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UPDATED ABSTRACT

PURPOSE: This study documents institution participation in the Antimicrobial Resistance Management Program (ARMP), begun in 1997 to compare antibiotic use and resistance rates, and demonstrates how the data collected from these institutions, available on www.armprogram.com, can be used to create custom reports on susceptibility of specific organisms to antibiotics over time.

METHODS: Institutions are enrolled in ARMP at no cost. Each provides a minimum of 3 years of antibiogram/sensitivity report data which, in a HIPAA-compliant non-identifying format, comprise a national aggregate database.

RESULTS: As of March 25, 2005, ARMP has enrolled 356 institutions, 282 (79%) nonteaching and 74 (20%) teaching, and collected 28.1 million isolates detailing 48 antibiotics and 19 organisms, including on Escherichia coli (11,424,793 isolates), Staphylococcus aureus (4,852,625), Pseudomonas aeruginosa (2,687,251) Klebsiella pneumoniae (2,717,761), and Proteus mirabilis (1,741,301). Institutions receive an analysis of antimicrobial susceptibility trends on an organism-by-organism basis, benchmarked against national, regional, and state comparators. At the ARMP Web site, the database was interrogated to determine whether an association existed between fluoroquinolone resistance and ESBL production. Nationally, between 1997 and 2003, E coli isolates became less susceptible to fluoroquinolones with the introduction of each new agent: susceptibility to ciprofloxacin declined from 98.1% to 86.5%; ofloxacin, 97.6% to 84.4%; levofloxacin, 96.5% to 87.2%; gatifloxacin from 90% (2000) to 88.8%; moxifloxacin was 79.9% for 2003. Susceptibility to extended-spectrum cephalosporin antibiotics also decreased slightly: cefotaxime, 99.2% to 98.9%; ceftriaxone, 99.6% to 97.9%; and cefepime, 100% to 98.9%. Similar results were noted for K pneumoniae and P mirabilis.

CONCLUSIONS: ARMP allows institutions to document trends in antimicrobial susceptibility before they become significant, allowing selection/modification of antibacterial agents. The Web-based aggregate database enables users to create custom reports demonstrating, as in the example above, low level ESBL activity is occurring, indicating fluoroquinolone resistance should be monitored.

Trends in Antimicrobial Resistance Documented at www.armprogram.com

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BACKGROUND

- ARMP is an ongoing study to
- Document trends in antimicrobial susceptibility patterns in inpatient and outpatient isolates
- Identify relationships between antibiotic use and resistance rates

METHODS

DATA COLLECTION

- $\bullet\;$ Qualifying hospitals/systems participate in ARMP at no cost
- Each provides ≥ 3 years of antibiogram or sensitivity report data
- The data, in a HIPAA-compliant non-identifying format, become part of the ARMP national aggregate surveillance resistance database
- Individual antibiotics and organisms collected include 48 antibiotics and 19 organisms (Table 1)

Table 1. Organism/Drug Matrix

	Acinetobacter species	Coagulase negative staphylococci	Enterobacter aerogenes	Enterobacter cloacae	Enterococcus faecalis	Enterococcus faecium	Enterococcus species	Escherichia coli	Haemophilus influenzae	Klebsiella pneumoniae	MRSA	MRSE	Proteus mirabilis	³ seudomonas aeruginosa	Serratia marcescens	Staphylococcus aureus	Staphylococcus epidermidis	Streptococcus pneumoniae
	⋖		_						Ŧ					_				
amikacin		•	•	•	•	•	•	•		•	•	•	•	•	•	•	•	٠
amoxicillin		•						٠	•	•			•		٠	•	•	٠
amoxicillin/clavulanate		•				•	•	•	•	•			•		•	•	•	•
ampicillin					•	•	•											•
ampicillin/sulbactam		•	٠	•				•	•	•			•		•	•	•	
azithromycin	-	٠						٠	٠	•			•		•	•	٠	٠
aztreonam	•		•	•				•	•	•			•	٠	•	_	_	_
cefaclor		•						•	•				•		•	•	•	•
cefazolin		•	•	•				•	•	•			•	_	•	•	•	٠
cefepime		•	•	•				•	•	•			•	•	•	•	٠	_
cefixime		•	•	•				:	•	:			•	:	:	•	•	٠
cefoperazone cefotaxime		:	•	•				÷	:	÷			•	•	÷	:	·	
cefotetan	•	•							•				•		·	•	•	·
cefoxitin								•		:			•					
cefpodoxime	-							•	•				•			•		٠
ceftazidime		÷	•					:	•	÷			:		÷	•	·	•
ceftriaxone		•	•	:					•	:			•	•	÷	•	•	
cefuroxime	·	:	•	•				:	•	:			•		:	•	:	÷
cephalothin	-	•						•	•				•		÷	•	•	•
chloramphenicol	-	•	•	•		•		•	•	÷		•	•		·	•	•	:
ciprofloxacin	-	•			•	•	•		•			•		•				•
clarithromycin		•	-	-	-			•	•	•	Ť	•	•	·	÷	•	•	·
clindamycin	-	•							•				•			•	•	
dalfopristin/quinupristin		Ť						•	•				•	•	·	•	-	·
doxycycline		•	Ť	Ť	•	•	•	•	Ť	•	•	•	Ť	Ť	Ť			•
erythromycin	-	•						•		•								
gatifloxacin		•						•	•	•	•	•	•	•		•	•	
gemifloxacin		•							•	•	•	•	•	•		•	•	•
gentamicin		•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	•	
imipenem		•	•	•	•	•	•	•	•	•	•	•	•	•		•	•	
levofloxacin		•			•			•	•	•		•	•	•	•	•	•	٠
meropenem		•		•	•	•	•		•				•	•		•	•	
moxifloxacin		•			Ė			•	•	•	•	•	•	•	•	•	•	٠
nafcillin/oxacillin		•								•			•		•	•	•	
nitrofurantoin					•	•	•	•		•								
ofloxacin		•		•								•		•		•	•	
penicillin		•			•			•	•	•			•		•	•	•	•
piperacillin/tazobactam		•														•		
piperacillin		•	•	•				•	•	•			•	•	•	•	•	
rifampin		•			•	•	•				•	•				•	•	
tetracycline	•	•			•	•	•	•		•	•	•						
ticarcillin		•	•	•				•	•				•		•	•	•	
ticarcillin/clavulanate		•	•	•				•	•				•			•	•	
tmp/smx		•						•	•	•	•	•	•		•	•	•	٠
tobramycin		•	•		•	•	•	•	•	•			•	•	•	•	•	
		•	_	-		_		•	•				•			•	•	

 Hospitals/systems receive a customized Antibiogram Report and Analysis detailing antimicrobial susceptibility trends benchmarked against national, regional, and state comparators

• Table 2 is a representative de-identified sample report

Table 2. Abridged Institutional Report

Hospital X Anytown, USA

Antiobiogram Report and Analysis

Notes: includes outpatient isolates; includes urinary isolates

I. Escherichia coli

Antibiotic	Year-2001	Year-2002	Year-2003
ampicillin	n=569	n=1111	n=1109
	68%	68%	63%
ampicillin/sulbactam	n=252	n=327	n=186
	71%	69%	56%
cefazolin	n=569	n=1109	n=1109
	96%	95%	94%
cefuroxime	n=321	n=771	n=882
	95%	94%	93%
cefotaxime	n=253	n=328	n=186
	100%	99%	98%
ceftriaxone	<i>n</i> =568	n=1111	n=1111
	100%	99%	98%
ceftazidime	n=254	n=332	n=201
	99%	98%	96%
ciprofloxacin	n=569	n=1101	n=1112
	95%	93%	89%
levofloxacin	n=567	n=1110	n=1109
	96%	93%	89%
imipenem	n=255	<i>n=334</i>	n=238
	100%	100%	100%
piperacillin	n=251	n=327	n=186
	71%	72 %	60%
pip/taz		n=5	n=36

Ampicillin susceptibilities have fluctuated between 63% and 68%. The current level of 37% resistance among 1,109 isolates is consistent with national and regional averages of 30%-40% resistance. Susceptibilities to ampicillin/sulbactam have mirrored those of ampicillin. This suggests that the majority of *E coli* pathogens are hyperproducing beta-lactamase. Through hyperproduction, resistant *E coli* pathogens create exponentially large concentrations of the enzyme. This renders suicidal agents such as sulbactam ineffective, resulting in combination therapy being no more active than single-agent therapy. The institution and the laboratory are encouraged to continue to follow the relationship between ampicillin and ampicillin/sulbactam as a

surrogate marker for hyperproduction of beta-lactamase.

The presence of extended-spectrum beta-lactamase (ESBL) activity is evaluated via surrogate markers of comparative cephalosporin susceptibilities across generations. Third-generation cephalosporins continue to exhibit enhanced activity over first or second-generation cephalosporins. This provides surrogate evidence to Hospital X that no significant ESBL activity is present within the institution.

Fluoroquinolone activity continues to leak. The 11% resistance to ciprofloxacin and levofloxacin is consistent with national averages, as well as peer-reviewed literature indicating that gram-negative bacilli resistance to the fluoroquinolones is increasing. The similarities in susceptibility patterns between the two fluoroquinolones indicate a class-mediated effect within Hospital X.

Sections II. - XII. omitted due to space limitations

XIII. Streptococcus pneumoniae

Antibiotic	Year-2001	Year-2002	Year-2003
cefuroxime	n=18	n=60	n=55
	83%	70%	76%
cefotaxime	n=18	n=60	n=58
	94%	90%	97%
ceftriaxone	n=18	n=60	n=58
	94%	92%	95%
clindamycin	n=18 89%	n=60 83%	
erythromycin	n=18	<i>n</i> =60	n=58
	78%	67%	78%
levofloxacin	<i>n=17</i>	<i>n=46</i>	n=58
	100%	100%	98%
penicillin	n=18	n=61	n=59
	72%	57%	68 %
vancomycin	n=18	n=61	<i>n=59</i>
	100%	98%	100%

The clinical laboratory is congratulated for spending the time and effort to record this offline community-based organism. The penicillin resistant Streptococcus pneumoniae (PRSP) rate within the isolates tested at Hospital X has ranged from 28% in 2001 to 43% in 2002. The current rate of 32% PRSP among 59 isolates is consistent with national and regional averages of 30%-40% PRSP

Consistent with the PRSP rate over the last three years, the macrolide resistance rate has also fluctuated. For 2001 and 2002, a comparison of erythromycin to clindamycin susceptibilities is possible. Making this comparison allows the institution to draw inference regarding the mechanism of resistance. For 2001, out of a total 22% macrolide resistance it is assumed that half (11%) is mediated through efflux mechanisms while the remaining 11% is methylation induced. For 2002, among the 33% total macrolide resistance, 17% is assumed to be methylation-induced, with the remaining 16% efflux mediated. This approximate 1:1 ratio between methylation and efflux mediated resistance among *Streptococcus pneumoniae* isolates in Hospital X is different than national averages which suggests that approximately 60%-70% of pneumococcal resistance is efflux mediated.

The institution is congratulated for incorporating an anti-pneumococcal fluoroquinolone to its reporting structure. Recent information from the PROTEKT US database shows *Streptococcus pneumoniae* increasing in resistance to the fluoroquinolones. Recent evidence from *Antimicrobial Agents and Chemotherapy* 2004 also suggests that this resistance may be class-mediated. Continued surveillance around this resistance is recommended.

The laboratory is congratulated for reporting both cefotaxime and ceftriaxone. Data from the ARM Program as well as the peer-reviewed literature (Antimicrobial Agents and Chemotherapy 2003) has previously suggested that these two third-generation cephalosporins are not interchangeable even though they share the same resistant breakpoint. While susceptibility differences within Hospital X between these two third-generation cephalosporins are minimal, differences have been noted in other hospitals throughout the country. Continued surveillance around both third-generation cephalosporins is recommended.

RESULTS

- As of March 25, 2005 ARMP has enrolled 356 institutions
- 282 (79%) nonteaching
- 74 (21%) teaching
- For the purposes of comparison, institutions are grouped in 6 geographic regions (Figure 2)

Figure 2. Geographic Distribution of Institutions



- The number of institutions from each region are:
- North Central: 52 (15%) South Central: 58 (16%)
- Northeast: 106 (30%) Southeast: 104 (29%)

Northwest: 8 (2%)

- Southwest: 28 (8%)
- 28.1 million isolates are represented in the ARMP resistance database
- The most significant organisms are summarized in Table 3

Table 3. Significant Organisms in the ARMP Aggregate Resistance Database

Organism	Isolates (n)
Escherichia coli	11,424,793
Staphylococcus aureus	4,852,625
Pseudomonas aeruginosa	2,687,251
Klebsiella pneumoniae	2,717,761
Proteus mirabilis	1,741,301

- www.armprogram.com, the ARMP Web site, allows comparative analysis between antibiotics used and resistance rates
- National and regional trends are available as figures and in tabular format for 1997-2003 for all organism/antibiotic combinations collected in the database
- Custom Reports can be created with up to 7 national, regional, and/or state comparators specified by collective or individual years
- For example, Table 4 summarizes a Custom Report run for 1997-2003 to determine whether there was an association between fluoroquinolone resistance and ESBL production, using comparative cephalosporin susceptibilities across generations as surrogate markers
- Nationally, no significant ESBL activity was detected; however, E coli, K pneumoniae, and P mirabilis isolates were less susceptible to each new fluoroquinolone as it was introduced

Table 4. Sample Custom Report: National Susceptibility of E Coli, K pneumoniae, and P mirabilis to First through Fourth-Generation Cephalosporins and Fluoroquinolones, by Year, 1997-2003

Organism/ Antibiotic	1997	1998	1999	2000	2001	2002	2003
E coli							
Cefazolin	n=88423	n=106105	n=106050	n=121608	n=142882	n=110471	n=64566
	92.8%	91.9%	91.0%	90.4%	90.0%	90.4%	90.2%
Cefuroxime	n=50222	n=57202	n=63013	n=76383	n=92105	n=64373	n=37807
	95.6%	94.2%	95.2%	94.9%	94.4%	92.6%	91.9%
Cefotaxime	n=23337	n=26238	n=18739	n=14101	n=22186	n=14172	=10994
	99.2%	99.3%	98.6%	99.3%	99.2%	98.3%	98.9%
Ceftriaxone	n=77460	n=92557	n=90987	n=95887	n=110087	n=93081	n=53737
	99.6%	99.6%	99.4%	99.0%	98.6%	98.1%	97.9%
Cefepime	n=48	n=11304	n=19273	n=39605	n=51125	n=54062	n=39603
	100%	99.3%	98.7%	99.5%	99.1%	98.9%	98.9%
Ciprofloxacin	n=75810	n=88236	n=91647	n=102831	n=116029	n=92973	n=49093
	98.1%	97.7%	95.7%	93.4%	93.1%	90.4%	86.5%
Levofloxacin	n=5534	n=36914	n=55509	n=81657	n=114723	n=83622	n=48047
	96.5%	95.8%	95.7%	93.6%	93.3%	91.3%	87.2%
Ofloxacin	n=50348	n=38678	n=23129	n=7743	n=2974	n=886	n=500
	97.6%	97.2%	94.2%	94.5%	90.1%	90.2%	84.4%
Gatifloxacin	_	_	_	n=542 90.0%	n=1 100%	n=10376 88.3%	n=11969 88.8%
Moxifloxacin	_	_	_	_	_	_	n=929

K pneumoniae

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Cefazolin	n=29884 $91.7%$	n=34174 91.4%	n=30796 91.3%	n=35226 91.0%	n=35490 90.4%	n=27582 90.0%	n=17046 87.5%
Cefuroxime	n=15592	n=16605	n=17614	n=22423	n=22411	n=15776	n=9707
	92.6%	90.7%	90.6%	90.5%	89.4%	89.0%	88.0%
Cefotaxime	n=7591	n=8229	n=5212	n=4535	n=6283	n=3794	n=2859
	98.9%	97.9%	96.0%	97.9%	97.3%	94.7%	96.3%
Ceftriaxone	n=26064	n=28464	n=25468	n=26705	n=27594	n=23461	n=14298
	98.3%	97.8%	97.5%	97.2%	96.0%	95.1%	94.5%
Cefepime	n=24	n=3574	n=5673	n=12648	n=14778	n=14870	n=10846
	100%	97.9%	96.7%	98.1%	96.7%	95.2%	94.0%
Ciprofloxacin	n=26871	n=29277	n=27325	n=29718	n=29092	n=22890	n=13254
	95.4%	94.8%	94.7%	95.6%	94.6%	93.6%	92.9%
Levofloxacin	n=2718	n=11715	n=15498	n=25022	n=28665	n=20481	n=12205
	94.7%	95.3%	95.5%	95.5%	93.8%	91.9%	88.7%
Ofloxacin	n=18287	n=14959	n=7953	n=2047	n=930	n=305	n=111
	94.8%	94.1%	92.7%	95.9%	92.8%	94.4%	91.9%
Gatifloxacin	_	_	_	n=120 90%	_	n=2778 94.0%	n=3149 91.6%
Moxifloxacin	_	_	_	_	_	_	n=332 88.3%

P mirabilis

Cetazolin	n=16342	n=18865	n=20144	n=32640	n=22725	n=17666	n=10447
	93.6%	92.4%	89.1%	90.8%	90.9%	90.4%	90.7%
Cefuroxime	n=8945	n=10318	n=11958	n=15805	n=14158	n=11349	n=6410
	97.4%	97.1%	97.1%	97.9%	97.1%	96.3%	96.2%
Cefotaxime	n=3754	n=4760	n=3247	n=2143	n=4079	n=2415	n=1591
	99.5%	99.2%	98.1%	98.7%	99.4%	99.5%	99.7%
Ceftriaxone	n=14137	n=15860	n=16406	n=18065	n=17556	n=14963	n=9341
	99.3%	99.4%	99.4%	99.3%	99.4%	99.1%	99.0%
Cefepime	n=6	n=1761	n=3319	n=7568	n=9928	n=10545	n=6388
	83.3%	98.6%	97.3%	97.9%	97.6%	97.7%	98.9%
Ciprofloxacin	n=13710	n=15293	n=17857	n=20342	n=19055	n=15908	n=8895
	91.8%	88.7%	82.7%	76.8%	75.1%	69.3%	68.7%
Levofloxacin	n=1169	n=6702	n=10218	n=15713	n=18584	n=12449	n=7888
	91.5%	90.9%	88.5%	81.7%	79.6%	74.7%	71.5%
Ofloxacin	n=9900 89.9%	n=8037 89.0%	n=4646 76.7%	n=1918 65.2%	n=468 78.2%	n=86 65.1%	_
Gatifloxacin	_	_	_	n=75 78.7%	_	n=1919 84.4%	n=1922 79.4%
Moxifloxacin	_	_	_		_	_	n=187 51 3%

CONCLUSION

- Through benchmarking at a variety of levels, ARMP can work with institutions/systems to delineate occurrence and extent of antimicrobial resistance before they become significant
- Allows for strategic intervention
- Provides data for local, regional, national benchmarks
- Has potential to reduce costs of antibiotics associated with inappropriate use.
- At www.armprogram.com, customized reports can be created utilizing
- the aggregate database that compare national to regional and state data
- Hospitals enrolling in ARMP may now provide rates of antibiotic utilization in addition to antibiogram/sensitivity data so that resistance patterns can be more clearly correlated

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