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Analytical study of the current Trends of Antibiotic Resistance Pattern among Bacterial Pathogens Isolates in Kuwait Hospital

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Abstract

Title: This paper is a review of all papers published during 2005-2015 concerning antibacterial resistance in Kuwaiti hospitals as ascertained by a literature search.

Background: Antibiotic resistance in hospitals is a serious problem worldwide, resulting in increases in morbidity, mortality and healthcare costs. This review was intended to derive an up-to-date picture of the situation in Kuwaiti hospitals, with the expectation that this might provide some guidance to authorities and involved medical and scientific workers in these institutions.

Methods and Findings: The PubMed database was searched using the following terms: antimicrobial resistance, antibiotic resistance, antibiotic stewardship, prevalence, epidemiology, mechanism of resistance and Kuwait.

Prevalence of resistant *E. coli* in Kuwait appears to be very high in Kuwait, with the figure of 77% being quoted in a 1990-2011 review. Resistance was higher in hospital-acquired (HA) urinary infections than in community-acquired (CA), with 2007 figures for cefotaxime being 17% in CA and 26% in HA and for gentamicin 15% and 26%. A 2010 analysis covering eight hospitals reported a range of 7.5% to 29% for third generation cephalosporin resistance and 14% to 40% for ciprofloxacin resistance. A 2002-2005 study found a prevalence of 11.7% ESBL-producing E. coli at one hospital, while figures for another hospital were 62%. The major strain of ESBL has been CTX-M-15 (90% of ESBL in a 2005-2006 study; 65.5% in a 2008 analysis). Carbapenem resistance was reported in *E. coli* in 2011.

Resistance in K. pneumonia is also prevalent in Kuwait, with a figure of 36.2% in the 1990-2011 review. A 2002-2005 study found 13.3% of clinically significant isolates from blood cultures to be ESBL-producing *K. pneumoniae*. At another hospital in 2010, 82.1% of K. pneumonia isolates were ESBL-producers. The predominant ESBL has again been CTX-M-15 (91% of ESBL in a 2005-2006 study). Outbreaks due to this clone were recorded in 2006 and 2008. The first reported finding of an OXA-48-producing *K. pneumoniae* (which hydrolyses carbapenems as well as penicillins) from the Arabian Peninsula was from a Kuwaiti patient in 2011. In the same year, the finding of a qnrA gene (conferring fluoroquinolone resistance) among ESBL-producing *K. pneumoniae* was first reported. A recent study reported *qnr* genes in 15.6 % of isolates from three major Kuwaiti hospitals.

The 1990-2011 literature survey revealed a comparatively low prevalence of 16.7% of resistance in *A. baumannii*. In the 2005-2007 survey of uropathogens, while resistance to amoxicillin/clavulanic acid increased from 54% to 77% in CA and 76% to 86% in HA, to cefotaxime from 65% to 88% in CA and 81% to 95% in HA, resistance to amikacin decreased from 12% to 4% in CA and 40% to 27% in HA, to ciprofloxacin from 15% to 4% in CA and 67% to 35% in HA, to cotrimoxazole from 12% to 8% in CA and 56% to 19% in HA, to gentamicin from 12% to 4% in CA and 57% to 22% in HA, and to piperacillin/tazobactam from 12% to 8% in CA and 55% to 32% in HA. A 2006-2007 outbreak of a carbapenem-resistant *A. baumannii* in an ICU unit was controlled with tigecycline but a 2011 study showed 13.6% resistance to tigecycline. Multi-drug-resistant (MDR) *A. baumannii* isolates are frequently carbapenemase producers (42.6% in a 2012 study). The diversity of such isolates is shown by the detection of 20 different sequence types in an analysis of 33 MDR isolates in a major hospital from 2011 and 2012, but bla (OXA-23) has become dominant, not only in Kuwait (85% in this series) but also through the Gulf Cooperation Council states (107 of 117 isolates in a 2011-2013 study).

CTX-M-15 type ESBL has also been documented in both *S. enterica* serotype typhi and nontyphoid Salmonella (2008), while the gyrA gene was found in *S. enterica* serotypes typhi and paratyphi A in 2010.

An analysis of 1,846 S. aureus isolates from 13 Kuwaiti hospitals during 2005 found 32% of these to be MRSA. Two outbreaks of MRSA in neonatal units in 2007 and 2011 were due to unusual strains not found in other hospitals, possibly indicating independent acquisition, especially given the diverse genetic backgrounds found in the latter instance.

Resistance prevalence in *S. pneumoniae* in Kuwait is very high, varying from 64% in one hospital to 54.5% in another.

Conclusions: Resistance is obviously a serious problem in Kuwaiti hospitals. This review gives some idea of the scope of the problem but there are many gaps and some anomalies. Some trends are apparent but the overall impression is of a constant state of flux. The extent to which the findings can be generalised to any particular hospital is limited. These factors make constant surveillance (including by molecular methods) by each hospital, as well as nationally, imperative. This, combined with well-instituted antibiotic stewardship, will assist in lessening the impact of resistance on morbidity, mortality and healthcare costs.

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Introduction

The World Health Organization has warned that the world is heading towards a post-antibiotic era, in which many common infections will no longer have a cure and, once again, kill unabated, and, with hospitals now the hotbeds for highly-resistant pathogens, such procedures as cancer treatments, sophisticated surgical operations and organ transplantations will become hazardous [1].

A Rand Report maintains that, by 2050, if the situation remains unabated, the world population will be between 11 million and 444 million lower than it would otherwise be, and the world economy smaller by between 0.06% and 3.1% [2].

Antibiotic resistance is usually associated with significant morbidity, longer hospitalisation and excess costs and mortality [3].

Excess costs associated with resistant microorganisms may be due to:

- Obligation to use more expensive antibiotics
- Longer hospital stay
- Higher mortality

- Delayed appropriate antibiotic therapy
- More common necessity to perform surgery [4].

A meta-analysis showed that bacteraemia due to extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae had a relative risk of death of 1.85 [5], while that due to methicillin resistant Staphylococcus aureus (MRSA) carried a relative death risk of 2.12 [6]. The increased mortality observed with resistant organisms appears to be due to delayed appropriate therapy or inappropriate therapy [4,5,7].

This analytical study is founded on the view that to defeat your enemy you must first know your enemy. It aims to discover the current situation with respect to antibiotic resistance in Kuwait hospitals, to the extent that this is possible by analyzing of reports in the literature. It must be admitted that, even restricting coverage to relatively recent papers, this is necessarily a historic view rather than an instant snapshot of the prevailing situation.

Methods

The PubMed database was searched using the following terms: antimicrobial resistance, antibiotic resistance, antibiotic stewardship, prevalence, epidemiology, mechanism of resistance and Kuwait. For the most part, this analytical study deals only with reports dealing with isolates from 2005 to 2015.

Results

Escherichia coli

E. coli is the most frequent cause of community- and hospital-acquired urinary tract infections and the most frequent cause of bloodstream infection at all ages. Resistance readily develops either through mutations or by acquisition of mobile elements [8].

A literature survey of articles published between 1990 and 2011 showed a prevalence of resistant *E. coli* in Kuwait (resistances to which antibiotics not cited) of 77%. This figure is easily the highest for any of the Gulf Cooperation Council countries, being more than five times that found for Bahrain and more than ten times that for Saudi Arabia [9].

An examination of resistances of isolates of *E. coli* from cases of urinary tract infections over a three year period (2005-2007) showed some interesting differences between isolates from outpatients and inpatients and between different antibiotics that may reflect changes in prescribing patterns: amikacin peak at 2% in community-acquired (CA) and 6% in hospital-acquired (HA) in 2006; amoxicillin/clavulanic acid lowest value at 25% in CA and 36% in HA in 2006; ampicillin fairly steady at average 66% in CA and increase from 72% to 78% in HA; cephalothin lowest value at 43% in CA and 57% in HA; cefotaxime increase from 9% to 17% in CA and fairly stable at average 26% in HA; ciprofloxacin increase from 26% to 30% in CA and 43% to 50% in HA; cotrimoxazole steady at 47% in CA and average 52% in HA; gentamicin increase from 12% to 15% in CA and 23% to 26% in HA; nalidixic acid increase from 10% to 44% in CA and 18% to 62% in HA; nitrofurantion increase from 5% to 9% in CA and stable at 8% in HA; piperacillin peak at 60% in CA and 70% in HA; piperacillin/tazobactam fairly steady at average 1% in CA and 4% in HA. Over the period, the prevalence of ESBL-producing *E. coli* increased from 9% to 17% in CA isolates but decreased from 30% to 27% in HA isolates [10].

Similar results were obtained for cefotaxime (28% resistant) and gentamicin (24% resistant) in an audit of isolates from neonatal sepsis cases in the main maternity hospital in Kuwait over the five-year period from January 2005 to December 2009 [11].

A three year prospective study (2002-2005) found a prevalence of 11.7% of ESBL-producing *E. coli* among clinically significant isolates from blood cultures at a major tertiary teaching hospital in Kuwait [12].

A study of isolates from clinical specimens at another hospital in 2010 detected ESBL production in 62% of *E. coli* isolates [13].

ESBL-producing *E. coli* isolates have been studied in detail. *E. coli* of phylogenic group B2, serotype O25:H4 and sequence type (ST) 131 is a major pandemic clone worldwide [14]. This clone was first reported from Kuwait in 2008 [15].Most strains exhibit the CTX-M ESBL. A study of ESBL-producing isolates from hospital and community patients in 2005 and 2006 found 90% to produce CTX-M-15, 5% CTX-M-9 and 5% CTX-M-14 [16]. An analysis from 2008 of 136 ESBL-positive isolates from the eight major hospitals in Kuwait found 77.9% harbouring *bla* (CTX-M) genes, with 84.1% of these being *bla* (CTX-M-15), 6.8% *bla* (CTX-M-14), 5.7% *bla* (CTX-M-14b) and 3.4% *bla* (TOHO-1). The study confirmed an explosive emergence of CTX-M-15 beta-lactamase in *E. coli* isolates and showed that the strains were clonally heterogeneous with no evidence of inter- or intra-hospital spread [17]. A 2010 report of isolates from eight government hospitals found consequent resistance to third generation cephalosporins varying from 7.5% to 29%. Ciprofloxacin resistance of these isolates ranged from 14% to 40% [18]. An analysis of a sample of 83 isolates of the clone from 832 multi-drug-resistant isolates obtained from 2010-2012 from three major Kuwait hospitals found 95.2% to harbour at least one *bla* gene, with *bla* (CTX-M-15) being the most prevalent. *Bla* (CTX-M-2) was identified for the first time in the Middle East and *bla* (CTX-M-56) for the first time outside Latin America [19]. Carbapenem resistance was reported in a strain in 2011 [20].

Klebsiella pneumoniae

Infections with *K. pneumoniae* are particularly common in hospitals among vulnerable individuals such as pre-term infants and patients with impaired immune systems, diabetes or alcohol-use disorders, and those receiving advanced medical care. *K. pneumoniae* carries a chromosomally located beta-lactamase gene that renders extended spectrum penicillins ineffective and acquires resistance to multiple antibiotics mainly through mobile genetic elements [8].

Resistance in *K. pneumonia* is high in Kuwait, with a figure of 36.2% being obtained from a literature finding covering the years 1990-2011 [9].

Interesting differences in trends were again seen in the study of resistant uropathogens from 2005 to 2007: amikacin peak in 2006 at 5% in CA and 8% in HA; amoxicillin/clavulanic acid increase from 18% to 24% in CA but decrease from 37% to 29% in HA; cephalothin increase from 20% to 31% in CA but peak at 46% in

2006 in HA; cefotaxime increase from 11% to 20% in CA and 17% to 33% in HA; ciprofloxacin increase from 16% to 26% in CA and from 29% to 43% in HA; cotrimoxazole lowest value in 2006 at 22% for CA and 27% for HA; gentamicin increase from 10% to 14% in CA but decrease from 27% to 13% in HA; nalidixic acid increase from 7% to 28% in CA and 14% to 33% in HA; nitrofurantoin lowest value in 2006 at 43% in CA but peak at 68% in the same year in HA; piperacillin peak in 2006 at 92% in both; piperacillin steady at 6% in CA but decrease from 19% to 14% in HA [10].

A three year prospective study (2002-2005) found a high prevalence (13.3%) of ESBL-producing *K. pneumonia* among clinically significant isolates from blood cultures at a major tertiary teaching hospital in Kuwait [12].

A study of isolates from clinical specimens at another hospital in 2010 detected ESBL production in 82.1% of *K. pneumoniae* isolates [13].

As with *E. coli*, the predominant ESBL has been CTX-M-15. In the 2005 to 2006 survey, this accounted for 91%, with CTX-M-9 constituting the other 9% [16].

An outbreak of bacteraemia due to a *K. pneumoniae* clone harbouring genes for CTX-M-15-like and SHV-12 ESBL in a neonatal intensive care unit of a Kuwaiti hospital in 2006 has been reported. The clone was also isolated from the hands of healthcare workers, suggesting they may have been involved in transmission [21].

Another outbreak, with a mortality rate of 21.4%, occurred in an intensive care unit in a teaching hospital during a two month period in 2008. All isolates harboured *bla* (CTX-M-15) and *bla* (TEM-1) genes. The same strain was obtained from a suction machine [22].

An audit of isolates from neonatal sepsis cases in the main maternity hospital in Kuwait over the five-year period from January 2005 to December 2009 found 24% of *K. pneumoniae* isolates resistant to cefotaxime and 20% to gentamicin [11].

A 2010 report documented an outbreak in a Kuwaiti hospital due to *K. pneumonia* producing the SHV-112 ESBL [23].

In 2012, the emergence of nosocomial New Delhi metallo-beta-lactamase-1- producing *K. pneumoniae* in patients admitted to a tertiary care hospital in Kuwait was reported [24].

In the same year, French workers reported the finding of the first OXA-48-producing *K. pneumoniae* from the Arabian peninsula in a patient with gangrene in her left foot who had been transferred to Paris from Kuwait. This finding is of great concern since this ESBL not only hydrolyses penicillins at a high level but also carbapenems at a low, but significant, level [25].

The emergence of the plasma-mediated *qnr* A gene, which confers fluoroquinolone resistance, among ESBL-producing nosocomial *K. pneumoniae* was reported for the first time in Kuwait in 2011 in a 2010 isolate [26].

A recent study of 173 ESBL-producing *K. pneumoniae* from three major hospitals found *qnr* genes in 15.6% of isolates [27].

Acinetobacter baumannii

A. baumannii is one of the most important opportunistic pathogens causing serious healthcare-associated complications in critically ill patients.

The 1990-2011 literature survey found a prevalence of 16.7% of resistant isolates in Kuwait less than 1/5 that recorded for Saudi Arabia [9].

In the 2005-2007 survey of uropathogens, while resistance to amoxicillin/clavulanic acid increased from 54% to 77% in CA and 76% to 86% in HA, to cefotaxime from 65% to 88% in CA and 81% to 95% in HA, resistance to amikacin decreased from 12% to 4% in CA and 40% to 27% in HA, to ciprofloxacin from 15% to 4% in CA and 67% to 35% in HA, to cotrimoxazole from 12% to 8% in CA and 56% to 19% in HA, to gentamicin from 12% to 4% in CA and 57% to 22% in HA, and to piperacillin/tazobactam from 12% to 8% in CA and 55% to 32% in HA [10].

Isolates of *A. baumannii* are frequently multiply resistant, including resistance to carbapenems. Some optimism was caused by the 2009 report of the success of controlling a carabapenem-resistant *A. baumannii* outbreak in an intensive care unit in Kuwait during 2006 and 2007 [28]. However, resistance was not long in developing and a 2011 study reported 13.6% resistance to tigecycline (and also to colistin) [29].

In the same year, a novel genetic structure harbouring *bla* PER-1 was identified in ceftazidime-resistant *A. baumannii* [30].

A 2012 study of multi-drug-resistant *A. baumannii* isolates collected from patients in two teaching hospitals in Kuwait found a high diversity of carbapenemases. Of the 94 isolates, 42.6% were resistant to imipenem or meropenem or both. Most (72.5%) of these isolates carried *bla* genes coding for MBL (VIM-2 and IMP-2) enzymes. Two harboured *bla* (OXA-23) [31].

The diversity of multi-drug-resistant (MDR) *A. baumannii* was confirmed in a study of isolates in a major Kuwaiti hospital from 2011 and 2012. Of 33 MDR isolates, 85% contained *bla* (OXA-23), 6% *bla* (OXA-24) and 18% *bla* (PER-1) genes. There were 20 different sequence types [32].

A study of 117 carbapenem-resistant *A. baumannii* isolates obtained from hospitals in various hospitals in the Gulf Cooperation Council states from July 2011 to January 2013 found OXA-23 in 107 and OXA-40 in five [33].

Another study, reported in 2013, found the wide dissemination of GES-type carbapenemases in *A.baumannii* isolates [34].

Pseudomonas aeruginosa

The 1990-2011 literature survey found a resistance prevalence of 2.6% much in line with other Gulf Cooperation Council countries but very much less than the 92.3% reported from Saudi Arabia [9].

The first report of ESBL-producing *P. aeruginosa* in the Middle East was from two isolates from the intensive care units of two different Kuwaiti hospitals in 1999 [35].

Salmonella

Salmonella is the main diarrhoeal pathogen transmitted by the food chain. Treatment of serious infections may be hampered by resistance to cephalosporins and/or fluoroquinolones. A 2008 report of a study over a two-year period in Kuwait and United Arab Emirates documented the emergence of CTX-M-15 type ESBL in both *S. enterica* serotype typhi and nontyphoidal *Salmonella* [36], while mutations in the *gyrA* gene resulting in fluoroquinolone resistance in *S. enterica* serotypes typhi and paratyphi A isolates from an infectious diseases hospital in Kuwait was reported in 2010 [37].

Shigella

Shigella is a major cause of diarrhoea and dysentery and causes more than a million deaths a year. Mobile genetic units are important in the spread of resistance determinants [8].

A 2010 report of a survey of isolates from stool samples of symptomatic patients at two Kuwaiti hospitals found high rates of resistance to the first line drugs (ampicillin 50%, cotrimoxazole 76%, tetracycline 76%) but little or no resistance to carbapenems, cephalosporins, fluoroquinolones or tigecycline [38].

Campylobacter jejuni

C. jejuni is a major cause of diarrhoea. Analysis of 85 isolates obtained during 2003-2006 from diarrhoeal stools at a teaching hospital in Kuwait found tetracycline resistance in 40%, with the resistance determinant carried on transmissible plasmids [39].

Staphylococcus aureus

Though a common commensal, *S. aureus* is also one of the most important human pathogens. The resistance of most concern is that due to acquisition of a *mecA* gene coding for a novel penicillin-binding protein, resulting in resistance to all beta-lactams and many other antibiotics so called methicillin-resistant *Staphylococcus aureus* (MRSA).

The prevalence of MRSA in Kuwait reported in the 1990-2011 survey was a low 3.3% (compared with 58.3% in Oman) [9]. However, an analysis of 1,846 *S. aureus* isolates from 13 Kuwaiti hospitals during 2005 found 32% of these to be MRSA (78% multi-resistant and 22% non-multi-resistant) [40].

Characterisation of 26 CA MRSA isolated from Kuwaiti hospitals from 2001 to 2003 showed two clones, ST30 and ST80, to be dominant [41].

Analysis of 135 CA MRSA isolates obtained from eight Kuwaiti hospitals throughout 2005 and 2006 showed the expansion of the ST80-SCC*mec*-IV clone, though nine other sequence types were detected [42].

The transmission of a rare clone of CA MRSA belonging to ST97 and with the SCC *mec*-V genotype among neonates in the neonatal intensive care unit and special care baby unit of a Kuwaiti hospital occurred between 10 and 30 April 2007 [43].

Between October and December 2011, CA MRSA was isolated from 20 of 21 babies in the Special Babies Care Unit. These belonged to diverse genetic backgrounds, suggesting they were acquired independently. However, the fact that ST60-SCC*mec*-IV, ST6-SC*mec*-IV and ST194-SCC*mec*-IV isolates were isolated from several babies suggests possible local transmission [44].

Streptococcus pneumoniae

S. pneumonia is a major cause of community-acquired pneumonia, meningitis and otitis media. Treatment is complicated by resistance to many beta-lactams due to chromosomally-mediated alteration of penicillin binding proteins.

The 1990-2011 survey reported a very high prevalence of resistance of 66.3% – more than twice that of the next highest for Gulf Cooperation Council countries [9].

Analysis of 397 consecutive clinical isolates collected during 2004 and 2005 in Kuwait showed 64% to be penicillin resistant [45]. Results of a similar study of 1,353 strains isolated from clinical specimens in a tertiary hospital in Kuwait gave the following results for the prevalence of resistance for the 2006-2007 period as: penicillin 54.5%, erythromycin 37.7%, tetracycline 41.3%, cotrimoxazole 62.8%, clindamycin 24.5% and chloramphenicol 3.7% [46].

Memish et al. have suggested that irrational and misguided use of antibiotics is the major driving force favouring the spread of penicillin resistant *S. pneumoniae* in Kuwait [47].

Group B Streptococcus (Streptococcus agalactiae)

Group B *Streptococcus* (GBS) is a leading cause of infections in neonates.

All 143 isolates of GBS isolates collected from mothers at the Maternity Hospital in Kuwait in 2006 and 2007 were susceptible to penicillin, ampicillin and cefotaxime but 92.3% were resistant to trimethoprim, 89.5% to tetracycline, 89.5% to minocycline, 76.9% to high level kanamycin, 30% to chloramphenicol, 12.6% to erythromycin, 7% to clindamycin, 3.5% to high level streptomycin and 0.7% to ciprofloxacin [48].

Application of molecular pathological epidemiology

Molecular Pathological Epidemiology (MPE) is an integrative science that so far has been applied mainly to analysing colorectal cancer [49-55]. No one has yet proposed using the MPE approach in microbiology, but it is possible to analyse molecular subtypes of microorganisms in relation to environment and host factors.

The emergence of MDR Gram-negative microorganisms has been largely associated with the excessive use of oxyimino-cephalosporins in clinical practice [21]. Resistance may be due to chromosomal mutations, acquisition of plasmids, or both. For instance, an A815G point mutation in the *bla* (SHV) gene causing an asparagine (AAT) to aspartic acid (GAT) mutation at position 253 of the enzyme resulted in the new SHV-112 ESBL [23]. Resistance to fluoroquinolones in *K. pneumoniae* may be due to emergence of the plasmid-mediated *qnr* A gene [26]. IncFII plasmids containing an MDR platform may acquire the *bla* (CTX-M-15) gene and contribute to the spread of CTX-M-15 [15]. Possession of the ISEcpl gene may also facilitate its spread [36].

Molecular epidemiological tools are important in developing

effective strategies for monitoring antibiotic resistance and may eventually help in devising methods for lessening its impact. Microorganisms, no less than larger organisms, are the product of their genes and their environment. Both of these can be quite fluid and interactions are undoubtedly complex. Nonetheless, MPE may well play a part in controlling antibiotic resistance and facilitating treatment of infectious disease.

Discussion

Compared to other Gulf Cooperation Council countries, Kuwait showed very high prevalence of resistance in E. coli and *S. pneumoniae* but comparatively low prevalence of MRSA in the analysis covering 1990-2011 isolates.

There appears to be an enormous increase in the prevalence of ESBL from 2002-2005 (11.7% in E. coli and 13.3% in *K.pneumoniae*) to 2010 (62% in E. coli and 82.1% in *K. pneumoniae*). However, these results are from two different hospitals and findings from eight hospitals indicated a range of 7.5-29% resistance to third generation cephalosporins and 14-40% to ciprofloxacin.

The predominant ESBL in both E. coli and *K. pneumoniae* has been CTX-M, with the explosive emergence of CTX-M-15 to reach 77.9% of ESBL in E. coli and 91% in *K. pneumoniae* in 2008. Clones have been heterogeneous, with no evidence of inter- or intra-hospital spread. The strain of *K. pneumoniae* isolated from an outbreak in 2006 in a neonatal ICU unit was also isolated from the hands of healthcare workers, while one involved in a 2008 outbreak in an ICU unit in a teaching hospital was isolated from a suction machine.

A carbapenemase was first reported in E. coli in 2011 and in 2012 (OXA-48) in *K. pneumoniae.*

A qnr gene coding for fluoroquinolone resistance was first encountered in *K. pneumoniae* in 2010and has recently been reported in 15.6% of ESBL-producing *K. pneumoniae*.

A wide diversity of carbapenemases has been detected in *A. baumannii*, belonging to 20 different sequence types, but with *bla* (OXA-23) predominant and GES-type also widely disseminated.

The first report of an ESBL-producing *P. aeruginosa* in the Middle East was made from a Kuwaiti hospital in 1999. Data on subsequent occurrences are missing.

The CTX-M-15 ESBL has also been reported in Salmonella and *gyrA* gene conferring fluoroquinolone resistance in 2010.

High resistance to first line drugs has been reported in Shigella and tetracycline resistance in *C. jejuni.*

The low prevalence of MRSA of 3.3% in the 1990-2011 survey does not accord with the 32% found in a 2005 examination of 1,846 *S. aureus* isolates from 13 Kuwaiti hospitals.

ST30 and ST80 have been the dominant clones, with the expansion of the ST80-SCC mec-11 clone through 2005 and 2006.

Two outbreaks in neonates in 2007 and 2011 involved strains with a diverse genetic background and lack of correspondence with strains in other hospitals, possibly indicating independent acquisition.

The decline in penicillin resistance in *S. pneumoniae* from 64% in 2004-2005 to 54.5% in 2006-2007 may be more apparent than real since the samples were different.

Resistance is obviously a serious problem in Kuwaiti hospitals. This analytical study gives some idea of the scope of the problem but there are many gaps and some anomalies. Some trends are apparent but the overall impression is of a constant state of flux. The extent to which the findings can be generalized to any particular hospital is limited. These factors make constant surveillance (including by molecular methods) by each hospital, as well as nationally, imperative. This, combined with well-instituted antibiotic stewardship, will assist in lessening the impact of resistance on morbidity, mortality and healthcare costs.

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