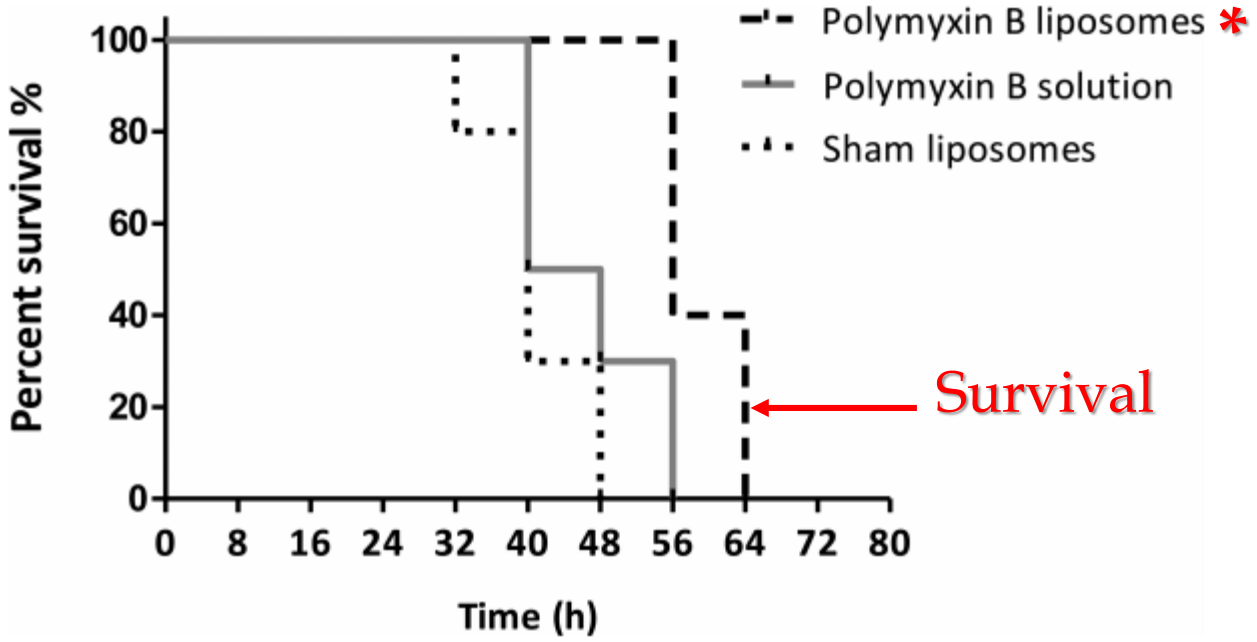
➢ Preliminary data on in vitro and in vivo activity, efficacy and safety of many preparations of polymyxins (e.g., liposomal polymyxins) in animal models are available

Liposomal polymyxin B in mice infected with *P.aeruginosa*

(Int J Antimicrob Agents 2013;42:559-64)



Bacterial burdens in lungs



Survival

Polymyxins

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Thailand AMR Containment and Prevention Program 2012-2016

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- **R & D of Antibiotics for AMR Infections**

✓ In Vitro Antibiotic Susceptibility Test of Innovative Compounds (Repository of ESBL+ve Enterobacteriaceae, XDR *A.baumannii*, *N.gonorrhoeae*, *B.pseudomallei*, MRSA)

✓ Clinical Study Phase I-IV including PK study

➢ Tebipenem & Polymyxin New Formulation

➢ Nitrofurantoin, Fosfomycin, Faropenem, Sitafloxacin, Mecillinam, Thiamphenicol, Colistin, Polymyxin B, Colistin+Meropenem, Colistin+Fosfomycin, Generic Antibiotics

Population Pharmacokinetics of Colistin Methanesulfonate and Formed Colistin in Critically Ill Patients from a Multicenter Study Provide Dosing Suggestions for Various Categories of Patients[▽]

S. M. Garonzik,[1]† J. Li,[2]† V. Thamlikitkul,[3] D. L. Paterson,[4] S. Shoham,[5] J. Jacob,[2] F. P. Silveira,[6]‡ A. Forrest,[1]‡ and R. L. Nation[2]*‡

Antimicrob Agents Chemother 2011;55:3284-94.

- Multinational study supported by NIH (USA) 2008 to 2012

✓ USA (U of Pittsburgh)

✓ Australia (Monash University)

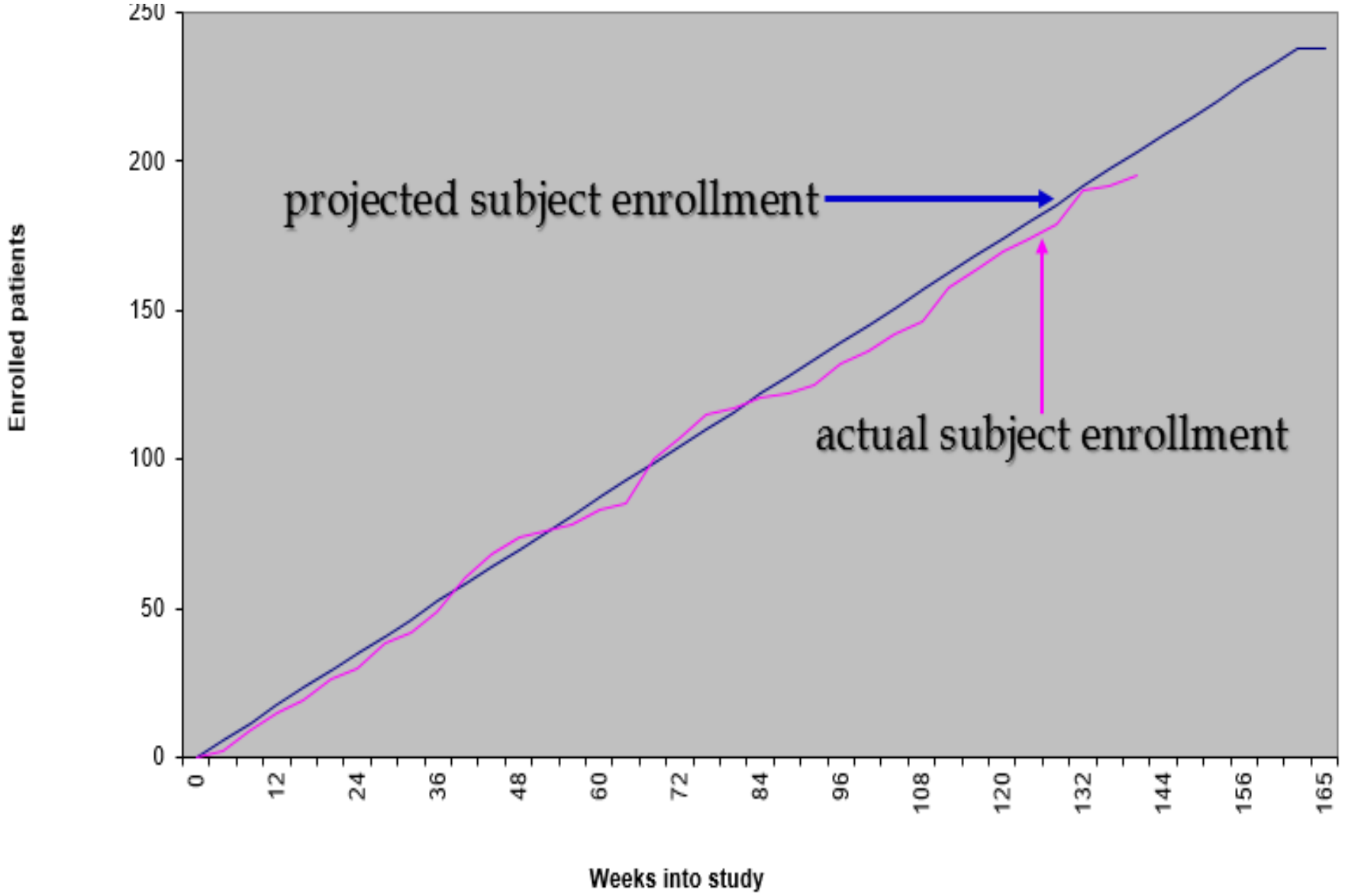
✓ Thailand (Siriraj Hospital, Mahidol University)

✓ Greece (Attikon University Hospital, Athens)

- 230 enrolled subjects with bacteremia or HAP due to XDR GNB who received IV colistin

✓ 170 subjects (74%) were Thai patients from Siriraj Hospital

Optimizing dosing of colistin for XDR Gram-negative infections supported by NIH (USA) 2008 to 2012



Alternatives to antibiotics—a pipeline portfolio review

Lancet Infect Dis 2016;16 (February):239-51.

- **Tier 1 approaches - translational funding to clinical evaluation at phase 2 :** Antibodies, Probiotics, Lysins, Vaccines, Wild-type bacteriophages, Engineered bacteriophages, Immune stimulation,
- **Tier 2 approaches - strong support for funding while monitoring for breakthrough insights regarding systemic therapy:** Antimicrobial peptides, Host defence peptides and innate defence peptides, Anti-biofilm peptides
- **Additional alternative approaches :** Immune suppression, Anti-resistance nucleic acids, Antibacterial nucleic acids, Toxin sequestration using liposomes, Antibiotic-degrading enzymes to reduce selection of resistance, Metal chelation, Alphamers, Apheresis of protective antibodies, Immune stimulation by P4 peptide

✓ Many compounds are very promising

✓ DNDi might want to explore these compounds

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