International Journal of Antimicrobial Agents 40 (2012) 389–397

Contents lists available at SciVerse ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: http://www.elsevier.com/locate/ijantimicag

Review

Antibiotic resistance amongst healthcare-associated pathogens in China

Saber Yezli[a,*], Han Li[b]

[a] Bioquell (UK) Ltd., 52 Royce Close, West Portway, Andover, Hampshire SP10 3RX, UK
[b] Institute for Disease Control & Prevention, Academy of Military Medical Sciences (AMMS), Beijing, China

ARTICLE INFO

Keywords:
Mycobacterium tuberculosis
Gram-positive organisms
Gram-negative organisms
Multidrug-resistant
China

ABSTRACT

The People's Republic of China, commonly known as China, comprises approximately one-fifth of the world's population. Because of the expanding size and density of its population and the frequent interaction of people with animals, China is a hotspot for the emergence and spread of new microbial threats and is a major contributor to the worldwide infectious disease burden. In recent years, the emergence and rapid spread of severe acute respiratory syndrome (SARS) generated considerable interest in the Chinese healthcare system and its infection control and prevention measures. This review examines antibiotic misuse and the status of antibiotic resistance in the Chinese healthcare system. China has high rates of antibiotic resistance driven by misuse of these agents in a healthcare system that provides strong incentives for overprescribing and in a country where self-medication is common. Tuberculosis remains a serious problem in China, with a high prevalence of multidrug-resistant and extensively drug-resistant strains. Drug resistance amongst nosocomial bacteria has been on a rapid upward trend with a strong inclination towards multidrug resistance. There is a need for effective infection prevention and control measures and strict use of antibiotics in China to control the rise and spread of antibiotic resistance in the country.

1. Introduction

The People's Republic of China, commonly known as China, is the largest country in East Asia and the most populous in the world with over 1.3 billion people, approximately one-fifth of the world's population. Since its establishment, China has seen an increase in life expectancy coupled with a decrease in infant mortality [1,2]. A significant reduction in rates of infectious diseases is thought to have been a major contributing factor [3–5]. However, because of the expanding size and density of its population, the increase in economic migration and the frequent interaction of people with animals, China is a major contributor to the worldwide infectious disease burden and is a hotspot for the spread of infectious diseases and the emergence of new microbial threats [4,6–8], e.g. the 2003 emergence and rapid spread of severe acute respiratory syndrome (SARS) in China and throughout the world [7,9]. The Chinese healthcare system has hence become a focus of the world's attention. Despite the Chinese government's efforts and improvements [4], the healthcare system still faces a number of challenges, including high cost restricting access to health services, increases in drug resistance amongst pathogens, and high rates of nosocomial infections driven by a poorly trained public health workforce with insufficient understanding of their role in disease control [4,10]. Relatively few studies have investigated antibiotic resistance and antibiotic misuse in China. This review will examine the status of antibiotic resistance in the Chinese healthcare system and the misuse of these agents in the country. Searches were performed in PubMed (until December 2011) using a combination of the search terms 'China', 'antibiotic', 'resistance', 'nosocomial infection' or 'surveillance'. References of relevant articles were also hand-searched. Articles were also selected from relevant peer-reviewed Chinese journals where local and national antimicrobial surveillance reports are published. We decided to focus the search to the last decade in order to review the current and recent trends in drug resistance amongst healthcare-associated pathogens in the country.

2. Antibiotic prescription and misuse in China

Widespread use and misuse of antibiotics worldwide has led to the emergence of drug-resistant bacteria [11,12] coupled with increased risk of side effects and increased treatment costs [13]. The problem is particularly acute in China because of its antibiotic prescribing practices, strong incentives for overprescribing, and over-the-counter availability of antibiotics [14,15]. Consequently, China has very high rates of antibiotic resistance [15]. Antibiotics are not only used incorrectly for susceptible bacterial infections, but also frequently for problems known not to have a bacterial

* Corresponding author. Tel.: +44 1264 835 867; fax: +44 1264 835 917.
E-mail address: saber.yezli@bioquell.com (S. Yezli).

0924-8579/$ – see front matter © 2012 Elsevier B.V. and the International Society of Chemotherapy. All rights reserved.
http://dx.doi.org/10.1016/j.ijantimicag.2012.07.009

aetiology [16]. In one report from Guizhou Province in southern China [14], coughs and diarrhoea were almost universally treated with antibiotics, whilst colds were normally treated with antivirals, antibiotics or both. Moreover, although antibiotic resistance was known by most physicians and many patients, it was not well understood, often being viewed as a property acquired by the patient and not the micro-organism. In another study [17], >98.0% of patients in the outpatient department of a Beijing children's hospital diagnosed with common cold were given antibiotics and >33% of the patients had been taking antibiotics before coming to the hospital. Economic factors also influence antibiotic prescribing in China. The heath system has strong financial incentives for drug prescription, including physicians profit-splitting with pharmaceutical suppliers and the fact that drug sales profits form a major part of a Chinese hospital's income [14].

Dong et al. [13] investigated antibiotic prescribing patterns in village health clinics in 40 counties in 10 provinces of western China. The percentage of prescriptions with antibiotics was 48.4% and as high as 57.4% in some provinces. A higher figure of 80.0% has already been reported in China [16]. These figures are much higher than those in developed countries such as the USA (15.3%) [18], Spain (32%) [19] and northern Europe (<1%) [20]. Dong et al. [13] found that prescriptions with one antibiotic comprised 40.6% of all prescriptions, whereas those with two antibiotics and with more than two antibiotics represented 7% and 0.7%, respectively, of all prescriptions. The number of antibiotics per 100 prescriptions was 54.6 and reached nearly 70 in some provinces. Moreover, because self-medication was not taken into consideration in the study, the true frequency and proportion of antibiotic use may have been underestimated [13]. In another study, Wu et al. [21] investigated antibiotic use in 151 Chinese hospitals on 1 day (7 August 2003). Over 54% of the 89 539 inpatients investigated were using antibiotics; 48.9% of these antibiotics were used for therapeutic purposes, whilst 35.4% were for prophylaxis and 15.5% were both for therapy and prophylaxis. Microbiological investigations before antibiotic prescription were rarely done, and amongst patients who were on therapeutic antibiotics only 23.9% of the samples were sent for pathogen detection [21]. Inappropriate antibiotic use not only adds to the growing antimicrobial resistance in the country but also adds to inpatient costs. Yang et al. [22] investigated antibiotic use amongst 946 cases of antibiotic treatment in 10 hospitals from five Chinese provinces. They reported that the rate of antibiotic misuse was 58.4%, adding 55% of unnecessary cost to inpatients.

3. Drug resistance amongst healthcare-associated pathogens in China

Drug resistance in China is most common with sexually transmitted diseases, including HIV/AIDS [23]. However, resistance amongst nosocomial bacteria has been on a rapid upward trend in the country. One study [15] compared the patterns of antibiotic resistance amongst bacteria of clinical relevance in China, Kuwait and the USA. It was reported that China had the highest level of antibiotic resistance and had the most rapid growth rate of resistance amongst the three countries; an average increase of 22% in 6 years (1994–2000) compared with 6% growth recorded for the USA (1999–2002).

3.1. *Mycobacterium tuberculosis*

Over the past two decades there has been an increase in the number of multidrug-resistant tuberculosis (MDR-TB) cases around the world [24]. MDR-TB is defined as a strain of *M. tuberculosis* with combined resistance to isoniazid and rifampicin [25]. Reports from the World Health Organization (WHO) rank China as having one of the world's largest number of TB cases with a high level of MDR-TB [26,27]. Based on recent national estimates, 120 000 new MDR-TB cases are diagnosed annually in China, accounting for ca. 24% of the global burden of MDR-TB [28]. One study [29] revealed that the mean prevalence of any drug resistance amongst new TB cases in 10 Chinese provinces was 24.3% and as high as 42.1% in some places. Amongst previously treated cases the mean was 51.8% and increased to 67.5% in some provinces. In a 6-year (2000–2006) surveillance on the prevalence of MDR-TB in Shanghai, of the 8419 pulmonary TB patients surveyed, 16.6% had resistance to any first-line anti-TB drug and 4% had MDR-TB [30]. Other studies showed much higher levels of MDR-TB in the country and means of 9.3–23.3% amongst all cases; 5.4–42.7% amongst new cases and 25.6–37.1% amongst previously treated cases have all been reported [29,31–35].

The emergence and spread of extensively drug-resistant (XDR)-TB in China is particularly problematic as it is difficult and expensive to treat, with a high mortality rate [36,37]. XDR-TB is defined as MDR-TB strains resistant to a fluoroquinolone and to at least one of the three injectable second-line drugs, including amikacin, kanamycin and capreomycin [38]. Sun et al. [39] characterised the first XDR-TB in China from clinical *M. tuberculosis* isolates collected from HIV-negative TB patients in a Beijing chest hospital. They also reported that 10.7% of the 1926 isolates collected were MDR-TB, and of these 6.3% (13/207) were XDR-TB. Wang et al. [40] found higher rates of MDR-TB and XDR-TB amongst *M. tuberculosis* strains isolated from patients in a Beijing hospital between 2007 and 2009. Amongst the 967 strains investigated, 19.4% were MDR-TB, and 14.9% of these were XDR-TB. Recently, the prevalence of XDR-TB amongst MDR-TB *M. tuberculosis* from the second largest province in China (Shandong) was reported to be 18.7% [41].

The TB situation in China needs particular attention. Measures should be taken to improve strategies for the prevention and control of TB transmission in the country. These include strengthening the existing TB infection control practices, improved antibiotic stewardship, and screening for latent TB infection. The latter is particularly important amongst healthcare workers (HCWs) who are at risk of TB transmission from patients, may have a high prevalence of latent TB and can become a source of active infection. He et al. [42] found the prevalence of latent TB infection amongst HCWs with and without Bacillus Calmette–Guérin (BCG) vaccine in a TB centre in Henan province in China to be 55.6% (432/777) and 49.0% (674/1376), respectively, with 20 cases of pulmonary TB detected amongst 3746 HCWs.

3.2. Gram-negative organisms

Gram-negative bacteria are amongst the most commonly isolated pathogens from nosocomial infections in China [43–47]. Studies and surveillance data report an increase in antimicrobial resistance amongst Gram-negatives (especially amongst the non-fermenting pathogens such as *Pseudomonas* and *Acinetobacter* spp.) in the country, with a tendency towards multidrug resistance and the emergence of carbapenem resistance and pan-resistance in Enterobacteriaceae, *Pseudomonas* and *Acinetobacter* spp. [48–51]. The drug resistance of 15 different species of Gram-negative bacilli isolated from 13 Chinese hospitals was investigated by Li et al. [52] for isolates both from hospital-acquired infections (HAIs) and community-acquired infections (CAIs) between 2000 and 2001. HAI isolates were more resistant to antimicrobial agents than those from CAIs, especially for *Enterobacter cloacae*, *Serratia* spp. and *Acinetobacter* spp. Resistance of *Pseudomonas aeruginosa* to fluoroquinolones increased, and >50% of *Escherichia coli* strains were found to be resistant to these agents. Another study concluded that antibiotic resistance rates for all bacteria investigated in a Chinese Intensive Care Unit (ICU) from 2002 to 2004 had been rising

Table 1
Rates of extended-spectrum β-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella* in China.

Location	Rate (%)		Study date	Reference
	E. coli	*Klebsiella*		
8 hospitals in six Chinese cities	64.9	31.9	2009	[61]
14 hospitals across China (CHINET 2009)	56.5	41.4	2009	[62]
Shanghai hospitals, China	58.9	49.6	2008	[116]
A children's hospital in Beijing, China	77.0	76.0[a]	2003–2008	[118]
12 hospitals across China (CHINET 2007)	55.0	45.0	2007	[77]
A hospital ICU in Wuhan, China	79.2	34.8	2007	[119]
Shanghai hospitals, China	58.0	53.9	2007	[100]
Shanghai hospitals, China	53.0	51.1	2006	[120]
8 hospitals across China (CHINET 2005)	38.9	39.1	2005	[98]
A hospital in Shanghai, China	47.6	69.6	2005	[121]
A hospital in Hangzhou, China	55.8	43.5[a]	2005	[122]
A hospital in Chongqing, China	37.5	31.4[a]	2004–2005	[123]
14 hospitals in Shanghai, China	36.5	45.0	2004	[124]
A hospital respiratory ICU in Guangzhou, China	–	47.8[a]	2004	[125]
A hospital ICU in Changsha, China	34.0	30.7[a]	2002–2004	[53]
A hospital surgical ICU in Guangzhou, China	66.2	58.5	2001–2004	[49]
Guangzhou hospitals, China	39.2	44.7	2003	[126]
Shanghai hospitals, China	33.6	44.2	2003	[127]
ICUs from 19 hospitals in seven Chinese central cities	45.7	34.9[a]	2002	[60]
4 hospitals in Kunming, China	37.9	36.3	2002	[128]
15 tertiary hospitals in Hubei, China	31.3	34.7	2002	[129]
ICUs from 19 hospitals in seven Chinese central cities	28.6	25.7[a]	2001	[60]

ICU, Intensive Care Unit.
[a] *Klebsiella pneumoniae*.

gradually with a strong inclination towards multidrug resistance. Gram-negative bacilli (mostly *P. aeruginosa* and *E. coli*) could resist four or more antibiotics, and the rate for resistance exceeded 40% [53].

Amongst the Gram-negatives, members of the Enterobacteriaceae family are frequently associated with nosocomial infections in Chinese hospitals [44,45,47]. These organisms may express extended-spectrum β-lactamases (ESBLs) that confer resistance to β-lactams [54]. This resistance is also commonly associated with resistance to aminoglycosides, sulfonamides and fluoroquinolones [55,56]. Until recently, carbapenems have been the treatment of choice for serious infections due to these ESBL-producers. However, carbapenem resistance has emerged in the Enterobacteriaceae family by various mechanisms and is now a major concern worldwide [57–59].

The China Nosocomial Pathogens Resistance Surveillance Study Group conducted a comprehensive 7-year study investigating antimicrobial resistance amongst Gram-negative clinical isolates from ICU patients in 19 hospitals [60]. During the study period, a decrease in the rate of susceptibility to cephalosporins, ciprofloxacin and cefoperazone/sulbactam was observed, particularly amongst *E. coli* to ciprofloxacin (from 42% to 25%) and cefotaxime (from 78% to 54%) and amongst *Enterobacter* spp. to ceftazidime (from 51% to 44%) and cefotaxime (from 50% to 37%) [60]. Another bacterial resistance surveillance study from 17 hospitals in China revealed that between 45% and 65% of *E. coli* and *Klebsiella* spp. strains were resistant to the first- and second-generation cephalosporin compounds. Resistance rates to third-generation cephalosporins, excluding ceftazidime, were in the range of 20–50%. *Escherichia coli* strains were particularly highly resistant to fluoroquinolones, with ca. 65% of strains being resistant to these drugs.

Yang et al. [61] reported antimicrobial resistance amongst Enterobacteriaceae isolated from patients with intra-abdominal infections (IAIs) in China between 2002 and 2009. They found that susceptibility rates of all tested third- and fourth-generation cephalosporins declined by nearly 30%. Increased resistance to fluoroquinolones in *E. coli* was also noted, with susceptibility to ciprofloxacin decreasing from 57.6% in 2002 to 24.2% in 2009, whilst susceptibility to levofloxacin decreased from 33.3% in 2003 to 27% in 2009. The occurrence of ESBLs increased rapidly in *E. coli* (from 20.8% in 2002 to 64.9% in 2009) and in *Klebsiella pneumoniae* (from 24% in 2002 to 31.9% in 2009). ESBL-producers showed higher antimicrobial resistance compared with non-ESBL-producers, as has been reported by other investigators [62]. A recent Chinese national drug resistance surveillance report found that the prevalence of ESBL-producers amongst *E. coli* and *Klebsiella* in 2009 was 56.5% and 41.4%, respectively [62]. These rates are in accordance with those reported by other Chinese investigations (Table 1). One-half of the ESBL-producers were resistant to ciprofloxacin and gentamicin and some of the *E. coli* strains were pan-resistant [62]. Yang et al. [61] found that carbapenems were active against Enterobacteriaceae, with susceptibility rates of >96% for the agents tested. However, carbapenem-non-susceptibility was detected in a small percentage of isolates, with 0.7% and 2.1% of isolates being non-susceptible to imipenem and ertapenem, respectively, in 2009 [61]. A similar carbapenem resistance (<2%) was found amongst Enterobacteriaceae isolates in a recent Chinese national drug resistance surveillance report [62]. However, a noticeable increase in the number of resistant isolates compared with data from 2007 was noted, particularly amongst *K. pneumoniae*. *Klebsiella pneumoniae* carbapenemase (KPC)-producing and pan-resistant strains have emerged in China and have been widely reported from various regions of the People's Republic [63–66].

Pseudomonas aeruginosa is another common pathogen in Chinese hospitals [44,45,47,67]. The organism is a uniquely problematic nosocomial pathogen because of its natural resistance to many drug families and its ability to acquire and rapidly develop resistance to multiple classes of antibiotics during the course of treating a patient [68,69]. Data from China suggest that over the past decades antibiotic resistance amongst *P. aeruginosa* clinical isolates has been on the increase, especially to carbapenems. An investigation into the changes in antimicrobial resistance amongst non-fermenting Gram-negative bacilli isolated from Chinese ICUs from 1994 to 2001 found that *P. aeruginosa* (46.9%) was the most predominant pathogen isolated and that the organism has become less susceptible to 11 antibiotics during the study period [67]. Another study of *P. aeruginosa* isolates from ICU patients in 19

Table 2
Rates of carbapenem resistance amongst *Pseudomonas aeruginosa* in China.

Location	Rate (%)		Study date	Reference
	Imipenem	Meropenem		
14 hospitals across China (CHINET 2009)	30.5	25.2	2009	[62]
Shanghai hospitals, China	22.8	19.2	2008	[116]
12 hospitals across China (CHINET 2008)	30.5	24.5	2008	[70]
12 hospitals across China (CHINET 2007)	36.0	28.5	2008	[77]
Shanghai hospitals, China	26.7	18.8	2007	[100]
A cancer centre in Guangzhou, China	21.4	–	2006–2007	[86]
A hospital in Xinjiang, China	24.2	18.5	2003–2007	[130]
Shanghai hospitals, China	24.4	15.5	2006	[120]
A hospital in Shanghai, China	39.3	59.6	2005	[121]
8 hospitals across China (CHINET 2005)	31.3	33.7	2005	[98]
7 teaching hospitals across China	31.3	33.7	2005	[131]
A hospital in Hangzhou, China	33.4	25.2	2005	[122]
A hospital in Chongqing, China	37.2	39.4	2004–2005	[123]
17 hospitals across 15 Chinese cities	10.6	–	2004–2005	[71]
A hospital ICU in Shenzhen, China	54.3	52.2	2002–2004	[132]
Shanghai hospitals, China	24.5	16.9	2003	[127]
A hospital in Guangzhou, China	10.5	–	2002–2003	[133]
A hospital in Tongling, China	6.0	–	1997–2003	[134]
ICUs from 19 hospitals in seven Chinese central cities	38.0	–	2002	[60]
11 hospitals in Shanghai, China	20.0	–	1999	[90]

ICU, Intensive Care Unit.

Chinese hospitals reported a marked decrease in *P. aeruginosa* susceptibility to imipenem (from 81% to 62%) between 1996 and 2002 [60].

Recent reports, however, show stable but high carbapenem resistance rates (Table 2), with a tendency towards multidrug resistance. A study of 286 *P. aeruginosa* isolates from IAIs between 2002 and 2009 found that ca. 30% and 25% of isolates were resistant to imipenem and meropenem, respectively [61]. Similar resistance rates were reported in a number of recent Chinese antimicrobial resistance surveillance publications [62,70]. The percentage of *P. aeruginosa* MDR strains, defined as isolates resistant to three or four antimicrobials amongst ceftazidime, ciprofloxacin, amikacin and imipenem, was reported to have increased from 11.5% to 20.5% in a 6-year period [60], and a recent national surveillance study found that >60% of *P. aeruginosa* isolates collected from 17 hospitals in China in 2008 were MDR [71]. Pan-resistance was found in 1.7% of the *P. aeruginosa* isolates tested in a recent 2009 Chinese national survey [50]. Amikacin remains one of the most active agents against *P. aeruginosa* in China, with 80–85% of isolates being susceptible to the drug [50,61].

Acinetobacter baumannii has recently gained increasing notoriety as a nosocomial pathogen [72] and is one of the most prevalent Gram-negative bacteria isolated from Chinese hospitals particularly in ICUs [44,47]. *Acinetobacter* is a serious pathogen in Chinese hospitals, especially with the emergence and spread of problematic strains such as the New Delhi metallo-β-lactamase (NDM-1)- and carbapenemase-producing isolates as well as the high prevalence of XDR and pan-resistant strains in the country [51,73–75]. Zhang et al. [76] reported the recent status of antimicrobial resistance amongst 4163 clinical isolates of *A. baumannii* from China in 2009. They found that amongst the antibiotics tested, cefoperazone/sulbactam and minocycline were the most active, with resistance rate of ca. 26%. Antimicrobial resistance to other agents was higher than 53%, especially amongst ICU isolates, and multidrug resistance and pan-resistance was noted in 44.4% and 17% of the isolates, respectively. Imipenem and meropenem resistance rates were 54.8% and 57.2%, respectively. These rates were higher than those reported in earlier national surveys (2008 and 2007) (<50%) [70,77] and were in line with the gradual increase over the years in carbapenem resistance in China [61,78]. Imipenem and meropenem resistance in *Acinetobacter* has seen a sharp increase in China in recent years (Table 3) and >50% of the isolates are now resistant to these agents. In one study it was reported that imipenem susceptibility amongst *A. baumannii* from IAIs in China decreased from 100% in 2002 to 21.6% in 2009 [61].

3.3. Gram-positive organisms

Gram-positive bacteria, particularly Gram-positive cocci of the genera *Staphylococcus*, *Enterococcus* and *Streptococcus*, contain important pathogenic species causing serious infections and associated with morbidity and mortality [79–84]. These species are commonly isolated from nosocomial infections in hospitals across China [44,47,85,86].

Staphylococcus aureus is a major pathogen associated with infections in hospital and community settings [79,80]. Most of these infections are caused by meticillin-sensitive *S. aureus*, however meticillin-resistant *S. aureus* (MRSA) is implicated in serious infections and outbreaks [87,88]. The prevalence of MRSA amongst *S. aureus* clinical isolates has increased sharply in China in the last few years (Table 4) and a rate as high as 94% has been reported from a Chinese surgical ICU [49]. Data from Shanghai showed that the prevalence of MRSA increased from 5% in 1980 to 24% during 1985–1986 [89] and reached 64% in 1999 [90]. Li et al. [91] investigated bacterial resistance both for HAIs and CAIs in China from 1998 to 1999. They reported that the prevalence of MRSA in *S. aureus* isolates was significantly higher in those from patients with HAIs (81.8%) than in those from patients with CAIs (21.8%). In a subsequent study [52,92], MRSA accounted for 37.4% (89/238) of *S. aureus* isolates, and the rate from HAI patients (89.2%; 33/37) was also significantly higher than that from CAI patients (30.2%; 42/139). The prevalence of meticillin resistance is even higher amongst coagulase-negative staphylococci (CoNS) (Table 4). Chen et al. [49] reported that meticillin-resistant CoNS represented 11.1% of all nosocomial infections in a Chinese surgical ICU. Meticillin resistance was present in 88.2% of CoNS isolates. A comprehensive report on bacterial resistance in China that investigated 4075 clinical bacterial isolates collected from 17 Chinese hospitals found that 62.9% of the *S. aureus* isolates were meticillin-resistant [71]. Resistance rates to fluoroquinolones and macrolides were high (41.7–64.4% and 70.1–84.5% of the isolates, respectively). CoNS showed higher resistance, with 82.8–89% of the strains being meticillin-resistant and with fluoroquinolone and macrolide resistance rates comparable with those of *S. aureus*.

Table 3
Rates of carbapenem resistance amongst *Acinetobacter* spp. in China.

Location	Rate (%)		Study date	Reference
	Imipenem	Meropenem		
14 hospitals across China (CHINET 2009)	57.1	58.3	2010	[135]
14 hospitals across China (CHINET 2009)	54.8[a]	57.2	2009	[76]
Shanghai hospitals, China	27.4	28.3	2008	[116]
12 hospitals across China (CHINET 2008)	48.1	49.3	2008	[70]
12 hospitals across China (CHINET 2007)	40.0[a]	35.0	2007	[77]
Shanghai hospitals, China	21.0	22.5	2007	[100]
Shanghai hospitals, China	15.5	17.0	2006	[120]
15 teaching hospitals across China	19.2[a]	23.8	2005	[48]
7 teaching hospitals across China	34.9[a]	43.2	2004–2005	[136]
A hospital in Chongqing, China	0.0[a]	0.0	2004–2005	[123]
17 hospitals across 15 Chinese cities	10.4[a]	–	2004–2005	[71]
A hospital in Tongling, China	10.3	–	1997–2003	[134]
ICUs from 19 hospitals in seven Chinese central cities	6.5	–	2002	[60]
11 hospitals in Shanghai, China	3.0	–	2000	[137]

ICU, Intensive Care Unit.
[a] *Acinetobacter baumannii*.

Streptococcus pneumoniae remains an important pathogen causing significant morbidity and mortality especially amongst young children [82–84]. The emergence and spread of penicillin-resistant and MDR strains around the world is of great concern [93–95]. Available data from China (Table 5) show that in the past few years, rates of penicillin and macrolide resistance in *S. pneumoniae* have been increasing significantly, especially amongst the paediatric population [96,97]. Rates of penicillin-non-susceptible (resistant + intermediately resistant) *S. pneumoniae* increased from <15% in 1997 [96] to 61% in 2005 [98]. Amongst the paediatric population, the rates more than doubled from 41% in 2000–2001 [99] to >88% in 2007 [77,100]. Increased *S. pneumoniae* resistance to penicillin in China has been mirrored by an increase in multidrug resistance especially to macrolides [96,101]. Resistance to macrolides is particularly problematic because these agents are the first-choice treatment for pneumonia. In a surveillance study from Beijing, resistance to erythromycin, clarithromycin and tetracycline was seen in 54%, 52% and 100% of *S. pneumoniae* isolates, respectively [102]. Xiao et al. [71] found >80% of *S. pneumoniae* clinical isolates to be resistant to macrolides and clindamycin. In a recent study, Yao et al. [103] reported that of the 279 *S. pneumoniae* strains isolated from Chinese children with pneumonia, 86% were penicillin-non-susceptible, 23.3% were penicillin-resistant and almost all isolates were resistant to erythromycin. Multidrug resistance is especially common amongst penicillin-resistant *S. pneumoniae* strains, and in one study >96% of these were reported to be MDR [104].

Enterococcus is a commonly isolated organism from Chinese hospitals [44,85]. *Enterococcus faecalis* and *Enterococcus faecium* account for most of the infections caused by this genus [81]. Vancomycin resistance is one of the most disturbing drug resistance trends to have emerged within these species [105]. Vancomycin-resistant enterococci (VRE) is a serious nosocomial pathogen because infections due to VRE have been associated with significant morbidity and mortality as well as increased hospital costs [106–108]. VRE infection or colonisation was first reported in France [109] and the UK [110], then throughout the world [111–114]. In China, surveillance data from 1999 on the bacterial resistance of clinical isolates from 11 Shanghai hospitals reported vancomycin-resistant *E. faecalis* and *E. faecium* frequencies of 3.6%

Table 4
Rates of meticillin resistance amongst *Staphylococcus aureus* and coagulase-negative staphylococci (CoNS) in China.

Location	Rate (%)		Study date	Reference
	S. aureus	CoNS		
14 hospitals across China (CHINET 2009)	52.7	71.7	2009	[62]
Shanghai hospitals, China	62.3	77.0	2008	[116]
12 hospitals across China (CHINET 2008)	55.9	75.9	2008	[70]
A children's hospital in Beijing, China	10.6	86.2	2003–2008	[118
A hospital ICU in Wuhan, China	84.0	90.0	2007	[119]
12 hospitals across China (CHINET 2007)	58.0	77.0	2007	[77]
Shanghai hospitals, China	61.1	75.9	2007	[100]
Shanghai hospitals, China	64.6	82.2	2006	[120]
A hospital in Shanghai, China	93.2	94.9	2005	[121]
8 hospitals across China (CHINET 2005)	69.0	82.0	2005	[98]
A hospital in Hangzhou, China	68.6	86.8	2005	[122]
17 hospitals in 15 Chinese cities	62.9	–	2004–2005	[71]
14 hospitals in Shanghai, China	63.9	82.9	2004	[124]
A hospital surgical ICU in Guangzhou, China	94.7	88.2	2001–2004	[49]
Guangzhou hospitals, China	70.8	82.4	2003	[126]
Shanghai hospitals, China	59.8	80.3	2003	[127]
A hospital in Guangzhou, China	65.3	70.7	2002–2003	[133]
4 hospitals in Kunming, China	36.3	–	2002	[128]
15 tertiary hospitals in Hubei, China	38.6	72.6	2002	[129]
13 hospitals across China	89.2	–	2000–2001	[92]
11 hospitals in Shanghai, China	64.0	77.0	1999	[90]
13 hospitals across China	81.8	–	1998–1999	[91]
Shanghai hospitals, China	54.9	70.7	1998	[138]

ICU, Intensive Care Unit.

Table 5
Rates of penicillin-non-susceptible *Streptococcus pneumoniae* in China.

Location	Rate (%)	Study date	Reference
Amongst all patients			
8 hospitals across China (CHINET 2005)	61.0	2005	[98]
17 hospitals in 15 cities across China	40.7	2004–2005	[71]
Beijing and Shenyang hospitals, China	42.7	2001–2002	[139]
13 hospitals across China	26.7	2000–2001	[92]
13 hospitals across China	22.5	1998–1999	[91]
4 teaching hospitals in Beijing, China	13.9	1997	[96]
Amongst adults			
12 hospitals across China (CHINET 2007)	26.4	2007	[77]
Shanghai hospitals, China	4.0	2006	[120]
7 hospitals in Shanghai, China	20.5	2004–2005	[140]
14 hospitals in Shanghai, China	8.8	2004	[124]
Shanghai hospitals, China	13.6	2003	[127]
Amongst children			
A children's hospital in Beijing, China	82.5	2003–2008	[118]
12 hospitals across China (CHINET 2007)	88.5	2007	[77]
Shanghai hospitals, China	88.3	2007	[100]
4 children's hospitals across China	86.0	2006–2007	[103]
Shanghai hospitals, China	87.0	2006	[120]
7 hospitals in Shanghai, China	63.1	2004–2005	[140]
14 hospitals in Shanghai, China	70.1	2004	[124]
Shanghai hospitals, China	62.8	2003	[127]
4 hospitals across China	41.0	2000–2001	[99]

Table 6
Rates of vancomycin-resistant enterococci in China.

Location	Rate (%)	Study date	Reference
A hospital in Beijing, China	5.6	2007	[141]
12 hospitals across China	1.1	2007	[142]
A hospital ICU in Wuhan, China	0.0	2007	[119]
A hospital in Beijing, China	7.0	2003–2007	[115]
17 hospitals in 15 cities across China	0.0	2004–2005	[71]
14 hospitals in Shanghai, China	0.0	2004	[124]
A hospital in Beijing, China	3.2	2001–2004	[143]
Shanghai hospitals, China	0.0	2003	[127]
A hospital in Guangzhou, China	4.6	2002–2003	[133]
4 hospitals in Kunming, China	0.0	2002	[128]
13 hospitals across, China	0.0	2000–2001	[92]
11 hospitals in Shanghai, China	2.6	1999	[90]
13 hospitals across, China	0.0	1998–1999	[91]
Shanghai hospitals, China	5.0	1998	[138]

ICU, Intensive Care Unit.

and 1.7%, respectively [90]. However, VRE was not a concern in mainland China until June 2003 when the first nosocomial infection was recognised in Beijing Chaoyang Hospital [115]. Since then, VRE has been reported in a number of Chinese studies [77,100,116]. From a total of 117 clinical isolates collected from Beijing Chaoyang Hospital between 2003 and 2007, 7.0% were confirmed as VRE and a correlation between vancomycin usage and misuse and VRE incidences was observed [115]. More worryingly, coexistence of MRSA and VRE in the same patient was reported in 7 of 129 cases, suggesting that this coexistence is not a rare occurrence [117]. Recent local and national reports (Table 6) suggest that VRE prevalence in China remains low; however, rates are on the increase.

4. Summary

China is a major contributor to the worldwide infectious disease burden and is a hotspot for the emergence and spread of new microbial threats. The 2003 SARS epidemic brought the world's attention to the emergence of infectious diseases and their control in the country. China has high rates of antibiotic resistance driven by misuse of antimicrobial agents in the community and in a healthcare system that provides strong incentives for overprescribing. The true frequency and proportion of antibiotic use may have been underestimated, especially in rural areas where over-the-counter antibiotics and self-medication are common. Drug resistance amongst nosocomial bacteria has been on a rapid upward trend in China, with a strong inclination towards multidrug resistance. Hospital strains show more resistance to antibiotics and are more likely to be MDR than non-hospital strains. MDR-TB rates are high and increasing, and the emergence and spread of XDR-TB in the country is particularly problematic as it is difficult and expensive to treat, with high mortality rates. Large proportions of Gram-negative nosocomial strains isolated in China are resistant to antibiotics, with the non-fermenters being highly resistant. The prevalence of ESBL-producers amongst Enterobacteriaceae is high and these strains showed higher antimicrobial resistance compared with non-ESBL-producers. There is also worrying evidence of the emergence and increased prevalence of carbapenem resistance and pan-resistance in Enterobacteriaceae, *Pseudomonas* and *Acinetobacter* spp. in China. The prevalence of MRSA amongst *S. aureus* clinical isolates has been increasing sharply in China, and rates as high as 94% have been reported. The prevalence of MRSA is significantly higher in isolates from patients with HAIs than in those from patients with CAIs. In the past few years, resistance rates to penicillin and macrolides amongst *S. pneumoniae* isolates have also been increasing significantly, especially amongst the Chinese paediatric population. VRE became a real concern in China since June 2003 when the first VRE nosocomial infection was recognised. Increased rates of VRE and the coexistence of MRSA and VRE in the same patient are particularly troubling. Despite the Chinese government's efforts and improvements, the healthcare system in the People's Republic still faces a number of challenges. There is a need for more effective infection prevention and control measures and a stricter use of antibiotics in China to control the rise in antibiotic resistance in the country.

Funding: No funding sources.

Competing interests: SY is employed by Bioquell (UK) Ltd. (Andover, UK). HL has no competing interests to declare.

Ethical approval: Not required.

References

[1] Rands G. Aspects of health care in China. J R Soc Health 1989;109:79–85.
[2] United Nations Development Programme. Human development report 2007/2008. New York, NY: Palgrave Macmillan; 2007.
[3] Cook IG, Dummer TJ. Changing health in China: re-evaluating the epidemiological transition model. Health Policy 2004;67:329–43.
[4] Wang L, Wang Y, Jin S, Wu Z, Chin DP, Koplan JP, et al. Emergence and control of infectious diseases in China. Lancet 2008;372:1598–605.
[5] Chinese Centre for Disease Control and Prevention. National database for notifiable diseases in China (1970–2007). Beijing, China: Chinese Centre for Disease Control and Prevention; 2009.
[6] World Health Organization. Cumulative number of confirmed human cases of avian influenza A/(H5N1) reported to WHO. Geneva, Switzerland: WHO; 2008.
[7] Shaw K. The 2003 SARS outbreak and its impact on infection control practices. Public Health 2006;120:8–14.
[8] Matsui S. Protecting human and ecological health under viral threats in Asia. Water Sci Technol 2005;51:91–7.
[9] Lam WK, Zhong NS, Tan WC. Overview on SARS in Asia and the world. Respirology 2003;8(Suppl.):S2–5.
[10] Yuan CT, Dembry LM, Higa B, Fu M, Wang H, Bradley EH. Perceptions of hand hygiene practices in China. J Hosp Infect 2009;71:157–62.
[11] Neu HC. The crisis in antibiotic resistance. Science 1992;257:1064–73.
[12] Russell AD, Tattawasart U, Maillard JY, Furr JR. Possible link between bacterial resistance and use of antibiotics and biocides. Antimicrob Agents Chemother 1998;42:2151.
[13] Dong L, Yan H, Wang D. Antibiotic prescribing patterns in village health clinics across 10 provinces of western China. J Antimicrob Chemother 2008;62:410–5.
[14] Reynolds L, McKee M. Factors influencing antibiotic prescribing in China: an exploratory analysis. Health Policy 2009;90:32–6.
[15] Zhang R, Eggleston K, Rotimi V, Zeckhauser RJ. Antibiotic resistance as a global threat: evidence from China, Kuwait and the United States. Global Health 2006;2:6.
[16] Zheng Y, Zhou Z. The root causes of the abuse of antibiotics, harm and the rational use of the strategy. Hosp Manag Forum 2007;123:23–7.
[17] Yang YH, Fu SG, Peng H, Shen AD, Yue SJ, Go YF, et al. Abuse of antibiotics in China and its potential interference in determining the etiology of pediatric bacterial diseases. Pediatr Infect Dis J 1993;12:986–8.
[18] Roumie CL, Halasa NB, Grijalva CG, Edwards KM, Zhu Y, Dittus RS, et al. Trends in antibiotic prescribing for adults in the United States—1995 to 2002. J Gen Intern Med 2005;20:697–702.
[19] Bjerrum L, Cots JM, Llor C, Molist N, Munck A. Effect of intervention promoting a reduction in antibiotic prescribing by improvement of diagnostic procedures: a prospective, before and after study in general practice. Eur J Clin Pharmacol 2006;62:913–8.
[20] Tiemersma EW, Bronzwaer SL, Lyytikainen O, Degener JE, Schrijnemakers P, Bruinsma N, et al. Methicillin-resistant *Staphylococcus aureus* in Europe, 1999–2002. Emerg Infect Dis 2004;10:1627–34.
[21] Wu AH, Ren N, Wen XM, Xu XH, Li J, Yi XY, et al. Study on the frequency of antibiotics use per day among inpatients in 151 hospitals in 2003. Zhonghua Liu Xing Bing Xue Za Zhi 2005;26:451–4 [in Chinese].
[22] Yang L, Xiao YH, Nie Y, Zheng YD, Wang J, Yan Q, et al. Impact of misuse of antimicrobial therapies on inpatient costs. Beijing Da Xue Xue Bao 2010;42:279–83 [in Chinese].
[23] Zhang FJ, Maria A, Haberer J, Zhao Y. Overview of HIV drug resistance and its implications for China. Chin Med J (Engl) 2006;119:1999–2004.
[24] Hutchison DC, Drobniewski FA, Milburn HJ. Management of multiple drug-resistant tuberculosis. Respir Med 2003;97:65–70.
[25] Mukherjee JS, Rich ML, Socci AR, Joseph JK, Viru FA, Shin SS, et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. Lancet 2004;363:474–81.
[26] World Health Organization. Global tuberculosis control: surveillance, planning, financing. Geneva, Switzerland: WHO; 2007. WHO/HTM/TB/2007.89.
[27] World Health Organization. Anti-tuberculosis drug resistance in the world. Report no. 4. Geneva, Switzerland: WHO; 2008.
[28] Ministry of Health of the People's Republic of China. Nationwide anti-tuberculosis drug resistant baseline surveillance in China (2007–2008). People's Public Health Press; 2010.
[29] He GX, Zhao YL, Jiang GL, Liu YH, Xia H, Wang SF, et al. Prevalence of tuberculosis drug resistance in 10 provinces of China. BMC Infect Dis 2008;8:166.
[30] Shen X, DeRiemer K, Yuan ZA, Shen M, Xia Z, Gui X, et al. Drug-resistant tuberculosis in Shanghai, China, 2000–2006: prevalence, trends and risk factors. Int J Tuberc Lung Dis 2009;13:253–9.
[31] Aziz MA, Wright A, Laszlo A, De Muynck A, Portaels F, Van Deun A, et al. Epidemiology of antituberculosis drug resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis. Lancet 2006;368:2142–54.
[32] Espinal MA, Laszlo A, Simonsen L, Boulahbal F, Kim SJ, Reniero A, et al. Global trends in resistance to antituberculosis drugs. World Health Organization–International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med 2001;344:1294–303.
[33] Pablos-Mendez A, Raviglione MC, Laszlo A, Binkin N, Rieder HL, Bustreo F, et al. Global surveillance for antituberculosis-drug resistance, 1994–1997. World Health Organization–International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. N Engl J Med 1998;338:1641–9.
[34] Wang G, Peng YL, Zhang G, Zhang L, Xing J, Li D, et al. Sample survey of drug-resistant tuberculosis in Henan, China, 1996. Respirology 2002;7: 67–72.
[35] Tang S, Zhang Q, Yu J, Liu Y, Sha W, Sun H, et al. Extensively drug-resistant tuberculosis at a tuberculosis specialist hospital in Shanghai, China: clinical characteristics and treatment outcomes. Scand J Infect Dis 2011;43:280–5.
[36] Gandhi NR, Moll A, Sturm AW, Pawinski R, Govender T, Lalloo U, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. Lancet 2006;368:1575–80.
[37] Kwon YS, Kim YH, Suh GY, Chung MP, Kim H, Kwon OJ, et al. Treatment outcomes for HIV-uninfected patients with multidrug-resistant and extensively drug-resistant tuberculosis. Clin Infect Dis 2008;47:496–502.
[38] World Health Organization. Case definition for extensively drug-resistant tuberculosis. Wkly Epidemiol Rec 2006;81:408.
[39] Sun Z, Chao Y, Zhang X, Zhang J, Li Y, Qiu Y, et al. Characterization of extensively drug-resistant *Mycobacterium tuberculosis* clinical isolates in China. J Clin Microbiol 2008;46:4075–7.
[40] Wang D, Yang C, Kuang T, Lei H, Meng X, Tong A, et al. Prevalence of multidrug and extensively drug-resistant tuberculosis in Beijing, China: a hospital-based retrospective study. Jpn J Infect Dis 2010;63:368–71.
[41] Deng Y, Wang Y, Wang J, Jing H, Yu C, Wang H, et al. Laboratory-based surveillance of extensively drug-resistant tuberculosis, China. Emerg Infect Dis 2011;17:495–7.
[42] He GX, van denHof S, van der Werf MJ, Wang GJ, Ma SW, Zhao DY, et al. Infection control and the burden of tuberculosis infection and disease in health care workers in China: a cross-sectional study. BMC Infect Dis 2010;10: 313.
[43] Liu MD, Cheng P. Analysis of nosocomial infection in hospitalized critical and serious patients. Zhonghua Liu Xing Bing Xue Za Zhi 1995;16:231–3 [in Chinese].
[44] Wang A, Fan S, Shen X. A retrospective study of nosocomial infections in a pediatric hospital: a seven-year experience at Beijing Children's Hospital. J Trop Pediatr 2008;54:281–2.
[45] Wang A, Fan S, Yang Y, Shen X. Nosocomial infections among pediatric hematology patients: results of a retrospective incidence study at a pediatric hospital in China. J Pediatr Hematol Oncol 2008;30:674–8.
[46] Han B, Di HX, Zhou DB, Zhao YQ, Wang SJ, Xu Y, et al. Infection pathogen analysis of 2388 patients in an open hematology ward from 1993 to 2004. Zhonghua Yi Xue Za Zhi 2006;86:664–8 [in Chinese].
[47] Ding JG, Sun QF, Li KC, Zheng MH, Miao XH, Ni W, et al. Retrospective analysis of nosocomial infections in the intensive care unit of a tertiary hospital in China during 2003 and 2007. BMC Infect Dis 2009;9:115.
[48] Yang QW, Xu YC, Chen MJ, Hu YJ, Ni YX, Sun JY, et al. Surveillance of antimicrobial resistance among nosocomial Gram-negative pathogens from 15 teaching hospitals in China in 2005. Zhonghua Yi Xue Za Zhi 2007;87:2753–8 [in Chinese].
[49] Chen J, Li LF, Guan XD, Chen DM, Chen MY, Ouyang B, et al. The drug resistance of pathogenic bacteria of nosocomial infections in surgical intensive care unit. Zhonghua Wai Ke Za Zhi 2006;44:1189–92 [in Chinese].
[50] Zhang YB, Ni YX, Sun JY, Zhu DM, Hu FP, Wang F, et al. CHINET 2009 surveillance of antibiotic resistance in *Pseudomonas aeruginosa* in China. Chin J Infect Chemother 2010;10:436–40.
[51] Chen Z, Qlu S, Wang Y, Wang Y, Liu S, Wang Z, et al. Coexistence of $bla_{\mathrm{NDM-1}}$ with the prevalent bla_{OXA23} and bla_{IMP} in pan-drug resistant *Acinetobacter baumannii* isolates in China. Clin Infect Dis 2011;52:692–3.
[52] Li JT, Li Y, Wang J. Surveillance on drug resistance of Gram-negative bacilli isolated from hospital acquired infections and community acquired infections (2000–2001). Zhonghua Yi Xue Za Zhi 2003;83:1035–45 [in Chinese].
[53] Dai CM, Zhou JD, Wu Y, Qi Y. Distribution of pathogen and resistance of nosocomial infections in the intensive care units. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2006;31:277–80 [in Chinese].
[54] Rupp ME, Fey PD. Extended spectrum β-lactamase (ESBL)-producing Enterobacteriaceae: considerations for diagnosis, prevention and drug treatment. Drugs 2003;63:353–65.
[55] Carattoli A. Resistance plasmid families in Enterobacteriaceae. Antimicrob Agents Chemother 2009;53:2227–38.
[56] Paterson DL. Resistance in Gram-negative bacteria: Enterobacteriaceae. Am J Infect Control 2006;34(5 Suppl. 1):S20–8.

[57] Grundmann H, Livermore DM, Giske CG, Canton R, Rossolini GM, Campos J, et al. Carbapenem-non-susceptible Enterobacteriaceae in Europe: conclusions from a meeting of national experts. Euro Surveill 2010;15, pii: 19711.
[58] Bratu S, Mooty M, Nichani S, Landman D, Gullans C, Pettinato B, et al. Emergence of KPC-possessing *Klebsiella pneumoniae* in Brooklyn, New York: epidemiology and recommendations for detection. Antimicrob Agents Chemother 2005;49:3018–20.
[59] Bratu S, Landman D, Haag R, Recco R, Eramo A, Alam M, et al. Rapid spread of carbapenem-resistant *Klebsiella pneumoniae* in New York City: a new threat to our antibiotic armamentarium. Arch Intern Med 2005;165:1430–5.
[60] Wang H, Chen M. Surveillance for antimicrobial resistance among clinical isolates of Gram-negative bacteria from intensive care unit patients in China, 1996 to 2002. Diagn Microbiol Infect Dis 2005;51:201–8.
[61] Yang Q, Wang H, Chen M, Ni Y, Yu Y, Hu B, et al. Surveillance of antimicrobial susceptibility of aerobic and facultative Gram-negative bacilli isolated from patients with intra-abdominal infections in China: the 2002–2009 Study for Monitoring Antimicrobial Resistance Trends (SMART). Int J Antimicrob Agents 2010;36:507–12.
[62] Wang F, Zhu DM, Hu FP, Ruan FY, Ni YX, Song JY. CHINET 2009 surveillance of bacterial resistance in China. Chin J Infect Chemother 2010;10:325–34.
[63] Chen S, Hu F, Xu X, Liu Y, Wu W, Zhu D, et al. High prevalence of KPC-2-type carbapenemase coupled with CTX-M-type extended-spectrum β-lactamases in carbapenem-resistant *Klebsiella pneumoniae* in a teaching hospital in China. Antimicrob Agents Chemother 2011;55:2493–4.
[64] Wei ZQ, Du XX, Yu YS, Shen P, Chen YG, Li LJ. Plasmid-mediated KPC-2 in a *Klebsiella pneumoniae* isolate from China. Antimicrob Agents Chemother 2007;51:763–5.
[65] Qi Y, Wei Z, Ji S, Du X, Shen P, Yu Y. ST11, the dominant clone of KPC-producing *Klebsiella pneumoniae* in China. J Antimicrob Chemother 2011;66:307–12.
[66] Huang ZM, Mi JR, Sheng YQ, Zou YX, Chu QJ, Ge LW, et al. Study on pan-resistant *Klebsiella pneumoniae* harboring bla_{KPC-2} type carbapenemase gene from a hospital outbreak in Huzhou, Zhejiang. Zhonghua Liu Xing Bing Xue Za Zhi 2010;31:559–62 [in Chinese].
[67] Wang H, Chen MJ; China Nosocomial Pathogens Resistance Surveillance Study Group. Changes of antimicrobial resistance among nonfermenting Gram-negative bacilli isolated from intensive care units from 1994 to 2001 in China. Zhonghua yi xue hui 2003;83:385–90 [in Chinese].
[68] Strateva T, Yordanov D. *Pseudomonas aeruginosa*—a phenomenon of bacterial resistance. J Med Microbiol 2009;58:1133–48.
[69] Lister PD, Wolter DJ, Hanson ND. Antibacterial-resistant *Pseudomonas aeruginosa*: clinical impact and complex regulation of chromosomally encoded resistance mechanisms. Clin Microbiol Rev 2009;22:582–610.
[70] Wang F, Zhu DM, Hu FP, Ruan FY, Ni YX, Sun JY, et al. CHINET 2008 surveillance of bacterial resistance in China. Chin J Infect Chemother 2009;05:321–9.
[71] Xiao YH, Wang J, Li Y. Bacterial resistance surveillance in China: a report from Mohnarin 2004–2005. Eur J Clin Microbiol Infect Dis 2008;27:697–708.
[72] Perez F, Hujer AM, Hujer KM, Decker BK, Rather PN, Bonomo RA. Global challenge of multidrug-resistant *Acinetobacter baumannii*. Antimicrob Agents Chemother 2007;51:3471–84.
[73] Chen Y, Zhou Z, Jiang Y, Yu Y. Emergence of NDM-1-producing *Acinetobacter baumannii* in China. J Antimicrob Chemother 2011;66:1255–9.
[74] Zhou H, Yang Q, Yu YS, Wei ZQ, Li LJ. Clonal spread of imipenem-resistant *Acinetobacter baumannii* among different cities of China. J Clin Microbiol 2007;45:4054–7.
[75] Liang W, Liu XF, Huang J, Zhu DM, Li J, Zhang J. Activities of colistin- and minocycline-based combinations against extensive drug resistant *Acinetobacter baumannii* isolates from intensive care unit patients. BMC Infect Dis 2011;11:109.
[76] Zhang XJ, Xu YC, Yu YS, Yang Q, Wang F, Zhu YX, et al. CHINET 2009 surveillance of antibiotic resistance in *Acinetobacter baumannii* in China. Chin J Infect Chemother 2010;10:441–6.
[77] Wang F, Zhu DM, Hu FP, Ruan FY, Ni YX, Sun JY, et al. CHINET 2007 surveillance of bacterial resistance in China. Chin J Infect Chemother 2008;05:325–33.
[78] Wang H, Chen M, Ni Y, Liu Y, Sun H, Yu Y, et al. Antimicrobial resistance among clinical isolates from the Chinese Meropenem Surveillance Study (CMSS), 2003–2008. Int J Antimicrob Agents 2010;35:227–34.
[79] Noskin GA, Rubin RJ, Schentag JJ, Kluytmans J, Hedblom EC, Jacobson C, et al. National trends in *Staphylococcus aureus* infection rates: impact on economic burden and mortality over a 6-year period (1998–2003). Clin Infect Dis 2007;45:1132–40.
[80] Lowy FD. *Staphylococcus aureus* infections. N Engl J Med 1998;339:520–32.
[81] Schaberg DR, Culver DH, Gaynes RP. Major trends in the microbial etiology of nosocomial infection. Am J Med 1991;91:72S–5S.
[82] O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by *Streptococcus pneumoniae* in children younger than 5 years: global estimates. Lancet 2009;374:893–902.
[83] Bridy-Pappas AE, Margolis MB, Center KJ, Isaacman DJ. *Streptococcus pneumoniae*: description of the pathogen, disease epidemiology, treatment, and prevention. Pharmacotherapy 2005;25:1193–212.
[84] McKenzie H, Reid N, Dijkhuizen RS. Clinical and microbiological epidemiology of *Streptococcus pneumoniae* bacteraemia. J Med Microbiol 2000;49: 361–6.
[85] Fan Y, Chang NB, Hu YJ, Ai XM, Xu SQ, Li JT, et al. Changes of pathogens and susceptibility to antibiotics in hematology ward from years 2001 to 2005. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2008;16:1455–8 [in Chinese].
[86] Sun YL, Zhao QY. Distribution and drug resistance of pathogenic bacteria strains in nosocomial infection in Sun Yat-sen University Cancer Center from 2006 to 2007. Ai Zheng 2009;28:543–8 [in Chinese].
[87] Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y. The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. Infect Control Hosp Epidemiol 2005;26:166–74.
[88] Engemann JJ, Carmeli Y, Cosgrove SE, Fowler VG, Bronstein MZ, Trivette SL, et al. Adverse clinical and economic outcomes attributable to methicillin resistance among patients with *Staphylococcus aureus* surgical site infection. Clin Infect Dis 2003;36:592–8.
[89] Shanghai Surveillance of Bacterial Resistance Working Group. Surveillance of bacterial resistance in Shanghai. Chin J Infect Chemother 2002;01: 1–9.
[90] Wang F, Zhu DM, Hu FP, Zhang YY. Surveillance of bacterial resistance among isolates in Shanghai in 1999. J Infect Chemother 2001;7:117–20.
[91] Li J, Weinstein AJ, Yang M. Surveillance of bacterial resistance in China (1998–1999). Zhonghua yi xue hui 2001;81:8–16 [in Chinese].
[92] Li JT, Li Y, Wang J. Surveillance on Gram-positive bacteria isolated from patients with hospital acquired infections or community acquired infections. Zhonghua yi xue hui 2003;83:365–74 [in Chinese].
[93] Musher DM. *Streptococcus pneumoniae*. In: Mandell GL, Bennett JE, Dolin R, editors. Principals and practice of infectious diseases. 6th ed. Philadelphia, PA: Churchill Livingstone; 2005. p. 197.
[94] Davies T, Goering RV, Lovgren M, Talbot JA, Jacobs MR, Appelbaum PC. Molecular epidemiological survey of penicillin-resistant *Streptococcus pneumoniae* from Asia, Europe, and North America. Diagn Microbiol Infect Dis 1999;34:7–12.
[95] Reinert RR, Ringelstein A, van der Linden M, Cil MY, Al-Lahham A, Schmitz FJ. Molecular epidemiology of macrolide-resistant *Streptococcus pneumoniae* isolates in Europe. J Clin Microbiol 2005;43:1294–300.
[96] Wang H, Huebner R, Chen M, Klugman K. Antibiotic susceptibility patterns of *Streptococcus pneumoniae* in China and comparison of MICs by agar dilution and E-test methods. Antimicrob Agents Chemother 1998;42:2633–6.
[97] Wang H, Yu YS, Liu Y, Li HY, Hu BJ, Sun ZY, et al. Resistance surveillance of common community respiratory pathogens isolated in China, 2002–2003. Zhonghua Jie He He Hu Xi Za Zhi 2004;27:155–60 [in Chinese].
[98] Wang F. CHINET 2005 surveillance of bacterial resistance in China. Chin J Infect Chemother 2006;5:289–95.
[99] Shen X, Lu Q, Ye Q, Zhang G, Yu S, Zhang H, et al. Prevalence of antimicrobial resistance of *Streptococcus pneumoniae* in Chinese children: four hospitals surveillance. Chin Med J (Engl) 2003;116:1304–7.
[100] Zhu BM, Zhang YY, Wang F. Surveillance of bacterial resistance from hospitals in Shanghai in 2007. Chin J Infect Chemother 2008;6:401–10.
[101] Wang M, Zhang Y, Zhu D, Wang F. Prevalence and phenotypes of erythromycin-resistant *Streptococcus pneumoniae* in Shanghai, China. Diagn Microbiol Infect Dis 2001;39:187–9.
[102] Li J, Zhang Y, Lu Y, Chen Y, Liu J, Chen Y, et al. A surveillance study on penicillin-resistant *Streptococcus pneumoniae* in China. Chin Med J (Engl) 1999;112:655–8.
[103] Yao KH, Wang LB, Zhao GM, Zheng YJ, Deng L, Zhao RZ, et al. Surveillance of antibiotic resistance of *Streptococcus pneumoniae* isolated from hospitalized patients with pneumonia in four children's hospitals in China. Zhongguo Dang Dai Er Ke Za Zhi 2008;10:275–9 [in Chinese].
[104] Yao KH, Yu SJ, Shen XZ, Tong YJ, Gao W, Yang YH. Molecular epidemiology of penicillin-nonsusceptible *Streptococcus pneumoniae* in Beijing, China, 2000–2002. Zhonghua Er Ke Za Zhi 2005;43:671–5 [in Chinese].
[105] Shepard BD, Gilmore MS. Antibiotic-resistant enterococci: the mechanisms and dynamics of drug introduction and resistance. Microbes Infect 2002;4:215–24.
[106] Edmond MB, Ober JF, Dawson JD, Weinbaum DL, Wenzel RP. Vancomycin-resistant enterococcal bacteremia: natural history and attributable mortality. Clin Infect Dis 1996;23:1234–9.
[107] Carmeli Y, Eliopoulos G, Mozaffari E, Samore M. Health and economic outcomes of vancomycin-resistant enterococci. Arch Intern Med 2002;162:2223–8.
[108] Lucas GM, Lechtzin N, Puryear DW, Yau LL, Flexner CW, Moore RD. Vancomycin-resistant and vancomycin-susceptible enterococcal bacteremia: comparison of clinical features and outcomes. Clin Infect Dis 1998;26:1127–33.
[109] Leclercq R, Derlot E, Duval J, Courvalin P. Plasmid-mediated resistance to vancomycin and teicoplanin in *Enterococcus faecium*. N Engl J Med 1988;319:157–61.
[110] Uttley AH, George RC, Naidoo J, Woodford N, Johnson AP, Collins CH, et al. High-level vancomycin-resistant enterococci causing hospital infections. Epidemiol Infect 1989;103:173–81.
[111] Korten V, Murray BE. The nosocomial transmission of enterococci. Curr Opin Infect Dis 1993;6:498–505.
[112] Heath CH, Blackmore TK, Gordon DL. Emerging resistance in *Enterococcus* spp. Med J Aust 1996;164:116–20.
[113] Marin ME, Mera JR, Arduino RC, Correa AP, Coque TM, Stamboulian D, et al. First report of vancomycin-resistant *Enterococcus faecium* isolated in Argentina. Clin Infect Dis 1998;26:235–6.
[114] Fujita N, Yoshimura M, Komori T, Tanimoto K, Ike Y. First report of the isolation of high-level vancomycin-resistant *Enterococcus faecium* from a patient in Japan. Antimicrob Agents Chemother 1998;42:2150.

[115] Cao B, Liu Y, Song S, Li R, Wang H, Wang C. First report of clinical and epidemiological characterisation of vancomycin-resistant enterococci from mainland China. Int J Antimicrob Agents 2008;32:279–81.
[116] Zhu BM, Zhang YY, Wang F, Guo Y, Ruan FY, Ni YX, et al. Surveillance of bacterial resistance from hospitals in Shanghai in 2008. Chin J Infect Chemother 2009;06:401–11.
[117] Wang Z, Cao B, Liu YM, Gu L, Wang C. Investigation of the prevalence of patients co-colonized or infected with methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci in China: a hospital-based study. Chin Med J (Engl) 2009;122:1283–8.
[118] Dong F, Xu XW, Song WG, Lu P, Feng DX, Liu XG, et al. The changing pattern and antibiotic resistance of clinical bacterial isolates in a pediatric clinic from 2003 to 2008. Chin J Infect Chemother 2009;06:440–5.
[119] Jian C, Sun ZY, Li L, Zhang B, Wang B, Chen ZJ, et al. Surveillance of antimicrobial resistance in clinical isolates from Wuhan Tongji Hospital in 2007. Chin J Infect Chemother 2009;01:42–7.
[120] Zhu DM, Zhang YY, Wang F. Surveillance of bacterial resistance in Shanghai hospitals during 2006. Chin J Infect Chemother 2007;06:393–9.
[121] Hu FP, Ye XY, Wu PC, Zhu DM, Wang F. Surveillance of antibiotic resistance in clinical isolates from Shanghai Huashan Hospital in 2005. Chin J Infect Chemother 2007;04:233–7.
[122] Zhuge XL, Teng M, Yang Q, Yun S. Surveillance of antibiotic resistance in clinical isolates from First Affiliated Hospital of Zhejiang University Medical College in 2005. Chin J Infect Chemother 2007;04:263–8.
[123] Zhuo C, Jia B, Huang WX, Zheng XP, Li CZ. Surveillance of bacterial resistance from a hospital in Chongqing from 2004 to 2005. Chin J Infect Chemother 2007;05:376–9.
[124] Zhu DM, Wang F, Hang YY. Surveillance of bacterial resistance from hospitals in Shanghai in 2004. Chin J Infect Chemother 2005;04:195–200.
[125] Ye F, Zhong SQ, Yuan JP, Yang L, Zhong NS. Surveillance of antimicrobial resistance in Gram-negative bacilli isolated from lower respiratory tract of patients in Respiratory Intensive Care Unit for 5 consecutive years. Chin J Infect Chemother 2007;5:367–71.
[126] Ye HF, Chen HL, Yang YM, Li HY, Su DH, Huang lX. Surveillance of common pathogenic bacterial resistance in Guangzhou in 2003. Chin J Infect Chemother 2005;01:29–32.
[127] Zhu D, Wang F, Zhang Y. Surveillance of bacterial resistance from hospitals in Shanghai in 2003. Chin J Infect Chemother 2005;01:4–12.
[128] Liu X, Yang X, San B, Du T, Huang Y, Wu F. Surveillance of antimicrobial resistance of clinical isolates in Kunming in 2002. Chin J Infect Chemother 2004;04:202–5.
[129] Shen Z, Sun B, Du T, Huang Y, Wu F. A surveillance study on antimicrobial resistance of clinical isolates from the tertiary hospitals in Hubei area. Chin J Infect Chemother 2004;05:263–7.
[130] Li J, Li ZW. Clinical distribution and antibiotics resistance surveillance of 1073 strains of *Pseudomonas aeruginosa* in People's Hospital of Xinjiang Autonomous Region, 2003–2007. Chin J Infect Chemother 2009;04:286–8.
[131] Ni YX. CHINET 2005 surveillance of antimicrobial resistance in *Pseudomonas aeruginosa* in China. Chin J Infect Chemother 2007;04:274–8.
[132] Wu WY, Chen SW, He L, Wu JS, Lu YM, Li WQ, et al. Antimicrobial susceptibility of *Pseudomonas aeruginosa* to 10 antimicrobial agents. Chin J Infect Chemother 2005;05:301–3.
[133] Zhang YB, Zhang KX, Zhao F, Xi Y, Wen B, Tang YC. Distribution and resistance of clinical isolates in our hospital during 2002–2003. Chin J Infect Chemother 2005;01:17–20.
[134] Fang P, Pan X, Chen L. Surveillance on antimicrobial resistance of 1 904 strains of Gram-negative bacilli. Chin J Infect Chemother 2004;05:271–4.
[135] Zhu DM, Wang F, Hu F, Jiang X, Ni Y, Sun J, et al. CHINET 2009 surveillance of bacterial resistance in China. Chin J Infect Chemother 2011;05:321–9.
[136] Wang Y, Xu YC. CHINET surveillance of antimicrobial resistance among *A. baumannii* isolates in China during 2004–2005. Chin J Infect Chemother 2007;04:279–82.
[137] Chen Z, Zhu D, Zhang Y, Hu F, Wu S, Wang F. Surveillance for distribution and resistance of 10992 *Acinetobacter* spp. isolates in Shanghai, 1995–2003. Chin J Infect Chemother 2005;03:129–32.
[138] Wang F, Wu S, Zhu D. Surveillance of bacterial resistance in Shanghai in 1998. Zhonghua Nei Ke Za Zhi 1999;38:729–32 [in Chinese].
[139] Tiemei Z, Xiangqun F, Youning L. Resistance phenotypes and genotypes of erythromycin-resistant *Streptococcus pneumoniae* isolates in Beijing and Shenyang, China. Antimicrob Agents Chemother 2004;48:4040–1.
[140] Yang F, Xu XG, Yang MJ, Zhang YY, Klugman KP, McGee L. Antimicrobial susceptibility and molecular epidemiology of *Streptococcus pneumoniae* isolated from Shanghai, China. Int J Antimicrob Agents 2008;32:386–91.
[141] Cao B, Sun LY, Liu K, Li RS, Liu YM, Tong ZH, et al. A hospital-wide intervention program to optimize the utilization quality of carbapenems and glycopeptides. Zhonghua yi xue hui 2009;89:2557–60 [in Chinese].
[142] Yang Q, Yu YS, Ni YX, Sun JY, Xu YC, Sun HL, et al. CHINET 2007 surveillance of antibiotic resistance in *Enterococcus* in China. Chin J Infect Chemother 2009;03:175–9.
[143] Li S, Zhang Z, Mi ZH. Vancomycin-resistant enterococci in a Chinese hospital. Curr Microbiol 2007;55:125–7.