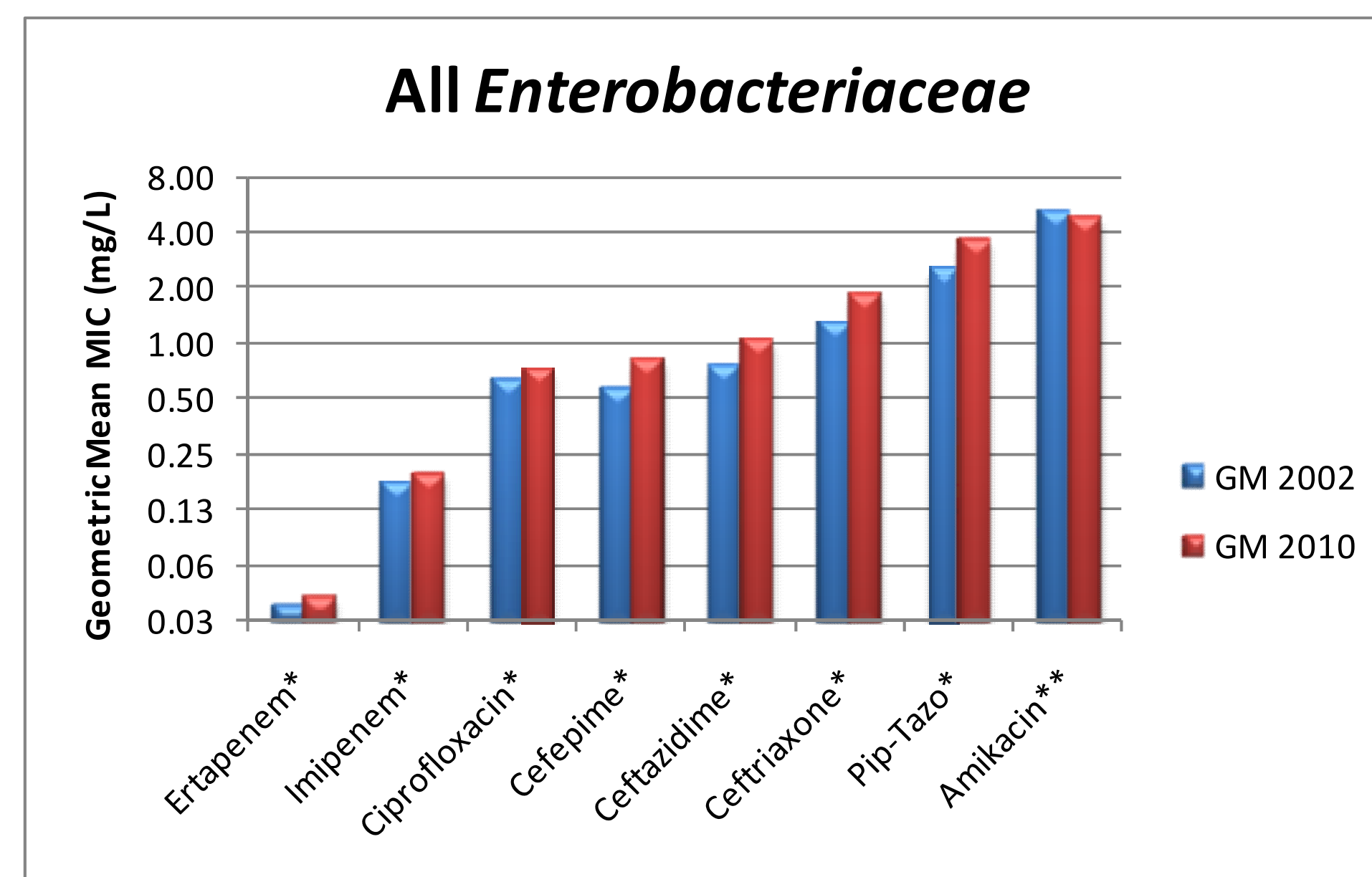


Revised Abstract

Objectives: The Study for Monitoring Antimicrobial Resistance Trends (SMART) is a global longitudinal surveillance study that has tracked activity of ertapenem and other drugs used to treat intra-abdominal infections (IA) since 2002. This report summarizes trends in susceptibility of *Enterobacteriaceae* over 9 years in Europe.

Methods: 86 hospitals in 15 European countries each collected up to 100 consecutively isolated gram-negative aerobic bacteria per year from IA. From 2002-2007, each site did susceptibility testing using MicroScan broth microdilution panels, following Clinical and Laboratory Standards Institute and MicroScan procedures and quality control. From 2008-2010 all susceptibility testing was done at a central lab (IHMA, Inc.), also using MicroScan panels. Minimum inhibitory concentrations (MICs) were interpreted using EUCAST guidelines. MIC frequency distributions were analyzed for trends using Spearman's correlation coefficient, and geometric mean (GM) MICs calculated. Percent susceptibility from 2002 and 2010 was compared using Fisher's exact test. Only drugs tested all 9 years of the study were evaluated.

Results: MICs of all drugs showed statistically significant ($p < .0001$) changes from 2002-2010: amikacin's GM MIC declined, but all other drugs increased. Percent susceptible values declined significantly ($p < 0.05$) from 2002-2010 except for ertapenem, imipenem, and amikacin. The figure below compares GM MICs in 2002 and 2010 for the 8 study drugs:



Conclusions: Although all drugs had statistically significant changes in MIC values over the course of the study, 3 (ertapenem, imipenem, and amikacin) did not show significant changes in their percent susceptible values, with all remaining >94% in 2010. The other 5 drugs had significantly reduced levels of susceptibility. Among the drugs studied, ertapenem, imipenem, and amikacin are the least affected by extended-spectrum beta-lactamases, and the loss of activity of the other study drugs is probably due largely to increases in ESBL-producing *Enterobacteriaceae* in Europe that have been documented in numerous reports.

Introduction

Antimicrobial resistance in bacteria is a global healthcare problem. Particularly troubling has been the spread of extended spectrum beta-lactamase producing (ESBL+) gram-negative pathogens that have rendered all but a few antibiotics ineffective, and which is associated with increased length of hospital stay, costs, and mortality [1,2]. Several collaborative studies have been established to monitor resistance [3-5]. The Study for Monitoring Antimicrobial Resistance Trends (SMART) was begun in 2002 and is the only surveillance study to globally monitor the *in vitro* antimicrobial susceptibility of aerobic and facultative gram-negative bacilli causing both hospital- and community-associated intra-abdominal infections (IA). This report focuses on trends in susceptibility of *Enterobacteriaceae* over 9 years in Europe.

Materials & Methods

- Participating sites each collected up to 100 consecutive, non-selected isolates of gram-negative aerobic or facultative bacilli from intra-abdominal infections each year of the study (1/patient); 18,076 *Enterobacteriaceae* isolates were collected between 2002 and 2010 at 86 institutions in 15 countries in Europe.
- From 2002-2007, each site did their own identification and susceptibility testing. From 2008-2010, all isolates were sent to a central laboratory (IHMA, Inc., Schaumburg, Illinois, USA) for confirmation of identification and susceptibility testing.
- Minimum inhibitory concentrations (MICs) and production of extended spectrum beta-lactamase (ESBL) were determined in all years of the study using MicroScan dehydrated broth microdilution panels (Siemens Medical Solutions Diagnostics, West Sacramento, CA), following manufacturer and CLSI guidelines [6,7]. MICs were analyzed using EUCAST susceptibility breakpoints [8].
- Quality control was done each day of testing following CLSI guidelines [6].
- Only drugs tested all nine years of the study were evaluated.
- Trends over time in MICs were assessed with Spearman's correlation, while the Cochran-Armitage test was used to assess linear trends in susceptibility.

References

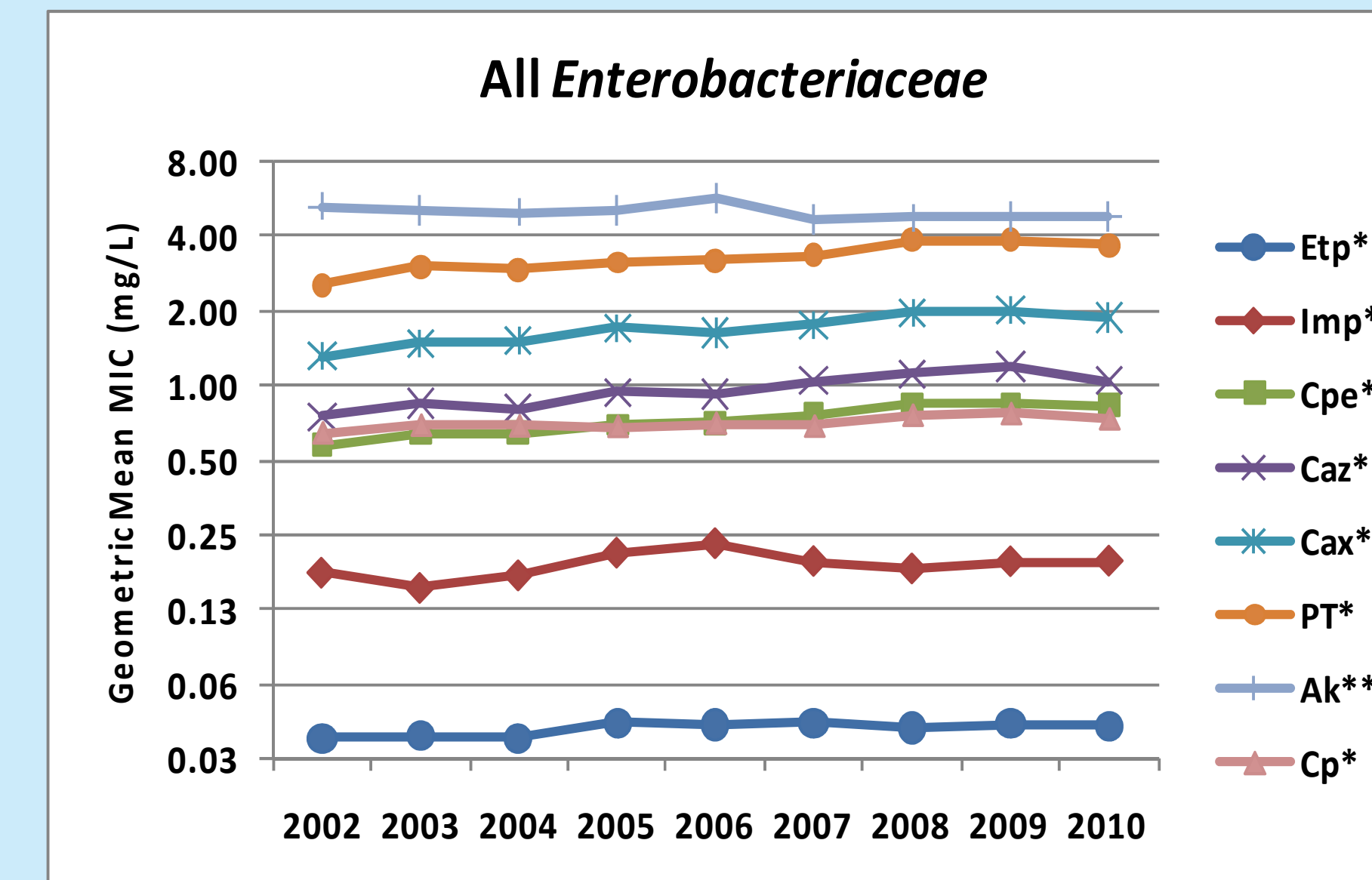
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Acknowledgements

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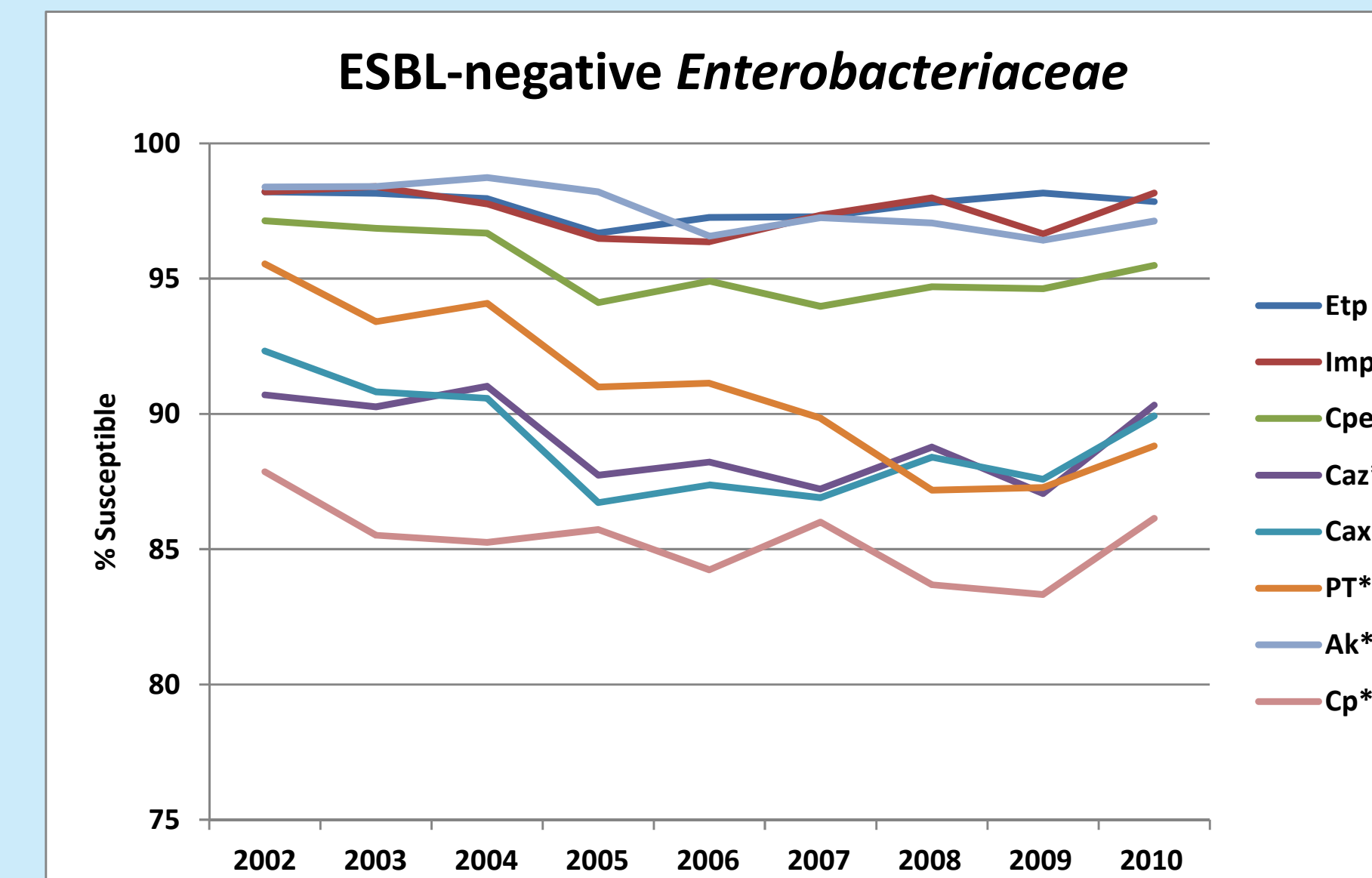
Results

Figure 1. Trends in geometric mean MICs for all *Enterobacteriaceae*, 2002-2010.



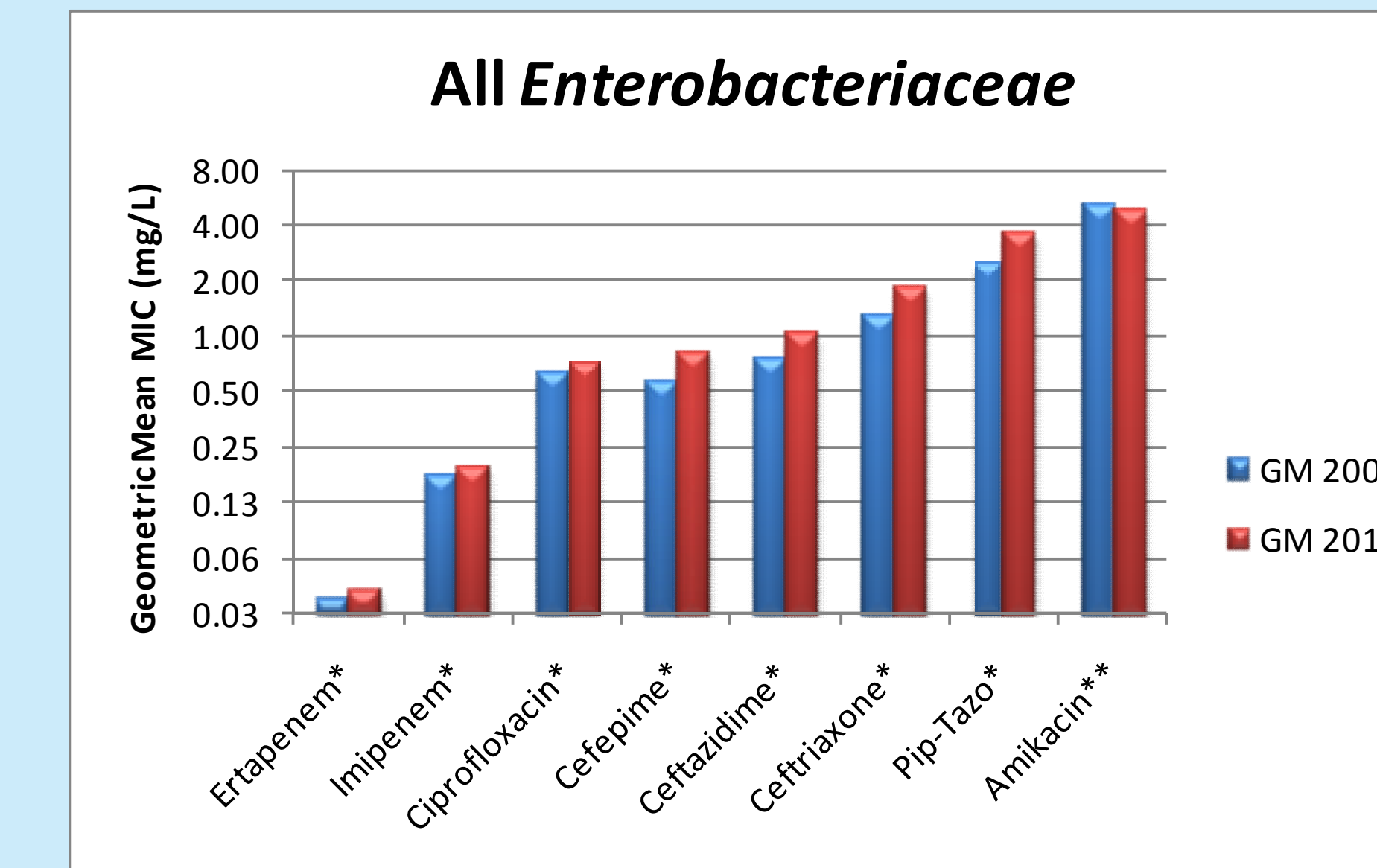
Etp=ertapenem, Imp=imipenem, Cpe=cefepime, Caz=ceftazidime, Cax=ceftriaxone, PT=piperacillin-tazobactam, Ak=amikacin, Cp=ciprofloxacin.
 * Statistically significant increase in GM MIC (p<0.05); ** statistically significant decrease in GM MIC (p<0.05).

Figure 4. Percent susceptible for ESBL-negative *Enterobacteriaceae*, 2002-2010.



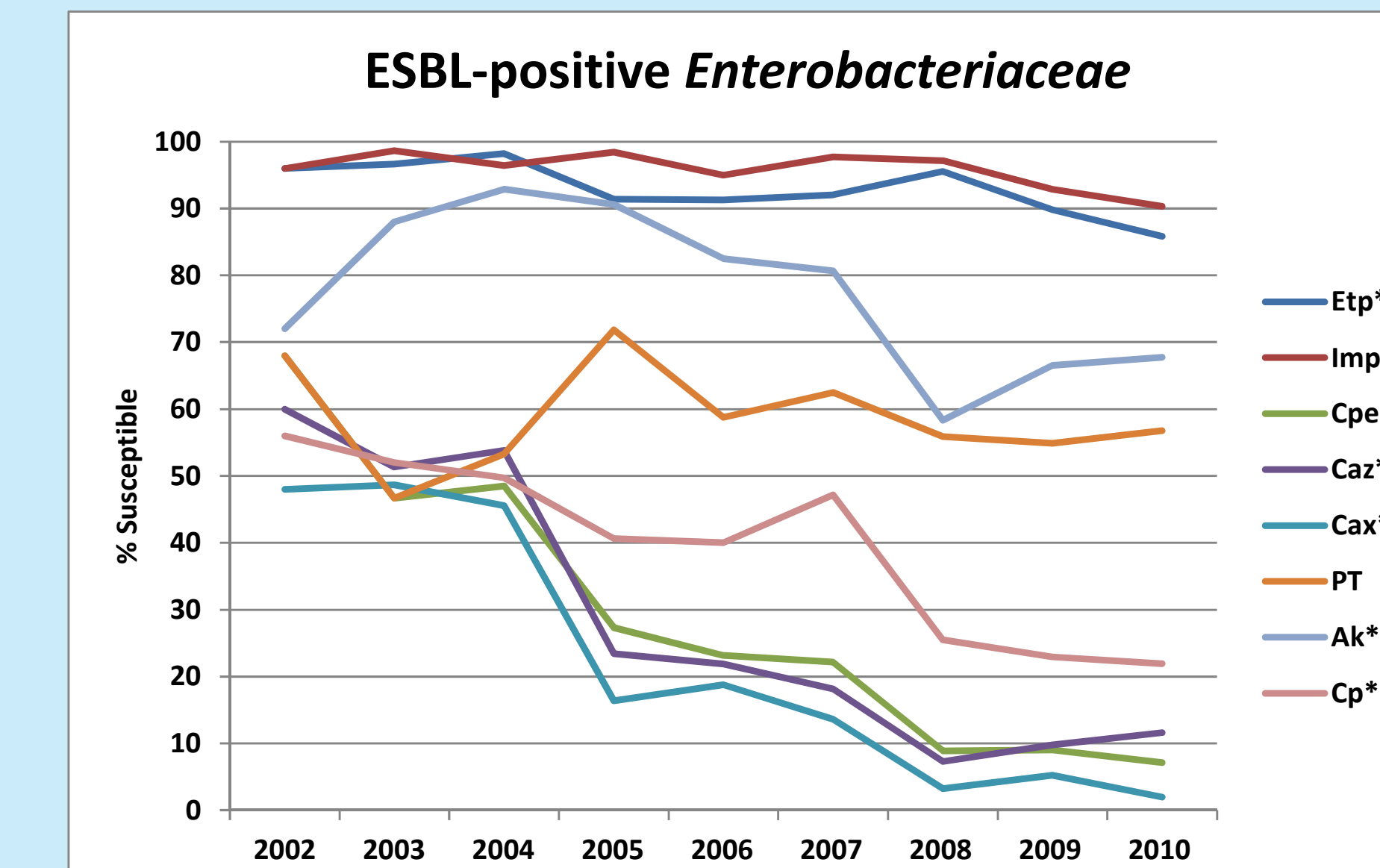
Etp=ertapenem, Imp=imipenem, Cpe=cefepime, Caz=ceftazidime, Cax=ceftriaxone, PT=piperacillin-tazobactam, Ak=amikacin, Cp=ciprofloxacin.
 * Statistically significant decrease (p<0.05).

Figure 2. Geometric mean MIC for all *Enterobacteriaceae* in 2002 and 2010.



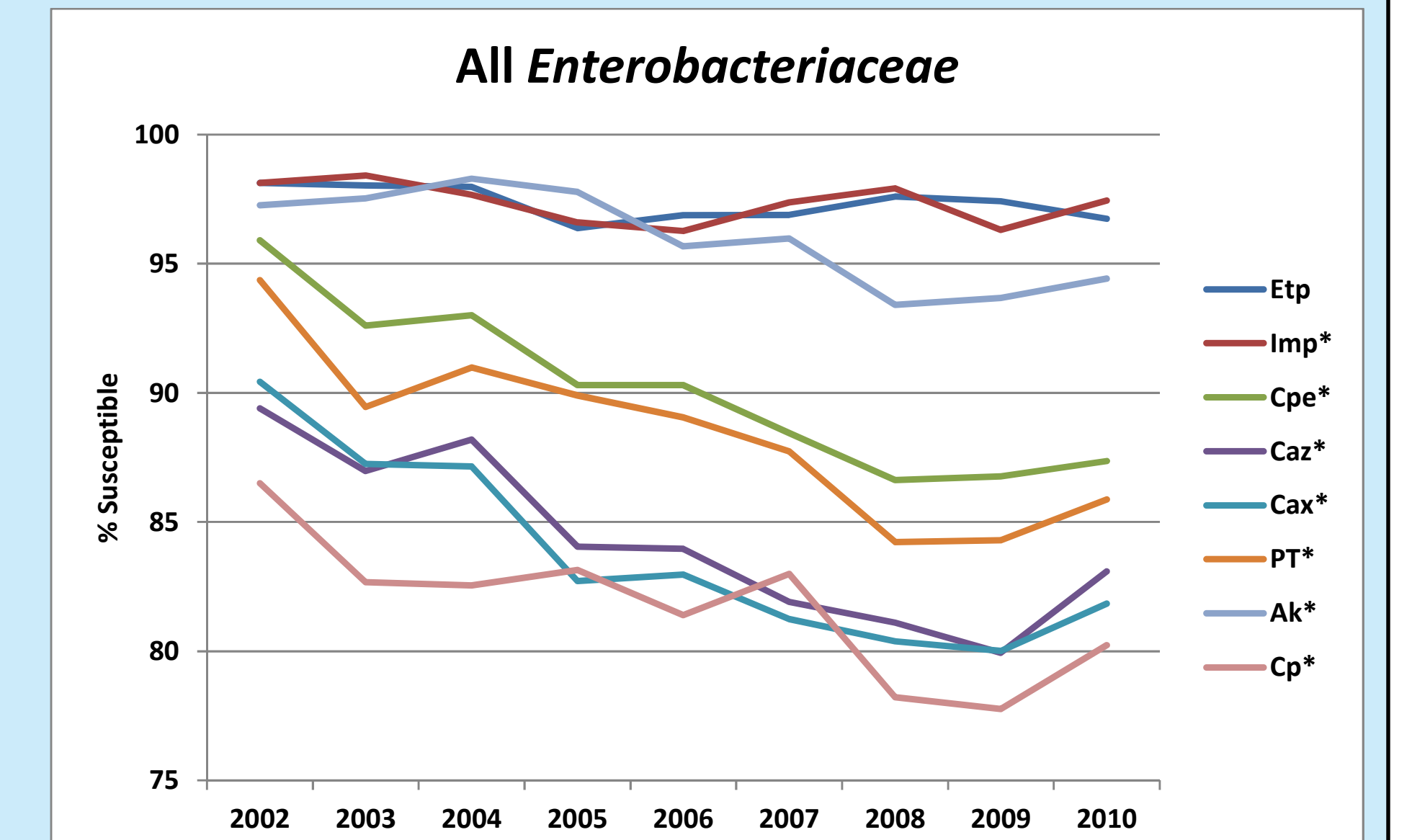
* Statistically significant increase in GM MIC (p<0.05); ** statistically significant decrease in GM MIC (p<0.05).

Figure 5. Percent susceptible for ESBL-positive *Enterobacteriaceae*, 2002-2010.



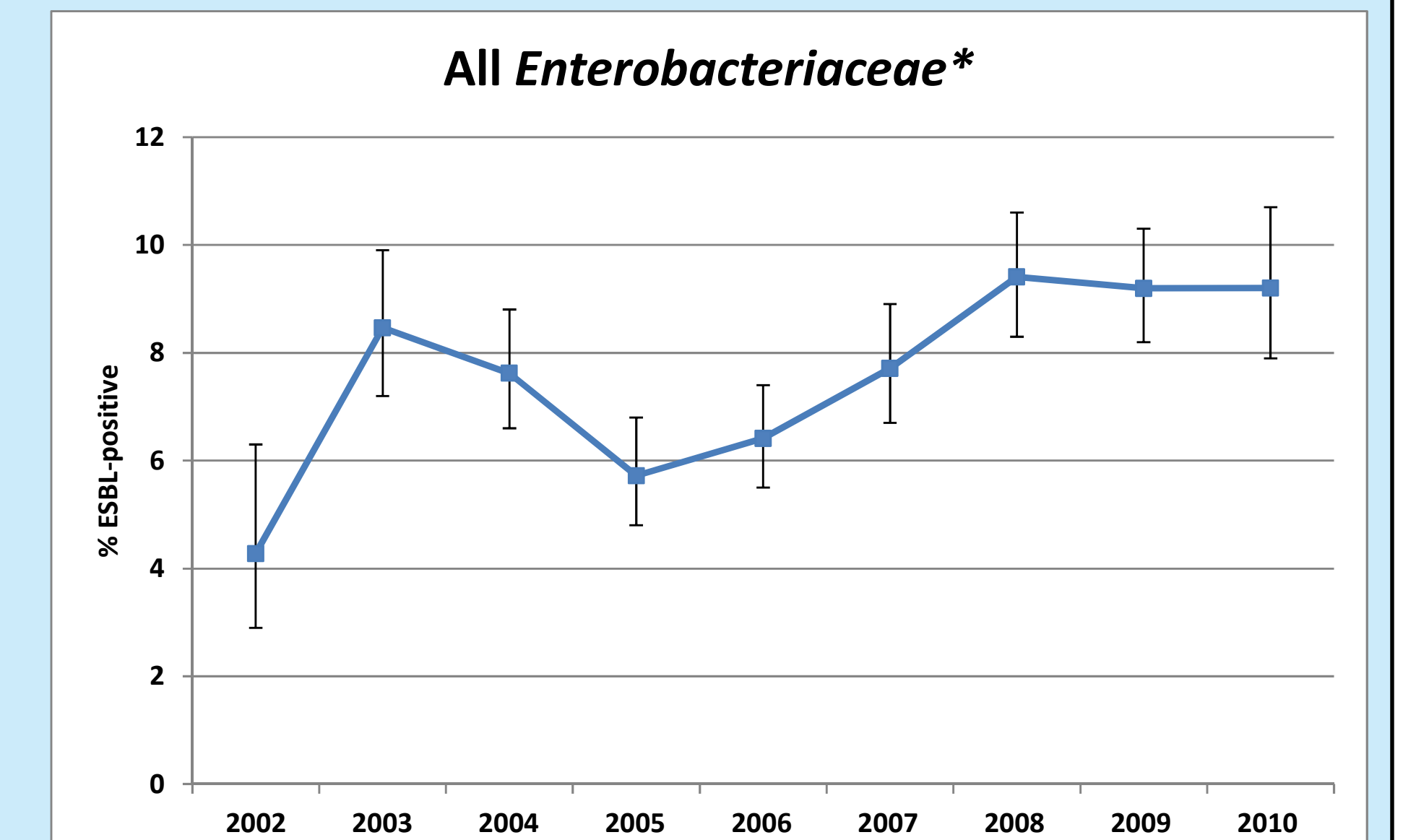
Etp=ertapenem, Imp=imipenem, Cpe=cefepime, Caz=ceftazidime, Cax=ceftriaxone, PT=piperacillin-tazobactam, Ak=amikacin, Cp=ciprofloxacin.
 * Statistically significant decrease (p<0.05).

Figure 3. Percent susceptible for all *Enterobacteriaceae*, 2002-2010.



Etp=ertapenem, Imp=imipenem, Cpe=cefepime, Caz=ceftazidime, Cax=ceftriaxone, PT=piperacillin-tazobactam, Ak=amikacin, Cp=ciprofloxacin.
 * Statistically significant decrease (p<0.05).

Figure 6. ESBL-positive rates with 95% confidence intervals for all *Enterobacteriaceae*, 2002-2010.



* Statistically significant increase (p<0.05).

Conclusions

- Although all drugs had statistically significant changes in MIC values for all *Enterobacteriaceae* combined over the course of the study, ertapenem did not show significant changes in percent susceptible values, and imipenem's decreasing trend was only marginally significant ($p=0.03$), with susceptibility to both agents remaining >96% in 2010. The other 6 drugs had significantly reduced levels of susceptibility.
- Amikacin showed a decrease in MIC for all *Enterobacteriaceae*, but also a decrease in percent susceptible. This seemingly paradoxical result was due to a divergent trend at the susceptible breakpoint, with slight shift of MICs in the susceptible isolates from an MIC of 8 mg/L to an MIC of 4 mg/L, and a concurrent increase in the proportion of isolates with MICs of 16 mg/L or greater.
- The decrease in susceptibility was much more obvious in the ESBL-positive subgroup, with all agents except piperacillin-tazobactam showing a clearly significant trend. This trend coupled with a statistically significant increase in the ESBL-positive rate in Europe between 2002 and 2010 probably explains a large portion of the decrease in susceptibility of *Enterobacteriaceae* overall.
- Among the drugs studied, ertapenem, imipenem, amikacin, and piperacillin-tazobactam were the least affected by extended-spectrum beta-lactamases. Ertapenem and imipenem were the only agents that did not show a significant decrease in susceptibility for ESBL-negative *Enterobacteriaceae*.