

Revised Abstract

**Background:** Resistance rates vary regionally, especially between “high-income” (HI) and “low-to-middle income” (LMI) countries. The SMART program has tracked susceptibility of gram-negative pathogens (GNP) of intra-abdominal infection (IAI) globally since 2002. This report summarizes susceptibility (%S) differences between HI and LMI countries from 2005-present.

**Methods:** Sites in 16 (2002) to 45 (2009) countries each collected up to 100 consecutively isolated GNP from IAI each year. Through 2007 susceptibility testing (AST) was done locally using MicroScan dehydrated MIC panels; from 2008 through 2009 it was done at a central lab in the US. Countries were categorized as HI or LMI using World Bank criteria. %S in 2005/2009 were compared with Fisher’s exact test.

**Results:** ESBL rates (%) in 2005/2009 were 8/8 and 19/36 for HI and LMI, respectively. Table 1 summarizes %S in 2005/2009.

Drug	High Income %S		p<0.05	Low-to-Middle Income %S		p<0.05
	2005 (n=1841)	2009 (n=2856)		2005 (n=809)	2009 (n=2150)	
Amikacin	99	99		97	95	x
Amp-Sulbactam	49	49		40*	28	x
Cefepime	95	93	x	86	64	x
Cefotaxime	88	87		78	58	x
Cefoxitin	92	91		88	85	x
Ceftazidime	93	91	x	86	66	x
Ceftriaxone	89	88		77	58	x
Ciprofloxacin	80	76	x	63	47	x
Ertapenem	98	99	x	98	96	x
Imipenem	98	100	x	100	98	x
Levofloxacin	81	77	x	66	49	x
Pip-Tazo	94	93		95	88	x

\*Shading denotes years with >10% difference between 2005 and 2009.

Conclusions:

- All drugs were significantly less active (p<.05) in LMI countries in 2009; ampicillin-sulbactam, both fluoroquinolones, and all cephalosporins except cefoxitin had relatively large differences (>10%) in %S values between HI and LMI; all other drugs were <6% lower in LMI.
- In vitro susceptibility levels remained fairly constant in HI countries from 2005-2009, but decreased in LMI countries, with only amikacin, ertapenem, and imipenem inhibiting >90% of *E. coli* by 2009.
- Given the much higher ESBL+ rates observed in LMI countries, these differences are not unexpected, as co-resistance in ESBL+ isolates to many of these drugs is well-documented.
- Data from SMART corroborate that resistance rates are higher in LMI than HI countries, and are increasing faster as well.

Introduction

Although antimicrobial resistance in bacteria is a global problem, resistance rates vary widely by country, drug, and species of bacteria. *Escherichia coli* is one of the most common causes of many infectious diseases, especially intra-abdominal and urinary tract infections. Although this species has largely remained susceptible to many antimicrobics, increasing resistance has been reported to many classes of drugs, and has reached alarming levels in some parts of the world. Increasing resistance can be attributed to many causes, including the spread of bacterial enzymes, such as extended spectrum beta-lactamases that render various antimicrobics inactive, widespread misuse of drugs, inappropriate prophylactic use, inadequate diagnostic capabilities, and poor hygiene conditions. The Study for Monitoring Antimicrobial Resistance Trends (SMART) tracks the susceptibility and resistance patterns of bacteria in many countries over time. In this report, we compared susceptibility rates of *E. coli* collected from “high income” and “low-to-middle income” countries (income levels defined by World Bank criteria).

Materials & Methods

- Hospitals in 16 (2005) to 45 (2009) countries each collected the first 100 consecutively isolated gram-negative aerobic pathogens from intra-abdominal infections (IAI) each year of study participation; a total of 38,201 isolates were collected, of which 18,218 (48%) were *E. coli*.
- Susceptibility testing was done using MicroScan dehydrated broth microdilution panels (Siemens Medical Solutions Diagnostics, West Sacramento, California), following manufacturer and Clinical and Laboratory Standards Institute (CLSI) guidelines [1].
- From 2005-2007, susceptibility testing was done at each participating hospital, using the same MicroScan panels; from 2008-2009 all isolates were sent to a central laboratory (IHMA, Inc., Schaumburg, Illinois) for confirmation of identification and susceptibility testing, again using the same MicroScan panels.
- Susceptibility testing results were interpreted using CLSI M100-S21 [2].
- Quality assurance was done each day of testing, following manufacturer and CLSI guidelines [2].
- Countries were combined into two groups: high-income, and low-to-middle income, using World Bank criteria of high income ≥\$12,276 per capita and low-to-middle income <\$12,276 [3, 4].
- Fisher’s exact test (two-tailed) was used to determine significance of changes in percent susceptibility observed between 2005 and 2009.

References

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Acknowledgements

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Results

Figure 1. 2009 Gross national income per capita, based on World Bank criteria of ≥\$12,276=high, <\$12,276=low-to-middle.

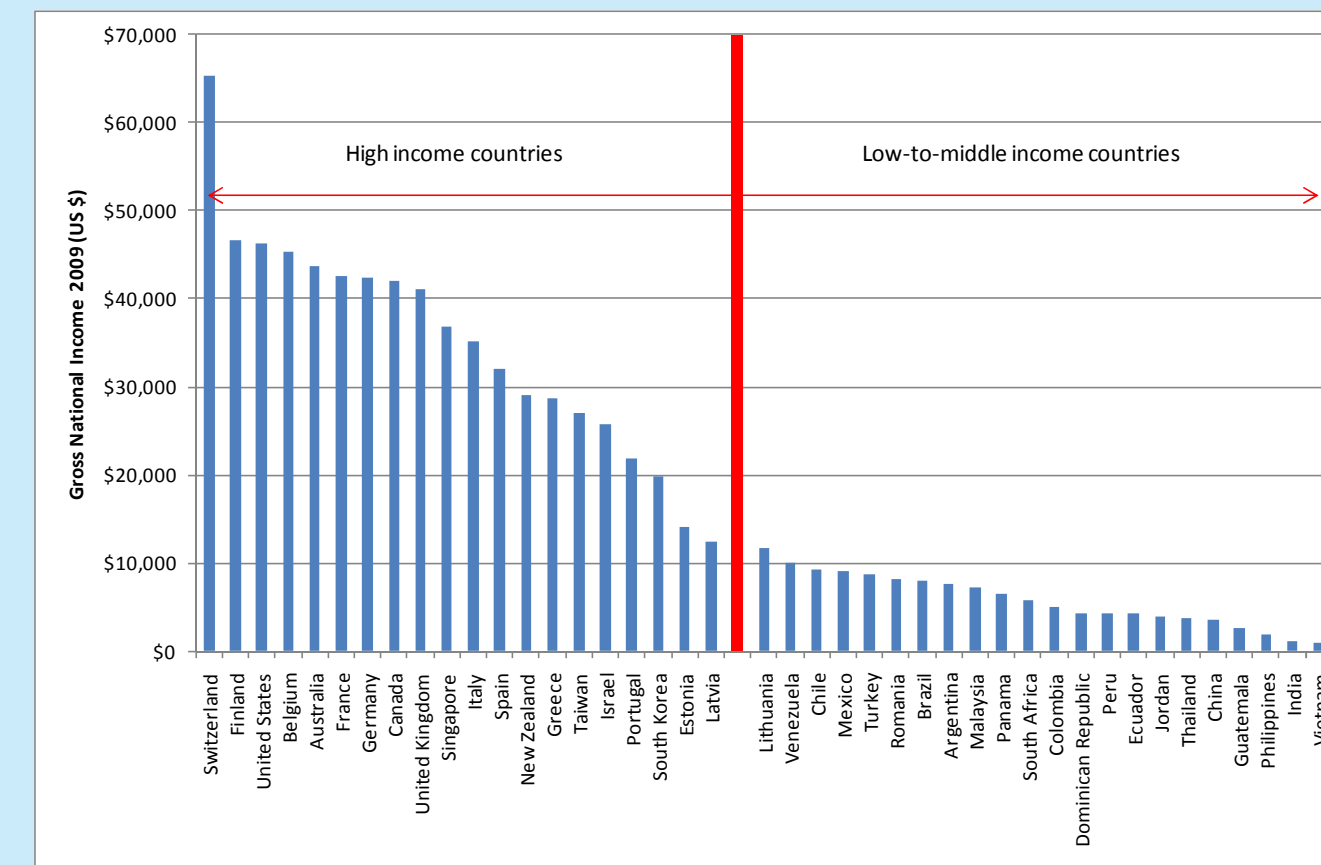


Figure 2. ESBL+ rates of *E. coli* in high- vs. low-to-middle income countries.

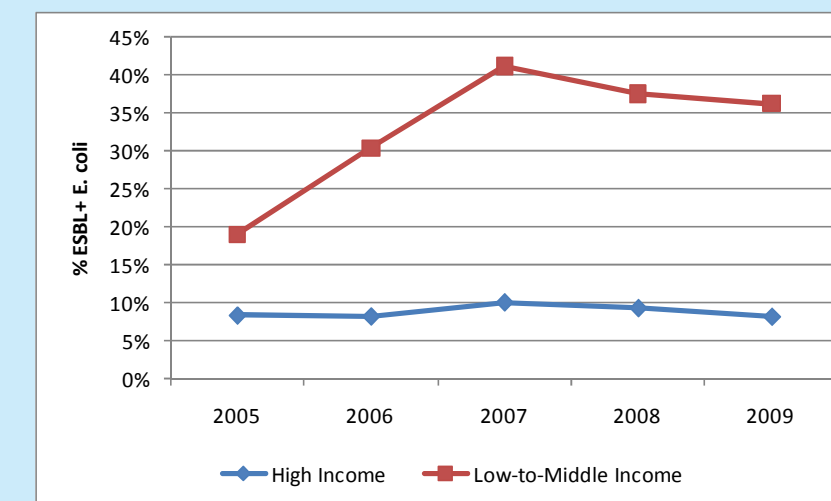
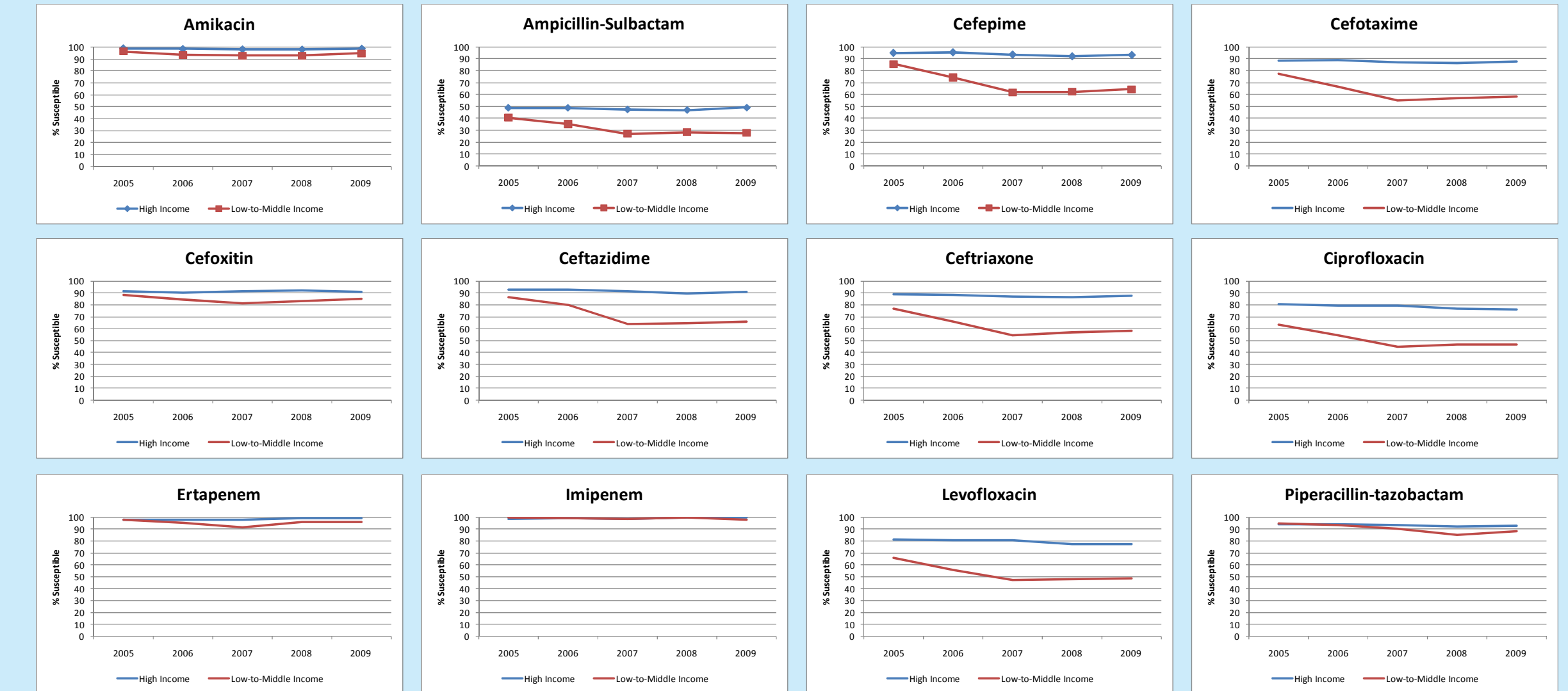


Table 1. Comparison of *E. coli* susceptibility rates in 2005 and 2009 from high-income and low-to-middle income countries.

Drug	HI <sup>1</sup> %S			LMI <sup>2</sup> %S			HI vs. LMI 2009 p <sup>3</sup>
	2005 (n=1841)	2009 (n=2856)	p <sup>3</sup>	2005 (n=809)	2009 (n=2150)	p <sup>3</sup>	
Amikacin	99.0	98.8	0.48	96.5	94.7	0.04	<.0001
Ampicillin-Sulbactam	48.9	49.1	0.95	40.4	27.8	<.0001	<.0001
Cefepime	94.7	93.1	0.02	85.5	64.4	<.0001	<.0001
Cefotaxime	88.3	87.4	0.39	77.6	58.1	<.0001	<.0001
Cefoxitin	91.7	91.1	0.46	88.0	85.1	0.04	<.0001
Ceftazidime	92.5	90.6	0.03	86.3	65.6	<.0001	<.0001
Ceftriaxone	88.7	87.8	0.31	77.0	58.1	<.0001	<.0001
Ciprofloxacin	80.4	76.2	0.001	63.4	46.8	<.0001	<.0001
Ertapenem	97.8	99.0	0.001	97.8	95.7	0.007	<.0001
Imipenem	98.4	99.9	<.0001	99.5	98.1	0.006	<.0001
Levofloxacin	81.3	77.3	0.001	65.8	48.6	<.0001	<.0001
Piperacillin-Tazobactam	93.9	93.0	0.26	94.8	88.3	<.0001	<.0001

<sup>1</sup>HI=high-income countries.  
<sup>2</sup>LMI=low-to-middle income countries.  
<sup>3</sup>p calculated comparing 2005 to 2009; values <.05 shaded in red.  
<sup>4</sup>p calculated comparing HI 2009 to LMI 2009; values <.05 shaded in red.  
Gray shading denotes >10% difference between 2005 and 2009.

Figure 3. *E. coli* susceptibility to 12 antimicrobics, 2005 through 2009.



Conclusions

- In 2009, all drugs showed significantly lower susceptibility rates in low-to-middle income countries (p<.0001). Ampicillin-sulbactam, both fluoroquinolones, and cephalosporins except for cefoxitin had relatively large differences (>10%) in %S values; all other drugs had differences of <6%.
- In vitro susceptibility levels remained fairly constant in high-income countries from 2005-2009, but decreased in low-to-middle income countries, with only amikacin, ertapenem, and imipenem inhibiting >90% of *E. coli* by 2009.
- Given the much higher ESBL+ rates observed in low-to-middle income countries, these differences are not unexpected, as co-resistance in ESBL+ isolates to many of these drugs is well-documented.
- Interestingly, after large increases in earlier years, *E. coli* ESBL and resistance rates in low-to-middle income countries seem to have stabilized in 2008 and 2009; further monitoring of the 2010-2011 data and beyond will determine if that is a real trend or just a temporary reprieve.
- Data from SMART corroborate that resistance rates are higher in low-to-middle countries than high-income countries, and have increased faster as well.
- Higher antimicrobial resistance rates observed in *E. coli* from low-to-middle income countries, combined with widespread global travel and commerce, will most likely contribute to increasing resistance rates in high income countries. To combat this, improving control and use of antimicrobial agents in low-to-middle income countries, improving the unsanitary conditions in which hundreds of millions of people now live, and developing new antimicrobial agents that can overcome bacterial mechanisms of resistance are all urgently needed.