Old Drugs….
New Bugs

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Outline

- Old bugs in new guises : Multidrug resistant bacteria
- The increasing problem of resistance and dwindling new antibiotic choices
- The revival of old drugs for drug-resistant Gram-negative and Gram-positive bacteria

Introduction

- Infections from resistant bacteria are now too common, and some pathogens have even become resistant to multiple types or classes of antibiotics
- World health leaders have described antibiotic-resistant microorganisms as “nightmare bacteria” that pose a catastrophic threat to people in every country in the world.

- In the United States, more than two million people are sickened every year with antibiotic-resistant infections, with at least 23,000 dying as a result.

- Regarding level of concern, CDC has for the first time prioritized bacteria into one of three categories: *urgent* (*C. difficile*, carbapenen-resistant Enterobacteriaceae, drug-resistant GC), *serious* (ESBL's,MRSA,MDR *P. aeruginosa*, MDR and XDR TB,etc) , and *concerning* (VRE,etc).

CDC: Antibiotic Resistance Threats in the US, 2013

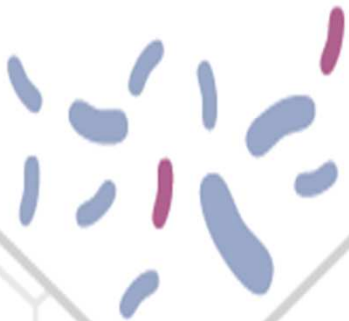
Acronym Definitions

- Multidrug-resistant MDR
  - resistance of an organism to at least 1 or more agents in 3 or more classes of antimicrobial categories
- Extensively drug-resistant XDR
  - resistance to at least 1 agent in all but 2 or fewer antimicrobial categories
- Pandrug-resistant PDR
  - resistance to all available antibiotics

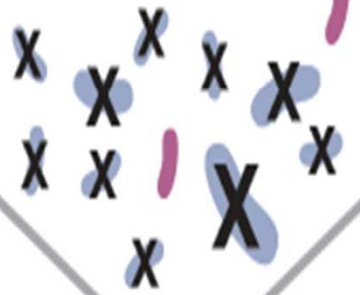
ARSP 2014

How Antibiotic Resistance Happens

1.
Lots of germs.
A few are drug resistant.



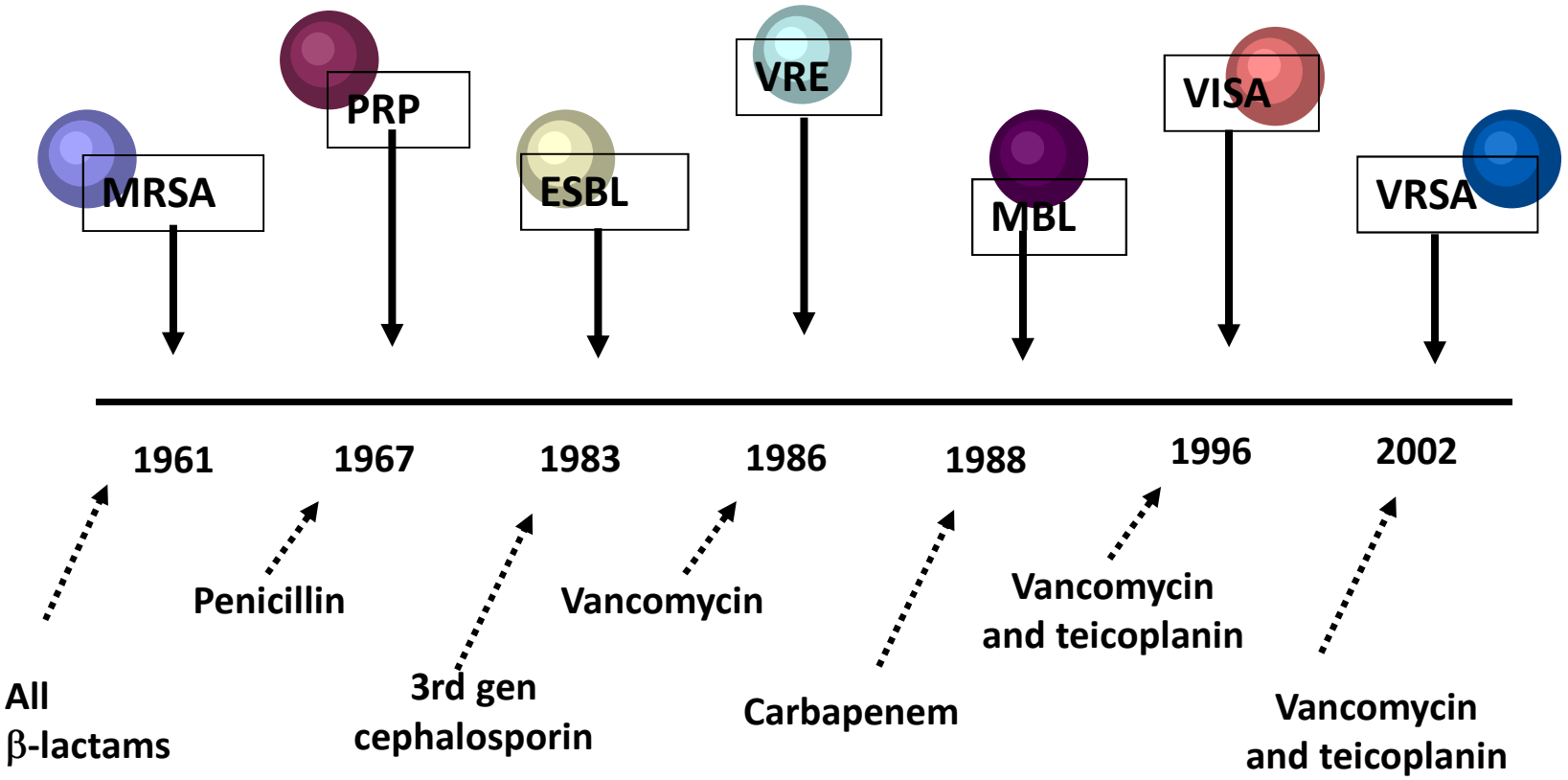
2.
Antibiotics kill bacteria causing the illness, as well as good bacteria protecting the body from infection.



3.
The drug-resistant bacteria are now allowed to grow and take over.

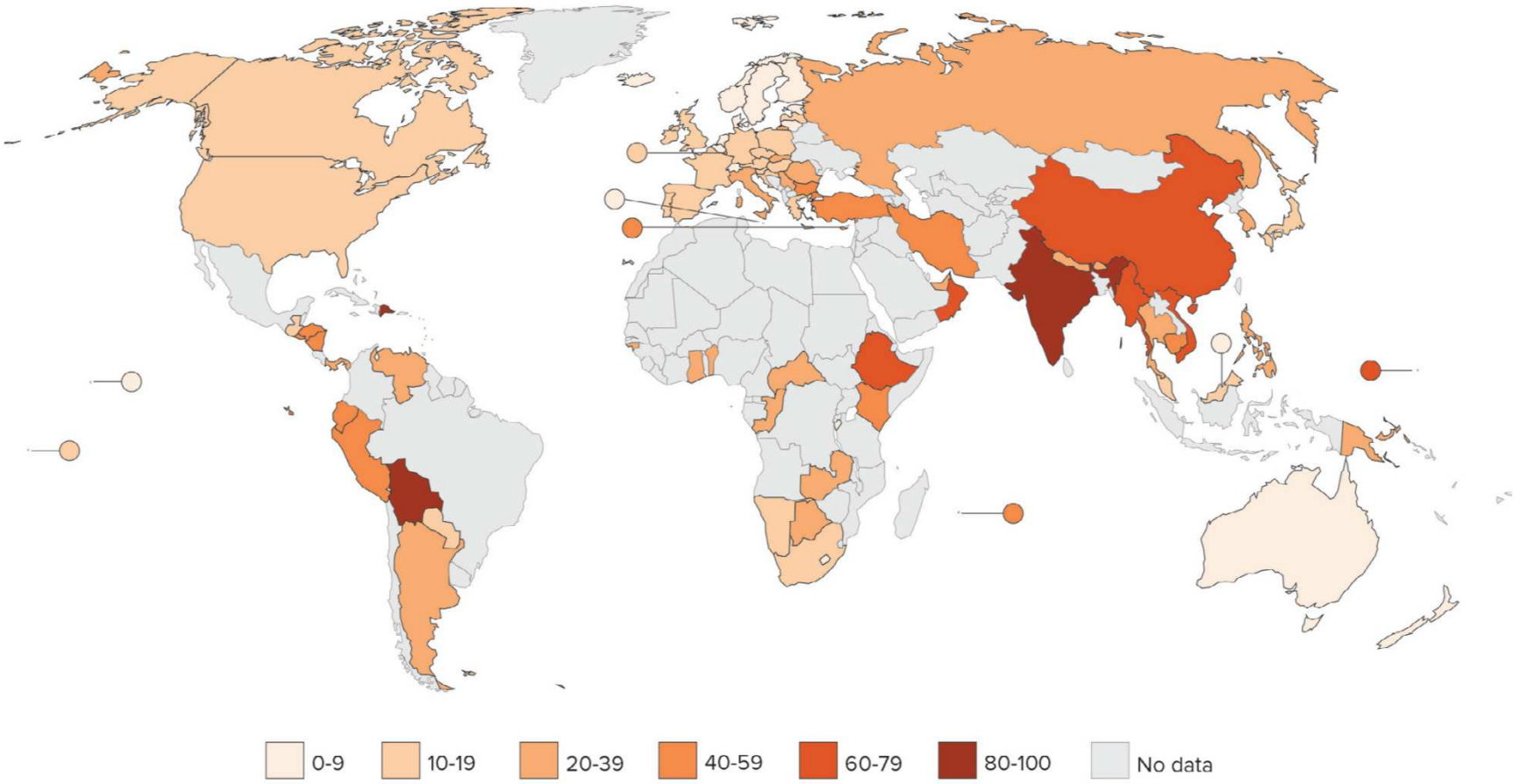
4.
Some bacteria give their drug-resistance to other bacteria, causing more problems.

Antibiotic Resistance – A Global Problem



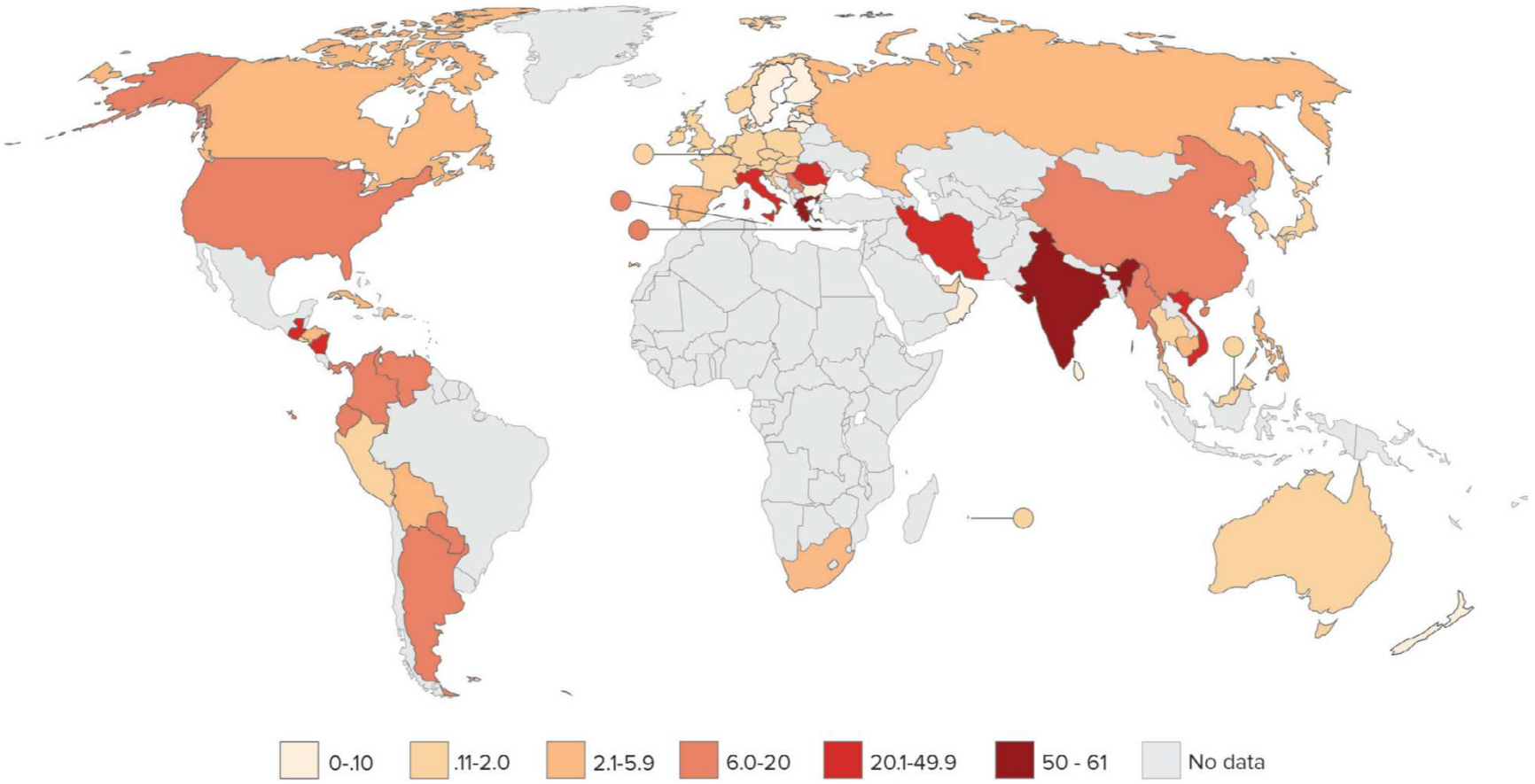
Emergence → Spread

Percentage of extended-spectrum beta-lactamase producing *Escherichia coli*, by country (2011–2014)



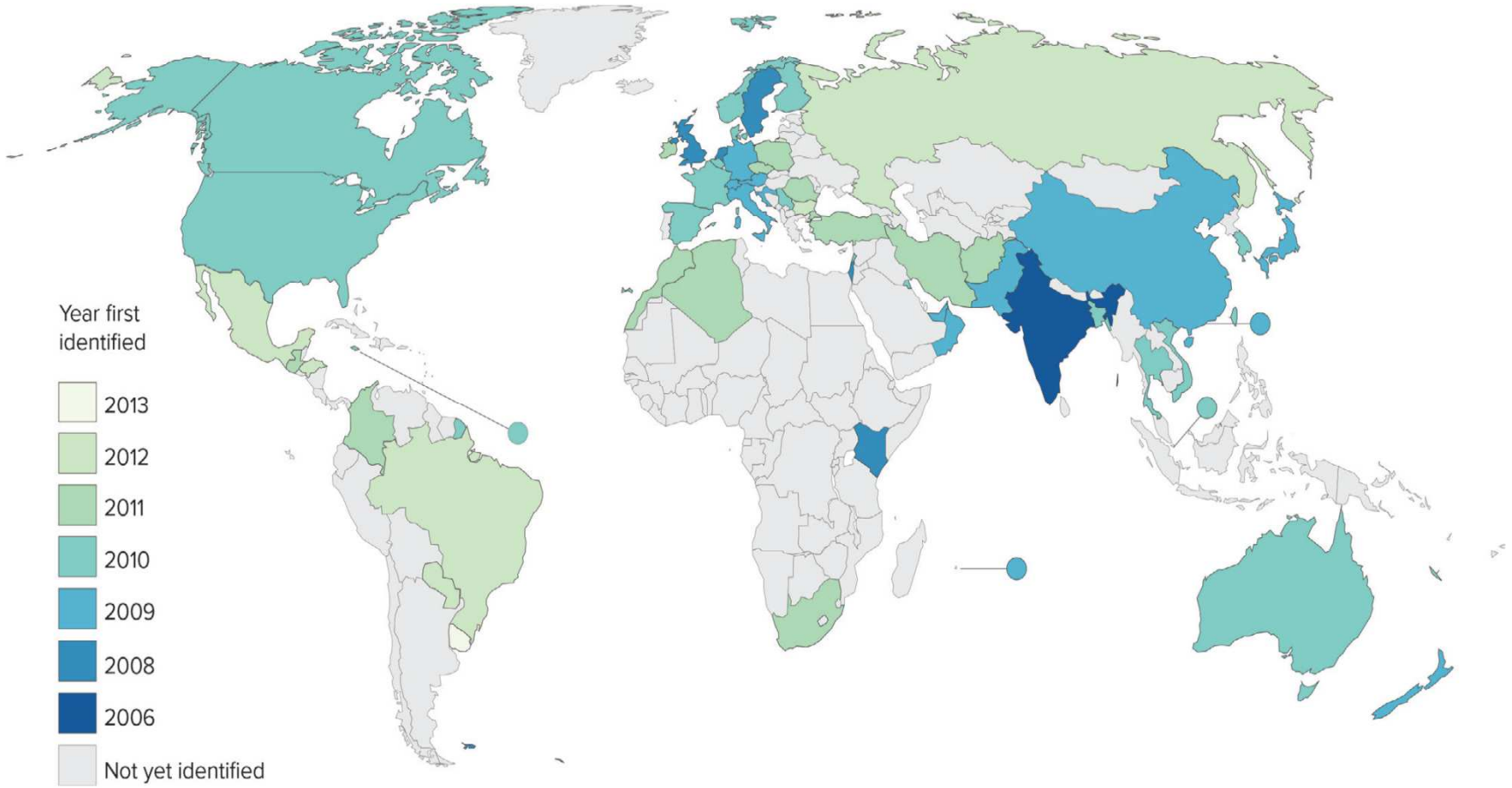
Source: CDDEP 2015, WHO 2014 and PAHO,

Percentage of carbapenem-resistant *Klebsiella pneumoniae*, by country (2011–2014)



Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

Spread of New Delhi metallo-beta-lactamase-1: first detection



Source: Johnson and Woodford 2013 (adapted)

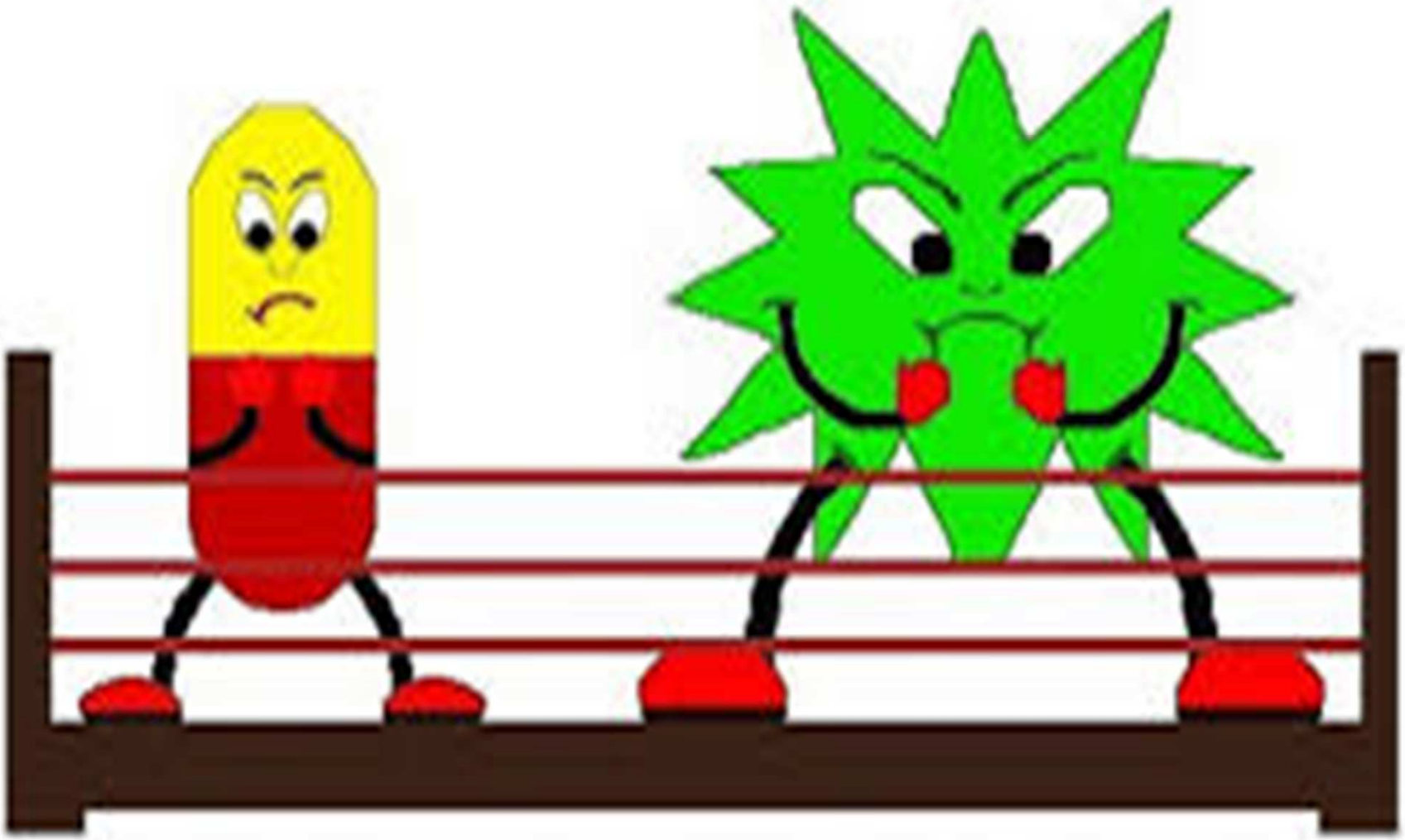
Most Commonly Isolated Multidrug Resistant Organisms

CDC	DOH-ARSP 2014
1. Methicillin-Resistant *S. aureus* (MRSA) 2. Vancomycin Resistant Enterococci (VRE) 3. Extended Spectrum Beta-Lactamase producing Enterobacteriaceae (ESBLs)	1. Methicillin-Resistant *S. aureus* (MRSA) 2. Extended Spectrum Beta-Lactamase producing Enterobacteriaceae (ESBLs) *3. Acinetobacter baumanii*

ARSP 2014 Data

- Multidrug-resistant
  - *P. aeruginosa* – 23%
  - *A. baumannii* – 61%
- Extensively drug-resistant
  - *P. aeruginosa* - 18%
  - *A. baumannii* - 46%

DRUGS VS. BUGS



Antibiotic Development is Dwindling

- Between 1983 and 1987, there were 16 New Antibacterial Agents
- Between 1988 and 1992, there were 14
- Between 1993 and 1997, there were 10
- Between 1998 and 2002, there were 7
- Between 2003 and 2007, there were 5
- Between 2008 and 20012, there were 2

The Epidemic of Antibiotic-Resistant Infections, CID 2008:46 (15 January) Clin Infect Dis. (2011) May 52 (suppl 5): S397-S328.doi: 10.1093/cid/cir 153

Why We Must Act Now

- The way we use antibiotics today in one patient directly impacts how effective they will be tomorrow in another patient; they are a shared resource.
- Since it will be many years before new antibiotics are available to treat some resistant infections, we need to improve the use of antibiotics that are currently available.
- In an era of increasing emergence of drug resistance and lack of new antibiotics there is a growing need to optimize the use of old and new antibiotics to treat infections

CDC Get Smart Program

- *In recent years, some older antibiotics that had been largely phased out have been returned to use to treat multidrug-resistant infections, particularly highly resistant Gram-negative infections, for which there are few alternatives.*

TABLE 4-1. INTRODUCTION OF ANTIBIOTIC CLASSES		
Antibiotic class	**Year introduced**	**Target or activity**
Sulfa drugs/sulfonamides (synthetic)	1936	Gram-positive
β-lactams (penicillins, cephalosporins, carbapenems, monobactams)	1938	Broad-spectrum
Aminoglycosides	1946	Broad-spectrum
Chloramphenicols	1948	Broad-spectrum
Macrolides	1951	Broad-spectrum
Tetracyclines	1952	Broad-spectrum
Lincosamides	1952	Gram-positive
Rifamycins (ansamycins)	1958	Gram-positive
Glycopeptides	1958	Gram-positive
Quinolones (synthetic)	1968	Broad-spectrum
Streptogramins	1998	Gram-positive
Oxazolidinones (synthetic)	2000	Gram-positive
Lipopetides	2003	Gram-positive
Fidaxomicin	2011	Gram-positive
Diarylquinolines	2013	Narrow-spectrum
Teixobactin	-	Gram-positive

Source: Adapted from Lewis, 2013

Infections caused by multidrug-resistant Gram-negative bacteria successfully treated with old antibiotics.

Molecule	Pathogens	Sites of infection
Colistin (IV)	MDR *A. baumannii* MDR *P.aeruginosa* MDR *K. pneumoniae* MDR *S.maltophilia*	Ventilator associated pneumonia HA-pneumonia Urinary tract infection Intraabdominal infections Bone and Joint Infections Bacteremia Wound infection Meningitis Prosthetic joint infection Diabetic foot infection

Cassir et al,A new strategy to fight antimicrobial resistance, doi: 10.3389/fmicb.2014.00551

Infections caused by multidrug-resistant Gram-negative bacteria successfully treated with old antibiotics.

Molecule	Pathogens	Sites of infection
Fosfomycin (IV)	ESBL *E. coli* ESBL *K. pneumoniae*/ Enterobacter sp./ Serratia sp. MDR *P.aeruginosa* OXA-48 *K. pneumonia* and *E. coli* KPC *K. pneumonia* Carbapenem-resistant *P. aeruginosa* MDR *S.enterica* serotype Typhimurium	Ventilator associated pneumonia HA-pneumonia Urinary tract infection Intraabdominal infection Bone and joint infections Bacteremia Wound infection Meningitis Brain abscess Lung abscess Cystic fibrosis (pulmonary exacerbation)
Fosfomycin (PO)	ESBL *E. coli* and *K. pneumoniae* KPC *K. pneumoniae* MDR *P.aeruginosa*	Lower UTI

Cassir et al,A new strategy to fight antimicrobial resistance, doi: 10.3389/fmicb.2014.00551

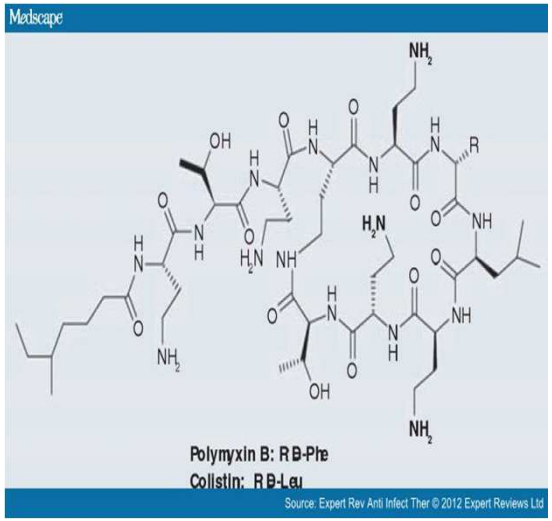
Infections caused by multidrug-resistant Gram-negative bacteria successfully treated with old antibiotics.

Molecule	Pathogens	Sites of infection
Pivmecillinam Mecillinam (PO)	ESBL *E. coli* and *K. pneumonia* CTX-M/ESBL *E. coli* ESBL Enterobacteriaceae	Lower UTI Relapsing pyelonephritis Complicated UTI
Temocillin (IV)	dAmpC/ESBL Enterobacteriaceae ESBL *E. coli* and *K. pneumonia* MDR *P. agglomerans*	HA pneumonia Urinary tract infection Bacteremia Severe sepsis (VAP, UTI, IAI) Epidural abscess Subacute synovitis
Nitrofurantoin (PO)	ESBL *E. coli*	Lower UTI

Cassir et al,A new strategy to fight antimicrobial resistance, doi: 10.3389/fmicb.2014.00551

Colistin – a polymyxin

- Synthesized by *Paenibacillus polymyxa* subspecies *colistinus*
- Discovered 1949 and introduced in 1950's
- concentration-dependent bactericidal effect; bind to LPS in outer cell membrane of Gm (-)'s
- In humans, mainly used topically due to severe neuro- and nephrotoxicity - until recently, where it was re-introduced as last-resort drug for multi-drug resistance (MDR)



Komura and Kurahashi,1979; Yahav, Colistin:New lessons on an old antibiotic, Clinical Microbiology and Infection, Volume 18 Number 1, January 2012

Colistin

- Recommended by the most recent American Thoracic Society Guidelines as a therapeutic option for the treatment of ventilator-associated pneumonia (VAP) caused by MDR Gram-negative organisms
- Evaluated for the treatment of serious MDR *P.aeruginosa*, *Acinetobacter baumannii* and Enterobacteriaceae infections of various types,including pneumonia, bacteremia, abdominal infections, bone and joint infections(BJIs), urinary tract infections(UTIs),and meningitis

A New Threat

- Up to recently, resistance to colistin has been chromosomally mediated
- New plasmid-mediated colistin resistance (MCR-1) in *E. coli* reported in China

Liu et al, Lancet Infectious Diseases, vol 16, no 2, Feb 2016

Fosfomycin

- an antimetabolite inhibitor that prevents the formation of N-acetylmuramic acid, a precursor of peptidoglycan in the bacterial wall
- first identified in Spain in 1969 in the fermentation broths of several strains of *Streptomyces* sp.(Raz, 2012)
- broad spectrum of activity with a rapid bactericidal effect against several Gram-negative and Gram-positive aerobic bacteria
- Generally well tolerated, with minimal toxicity (excepting thrombophlebitis when administered via peripheral venous catheter).

Pivmecillinam

- Prodrug of mecillinam, a β-lactam with high specificity against penicillin-binding protein 2(PBP-2) in the Gram-negative cell wall ; introduced in the 1970s
- Highly active against Enterobacteriaceae and resistant to β-lactamases.
- lack of activity against Gram-positive organisms and *P. aeruginosa*
- use of pivmecillinam as first- line treatment for uncomplicated UTIs is recommended by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

Temocillin

- Developed and first marketed in the UK in the 1980s
- 6-α-methoxy derivative of ticarcillin, characterized by its resistance to most beta-lactamases with an extended spectrum and some carbapenemases
- abandoned because of lack of activity against Gram-positive organisms, anaerobes and *Pseudomonas aeruginosa*
- Mainly excreted renally and therefore requires dosage adjustment in patients with renal impairment
- Appropriate for use in microbiologically directed therapy, particularly for the UTIs caused by confirmed ESBL producers

Nitrofurantoin

- synthetic antimicrobial derived from furan by the addition of a nitro group and a side chain containing hydantoin
- Introduced into clinical practice in its microcrystalline form in 1952
- Macrocrystalline form has less gastrointestinal side
- broad-spectrum activity against the main uropathogens (i.e., *Escherichia coli*, *Citrobacter* species, group-B streptococci, entero-cocci, *Staphylococcus aureus*, *S. epidermidis*, *Klebsiella pneumoniae*, and *Enterobacter* sp.)
- Active against ESBL-producing Enterobacteriaceae and vancomycin-resistant enterococci.
- Currently, NFT is recommended as a first-line treatment for uncomplicated UTIs by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases

Infections caused by multidrug-resistant Gram-positive bacteria successfully treated with old antibiotics.

Molecule	Pathogens	Sites of infection
Trimethoprim-sulfamethoxazole (TMP/SMX) (IV, PO)	CA and HA-MRSA *E. americana*	Skin and soft tissue infections Bone and joint infections Osteomyelitis Infective endocarditis (prosthetic valve) Meningitis Bacteremia COPD exacerbation
Minocycline (IV, PO)	MRSA	Skin and soft tissue infections Bone and joint infections Osteomyelitis Infective endocarditis (prosthetic valve) Bacteremia
Doxycycline (IV, PO)	MRSA VRE*f*	Skin and soft tissue infections UTI Bacteremia

Cassir et al,A new strategy to fight antimicrobial resistance, doi:

10.3389/fmicb.2014.00551

Infections caused by multidrug-resistant Gram-positive bacteria successfully treated with old antibiotics.

Molecule	Pathogens	Sites of infection
Chloramphenicol (IV)	VRE VRE*f* *Stenotrophomonas maltophilia*	Meningitis Ventriculitis Bacteremia Intraabdominal infections Infective endocarditis (prosthetic valve)
Clindamycin (IV, PO)	MRSA MRSA(PVL+)	Skin and soft tissue infections Bone and joint infections Mandible osteomyelitis Necrotizing fasciitis Necrotizing pneumonia Bacteremia
Pristinamycin (PO)	MRSA VRE CoNS	Pneumonia Skin and soft tissue infections Urinary tract infections Bone and joint infections Epidural abscess

Cassir et al,A new strategy to fight antimicrobial resistance, doi:

10.3389/fmicb.2014.00551

Infections caused by multidrug-resistant Gram-positive bacteria successfully treated with old antibiotics.

Molecule	Pathogens	Sites of infection
Fusidic acid (PO)	MRSA	Bone and joint infections Prosthetic joint infections Chronic osteomyelitis Epidural abscess

Cassir et al,A new strategy to fight antimicrobial resistance, doi: 10.3389/fmicb.2014.00551

TRIMETHOPRIM-SULFAMETHOXAZOLE

- broad-spectrum bactericidal agent introduced clinically in the early 1970s
- Trimethoprim is a tetrahydrofolate reductase inhibitor that, when added to sulfamethoxazole, provides a second-step block in the folate biosynthetic pathway
- According to its good oral bioavailability, high- dosage regimen of TMP/SMX represents a suitable alternative for methicillin-resistant *S. aureus* (MRSA) infections

TRIMETHOPRIM-SULFAMETHOXAZOLE

- In a recent study with a cohort of 328 patients with infections due to MRSA with a MIC to vancomycin of 2µg/mL, TMP/SMX alone compared favorably to linezolid and daptomycin in terms of treatment efficacy, mortality, and reduced antibiotic costs (Campbell et al., 2012)
- TMP/SMX alone has been shown to be less effective than current treatment for MRSA endocarditis in combination with other antibiotics (Fujino et al., 2009; Casalta et al., 2013; Di Carlo et al., 2013)

Minocycline

- is an “old drug” that was first introduced in the 1960s.
- It is available both intravenously and orally with United States Food and Drug Administration approval for the treatment of infections caused by *A. baumannii*

Tigecycline – a glycylcycline

Glycylcyclines are ‘3rd generation’ tetracyclines

- Less affected by bacterial resistance mechanisms
- Broad-spectrum, lower MICs

Only tigecycline is in clinical use (2006) – complicated skin and soft tissue infections in humans

- More toxic, higher mortality and more adverse effects than comparators
- Recommended only when other treatment options are not available

Chloramphenicol

- produced by *Streptomyces venezuelae*, inhibits protein synthesis by binding reversibly to the 50S subunit of the bacterial ribosome
- Has good oral bioavailability and excellent tissue penetration
- Broad-spectrum: Gram-positive and Gram-negative bacteria, anaerobes, spirochetes, rickettsiae, chlamydiae, and mycoplasma
- Released in the United States in 1949, reports linked this drug to rare but potentially lethal hematological side effects that restricted its use as last resort therapy
- Found to be effective against vancomycin-resistant *Enterococcus faecium* (VRE*f*), with bacteriostatic activity (Norris et al, 1995; Zhanel et al 2003)

Clindamycin

- produced by chemical modification of lincomycin, which was isolated in 1962 from *Streptomyces lincolnensis* (McGehee et al., 1968)
- binds to 50S ribosomal subunit
- Concern about *C.difficile* colitis has limited the use of clindamycin, but remains an important antibiotic in the treatment of severe anaerobic infections.
- main advantage is its potential anti-exotoxin activity in necrotizing Panton-Valentin leucocidin (PVL)-positive CA-MRSA-complicated pneumonia or SSTIs, and it is usually used with another anti-MRSA antibiotic (Hidron et al., 2009).
- recommended by clinical practice guidelines as monotherapy for CA-MRSA SSTIs (Stevens et al., 2014).

Pristinamycin

- Derived from *Streptomyces pristinae spiralis*
- An oral streptogramin antibiotic made up of two synergistic but structurally unrelated components, pristinamycin IA and pristinamycin IIA
- Discovered over 50 years ago
- A well-tolerated and effective alternative for the treatment of bone and joint infections due to Gram-positive bacteria including MRSA and VRE

Rifampicin

- A semisynthetic compound derived from *Streptomyces mediterranei*
- Introduced in 1967 as major part of the anti-tuberculous treatment
- Has an excellent tissue penetration and a unique activity on bacteria in biofilms growing on the surface of prosthetic devices.
- Despite the excellent bactericidal activity and oral bioavailability, the rapid emergence of resistance in bacteria constitutes a major limitation and therefore should be used in combination with other antimicrobial agents

Rifampicin

- Despite the lack of a control group and the limited number of patients, colistin and rifampicin appeared to be an effective and safe combination therapy for severe infections caused by MDR *Acinetobacter baumanii* (Motaouakkiletal.,2006;Bassettietal., 2008) or MDR *Pseudomonas aeruginosa*
- Rifampicin with fusidic acid or rifampicin with fluoroquinolones treatment has been shown to be effective, in combination with surgical debridement, on early prosthesis joint infections (PJI) caused by MRSA (Aboltins et al., 2007).

Fusidic acid

- Derived from the fungus *Fusidium coccineum*, introduced into clinical practice in 1962
- Inhibits polypeptide-chain elongation by binding to the ribosome elongation factor G (EF-G)–GDP complex.
- excellent oral bioavailability; metabolized in liver
- mainly bacteriostatic against Gram-positive bacteria, but has bactericidal activity at higher concentrations
- no randomized controlled trials as treatment for BJIs due to MRSA, but several case series have reported its effectiveness, mostly in combination with another oral antibiotic
- Must be used in combination with rifampin or other agents to prevent the emergence of resistance

Something old, something new

- Notably, the three recently approved new antibiotics – linezolid (2000), daptomycin (2003) and retapamulin (2007) – actually belong to chemical classes first reported in 1978, 1987 and 1952, respectively.

Back to the future: breathing new life into old antibiotics to fig...

Linezolid

- A member of a class of chemicals discovered by DuPont in 1970
- Kill bacteria by blocking the production of proteins.
- Early clinical trials revealed the antibiotic produced liver toxicity, and their development was discontinued.
- Twenty years later, a new version of the antibiotic that was no longer toxic was generated, and was effective in treating resistant skin infections and pneumonia, including the superbugs vancomycin-resistant enterococci (VRE), and methicillin-resistant Staphylococcus aureus (MRSA).

Back to the future: breathing new life into old antibiotics to fig...

Daptomycin

- Daptomycin is an antibiotic isolated from a soil bacterium in the early 1980s by Eli Lilly.
- Preliminary studies showed the compound to be highly effective in treating infections, killing bacteria by blocking protein synthesis.
- Due to the presence of mild but reversible side, effects, it was also shelved.
- In 1997, Cubist Pharmaceuticals looked more carefully at these side effects.
- By using of a new form of giving the antibiotic (called a dosing regimen), it was able to get a safe drug approval by the United States Food and Drug Administration in 2003.

Back to the future: breathing new life into old antibiotics to fig...

Retapamulin

- Retapamulin was first isolated in 1952 by members of the New York Botanical Garden.
- It was not suitable to be taken orally (in tablet form) and was shelved.
- Some 25 years later, it was resurrected as a topical preparation for infections such as impetigo.
- It is the first new topical antibiotic to be approved in almost 20 years.

Back to the future: breathing new life into old antibiotics to fig...

MESSAGE

- Unjustified antibiotic use is a much bigger issue than AIDS and terrorism put together
- Adherence to judicious antibiotic use and infection control measures is, more than ever, an urgent matter
- The consequences can affect all of us and, in fact, we are already feeling its effects.
- *We are hurtling fast into the pre-antibiotic era*

Bad Bugs….

No Drugs!

Thank You!