UNIVERSITI PUTRA MALAYSIA

MOLECULAR EPIDEMIOLOGY AND ANTIMICROBIAL RESISTANCE PROFILE OF ESBL-PRODUCING Escherichia coli *ISOLATED AT POULTRY FARMS AND POULTRY MEAT WET-MARKETS IN SELANGOR, MALAYSIA*

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By

ALIYU ABDULRASHEED BELLO

Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfillment of the Requirements for the Degree of Doctor of Philosophy

September 2016

DEDICATION

This work is dedicated to:

My late grandparents

Alh. Abubakar Sidiku Tunga (Mutawallen Gwandu)

Haj. Gado (Fadimatu)

Haj. Yaya (Rakiya)

My parents

Late Engr. Alh. Bello Aliyu

Haj. Aisha Abubakar Sidiku Tunga

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfillment of the requirement for the Degree of Doctor of Philosophy

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September 2016

Chairman : Professor Saleha Abdul Aziz, PhD
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Extended spectrum β-lactamase-producing- *Escherichia coli* (ESBL-EC) are emerging multidrug resistant zoonotic bacteria that threaten animal production, food safety and global antimicrobial therapy. It confers resistance to first line and most widely used antibiotic in both human and veterinary chemotherapeutics. ESBL-EC is a major public health problem challenging worldwide health care facilities including Malaysia. Poultry has been suggested to serve as a major pathway for human exposure to ESBL-EC. To date, there has been little to no research on the occurrence of ESBL-EC within the Malaysian poultry food chain. Hence, the objectives of the study were to determine the occurrence and distribution of ESBL-EC in broiler chickens and chicken meat, to assess their antimicrobial resistance profiles, to identify the potential risk factors associated with the occurrence of ESBL-EC, and to conduct molecular characterization and phylogenetic analysis on the ESBL-EC isolates. A cross-sectional study was conducted with 640 samples collected to determine the presence of ESBL-EC from broiler poultry farms (400 samples) and wet-markets (240 samples) in Selangor, Malaysia using culture and disk combination methods and polymerase chain reaction assays. The overall study was carried out between July-2012 to February 2015.

The findings demonstrated the wide distribution of ESBL-EC across the eight district areas of Selangor, Malaysia. At poultry farms, the overall proportion of ESBL-EC occurrence was 37.2%. There were significant differences in the proportions of ESBL-EC that occurred among poultry farms as well as within the type of study samples. Of the eight farms, Farm A (Gombak), Farm B (Klang) and Farm C (Hulu Selangor), had the highest occurrence rate at 62%, 50%, and 50% respectively, followed by Farm D (Petaling) 38%, Farm E (Sepang) 34%, Farm F (Kuala Langat) 26% and Farm G (Kuala Selangor) 24%, and the lowest was in Farm H (Hulu Langat) 14%. Among the study samples, chicken had the highest occurrence rate at 45.4%, followed by the chicken house floor at 40%, and flies 30%, while feed and water samples were at

17.5%, and 12.5% respectively. Two hundred and forty samples (240) were collected from 40 broiler poultry stalls at wet-markets, with five stalls representing each district area. The overall prevalence was 48.8%. Among the district areas, Hulu Selangor had the highest occurrence rate at 66.7%. Moderate proportion was seen in Hulu Langat 56.7%, and Kuala Selangor 50%. The lowest proportions were found in Klang 46.7%, Sepang 46.7%, Petaling 43.3%, Gombak 40%, and Kuala Langat 40%.

To determine possible factors associated with the presence of ESBL-EC at poultry farms and poultry meat wet-markets, a questionnaire was used as an instrument to obtain information and the data were analyzed using Chi-square test and logistic regression analysis at p-value of less than 0.05. At poultry farms, ten factors were found to be significantly associated in the occurrence of ESBL-EC, which were broadly classified into farm management, biosecurity, and medical history such as antibiotic usage. At the poultry meat wet-markets, only four factors had the significant association with ESBL-EC contamination, which included stall sanitation, type of counter top, source of cleaning water, and type of cutting board.

The antimicrobial resistant profiles of ESBL-EC isolated from poultry farm and wet-markets were determined using the standard disc diffusion method, according to CLSI guidelines. The ESBL-EC isolates were screened for susceptibility against 11 panels of antibiotics and 98% of the isolates showed resistance to tetracycline, 91.9% to cefotaxime, 85.2% to sulfamethoxazole/trimethoprim, 78.5% to nalidixic acid, 73.8% to chloramphenicol, 65.1% to cefpodoxime, 64.4% to ciprofloxacin, 61.1% to ceftriaxone, 59.7% to gentamicin, 53.7% to ceftazidime, and the least resistance was to aztreonam at 30.2%. At the wet-markets, ESBL-EC isolates were also tested against the same panels of 11 antibiotics and 99.1% showed resistance to tetracycline, 94.9% to cefotaxime, 93.2% to nalidixic acid, 82.1% to sulfamethoxazole/trimethoprim, 80.3% to chloramphenicol, 78.6% to ciprofloxacin, 59.8% to cefpodoxime, 41.0% to ceftriaxone, 23.9% to gentamicin, and the least resistance was to aztreonam at 21.4%.

For the molecular characterization and phylogenic analysis of ESBL-EC, representative isolates from the poultry farms and wet-markets, pulsed-field gel electrophoresis (PFGE) were used. To analyse the PFGE results, 85% similarity was used as the study cut-off point. Although there is wide genomic diversity between, within and across the poultry farms and poultry meat wet- markets isolates. However, the PFGE molecular epidemiological results had evidently demonstrated genomic relationship within the selected study isolates. At the poultry farms, PFGE molecular fingerprinting revealed four major phylogroupings, with 16 isolates demonstrating genomic relationship that ranges 100% to 85% genetic similarity, between and within the poultry farms. Similarly, at the poultry meat wet-markets, four major phylogroups were detected, with 11 isolates demonstrating genomic relationship that ranges from 100% to 86% genetic similarity, between and within the poultry farms. Phylogenetic analysis for the combination of poultry farms and poultry meat wet-markets isolates revealed six major phylogroups, with eight isolates demonstrating genomic relationship across the poultry farms and poultry meat wet-markets, which range from 92% - 85% genetic similarity.

In conclusion, the present study indicated the high occurrence and wide dissemination of multidrug resistant ESBL-EC at the poultry farms and wet-markets. The ESBL-EC occurrence was associated with several factors that can be broadly classified under imprudent use of antibiotics, poor husbandry, management and biosecurity practices at the farms; while the poultry meat wet-market factors included poor personal hygiene and sanitary practices, poor environmental sanitation and lack of good manufacturing practices. Thus, the findings of the study can assist to serve as a useful guide to Veterinary/Public Health authority in designing evidence-based mitigation strategies for effective control of ESBL-EC at poultry farms and poultry meat wet-markets.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Doktor Falsafah

EPIDEMIOLOGI MOLEKUL DAN PROFIL RINTANGAN ANTIMIKROBIA ESBL-*Escherichia coli* TERASING DI LADANG AYAM DAN PASAR BASAH DAGING AYAM DI NEGERI SELANGOR, MALAYSIA

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Spektrum terluas pengeluaran β-laktamase- *Escherichia coli* (ESBL-EC) merupakan bakteria zoonotik rintangan berbilang ubatan yang muncul yang mengancam pengeluaran haiwan, keselamatan makanan, dan terapi antimikrobia global. Ubatan tersebut memberikan rintangan kepada antibiotik barisan pertama dan antibiotik yang paling banyak digunakan dalam kemoterapi manusia dan veterinar. ESBL-EC merupakan masalah utama kesihatan awam yang mencabar kemudahan penjagaan kesihatan sejagat, termasuk Malaysia. Poltri merupakan laluan utama bagi pendedahan manusia kepada ESBL-EC. Sehingga kini, kurang terdapat atau boleh dikatakan tiada penyelidikan mengenai kehadiran ESBL-EC dalam lingkungan jaringan makanan poltri terutama ayam di Malaysia. Oleh sebab itu, objektif kajian ini adalah untuk menentukan kadar kehadiran ESBL-EC pada ayam dan daging ayam, untuk menilai profil rintangan antimikrobia, mengenalpasti faktor risiko potensi yang berkaitan dengan kehadiran ESBL-EC, dan untuk menjalankan pencirian molekul serta analisis filogenetik terhadap isolat ESBL-EC. Kajian keratanrentas telah dilaksanakan ke atas 640 sampel yang dikumpul untuk menentukan kehadiran ESBL-EC di ladang ayam pedaging (400 sampel) dan daging ayam di pasar basah (240 sampel) di Selangor, Malaysia dengan menggunakan kaedah kombinasi kultur dan disk dan assai reaksi jarring polymerase (PCR). Keseluruhan kajian telah dijalankan antara Julai 2012 hingga Februari 2015.

Hasil kajian menunjukkan bahawa sebaran ESBL-EC yang meluas merentasi lapan kawasan daerah di Selangor, Malaysia. Di ladang ayam, keseluruhan kadar kehadiran ESBL-EC ialah 37.2%. Terdapat perbezaan yang signifikan daripada segi kadar ESBL-EC yang hadir dalam kalangan ladang ayam dan dalam lingkungan jenis sampel kajian. Antara lapan ladang, Ladang A (Gombak), Ladang B (Klang) dan Ladang C (Hulu Selangor), mempunyai kehadiran yang paling tinggi, iaitu masing-masing 62%, 50% dan 50%, diikuti oleh Ladang D (Petaling) 38%, Ladang E (Sepang) 34%, Ladang F (Kuala Langat) 26% dan Ladang G (Kuala Selangor) 24%, dan yang paling rendah ialah Ladang H (Hulu Langat) 14%. Antara sampel kajian, ayam mempunyai

kadar kehadiran paling tinggi, iaitu 45.4%, diikuti oleh lantai rumah ayam iaitu 40%, dan lalat 30%, manakala sampel makanan dan air adalah masing-masing 17.5%, dan 12.5% . Dua ratus dan empat puluh sampel (240) telah dikumpulkan daripada 40 gerai daging ayam di pasar basah, dengan lima gerai mewakili setiap kawasan daerah. Keseluruhan kehadiran ialah 48.8%. Antara kawasan daerah, Hulu Selangor mempunyai kadar yang paling tinggi, iaitu 66.7%. Kadar yang sederhana didapati di daerah Hulu Langat, iaitu 56.7%, dan Kuala Selangor 50%. Kadar yang paling rendah ialah daerah Klang 46.7%, Sepang 46.7%, Petaling 43.3%, Gombak 40%, dan Kuala Langat 40%.

Bagi menentukan faktor risiko yang mungkin berkaitan dengan kewujudan ESBL-EC di ladang ayam dan pasar basah daging ayam, soalselidik telah digunakan sebagai instrument untuk memperoleh maklumat dan data telah dianalisis menggunakan ujian khi kuasa dua (*chi-square test*) dan analisis regresi logistik pada nilai $p < 0.05$. Di ladang ayam, sepuluh faktor risiko telah dikenalpasti secara signifikan yang berkaitan dengan kehadiran ESBL-EC, yang telah diklasifikasikan secara kasar kepada pengurusan ladang, biokeselamatan, dan sejarah perubatan seperti penggunaan antibiotic. Di pasar basah daging ayam, hanya empat faktor mempunyai kemungkinan secara signifikan sebagai penyebab kontaminasi dengan ESBL-EC, termasuk sanitasi gerai, jenis permukaan kaunter, sumber air pembersihan, dan jenis papan memotong daging.

Profil rintangan antimikrobia isolat ESBL-EC daripada ladang ayam dan pasar basah telah ditentukan menggunakan kaedah difusi disk standard, berdasarkan garispanduan CLSI . Isolat ESBL-EC telah uji kepekaan terhadap 11 panel antibiotik dan 98% isolat daripada ladang ayam menunjukkan rintangan terhadap *tetracycline,* 91.9% *cefotaxime*, 85.2% *sulfamethoxazole/trimethoprim*, 78.5% *nalidixic acid*, 73.8% *chloramphenicol*, 65.1% *cefpodoxime,* 64.4% *ciprofloxacin*, 61.1% ceftriaxone, 59.7% *gentamicin*, 53.7% *ceftazidime*, dan rintangan paling rendah adalah terhadap *aztreonam*, 30.2%. Isolat ESBL-EC daripada pasar basah menunjukkan rintangan antibiotik seperti berikut: *tetracycline* 94.9%, *cefotaxime* 93.2%, *nalidixic acid* 82.1%, *sulfamethoxazole/trimethoprim* 80.3%, *chloramphenicol* 78.6%, *ciprofloxacin* 59.8%, *cefpodoxime* 41.0%, *ceftriaxone* 23.9% *gentamicin* dan rintangan paling rendah adalah terhadap *aztreonam* 21.4%.

Bagi pencirian molekul dan analisis filogenik isolat ESBL-EC, isolat daripada ladang ayam dan pasar basah, elektrophoresis gel medan denyut (PFGE) telah digunakan. Bagi menganalisis keputusan PFGE, 85% persamaan telah digunakan sebaga ititik pemisah.Terdapat kepelbagaian genomik yang merentasi isolat ladang ayam dan pasar basah daging ayam .Walaubagai mana pun, keputusan epidemiologi molekul PFGE telah terbukti menunjukkan hubungan genomik dalam lingkungan isolat terpilih yang dikaji. Di ladang ayam, pencapjarian molekul PFGE memperlihatkan empat filokumpulan utama, dengan 16 isolat mempamerkan hubungan genomik yang berjulat 100% hingga 85% persamaan genetik, antara dan dalam ladang ayam. Begitu juga di pasar basah daging ayam, empat filokumpulan utama telah dikesan, dengan 11 isolat mempamerkan hubungan genomik yang berjulat daripada 100% hingga 86% persamaan genetik, antara dan dalam pasar basah. Analisis filogenetik bagikombinasi isolat ladang ayam dan pasar basah daging ayam menunjukkan enam filokumpulan utama, dengan lapan isolat mempamerkan hubungan genomic merentasi ladang ayam dan pasar basah daging ayam, dengen persamaan genetik berkisar 92% - 85%.

Sebagai kesimpulan, kajian ini memperlihatkan kehadiran ESBL-EC yang tinggi dan sebaran ESBL-EC rintangan berbilang ubatan (MDR) yang luas di ladang ayam dan di pasar basah. Kehadiran ESBL-EC telah dikaitkan dengan pelbagai faktor risiko yang secara kasar dapat diklasifikasikan sebagai penggunaan antibiotik yang tak berhemah, amalan penternakan, amalan pengurusan dan amalan biokeselamatan yang lemah di ladang ayam; mana kala faktor di pasar basah daging ayam pula adalah termasuk amalan kebersihan yang lemah dan juga sanitasi persekitaran yang kurang. Oleh sebab itu, daripada hasil kajian ini diharapkan dapat membantu pihak berkuasa Kesihatan Awam / Veterinar dalam merekabentuk strategi mitigasi kawalan ESBL-EC yang berkesan di ladang ayam dan di pasar basah daging ayam.

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This thesis was submitted to the Senate of the Universiti Putra Malaysia and has been accepted as fulfillment of the requirement for the degree of Doctor of Philosophy. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

AMR	Antimicrobial resistance
APEC	Avian pathogenic *E. coli*
CDC	Centers for Disease Control and Prevention
CI	Confidence Interval
CIPARS	Canadian Integrated Program for Antimicrobial Resistance Surveillance
CLB	Cell lysis buffer
CLSI	Clinical and Laboratory Standards Institute
DAEC	Diffusely adherent *E. coli*
DNA	Deoxyribonucleic acid
Dntp	Deoxyribonucleotide triphosphate
DSC	Decreased susceptibility to cephalosporins
DSM	Department of Statistics Malaysia
DVS	Department of Veterinary Services
EAEC	Enteroaggregative *E. coli*
EDTA	Ethylenediaminetetraacetic acid
EHEC	Enterohaemorrhagic *E. coli*
EIEC	Enteroinvasive *E. coli*
ELISA	Enzyme-linked immunosorbent assay
EPEC	Enteropathogenic *E. coli*
ESBL-EC	Extended-spectrum beta-lactamase producing *Escherichia coli*
ESBLs	Extended-spectrum beta-lactamases
ESC	Extended-spectrum cephalosporins
ETEC	Enterotoxigenic *E. coli*

FAO	Food and Agricultural Organization of United Nation
HPAI	Highly Pathogenic Avian Influenza
IDSA	Infectious Diseases Society of America
MDR	Multidrug resistant
MHA	Mueller-Hinton agar
MIC	Minimum Inhibitory Concentration
MMT	Million Metric Tons
MRSA	Methicillin resistance *Staphylococcus aureus*
MT	Metric Tons
NAG	N-acetylglucosamine
NAM	N-acetylmuramic acid
NARMS	Antimicrobial Resistance Monitoring System
NMEC	Neonatal meningitis *E. coli*
OIE	International Organization for Animal Health
OR	Odds ratio
PBPs	Penicillin-binding proteins
PCR	Polymerase chain reaction
PFGE	Pulsed field gel electrophoresis
PPE	Personal Protective Equipment
REF	Reference variable
RM	Malaysian Ringgit
rRNA	Ribosomal ribonucleic acid
SSC*mec*	Staphylococcus cassette chromosome mec
TBE	Tris-Borate-EDTA
UPEC	Uropathogenic *E. coli*

UPM	Universiti Putra Malaysia
USDA	United States Department of Agriculture
UTI	Urinary tract infection
VRI	Veterinary Research Institute
WHO	World Health Organization
WPR	World Poultry Report

CHAPTER 1

INTRODUCTION

Extended-spectrum beta-lactamase producing *Escherichia coli* (ESBL-EC) are plasmid mediated emerging zoonotic and multidrug resistant bacteria. ESBL-EC bear resistance to β-lactams, the penicillins first-, second-, third- and fourth-generation cephalosporins and monobactam; with the exception of cephamycins and carbapenems. At the same time they possess co-resistance to several other groups of antibiotics. However, ESBL-EC are inhibited by clavulanic acid and tazobactam (Rawat & Nair, 2010).

Beta-lactams (β-lactams) are first line antibiotics in human and veterinary medicine (Ewers et al., 2011; Liu et al., 2007). Over the last six decades, β-lactams are considered as the most widely used antibiotic (Livermore et al., 2006). WHO (2009) have categorized β-lactams as critically important antimicrobials for veterinary medicine and highly important antimicrobials in human medicine, with high efficacy and safety in clinical drug therapy. Thus resistance to this group of antibiotics serves as a great threat to public and animal health (Sahu et al., 2011).

The continuous exposure of bacterial strains to the first and second generation cephalosporins has induced a dynamic mutation, with an increase selective pressure and dramatic expansion of β-lactamases spectrum of activity and formation of a newly hydrolytic enzyme known as extended-spectrum beta-lactamases (ESBLs) (Shaikh et al., 2015). These are enzymes that confer resistance to the newly developed extended spectrum β-lactams (third- and fourth-generation cephalosporins). ESBLs are primarily produced by Enterobacteriaceae, particularly *Klebsiella pneumoniae* and *E. coli*. *Escherichia coli* has been reported as the most dominant ESBLs producing organism across the world (Kassakian et al., 2014).

The distribution of ESBLs producing organisms showed endemic level in several countries across the globe (Cantón & Coque, 2006), with several studies consistently reporting relatively high prevalence of ESBLs-positive organisms worldwide; however, Asia has been reported to have the highest proportion of ESBL-EC (Paterson et al., 2005; Dhillon and Clark 2011).

The misuse of extended-spectrum cephalosporins (ESC) in human and veterinary medicine has been considered as the major factor facilitating the development and global dissemination of ESBLs (Ewers et al., 2012). This alarming trend is further favored by the horizontal transfer of plasmid mediated ESBLs encoding gene among different bacterial populations, and the ability of *E. coli* to survive and proliferate across human and animal populations, and in their environment (Cantón et al., 2012; Zurfluhet al., 2014).

Food safety and antimicrobial resistance have recently received international attention, over their huge impact on economy, public health, and their potential threat to post-antibiotic era (WHO, 2014). ESBL-EC is the most frequent cause of blood stream infections, community and hospital acquired urinary tract infection, also associated with increased mortality, prolonged hospitalization, and increased cost of hospitalization, limited therapeutic option, high rate of treatment failure, co-resistance to several groups of antibiotics, and the world most leading cause of foodborne infection (Kotapati et al., 2005; Schwaber et al., 2006; Kraker et al., 2011; Rottier et al., 2012; WHO, 2014).

The incidence of outbreaks and nosocomial infections caused by ESBLs-producing *K. pneumoniae* harboring SHV-5 β-lactamase was reported in a Malaysian tertiary hospital in 1995- 1996 (Subramaniam et al., 2006). Two years later, another variant of SHV-5-β-lactamase was detected from the same hospital; thus it was postulated to be acquired via the horizontal transfer of plasmid encoding SHV-5 ß-lactamase genes from the predominance threat of SHV-5 ß-lactamases in *K. pneumoniae* isolates that were persistently experienced in the hospital (Subramaniam et al., 2006). Since the first identification of ESBL-EC, it has continue to be a major problem affecting the health care settings in Malaysia (Lim et al. 2009; Sekawi et al. 2008), thus threatening the efficacy of clinical drug therapy.

Poultry industry constitutes a greater percentage of human food animal protein source and poultry has been questioned as a major reservoir for the dissemination of ESBL-EC among humans, which were acquired directly or indirectly through poultry production, handling, processing and consumption of contaminated poultry product (Kola et al., 2012; Hille et al., 2013; Sharp et al., 2013). However, little or no research has been conducted in Malaysia in order to understand the potential role of poultry industry in the dynamic rise and dispersal of ESBL- *E. coli* within the community. Thus, there is a need to understand the role of poultry food chain as an important exposure pathway for acquisition and transmission of ESBL-EC into human populations. Hence, this warrants the study on the prevalence and operational and management practices that may significantly contribute to the occurrence of ESBL-EC in poultry farms and poultry-meat retail-markets. Understanding this phenomenon is very crucial in designing an effective and evidence-based veterinary and public health intervention, which will serve as a useful guide for the control and prevention of ESBL-EC along the poultry food chain.

The study was designed to answer the following questions:

1. What is the prevalence of ESBL-EC in poultry farms and poultry-meat retail-markets in Selangor, Malaysia?
2. What types of β-lactamase encoding genes are associated with the phenotypically detected ESBL-EC from poultry farms and poultry meat wet-markets in Selangor, Malaysia?
3. What types of antibiotics were the isolates resistant to?
4. What factors were possibly associated with the occurrence of ESBL-EC in poultry farms and poultry meat retail-markets?

5. Is there any molecular relationship between and within the ESBL-EC isolated from the farms and markets?

The hypotheses were:

1. There is a variation in the occurrence of ESBL-EC between and within the poultry farms and poultry meat wet-markets of Selangor, Malaysia.
2. There is a difference in the level of antibiotic resistance among the isolates of poultry farms and poultry meat wet-markets.
3. Several risk factors play a vital role in the occurrence of ESBL-EC at poultry farms and poultry meat wet-markets.
4. There are genetic similarities between and within the ESBL-EC isolated from the poultry farms and poultry meat wet-markets.

General objective

The study aimed to determine the prevalence, antimicrobial resistant profile, genetic similarities and risk factor associated with ESBL-EC in poultry farms and poultry-meat retail-markets in Selangor, Malaysia.

Specific objectives

1. To determine the prevalence of ESBL-EC in poultry farms and poultry meat wet-markets in Selangor, Malaysia.
2. To determine the level of antibiotic resistance of the ESBL-EC isolates.
3. To determine the risk factors associated with the occurrence of ESBL-EC in the poultry farms and poultry meat wet-markets.
4. To conduct molecular characterization and cluster analysis among the ESBL-EC isolates.

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