Minireview

The public health risks of multiple-drug resistant (MDR) Enterococcus spp. in Southeast Asia

Diane Sunira Daniel a,b #*, Sui Mae Lee a,b, Gary A. Dykes a, and Sadequr Rahman a,b

School of Science, Monash University Malaysia, Selangor, Malaysia a; Tropical Medicine and Biology Platform, Monash University Malaysia, Selangor, Malaysia b

Running Head: Multiple drug resistant (MDR) Enterococcus spp.

Keywords: Antibiotics, Enterococcus spp, Public health, Southeast Asia, Transmission.

#Address correspondence to Diane Sunira Daniel, dsdan2@student.monash.edu

* Present address: Diane Sunira Daniel, School of Science, Monash University Malaysia, Selangor, Malaysia.
Abstract – 130 words

Enterococci rank as one of the leading causes of nosocomial infections, such as urinary tract infection, surgical wound infection and endocarditis in humans. These infections can be hard to treat due to the rising incidence of antibiotic resistance. Enterococci inhabiting nonhuman reservoirs appear to play a critical role in the acquisition and dissemination of antibiotic resistance determinants. The spread of antibiotic resistance has become a major concern in both human and veterinary medicine, especially in Southeast Asia where many developing countries have poor legislations and regulations to control the supply and excessive use of antimicrobials. This review addresses the occurrence of antibiotic resistant enterococci in ASEAN (Association of Southeast Asian Nations) countries and proposes infection control measures that should be applied to limit the spread of multiple drug resistant enterococci.
The enterococci are a complex and diverse group of bacteria. They are commonly found in the gastrointestinal tract, female genital tract, oral cavity and skin of humans and other animals. Enterococci are also found in soil, water, and foods. Different species of enterococci are able to grow between 10°C to 45°C and in environments with a broad range of pH values (1). These characteristics present a challenge to those who wish to control the spread of the pathogenic species of these organisms which can pose serious infections in humans and animals. In addition, enterococci have the capacity to acquire a wide variety of antimicrobial resistant factors through horizontal exchange of mobile genetic material which presents further problems in the management of patients with enterococcal infections (2). Enterococci can be transmitted to humans by various means including contaminated food and water sources (3). The presence of antibiotic resistant enterococci in the faecal material of animals has therefore become a major global concern in both human and veterinary medicine. Most of the studies concerning the transmission of microorganisms from food animals to humans have focused on pathogens that pose a direct threat to human health (4). Given the significant importance of *Enterococcus* spp. to public health and the farming industry, additional information on the genetics and transmission of multi-drug resistance in these species is essential.

Legislation and regulations to control the supply and excessive use of antimicrobials are very poor in many developing Southeast Asian countries (5, 6, 7) and the prevalence of antimicrobial resistance of major bacterial pathogens such as enterococci has been rapidly increasing in Asia (8, 9, 10, 65). In particular the rise of multi drug resistant (MDR) enterococci is of great concern.
This review briefly summarises the classification of enterococci and discusses the incidence and causes of MDR enterococci in non-human reservoirs, particularly farm animals and water supplies. The prevalence in hospitals is also reviewed and possible control measures are suggested with a particular focus on the Association of Southeast Asian Nations (ASEAN).

**Human Reservoirs of Enterococcus spp.**

*Enterococcus* spp. are normal flora of the human gastrointestinal tract (11). Enterococci are minority members of the bacterial community in humans, as molecular analysis has shown that these bacteria make up no more than 1% of the intestinal microflora of an adult (1, 12). However, the medical importance of these bacteria overshadows their relative numbers in the intestinal tract. This is due to *Enterococcus* spp. now ranking as among the leading causes of nosocomial infections in humans (13).

Enterococci are well adapted for living in biofilms where adhesion to extracellular matrix proteins of the human gut is the first step in colonization and infection (14, 15). The ability to form biofilms is a critical factor in causing endodontic and urinary tract infections as well as endocarditis. According to the National Institutes of Health, biofilms are involved in over 80% of microbial infections in the body (16). A mature biofilm can tolerate antibiotics at concentrations of 10 to 1000 times more than are required to kill planktonic bacteria (17). A recent study in Australia determined significant clonal variation of clinical *Enterococcus faecalis* isolates in their capacity to form biofilms when subjected to sub-minimum inhibitory concentration (MIC) levels of antimicrobial compounds, Clindamycin and Tetracycline, found in endodontic medicaments (18). A strong correlation between the presence of the virulence gene, *esp*, and the ability of enterococci to form biofilms in vitro has also been reported (19, 20, 21). The
contribution of *esp* to biofilm formation was found to be most pronounced in the presence of 0.5% (wt/vol) or greater glucose (19). These results suggest that, whereas *esp* is important in biofilm formation, additional determinants in *E. faecalis* may also contribute to biofilm formation (19). Studies on antibiotic resistance and biofilm production of enterococci with relevance to Southeast Asia have not been focused on due to fragmented information.

Certain strains of enterococci have long been known as important causes of endocarditis and in the 1970’s began to be recognized as common causes of hospital-acquired urinary tract and wound infections (13). While traditionally 90% of all enterococcal infections were caused by *E. faecalis* and only 10% by *E. faecium*, the proportion of *E. faecium* has gradually increased over the years to 40% (1). Other enterococcal species, including *E. avium, E. casseliflavus, E. cecorum, E. dispar, E. durans, E. gallinarum, E. hirae, E. malodoratus, E. mundtii, E. pseudoavium, E. raffinosus, E. saccharolyticus, E. seriocoida* and *E. solitarius* are primarily found in the gastrointestinal tract of various animals but occasionally isolated from human infections (1).

**Non-human Reservoirs of *Enterococcus* spp.**

Apart from humans, *Enterococcus* spp. are a natural part of the intestinal flora in most mammals and birds (22). The livestock industries of Southeast Asia, China and Papua New Guinea play a major role globally in terms of meat production, contributing roughly 13 to 33% of global meat production from 1979 to 2004 (23). Southeast Asia also imports livestock from China, India, Australia and the US. The large importers of livestock, mainly cattle and pigs, are Singapore, Malaysia and Indonesia (23). Studies carried out in Malaysia, Thailand, Vietnam, Indonesia, and other Southeast Asian countries reported MDR enterococci isolated from livestock and animal...
related products (22, 24). Many Southeast Asian nations such as Malaysia, Myanmar, Indonesia, Thailand and Vietnam have flourishing poultry and livestock industries, and are also major exporters around the Asian region (25). Countries that either export or import livestock or chickens could be inadvertently involved in the spread of MDR *E. faecalis* due to the widespread use of antimicrobials in these industries as discussed later (26).

**Use of antimicrobials in Southeast Asia**

In addition to the treatment of human infection, antimicrobial agents are used on food animals, on pets and for laboratory use. In modern food animal production, antimicrobial agents are used in four different ways: (i) therapy, the treatment of infections of animals; (ii) metaphylactics, the treatment of clinically healthy animals belonging to the same flock or pen as animals with clinical signs; (iii) prophylactics, the treatment of healthy animals in a period of stress to prevent disease, such as during early weaning; and (iv) growth promotion, the inclusion of antimicrobial agents continuously in animal feed to prevent infections and improve growth (27, 28).

It is challenging to obtain reliable data on quantities of antimicrobial agents used on food animals worldwide. In the US, the farm animal population (consisting of approximately 5.34 million lamb and sheep, 89.3 million cattle, 113.2 million pigs and 479 million poultry in 2012) used an estimated quantity of antimicrobial agents of 13542 tonnes, while the usage for humans was estimated to be approximately 3289 tonnes, in 2011 (29, 30). According to a 2013 report in the UK from the Department for Environmental Food and Rural Affairs (DEFRA), it was estimated that approximately 290 tonnes of antimicrobial agents were sold for food animals in 2011 (31). The UK farm animal population consisted of approximately 32 million lamb and sheep, 9.7 million cattle, 4.8 million pigs and 162 million poultry in 2012 (32). Antimicrobial
consumption data are lacking in many developing countries including ASEAN countries (33).

Table 1 shows the livestock population in ASEAN countries from the year 2010 as well as the estimated antimicrobial consumption in cattle, chicken and pigs (34). The estimates of antimicrobial consumption presented in Table 1 are based on antimicrobial consumption per population correction unit (PCU) as devised by Van Boeckal (35) for Organization for Economic Co-operation and Development (OECD) countries. The mean of the posterior for antimicrobial consumption in cattle was 45 mg/PCU, 148 mg/PCU for chickens and 172 mg/PCU for pigs (35). PCUs are used to compare population and production of different types of livestock across countries and correspond to 1kg of living or slaughtered animals (36) using an estimate of 2.5 kg per chicken (37), 100 kg per pig (38) and 600 kg per cattle (39). Assuming that antimicrobial consumption in chicken, cattle and pigs represent majority of antimicrobial consumption in food-producing animals, the total consumption of antimicrobials was calculated for each country by pooling the estimates collected by multiplying the per PCU figure by the total national livestock population for each type of livestock (35). Based on the estimated values of antimicrobial consumption in Table 1, Indonesia, Vietnam and Myanmar are the three leading users of antimicrobials for farm use on a total per country basis.

Although there is a large amount of data about the emergence of antimicrobial resistance enterococci in Southeast Asian countries, most of this information is fragmented since it has been published in different papers from different countries over several decades (40, 41, 42, 43). However, several studies show the extent of unregulated and inappropriate use of antimicrobials in food animals in developing Southeast Asian countries such as Vietnam and Malaysia (22, 24, 44). Usui et al. (24) obtained results that demonstrate the use of antimicrobials in chickens in Southeast Asian countries, especially Vietnam, to be higher than developed countries (44).
Vietnam, Colistin was reported as a commonly used antibiotic on poultry, representing 4 to 7% of those used in quantitative terms compared with 1.6% reported from nine European countries (45). The use of antimicrobials in Vietnamese aquaculture has also been reported to be high with 700g per tonne of production compared to 1 to 200g per tonne in three European countries, Canada and Chile (46). In Malaysia, there are currently 97 antimicrobials registered for use according to the National Pharmaceutical Control Bureau (NPCB) of the Ministry of Health, Malaysia. Most of these registered drugs are used in poultry and pig farms. Unfortunately, more than half of the antibiotics registered with the Ministry of Health for food animals are not recommended for veterinary use by the World Health Organization (WHO). These antibiotics include Ampicillin, Amoxycillin, Cefadroxil, Chlorotetracycline, Oxytetracycline, Doxycycline, Sulfadiazine, Sulfadimethoxine, Erythromycin, Spiramycin, Neomycin, Gentamicin and Flumequine (47). Macrolides, Trimethoprim, Sulfonamides, Fluoroquinolones and Tetracyclines are classes of antibiotics that are commonly used in animal husbandry and human medicine in the Southeast Asian region (6, 7, 48).

To summarise, in comparison with western countries, geographic variations in the use of antimicrobials for poultry and livestock are notable in Southeast Asia due to different standards and fragmented policies for antimicrobial usage between countries (40). Countries such as Indonesia have a well designed and established system for the control of residues of veterinary drugs, however, issues relating to facilities, human resources and law enforcement need to be controlled (49). The department of livestock and fisheries in Laos lack consistent methods in evaluating and addressing antimicrobial resistant issues (50). Myanmar also has a major existing problem of inappropriate usage of antimicrobials and most farmers use antimicrobials without any consultation by veterinarians (51). Much work is needed in elucidating the level of...
antimicrobial resistance in these countries entailing cost, man power resources, and policy reviews (6, 7).

Monitoring systems in developed countries, such as The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme in Denmark established in 1995, are used to assess antimicrobial resistance in bacteria, including enterococci, from healthy food producing animals (41). Control measures set by the World Organization for Animal Health (OIE) and the Food and Agricultural Organization (FAO) in 2010 includes published guidelines for national antimicrobial surveillance programs in animals and the responsible use of antimicrobials in them (42). The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme reported a decrease in MDR \textit{E. faecalis} from 40\% in 2011 to 34\% in 2012 from pigs. Prevalence of MDR \textit{E. faecalis} in broilers has also decreased from 13\% in 2009 to 5\% in 2013 (41).

In December 1998, the European Commission decided to ban the use of Bacitracin, Spiramycin, Tylosin, and Virginiamycin for growth promotion beginning July 1 1999 (52). These initiatives follow the recommendations by the WHO and have had significant effects on the types and amounts of antimicrobial agents used. In comparison to the legislation and policies in most ASEAN nations, the European Union has a stronger control over regulating non-therapeutic uses of antibiotics in animals. The European Union leads the world in reducing antibiotic use in healthy animals. Sweden, Denmark and Switzerland were the first countries to unilaterally ban all non-therapeutic antibiotic growth promoters in animal feed (47). A more organized monitoring system of antimicrobial resistance in both agricultural and clinical settings and restricting their use is essential for preserving the therapeutic value of antibiotics in Southeast Asia.
Enterococcus spp. in the Environment and Water

Environmental and water samples often contain enterococci (53). Large amounts of human and animal wastes are distributed into the environment through sewage or non-sewage systems. For almost a century, enterococci have been used as indicators of faecal contamination of water and food for human consumption (1). Pathogenic bacteria in environmental surface waters originate mainly from the final effluent discharge from sewage wastewater treatment plants. Treated sludge, a by-product from treated sewage waste water containing the faecal contents of animals and humans, can be used as fertilizers on agricultural land which could potentially pass on MDR strains to food supply (54). Challenges for effective wastewater management differ in South East Asian countries as well. These include poor sanitation levels, especially in rural areas, inadequate sewerage network coverage, and lack of sewage treatment facilities (55). Many countries in Southeast Asia still depend on septic tanks and other low cost onsite sanitation facilities. However, most of these countries do not have specific policies, legal and institutional framework for appropriate septage management. Unfortunately septic tanks are poorly designed and not accurately constructed, operated and maintained in many cases. In Vietnam (56) a low treatment performance efficacy of only 20 to 30% BOD removal was observed. According to the AECOM and SANDEC 2010, the amount of generated septage that has been treated varies among different Southeast Asian countries include 4% in Indonesia, 5% in Metro Manila of Philippines, less than 4% in Vietnam and 30% in Thailand (57). In environmental water such as agricultural wells on animal farms, coastal waters, rivers and canals, the species considered as faecal contaminants are mainly *E. faecalis* and *E. faecium*, but other species can also be recovered (1). The water cycle has been suggested as a transmission route for resistance to antibiotics (54) and this may be particularly true if incentives for monitoring the water quality are lacking and the...
possibility of direct discharge of poorly treated sewage into seawater and rivers is present. Two
studies (58, 59) have isolated MDR enterococci in coastal bathing waters and storm waters
which lead to recreational beaches around Malaysia. The findings suggest that these recreational
beaches may contribute to the dissemination of MDR enterococci and virulence characteristics.
Another study carried out in Thailand found a high prevalence of MDR enterococci, out of which
10.3% were VRE isolates, from environmental water including agricultural wells on animal
farms, rivers and canals (54). This again suggests a potential transfer route of MDR enterococci
and resistance genes into the human-food chain and environment which could potentially pose a
threat to public health. Table 2 summarizes studies carried out in Southeast Asian countries
investigating incidences on antibiotic resistant Enterococcus species in the environment, namely
water sources and farm animals.

Transfer of Resistance between Nonhuman and Human Reservoirs
Infections with enterococci in animals are rarely specifically targeted with antimicrobial agents.
However, as normal inhabitants of the intestinal tract, enterococci are exposed to antimicrobial
selection every time animals are subjected to antimicrobial therapy or are given antimicrobial
agents for growth promotion (60).

Enterococci are one of the traditional bacterial markers for faecal contamination of food
and water for human consumption, and it has been accepted for several decades that enterococci
from nonhuman sources could contaminate food intended for human consumption (54). Clearly
enterococci with resistance genes may reach humans in several ways, including direct contact
with farm personnel (22, 61), via waste and surface water (54, 58, 59), or by contact with or
consumption of food animals and food of animal origin (22, 24). Although the hygienic
standards of meat production are high in most developed countries, faecal contamination of meat products cannot be completely eliminated (62). Figure 1 shows the complex epidemiology of enterococci and its ecological relationship between different reservoirs (63). The interaction between the different reservoirs contributes to the widespread of MDR enterococci.

Transmission of resistance can take place through food animals or directly through contact between animals and humans. Studies have suggested the potential for zoonotic transmission of enterococci. Research in Vietnam documented the isolation of the same clone of *E. faecalis* in a patient’s urine and poultry from the same households in which patients had close contact with the poultry. In 23% of urinary tract infection cases, identical or closely related pulsed-field gel electrophoresis patterns to that found in poultry were detected (64). In another study carried out in Malaysia, one vancomycin-resistant *E. faecium* strain isolated from a chicken was found to be clonal to that of humans (22). Treated sewage sludge, a by-product from treated sewage waste water containing the faecal contents of animals and humans, can be used as fertilizers which potentially pass on MDR strains to food supply. A study conducted in Vietnam found similar relative occurrences of *E. faecium*, *E. faecalis* and other *Enterococcus* spp. in the water–sediment of ponds and manure samples of pigs, suggesting that *Enterococcus* spp. isolated in the ponds originated mainly from the pig manure (65). Insufficient data on the interaction between different reservoirs concerns the widespread of MDR enterococci in Southeast Asian countries.

**Use of Antimicrobials in Hospitals and Antimicrobial Resistance**

Generally, the antibiotic of choice for the treatment of enterococcal infections in humans is Ampicillin, and Vancomycin is an alternative agent (66). Prudent antibiotic use is an essential component for control of the spread of vancomycin-resistant enterococci (VRE). The Healthcare
Infection Control Practices Advisory Committee (HICPAC) guidelines insist on curtailing the use of antibiotics for routine surgical prophylaxis and empiric therapy (67).

Although the full extent of MDR Enterococcus spp. in Southeast Asia remains undiscovered, data is available from some countries. A linezolid-resistant *E. faecalis* strain was isolated in July 2010 from a diabetic patient in Thailand who received Linezolid for at least 3 months prior to the isolation of the resistant strain (68). From 1999 to 2009, 1.9% of VRE isolates were recovered from patients in the Rajavithi Hospital, Thailand. Out of this 1.9%, there was a significantly higher prevalence of VRE isolates from the inpatient department compared to the outpatient department (10). In Indonesia, antibiotics can easily be obtained without a prescription from medical retailers despite existing regulations (69). According to the National Surveillance of Antimicrobial Resistance in Malaysia, antibiotic susceptibility testing was carried out on bacterial isolates from hospitalized patients whereby analysis was based on one isolate per patient (70). This analysis revealed that roughly 1.2% of the *E. faecalis* isolates was vancomycin-resistant in 2012 and 1.4% in 2013, a longer time-frame is required to determine if the rate is increasing over time. There was also an increase in Ciprofloxacin resistant *E. faecalis* from 248 patients (20.6%) in 2012 to patients 437 (21.1%) in 2013 and Penicillin resistant *E. faecium* from 309 patients (84.4%) in 2012 to 415 patients (89.6%) in 2013 (70). A study in Malaysia isolated Tazobactam-Piperacillin, Ampicillin, Penicillin and high-level Gentamicin resistant Enterococci strains from hospitalised patients (66). Another case study in 2008 discovered Vancomycin, Teicoplanin, Ampicillin and Gentamicin resistant *E. faecium* strains from two patients with chronic diabetes mellitus and urinary tract infection under a 3 to 12 days course treatment of Cloxacilin, Ceftriaxone, Erythromycin and Vancomycin (71). The first VRE isolated in Singapore was observed in 1994 from a patient at the Singapore National Burns...
Centre (72). Two consecutive outbreaks followed later on in 2004 (73) and 2005 (74). According to the Network for Antimicrobial Resistance Surveillance in Singapore (NARSS) in 2006, VRE constitutes 0.8% of all enterococci isolates in Singapore public hospitals (75). An epidemiology study in Singapore documenting VRE in public hospitals from 2006 to 2010 reported 24.4% clinical VRE isolates (9). While the prevalence of VRE clinical isolates remain low in Singapore public hospitals the need for continued vigilance is necessary to prevent any further increase in VRE prevalence. Documented cases of antibiotic resistant *Enterococcus* species were reported in Myanmar from hospitalized patients during 2009 to 2013 in which 30.8% were found to be resistant to Ampicillin and 68.8% were resistant to Erythromycin (76). In 2012, a case study in Vietnam reported vancomycin-resistant *E. faecium* in a patient with liver cirrhosis undergoing antimicrobial therapy consisting Imipenem and Vancomycin for one week (77). Thus not only regulation of antibiotic, but also diligent prescribing of other broad-spectrum antimicrobials should be carried out in hospitals around the region in an attempt to decrease colonization with MDR *E. faecalis*.

**Source Control for Infections**

In past years, the source of infection for most patients was thought to be their own endogenous enterococci (1). However, with the increase of sophisticated molecular typing techniques and the rise in nosocomial acquisition of antibiotic resistant enterococci in the 1980s and 1990s, studies have clearly demonstrated transmission of enterococci among patients in acute care hospital settings (2). A recent study in Malaysia discovered clinical strains of MDR *E. faecium* with the presumed mode of spread from patient to patient via the hands of health care workers (22). Transient carriage of *E. faecalis* on the hands of health care workers has also been documented...
Transmission of enterococci from transiently colonised health care worker’s hand to a patient may involve direct contact with hands, environmental surfaces or medical equipment, but it is more likely that transmission results in colonization of the patient’s gut (78). The acquired antibiotic resistant strain is able to survive in the gastrointestinal tract of humans with the aid of selective pressure of broad-spectrum antibiotics which is used frequently in hospitalized patients (78). Infections consequently arise from these newly acquired enterococcal strains.

Various guidelines have been set up by countries in Southeast Asia to provide infection control information for hospitals, healthcare facilities, and livestock/animal health to prevent the spread of MDR enterococci. Indonesia aims to strengthen the implementation of regulations for the production, distribution, sale and prescription of antibiotics as well as establish the Antimicrobial Resistance Control Programme as a national programme. This programme will aid in developing regulations for antibiotic use in veterinary practices as well as guidelines for community acquired infection and public access to it (47). Myanmar is currently establishing a national multisectoral steering committee for antimicrobial resistance and is in the process of constituting a national policy for antibiotic use in humans and animals. Data collection is ongoing in Thailand to understand trends in antimicrobial resistance and develop antibiotic policy of MDR (47). Treatment options for antibiotic resistant Enterococcus spp. especially those due to VRE are limited. Therefore measures to minimize the spread of these resistant organisms within a facility are essential. Each facility should establish a comprehensive infection control program aimed at decreasing transmission of VRE among patients (79). Specific policies should be based on the rates of resistance within the facility and should be appropriate for the specific health care setting. In 1995, the Centers for Disease Control and Prevention Hospital
Infection Control Practices Advisory Committee (HICPAC) published recommendations aimed at controlling the nosocomial transmission of VRE (67). These recommendations provide a base on which specific policies can be developed for individual facilities. The major recommendations of HICPAC focus on (i) prudent use of Vancomycin to decrease the selective pressure for emergence of VRE; (ii) education of health care personnel about the importance of VRE and its mode of transmission; (iii) use of the microbiology lab to quickly identify patients with VRE; and (iv) infection control measures that minimize transmission to other patients. The emergence and severity of VRE has also been reported in other regions of Southeast Asia (5, 40). These findings suggest that early detection of VRE is necessary in preventing further spread in healthcare settings.

Conclusion

Enterococci inhabiting nonhuman reservoirs appear to play a critical role in the acquisition and distribution of antibiotic resistance determinants (60, 80). The introduction of antimicrobial agents in clinical medicine and animal husbandry has been one of the most important medical achievements, however surveillance and enforcement of the use of antibiotics in hospital settings and farms is often lax in most Southeast Asian countries. In addition, the Southeast Asian region lacks in systemic studies to understand the epidemiology of MDR enterococci. The most effective way to limit the spread of antimicrobial resistance, and thereby extend the usefulness of antimicrobials, is through their restricted use (47). As a consequence, it has been recommended that antimicrobial agents that select for resistance to antibiotics used for human therapy should not be used for growth promotion in animal husbandry. Growth promoters should be limited to agents that are of no value for therapeutic use (47). To limit the emergence of antimicrobial
resistance and the consequences for human and animal health, it is necessary to collect data on factors affecting the occurrence, emergence, and spread of resistance. At the present, knowledge of antimicrobial resistance among food animals in Southeast Asia is fragmentary. This review highlights the need of health care settings, industries and governments in Southeast Asian countries to strictly regulate the use of antibiotics to curb the emerging threat of MDR enterococci.

**Word count: 4042**

**References**


30. United States Department of Agriculture. 2012. Overview of U.S. Livestock, Poultry, 

31. Veterinary Medicines Directorate. 2013. United Kingdom Veterinary Antibiotic 
Resistance and Sales Surveillance 2013. Government Department for the Environment, 
Food and Rural Affairs, U.K. 
ARSS.pdf

32. Agriculture in the United Kingdom. 2012. Department of Environment, Food and 
Rural Affairs. Department of Agriculture and Rural Development (Northern Island). The 
Scotish Government, Rural and Environment Research and Analysis Directorate. Welsh 
Assembly Government, The Department for Rural Affairs and Heritage. 
k-2012-25jun13.pdf

Antimicrobial resistance: a global view from the 2013 World Healthcare-Associated 

34. Food and Agricultural Organisation. 2010. FAOSTAT on livestock population in 


41. The Danish Integrated Antimicrobial Resistance Monitoring and Research Programme (DANMAP). 2013. Use of antimicrobial agents and occurrence of
antimicrobial resistance in bacteria from food animals, food and humans in Denmark.

Rosendahls-Schultz Grafisk, Denmark.


http://pubs.acs.org/doi/abs/10.1021/es0709021


549
550 55. McIntosh AC. 2014. Urban water supply and sanitation in Southeast Asia: A guide to
552 http://www.adb.org/sites/default/files/publication/42583/urban-water-supply-sanitation-
553 southeast-asia.pdf
554
556 Decentralised wastewater treatment - new concept and technologies for Vietnamese
557 conditions. Proceedings of the 5th Specialised Conference on Small Water and
558 Wastewater Treatment Systems, Istanbul, Turkey.
559 http://www2.gtz.de/Dokumente/oe44/ecosan/en-decentralised-wastewater-treatment-
560 vietnam-2002.pdf
561
562 57. AECOM International Development, Inc. and the Department of Water and
563 Sanitation in Developing Countries (Sandec) at the Swiss Federal Institute of
564 Aquatic Science and Technology (Eawag). 2010. A Rapid Assessment of Septage
565 Management in Asia: Policies and Practices in India, Indonesia, Malaysia, the
566 Philippines, Sri Lanka, Thailand, and Vietnam. AECOM and SANDEC/EAWAG,
568
570 Susceptibility for antibiotics among fecal indicators and pathogenic bacteria in sewage
572 http://www.iwaponline.com/wpt/008/wpt0080001.htm


http://trstmh.oxfordjournals.org/content/early/2014/09/23/trstmh.tru151.short


http://europepmc.org/abstract/med/8799020


Table 1. Livestock population and total antimicrobial consumption in chicken, cattle and pigs from ASEAN countries

Table 2. Summary of key studies investigating incidences of antibiotic resistant Enterococcus species in the environment.

Figure 1. Ecological relationships between different reservoirs (63)
<table>
<thead>
<tr>
<th>Country</th>
<th>Livestock population (in thousands)</th>
<th>PCU (in thousands)</th>
<th>Total amount of antimicrobial consumption in chicken, cattle and pigs in mg/PCU (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chicken</td>
<td>Cattle</td>
<td>Pig</td>
</tr>
<tr>
<td>Brunei</td>
<td>16,000</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Cambodia</td>
<td>17,448</td>
<td>3,484</td>
<td>2,057</td>
</tr>
<tr>
<td>Indonesia</td>
<td>1,622,750</td>
<td>1,363</td>
<td>7,212</td>
</tr>
<tr>
<td>Lao PDR</td>
<td>23,000</td>
<td>1,400</td>
<td>3,400</td>
</tr>
<tr>
<td>Malaysia</td>
<td>225,790</td>
<td>909</td>
<td>1,711</td>
</tr>
<tr>
<td>Myanmar</td>
<td>125,000</td>
<td>13,000</td>
<td>7,900</td>
</tr>
<tr>
<td>Philippines</td>
<td>158,984</td>
<td>2,570</td>
<td>13,398</td>
</tr>
<tr>
<td>Singapore</td>
<td>3,300</td>
<td>0.2</td>
<td>270</td>
</tr>
<tr>
<td>Thailand</td>
<td>231,918</td>
<td>6,498</td>
<td>7,623</td>
</tr>
<tr>
<td>Vietnam</td>
<td>218,201</td>
<td>5,916</td>
<td>27,373</td>
</tr>
</tbody>
</table>

FAOSTAT – FAO Statistics Division 2010
Table 2. Summary of key studies investigating incidences of antibiotic resistant Enterococcus species in the environment.

<table>
<thead>
<tr>
<th>Study</th>
<th>Country</th>
<th>Location</th>
<th>Resistance rate (%)</th>
<th>Reference number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tansuphasiri et al. 2006</td>
<td>Thailand</td>
<td>Environmental water (Agricultural wells on animal farm, rivers and canals)</td>
<td>48.4% resistant to Ciprofloxacin, 46.8% resistant to Tetracycline</td>
<td>54</td>
</tr>
<tr>
<td>Getachew et al. 2009</td>
<td>Malaysia</td>
<td>Feces from live broiler chickens</td>
<td>VRE [Enterococcus faecalis (48%), Enterococcus faecium (25.7%), Enterococcus gallinarum (12.1%), Enterococcus casseliflavus (1.4%) and other Enterococcus species (12.8%)]</td>
<td>81</td>
</tr>
<tr>
<td>Dada et al. 2013</td>
<td>Malaysia</td>
<td>Coastal bathing waters</td>
<td>76.63% resistant to Kanamycin, 10.87% resistant to novobiocin, 8.38% resistant to chloramphenicol</td>
<td>59</td>
</tr>
<tr>
<td>Al-Geethi et al. 2013</td>
<td>Malaysia</td>
<td>Sewage treated effluent</td>
<td>71.4% resistant to Ampicillin, 4.7% resistant to Ciprofloxacin, 95.2% resistant to Cefuroxime</td>
<td>58</td>
</tr>
<tr>
<td>Usui et al. 2014</td>
<td>Vietnam</td>
<td>Feces from live chicken</td>
<td>E. faecalis (86.3% resistant to chloramphenicol, 90.9% resistant to erythromycin and lincomycin, 100% resistant to oxytetracycline)</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>E. faecium (97.8% resistant to oxytetracycline, 88.8% resistant to lincomycin, 86.5% resistant to enrofloxacin)</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>Sample Type</td>
<td>Enterococcus Species</td>
<td>Resistance Details</td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>---------------------</td>
<td>---------------------------------------</td>
<td>-------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Indonesia</td>
<td>Feces from live chicken</td>
<td><strong>E. faecalis</strong></td>
<td>79.3% resistant to Lincomycin, 77.6% resistant to erythromycin, 65.5% resistant to oxytetracycline</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>E. faecium</strong></td>
<td>(81% resistant to oxytetracycline, 69% resistant to enrofloxacin, lincomycin and kanamycin)</td>
<td></td>
</tr>
<tr>
<td>Thailand</td>
<td>Feces from live chicken</td>
<td><strong>E. faecalis</strong></td>
<td>56.8% resistant to oxytetracycline, 54% resistant to lincomycin, 48.5% resistant to erythromycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>E. faecium</strong></td>
<td>(92.2% resistant to oxytetracycline, 83.9% resistant to lincomycin, 82.8% resistant to enrofloxacin)</td>
<td></td>
</tr>
<tr>
<td>Vietnam</td>
<td>Pig manure</td>
<td>100% resistant to tetracycline, 32% resistant to enrofloxacin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Water-sediment from pond</td>
<td>90% resistant to tetracycline, 45% resistant to enrofloxacin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Use of antibiotics as growth promoters and for therapeutic use

Food animals

Spread of manure on fields

Wildlife
Soil and water
Fruits and vegetables

Food animal products

Farmers

Hospitalized patients

Humans in the community

Sewage treatment plant

Use of antibiotics for humans