

Trends in Levofloxacin and Ciprofloxacin Resistance Rates in *E. coli* from Intra-abdominal Infections in Asia/Pacific – SMART 2005 to the Present

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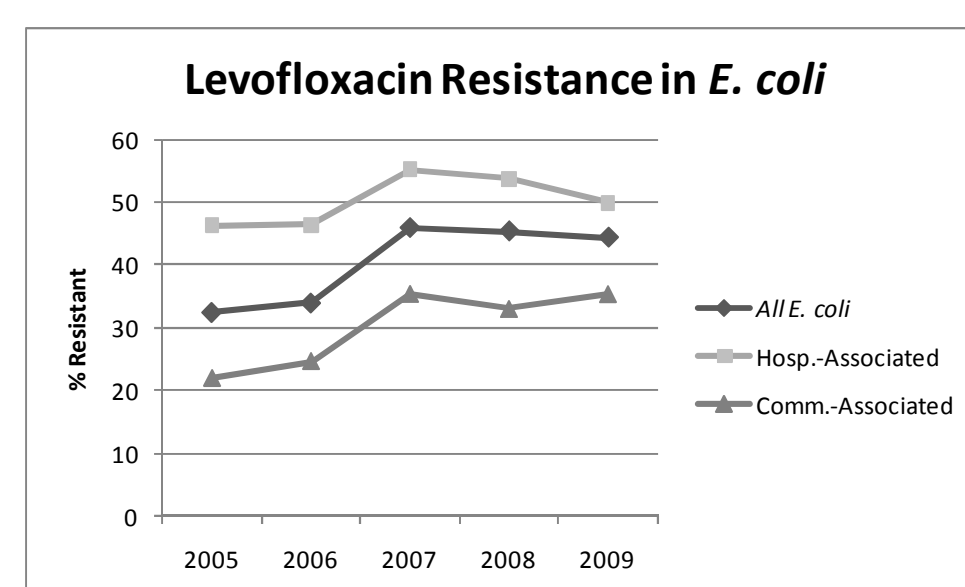
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Revised Abstract

Background: Widespread use of ciprofloxacin and levofloxacin (FQ) to treat many infectious diseases has contributed to increased rates of resistance to these agents. Increasing rates of extended spectrum beta-lactamase producing *E. coli* in Asia have further exacerbated FQ resistance due to frequent presence of FQ resistance determinants in these isolates. This report from the Study for Monitoring Antimicrobial Resistance Trends (SMART) describes trends in FQ resistance rates in *E. coli* from intra-abdominal infections (IAI) in Asia/Pacific from 2005 to 2010.

Methods: 6,627 isolates of *E. coli* from IAI were collected in hospitals in 11 Asia/Pacific countries from 2005-2010. Susceptibility was determined using custom MicroScan broth microdilution panels, and interpreted using CLSI M100-S21 guidelines. Isolates were deemed hospital-associated (HA) or community-associated (CA) if specimens were collected ≥ 48 or < 48 hours from admission, respectively.

Results: Levofloxacin resistance rates for all *E. coli*, HA only, and CA only are shown in the graph below. Ciprofloxacin resistance rates were about 4% higher than those of levofloxacin.



Conclusions: After increasing in earlier years, FQ resistance rates in *E. coli* seem to have leveled off at 45-50%. The HA levofloxacin resistance rate was 24% higher than CA in 2005, but by 2009 the gap had narrowed to 14%. Since 40-50% of *E. coli* from IAI in Asia/Pacific are resistant to levofloxacin and ciprofloxacin, the utility of these drugs in *E. coli*-associated IAI in several countries of this region appears to be limited.

Introduction

Fluoroquinolones (FQs) have been widely used in treatment of a variety of infectious diseases for many years; however, their utility in many countries has diminished over time as resistance has developed. There are several proposed contributors to development of fluoroquinolone resistance, including their widespread use in outpatients for more than 20 years, their use in animal feeds, and even use of sub-standard or counterfeit preparations of drugs. The spread of extended-spectrum beta-lactamase (ESBL) producing organisms, with frequent co-resistance to fluoroquinolones, has exacerbated this problem. The Study for Monitoring Antimicrobial Resistance Trends (SMART) tracks resistance rates among intra-abdominal infection pathogens to several drugs, including ciprofloxacin and levofloxacin. Since *E. coli* represents approximately 40% of aerobic gram-negative IAI pathogens, its susceptibility to antimicrobials must be taken into account when selecting appropriate empiric therapy for such infections. This report summarizes data from SMART in the Asia/Pacific region from 2005-2010, specifically for fluoroquinolone resistance and ESBL-positive rates observed in *E. coli*.

Materials & Methods

- Participating sites each collected up to 100 consecutive, non-selected isolates of gram-negative aerobic bacilli from intra-abdominal infections each year of the study; 6,627 clinical isolates of *E. coli* were collected from 2005-2010 at 60 institutions in 11 countries in Asia/Pacific. Isolates were deemed hospital-associated (HA) or community-associated (CA) if specimens were collected ≥ 48 or < 48 hours from admission, respectively.
- From 2005-2007, sites identified isolates and conducted the susceptibility testing; however, from 2008-2010 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 using MicroScan dehydrated broth microdilution panels (Siemens Medical Solutions Diagnostics, West Sacramento, CA), following manufacturer and CLSI guidelines [1,2]. MICs were analyzed using CLSI M100-S21 susceptibility breakpoints [1].
- Quality control was done each day of testing following CLSI guidelines [1].
- Linear trends in percent resistant over time were assessed with the Cochran-Armitage test. The chi-square test for independence was used to test whether FQ resistance was associated with ESBL+ rates.

References

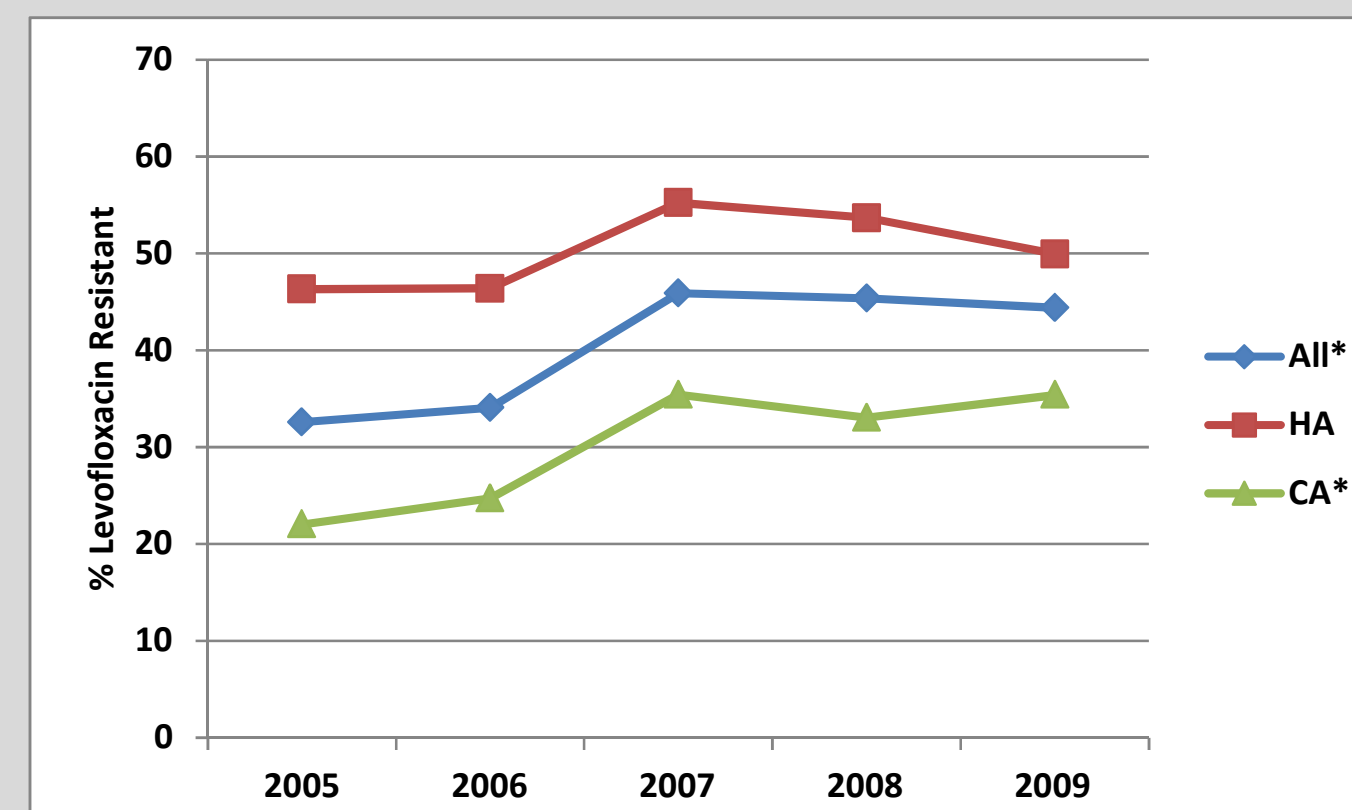
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Acknowledgements

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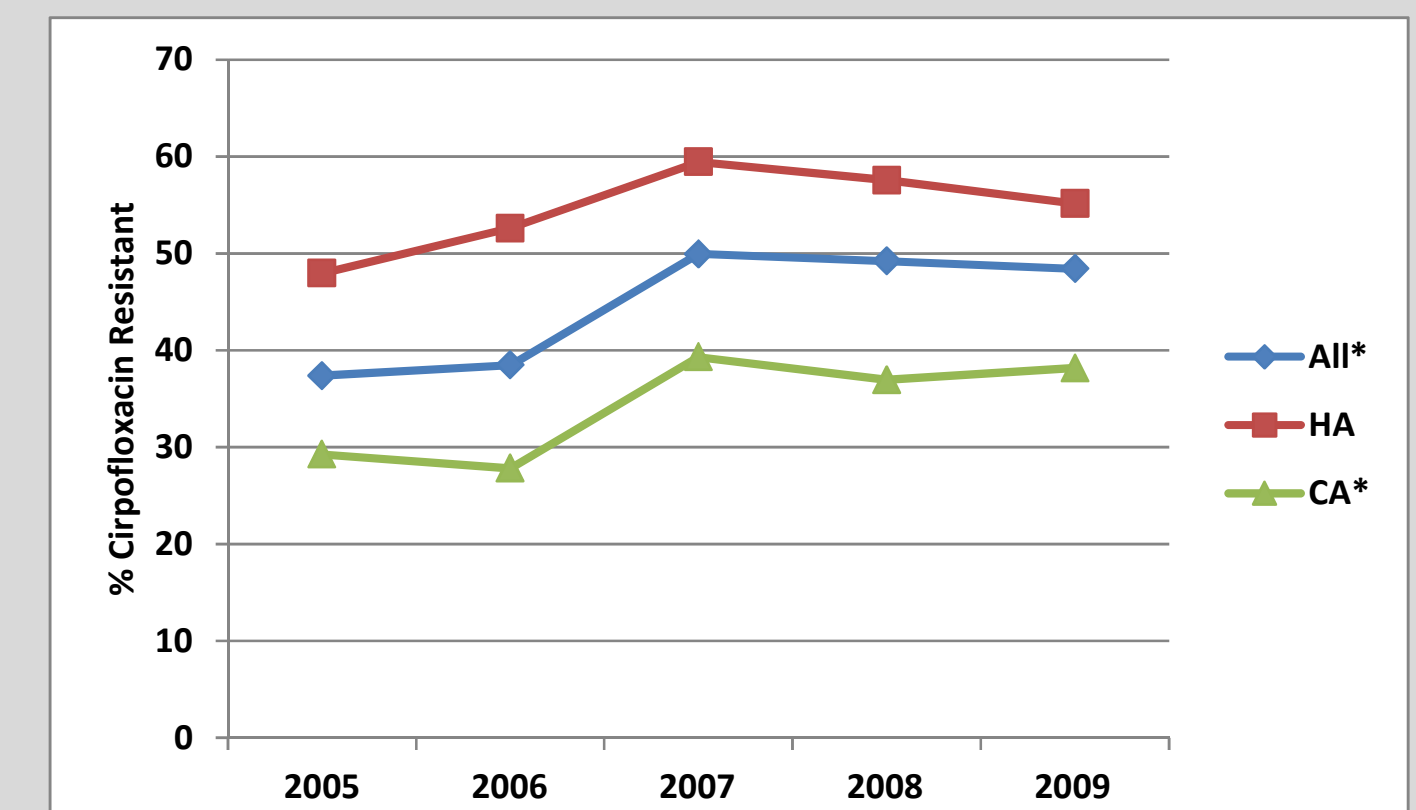
Results

Figure 1. Levofloxacin resistance trends for *E. coli* in hospital-associated (HA) and community-associated (CA) infections, Asia/Pacific 2005-2009^a.



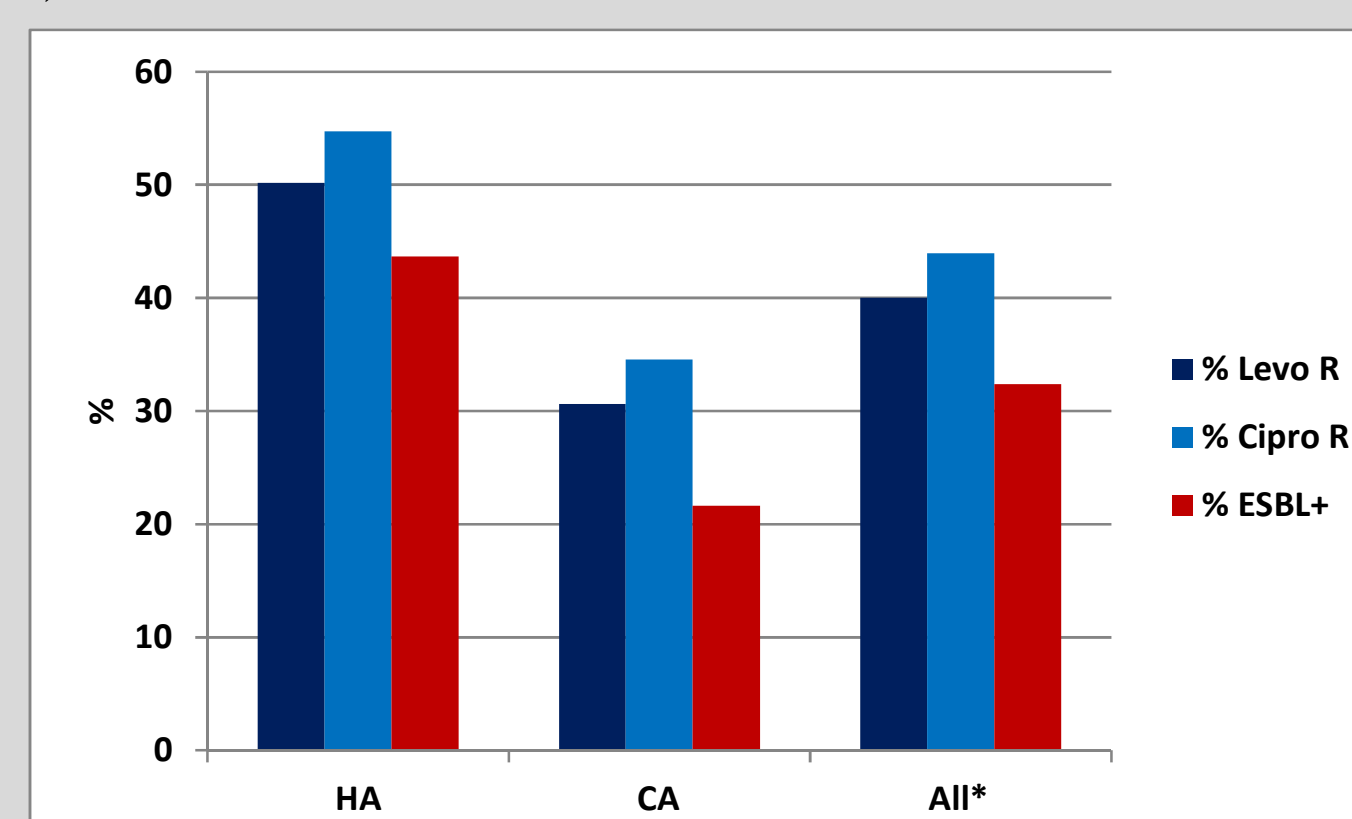
* p for trend < 0.05.
*Note: Because of pending data for China and India, 2010 is not included for the overall region.

Figure 2. Ciprofloxacin resistance trends in *E. coli* in hospital-associated (HA) and community-associated (CA) infections, Asia/Pacific 2005-2009^a.



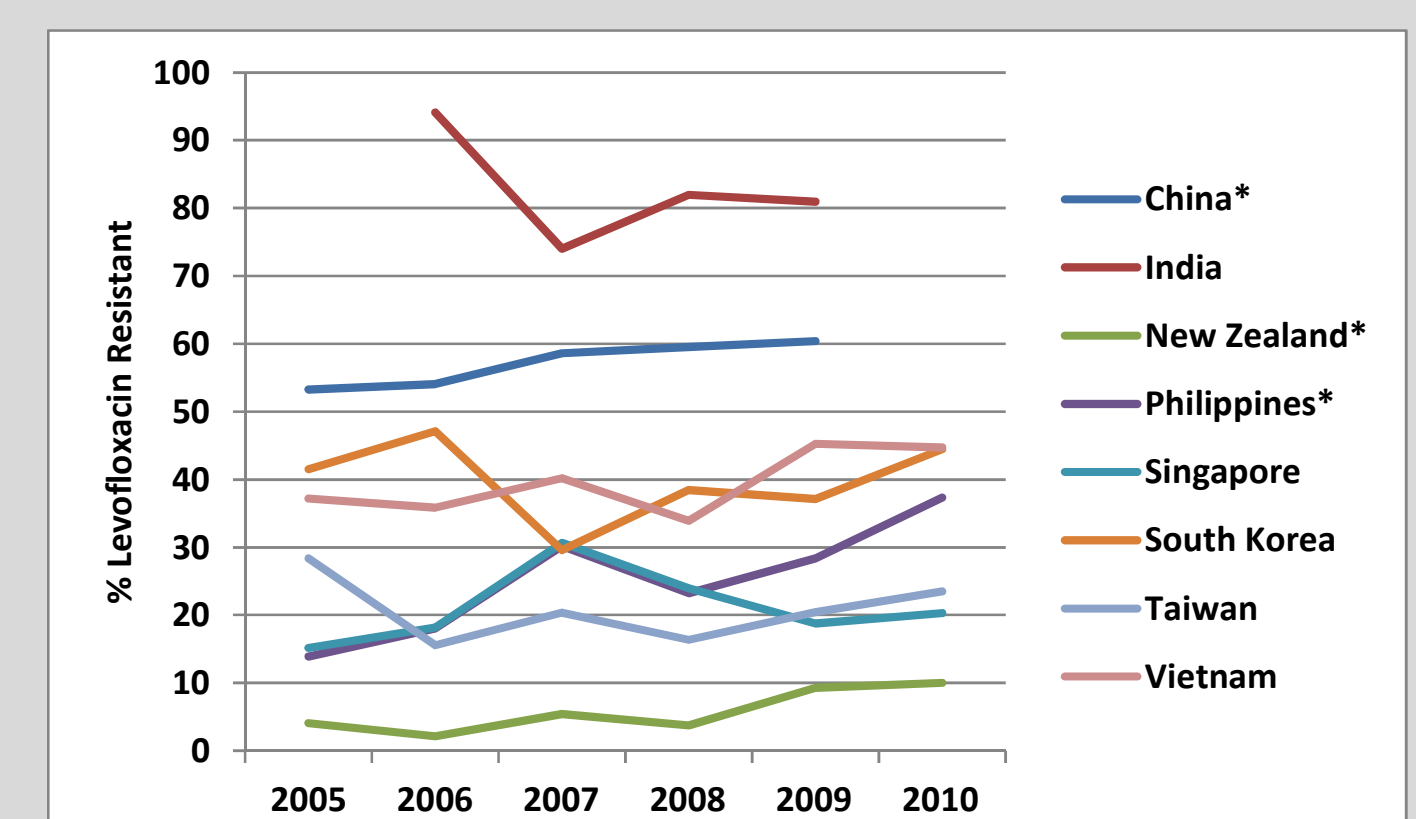
* p for trend < 0.05.
*Note: Because of pending data for China and India, 2010 is not included for the overall region.

Figure 3. Fluoroquinolone resistance and ESBL+ rate for *E. coli* in hospital-associated (HA), community-associated (CA) infections, and overall, 2005-2010.



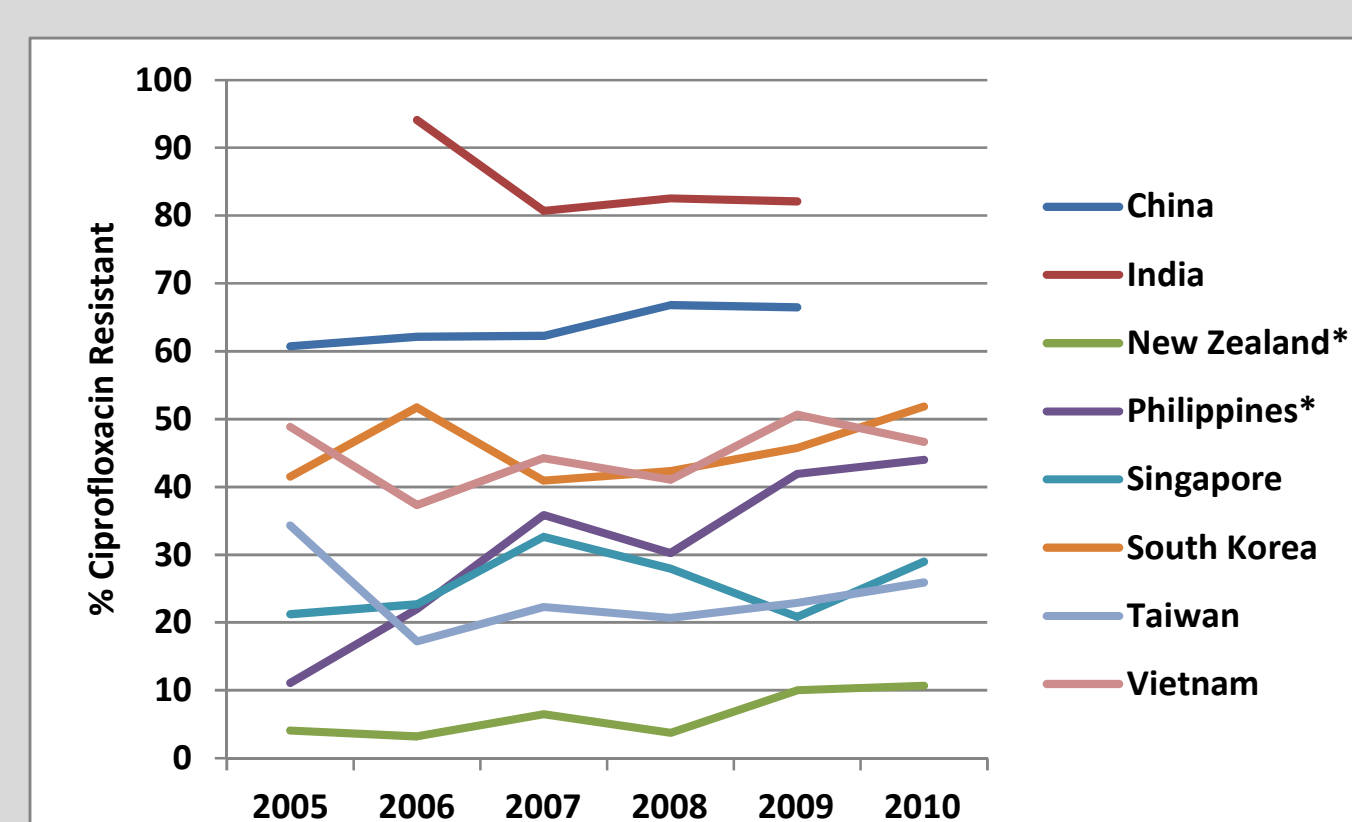
*Chi square test for independence done on all *E. coli* (i.e., not HA or CA individually) shows a significant association between levofloxacin/ciprofloxacin resistance and ESBL+ rate (p<0.0001).

Figure 4. Levofloxacin resistance trends for all *E. coli* by country, Asia/Pacific 2005-2010.



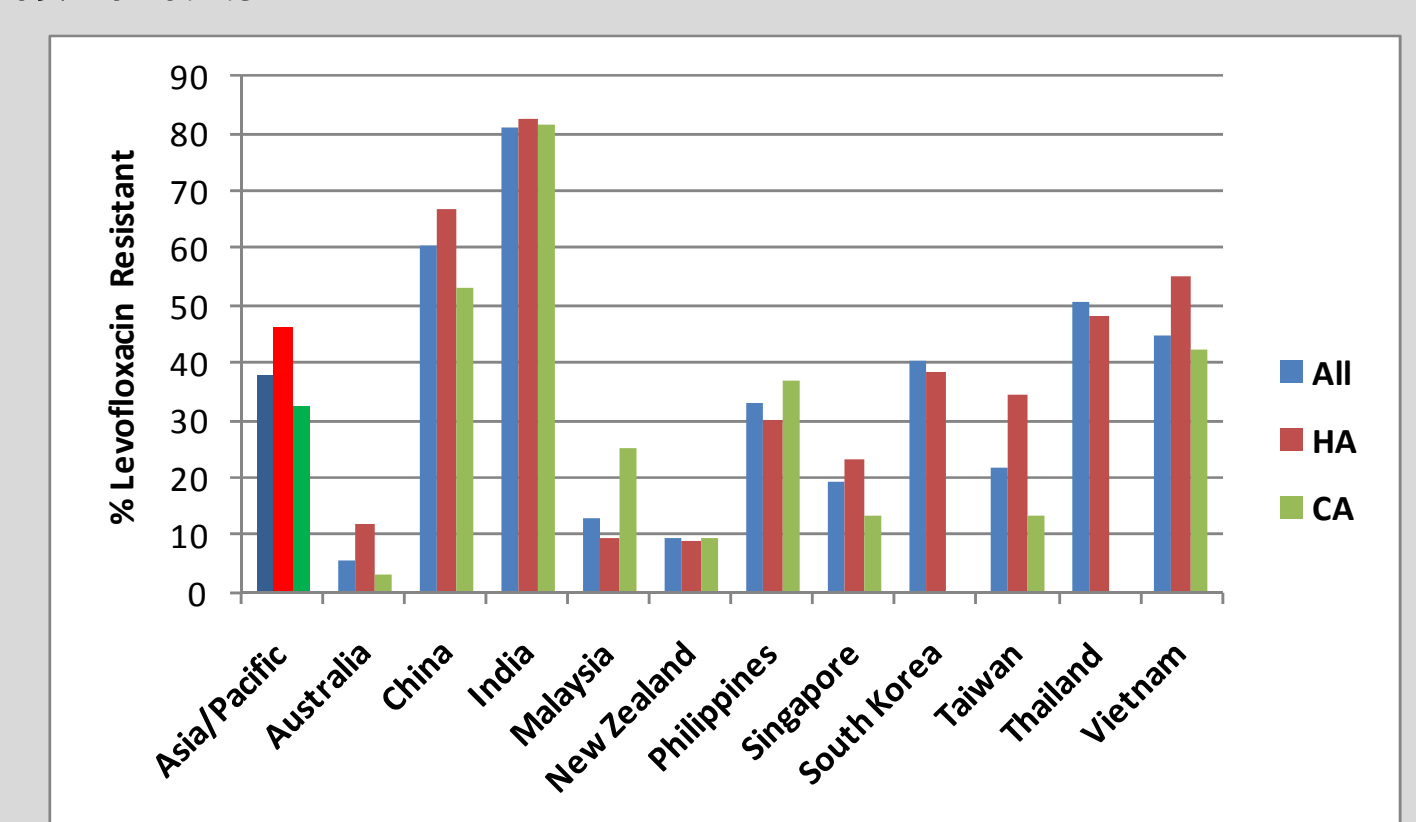
* p for trend < 0.05.
Only countries with data from contiguous years were included in this analysis.
n by year: China 186/222/331/304/346/-, India -/17/331/327/346/-, New Zealand 49/94/92/133/140/140, Philippines 36/50/53/43/74/75, Singapore 33/66/49/75/96/69, South Korea 33/66/49/75/96/69, South Korea 53/87/44/26/35/27, Taiwan 67/186/260/232/240/247, Vietnam 43/67/122/56/148/208.

Figure 5. Ciprofloxacin resistance trends for all *E. coli* by country, Asia/Pacific 2005-2010.



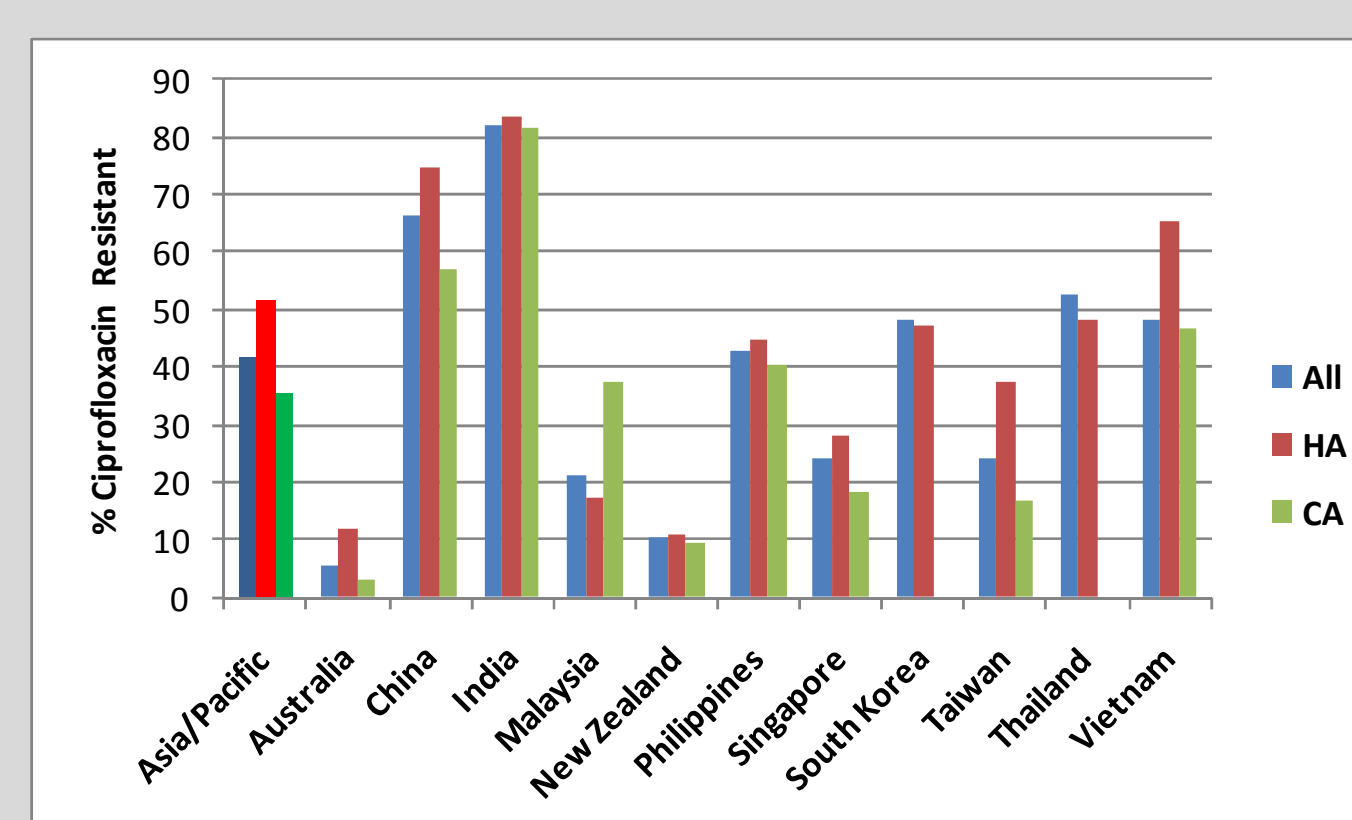
* p for trend < 0.05.
Only countries with data from contiguous years were included in this analysis.
n by year: China 186/222/331/304/346/-, India -/17/331/327/346/-, New Zealand 49/94/92/133/140/140, Philippines 36/50/53/43/74/75, Singapore 33/66/49/75/96/69, South Korea 33/66/49/75/96/69, South Korea 53/87/44/26/35/27, Taiwan 67/186/260/232/240/247, Vietnam 43/67/122/56/148/208.

Figure 6. Current levofloxacin resistance levels for *E. coli* in hospital-associated (HA) and community-associated (CA) infections by country, 2009/2010.4.54



n (All/HA/CA): Asia/Pacific 2559/977/828, Australia 121/34/31, China (only 2009) 346/188/156, India (only 2009) 346/215/70, Malaysia 109/86/16, New Zealand 280/65/73, Philippines 149/87/62, Singapore 165/99/66, South Korea 62/34/1, Taiwan 487/101/213, Thailand 61/25/-, Vietnam 356/29/118.

Figure 7. Current ciprofloxacin resistance levels for *E. coli* in hospital-associated (HA) and community-associated (CA) infections by country, 2009/2010.



n (All/HA/CA): Asia/Pacific 2559/977/828, Australia 121/34/31, China (only 2009) 346/188/156, India (only 2009) 346/215/70, Malaysia 109/86/16, New Zealand 280/65/73, Philippines 149/87/62, Singapore 165/99/66, South Korea 62/34/1, Taiwan 487/101/213, Thailand 61/25/-, Vietnam 356/29/118.

Conclusions

- After increasing in earlier years, FQ resistance rates in *E. coli* seem to have leveled off at about 45-50%. Nevertheless, the trend of increasing resistance between 2005 and 2009 is significant for both levofloxacin and ciprofloxacin for all *E. coli* and for community-associated *E. coli* infections in the Asia/Pacific region (p<0.05). A statistically significant trend of increasing resistance can also be found in China (levofloxacin only) and New Zealand and the Philippines (both FQs).
- The levofloxacin resistance rate in hospital-associated infection was 24% higher than that in community-associated infection in 2005, but by 2009 the gap had narrowed to 14%. Higher FQ resistance rates in hospital-associated infections are associated with a higher ESBL+ rate (p<0.05).
- FQ resistance rates in 2009/2010 vary by country, with the highest rates still in India and China, and the lowest in Australia and New Zealand.
- Since 40-50% of *E. coli* from IAI in Asia/Pacific are resistant to levofloxacin and ciprofloxacin, the utility of these drugs in *E. coli*-associated IAI in many countries of this region appears to be limited, especially in China, India, Vietnam, South Korea, the Philippines, and Thailand; less so in Australia and New Zealand.