MDROS: What, Why, and How?

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Disclosure

No conflicts of interest to disclose

Objectives

- To define WHAT MDROs are.
- To provide current data on MDROs.
- To explain WHY MDROs exist.
- To discuss the *relevance* of MDROs to clinical practice.
- To discuss HOW pediatricians can help prevent the spread of MDROs.

Outline

What are MDROs?

What is the burden of MDROs?

What brings about MDROs?

What is the implication of MDROs in clinical practice?

What can we do to prevent MDROs?

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MULTIDRUG RESISTANT ORGANISMS

Microorganims, predominantly bacteria that are resistant to one or more classes of antimicrobial agents.

MRSA Methicillin-resistant *Staphylococcus aureus*

VRE Vancomycin-resistant enterococci

ESBLS Extended-spectrum Beta-lactamases (resistant to cephalosporins and monobactams)

PRSP Penicillin-resistant *Streptococcus pneumoniae*

IOM (1998), eds. Harrison, P.F. & Lederberg, J. (National Academy Press, Washington, D.C), pp. 8-74.

"ESKAPE" pathogens

Enterococcus faecium Staphylococcus aureus Klebsiella pneumoniae Acinetobacter baumanii Pseudomonas aeruginosa Enterobacter species

What are MDROs?

Although the names of certain MDROs describe resistance to only one agent,

i.e. MRSA, VRE, these are frequently resistant to **MOST** available antimicrobial agents.

Shlaes, D. M., Gerding, D. N., John, J. F., Jr., Craig, W. A., Bornstein, D. L., Duncan, R. A., Eckman, M. R., Farrer, W. E., Greene, W. H., Lorian, V., et al. (1997) Infect Control Hosp Epidemiol 18, 275-291.

What are MDROs?

ARSP, DOH Philippines:

Resistance to one or more agents (drugs) in 3 or more classes of antimicrobial categories

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ARSP, DOH Philippines:

Resistance to one or more agents (drugs) in 3 or more classes of antimicrobial categories

K. pneumoniae, Resistant to:

B-lactam (Ceftazidime, Piperacillin-Tazobactam) Aminoglycosides (Amikacin, Gentamicin) Carbapenem (Meropenem)

Outline

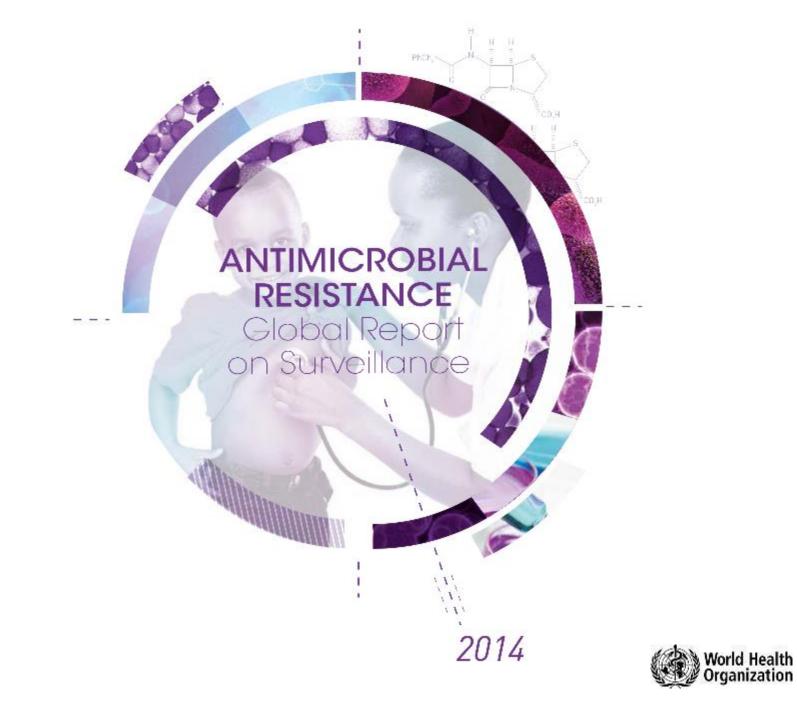
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AMR Global Report on Surveillance, 2014

High proportion of resistance to common treatments reported in all regions

Bacteria commonly causing infections in hospitals and in the community

Bacterium/ Resistance	Typical Diseases	No. out of 194 Member States Providing Data	No. of WHO Regions with National Reports of 50% Resistance or More
E. coli vs 3 rd gen. CPN vs FQ	UTI BSI	86 92	5/6 5/6
K. pneumoniae vs 3 rd gen. CPN vs Carbapenems	Pneumonia UTI BSI	87 71	6/6 2/6
S. aureus	Wound infections BSI	85	5/6

Bacteria commonly causing infections in the community

Bacterium/ Resistance	Typical Diseases	No. out of 194 Member States Providing Data	No. of WHO Regions with National Reports of 50% Resistance or More
S. pneumoniae R to Penicillin	Pneumonia Meningitis Otitis	67	6/6
Nontyphoidal Salmonelle vs FQ	Foodborne diarrhea BSI	68	3/6
Shigella sp. vs FQ	Diarrhea	35	2/6

Antibiotic Resistance Threats

Burden of MDROs & Economic Impact:

<u>US:</u>

2 M people are affected/yr., 23,000 die
20 Billion direct costs, 35 Billion indirect costs

European Union 25,000 deaths/yr.

Overall societal costs about 1.5 billion Euros/year

<u>Thailand</u>

40,000 AMR infected patients/yr. >30,000 deaths from blood infection 2.0 billion USD/year

http://www.tufts.edu/med/apua/consumers/personal_home_5_1451036133.pdf (accessed 8-5-2013); extrapolated from Roberts RR, Hota B, Ahmad I, et al.Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship.Clin Infect Dis.2009 Oct 15;49(8):1175-84



ANTIMICROBIAL RESISTANCE SURVEILLANCE PROGRAM 2015 Data Summary Report

Antimicrobial Resistance Surveillance Reference Laboratory

Research Institute for Tropical Medicine Department of Health Philippines

E. coli

E. coli rates of resistance against the fluoroquinolones and 3rd generation CPNs have been increasing for the past years with resistance rates against ciprofloxacin at 39.2% (n=5,618) and ceftriaxone at 34.6% (n=5,458) for 2015.

Emerging resistance against the carbapenems are also reported for 2015 with rates of resistance at 4.2% for ertapenem (n=3,036); 3.5% for imipenem (n=6,132); and 3.4% for meropenem (n=5,794).

E. coli

Urinary *E. coli* isolates from outpatients remain susceptible to nitrofurantoin with rate of resistance at 3.1% (n= 814). Comparatively, urinary *E. coli* isolates from hospitalized patients show variable susceptibility to parenteral agents with rates of resistance ranging from 4.2% against amikacin (n=2105); and 5.7% against ertapenem (n=1241); to as high as 40.4% against ceftriaxone (n=1973).

ESBL E. coli

ESBL suspect rate is at 27% (5578 isolates).

Escherichia coli

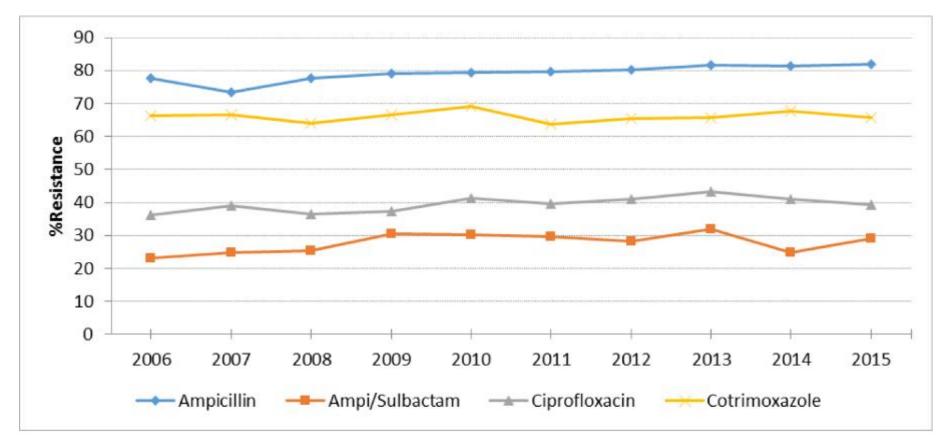


Figure 44. Yearly ampicillin, ampi-sulbactam, ciprofloxacin and co-trimoxazole resistance rates of *Escherichia coli*, ARSP, 2006-2015

Escherichia coli

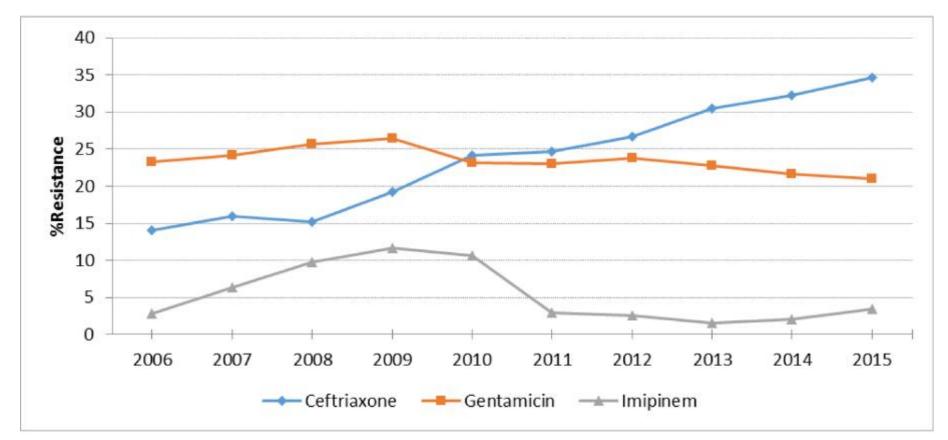


Figure 45. Yearly ceftriaxone, gentamicin and imipinem resistance rates of *Escherichia* coli, ARSP, 2006-2015

K. pneumoniae

Resistance to the carbapenems are rising with 2015 Klebsiella species resistance rates as high as 15.3% for ertapenem (n=4,041), 11.1% for imipenem (n=8,068) and 11.9% for meropenem (n=7,663).

ESBL K. pneumoniae

Extended-spectrum β -lactamase suspect rates for 2015 is at 38% (n=8,407).

Klebsiella pneumoniae

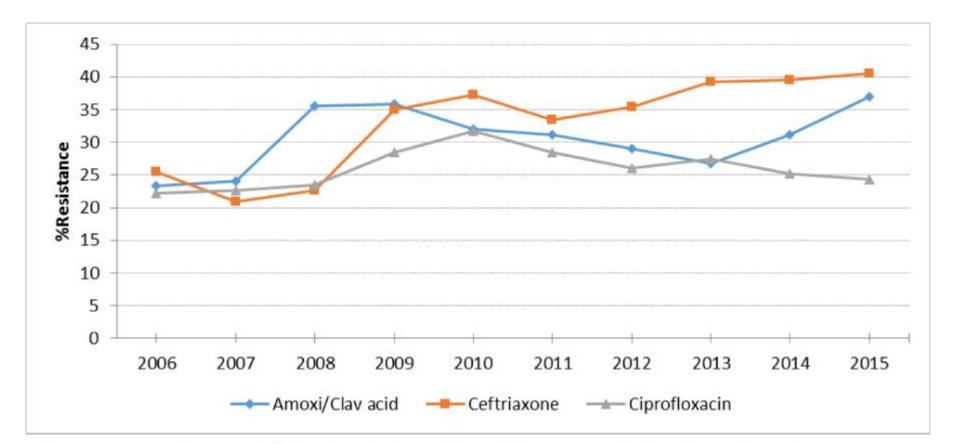


Figure 49. Yearly amoxicillin-clavulanic acid, ceftriaxone and ciprofloxacin resistance rates of *Klebsiella pneumoniae*, ARSP, 2006-2015

Klebsiella pneumoniae

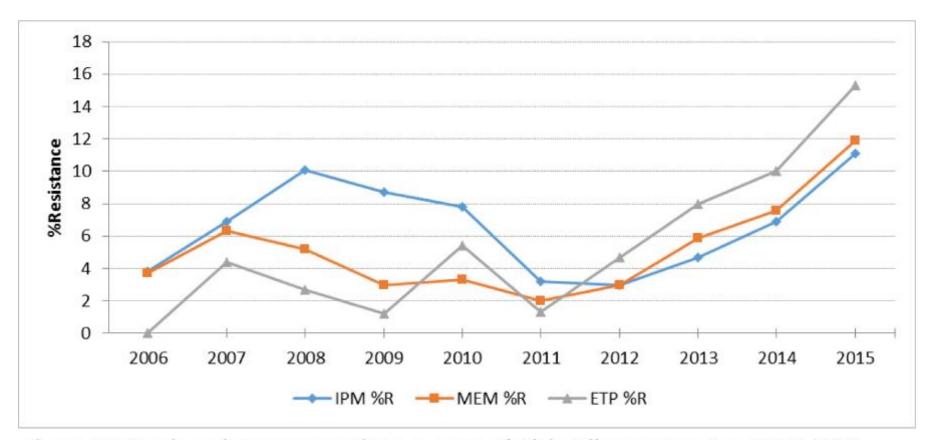


Figure 50. Yearly carbapenems resistance rates of *Klebsiella pneumoniae*, ARSP, 2006-2015

A. baumannii

Rate of resistance of *A. baumannii* is reported at 46.3% for ampicillin-sulbactam (n= 2,586) for 2015.

A. baumannii aminoglycoside resistance rates are at 31% for amikacin (n=2,827) and 36.4% for gentamicin (n=3,358).

Resistance of *A. baumannii* against imipenem have been increasing in the past 10 years with rates of resistance for 2015 reported as high as 54.1% (n=3,421).

Acinetobacter baumanii

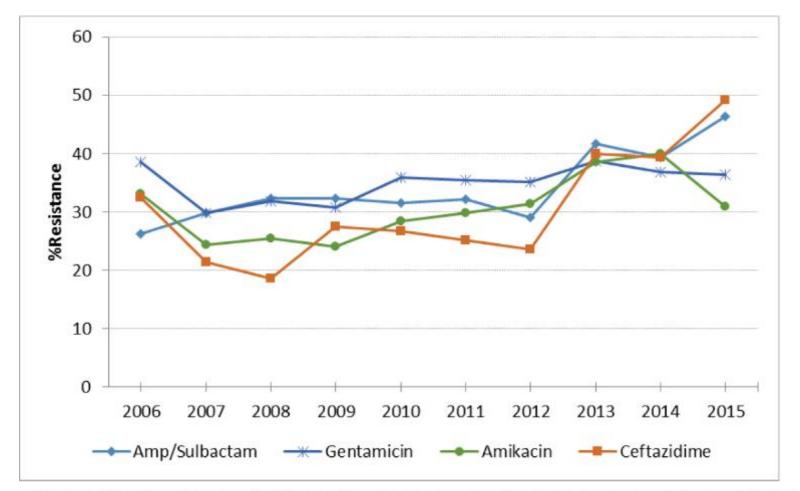


Figure 58. Yearly ampicillin-sulbactam, amikacin and gentamicin resistance rates of *Acinetobacter baumannii*, ARSP, 2006-2015

Acinetobacter baumanii

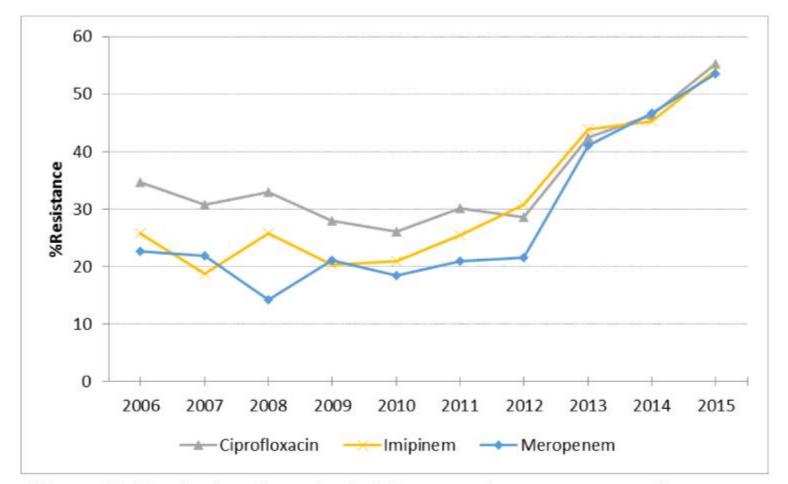


Figure 59. Yearly ciprofloxacin, imipinem and meropenem resistance rates of *Acinetobacter baumannii*, ARSP, 2006-2015

MDR P. aeruginosa & A. baumannii

P. aeruginosa MDR rates for all isolates were at 22%.

A. baumanii MDR rates for all isolates were at 66%.

S. pneumoniae

Cumulative resistance rate of *S. pneumoniae* isolates from all specimen types reported for 2014 against penicillin, using meningitis breakpoints, was at 7.6% (n=369); 5% in 2013, 0% in 2010

S. pneumoniae

Penicillin resistance was at 9% for invasive (blood and CSF) isolates when analyzed using meningitis breakpoints but only 1% penicillin resistance rate for non-invasive isolates (non-CSF and non-blood) when analyzed using non-meningitis breakpoints.

There was no ceftriaxone-resistant *S. pneumoniae* reported for 2015.

Streptococcus pneumonia

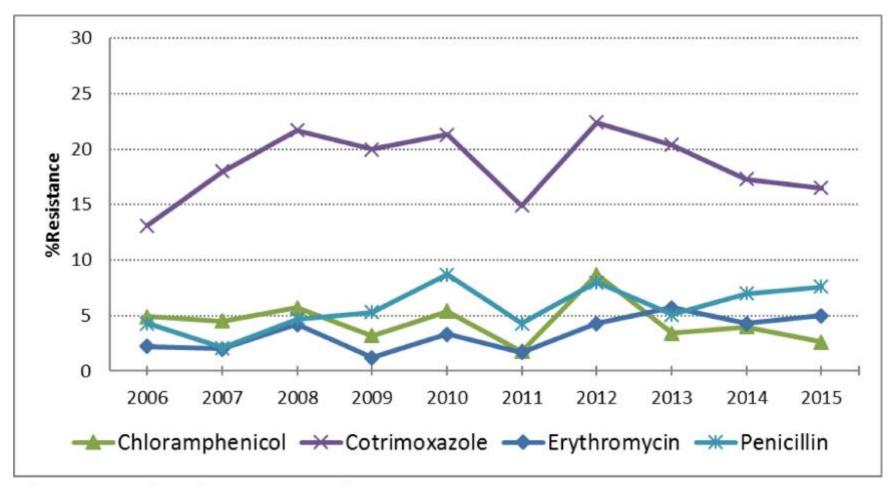


Figure 7. Yearly resistance rates of Streptococcus pneumoniae, ARSP, 2006-2015

MRSA

MRSA rate is at 62.6% (n= 3,555); 60.3% in 2014.

No confirmed vancomycin-resistant S. aureus.

Staphylococcus aureus

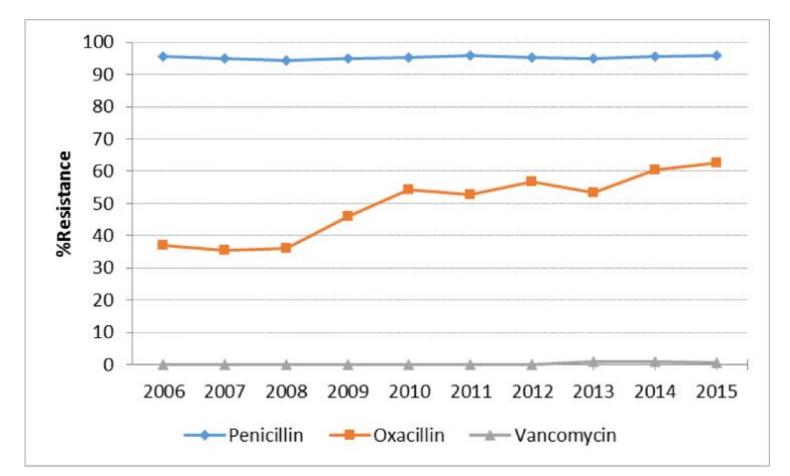


Figure 34. Yearly penicillin, oxacillin and vancomycin resistance rates of Staphylococcus aureus, ARSP, 2006-2015

ARSP 2015, DOH

VRE

Higher rates of ampicillin resistance 10.9% for *E. faecalis* (n=817), 78.1% for *E. faecium* (n=301).

There were no confirmed reports of vancomycin-resistant *E. faecalis or E. faecium*.

Antibiotic-resistant infections can happen anywhere.

Most infections happen in the general community.

Most deaths related to antibiotic resistance happen in healthcare settings.

Prevalence of MDROs varies temporally, geographically, and by healthcare setting

Zinn, C. S., Westh, H., & Rosdahl, V. T. (2004) Microb Drug Resist 10, 160-168.

Type and level of care influence the prevalence of MDROs

ICUs at tertiary care facilities have a higher prevalence of MDRO infections than do non-ICU settings

Resistance rates are strongly correlated with hospital size, tertiary-level care, and facility type

Fridkin, S. K. (2001) Crit Care Med 29, N64-68.

MDRO burden is greatest in adult hospital patients, but MDRO require similar control efforts in pediatric populations.

Saiman, L., Cronquist, A., Wu, F., Zhou, J., Rubenstein, D., Eisner, W., Kreiswirth, B. N., &Della-Latta, P. (2003) Infect Control Hosp Epidemiol 24, 317-321.

Point prevalence surveys, Pediatric Prevention Network (8 US PICUs & 7 NICUs, 2000)

 ✓ 10-24% of patients were colonized with Ceftazidime or Aminoglycoside-resistant gram negative bacilli

 $\checkmark < 4\%$ of patients were colonized with MRSA or VRE

✓< 3% of patients were colonized with ESBL-producing gram negative bacilli

Siegel, et. Al. Management of Multidrug-Resistant Organisms in Healthcare Settings, 2006.

Risk Factors

Severe illness

Underlying disease or condition such as diabetes, chronic kidney disease

Previous prolonged use of antibiotics

Invasive procedures (dialysis, use of medical devices)

Repeated contact with the healthcare system

Previous colonization with a MDRO

Elderly

Siegel, et. Al. Management of Multidrug-Resistant Organisms in Healthcare Settings, 2006.

Outline

What are MDROs?

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What can we do to prevent MDROs?

Why do they exist?

Why do they exist?

Widespread use of antibiotics, plus the natural growth of bacteria over time, has created a number of MDROs.

Use of antibiotics puts biological pressure on bacteria that promotes the development of resistance.

CDC Antibiotic Resistance Threats in the US, 2013

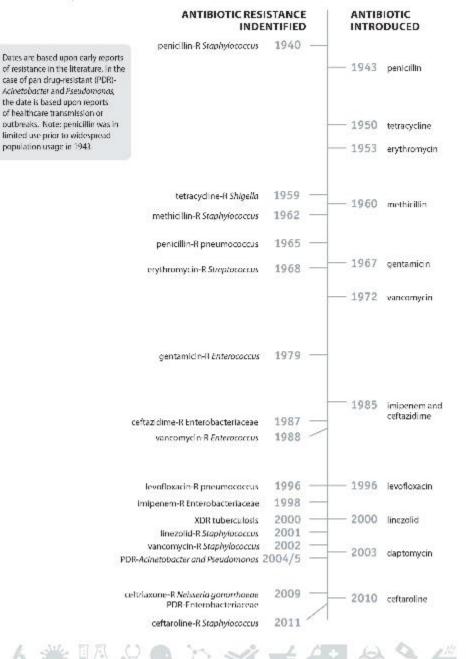
Every time someone takes an antibiotic they don't need, they increase their risk of developing a resistant infection in the future.

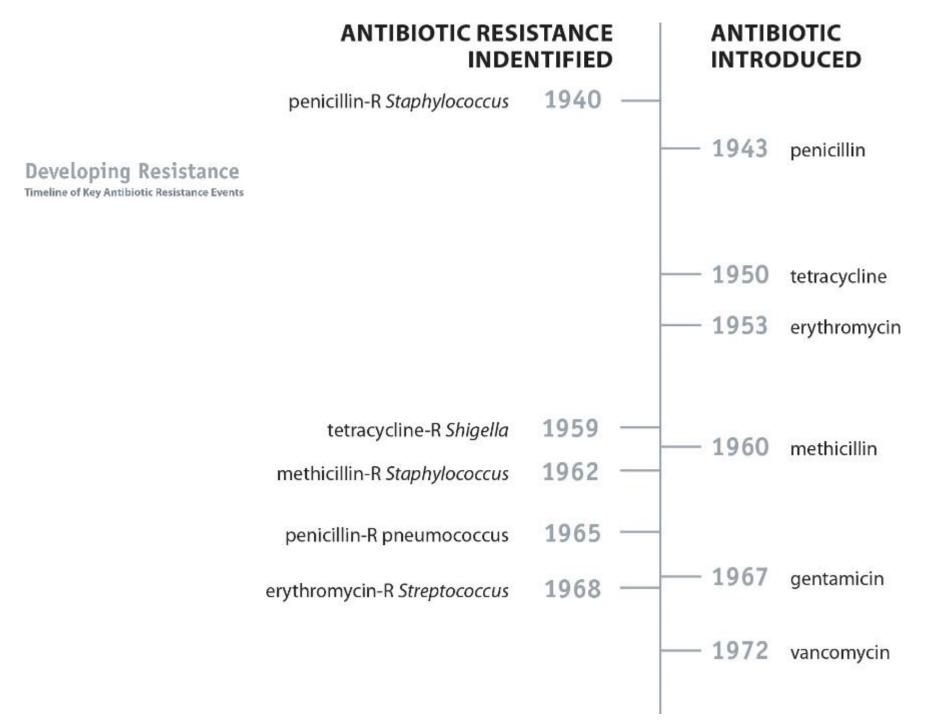
Evolution of MDROs

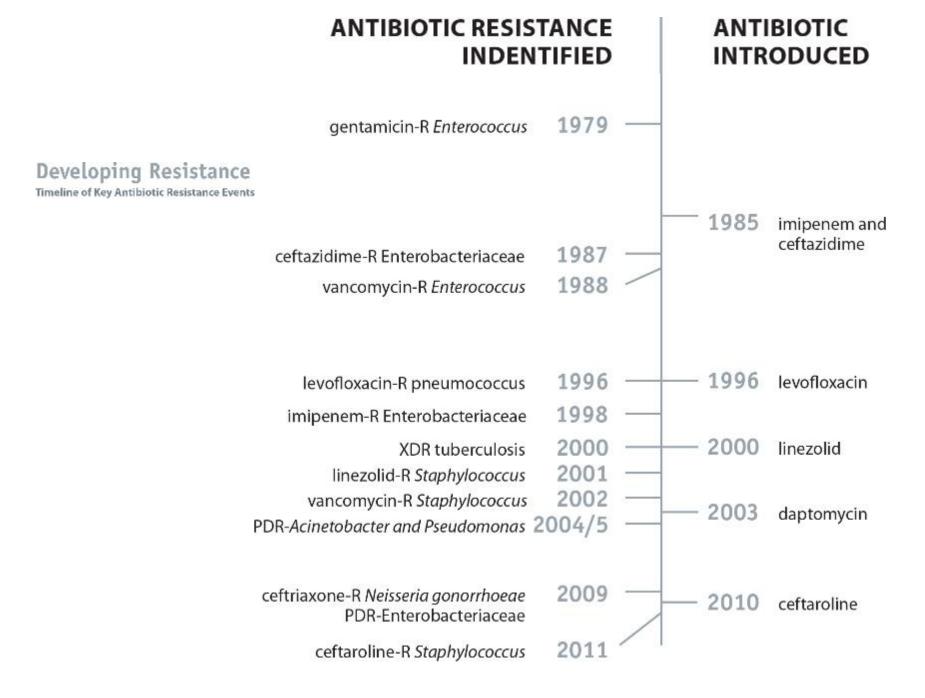
Developing Resistance

Timeline of Key Antibiotic Resistance Events

28







The more we use them, the more we lose them.

Albrich et al EID 2004

How are MDROs Transmitted?

Epidemiologic evidence suggests that MDROs are carried from one person to another via the hands of healthcare personnel.

CDC (2002) MMWR 51(16), 1-44.

How are MDROs Tranmsitted?

In the healthcare setting, once MDROs are introduced, transmission and persistence of the organism is determined by:

Availability of vulnerable patients

 ${f S}$ elective pressure exerted by antimicrobial use

Increased potential for transmission from colonized or infected patients

Impact of implementation and adherence to prevention efforts

CDC (2002) MMWR 51(16), 1-44.

How are MDROs Tranmsitted?

They can also spread from person-to-person through direct contact (touching oozing sores).

MDROs can also spread on objects such as medication cart handles, bed rails, bedside tables, IV poles, and catheters, to name a few.

CDC (2002) MMWR 51(16), 1-44.

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Implication

MDROs deserve special attention in healthcare facilities

In most instances (with the exception of MRSA), they have clinical manifestations similar to infections caused by susceptible pathogens

OPTIONS FOR TREATING PATIENTS ARE EXTREMELY LIMITED.

Stone, P. W., Gupta, A., Loughrey, M., Della-Latta, P., Cimiotti, J., Larson, E., Rubenstein, D., Saiman, L. (2003) Infect Control Hosp Epidemiol 24, 601-606.

Implication

Antibiotic-resistant infections add considerable and avoidable costs to the healthcare system.

They require prolonged treatments, extend hospital stays, necessitate additional doctor visits and healthcare use, and result in greater disability and death compared with infections that are easily treatable with antibiotics.

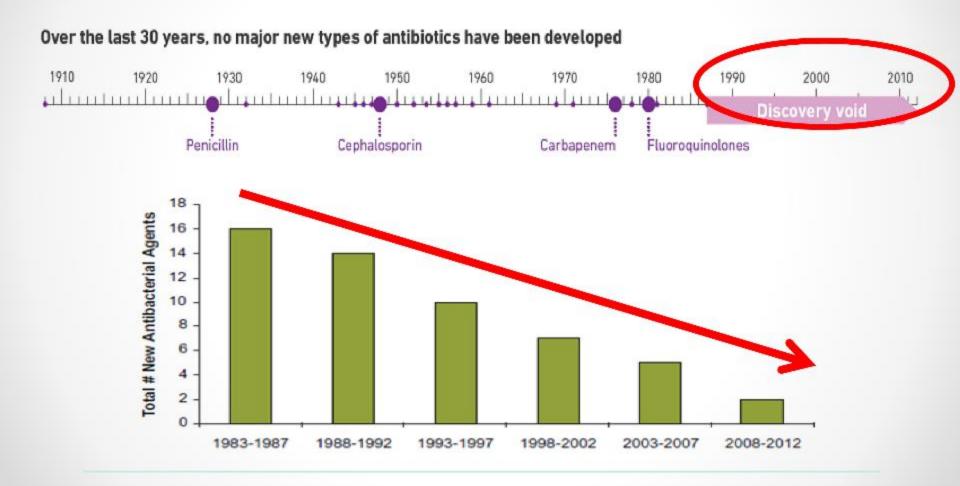
> <u>http://www.tufts.edu/med/apua/consumers/</u>personal_home_5_1451036133.pdf (accessed 8-5-2013); extrapolated from Roberts RR, Hota B, Ahmad I, et al.Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship.Clin Infect Dis.2009 Oct 15;49(8):1175-84

Site of MDRO Infections

MDROs can cause infections in almost any part of the body:

- ✓ Bloodstream
- ✓ Lungs
- ✓ Urinary tract
- ✓ Wounds
- ✓ Skin
- ✓ Surgical site

New antibiotics are scarce



World Health Organization (2014). Antimicrobial resistance. Global report on surveillance infographic

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Drug	Year Approved	Targeted Pathogens	Use & Resistance Trends
Quinupristin/ Dalfopristin	1999	Staphylococcus Streptococcus	gram-positive side effects are common, not a first choice
Moxifloxacin	1999	Enterobacteria* Staphylococcus Streptococcus	Broad-spectrum Cross-resistance among FQ
Linezolid	2000	Staphylococcus Enterococcus	Gram-positive
Ertapenem	2001	Enterobacteria Staphylococcus Streptococcus	CRE impacting drugs effectiveness
Gemifloxacin	2003	Enterobacteriaceae Streptococcus	Cross-resistance among FQ

Drug	Year Approved	Targeted Pathogens	Use & Resistance Trends
Daptomycin	2003	Staphylococcus Streptococcus Enterococcus	gram-positive resistance emerging, low
Tigecycline	2005	Enterobacteria Staphylococcus Streptococcus Enterococci	MDR Gram- negatives resistance emerging, uncommon

Drug	Year Approved	Targeted Pathogens	Use & Resistance Trends
Doripenem	2007	Enterobacteriaceae <i>Pseudomonas</i> <i>aeruginosa</i> Acinetobacter spp. Streptococcus spp.	Gram-negative
Telavancin	2008	Staphylococcus Streptococcus Enterococcus	Gram-positive SSTI
Ceftaroline	2010	Enterobacteriaceae Staphylococcus Streptococcus	MRSA NOT for ESBLs resistance emerging, low

Polymyxins (Colistin)

Older class of antibiotics

Fell out of favor because of toxicity concerns

Now used as a "last resort" agent for treatment MDR gram-negative infections

There are currently no antibacterials in advanced development for highly resistant pathogens.

Paterson DL, Doi Y. A step closer to extreme drug resistance (XDR) in gram-negative bacilli. Clin Infect Dis 2007; 45:1179–81.

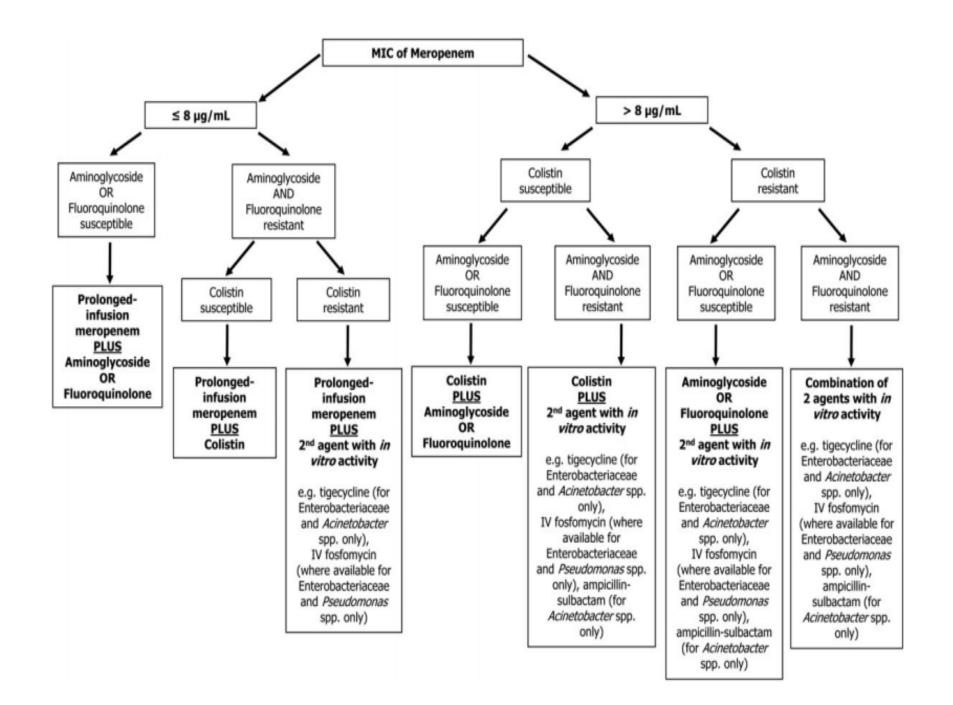
INVITED ARTICLE REVIEWS OF ANTI-INFECTIVE AGENTS

Louis D. Saravolatz, Section Editor

Treatment of Multidrug-Resistant Gram-Negative Infections in Children

Alice J. Hsu¹ and Pranita D. Tamma²

¹Department of Pharmacy, Division of Pediatric Pharmacy, The Johns Hopkins Hospital, and ²Department of Pediatrics, Division of Infectious Diseases, Johns Hopkins University School of Medicine, Baltimore, Maryland



LIMITED TREATMENT OPTIONS FOR MDROs.

Bacteria will inevitably find ways of resisting the antibiotics we develop, which is why aggressive action is needed NOW!

Outline

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How Can Infection Be Prevented?

Four Core Actions to Prevent Antibiotic Resistance:

- 1. Prevent Infections and Prevent the spread of Resistance Immunization Guidelines, safe food preparation, hand hygiene
- 2. Tracking

ARSP, DOH Philippines is used by healthcare facilities to report infections, antibiotic use, and resistance.

How Can Infection Be Prevented?

Four Core Actions to Prevent Antibiotic Resistance:

- Improving Antibiotic Prescribing (Stewardship)
 Get cultures before starting antibiotics
 Antibiotic Best Practices (indication, dose, duration)
- 4. Developing New Drugs and Diagnostic Tests

Prevention and Control of MDROs

Successful control of MDROs has been documented using a variety of combined interventions:

Improvements in hand hygiene practices

Use of Contact Precautions until patients are culture-negative for a target MDRO, use of proper PPE

Temporary unit closure

Prevention and Control of MDROs

Successful control of MDROs has been documented using a variety of combined interventions:

Active surveillance cultures (to identify those who are colonized)

Enhanced environmental cleaning (for frequently touched surfaces)

Adequate staff to patient ratio

In-service education of staff

Improvements in communication about patients with MDROs within and between healthcare facilities

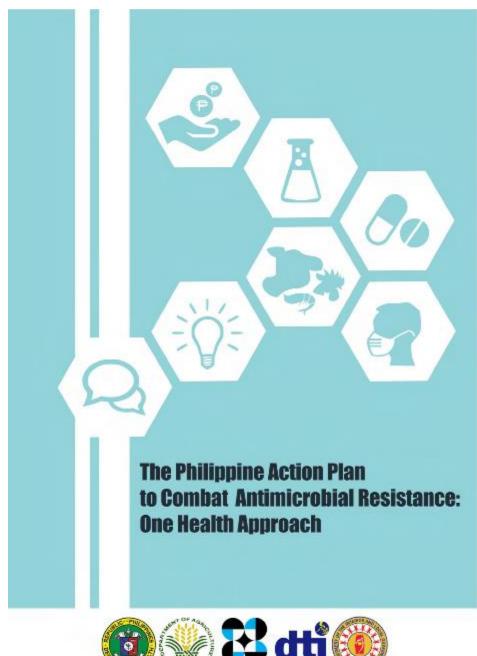
Philippine Situation

Country Situation Analysis, 2012

- 1. No comprehensive AMR plan
- 2. Need to improve surveillance
- 3. Securing the drug supply chain
- 4. Need for positive changes in knowledge and practices of prescribers, dispensers and patients
- 5. Strengthen sanitation, infection control and prevention
- 6. Research on discovery and development

Administrative Order no. 42 s. 2014,

Creating an Inter-Agency Committee for the Formulation and Implementation of the National Plan to Combat Antimicrobial Resistance in the Philippines



Philippine Action Plan to Combat AMR: One Health Approach

3-year comprehensive plan

Emphasis on "One Health Strategy"

The causation of AMR is interrelated and inter-sectoral thereby requiring collaborative multidisciplinary work at local, national, and global levels to attain optimal health for humans, animals and the environment

Key Strategies:

- 1. Commit to a comprehensive, financed national plan with accountability and civil society engagement.
- 2. Strengthen surveillance and laboratory capacity.

Key Strategies:

- 3. Ensure uninterrupted access to essential medicines of assured quality.
- 4. Regulate and promote rational use of medicines in the human and animal health sectors and ensure proper patient care.

Key Strategies:

- 5. Enhance infection prevention and control across all settings
- 6. Foster innovations and research and development.
- 7. Development of a Risk Communication Plan to combat AMR.

Department Personnel Order No. 2014-4245

Creation of the National Antibiotic Guidelines Committee (NAGCom)

NAGCom

FUNCTION:

- 1. Develop the National Antibiotic Guidelines for Primary Care and for Hospitals
- 2. Provide trainings/lectures on the dissemination of the Guidelines

NAGCom

Chair: Dr. Estrella Paje-Villar/Mediadora Saniel

Members:

PIDSP 😳 PSMID (Dr. Mari Rose De Los Reyes) RITM (Dr. Celia Carlos) National Center for Disease Prevention and Control (Dr. Rosalind Vianzon) Formulary Executive Council (Dr. Cecilia Lazarte) Philippine Pharmacists Association (Dr. Olivia Limuaco) Philippine Hospital Infection Control Society (Dr. Benilda Galvez) UP College of Medicine (Dr. Mary Ann Lansang) National Epidemiology Center (Dr. Vito Roque) National Center for Health Facilities and Development (Dr. Cynthia Fabregas)

NAGCom

PIDSP Board Members

PIDSP Fellows/Diplomates: Bone and Joint: Grace Go/Edna Mallorca CV: Mercy Aragon/Ruth Sengson Dental: Cecilia Lazarte GI: Celia Carlos Ocular: Carmina delos Reyes **RTI:** Carmina delos Reyes Sepsis: Mary Ann Banez/Pia Torres SSTI: Grace Go/Edna Mallorca STI: Rosemarie Arciaga/Joanne de Jesus/Tricia Carino

Guideline	Status	
Filariasis & Schistosomiasis	Finished and should be available	
GIT Infections	Finished and should be available	
Surgical Prophylaxis	Finished and should be available	
UTI	Finished and should be available	
Tuberculosis	For lay-outing, will be out soon	

Guideline	Status
Dental & Oral	For Finalization by the Committee
Leprosy	For Finalization by the Committee
Malaria	For Finalization by the Committee
RTI	For Finalization by the Committee
STI	For Finalization by the Committee

Guideline	Status
Blood/Cardiovascular	For Public Consultation due by March 10, 2017
Bone & Joints	due by Feb. 20, 2017
CNS	due by Feb. 10, 2017
Eye	due by Feb. 20, 2017
SSTI	due by Feb. 20, 2017

http://icamr.doh.gov.ph

http://pharmadiv.doh.gov.ph

NAGCom Guidelines, Sepsis

Sepsis in Children

Systemic Inflammatory Response Syndrome (SIRS)

The presence of two or more of the following four criteria, one of which must be abnormal temperature or white blood cell count:

- 1. Core temperature (rectal, bladder, oral, or central catheter probe) > $38.5^{\circ}C(101.3^{\circ}F)$ or $< 36^{\circ}C(96.8^{\circ}F)$
- 2. Tachycardia or bradycardia
- 3. Mean RR > 2 standard deviations for age or mechanical ventilatin for an acute process not related to an underlying neuromuscular disease or to general anesthesia
- 4. Abnormal WBC count or > 10% immature neutrophils

Sepsis: SIRS in the presence of or caused by suspected or proven infection

NAGCom Guidelines, Sepsis

Healthcare-associated sepsis

Etiology	Preferred Regimen	Comments
Gram-negative bacilli <i>S. aureus</i>	Ceftazidime 150-200 mg/kg/d q8h (max 6 g/d) OR Cefepime 100-150 mg/kg/d q8h, max 4-6 g/d OR Piperacillin-Tazobactam 300 mg/kg/d of piperacillin q8h (max 9-16 g/d) OR Meropenem 60-120 mg/kg/d q8h (max 1.5-6g/d)	Choice of empiric antibiotic therapy should be based on current antimicrobial susceptibility pattern within an institution
	WITH OR WITHOUT Aminoglycoside Amikacin 15 mg/kg/d OD WITH OR WITHOUT Vancomycin 40-60 mg/kg/d q6h (max 2-4 gm/d)	For severe infections with Pseudomonas and/or if antimicrobial resistance is suspected If with previous surgery, IV therapy or other instrumentation and staphylococcal infection is suspected

The Threat is REAL!



What MDs can do

What MDs can do

Know if patients with MDROs are hospitalized at your facility, and be aware of MDRO risks.

Ask if your patients have received medical care somewhere else.

Follow infection control recommendations with every patient – (Standard and contact precautions for MDROs). What MDs can do

Whenever possible, dedicate rooms, equipment, and staff to MDRO patients.

Prescribe antibiotics wisely.

Use culture results to modify prescriptions if needed.

Remove temporary medical devices as soon as possible.

What Patients Can Do

Tell your doctor if you have been hospitalized in another facility.

Take antibiotics only as prescribed; do not recycle or share prescriptions

Insist that everyone wash their hands before touching you.

Do not demand treatment for conditions when antibiotics are not needed and will not help.

Call for Stewardship

Antibiotics are a limited resource.

The more that antibiotics are used today, the less likely they will still be effective in the future.

Health professionals should adopt the principles of responsible antibiotic use (antibiotic stewardship).

Stewardship is a commitment to always use antibiotics only when they are necessary to treat, and prevent disease; to choose the right antibiotics; and to administer them in the right way in every case.

Call for Stewardship

Effective stewardship ensures that every patient gets the maximum benefit from the antibiotics, avoids unnecessary harm, helps preserve the life-saving potential of these drugs for the future and prevent the emergence of MDROs.

Responsible use of antibiotics have not only demonstrated these benefits but have also been shown to improve outcomes and save healthcare costs.

Think Before You Ink!

Mission: Disaster Response Officer

HELP FIGHT Multi Drug Resistant Organisms

What we learned in the last 30 minutes...

MDROs are organisms which are resistant to one or more agents (drugs) in 3 or more classes of antimicrobial categories

There is a high proportion of resistance to common treatments reported in all regions (AMR Global Report on Surveillance, 2014)

MDROs exist because use of antibiotics puts biological pressure on bacteria that promotes the development of resistance.

What we learned in the last 30 minutes...

Infections with MDROs deserve special attention.

There are currently no antibacterials in advanced development for highly resistant pathogens.

There are core actions to prevent the development of resistance and and there are proven control interventions once MDRO infection has set in.

We hold the solution to this problem.

Thank you!