A 10 year surveillance for antimicrobial susceptibility of *Escherichia coli* and *Klebsiella pneumoniae* in community- and hospital-associated intra-abdominal infections in China

Qiwen Yang,[1] Hui Zhang,[1] Yao Wang,[1] Yingchun Xu,[1] Minjun Chen,[1] Robert E. Badal,[2] Hui Wang,[3] Yuxing Ni,[4] Yunsong Yu,[5] Bijie Hu,[6] Ziyong Sun,[7] Wenxiang Huang,[8] Yong Wang,[9] Anhua Wu,[10] Xianju Feng,[11] Kang Liao,[12] Dingxia Shen,[13] Zhidong Hu,[14] Yunzhuo Chu,[15] Juan Lu,[16] Bin Cao,[17] Jianrong Su,[18] Bingdong Gui,[19] Qiong Duan,[20] Shufang Zhang,[21] Haifeng Shao,[22] Haishen Kong,[23] Yunjian Hu[24] and Huifen Ye[25]

Correspondence
Yingchun Xu
xycpumch@yahoo.com.cn

[1]Department of Clinical Laboratory, Peking Union Medical College Hospital, Peking Union Medical College, Chinese Academy of Medical Sciences, Beijing 100730, China

[2]International Health Management Associates, Inc., Schaumburg, Illinois 60173-3817, USA

[3]People's Hospital of Peking University, Beijing 100044, China

[4]Ruijin Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai 200025, China

[5]Sir RunRun Shaw Hospital, School of Medicine, Zhejiang University, Hangzhou 310016, China

[6]Zhong Shan Hospital of Fu Dan University, Shanghai 200032, China

[7]Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, China

[8]First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, China

[9]Shandong Provincial Hospital, Jinan 250021, China

[10]Xiangya Hospital, Central Southern University, Changsha 410008, China

[11]First Affiliated Hospital of Zhengzhou University, Zhenzhou 450052, China

[12]First Affiliated Hospital, Sun Yat-Sen University, Guangzhou 510080, China

[13]General Hospital of PLA, Beijing 100853, China

[14]General Hospital of Tianjin Medical University, Tianjing 300052, China

[15]First Affiliated Hospital of Chinese Medical University, Shenyang 110001, China

[16]First Affiliated Hospital of Harbin Medical University, Harbin 150001, China

[17]Chaoyang Hospital of Capital Medical College, Beijing 100020, China

[18]Friendship Hospital of Capital Medical College, Beijing 100020, China

[19]Second Affiliated Hospital of Nanchang University, Nanchang 330006, China

[20]People's Hospital of Jilin Province, Jilin 130021, China

[21]People's Hospital of Haikou City, Haikou 570208, China

[22]General Hospital of Nanjing Military Command, Nanjing 210002, China

[23]First Affiliated Hospital of Zhejiang University, Hangzhou 310003, China

[24]Beijing Hospital, Beijing 100730, China

[25]Guangzhou First Municipal People's Hospital, Guangzhou 510180, China

Abbreviations: ATCC, American Type Culture Collection; CA, community-associated; CLSI, Clinical and Laboratory Standards Institute; ESBL, extended-spectrum beta-lactamase; HA, hospital-associated; IAI, intra-abdominal infection; MIC, minimal inhibitory concentration; QC, quality control; SMART, The Study for Monitoring Antimicrobial Resistance Trends.

The objective of this study was to investigate the susceptibility of hospital-associated (HA) and community-associated (CA) *Escherichia coli* and *Klebsiella pneumoniae* isolated from patients with intra-abdominal infections (IAIs) in China. From 2002 to 2011, the minimum inhibitory concentrations (MICs) of 12 antibiotics against 3074 *E. coli* and 1025 *K. pneumoniae* from 23 centres located in 16 cities were determined by the broth microdilution method. During the 10 year study period, ertapenem, imipenem, amikacin and piperacillin-tazobactam retained high and stable activity against *E. coli* and *K. pneumoniae* isolates regardless of whether their source was HA or CA and regardless of their extended-spectrum beta-lactamase (ESBL) production. However, the susceptibility of *E. coli* to cephalosporins and ampicillin-sulbactam decreased dramatically during the 10 years, especially for the CA isolates. Fluoroquinolones showed low activity against *E. coli*. During the whole study period, the ESBL rates for *E. coli* isolates from IAIs increased from 36.1 % in 2002–2003 to 68.1 % in 2010–2011 ($P<0.001$). Correspondingly, the ESBL rates in HA isolates increased from 52.2 % in 2002–2003 to 70.0 % in 2010–2011 ($P=0.001$), and in CA isolates from 19.1 % in 2002–2003 to 61.6 % in 2010–2011 ($P<0.001$). The ESBL-positive rate in *K. pneumoniae* remained between 30.1 and 39.3 % of the total isolates with no significant change during the 10 years. In conclusion, carbapenems retained the highest susceptibility rates against HA and CA *E. coli* and *K. pneumoniae*. High prevalence of ESBL in HA *E. coli* and fast-growing resistance in CA *E. coli* severely limit the empirical use of the third- and fourth-generation cephalosporins in the therapy of IAIs.

Received 28 February 2013
Accepted 4 June 2013

INTRODUCTION

A number of surveillance programmes exist to monitor the susceptibility of clinically important pathogens on a national or international scale. The Study for Monitoring Antimicrobial Resistance Trends (SMART) is a global surveillance programme initiated in 2002 and designed to monitor the susceptibility of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections (IAIs). *E. coli* and *K. pneumoniae* are the most common pathogens causing community-associated (CA) and hospital-associated (HA) IAIs. Although there have been other reports from the SMART programme describing susceptibility levels observed globally (Baquero *et al.*, 2009; Hawser *et al.*, 2009a; Hoban *et al.*, 2010; Ko & Hseuh, 2009; Rossi *et al.*, 2006), this report is the first to provide an overview specifically of the antimicrobial susceptibility of CA and HA *E. coli* and *K. pneumoniae* in China from 2002 to 2011.

METHODS

Clinical isolates. Over the study period (2002–2011), a total of 3074 *E. coli* and 1025 *K. pneumoniae* were isolated consecutively from IAIs from 23 centres located in 16 cities (Beijing, Shanghai, Hangzhou, Wuhan, Guangzhou, Chongqing, Changchun, Changsha, Harbin, Haikou, Jinan, Nanchang, Nanjing, Shenyang, Tianjin and Zhengzhou) in China. Isolates were cultured from intra-abdominal body sites. The majority of intra-abdominal specimens were obtained during surgery, though some paracentesis specimens were also accepted. By protocol, duplicate isolates (the same genus and species from the same patient) were excluded. Isolates obtained from abdominal drains or drainage bottles, stool, superficial wounds, blood, urine, or perirectal abscesses were excluded. Bacteria were identified by standard methods used in the participating clinical microbiology laboratories. All organisms were deemed clinically significant by local participant criteria. Isolates were considered to be CA if they were recovered from a specimen taken less than 48 h after the patient was admitted to the hospital, or HA if the specimen was taken 48 or more hours after hospital admission, as described previously (Hawser *et al.*, 2009b).

Antimicrobial susceptibility test method. Minimum inhibitory concentrations (MICs) were determined using custom dehydrated MicroScan broth microdilution (Siemens Medical Solutions Diagnostics) by following Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2012). Susceptibility interpretations were based on CLSI clinical breakpoints (CLSI, 2013). Twelve antimicrobial agents commonly used to treat IAIs were tested although some of them were not tested over the whole study period because of the changes in protocols, which included cefotaxime (2005–2011), ampicillin-sulbactam (2002, 2005–2011) and levofloxacin (2003–2011). Reference strains *E. coli* ATCC (American Type Culture Collection) 25922, *Pseudomonas aeruginosa* ATCC 27853 and *K. pneumoniae* ATCC 700603 (positive ESBL control) were used as quality control (QC) strains for each batch of MIC tests. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI guidelines.

Extended-spectrum β-lactamases (ESBLs) detection. Phenotypic identification of ESBL production among *E. coli* and *K. pneumoniae* was detected by the method recommended by CLSI (CLSI, 2013). If the cefotaxime or ceftazidime MIC was $\geqslant 2$ μg ml^{-1}, then the MIC of cefotaxime or ceftazidime was compared to the MIC of cefotaxime + clavulanic acid (4 μg ml^{-1}) or ceftazidime + clavulanic acid (4 μg ml^{-1}). A positive test for ESBL production was defined as a $\geqslant$ eightfold (i.e. three doubling dilution) decrease in the MIC for cefotaxime or ceftazidime when tested in combination with clavulanic acid versus their MICs when either drug was tested alone.

Statistical analysis. The study period (2002–2011) was segmented into five 2-year periods. Statistical methods were used to compare the susceptibility rates of CA and HA isolates to different antimicrobial

agents. Fisher's exact test (two tailed) and the Pearson chi-squared test (two tailed) were used to determine significance. A *P*-value of <0.05 was considered to represent statistical significance.

RESULTS

In vitro susceptibility of HA and CA *E. coli* isolates

Against HA *E. coli* isolates from IAIs, ertapenem, imipenem, amikacin and piperacillin-tazobactam retained the highest and most stable activity, with susceptibility rates of 94.9–98.7 %, 98.6–100 %, 87.6–93.1 % and 89.3–92.2 %, respectively. Cefoxitin showed moderate activity against this species and showed little difference in susceptibility rates among years (69.2–76.2 %). For the third- and fourth-generation cephalosporins, dramatic decreases were found in the susceptibility rates, with susceptibility rates of most of the tested cephalosporins decreasing by 20 % during the 10 year study period (cefepime: from 55.1 % in 2002–2003 to 34.7 % in 2010–2011; ceftazidime: from 77.5 % to 54.3 %; ceftriaxone: from 48.6 % to 26.7 %; cefotaxime was not tested in 2002–2004, however, the susceptibility rate was only 26.9 % in 2010–2011). Two tested fluoroquinolones (ciprofloxacin 2002–2011, levofloxacin 2005–2011) exhibited stable but low activity, with susceptibility rates of 20.4–30.4 % during the 10 years. Ampicillin-sulbactam was the least active antimicrobial agent against *E. coli* isolates.

Against CA *E. coli* isolates, ertapenem, imipenem, amikacin and piperacillin-tazobactam also retained the highest and most stable activity, and the susceptibility rates of these four antimicrobial agents showed no significant differences when compared to those of HA *E. coli* isolates except for some occasional study periods (Table 1). The susceptibility rates of CA isolates to other antimicrobial agents were mostly higher than those of HA isolates ($P<0.05$). Cefoxitin susceptibility rates were 73.9–89.6 %. The susceptibility rates of CA isolates to the cephalosporins exhibited greater decreases than those of HA isolates during the 10 year study period (cefepime: from 85.5 % in 2002–2003 to 46.1 % in 2010–2011; ceftazidime: from 92.4 % to 63.9 %; ceftriaxone: from 80.9 % to 37.1 %; cefotaxime was not tested in 2002, however, the susceptibility rate was 36.5 % in 2010–2011).

In vitro susceptibility of HA and CA *K. pneumoniae* isolates

Against HA *K. pneumoniae* isolates from IAIs, ertapenem, imipenem, amikacin and piperacillin-tazobactam retained the highest and most stable activity, with susceptibility rates of 90.1–96.5 %, 94.2–100 %, 81.0–94.4 % and 75.0–89.0 %, respectively. Cefoxitin susceptibility rates were 68.0–81.3 %. For the third- and fourth-generation cephalosporins, the susceptibility rates ranged from 43.8 % to 75.4 % (cefepime, 52.1–71.9 %; ceftazidime, 64.5–75.4 %; cefotaxime, 44.4–59.8 % and ceftriaxone, 43.8–64.9 %), while only the isolates from 2004–2005 had relatively lower susceptibility. Ciprofloxacin and levofloxacin showed stable and higher activity against *K. pneumoniae* than against *E. coli*, with susceptibility rates of 59.5–75.0 % during the 10 years. Ampicillin-sulbactam was the least active antimicrobial agent against *K. pneumoniae* isolates.

Against CA *K. pneumoniae* isolates, ertapenem, imipenem, amikacin and piperacillin-tazobactam also retained the highest and most stable activity. Cefoxitin susceptibility rates were 77.0–92.7 %. Ciprofloxacin and levofloxacin showed moderate activity with susceptibility rates of 62.2–83.7 % and 70.3–90.7 %, respectively. During most of the study period (except 2006–2007), the susceptibility rates of CA *K. pneumoniae* isolates to ertapenem, imipenem, amikacin, piperacillin-tazobactam, cefoxitin, ciprofloxacin and levofloxacin showed no significant differences compared to those of HA *K. pneumoniae* ($P>0.05$) (Table 1). In contrast, the susceptibility rates of CA isolates to cephalosporins and ampicillin-sulbactam were always higher than those of HA isolates during most of the periods ($P<0.05$).

ESBL production in HA and CA *E. coli* and *K. pneumoniae*

During the 10 year study period, the ESBL-positive rates for *E. coli* from IAIs nearly doubled from 36.1 % in 2002–2003 to 68.1 % in 2010–2011 ($P<0.001$). While the ESBL-positive rates increased from 52.2 % in 2002–2003 to 70.0 % in 2010–2011 in HA isolates ($P=0.001$), and rates among CA isolates more than tripled from 19.1 % in 2002–2003 to 61.6 % in 2010–2011 in CA isolates ($P<0.001$) (Fig. 1).

Trends in ESBL prevalence in *K. pneumoniae* were quite different from *E. coli*. The ESBL-positive rate remained at 30.1–39.3 % of the total isolates during the 10 years with no significant difference. Even though there was some fluctuation in the ESBL rates during the periods for HA and CA isolates, differences were not statistically significant (Fig. 2).

DISCUSSION

IAIs are commonly encountered in clinical practice. These infections include a variety of conditions including peritonitis, appendicitis, intra-abdominal abscesses, and intra-hepatic infection (Guembe *et al.*, 2008). Although many species of pathogens are known to cause IAIs, *E. coli* and *K. pneumoniae* have been reported to be the most common causative agents (Nicoletti *et al.*, 2009). Thus, the development of antibiotic resistance among these two species, especially strains that produce ESBL, severely limits the choices of appropriate empirical antibiotics. ESBLs have been widely reported among HA *Enterobacteriaceae*. However, some recent studies showed that this resistance determinant has also been found in CA isolates (Dias *et al.*, 2012; Park *et al.*, 2012). Because *E. coli* and *K. pneumoniae*

Table 1. Susceptibility rates of *E. coli* and *K. pneumoniae* isolates from IAIs by isolate source (HA versus CA) in 2002–2011 in China

Organism/Drug	2002–2003			2004–2005			2006–2007			2008–2009			2010–2011		
	HA	CA	*P*-value	HA	CA	*P*-value	HA	CA	*P*-value	HA	CA	*P*-value	HA	CA	*P*-value
E. coli	(***n*=138**)	(***n*=131**)		(***n*=167**)	(***n*=125**)		(***n*=354**)	(***n*=218**)		(***n*=366**)	(***n*=188**)		(***n*=1077**)	(***n*=310**)	
Ertapenem	94.9	100.0	**0.015**	97.6	100.0	0.138	96.1	99.1	**0.036**	96.2	96.3	1.000	98.7	99.7	0.213
Imipenem	100.0	100.0	1.000	99.4	99.2	1.000	98.6	99.5	0.415	98.6	98.4	1.000	99.6	100.0	0.581
Amikacin	90.6	93.1	0.509	89.8	95.2	0.124	87.6	95.0	**0.003**	89.3	88.3	0.775	93.1	94.2	0.605
Piperacillin-tazobactam	91.3	98.5	**0.011**	92.2	96.0	0.224	89.3	96.3	**0.002**	92.1	93.1	0.737	90.3	95.2	**0.006**
Cefoxitin	70.3	84.0	**0.009**	71.3	89.6	**0.000**	69.2	86.2	**0.000**	76.2	73.9	0.602	71.7	82.3	**0.000**
Ciprofloxacin	29.7	56.5	**0.000**	20.4	43.2	**0.000**	21.2	47.7	**0.000**	23.0	31.4	**0.040**	26.6	32.6	**0.044**
Levofloxacin	ND	ND	ND	23.4	45.6	**0.000**	23.7	52.3	**0.000**	25.4	33.0	0.072	30.4	36.8	**0.038**
Cefepime	55.1	85.5	**0.000**	43.1	88.8	**0.000**	38.7	70.6	**0.000**	33.3	51.6	**0.000**	34.7	46.1	**0.000**
Ceftazidime	77.5	92.4	**0.001**	69.5	88.8	**0.000**	60.7	87.6	**0.000**	51.6	65.4	**0.002**	54.3	63.9	**0.003**
Cefotaxime	ND	ND	ND	25.9	88.3	**0.000**	29.7	66.1	**0.000**	28.1	44.2	**0.000**	26.9	36.5	**0.001**
Ceftriaxone	48.6	80.9	**0.000**	32.9	81.6	**0.000**	28.8	65.1	**0.000**	27.6	44.7	**0.000**	26.7	37.1	**0.000**
Ampicillin-sulbactam	23.3	61.5	**0.000**	11.8	45.0	**0.000**	14.7	38.5	**0.000**	12.6	27.1	**0.000**	14.5	20.7	**0.010**
K. pneumoniae	(*n*=57)	(*n*=56)		(*n*=48)	(*n*=41)		(*n*=97)	(*n*=86)		(*n*=121)	(*n*=74)		(*n*=373)	(*n*=72)	
Ertapenem	96.5	98.2	1.000	95.8	100.0	0.497	91.8	100.0	**0.007**	90.1	89.2	0.814	95.4	100.0	0.088
Imipenem	100.0	100.0	1.000	97.9	100.0	1.000	99.0	100.0	1.000	94.2	89.2	0.268	96.5	100.0	0.141
Amikacin	87.7	98.2	0.061	83.3	95.1	0.100	85.6	98.8	**0.001**	81.0	85.1	0.561	94.4	100.0	**0.033**
Piperacillin-tazobactam	87.7	94.6	0.321	75.0	95.1	**0.017**	76.3	94.2	**0.001**	80.2	82.4	0.851	89.0	93.1	0.399
Cefoxitin	79.0	82.1	0.813	81.3	92.7	0.134	68.0	86.1	**0.005**	72.7	77.0	0.613	81.2	91.7	**0.039**
Ciprofloxacin	61.4	76.8	0.104	68.8	78.1	0.349	59.8	83.7	**0.001**	59.5	62.2	0.764	70.2	77.8	0.254
Levofloxacin	ND	ND	ND	75.0	80.5	0.615	67.0	90.7	**0.000**	62.0	70.3	0.279	74.8	80.6	0.368
Cefepime	71.9	92.9	**0.006**	52.1	90.2	**0.000**	66.0	90.7	**0.000**	66.9	67.6	1.000	69.7	81.9	**0.045**
Ceftazidime	75.4	92.9	**0.019**	64.6	90.2	**0.006**	70.1	91.9	**0.000**	64.5	73.0	0.270	75.1	88.9	**0.009**
Cefotaxime	ND	ND	ND	44.4	91.7	**0.000**	50.5	84.9	**0.000**	57.9	62.2	0.652	59.8	80.6	**0.001**
Ceftriaxone	64.9	82.1	0.055	43.8	85.4	**0.000**	49.5	83.7	**0.000**	58.7	62.2	0.654	58.7	76.4	**0.005**
Ampicillin-sulbactam	68.0	72.0	0.838	27.8	75.0	**0.000**	39.2	72.1	**0.000**	47.9	54.1	0.461	47.5	73.6	**0.000**

ND, Not determined.

P-values <0.05 are shown in bold.

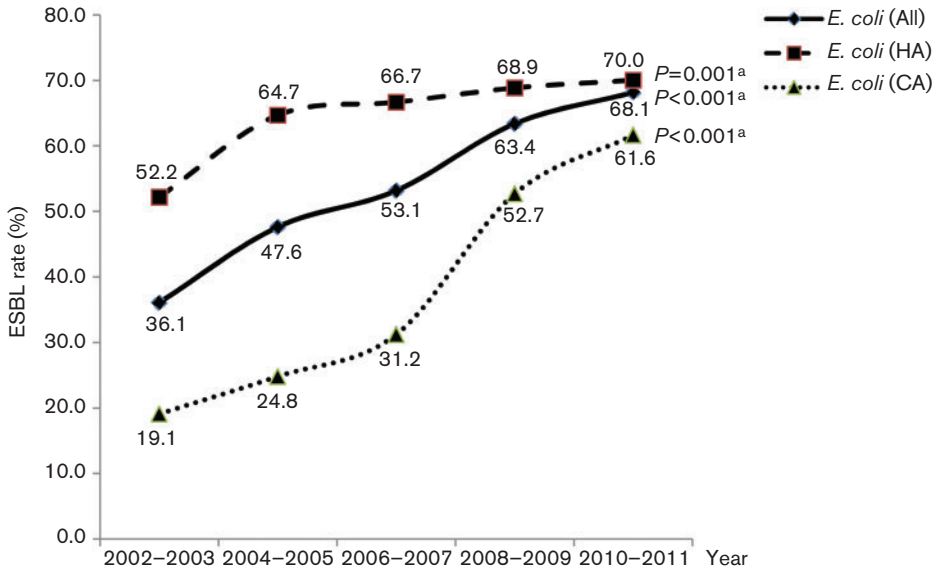

Fig. 1. Occurrence of ESBL-producing *E. coli* (%) in 2002–2011 from IAIs in China. ESBL rate (%) is compared by using Fisher's exact test (two tailed).

comprise the major aerobic and facultative anaerobic pathogens associated with IAIs, knowledge of their resistance patterns and ESBL prevalence in HA and CA settings is critical.

ESBL production is the predominant resistance determinant of *E. coli* and *K. pneumoniae* to cephalosporins. In this study, the susceptibility rates of HA *E. coli* strains to all tested third- and fourth-generation cephalosporins declined by more than 20 % over the 10 year study period, with susceptibility of 26.7 %, 26.9 %, 54.3 % and 34.7 % for ceftriaxone, cefotaxime, ceftazidime and cefepime, respectively, in 2010–2011. Against CA *E. coli*, the susceptibility to cephalosporins decreased even more severely, with drops of 28.5–43.8 % in susceptibility rates during the 10 years. These results indicate that the third- and fourth-generation cephalosporins should no longer be considered first line choices for the empirical therapy of IAIs in China, even for CA settings. We also found that no statistically significant

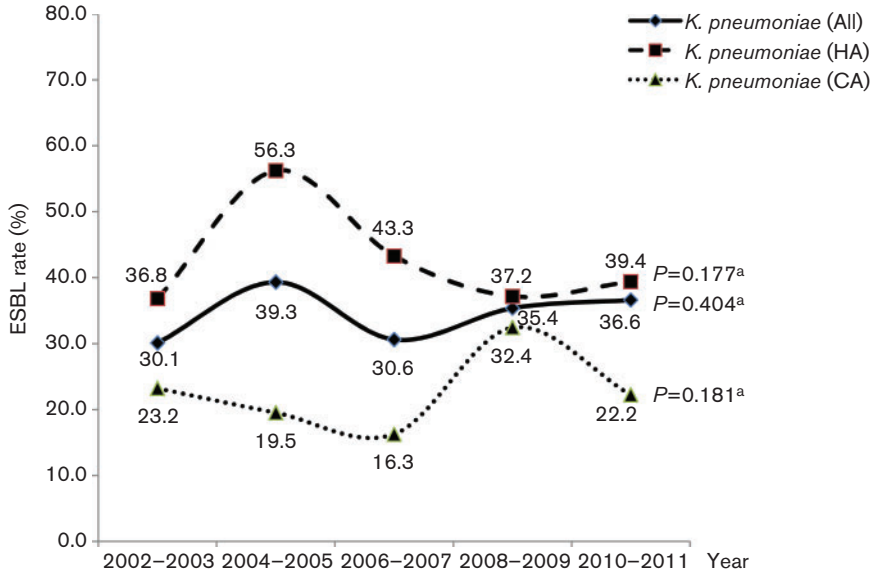

Fig. 2. Occurrence of ESBL-producing *K. pneumoniae* (%) in 2002–2011 from IAIs in China. ESBL rate (%) is compared by using Fisher's exact test (two tailed).

difference was seen for the ESBL rates in HA *E. coli* during the years after 2003 ($P>0.05$), which indicates that ESBL prevalence in HA *E. coli* remained stable during the years 2004–2011 (64.7–70.0 %). However, the significant differences in the ESBL rates among CA *E. coli* during the study period indicate fast-growing ESBL prevalence (19.1 % in 2002–2003 to 61.6 % in 2010–2011, an increase of over 300 %). We believe that the cephalosporin resistance development in *E. coli* overall during the years 2004–2011 was driven largely by the fast-growing ESBL prevalence in CA isolates. In contrast, the susceptibility of *K. pneumoniae* to cephalosporins was stable with no significant differences during the 10 years. In 2010–2011, the susceptibility of HA and CA *K. pneumoniae* to cefepime, ceftazidime, cefotaxime and ceftriaxone were 69.7 % (HA) and 81.9 % (CA), 75.1 % (HA) and 88.9 % (CA), 59.8 % (HA) and 80.6 % (CA) and 58.7 % (HA) and 76.4 % (CA), respectively. The relatively stable susceptibility can be explained by the mostly unchanged and relatively lower ESBL rates (compared with that of *E. coli*) among HA and CA *K. pneumoniae* (HA was 36.8 % in 2002–2003 to 39.4 % in 2010–2011; CA was 23.2 % in 2002–2003 and 22.2 % in 2010–2011). We also observed some fluctuation of ESBL rates in *K. pneumoniae* and susceptibility to some antimicrobial agents in some time periods, which may have resulted from the somewhat limited number of isolates in early stages of this study. Researchers in China have previously determined that the ESBL genotypes in Beijing, Guangdong and Hangzhou were mainly CTX-M types (Chanawong *et al.*, 2002; Wang *et al.*, 2003), which preferentially hydrolyse cefotaxime and ceftriaxone over ceftazidime. This may explain why ceftazidime always showed the highest susceptibility rates among cephalosporins against ESBL-producing *E. coli* and *K. pneumoniae*. We also noticed a decline of ceftazidime activity against ESBL-producing *E. coli* and *K. pneumoniae*. This may have resulted from increases in both ESBL prevalence and other β-lactamase types among the two species, especially SHV-type ESBLs and AmpC cephalosporinases.

Fluoroquinolone-resistant *E. coli* is a very big problem in China. The susceptibility to ciprofloxacin of HA *E. coli* decreased from 29.7 % in 2002–2003 to 26.6 % in 2010–2011($P=0.075$), and from 56.5 % in 2002–2003 to 32.6 % in 2010–2011 against CA strains ($P<0.001$). Wang *et al.* (2001) found that ciprofloxacin-resistant *E. coli* had multiple substitutions in the gyrA and parC genes. In light of the poor activity of fluoroquinolones against *E. coli*, ciprofloxacin and levofloxacin should not remain first line choices for empirical therapy of complicated IAIs. We also found that susceptibility to ciprofloxacin among ESBL-producing *E. coli* and *K. pneumoniae* was significantly lower than that of ESBL-non-producing isolates, as has been reported by other investigators (Ben-Ami *et al.*, 2009). Ben-Ami *et al.* (2009) and Pitout *et al.* (2005) reported that isolates producing CTX-M-type ESBLs were significantly more resistant to fluoroquinolones than the isolates producing other types of ESBLs. This may partly explain the dramatic development of resistance to fluoroquinolones among CA *E. coli*, given the fast-growing CTX-M type ESBL prevalence in CA *E. coli* reported in China (Sun *et al.*, 2010; Tian *et al.*, 2011).

Carbapenems have always been considered a good treatment option for severe infections and the empiric therapy alternative of choice for infections with high suspicion of being caused by ESBL-producing or AmpC-derepressed *Enterobacteriaceae* (Essack, 2000; Livermore *et al.*, 2001; Paterson, 2000). In this study, carbapenems, including ertapenem and imipenem, demonstrated high and stable activity against *E. coli* and *K. pneumoniae* isolates, regardless of ESBL production and isolate background (HA or CA). However, carbapenem-resistant *Enterobacteriaceae* have emerged. Based upon our analysis of the resistance mechanisms of ertapenem-non-susceptible isolates, nearly one-third of isolates produced carbapenemases (mainly KPC-2 and IMP-4), while two-thirds of isolates showed resistance due to loss of porins (OmpK35/36 for *K. pneumoniae* and OmpF/C for other *Enterobacteriaceae*) combined with hyper-production of ESBLs or AmpC (data not shown).

In conclusion, the SMART programme is a specific resistance surveillance study focused on IAIs. During 2002–2011, the carbapenems retained the highest activity against both HA and CA *E. coli* and *K. pneumoniae*, followed by amikacin and piperacillin-tazobactam. ESBL-positive rates showed stable and high prevalence in HA *E. coli* and a dramatic increase in CA *E. coli* during the past 10 years, which complicates the treatment of IAIs in both HA and CA settings. Dramatic decreases in the susceptibility to cephalosporins and fluoroquinolones suggest that those drugs are no longer suitable as first line choices for empirical therapy of IAIs in China.

ACKNOWLEDGEMENTS

We thank all the investigators for their participation in the SMART programme. This study was sponsored by Merck & Co., Inc., and was partially supported by grant 81101287 from the National Natural Science Foundation of China and grant 201002021 from the Research Special Fund for Public Welfare Industry of Health of China.

REFERENCES

Baquero, F., Hsueh, P. R., Paterson, D. L., Rossi, F., Bochicchio, G. V., Gallagher, G., Lantz, K., Villasenor, J. B., McCarroll, K. & other authors (2009). *In vitro* susceptibilities of aerobic and facultatively anaerobic gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: 2005 results from Study for Monitoring Antimicrobial Resistance Trends (SMART). *Surg Infect (Larchmt)* **10**, 99–104.

Ben-Ami, R., Rodríguez-Baño, J., Arslan, H., Pitout, J. D., Quentin, C., Calbo, E. S., Azap, O. K., Arpin, C., Pascual, A. & other authors (2009). A multinational survey of risk factors for infection with extended-spectrum beta-lactamase-producing *Enterobacteriaceae* in nonhospitalized patients. *Clin Infect Dis* **49**, 682–690.

Chanawong, A., M'Zali, F. H., Heritage, J., Xiong, J. H. & Hawkey, P. M. (2002). Three cefotaximases, CTX-M-9, CTX-M-13, and CTX-M-14, among *Enterobacteriaceae* in the People's Republic of China. *Antimicrob Agents Chemother* **46**, 630–637.

CLSI (2012). *Method for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically*; Approved Standard, 9th edn, M7-A9. Wayne, PA: Clinical and Laboratory Standards Institute.

CLSI (2013). *Performance Standards for Antimicrobial Susceptibility Testing.* 23rd Informational Supplement M100-S23. Wayne, PA: Clinical and Laboratory Standards Institute.

Dias, V. C., da Silva, V. L., Firmo, E. O., Bastos, L. Q., Bastos, A. N., Bastos, R. V. & Diniz, C. G. (2012). Distribution of ESBL-producing enterobacteria associated to community-acquired monomicrobial urinary tract infections and antimicrobial susceptibility trends over a 9-year period. *J Chemother* **24**, 178–181.

Essack, S. Y. (2000). Treatment options for extended-spectrum beta-lactamase-producers. *FEMS Microbiol Lett* **190**, 181–184.

Guembe, M., Cercenado, E., Alcalá, L., Marín, M., Insa, R. & Bouza, E. (2008). Evolution of antimicrobial susceptibility patterns of aerobic and facultative Gram-negative bacilli causing intra-abdominal infections: results from the SMART studies 2003-2007. *Rev Esp Quimioter* **21**, 166–173.

Hawser, S. P., Bouchillon, S. K., Hoban, D. J. & Badal, R. E. (2009a). *In vitro* susceptibilities of aerobic and facultative anaerobic Gram-negative bacilli from patients with intra-abdominal infections worldwide from 2005-2007: results from the SMART study. *Int J Antimicrob Agents* **34**, 585–588.

Hawser, S. P., Bouchillon, S. K., Hoban, D. J., Badal, R. E., Hsueh, P. R. & Paterson, D. L. (2009b). Emergence of high levels of extended-spectrum-β-lactamase-producing Gram-negative bacilli in the Asia-Pacific region: data from the Study for Monitoring Antimicrobial Resistance Trends (SMART) program, 2007. *Antimicrob Agents Chemother* **53**, 3280–3284.

Hoban, D. J., Bouchillon, S. K., Hawser, S. P. & Badal, R. E. (2010). Trends in the frequency of multiple drug-resistant *Enterobacteriaceae* and their susceptibility to ertapenem, imipenem, and other antimicrobial agents: data from the Study for Monitoring Antimicrobial Resistance Trends 2002 to 2007. *Diagn Microbiol Infect Dis* **66**, 78–86.

Ko, W. C. & Hsueh, P. R. (2009). Increasing extended-spectrum β-lactamase production and quinolone resistance among Gram-negative bacilli causing intra-abdominal infections in the Asia/Pacific region: data from the SMART Study 2002-2006. *J Infect* **59**, 95–103.

Livermore, D. M., Oakton, K. J., Carter, M. W. & Warner, M. (2001). Activity of ertapenem (MK-0826) versus *Enterobacteriaceae* with potent beta-lactamases. *Antimicrob Agents Chemother* **45**, 2831–2837.

Nicoletti, G., Nicolosi, D., Rossolini, G. M. & Stefani, S. (2009). Intra-abdominal infections: etiology, epidemiology, microbiological diagnosis and antibiotic resistance. *J Chemother* **21** (Suppl 1), 5–11.

Park, S. H., Byun, J. H., Choi, S. M., Lee, D. G., Kim, S. H., Kwon, J. C., Park, C., Choi, J. H. & Yoo, J. H. (2012). Molecular epidemiology of extended-spectrum β-lactamase-producing *Escherichia coli* in the community and hospital in Korea: emergence of ST131 producing CTX-M-15. *BMC Infect Dis* **12**, 149.

Paterson, D. L. (2000). Recommendation for treatment of severe infections caused by Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs). *Clin Microbiol Infect* **6**, 460–463.

Pitout, J. D., Nordmann, P., Laupland, K. B. & Poirel, L. (2005). Emergence of *Enterobacteriaceae* producing extended-spectrum beta-lactamases (ESBLs) in the community. *J Antimicrob Chemother* **56**, 52–59.

Rossi, F., Baquero, F., Hsueh, P. R., Paterson, D. L., Bochicchio, G. V., Snyder, T. A., Satishchandran, V., McCarroll, K., DiNubile, M. J. & Chow, J. W. (2006). *In vitro* susceptibilities of aerobic and facultatively anaerobic Gram-negative bacilli isolated from patients with intra-abdominal infections worldwide: 2004 results from SMART (Study for Monitoring Antimicrobial Resistance Trends). *J Antimicrob Chemother* **58**, 205–210.

Sun, Y., Zeng, Z., Chen, S., Ma, J., He, L., Liu, Y., Deng, Y., Lei, T., Zhao, J. & Liu, J. H. (2010). High prevalence of $bla_{\text{CTX-M}}$ extended-spectrum β-lactamase genes in *Escherichia coli* isolates from pets and emergence of CTX-M-64 in China. *Clin Microbiol Infect* **16**, 1475–1481.

Tian, S. F., Chu, Y. Z., Chen, B. Y., Nian, H. & Shang, H. (2011). ISEcp1 element in association with $bla_{\text{CTX-M}}$ genes of E. coli that produce extended-spectrum β-lactamase among the elderly in community settings. *Enferm Infecc Microbiol Clin* **29**, 731–734.

Wang, H., Dzink-Fox, J. L., Chen, M. & Levy, S. B. (2001). Genetic characterization of highly fluoroquinolone-resistant clinical *Escherichia coli* strains from China: role of *acrR* mutations. *Antimicrob Agents Chemother* **45**, 1515–1521.

Wang, H., Kelkar, S., Wu, W., Chen, M. & Quinn, J. P. (2003). Clinical isolates of *Enterobacteriaceae* producing extended-spectrum beta-lactamases: prevalence of CTX-M-3 at a hospital in China. *Antimicrob Agents Chemother* **47**, 790–793.