ANTIMICROBIAL RESISTANCE AMONG OTHER BACTERIAL PATHOGENS OF PUBLIC HEALTH IMPORTANCE

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Once upon a time...

Alexander Fleming in 1928 accidentally discovers PENICILLIN

www.nobelprize.org
Thanks to PENICILLIN
...He Will Come Home!
Timeline of Antibiotic Deployment and the Evolution of Antibiotic Resistance

Antimicrobial Resistance

• Antimicrobial resistance occurs when bacteria changes in ways that reduces/eliminates the effectiveness of the drug designed to cure/prevent the infection

“Survival of the Fittest”

1. Population of Dividing Microbes

(20 minutes to many months)

2. Process of growth and division produces naturally occurring mutants

5. Mutants continue to grow and divide in the presence of the antimicrobial and begin to spread throughout the environment

4. Microbes are killed or prevented from growing by antimicrobial except for specific, resistant mutants

“Selective Pressure”

Microbes are Exposed to Antimicrobial Compound

3. Microbial population continues to multiply, occasionally giving rise to more mutants

Antimicrobial Resistance

National Institute of Allergy and Infectious Diseases
http://www.usc.edu
Antimicrobial Resistance: The Bugs Fight Back

**WARNING:** Antibiotics don’t work for viruses like colds and the flu. Using them for viruses will **NOT** make you feel better or get back to work faster.

Antibiotics are strong medicines. Keep them that way. Prevent antibiotic resistance. Antibiotics don’t fight viruses—they fight bacteria. Using antibiotics for viruses can put you at risk of getting a bacterial infection that is resistant to antibiotic treatment. Talk to your healthcare provider about antibiotics, visit www.cdc.gov/getsmart or call 1-800-CDC-INFO to learn more.
Consequences of Antimicrobial Resistance

- Mortality

- Morbidity - prolonged illness, greater chance of resist organisms to spread to others

- Cost - increase cost of care, newer and more expensive antibiotics

- Limited Options - few new drugs on the horizon
Antimicrobial Resistance Surveillance Program (ARSP)

- Department Order No. 339J- Department of Health Created the Antimicrobial Resistance Surveillance Committee (December 1, 1988)
- Objective: To provide critical inputs to the DOH’s effort to promote rational drug use by determining the current status and developing trends on antimicrobial resistance of selected bacteria to specific antimicrobials.
Antimicrobial Resistance Surveillance Program (ARSP)

1988: Philippine General Hospital (PGH), National Kidney Institute (NKI), Lung Center of the Philippines (LCP), Research Institute for Tropical Medicine (RITM), San Lazaro Hospital (SLH), Bureau of Research Laboratory (BRL), Far Eastern University (FEU) and Jose Reyes Memorial Medical Center (JRMMC)

1994: Rizal Medical Center (RMC), Governor Celestino Gallares Memorial Medical Center (GMH) and Zamboanga medical Center (ZMC)

1998: Eastern Visayas Regional Medical Center (EVR), Corazon Locsin Montelibano Memorial Medical Center (MMH), Vicente Sotto Memorial Medical Center (VSM) and Davao Medical Center (DMC)

2000- Cotabato General Hospital and Medical Center (CMC), Baguio General Hospital and Medical Center (BGH), Bicol Regional Teaching and Training Hospital; Gonorrhea Surveillance- Pangasinan Provincial Hospital (PPH), Zamboanga del Norte Provincial Hospital (ZPH), Dr. Rafael S. Tumbokon Memorial Hospital (RTH) and Bicol Regional Teaching and Training Hospital (BRT)

2008- Mariano Marcos Memorial Hospital (MAR) and Medical Center and Batangas Regional Hospital (BRH)

2009- Cagayan Valley Medical (CVM), Jose B. Lingad Memorial General Hospital (JBL) and Northern Mindanao Medical Center (NMC)
Antimicrobial Resistance Surveillance Program (ARSP)
Pathogens of Public Health Importance Covered by this Presentation

- **Diarrheal Diseases**
  - Salmonella species
  - Shigella species
  - *Vibrio cholerae*

- **Respiratory Tract Infections**
  - *Streptococcus pneumoniae*

- **Sexually Transmitted Infections**
  - *Neisseria gonorrhoeae*

- **Urinary Tract Infections**
  - *Escherichia coli*

- **Skin/Lung/Bloodstream Infections**
  - *Staphylococcus aureus*

- **Hospital Acquired Infections**
  - *Klebsiella spp.*
  - *Pseudomonas aeruginosa*
ANTIMICROBIAL RESISTANCE SURVEILLANCE PROGRAM
2009 REPORT
Penicillin cures gonorrhea in 4 hours. See your doctor today.
Enteric Pathogens

- Diarrhea remains one of the top 5 causes of morbidity and mortality amongst Filipino children < 5 years old

- Key Bacterial Causes of Diarrhea:
  1. *Vibrio cholera*
  2. *Salmonella sp.*
  3. *Shigella sp.*

World Health Statistics 2010
Salmonella Infections

- Typhoid Fever - Salmonella Typhi
- Diarrhea - Nontyphoidal Salmonella
Trends in Antimicrobial Resistance among *Salmonella Typhi* Isolates 1988-2009 ARSP

- **Ampicillin**
- **Ciprofloxacin**
- **Cotrimoxazole**
Burden and Epidemiology of Pneumonia

- Pneumonia is the leading killer of children under 5 years of age worldwide.

- Although bacterial infections account for no more than 50% of cases of pneumonia, they cause nearly 70% of deaths due to pneumonia.


Burden and Epidemiology of Pneumonia

- *Streptococcus pneumoniae* and *Haemophilus influenzae* are the most common bacteria causing pneumonia and these two organisms account for more than half of all deaths due to pneumonia in children under five years of age.

- Penicillin nonsusceptible *S. pneumoniae* (PNSP) was initially detected in the 1970s, but resistance to the antimicrobial has since spread worldwide.

Lynch et al. Curr Opin Pulm Med. 2010

ARSP

![Graph showing trends in antimicrobial resistance among *Streptococcus pneumoniae* isolates from 1988 to 2009. The graph plots the percentage of isolates resistant to benzylpenicillin across the years.](image)
**Escherichia coli**

- Most common cause of UTIs

- Other infections: neonatal meningitis, hospital acquired pneumonia, gallbladder and biliary tract infections, skin, bone and joint infections and bloodstream infections
Resistance Rates of *Escherichia coli*
All Sites 1988-2009
SuperBugs and Hospital-acquired Infections

*Staphylococcus aureus*, *Klebsiella* spp. and *Pseudomonas aeruginosa*

Hospital bugs are exposed to wide range of antibiotics

Hospital bugs are more resistant

- higher mortality rates
- longer length of hospital stay
- higher cost

Cosgrove SE. CID 2006
Zoleta et al. Phil J Microbio Infect Dis 2004
## Presumptive Nosocomial Infections

ARSP 2009 Data from All Sites

<table>
<thead>
<tr>
<th># of Isolates 2009 with Date of Admission Data</th>
<th># of Isolates from Specimens Submitted 48 Hours Admission</th>
<th>% of Isolated Presumed to Be of Nosocomial Origin</th>
</tr>
</thead>
<tbody>
<tr>
<td>13776</td>
<td>4995</td>
<td>36%</td>
</tr>
</tbody>
</table>

### Presumptive Nosocomial Infections (N= 4995)

<table>
<thead>
<tr>
<th>Organism</th>
<th># of Isolates</th>
<th>% of Presumed Nosocomial Infections</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Klebsiella</em> spp.</td>
<td>1142</td>
<td>23</td>
</tr>
<tr>
<td><em>Escherichia coli</em></td>
<td>850</td>
<td>17</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>789</td>
<td>16</td>
</tr>
<tr>
<td><em>Enterobacter</em> spp</td>
<td>662</td>
<td>13</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>320</td>
<td>6</td>
</tr>
<tr>
<td>Others</td>
<td>683</td>
<td>14</td>
</tr>
</tbody>
</table>
MRSA (Methicillin-Resistant *Staphylococcus aureus*)

Skin and soft tissue infections, bone infections, pneumonia, catheter-related infections, bloodstream infections
MRSA (Oxacillin) Trends
All ARSP Sites 1998-2009

Oxacillin Resistance
## MRSA: 2009 ARSP and the ANSORP Surveillance

<table>
<thead>
<tr>
<th>MRSA Rates</th>
<th>ARSP 2009</th>
<th>ANSORP 2004-2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Over-all</td>
<td>45%</td>
<td>53%</td>
</tr>
</tbody>
</table>

ANSORP (Asian Network for Surveillance of Resistant Pathogens) Countries participating: Korea, Taiwan, Hong Kong, Thailand, Philippines, Vietnam, India and Sri Lanka.

Song J et al., J Antimicrob Chemother. 2011
S. Aureus Oxacillin Resistance Rates
All Sites 2009 ARSP

Oxacillin
Community-acquired MRSA

- Skin infections
- Younger population
- No hospital exposure
- No previous antibiotic treatment
- No risk factors of underlying disease
# Distribution of MRSA Isolates Among Admitted Patients with Date of Admission

All ARSP Sites 2009

<table>
<thead>
<tr>
<th>Admitted Patients with Information on Date of Admission</th>
<th>MRSA</th>
<th>% MRSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community Acquired</td>
<td>99</td>
<td>57</td>
</tr>
<tr>
<td>Presumptive Nosocomial Infection *</td>
<td>74</td>
<td>46</td>
</tr>
</tbody>
</table>

* Presumptive Nosocomial Infection- “specimen date” was 48 hours after “date of admission”
Gram-negative Superbugs and Hospital-Acquired Infections

- Gram-negative bacteria are highly efficient in developing mechanisms of antimicrobial resistance

- Absence of new drug development with activity against drug-resistant gram-negative bacteria

- *Klebsiella* spp. and *Pseudomonas aeruginosa* – representative of gram-negative hospital pathogens

WHO: Surveillance Standards for Antimicrobial Resistance
Klebsiella spp.

New superbug in UK

New Delhi metallo-β-lactamase-1, or NDM-1 for short, is an enzyme that can live inside different bacteria. Any bacteria that carry it will be resistant to antibiotics.

Countries where NDM-1 has spread

- Islamabad
- New Delhi
- Dhaka
- Pakistan
- India
- Bangladesh
- Lungs: Klebsiella pneumonia
- Gut: E.coli

Two types of bacteria have been host to NDM-1: the gut bacterium E.coli and another that can invade the lungs called Klebsiella pneumonia. Both can lead to urinary tract infections and blood poisoning.

Press Association Graphic

- Ceftriaxone
- Ciprofloxacin
- Imipenem
- Cefepime
Trends in Resistance of *Pseudomonas aeruginosa* 1988-2009 ARSP
AND THE STORY GOES ON...

Antibiotic resistance now has been universally identified as public health priority and necessary plan of action to combat resistance should be developed.
ANTIMICROBIAL RESISTANCE SURVEILLANCE PROGRAM
**ARSP Achievements**

To assure the quality of our data:

The ARSRL participate regularly in International External Quality Assurance Programs for the ARSRL

Sentinel sites’ microbiology laboratories perform culture and susceptibility tests according to international standards and refer data to the central coordinating laboratory of the program

Regular feedback with alert reports for possible outbreaks are reported to the sentinel sites
ARSP annual reports from 1988-2009 distributed to relevant stakeholders

**ANTIMICROBIAL RESISTANCE SURVEILLANCE PROGRAM**

**PROGRESS REPORT**
January - December 2008

Research Institute for Tropical Medicine
Filinvest Corporate City
Alabang, City of Muntinlupa

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**The Antimicrobial Resistance Surveillance Program (ARSP) Program Report**

(December 2008)

**Executive Summary**

By CELIA C. CARLOS, M.D.

**Highlights of Year 2008 Antimicrobial Resistance Surveillance Program (ARSP)**

Data

1. Overall, methicillin-resistant *Staphylococcus aureus* (MRSA) rate at 31% was the same compared to that of the 2007. The resistance rate from Metro Manila increased from 25% in 2006 to 33% in 2007. MRSA rates were high and increasing for most sentinel sites. Among the regional sentinel sites, MRSA rates were as follows: ZMC (32%), VAMC (45%), CMH (24%), EVR (45%), BCH (41%), MGH (25%), RCT (10%), CMC (5%), and DMC (3%). There have been clinical cases of community-acquired MRSA reported by infectious disease specialists from within and outside Metro Manila. There were no confirmed isolates of vancomycin-resistant *Staphylococcus aureus* reported in 2008.

2. Among the respiratory and invasive isolates of *Streptococcus pneumoniae*, there was no resistance to penicillin (as determined by screening with 1 µg oxacillin disk).

3. Resistance rates of all *Salmonella typhi* isolates to ampicillin, and ceftriaxone remained low at <5% each.

4. As has been previously observed, non-typhoidal *Salmonella* showed higher resistance rates to chloramphenicol 5%, ampicillin 18%, and ceftriaxone 14% compared to rates for *S. Typhi*. There was no observed resistance to ciprofloxacin for 2008.

5. The resistance rate of *Shigella* to ceftriaxone was 54% which was lower than the figure of 65% in 2007 but the presence of 8% resistance to ciprofloxacin is a big concern.

6. In contrast to data on Salmonella and *Shigella*, resistance rates of *Vibrio cholerae* to tetracycline and chloramphenicol remained low at 0% and 1%, respectively.

7. Among the isolates of *Haemophilus influenzae* – 22%, 10%, and 15% of the isolates were resistant to ceftriaxone, ampicillin and chloramphenicol, respectively. It was lower for ampicillin whose resistance rate was only 11% in 2007 but higher for ceftriaxone and chloramphenicol whose resistance rates were 13% and 8%, respectively, in 2007.

*Chairperson, Department of Health Committee on Antimicrobial Resistance Surveillance; Consultant in Pulmonary and Critical Care Medicine, Head, Infectious Disease Research Group, Pathological and Forensic Reference Laboratory, Research Institute for Tropical Medicine*
Philippine CAP and UTI Guidelines
Philippine National Drug Formulary

- reassessing the national formulary
- assuring that drug supplies are appropriate for needs
The 2001 Antimicrobial Susceptibility Data
Celia C. Carlin, M.D.*

ARSP PUBLICATIONS, LOCAL AND INTERNATIONAL

Antimicrobial Resistance Surveillance in the Philippines

The most common species of bacteria were blood—20%, urine—21%, respiratory—18%, wounds—15%, and peritonitis—12%. 16 species were identified and 12 were classified as sensitive. The distribution of pathogens isolated was follows: E. coli (31.5%) 15% of those coming from urine, Staphylococcus aureus (10%) and Pseudomonas aeruginosa (10%). Fungi (7%) were positive for Candida (7%), Pseudomonas aeruginosa (10%) and Aspergillus (7%). A. candida was found in 3% of the isolates. In total, 14.8% of the isolates were identified as resistant. The resistance rate of E. coli was 1% (12%) and P. aeruginosa was 10% (14%).

Major Article
Clinical Outcomes of Pneumococcal Pneumonia Caused by Antibiotic-Resistant Strains in Asian Countries: A Study by the Asian Network for Surveillance of Resistant Pathogens

To evaluate the clinical outcomes of pneumococcal pneumonia caused by antibiotic-resistant strains in Asian countries, we performed a prospective observational study of 233 cases of adult pneumococcal pneumonia in 9 Asian countries from January 2000 to June 2001. Among 233 isolates, 125 (53.5%) were susceptible to penicillin (24.9% were intrinsically susceptible, and 29.6% were resistant). Clinical severity of pneumococcal pneumonia was not significantly different between antibiotic-resistant and antibiotic-susceptible groups. Mortality rates among patients with pneumococcal pneumonia caused by penicillin-resistant or macrolide-resistant strains were not higher than those with antibiotic-susceptible pneumococcal pneumonia. Bacteremic and mechanical ventilation were significant risk factors for death, but any kind of antibiotic resistance was not associated with increased mortality due to pneumococcal pneumonia. Outcome of pneumococcal pneumonia was not significantly affected by drug resistance and current antibiotic regimen are mostly effective in the treatment of pneumococcal pneumonia, despite the widespread emergence of in vitro resistance.

Pneumococcal pneumonia remains one of the most important bacterial pathogens causing community-acquired pneumonia, meningitis, otitis media, and sinusitis. Since the 1980s, global emergence of in vitro resistance to penicillin, other β-lactam agents, and macrolides has been reported from many parts of the world during the previous 2 decades (1–4). In some Asian countries in particular, the reported prevalence of penicillin and macrolide resistance was the highest in the world (5–7). With the increasing prevalence of in vitro resistance to multiple antibiotics among S. pneumoniae, questions and concerns about the clinical impact of resistance have been raised. Treatment failure associated with antibiotic-resistant pneumococci has been reported for patients with otitis media and meningitis.

CID Journal

PSMID Journal
ARSP Achievements

Relevant researches and publications by Dr. Celia C. Carlos and ARSP staff:


ARSP Achievements

Relevant researches and publications by Dr. Celia C. Carlos and ARSP staff:


• Surveillance of antimicrobial resistance of Salmonella enterica serovar Typhi in seven Asian countries. Epidemiology and Infection 12:1-4, 2008 (May).


• Clinical impact of methicillin resistance on outcome of patients with Staphylococcus aureus infections: a stratified analysis according to underlying diseases and site of infection in a large prospective cohort, J of Infection (2010) 61: 299-306.
ARSP Achievements

Relevant researches and publications by Dr. Celia C. Carlos and ARSP staff:

- Hospital-based Surveillance to Estimate the Economic Burden of Rotavirus Gastroenteritis in Children Under 5 years of age in the Philippines
- A prospective multinational surveillance of hospital-acquired pneumonia (HAP) and ventilator-associated pneumoniae (VAP) in adults in Asian countries: etiology, clinical outcome, and impact of antimicrobial resistance
- Prospective, hospital-based, multinational surveillance on antimicrobial resistance and serotypes of Streptococcus pneumoniae and disease burden of pneumococcal infections in Asian countries in the era of pneumococcal conjugate vaccine