Analysis of Long Term (20 Years) *In Vitro* Susceptibility to Antibacterial Drugs of the Most Prevalent Animal Bacterial Pathogens Isolated in Israel. Part 2: Multi-Drug Resistance

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ABSTRACT

This part of the study is based on the data presented in Part 1 in the Israel Journal of Veterinary Medicine. Changes in the number of antibacterial drugs to which each microorganism was susceptible and possible correlation between all the combinations of susceptibility curves were evaluated. Results indicated a decrease in the number of drugs to which the microorganisms were resistant to, for *Salmonella enterica* serogroup B and *Proteus* spp. The number of drugs to which *E. coli* showed resistance decreased but returned to the original level. The low number of drugs (n=4) that were used for *Pseudomonas aeruginosa* made the identification of variations difficult. It was found that while stability was maintained until 2007, the number of resistant drugs decreased steeply in 2008 and somewhat increased in 2009. For *Pasteurella multocida* and *Mannheimia haemolytica*, the number of antibacterial drugs to which there was a resistance remained practically unchanged. No noteworthy patterns of correlation between susceptibility curves were observed with the exception of chloramphenicol and sulfamethoxazole/trimethoprim that had a high correlation coefficient for 3 out of the 6 included microorganisms: *E. coli*, *Proteus* spp. and *P. multocida*.

These findings are in general in agreement with those of Part 1 of this study and stress the importance of conducting long term surveys before reaching conclusions regarding the evolution of bacterial resistance and multi-resistance.

Key words: Multi drug resistant, long term, *in vitro* susceptibility, animal.

INTRODUCTION

During the last decades, multi-drug resistant (MDR) bacteria have become one of the most problematic topics of human and veterinary medicine (1). A clear definition of the term exists for *Mycobacterium tuberculosis* – an isolate resistant at least to isoniazid and rifampin is considered multi-drug resistant (2). The definition of other bacteria as MDR is more vague (3). In addition to the term MDR other expressions such as Extensive Drug Resistant (XDR) (4) and Pan Drug Resistant (PDR) (5) have been used to define, respectively, strains of *Mycobacterium tuberculosis* (4) and Gram negative bacteria showing exceptionally marked resistance to antibacterial drugs (3).

The establishment of MDR bacteria has been associated with the intensive subtherapeutic concentrations of antibacterial drugs in hospitals (6, 7), but more recently such strains have been reported with increased frequency in the community as well (8, 9). Bacteria may become MDR following prolonged exposure to the relevant drugs (10), horizontal gene transfer (11) or by a resistance mechanism that develops for one drug but affects indirectly several others as well (12). The latter may be assessed by evaluating eventual

associations between the resistances to two or more drugs. In this second part of the study we examined the long term variations in the prevalence of MDR bacteria and associations between their resistance patterns.

MATERIALS AND METHODS

This part of the study is based on the data presented in Part 1 (13). The following parameters were assessed:

1. Changes over time of the number of antibacterial drugs to which each microorganism was susceptible. Annual trends were assessed by the LINEST() function of MS Excel® and their statistical significance determined according to *F* percentile distribution tables (Dixon, 1957). Only antibacterial drugs examined during the whole period of 20 years were included and presented in Table 1.
2. Correlations between all the combinations of susceptibility curves were evaluated by the CORREL() function of MS Excel®.

Results

Results of the changes in the number of antibacterial drugs to which each microorganism was susceptible are shown in Tables 2-7 and Figures 1-3. For *Salmonella enterica* serogroup (sgr.) B (Figure 1) a decrease in the statistical mode from resistance to 4 drugs in 1990 to 1 in 2004 (0 in 2003) was noted. This decrease was highly significant ($p<0.01$). Interestingly, this decrease was not uniform in time, but proceeded in a stepwise mode between 1990 and 1993 (with a temporary increase in 1993) and 2001 and 2003, remaining stable between the years 1993 to 2001. A highly signifi-

Table 1: Bacteria and antibacterial drugs included in the study:

	Pseudomonas. aeruginosa	*Salmonella enterica sgr. B Escherichia coli Proteus spp.*	*Pasteurella multocida Mannheimia haemolytica*
Gentamicin	+	+	+
Amikacin	+	+	
Polimixin B	+	+	
Fluoroquinolones	+	+	+
Ampicillin		+	+
Chloramphenicol		+	
Sulfamethoxazole-trimethoprim		+	+
Cefotaxime		+	
Cephalothin			+
Tetracyclines			+

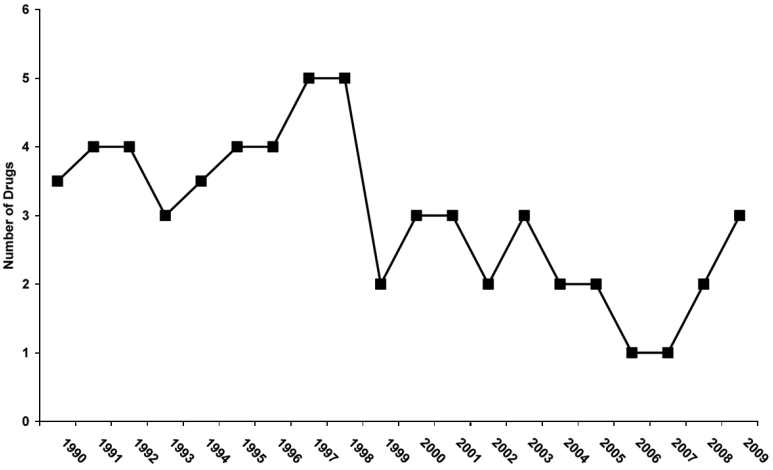

Figure 2: Mode of number of antibacterial drugs *Proteus* spp. isolates were resistant to.

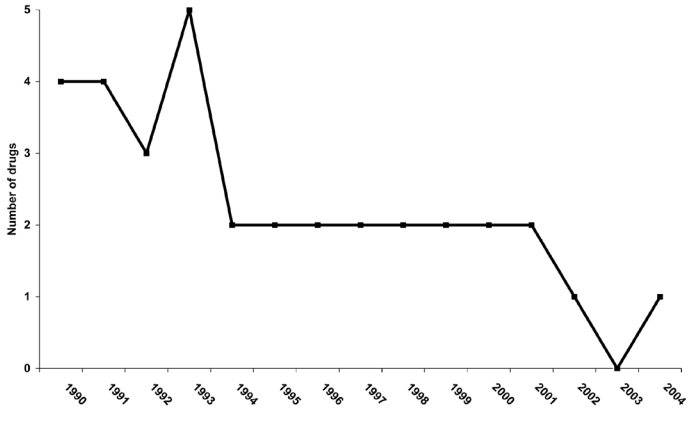

Figure 1: Mode of number of antibacterial drugs *Salmonella enterica* sgr. B isolates were resistant to. Decrease statistically highly significant ($p<0.01$)

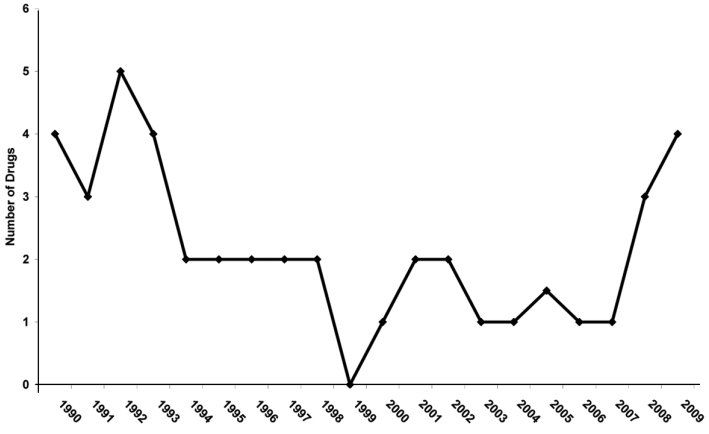

Figure 3: Mode of number of antibacterial drugs *Escherichia coli* isolates were resistant to.

cant ($p<0.01$) decrease in the number of resistant drugs was observed for *Proteus* spp. (Figure 2) as well, but, unlike *S. enterica* sgr. B, this decrease was more or less constant. An increase in the statistical mode was observed between 1993 and 1997 and starting 2007. The number of resistant drugs to *E. coli* followed a completely different pattern to that of other drugs. While the mode values for *S. enterica* sgr, B and *Proteus* spp. followed a general trend, *E. coli* values evolved in a curve (Figure 3): mode values went from resistance to 5 drugs in 1992, decreased to 0 in 1999 and returned to 4 drugs in 2009.

Due to its intrinsic resistance to most antibacterial drugs used in our laboratory, the susceptibility of *Pseudomonas aeruginosa* was tested to only 4 drugs. While this low number could make it difficult to identify the more subtle variations, in this survey we found that until 2007 the mode was stable (without resistance to any drug between 1993 and 2007). Interestingly within one year the mode increased to resistance to 3 out of 4 tested drugs, returning to one drug in 2009.

For the respiratory pathogens, *Pasteurella multocida* and *Mannheimia haemolytica*, the mode remained practically unchanged at a resistance of only one to two drugs.

Correlation coefficients between the various susceptibility curves are presented in Tables 8-13. While high (>0.7) coefficients were found in several cases, no noteworthy patterns emerged. The only couple of drugs that showed a high correlation coefficient in more than one microorganism were those observed between chloramphenicol and sulfamethoxazole/trimethoprim: 0.822, 0.717 and 0.772 in *E. coli*, *Proteus* spp. and *P. multocida*, respectively.

DISCUSSION

The results of the survey on multidrug resistance are generally in accordance with those found the previous study covering drug resistance of bacteria in Israel (13), namely that the number of antibacterial drugs the microorganisms were resistant to did not increase. In fact in two cases, *Salmonella enterica* sgr. B and *Proteus* spp., these values decreased. In the case of *E. coli*, the importance of long term surveys emphasized in Part 1 of this study was underscored once more

Table 2: Number of antibacterial drugs *Salmonella enterica* sgr. B isolates were resistant to (percent). Mode emphasized.

N	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
0	19.1	12.2	12.0	12.4	24.5	19.5	13.8	14.4	14.3	18.5	19.4	24.7	27.7	**26.2**	12.5
1	2.2	7.0	9.8	15.2	9.6	8.6	10.6	8.5	11.7	11.1	18.1	20.8	**34.9**	23.8	**22.5**
2	7.9	7.8	9.8	15.2	**28.7**	**28.9**	**38.1**	**31.4**	**35.1**	**24.1**	**23.6**	**29.9**	15.7	21.4	15.0
3	13.5	12.2	**21.7**	15.2	16.0	19.5	17.5	20.3	16.9	22.2	20.8	11.7	10.8	9.5	17.5
4	**23.6**	**34.8**	19.6	14.3	13.8	17.2	9.4	10.2	11.7	14.8	12.5	7.8	4.8	7.1	7.5
5	15.7	14.8	16.3	**17.1**	6.4	5.5	5.6	8.5	6.5	5.6	2.8	1.3	6.0	7.1	5.0
6	12.4	6.1	7.6	8.6	0.0	0.8	4.4	3.4	3.9	3.7	0.0	3.9	0.0	4.8	15.0
7	4.5	3.5	3.3	1.9	1.1	0.0	0.6	2.5	0.0	0.0	2.8	0.0	0.0	0.0	5.0
8	1.1	1.7	0.0	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0

N: number of antibacterial drugs

Table 3: Number of antibacterial drugs *Proteus* spp. isolates were resistant to (percent). Mode emphasized.

N	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
0	1.5	0.0	0.0	0.0	3.2	0.0	0.0	1.3	0.0	2.1	2.6	1.8	0.0	0.0	2.4	3.4	3.9	0.0	0.0	1.1
1	3.1	5.9	0.0	3.6	16.1	12.7	7.9	6.3	8.7	8.2	12.8	10.1	6.4	5.3	4.9	24.1	**28.4**	**43.8**	18.0	26.9
2	21.5	8.8	8.5	14.3	12.9	25.4	15.8	11.3	15.2	**27.8**	24.8	21.1	**28.0**	19.5	**23.2**	**26.4**	22.5	25.0	**31.1**	17.2
3	**23.1**	27.9	23.7	**25.0**	**19.4**	15.5	17.1	15.0	14.1	18.6	**25.6**	**22.0**	22.4	**25.7**	18.3	12.6	19.6	12.5	16.4	**28.0**
4	**23.1**	**32.4**	**23.7**	21.4	**19.4**	**29.6**	**23.7**	20.0	18.5	18.6	22.2	16.5	18.4	22.1	17.1	18.4	13.7	10.4	19.7	14.0
5	12.3	10.3	23.7	21.4	14.5	7.0	22.4	**21.3**	**25.0**	16.5	10.3	14.7	13.6	18.6	13.4	10.3	4.9	4.2	8.2	9.7
6	9.2	7.4	15.3	8.9	11.3	7.0	6.6	13.8	9.8	7.2	0.9	11.9	8.8	3.5	9.8	3.4	4.9	4.2	4.9	1.1
7	3.1	7.4	5.1	3.6	3.2	1.4	6.6	6.3	7.6	1.0	0.9	1.8	1.6	4.4	7.3	0.0	2.0	0.0	1.6	1.1
8	3.1	0.0	0.0	1.8	0.0	1.4	0.0	5.0	1.1	0.0	0.0	0.0	0.8	0.9	3.7	1.1	0.0	0.0	0.0	1.1

N: number of antibacterial drugs

Table 4: Number of antibacterial drugs *Escherichia coli* isolates were resistant to (percent). Mode emphasized.

N	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
0	3.6	7.4	0.0	6.7	11.5	0.0	5.2	6.4	11.4	**21.2**	**18.5**	19.4	16.8	16.5	9.0	12.3	14.2	15.2	5.6	4.5
1	8.9	11.9	16.3	13.5	20.9	12.1	17.6	16.5	17.8	17.0	17.3	15.8	17.4	**19.6**	**21.1**	**19.6**	**21.8**	**19.1**	12.4	10.7
2	17.2	15.6	12.6	19.0	**22.1**	**27.2**	**20.5**	**21.9**	**22.1**	18.7	**18.5**	**21.2**	**22.6**	18.3	17.5	**19.6**	16.2	17.3	17.4	10.4
3	16.7	**32.6**	17.8	15.3	19.1	23.8	18.8	17.2	19.2	15.7	17.0	13.7	13.9	16.5	19.8	15.8	14.2	14.4	**19.1**	16.2
4	**18.8**	14.8	14.8	**20.9**	14.9	20.0	13.9	13.8	11.4	12.9	15.0	12.8	16.0	13.0	14.1	12.5	12.7	16.2	12.9	**16.4**
5	17.7	9.6	**22.2**	13.5	6.4	8.6	10.7	11.1	13.2	11.5	9.1	10.4	8.2	9.3	9.5	8.4	12.5	8.7	15.7	15.7
6	11.5	3.7	10.4	8.6	2.6	6.2	9.0	8.1	3.6	1.9	3.5	4.5	4.1	3.3	5.7	5.7	4.4	5.1	9.0	13.7
7	3.6	1.5	5.2	2.5	0.9	1.4	2.3	3.0	1.1	0.8	1.2	0.9	1.1	1.8	2.8	5.2	3.4	2.9	6.2	9.0
8	2.1	3.0	0.7	0.0	1.7	0.7	2.0	2.0	0.4	0.3	0.0	1.2	0.0	1.8	0.5	0.8	0.5	1.1	7.3	3.5

N: number of antibacterial drugs

Table 5: Number of antibacterial drugs *Pseudomonas aeruginosa* isolates were resistant to (percent). Mode emphasized. Note steep increase in multi-drug resistant isolates in 2008.

N	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
0	27.6	33.3	31.1	**51.9**	**60.9**	**68.4**	**57.1**	**48.0**	**61.9**	**49.6**	**49.1**	**51.0**	**47.9**	**42.7**	**34.3**	**55.9**	**67.6**	**68.2**	2.7	9.6
1	**37.9**	24.0	**37.8**	22.2	20.3	17.5	23.4	24.0	31.0	29.9	35.3	31.5	24.8	32.1	30.5	20.7	20.9	22.7	9.5	**69.3**
2	31.0	**36.0**	24.4	20.4	17.2	10.5	13.0	16.0	6.0	12.0	10.3	8.7	18.8	18.3	22.9	13.5	5.4	4.5	25.7	7.0
3	1.7	6.7	6.7	5.6	1.6	3.5	5.2	10.7	1.2	7.7	4.3	7.4	7.7	6.1	11.4	6.3	6.1	4.5	**47.3**	9.6
4	1.7	0.0	0.0	0.0	0.0	0.0	1.3	1.3	0.0	0.9	0.9	1.3	0.9	0.8	1.0	3.6	0.0	0.0	14.9	4.4

N: number of antibacterial drugs

Table 6: Number of antibacterial drugs *Pasteurella multocida* isolates were resistant to (percent). Mode emphasized.

N	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
0	**43.0**	**66.7**	**51.6**	**58.4**	**39.4**	**39.5**	**44.6**	27.8	**43.4**	**41.7**	**58.4**	**53.8**	**59.6**	**40.5**	**49.0**	**41.3**	**54.0**	**67.6**	**40.6**	**71.1**
1	26.0	17.5	26.6	18.2	38.4	34.0	27.3	**37.3**	22.1	35.2	23.8	28.8	24.1	35.1	32.7	34.9	27.0	16.7	31.3	15.6
2	11.0	10.5	9.4	11.7	11.1	11.6	17.4	16.7	18.0	12.0	6.9	9.6	7.8	14.4	10.2	12.8	9.5	10.2	18.8	6.7
3	10.0	3.5	9.4	5.2	6.1	8.8	3.3	8.7	5.7	5.6	6.9	2.9	4.3	4.5	5.1	6.4	7.3	3.7	6.3	4.4
4	7.0	1.8	3.1	3.9	4.0	4.8	1.7	4.8	5.7	2.8	3.0	2.9	3.5	3.6	1.0	2.8	0.0	0.0	3.1	0.0
5	3.0	0.0	0.0	2.6	1.0	1.4	4.1	4.0	3.3	2.8	1.0	1.0	0.7	0.9	2.0	1.8	2.2	0.9	0.0	0.0
6	0.0	0.0	0.0	0.0	0.0	0.0	1.7	0.8	1.6	0.0	0.0	1.0	0.0	0.9	0.0	0.0	0	0.9	0.0	2.2

N: number of antibacterial drugs

Table 7: Number of antibacterial drugs *Mannheimia haemolytica* isolates were resistant to (percent). Mode emphasized.

N	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
0	**63.2**	**60.0**	**66.7**	**50.5**	**41.2**	**46.1**	**46.9**	**36.6**	**43.8**	**54.8**	**50.0**	**54.0**	**53.8**	**39.6**	36.8	**40.7**	**42.4**	**49.3**	**32.7**	**46.3**
1	22.6	20.0	17.5	16.5	21.6	32.4	21.9	31.0	20.3	21.0	16.0	14.3	26.9	**39.6**	**40.4**	37.3	39.0	21.9	26.5	39.0
2	6.6	8.0	6.3	6.6	18.6	12.7	10.9	9.9	7.8	8.1	12.0	19.0	3.8	15.1	10.5	10.2	13.6	19.2	18.4	9.8
3	3.8	10.7	6.3	16.5	14.4	6.9	15.6	14.1	20.3	12.9	16.0	11.1	9.6	3.8	8.8	6.8	3.4	9.6	14.3	2.4
4	2.8	1.3	3.2	5.5	1.0	1.0	1.6	2.8	1.6	3.2	0.0	1.6	3.8	1.9	0.0	3.4	0.0	0.0	6.1	2.4
5	0.9	0.0	0.0	4.4	3.1	1.0	3.1	4.2	4.7	0.0	2.0	0.0	1.9	0.0	3.5	1.7	1.7	0.0	2.0	0.0
6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.4	1.6	0.0	4.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

N: number of antibacterial drugs

Table 8: Correlation coefficients for *Salmonella enterica* sgr. B susceptibility curves. Values above 0.7 emphasized.

	SxT	Ceph*	Amp	AmC*	Gen	Flq	Ctx	PB	Clm
Ceph*	0.368								
Amp	0.214	0.157							
AmC*	-0.460	0.175	0.639						
Gen	**0.891**	0.544	0.503	-0.124					
Flq	0.310	0.284	0.099	-0.157	0.377				
Ctx	0.631	0.522	0.129	-0.037	0.547	0.265			
PB	0.472	0.592	-0.222	-0.450	0.421	0.115	0.281		
Clm	0.122	-0.414	0.723	0.447	0.261	-0.007	-0.128	-0.619	
Amk	0.539	**0.715**	0.344	0.326	0.578	0.104	0.568	0.145	0.203

SxT: Sulfamethoxazole-trimethoprim, Ceph: Cephalothin, Amp: Ampicillin, AmC: Amoxicillin/clavulanic acid, Gen: Gentamicin, Flq: Fluoroquinolones, Ctx: Cefotaxime, PB: Polymyxin B, Clm: Chloramphenicol, Amk: Amikacin; *Starting 1992

Table 9: Correlation coefficients for *Escherichia coli* susceptibility curves. Values above 0.7 emphasized.

	SxT	Ceph*	Amp	AmC*	Gen	Flq	Ctx	PB	Clm
Ceph*	0.055								
Amp	0.411	0.418							
AmC*	0.175	0.604	0.255						
Gen	0.239	0.349	0.338	0.336					
Flq	-0.454	0.547	0.064	0.069	0.179				
Ctx	0.467	0.136	0.582	-0.023	0.311	-0.347			
PB	0.340	0.691	0.521	0.150	0.523	0.072	0.638		
Clm	**0.822**	-0.180	0.321	-0.027	0.152	**-0.751**	0.673	0.352	
Amk	0.639	0.198	0.278	0.430	0.239	-0.624	0.689	0.484	**0.798**

SxT: Sulfamethoxazole-trimethoprim, Ceph: Cephalothin, Amp: Ampicillin, AmC: Amoxicillin/clavulanic acid, Gen: Gentamicin, Flq: Fluoroquinolones, Ctx: Cefotaxime, PB: Polymyxin B, Clm: Chloramphenicol, Amk: Amikacin; *Starting 1992

Table 10: Correlation coefficients for *Proteus* spp. susceptibility curves. Values above 0.7 emphasized.

	SxT	Ceph*	Amp	AmC*	Gen	Flq	Ctx	PB	Clm
Ceph*	**0.754**								
Amp	**0.725**	0.674							
AmC*	0.505	**0.792**	0.593						
Gen	0.130	0.218	0.259	0.430					
Flq	-0.237	-0.433	-0.076	-0.354	0.082				
Ctx	0.806	0.835	0.643	0.459	0.029	-0.329			
PB	-0.407	-0.521	-0.387	-0.270	0.344	0.337	-0.517		
Clm	**0.717**	**0.806**	0.574	**0.712**	0.403	-0.486	0.649	-0.365	
Amk	0.400	0.565	0.437	**0.745**	0.463	-0.206	0.362	0.191	0.548

SxT: Sulfamethoxazole-trimethoprim, Ceph: Cephalothin, Amp: Ampicillin, AmC: Amoxicillin/clavulanic acid, Gen: Gentamicin, Flq: Fluoroquinolones, Ctx: Cefotaxime, PB: Polymyxin B, Clm: Chloramphenicol, Amk: Amikacin; *Starting 1992

since the decrease in the number of antibacterial drugs this microorganism was susceptible to was followed by an increase during the following years, to a level almost identical to the original stage.

Whether the increase in multiresistance observed for *Proteus* spp. in 2008-2009 indicates a trend or a temporary fluctuation, similar to the rise observed between 1993 and 1996, may be determined in the future. The same considerations may be made for *Pseudomonas aeruginosa* regarding the results of 2008 in which almost half of the isolates tested were resistant to 3 out of 4 drugs examined and 14.9% were resistant to all 4. Although the results of 2009 indicate that this may have been an exceptional phenomenon, its amplitude (decreasing from a mode of 0 resistances to 3/4) is significant enough to warrant further monitoring.

Correlation coefficients between the various susceptibility curves did not indicate a noteworthy pattern. Interestingly when high correlation coefficients were found they were between different drug groups while high coefficients between drugs belonging to the same (the aminoglycoside gentamicin and amikacin) or similar (the beta-lactam penicillins and cephalosporins) groups were rare. Another noteworthy observation regards the correlation between chloramphenicol

Table 11: Correlation coefficients for *Pseudomonas aeruginosa* susceptibility curves. Values above 0.7 emphasized.

	Gen	Flq	PB
Gen			
Flq	-0.176		
PB	0.552	0.048	
Amk	**0.866**	-0.177	0.540

Gen: Gentamicin, Flq: Fluoroquinolones, PB: Polymyxin B, Amk: Amikacin

Table 12: Correlation coefficients for *Pasteurella multocida* sceptibility curves. Values above 0.7 emphasized.

	SxT	Ceph	Amp	AmC*	Gen	Flq*	Ctx*	Tet
Ceph	0.389							
Amp	-0.173	0.371						
AmC*	-0.268	0.163	-0.051					
Gen	-0.048	0.281	0.194	**0.729**				
Flq*	0.258	-0.226	-0.220	0.024	0.033			
Ctx*	-0.278	-0.273	0.183	0.461	0.356	0.556		
Tet	0.445	0.148	-0.179	-0.148	-0.239	0.569	0.262	
Clm	**0.772**	0.357	-0.442	-0.194	-0.120	0.334	-0.280	0.480

SxT: Sulfamethoxazole-trimethoprim, Ceph: Cephalothin, Amp: Ampicillin, AmC: Amoxicillin/clavulanic acid, Gen: Gentamicin, Flq: Fluoroquinolones, Ctx: Cefotaxime, Tet: Tetracyclines, Clm: Chloramphenicol; *Starting 1992

Table 13: Correlation coefficients for *Mannheimia haemolytica* susceptibility curves. Values above 0.7 emphasized.

	SxT	Ceph	Amp	AmC*	Gen	Flq*	Ctx*	Tet
Ceph	-0.070							
Amp	0.677	0.234						
AmC*	-0.313	0.553	-0.315					
Gen	-0.101	-0.074	-0.016	-0.246				
Flq*	0.415	0.273	0.430	-0.114	-0.043			
Ctx*	0.470	-0.102	0.524	-0.012	0.181	0.240		
Tet	0.302	0.116	0.289	0.326	-0.240	-0.089	0.015	
Clm	0.068	-0.040	-0.108	-0.118	-0.049	0.053	-0.182	-0.063

SxT: Sulfamethoxazole-trimethoprim, Ceph: Cephalothin, Amp: Ampicillin, AmC: Amoxicillin/clavulanic acid, Gen: Gentamicin, Flq: Fluoroquinolones, Ctx: Cefotaxime, Tet: Tetracyclines, Clm: Chloramphenicol; *Starting 1992

and sulfamethoxazole/trimethoprim. The curves of these two antibacterial drugs were the only ones to be significant in more than one case. In fact they correlated for *E. coli*, *Proteus* spp. and *P. multocida*. Interestingly this seems to indicate that if a common mechanism of resistance exists, the microorganisms' taxonomic affiliation is not the only determining factor: the correlation was observed for *E. coli*, *Proteus* spp. which belongs to the Enterobacteriaceae but not for another member of the same family, *Salmonella enterica* sgr. B. On the other hand, a third microorganism for which a high correlation coefficient was found, *Pasteurella multocida*, belongs to a completely different family, the *Pasteurellaceae*.

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