PEDIATRIC INFECTIOUS DISEASE SOCIETY OF THE PHILIPPINES

Vol.11 No.2
July-December 2010

PIDSP JOURNAL

Vol.10 No.2t
July-December 2010

THE 2009 ANTIMICROBIAL RESISTANCE SURVEILLANCE PROGRAM: PROGRESS REPORT

AUTHORS: Celia C. Carlos, MD
Research Institute of Tropical Medicine

KEYWORDS
Antimicrobial resistance, enteric pathogens, respiratory pathogens, *Streptococcus pneumoniae, Haemophilus influenzae, Staphylococcus aureus, Neisseria gonorrhea, E. coli*

Resistance data for 24, 684 isolates were reported and analyzed. The most common specimen sources were respiratory and urine which accounted for 29% and 23% of all specimens respectively. The rest of the specimen sources were blood 18% and wounds 16%. There were 197 genital tract, 315 CSF, and 431 stool isolates reported.

The distribution of pathogens reported were as follows: *E. coli* –18%, *Klebsiella* – 16%, coagulase negative Staphylococci – 12%, *Pseudomonas aeruginosa* – 11%, *Enterobacter –9%*, *Staphylococcus aureus* – 7%, *Acinetobacter* – 6% and others. There were 384 isolates of *Moraxella catarrhalis* and 73 isolates of *Neisseria gonorrhea*. The number of *Moraxella* isolates decreased from 477 isolates in 2008 to 384 in 2009 while the number of gonococcal isolates decreased by 14% from 83 in 2008 to 73 in 2009. LCP contributed 97% of the total isolates of *M. catarrhalis,* DMC 2%, and MAR and NKI together contributed an aggregate of less than 1%. Sixty four percent (51%) of the gonococcal isolates came from the patients of Zamboanga Provincial Hospital (ZPH) followed by Vicente Sotto Memorial Medical Center (VSM) 21%. The other sentinel sites contributing gonococcal isolates were MMH – 8, STU – 7, GMH – 3, BGH -1, DMC – 1 and RMC – 1. There were less isolates of *Salmonella* Typhi and *Vibrio cholerae* in 2009 at 203 and 88, respectively, compared to 260 and 91in 2008. The top three contributors of *Salmonella* Typhi isolates were GMH 19%, CMC 18% and VSM 15%. RTM ranked as the highest contributor of *Vibrio cholerae* at 27%, BRH 18%, and EVR 14%. There was one *Campylobacter jejuni* isolate reported in 2009. This was reported by RTM.

There were 6 isolates of *Neisseria meningitides* which were reported by the following hospitals: SLH – 4 and VSM – 2. One isolate referred by VSM was non typeable. The following hospitals were the main contributors of data for *H. influenzae*: MAR 32%, VSM 20%, NKI 9%, RMC 6%, and RTM 6%. There was a 40% increase in the total number of *Streptococcus pneumoniae* isolates noted for 2009 at 208 as against the 128 contributed in 2008. The main contributors of data on *S. pneumoniae* were VSM 22%, LCP 13%, STU 10%, NKI 9%, and BGH 7%. There were 18 isolates of *Shigella* which were reported by 5 hospitals with GMH 6 isolates, MAR 2 isolates, NKI 1 isolates, SLH 4 isolates, STU 4 isolates, and VSM 1 isolate.

1. Enteric pathogens

Resistance rates of all *Salmonella* Typhi isolates to ampicillin, and cotrimoxazole remained low at <5% each as was in 2008 at 0.4% and 0.9%, respectively. Resistance rate was the same for ampicillin at 0.5% and was slightly increased at 1.5% for cotrimoxazole. There was no chloramphenicol resistance reported for 2009. There were no ciprofloxacin resistant *S.* typhi isolates reported for 2009 as in the past many years.

The resistance rate of *S.* Typhi gathered from regional hospitals show that the organism remains to be sensitive to chloramphenicol,

cotrimoxazole and ampicillin, where very low resistance was observed to the 3 antibiotics. Based on the above epidemiologic information, empiric therapy for suspected uncomplicated typhoid fever could still consist of chloramphenicol, cotrimoxazole, or amoxicillin.

As has been previously observed, nontyphoidal S*almonellae* showed higher resistance rates to chloramphenicol 10%, ampicillin 17%, and cotrimoxazole 17% compared to rates for *S.* Typhi. Resistance to ampicillin decreased compared to their rates in 2008(18%) while resistance to chloramphenicol and cotrimoxazole increased from 5% and 14%, respectively, in 2008. One isolate from STU was confirmed to be resistant to ciprofloxacin for 2009. Eleven nontyphoidal salmonella were nalidixic acid resistant by MIC. Of the referred isolates, 4 *Salmonella* typhimurium (2 from STU, 1 each from MAR and VSM), 3 *Salmonella* enteritides (1 each from EVR, Jose B. Lingad Memorial Regional Hospital (JLM), and STU), 1 *Salmonella* Group B from BRH, 1 *Salmonella* albany from JLM, 1 *Salmonella* schwarzengrund from STU, *and 1 Salmonella* choleraesuis from SLH were confirmed to be nalidixic acid resistant.

There were 149 & 33 viable *S*. Typhi and non-typhoidal *Salmonella* isolates, respectively, confirmed at the ARSRL. The most common nontyphoidal *Salmonella* serotypes identified were *Salmonella* enteritides (11 isolates) and *Salmonella* Typhimurium (9 isolates).

The resistance rate of *Shigella* to cotrimoxazole was 75% which was higher than the figure of 54% in 2008. There was no ciprofloxacin or nalidixic acid resistance reported for 2009. Nine out of 18 of the *Shigella* isolates came from Metro Manila. Of the regional sites, GMH reported 6 *Shigella* isolates, MAR 2 isolates and VSM 1 isolate. Nalidixic acid had become the first line treatment of Shigellosis in areas of the world where cotrimoxazole resistance is high.

There was no resistance of *V. cholera* 01 to tetracycline, cotrimoxazole and chloramphenicol in 2009.

2. ARI pathogens

Among the respiratory and invasive isolates of *Streptococcus pneumoniae,* there was 0% resistance to penicillin (as determined by screening with 1 ug oxacillin disk) in 2009. There was a decrease in resistance to cotrimoxazole at 22% from 23% in 2008, and resistance to chloramphenicol remained the same at 5% (Figure 1).

Among the isolates of *Haemophilus influenzae* – 39%, 17%, and 21% of the isolates were resistant to cotrimoxazole, ampicillin and chloramphenicol, respectively. Resistance rates were higher for cotrimoxazole and ampicillin whose resistance rates were 22% and 10%, respectively, in 2008. Resistance to chloramphenicol remained the same at 21%.

3. Staphylococci and other Gram positive cocci

Only fifty five percent (55%) of *Staphylococcus aureus* isolates remained sensitive to oxacillin as compared to the 69% in 2008. There were 395 MRSA tested of which 153 came from Metro Manila. Those of the regional hospitals totaled 242 which were as follows: BGH (69), MAR (51), GMH (25), CVM (20), EVR (18), BRH (17), JLM (12), DMC (8), MMH (6), NMC (6), VSM (6), BRT (2) and CMC (2). Results of MICs done by ARSRL on 395 oxacillin-resistant isolates showed that 361 (91 %) were truly methicillin-resistant (MRSA)

Overall MRSA rate increased at 45% compared to 31% in 2008 (Figure 2). Resistance rate from Metro Manila increased from 31% in 2008 to 38% in 2009. Among the regional sentinel sites, MRSA rates were as follows: ZMC (86%), CVM (77%), JLM (75%), MAR (73%), BRH (67%), NMC (58%), GMH (52%), EVR (52%), VSM (50%), BGH (38.8%), DMC (19.4%), CMC (18.2%), MMH (12%) and BRT (4%).

Resistance rate of *Staphylococcus epidermidis* to oxacillin increased to 70% from 65% in 2008 and resistance to cotrimoxazole

increased to 48% from 43% in 2008. Resistance to erythromycin also increased to 54% from 52%. There was no vancomycin resistant *Staphylococcus epidermidis* reported in 2009. Likewise, there was no vancomycin resistant *S. aureus* reported for 2009.

There were 298 and 38 isolates of *Enterococcus faecalis* and *E. faecium*, respectively. Majority of *E. faecalis* (144 isolates) came from NKI while most of *E. faecium* (9 isolates) came from STU. Vancomycin and ampicillin resistance among *E. faecalis* and *E. faecium* were 1% and 8%, respectively for vancomycin and 8% and 64%, respectively for ampicillin.

4. Gram negative bacilli

For *Pseudomonas aeruginosa,* overall resistance to ceftazidime remained the same at 15% while resistance to ciprofloxacin decreased from 28% (2008) to 22% (Figure 3). There was an increase in resistance to piperacillin/tazobactam (from 11% to 16%). Among aminoglycosides, there was 0% resistance to netilmycin while resistance rates for amikacin, tobramycin and gentamicin which ranged from 12-21%. Comparing resistance rates among regions, imipenem resistance was highest in NMC at 25%. Ceftazidime resistance was highest in NMC, Metro Manila, and ZMC at 30%, 22%, and 19%, respectively. Cefepime resistance was highest in ZMC and BGH at 27% and 19%, respectively.

Many of the Enterobacteriaceae showed high resistance rates to several antibiotics tested but resistance rates of *E. coli* to cotrimoxazole increased to 67% from that of 2008 (65%) (Figure4). There was an increase in the resistance rate to ampicillin from 78% to 80% while the resistance rates to the third generation cephalosporin (ceftriaxone) increased from 12% in 2008 to 18% in 2009. Resistance to fourth generation cephalosporin (cefepime) also increased at 21% in 2009. A resistance rate to the second generation cephalosporin was noted at 20% (which increased from 14% in 2008) while beta lactam-beta lactamase inhibitors (i.e. ampicillin-sulbactam) increased to 30% from 25% in 2008.

No significant change was observed in comparing data for *E. coli* among regions. As had been seen in 2008, very high resistance rates existed against cotrimoxazole (range: 34% in BRT to 75% in DMC), cephalothin (range: 30% in VSM to 100% in CMC), but were variable for co-amoxiclav (range: 27% in BRH to 61% in BRT). Other sentinel sites with high resistance rates to co-amoxiclav were ZMC (55%), CVM (54%), MAR (53%), and NMC (50%), An abrupt increase in resistance rate of *E. coli* to co-amoxiclav was observed for GMH (from 11% to 41%), and ZMC (from 29% to 55%) but a decrease was observed for CMC (from 50% to 28%) and VSM (from 66% to 30%) . An abrupt increase in resistance rate of *E. coli* to cephalothin (from 52% to 77%) was observed for ZMC. For CMC, 100% (6 out 6) of *E coli* isolates were ESBL producing, 91% (10 out of 11) for GMH, 90% (17 out of 19) for MMH and 84% (38 out of 45) for DMC.

Resistance rates of *Klebsiella* against 8 out of the 9 antibiotics increased for 2009. Resistance rate for ceftriaxone increased from 19% in 2008 to 29% while cefepime increased from 8% to 14%, ampicillin-sulbactam (from 25% to 26%) and cefepime (from 7% to 8%). High resistance rates were exhibited against first generation cephalosporins like cephalothin (53%) and second generation cephalosporins like cefuroxime (29%) and beta lactam-beta lactamase inhibitors like ampicillin-sulbactam at 32%. There was a high resistance rate (31%) against gentamicin but lower for amikacin where the resistance rate was 20%. Resistance rate remained the same for imipenem (0.7%).

VSM had the most number of confirmed ESBL (+) isolates at 78 (68% of referred suspected ESBL producing isolates) followed by BGH at 74, MMH at 72, DMC at 68 and STU at 68. There is a need to closely monitor the presence of this enzyme among the *Enterobacteriaceae* in view of the very limited antibiotics (i.e. carbapenems, beta lactam-beta lactamase inhibitors) which can be utilized for

patient therapy in the presence of such enzyme. Hospitals reporting many of these organisms should investigate whether there cases were associated with outbreaks and if so, investigated.

Resistance rates of urinary *E. coli* from outpatients versus inpatients showed no significant difference in rates for most antibiotics except for higher resistance rates among inpatient compared to outpatient isolates against cefotaxime (27% versus 13%) and against nalidixic acid (46% versus 34%). In isolates obtained from outpatients, least resistance was observed against nitrofurantoin among oral antibiotics at 7% while there was a remarkable increase in the resistance rate for cefuroxime axetil (from 28% in 2008 to 44% in 2009). For parenteral antibiotics, amikacin had the least resistance at 9% followed by cefotaxime and ceftriaxone at 13%. Among in-patients, there was a remarkable increase in resistance to cefotaxime (from 12% to 27%).

In contrast, resistance rates of *Klebsiella* from respiratory specimens showed higher rates among most isolates from inpatients which was also the trend observed in 2008. Among outpatient isolates, there was a noted increase in resistance rates compared to 2008 data to cephalothin (from 19% to 29%) and cefuroxime (from 12% to 18%). Among inpatient isolates there was a significant increase in resistance rate for cefuroxime axetil (from 33% to 50%) while there was a significant decrease in resistance to co-amoxiclav, from 41% to 14%. For *Pseudomonas aeruginosa*, the rates between in and outpatient isolates tended to be similar. Among in-patients, there was a decrease in resistance rate to netilmycin from 11% in 2008 to 0% in 2009.

5. *Neisseria gonorrheae*

Resistance to ciprofloxacin and ofloxacin increased to 83% and 79% in 2009 from 48% and 54%, in 2008, respectively. Resistance to tetracycline decreased from 82% to 47%. There were no spectinomycin, ceftriaxone and cefixime resistant isolates reported for 2009.

Recommendations

Based on the above-mentioned anti-microbial resistance surveillance data:

a. In view of the continued high rates of methicillin/oxacillin resistance among staphylococci in 2008, there may be an indication to shift empiric treatment of suspected staphylococcal infections from oxacillin to vancomycin. However, in order to ensure prudent use of vancomycin, guidelines for judicious use of vancomycin should be followed.

b. Infections secondary to *Streptococcus pneumoniae* can be covered with penicillin or chloramphenicol although there is a need to closely monitor the changing trends of resistance among pneumococci.

c. Empiric treatment for suspected uncomplicated typhoid fever could still consist of either chloramphenicol or cotrimoxazole or amoxicillin/ampicillin.

d. The fluoroquinolones and 3rd generation cephalosporins are better treatment options for non-typhoidal *Salmonella*. However, physicians should be aware of the existence of fluoroquinolone resistant nontyphoidal *Salmonella* in a small proportion of isolates.

e. Ciprofloxacin may be considered as the drug of choice for treatment of suspected shigellosis among adult patients while nalidixic acid may be considered as empiric treatment for the pediatric age group. In view of the emerging resistance of *Shigella* to the quinolones, continued surveillance of the resistance pattern of this organism should be pursued with the possibility of considering alternative antimicrobial

treatment such as ceftriaxone or azithromycin if the rates continue to rise.

f. Tetracycline, chloramphenicol and cotrimoxazole remain good treatment options for cholera cases.

g. Due to the significant increase in resistance of *Haemophilus influenza* to ampicillin in 2009 (10% in 2008 to 17% in 2009) and since ampicillin resistance in *H. influenzae* is usually mediated by beta lactamase production, empiric treatment for suspected *H. influenza* infections may consist of beta lactam-beta lactamase inhibitor combinations, extended spectrum oral cephalosporins and the newer macrolides. Laboratories should therefore screen all isolates of *H. influenzae* for beta lactamases as part of its antimicrobial susceptibility test procedure.

h. Hospitals should base their treatment recommendations for the Enterobacteriaceae on their institution's prevailing resistance patterns as these patterns have been found to be variable from hospital to hospital. There is need to closely monitor the presence of ESBLs from among the Enterobacteriaceae in hospitals in view of the very limited antibiotics (i.e. carbapenems, beta lactam-beta lactamase inhibitors) which can be utilized for patient therapy in the presence of such enzyme.

i. The continued rise in MRSA rates and cases of infection secondary to ESBL may indicate very inadequate implementation of infection control procedures in some hospitals, which the Department of Health (DOH) should look into.

j. Cefixime and ceftriaxone can remain as empiric antibiotics of choice for gonococcal infections.

Acknowledgments

For the year 2009, financial supports for the activities of the ARSP were derived mainly from suballotted funds from the Department of Health (Pharma 50, National Epidemiology Center, and Vaccine Self-sufficiency funds) and World Health Organization Western Pacific Regional Office. Research funds were also received from the Asian Network for Surveillance of Resistant Pathogens (ANSORP) for the HAP/VAP and *Streptococcus pneumoniae* studies.

Antimicrobial Resistance Rates by DISC DIFFUSION,
Department of Health Antimicrobial Resistance Surveillance, Jan- Dec., 2009
Prepared by the Antimicrobial Resistance Surveillance Reference Laboratory,
Research Institute for Tropical Medicine

PERCENT RESISTANCE (NUMBER TESTED)

ORGANISMS	Ampicillin	Chloramphenicol	Ciprofloxacin	Cotrimoxazole	Tetracycline	Nalidixic Acid
A. Enteric Pathogens						
Salmonella typhi	0.5 (197)	0 (202)		1.5 (196)		
Nontyphoidal Salmonella	16.5 (115)	10.4 (96)	2.9 (105)	17.4 (92)		
Shigella	76.5 (17)	50 (16)	0 (15)	75 (16)		0 (14)
Vibrio cholera		0 (84)		0 (85)	0 (86)	

ORGANISMS	Ampicillin	Cefuroxime	Chloramphenicol	Ciprofloxacin	Co-amoxiclav	Cotrimoxazole	Erythromycin	Penicillin	Ampisulbactam
B. ARI Pathogens									
Streptococcus pneumoniae			4.8. (188)			21.7 (189)		0 (170)	
Haemophilus influenzae	17.4 (92)		20.9 (86)			38.5 (78)			
Moraxella catarrhalis	24.2 (120)				17.1 (123)	47.6 (124)	45.9 (122)		

ORGANISMS	Ampicillin	Benzylpenicillin	Ciprofloxacin	Cotrimoxazole	Erythromycin	Oxacillin	Vancomycin
C. Staphylococci and Enterococci							
Staphylococcus aureus		95.6 (1595)	5.5 (1447)	5.3 (1479)	9.2 (1520)	44.8 (1620)	0 (1421)
Staphylococcus epidermidis		92.4.(699)		47.6 (611)	54.3 (648)	69.9 (599)	0 (572)
Enterococcus faecalis	7.7 (234)						1.4 (290)

PERCENT RESISTANCE (NUMBER TESTED)

ORGANISMS	Amikacin	Ampicillin	Ampi-Sulbactam	Cefuroxime	Ciprofloxacin	Ceftriaxone	Cephalothin	Gentamicin	Cotrimoxazole	Cefepime	Imipenem
D. Enterobacteriaceae											
E. coli	10.8 (3717)	79.7 (3997)	29.9 (3502)	20.3 (2341)	38.2 (3879)	17.6 (3665)	48.6 (2126)	26.9 (3976)	67.1 (3794)	21.4 (2591)	
Klebsiella	20.3(3392)		31.7 (2638)	28.9 (1694)	27.9 (3484)	29.7 (3355)	53.4 (2084)	31.4 (3414)		14.3 (2757)	0.7 (3495)
Enterobacter	11.2(1950)				20.3 (1850)	27.4 (1908)	85.3 (1276)	28.3 (1929)		14.4 (1705)	2.3 (1913)

ORGANISMS	Amikacin	Cefepime	Ceftazidime	Ciprofloxacin	Gentamicin	Imipenem	Netilmicin	Piper-Tazo	Tobramycin
E. **Gram negative nonfermentative bacilli**									
Pseudomonas aeruginosa	11.5 (2659)	11.2 (2292)	15.4 (2660)	22.1 (2579)	20.6 (2556)	13.5 (2473)	0 (22)	15.8 (1647)	19.2 (2428)

ORGANISMS	Cefixime	Ceftriaxone	Ciprofloxacin	Ofloxacin	Penicillin	Spectinomycin	Tetracycline
Neisseria gonorrheae	0 (65)	0 (71)	82.8 (64)	79.1 (67)	90.4 (73)	0 (64)	46.6 (73)

ABBREVIATIONS

BGH - Baguio General Hospital
BRH – Batngas Regional Hospital M
BRT- Bicol Regional Training and Teaching Hospital
CMC- Cotabato Regional Hospital and Medical Center
CVM- Cagayan Valley Medical Center
DVM- Davao Medical Center
EVR- Eastern Visayas Medical Center
GMH- Celestino Gallares Memorial Hospital
LCP- Lung Center of the Philippines
JLM- Jose Lingad Memorial Regional Hospital
MAR - Mariano Marcos Memorial Hospital
MMH- Corazon Locsin Memorial Hospital and Medical Center
NKI- National Kidney and Transplant Institute
NMC Northern Mindanao Medical Center
RMC- Rizal Medical Center
RTM- Research Institute of Tropical Medicine
SLH- San Lazaro Hospital
STU- Santo Tomas University Hospital
VSM- Vicente Sotto Memorial Medical Center
ZPH- Zamboanga Del Norte Provincial Hospital