

THE ANTIMICROBIAL RESISTANCE SURVEILLANCE PROGRAM

PROGRESS REPORT (January – December 2011)

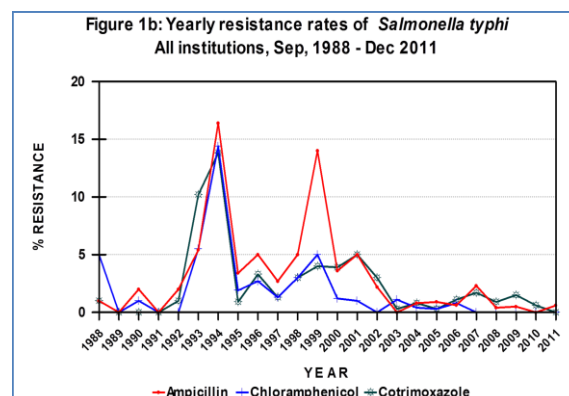
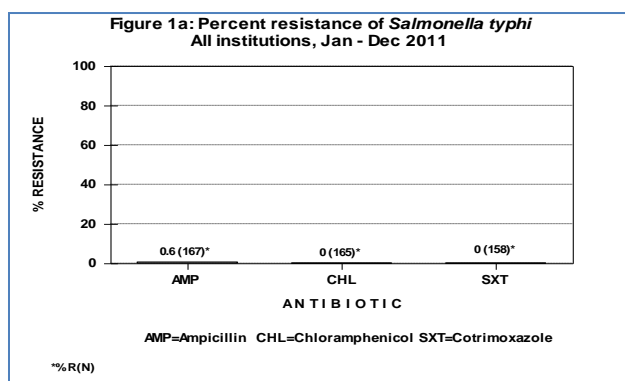
Resistance data for 23, 754 isolates at one isolate per patient were reported and analyzed. The most common specimen sources were respiratory and blood which accounted for 27% and 22% of all specimens respectively. The rest of the specimen sources were urine 22% and wounds 18%. There were 134 genital tract isolates reported, 357 CSF isolates, and 264 stool specimens.

The distribution of pathogens reported were as follows: *E. coli* –16%, *Klebsiella* – 15%, coagulase negative Staphylococci – 13%, *Pseudomonas aeruginosa* – 9%, *Enterobacter spp* – 9%, *Staphylococcus aureus* – 7%, *Acinetobacter spp* – 7%, *Staphylococcus epidermidis* – 4%, *Proteus sp.* – 3%, *Enterococcus faecalis* – 1%, and others - 15%. There were 39 isolates of *Moraxella catarrhalis* and 30 isolates of *Neisseria gonorrhoea*. There were 171 isolates of *Salmonella Typhi* and 82 *Vibrio cholerae* in 2011.

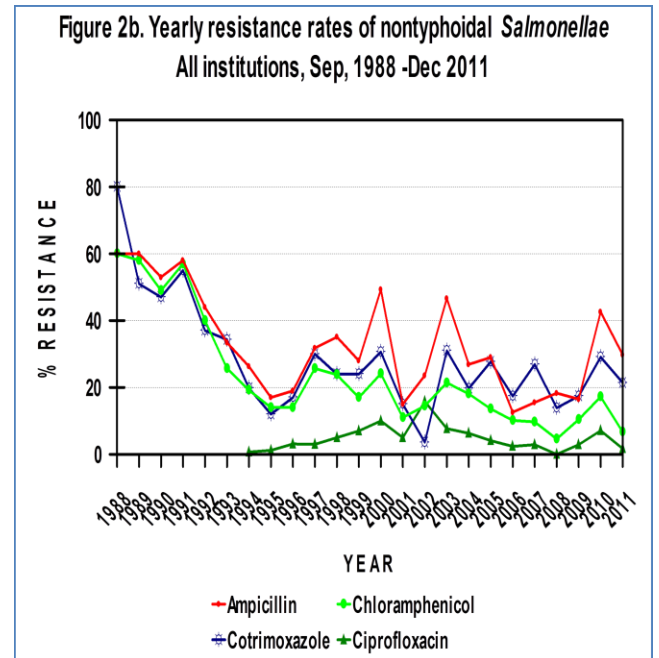
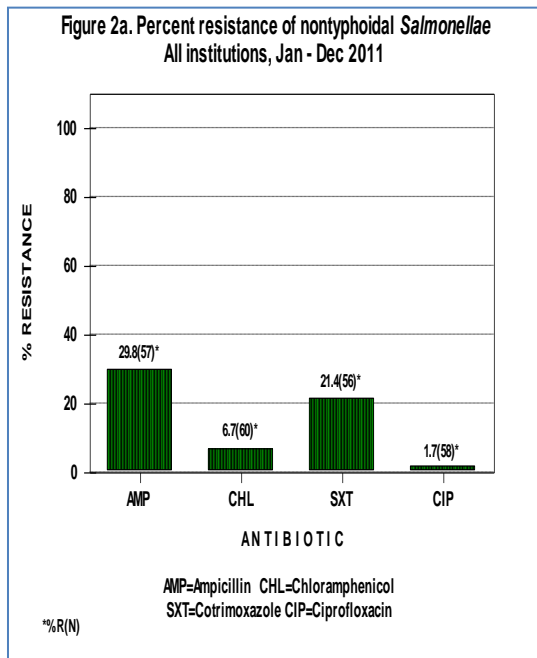
There were 10 isolates of *Neisseria meningitides*, 139 *Haemophilus influenzae* isolates, and 176 *Streptococcus pneumoniae* isolates.

1. Enteric pathogens

Resistance rates of all *Salmonella Typhi* isolates to ampicillin increased from zero in 2010 but remained low at 0.6% (95%CI:0-3.8) in 2011. The increase was not statistically significant ($p=0.5107$). There was no chloramphenicol nor cotrimoxazole resistance reported for 2011 (95%CI:0-2.8; 0-3) (Figures 1a and 1b). There was no ciprofloxacin resistant *S. Typhi* reported for 2011 (95%CI: 0-2.8) as in the past many years. Resistance to ceftriaxone was at 1% (95%CI: 0.2-4.7) from zero in 2010.



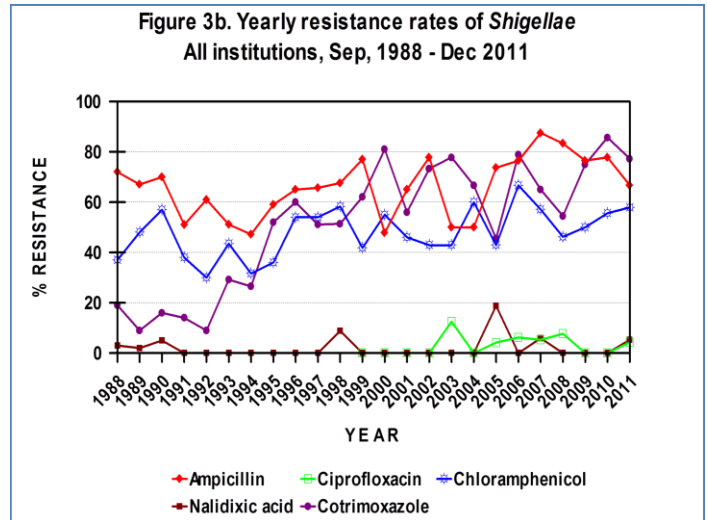
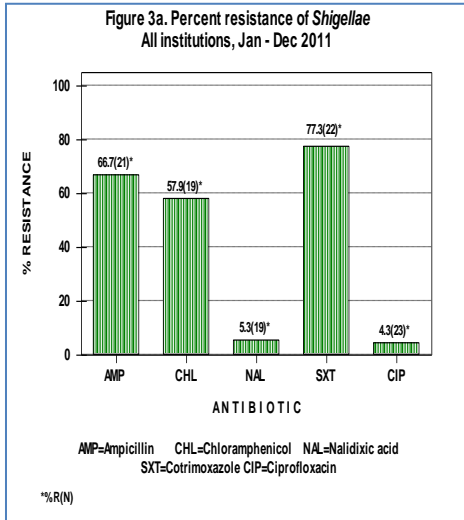
As has been previously observed, nontyphoidal *Salmonellae* showed higher resistance rates to chloramphenicol 7% (95%CI: 2.2-17), ampicillin 30% (95%CI:18.8-43.5) , and cotrimoxazole 21% (95%CI: 12-34.8) compared to rates for *S. Typhi* (Figures 2a and 2b). Resistance to ampicillin decreased at 30% in 2011 compared to the rate in 2010(43%). This decrease in rate is not statistically significant (p=0.105). There was likewise a decrease in the resistance to chloramphenicol and cotrimoxazole from 17% in 2010 to 7% in 2011 and from 29% in 2010 to 21% in 2011, respectively. Both changes in rates are not statistically significant(p=0.0522; p=0.2388). One isolate of *Salmonella* Paratyphi from NKI was reported to be ciprofloxacin resistant but was not confirmed.



Thirteen of the nineteen nontyphoidal salmonella isolates reported for 2011 were confirmed to be nalidixic acid resistant. Of the confirmed nalidixic acid resistant isolates, 6 isolates were *Salmonella* Typhimurium, 4 were *S. Enteritidis*, 1 *S. Albany*, 1 *S. Choeraesuis* var *Kurzendorf* and 1 *S. Hissar*.

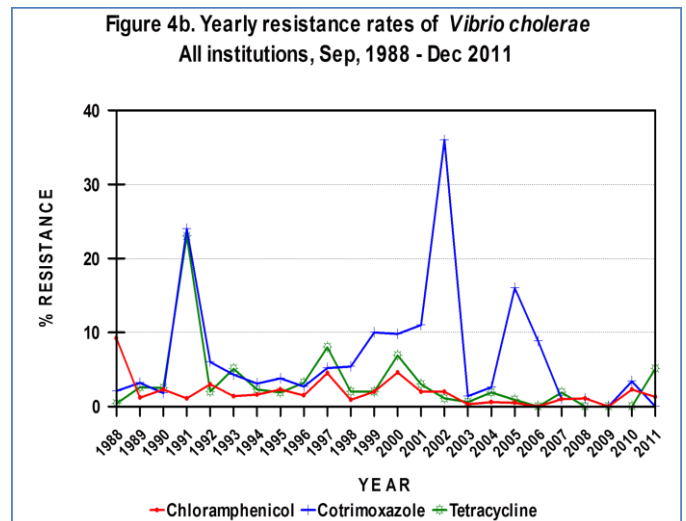
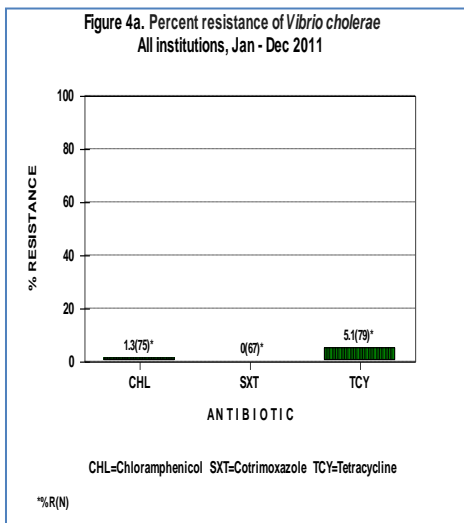
There were 139 & 28 viable *S. Typhi* and non-typhoidal *Salmonella* isolates, respectively, confirmed at the ARSRL. The most common nontyphoidal *Salmonella* serotypes identified were *Salmonella* Enteritidis (10 isolates) and *Salmonella* Typhimurium (6 isolates).

The resistance rate of *Shigella* to cotrimoxazole was 77% (95%CI: 54.2-91.3) which was lower than the figure of 86% in 2010. The decrease was not statistically significant ($p=0.5454$). Resistance to ciprofloxacin and nalidixic acid were 5% (95%CI: 0.2-23.9) and 4% (95%CI: 0.3-28.2), respectively (Figures 3a and 3b).



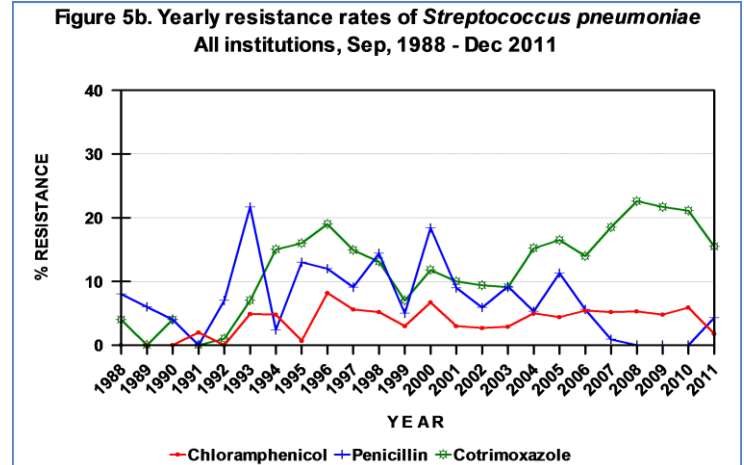
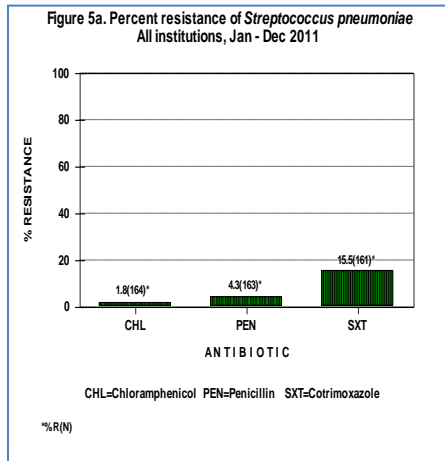
In order to obtain a reasonable statistical estimate of cumulative %R for *Shigella*, we combined the results of isolates from 2010 to 2011 to obtain a total required number of isolates (>30 isolates). The resistance rate of *Shigella* for the combined 2010 to 2011 isolates are as follows: resistance to cotrimoxazole is 79%(95%CI: 59.7-91.3), ciprofloxacin 3%(95%CI: 0.2-17.5) and nalidixic acid 4%(95%CI: 0.2-20.3).

There was an increase in the resistance of *Vibrio cholerae* 01 to tetracycline at 5% (95%CI: 1.7-13.2) in 2011 compared to zero for 2010 (Figures 4a and 4b). This increase was not statistically significant ($p=0.1769$). There was a decrease in resistance to cotrimoxazole and chloramphenicol at 0% (95%CI: 0-6.8) in 2011 against 3% in 2010 and at 1%(95%CI: 0.1-8.2) in 2011 against 2% in 2010, respectively. Both decreases were not statistically significant ($p=0.3021$; $p=0.6048$).

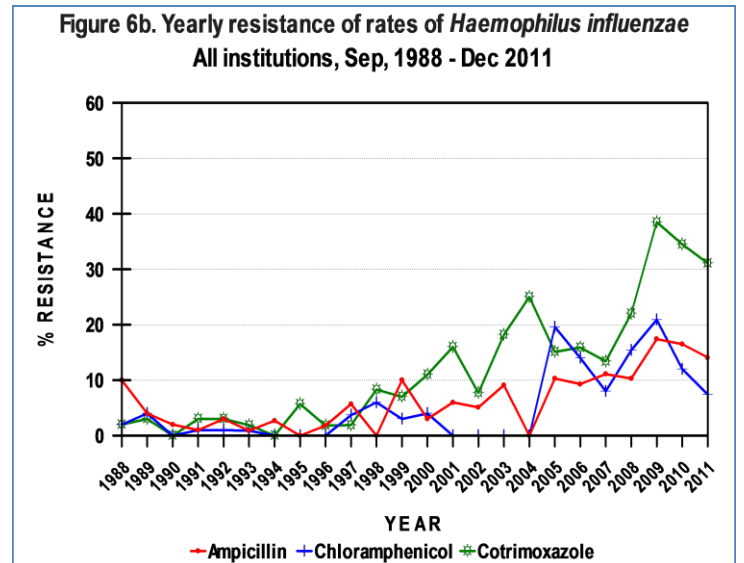
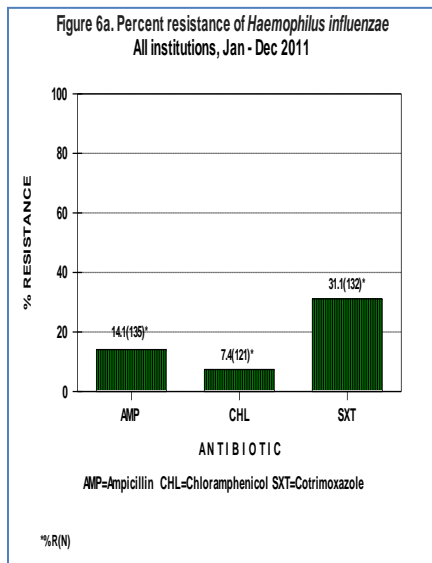


2. ARI pathogens

Among the respiratory and invasive isolates of *Streptococcus pneumoniae*, there was an increase in resistance to penicillin at 4% (95%CI: 1.9-9) in 2011 compared to 0% in 2010. This increase is statistically significant ($p=0.0076$). Five of the seven reported penicillin resistant *S. pneumoniae* were confirmed to be resistant. There was a decrease in resistance to cotrimoxazole at 16% (95%CI: 10.5-22.2) from 21% in 2010. This decrease is not statistically significant ($p=0.1229$). Resistance to chloramphenicol likewise decreased from 6% in 2010 to 2% (95%CI:0.5-5.6) in 2011(Figures 5a and 5b). Decrease in %R to chloramphenicol was statistically significant ($p=0.0445$).

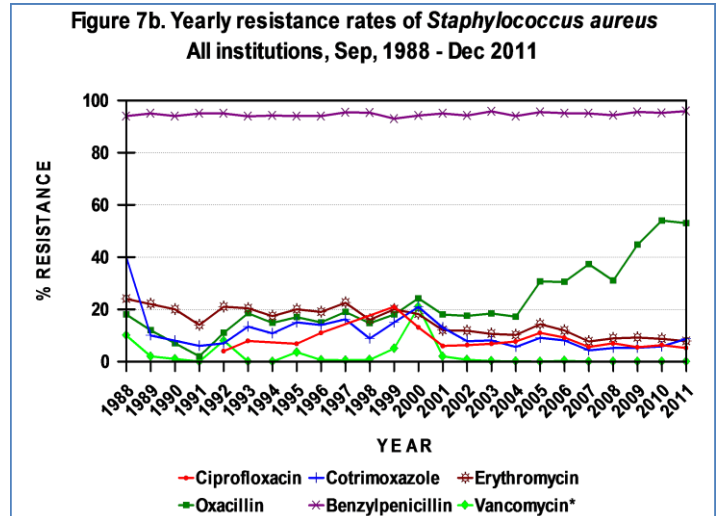
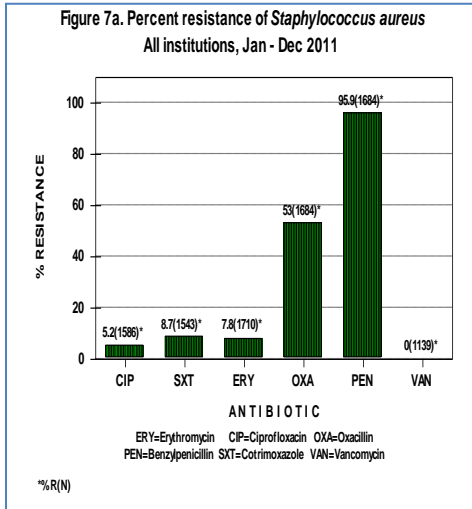


Among the isolates of *Haemophilus influenzae* – 31% (CI 23.5-39.8), 14%(CI 8.9-21.4), and 7%(CI: 3.6-14) of the isolates were resistant to cotrimoxazole, ampicillin and chloramphenicol, respectively (Figures 6a&b). Resistance rate was lower for ampicillin in 2011 at 14% compared to 16% in 2010 ($P=0.3821$). Resistance to cotrimoxazole and chloramphenicol likewise decreased at 31% and 7% from 34% and 12%, respectively, in 2010 ($p=0.3504$; $p=0.1921$).



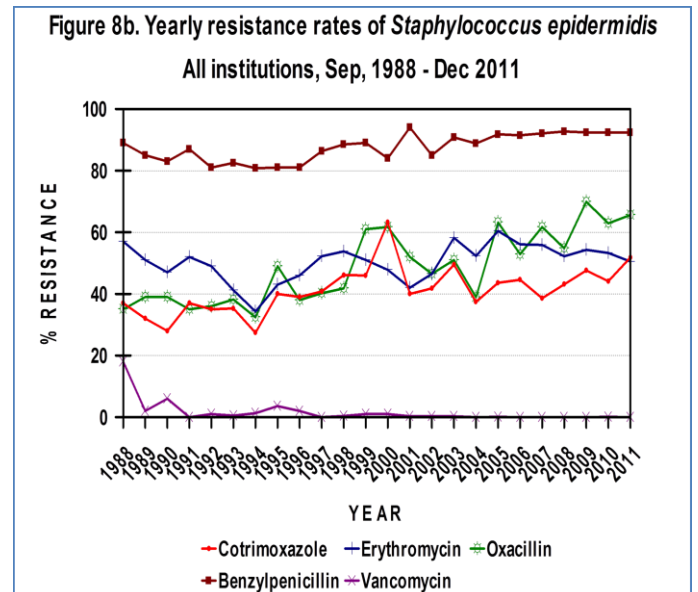
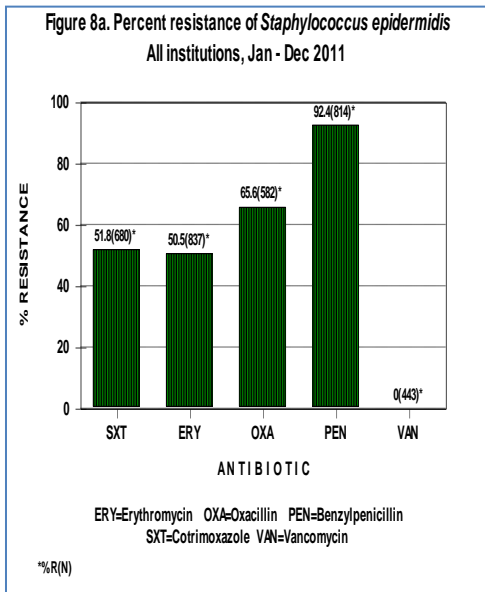
3. Staphylococci and other Gram positive cocci

Forty seven percent (47%) of *Staphylococcus aureus* isolates remained sensitive to oxacillin as compared to 46% in 2010 (Figures 7a&b).



Overall MRSA rate decreased at 53% (95%CI: 50.6-55.4) compared to 54% in 2010. This decrease is not statistically significant ($p=0.2968$).

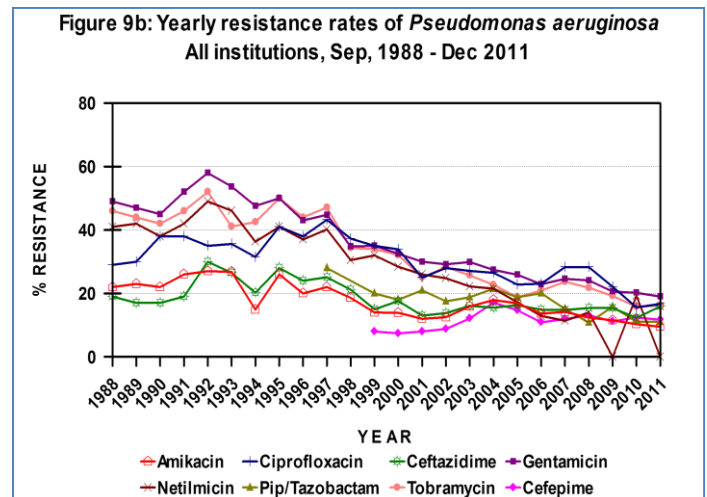
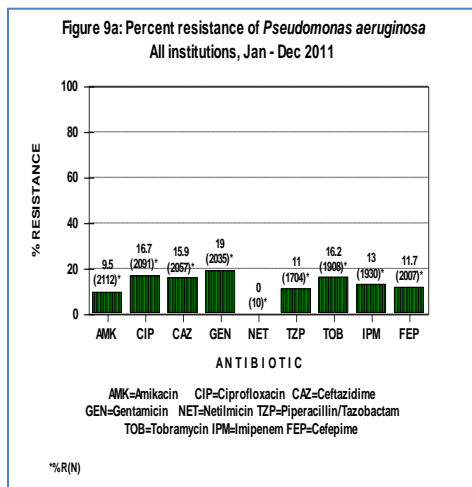
Resistance rate of *Staphylococcus epidermidis* to oxacillin increased ($p=0.1712$) to 66% (95%CI:61.6-69.4) from 63% in 2010 as well as resistance to cotrimoxazole ($p=0.0019$) at 52% (95%CI:48-55.6) from 44% in 2010. Resistance to erythromycin also decreased ($p=0.0309$) to 51% (95%CI:47.1-53.9) from 53% in 2010. There was no vancomycin resistant *Staphylococcus epidermidis* isolate reported in 2011 (95%CI 0-1.1)(Figures 8a&b). There was also no vancomycin resistant *S. aureus* reported for 2011 (95%CI 0-0.4).



There were 54 and 11 isolates of *Enterococcus faecalis* and *E. faecium*, respectively. Vancomycin and ampicillin resistance among *E. faecalis* and *E. faecium* were 0.4% (95%CI:0-2.5) and 0% (95%CI:0-6.4), respectively for vancomycin and 10% (95%CI:6.3-14) and 69% (95%CI:56.8-79.2), respectively for ampicillin.

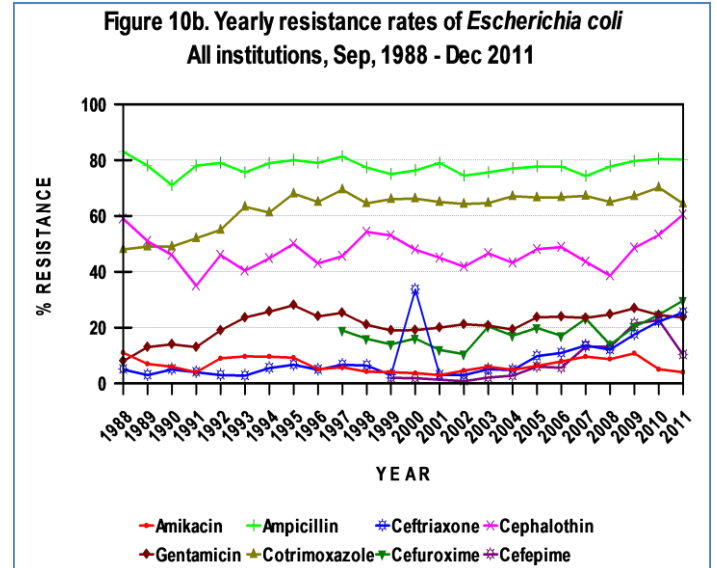
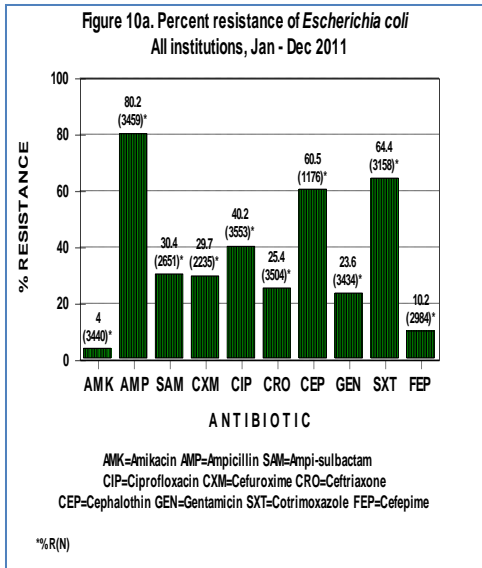
4. Gram negative bacilli

For *Pseudomonas aeruginosa*, overall resistance to ceftazidime increased at 16% (95%CI:14.4-17.6) in 2011 from 12% in 2010 while resistance to ciprofloxacin likewise increased from 16% (2010) to 17% (95%CI:15.1-18.4) in 2011 (Figures 9a & b). The increase in resistance rate for ceftazidime is statistically significant ($p=0.0007$).



Resistance to piperacillin/tazobactam remained the same at 11 % (95%CI:9.6-12.6). Among aminoglycosides, there was 19% (95%CI:17.3-20.8) resistance to gentamycin while resistance rates for amikacin, and tobramycin were 10% (95%CI:8.3-10.9), and 16% (95%CI:14.6-17.9), respectively. Imipenem resistance increased from 9.7% in 2010 to 13% (95%CI 11.5-14.6) in 2011. This increase is statistically significant ($p=0.0008$).

Many of the Enterobacteriaceae showed high resistance rates to several antibiotics tested but resistance rates of *E. coli* to cotrimoxazole decreased to 64% (95%CI 62.7-66.1) from that of 2010 (70%) (Figures 10a and b)($p=0.0001$). Resistance rate to ampicillin remained the same at 80% (95%CI 78.8-81.5)($p=0.4341$) while the resistance rates to the third generation cephalosporin (ceftriaxone) increased from 22% in 2010 to 25% (95%CI 24-26.9)($p=0.00013$) in 2011. Resistance to fourth generation cephalosporin (cefepime) decreased at 10%(95%CI 9.1-11.4) in 2011 compared to 23% in 2010 ($p=0.0001$). A resistance rate to the second generation cephalosporin (cefuroxime) was noted at 30% (95%CI 27.8-31.7) (which decreased from 25% in 2010; $p=0.0002$) while beta lactam-beta lactamase inhibitors (i.e. ampicillin-sulbactam) decreased to 30% (95%CI 28.7-32.2) from 32% in 2010 ($p=0.1468$).



The first confirmed NDM-1 positive case of *E. coli* from the Philippines.

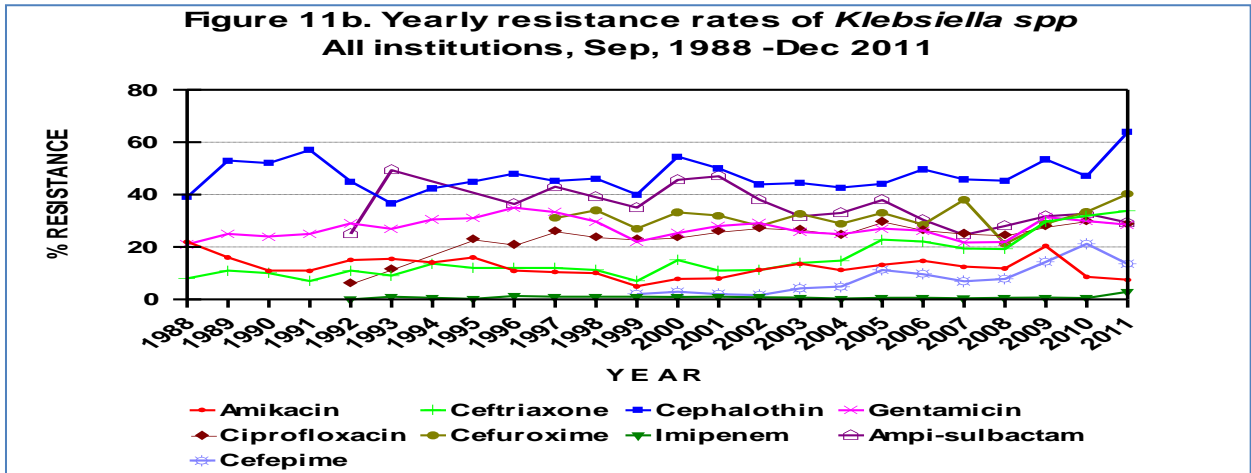
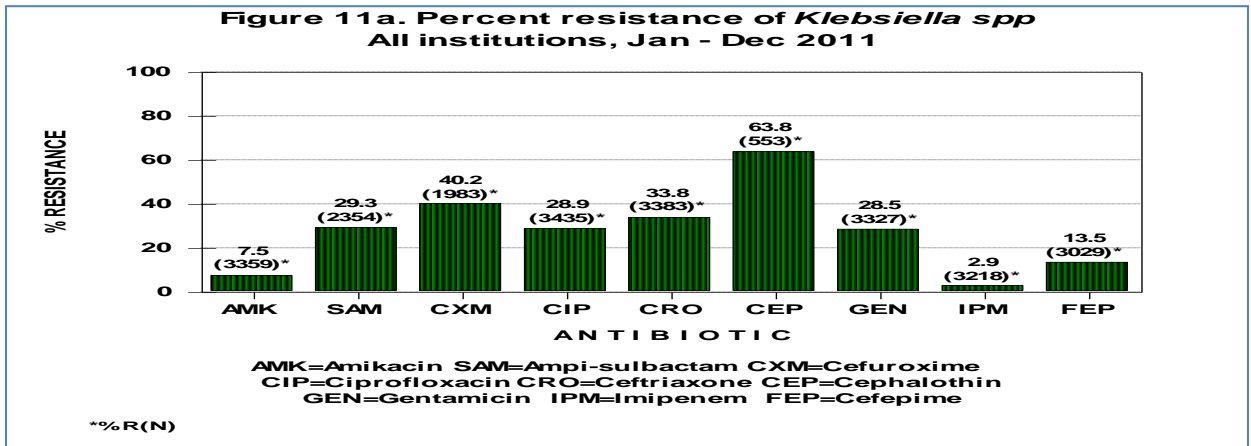
The ARSRL confirmed the first NDM-1 positive case from the Philippines. The clinical isolate is an *E. coli* from a urine specimen from a 33 year old female. The isolate was sent to the ARSRL for confirmation in March 2011. Results of disc diffusion tests done by ARSRL showed the isolate to be resistant co-amoxiclav, ampicillin, aztreonam, ceftazidime, cefepime, cefixime, cefotaxime, ceftriaxone, ciprofloxacin, cephalothin, cotrimoxazole, **imipenem**, nitrofurantoin, norfloxacin, ofloxacin, piperacillin, tetracycline, piperacillin-tazobactam, ticarcillin-clavulanic, tobramycin, **ertapenem**, cefturoxime axetil and sensitive to gentamicin and amikacin. In addition, the ARSRL performed quantitative antimicrobial susceptibility tests (minimum inhibitory concentration) which showed the isolate to be resistant to co-amoxiclav, ampicillin, ceftazidime, ciprofloxacin, cotrimoxazole, **imipenem (32 ug/ml)**, nitrofurantoin, norfloxacin, piperacillin, tetracycline, piperacillin-tazobactam, and **ertapenem (≥ 32 ug/ml)**.

Modified Hodge test (phenotypic test for carbapenemase production) done by ARSRL came out positive. Since the ARSRL staff suspected that the isolate could be a New Delhi metallo- β -lactamase (NDM-1) producer, the staff planned to perform further confirmatory tests which included screening for the NDM genes (F/R) by multiplex PCR and NDM A/B for amplification of the entire gene to confirm the NDM-1 or its variants by sequencing. The PCR procedures for NDM detection **were initially established by the laboratory staff last June** before actual runs were performed. PCR results were positive for NDM thus the laboratory staff thought of having the PCR product (the amplified DNA gene) sent to a laboratory abroad for DNA sequencing since RITM does not have a functional DNA sequencing machine. Single pass DNA sequencing was performed at a DNA sequencing facility in Singapore. Results showed 99% identity of the Philippine *E. coli* isolate with NDM-1 positive isolates of *E. coli*, *Klebsiella*, *Pseudomonas* and *Acinetobacter baumannii* from India (mostly), Japan, Australia, Hong Kong, and Germany when searched at the National Center for Biotechnology Information database (NCBI), a big repository

of DNA sequence data housed in the United States. The ARSRL then sent the isolate to the National Microbiology Laboratory, Canada where additional tests confirmed that the isolate was indeed NDM-1 positive.

As we know, the emergence of multidrug resistant (MDR) pathogens has become a serious global concern in recent years. Among the more recent multidrug resistant (MDR) genes that have caused a global concern is NDM-1 among gram negative bacteria. Isolation of bacteria with this gene is considered an important public health concern because of its resistance to broad-spectrum antibiotics especially carbapenems which we all know is an antibiotic reserved for drug resistant bacteria.

Resistance rates of *Klebsiella* against 4 out of the 9 antibiotics increased for 2011 (Figures 11 a & b). Resistance rate for cefuroxime increased from 33% in 2010 to 40% (95%CI:38-42.2)(p=0.0001) while ceftriaxone increased from 32% to 34%(95%CI:32.2-35.4)(p=0.0561), cephalothin from 47% to 64%(95%CI:59.6-67.8)(p=0.0001) and imipenem from 0.5% to 3%(95%CI:2.4-3.6)(p=0.0001) (Figure 15a). High resistance rates were exhibited against beta lactam-beta lactamase inhibitors like ampicillin-sulbactam at 29% (95%CI:27.5-31.2), ciprofloxacin at 29% (95%CI:27.4-30.5), and gentamicin 28%(95%CI:27-30.1).



The presence of extended spectrum beta lactamases had been confirmed from bacterial isolates of *E. coli* and *Klebsiella* referred by 18 tertiary care sentinel sites of the ARSP to ARSRL as follows:

Table 1. Bacterial Isolates screened and confirmed for ESBL production from sentinel sites, DOH ARSP, January to December 2011

Organism	Total No. Of Isolates from all Sentinel Sites (A)	Total No. of CAZ Resistant Isolates by Disk Diffusion (ESBL suspect) (B)	% of CAZ Resistant Isolates (ESBL suspect) (B/A)	No. of CAZ Resistant Isolates Referred to ARSU*	% of CAZ Resistant Isolates Referred to ARSU (C/B)	No. of CAZ resistant referred Isolates Confirmed by ARSRL to be ESBL (+)** (D)	No. of referred CAZ resistant Isolates w/ Non-Determinable Results (F)	No. of Negative ESBL Isolates (G)
<i>Escherichia coli</i>	3824	696	18.2 0%	479	68.8 2%	324	44	2
<i>Klebsiella sp.</i>	3653	1038	28.4 2%	686	66.0 9%	419	87	6

CAZ - Ceftazidime

*based on site ceftazidime test results on disk diffusion

** includes referred isolates not suspected to be ESBL(+) but were later on confirmed at ARSRL to be ESBL(+)

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 these 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 outpatient compared to inpatient isolates against nalidixic acid (58.1% versus 53.5%), ciprofloxacin (49% versus 45.1%), and cephalotin (64.6% versus 59.3%)(Table 2).

Table2. Percent Resistance of *E. coli* from Urine, Outpatients vs Inpatients, ALL Institutions, DOH ARSP for Jan – Dec, 2011

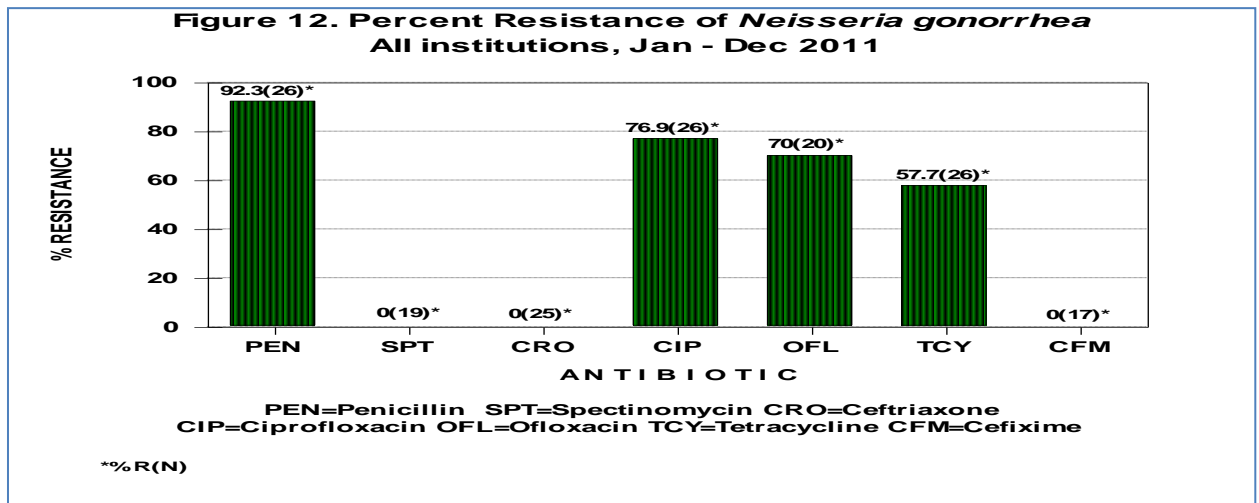
ANTIMICROBIAL AGENT	PERCENT RESISTANCE			
	OUTPATIENT (n=775)	95%CI	INPATIENT (n=1528)	95%CI
1. AMPICILLIN	81.5	78.4-84.2	83	80.9-84.9
2. CO-AMOXICLAV	27	23.8-30.4	30.3	28.0-32.8
3. CEPHALOTHIN	64.6	59.4-69.4	59.3	55.6-62.9
4. CEFUROXIME AXETIL	38.9	31.7-46.6	42.7	37.6-48.0

5. CEFTRIAXONE	25.3	22.1-28.7	27.7	25.4-30.1
6. CEFOTAXIME	30.9	26.8-35.3	35.6	32.5-38.8
7. COTRIMOXAZOLE	65.8	62.0-69.4	68.2	65.6-70.7
8. GENTAMICIN	25.4	22.3-28.8	25.3	23.0-27.7
9. AMIKACIN	2.9	1.8-4.5	5	3.9-6.3
10. CIPROFLOXACIN	49	46.2-53.6	45.1	42.5-47.7
11. NALIDIXIC ACID	58.1	53.4-62.7	53.5	50.2-56.8
12. NITROFURANTOIN	11.8	9.5-14.5	11.3	9.7-13.2

In isolates obtained from outpatients, least resistance was observed against nitrofurantoin among oral antibiotics at 11.8% while there was an increase in the resistance rate for nitrofurantoin (from 7.6% in 2010 to 11.8% in 2011). For parenteral antibiotics, amikacin had the least resistance at 2.9% followed by gentamycin at 25.4%. Among in-patients, there was a decrease in resistance to cotrimoxazole (from 72.7% in 2010 to 68.2% in 2011).

5. *Neisseria gonorrhoeae*

Resistance to ciprofloxacin and ofloxacin decreased to 77% (95%CI 55.9-90.2) and 70%(95%CI 45.7-87.2) in 2011 from 85% and 89% in 2010, respectively(p=0.3089; p=0.0954). Resistance to tetracycline increased from 33% in 2010 to 58%(95%CI 37.2-76) in 2011 (p=0.0538). There were no spectinomycin (95% CI 0-20.9), ceftriaxone (95% CI 0-16.6) and cefixime (95%CI 0-22.9) resistant isolates reported for 2011 (Figure 12).



In order to obtain a reasonable statistical estimate of cumulative %R for *Neisseria gonorrhoeae*, we combined the results of isolates from 2010 to 2011 to obtain a total required number of isolates (>30 isolates). The resistance rate of *N. gonorrhoeae* for the combined 2010 to 2011 isolates (n=64) are as follows: resistance to ciprofloxacin is 82% (95%CI: 69.2-90.1), ofloxacin 81%(95%CI: 66.8-90.5) and tetracycline 44%(95%CI: 31.4-57.6). There were no spectinomycin (95% CI 0-10.2), ceftriaxone (95%CI 0-7.7) and cefixime (95% CI 0-10.4) resistant isolates reported for the combined 2010 and 2011 *N. gonorrhoeae* isolates.

7. Multidrug resistant pathogens

In the recent years, there had been a growing recognition of the emergence of gram-negative bacteria resistant to many classes of antibiotics. Among these are *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.

ARSP 2011 data shows that 19% (481 out of 2566) of *Pseudomonas aeruginosa* isolates are multidrug resistant (MDR; resistant to at least 3 classes of antimicrobial agents among those that are available at the time of the definition in most parts of the world and are regarded as potentially effective against the pathogen) and 3% (78 out of 2566) are extensively drug resistant (XDR; resistant to all but 1 or 2 classes of antimicrobial agents among those that are available at the time of the definition in most parts of the world and are regarded as potentially effective against respective pathogens). MDR *P. aeruginosa* were reported by 21 out of the 22 sites.

Among the MDR *P. aeruginosa* isolates with information on date of admission, 43% (208 out of 481) are presumptively nosocomial.

Among *Acinetobacter baumannii* isolates, 50% (549 out of 1102) are multidrug resistant (resistant to at least 3 classes of antimicrobial agents among those that are available at the time of the definition in most parts of the world and are regarded as potentially effective against the pathogen) and 13% (138 out of 1102) are extensively drug resistant (XDR; resistant to all but 1 or 2 classes of antimicrobial agents among those that are available at the time of the definition in most parts of the world and are regarded as potentially effective against respective pathogens). These isolates were reported by 21 sentinel sites.

Among the MDR *A. baumannii* isolates with information on date of admission, 43% (237 out of 549) are presumptively nosocomial.

RECOMMENDATIONS

Based on the above-mentioned antimicrobial resistance surveillance data:

- a. In view of the continued high rates of methicillin/oxacillin resistance among staphylococci in 2011, 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 high resistance rate of *Haemophilus influenzae* to ampicillin in 2011 (16% in 2010 to 14% in 2011) and since ampicillin resistance in *H. influenzae* is usually mediated by beta lactamase production, empiric treatment for suspected *H. influenzae* 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 for epidemiologic purpose and 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. There is a need to closely monitor the emergence of gram-negative bacteria such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* with advanced antimicrobial resistance rendering them resistant to many classes of antibiotics. These pathogens have become global public health threat as they can be observed to be resistant to the most commonly used empiric antibiotics, such as cephalosporins, penicillins with beta-lactamase inhibitors and carbapenems, and are associated with high mortality. Treatment options for these pathogens are very limited as they are usually susceptible only to tigecycline and polymyxins.
- j. **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.**
- k. Cefixime and ceftriaxone can remain as empiric antibiotics of choice for gonococcal infections.

ACKNOWLEDGMENTS

For the year 2011, financial support for the activities of the ARSP was derived mainly from suballotted funds from the Department of Health (National Epidemiology Center, and Vaccine Self-sufficiency funds).