Perspectives on Antimicrobial Resistance in Livestock and Livestock Products in ASEAN Countries

Amornthep Archawakulathep1 Chung Ta Thi Kim2 Dethaloun Meunsene3
Didik Handijatno4 Hasliza Abu Hassim5 Hope R. G. Rovira6 Khin Sandar Myint7
Loinda R. Baldrias6 Meas Sothy8 Min Aung7 Nenny H. Wahyu4 Rortana Chea8
Sookruetai Boonmasawai9 Soulsack Vannamahaxay3 Sunpetch Angkititrakul10
Therese M. A. Collantes6 Tho Nguyen Van2 Veerasak Punyapornwithaya11
Zunita Zakaria5 Runtip Chuanchuen12*

Abstract

Antimicrobial resistance (AMR) in bacteria, particularly in foodborne pathogens, has increasingly become apparent in most parts of the world including ASEAN countries, creating great impact on economy, human and animal health and international food trade. The tendency of bacterial pathogens to become multidrug resistant (MDR) is the most serious concern in AMR. The ASEAN Economic Community (AEC) will be fully established in 2015 and ASEAN cooperation has acknowledged the significance of food safety, of which AMR is one of the major concerns. There is a need for all ASEAN nations to harmonize its AMR monitoring and surveillance programmes in order to strengthen the control and institute prevention strategies in the region. Currently, public health systems dealing with monitoring and control in ASEAN countries are still highly diverse and require a unifying action. National monitoring and control programmes for AMR have not been successfully established in most ASEAN countries and a regional-cooperative programme has yet to be set in place. Therefore, a review of current AMR situations in ASEAN member states shall be useful for future development and establishment of monitoring and control programmes within the region.

Keywords: antimicrobial resistance, ASEAN, livestock, livestock products

1Faculty of Veterinary Medicine, Kasetsart University, Bangkok, Thailand
2Faculty of Veterinary Medicine, Hanoi University of Agriculture, Hanoi, Vietnam
3Faculty of Agriculture, National University of Laos, Vientiane Capital, Lao PDR
4Faculty of Veterinary Medicine, Airlangga University, Surabaya, Indonesia
5Faculty of Veterinary Medicine, Universiti Putra Malaysia, Selangor, Malaysia
6Department of Veterinary Paraclinical Sciences, College of Veterinary Medicine, University of the Philippines Los Banos, Laguna, Philippines
7Department of Animal Science, University of Veterinary Science, Nay Pyi Taw, Myanmar
8Division of Research and Extension, Royal University of Agriculture, Phnom Penh, Cambodia
9Faculty of Veterinary Science, Mahidol University, Nakhonpathoom, Thailand
10Faculty of Veterinary Medicine, KhonKaen University, KhonKaen, Thailand
11Faculty of Veterinary Medicine, Chiang Mai University, Chiang Mai, Thailand
12Faculty of Veterinary Science, Chulalongkorn University, Bangkok, Thailand
*Correspondence:rchuanchuen@yahoo.com

Introduction

Antimicrobial resistance (AMR) has increasingly emerged and re-emerged as a major threat to public health and economy in various countries throughout the world including in ASEAN communities (Padungtod and Kaneene, 2006; Lay et al., 2011; Boonmar et al., 2013). The problem is currently a major concern for both animal and human health and becoming more complicated due to the rapid emergence of the pathogenic strains resistant to many clinically-important antimicrobial agents simultaneously (so called multidrug resistance, MDR). AMR directly affects animal and human health when infection with bacterial pathogens leads to illness that requires antimicrobial treatment and the selected therapeutic drug is ineffective owing to resistance, resulting in prolonged treatment period, higher cost, inefficient therapy and eventually, treatment failure. This marks the critical economic burden of AMR despite the difficulties in assessing the exact costs. Increasing concerns on AMR have caused some trading partners and competitors of ASEAN members to implement restrictions and prohibitions on the use of certain antimicrobials in livestock production that could become an issue affecting ASEAN export markets for livestock and livestock products in the future.

Evidences showed that the extensive-overuse and misuse of antimicrobial agents in livestock has irrefutably led to AMR in various pathogenic and commensal bacteria (Rosengren et al., 2009). Due to the rapid-growing global health crisis of AMR, national and international regulatory authorities have become highly concerned and have issued various policy, guidelines and regulations to minimize the emergence and spread of AMR in bacteria associated with livestock and livestock products with varying degrees of evidence and efficacy. For example, Codex has issued “Code of practice to minimize and contain antimicrobial resistance” stating responsibilities of relevant authorities (Codex, 2005). EU has completely banned antibiotic use for growth promoter in food animals (EU, 2006) and has launched technical guideline for AMR monitoring in bacteria associated with food animals (i.e. Salmonella, Campylobacter, Esherichia coli and Enterococcus) for the member states (EFSA, 2012). OIE has released Terrestrial Animal Health Code (2012), which describes recommendations for controlling AMR, national AMR surveillance and monitoring programmes, responsible and prudent use of antimicrobial agents in veterinary medicine and contributed a web space dedicated to AMR (OIE, 2012). It is certain that veterinary programmes to monitor AMR in animal and zoonotic pathogens are essential to effectively control AMR. However, differences in concern, perceptions and resources in different organizations and countries have been a major obstacle and created much controversy regarding control strategic scheme as a result of the complexity of AMR problem.

By 2015, ASEAN Economic Community (AEC) will be fully established with key characteristics including a single market and production base, a highly competitive economic region, an equitable economic development region and a region fully integrated into the global economy (Secretariat, 2012). ASEAN cooperation has recognized the importance of food safety to maintain stability and prosperity of the member states. For this matter, AMR is a major challenge in food safety. However, national monitoring and control programme for AMR and foodborne pathogens has not been successfully established in ASEAN countries and that for the regional level is even far. The root causes and true cost of the problem are still unclear in all ASEAN members due to limited data on the burden of AMR in livestock. Each ASEAN country has different perspectives and uses different approaches, methods of surveillance and regulation to deal with AMR problem. Therefore, non-standardized and non-harmonized AMR monitoring is recognized as a primary weakness in comparison with AMR monitoring data across the regional countries. These limitations have become a major hindrance for development and implementation of effective and efficient control and prevention strategic programme for AMR in this part of the world. Therefore, current situation of and approaches to limiting AMR in ASEAN member states are reviewed to provide useful data for future development of monitoring and control programme in the region. This is the first step to fulfill the gaps of standardization and harmonization of AMR monitoring in ASEAN livestock and its products.

Aspects of antimicrobial resistance

While antimicrobial agents have been implicated in development and dissemination of AMR, the relationship between antimicrobial use (AMU) and AMR is complicated and inconsistent. Use of some antimicrobial agents may result in resistance in some bacterial species in certain circumstances, however, this may not always be the case other bacterial or animal species.

Resistant foodborne pathogens directly affect human health. At the same time, resistant-commensal bacteria indirectly pose a health risk by carrying and spreading resistance determinants to bacterial pathogens. Such resistance determinants can be transferred from commensal bacteria originating in livestock to pathogenic bacteria in humans, or vice versa. Commensal bacteria are ubiquitous in healthy animals and may possibly contaminate carcasses in slaughterhouses and eventually enter food chain. Therefore, the indirect risk posed by commensal bacteria can be equal to or even greater than that posed by bacterial pathogens.

In the process of AMR development, antimicrobial agents contribute to the emergence of AMR by selection and enrichment of resistant
bacteria. Susceptible bacteria become resistant after antimicrobial exposure and only resistant cells will be selected to survive and multiply. A bacterium can be rendered naturally resistant because of its inherent structural or functional characteristics; for example, inaccessibility of the drug into the bacterial cell, lack of the drug affinity for the bacterial target, natural production of inactivating enzymes or extrusion of the drug molecule by chromosomally encoded active efflux (Russell and Chopra, 1996). Concurrently, bacteria may acquire AMR by means of mutation in its own chromosomal DNA relevant for the activity of the antimicrobials or acquisition of new genetic material containing resistance conferring DNA from another source (Dzidic et al., 2008). Bacteria are capable of developing several mechanisms to acquire resistance to antimicrobials and can collect multiple resistance traits over time. Therefore, they can become resistant to many different classes of antimicrobials.

In AMR spreading process, transmission of AMR occurs vertically and horizontally through bacteria populations. Vertical transfer or clonal spread is the spreading process that bacteria pass their resistance trait directly to their offspring during DNA replication (Dzidic et al., 2008). This resistance is stably maintained even in the absence of antibiotic selective pressure.

Horizontal-resistance transfer happens when resistance genes are transferred from resistant-donor to susceptible-recipient cells via conjugation, transformation and transduction and can occur among bacteria of the same or different species (Dzidic et al., 2008).

A single antimicrobial agent can select MDR bacteria resistant for many antimicrobials simultaneously by co-selection (different resistance determinants present on the same genetic element) and cross-resistance (the same genetic determinant responsible for resistance to different classes of antimicrobials) (Russell and Chopra, 1996). Co-selection and cross-resistance are the important processes contributing to the persistence of resistance to certain antimicrobials that are no longer used.

**Antimicrobial use in livestock production**

Most drugs are used for both treatment and as feed additives for sub-therapeutic prophylaxis and growth promoter. Veterinary drug formulas often contain a combination of different antibiotics although their therapeutic effect is not clearly stated (OIE, 2003; OIE, 2007). Like many other developing regions, antimicrobial agents are still commonly used in livestock production in most ASEAN countries due to widespread of bacterial infections. Type and extent of antimicrobial use (AMU) are different from one country to another based on economy, level of antimicrobial use (AMU) are different from one country to another based on economy, level of development, animal husbandry and animal species. In addition to the prevalence of AMR, extent of AMU needs to be monitored to provide useful information for prediction of antimicrobial resistance trend. However, the data is neither systematically recorded nor clearly stated in most ASEAN countries. Concurrently, limited data on the amount of antimicrobial importations and use exist. In some particular countries (e.g. Laos), antibiotics are not commonly used in livestock due to increasing investment cost and this could be the explanation of deficient data on AMU in the country (Boonmar et al., 2013).

Based on the available data, the major classes of antimicrobials used in Myanmar livestock production include β-lactams, tetracycline, fluoroquinolones, aminoglycosides, macrolides and sulphonamides and most are imported from Asian and European countries (Aung and Myint, 2013). Most veterinary drugs in the Philippines are imported as well (Cresencio, 2012) but no formal data on AMU in livestock could be reached. In Thailand, types and amounts of veterinary drugs used vary widely upon the level and type of farm. A variety of antibiotics have been produced in and imported into this country. Reports on AMU are occasionally observed but not systematically recorded. Antibiotics are frequently used in livestock in Vietnam as well and veterinary drug sales are approximately 50% of total drug sales. The country has faced a serious problem of counterfeit drugs with limited data on the amount of antimicrobial importations and use (Wondemagegnehu, 1999). In Malaysia, routine monitoring of selected antimicrobial classes used in human medicine is performed in government hospitals but not for veterinary medicine (WHO, 2011). In Indonesia, monitoring and surveillance programs have been conducted to confirm the quality of veterinary drugs in distribution, in storages, in the markets, and at the farms (FAO/WHO, 2004). Still, no published data is available for AMU in livestock.

**Prevalence of antimicrobial resistance in bacteria associated with livestock and livestock products**

Like countries in other regions of the world, most ASEAN member states have confronted a similar challenge in lack of data on the AMR load in livestock. Research on AMR is still limited. The number of published data varies from one country to another and no data are publicly available in some countries. There is no systematic data collection existing at national and international level in the countries.

Foodborne pathogens, especially *Salmonella enterica*, *Campylobacter* and pathogenetic *Escherichia coli* are common and particularly concerned in ASEAN and MDR bacteria associated with livestock and livestock products have been increasingly reported in Thailand (Chuanchuen and Padungtod, 2009), Malaysia (Hamid, 2012; Rejab et al., 2012), Philippines (Baldrias and Raymundo, 2009), Vietnam (Trung et al., 2012) and Myanmar (Aung, 2005). While overall published data are still few in most countries, AMR in *Salmonella* has been the most studied in comparison with other pathogens. Most *Salmonella* isolates were resistant to common antibiotics, e.g. ampicillin, tetracycline, streptomycin, sulfamethoxazole and trimetroprim (Padungtod and Kaneene, 2006;
Resistance rates to norfloxacin and ciprofloxacin varied upon type of animals, type of products and countries. In Thailand, Salmonella is the second most common foodborne illness (Bodhidatta et al., 2002). Therefore, it is not surprising that AMR has been extensively studied in Salmonella isolated from various food animals in the country. Previous studies suggested that pork and chicken meat played a major role as sources of AMR salmonellosis in humans (Angkititrakul et al., 2005). A recent study in Thailand highlighted the high prevalence of MDR bacteria including Salmonella and Escherichia coli in healthy chicken from selected poultry farms and all the Salmonella isolates exhibited resistance to tetracycline and clindamycin (Geidak et al., 2012).

Campylobacter species, in particular C. jejuni and C. coli resistant to multiple drugs was increasingly reported in broilers and pigs (Ekkapobyotin et al., 2008; Baldrias and Raymundo, 2009). Previous studies demonstrated that Campylobacter species from broilers in Thailand and the Philippines exhibited MDR phenotype with the lowest level of resistance to erythromycin and resistance to ciprofloxacin, tetracycline and ampicillin was also common (Padungtod et al., 2006; Ekkapobyotin et al., 2008; Baldrias and Raymundo, 2009). A recent study reported the presence of MDR Campylobacter in chicken sold in retail market in Cambodia (Lay et al., 2011).

Data on AMR and foodborne pathogens are limited in Laos and Myanmar. Previous studies reported high prevalence of Salmonella in pigs (76%), pork carcass in slaughterhouses (66%) and patients (51%) in Laos (Phetsouvanh et al., 2006; Boonmar et al., 2008). It is interesting to observe that resistance rates in pig isolates in Laos is much lower when compared to those reported in countries of the same region. Even though the use of antimicrobial agents in food animals is not well regulated, such use is still not common due to increasing costs. A study demonstrated that Salmonella contamination rate was higher in pig carcasses than in those before being slaughtered, indicating poor hygiene and cross-contamination during the slaughtering process (Inthavong et al., 2006). Based on a student thesis, Salmonella strains in raw food products in retail markets in Yangon, Myanmar were all resistant to tetracycline (Aung, 2005).

Legislation, policy and regulations for antimicrobial use in livestock

Regulations, guidelines or policies on AMR in livestock and livestock products in ASEAN countries quite vary. Different laws and regulations have been issued to control veterinary drugs in each country. National policy on the sale or use of antimicrobials in animals and animal feed is not well established in most countries and does not exist in some countries, e.g. Myanmar. There are currently not much relevant data publicly available, while some existing publications are in native languages.

In Indonesia, veterinary drugs (e.g. hormones and antimicrobials) intended for human medicine are regulated under the Animal Health and Animal Husbandry Law No. 18/2009, article 22 (FAO, 2012) and the Government Regulation no. 78/1992. Veterinary drugs can be used as feed additives and growth promoters in food producing animals by the Government Regulation no. 806, 1994 (FAO, 2012). Code of practice for using veterinary drugs was prepared to be harmonized with the Codex Code of Practice for Control of the Use of Veterinary Drugs (CAC/RCP 38-1993) and assigned to cover regulations on the use of veterinary drugs in feed and to promote prudent use of veterinary drugs (FAO/WHO, 2004).

In Laos, Ministry of Agriculture and Forestry issued Technical Norms on Livestock and Livestock Product Management, No. 0313/MAF or 0036/DLF in 2000 to provide the same monitoring protocol and livestock management for the whole country (MAF, 2000; Theungphachan, 2012). This regulation is very comprehensive and governs most aspects of animal raising and management, including importation of veterinary drugs in the country (Stir et al., 2002). However, AMR is not stated in this regulation.

In Malaysia, drugs that are used on humans or animals are required to be registered with the Drug Control Authority (DCA). Animal feed containing drug(s) is exempted from the registration requirements until a separate regulatory control is established (MOH, 2009). National Pharmaceutical Control Bureau, Ministry of Health regulates veterinary drugs in most aspects by Registration Guideline of Veterinary Products (REGOVP); Version 2, March 2009 (MOH, 2009).

There are two agencies in the Philippines that are involved in the regulations on AMU; the Department of Agriculture (DA) through the Bureau of Animal Industry (BAI) and the Department of Health through its Food and Drug Administration (DOH-FDA). Both agencies work in cooperation based on their respective regulatory functions. FDA regulates all veterinary drugs for injections and individual administration for animals. The BAI regulates veterinary drugs and products that are used or mixed or incorporated in feeds and drinking water. RA No. 9711 or the Food and Drug Administrative Act of 2009 is the most current law on regulating and monitoring of establishments and products including veterinary drugs and other health products (FDA, 2009). DA issued an Administrative Order No. 24 establishing the National Veterinary Drug Residues Control Program to ensure rational use of antimicrobials and other veterinary drugs and chemicals in animal production. This regulation specifies the responsibilities of various stakeholders, including livestock and poultry producers and Local Government Units, on the rational use of veterinary drugs. Currently, the Food Safety Act of the Philippines is proposed. This act will cover food safety issues including controlling veterinary drug residues and AMR.
Thailand is an outstanding exporter of chicken meat and shrimp. The country is one of the largest poultry exporters of the world. Department of Livestock Development (DLD), Ministry of Agriculture and Cooperatives is the major organization that plays a very important role in regulations and control of all matters regarding livestock and livestock products. DLD also issues importation standards of livestock and livestock products and environmental and animal welfare concerns are addressed in the standards. DLD works in cooperation with Food and Drug Administration (FDA), Ministry of Public Health in regulation of veterinary drugs. FDA is responsible for licensing and registrations of veterinary medicinal products and authorizes relevant officials of DLD to enforce Drug Act relating to post-marketing of veterinary drugs/biologics. DLD is responsible for controlling the usage and post-marketing surveillance of veterinary medicinal products. Veterinary drugs are regulated by Drug Act B.E. 2510 (1967) (DLD, 1967). DLD also listed drugs and chemicals that are not allowed to be used in food animals (MOH, 2009). Currently, FDA has banned all antibiotics used for growth promoters in food animals.

The National Bureau of Agricultural Commodity and Food Standards (ACFS) is another governmental agency under the Ministry of Agriculture and Cooperatives that is involved in standards and policies of the country. ACSFs issued Code of Practice for Control of Use of Veterinary Drugs (THAI AGRICULTURAL STANDARD, TAS 9032-2009), which describes good practices for the use of veterinary drugs for food producing animals to avoid excess of maximum residue limits of veterinary drugs in animals, animal produce and animal products for human consumption (ACFS, 2009). Recently, ACF has drafted guidelines for judicious use of antimicrobials in broiler farms that will be effective soon.

A serious problem of drugs in Vietnam is the wide distribution of counterfeit drugs. In the same time, drug control policy and regulations in this country is under the Veterinary Drug Management division, Department of Health (DOH), which may not be perfectly efficient. Veterinary drugs are regulated by Ministry of Agriculture and Rural Development by “Regulations on registration procedures of production, import and circulation of veterinary drugs, raw materials for veterinary drugs, biological products, microorganisms, chemicals used in veterinary medicine”, No: 10/2006/QD - BNN/2006 (Anonymous, 2005).

**Programmes for antimicrobial resistance control and monitoring**

Despite the emergence and re-emergence of AMR, national AMR monitoring and surveillance programme has not been successfully established in all ASEAN countries. The programme is needed to be harmonized at national, regional and international level to strengthen the control and prevention strategies. Conversely, most countries lack standardized and harmonized protocol for national monitoring of AMU and AMR. At the regional level, each ASEAN Member State has its own public health systems different from one country to another and most work independently, leading to a wide variation in surveillance and control systems. Knowledge and technology among ASEAN Member States greatly vary and may not be comparable.

AMR in bacteria associated with livestock and livestock products has been extensively studies in Thailand by governmental and non-governmental organizations. AMR in livestock and livestock products is routinely monitored but data are scattered. Currently, the major institute that is involved in national AMR monitoring is National Institute of Health, DLD. Attempting to control AMR associated with food animals, FDA proposed to include antimicrobial risk assessment as document required for drug registration. The control of veterinary drugs in Vietnam is fully supported by government and private laboratories. However, most laboratories still need to be standardized and ISO accredited. National data base through National Animal Health Information in near future is expected (OIE, 2007).

**Discussion**

AMR is a global problematic issue that requires global attention and cooperation. Both human and animal sectors have a shared responsibility to prevent and diminish AMR. Even though antibiotic use is most likely posing a serious risk to human health, antibiotic treatment is still continued in livestock due to lack of better alternatives for infection treatment and animal welfare. Antibiotics should be prudently and responsibly used in such a way that their therapeutic efficacy is optimized and development and spread of AMR microorganisms is minimized. For this matter, guidelines on responsible use of antimicrobial agents in livestock production are recommended and have been mostly developed by relevant authorities in developing countries. The guidelines should cover the responsibilities of all levels including national regulatory authorities, veterinarians, and food animal producers and must be strictly followed. At least two ASEAN countries, including Thailand and Philippines, have started development of the prudent use guidelines for antimicrobial use in food animals.

From this review, one of the major findings is that most ASEAN countries do not have or inadequately have national monitoring and control programmes. Some may have an existing programme that is conducted only in some parts of the countries and is not efficient. Overall, the ASEAN countries have encountered several challenges that hamper AMR control and management of which the major problems are as follows:

1. AMR is not concerned as a major public health problem and a priority of the country.
2. There is no standardization and harmonization on antimicrobial susceptibility test and monitoring protocol. Each country uses different approaches, e.g. sampling and testing methodology, and different clinical breakpoints and/or epidemiological cutoff. Therefore, data from different laboratories are not comparable.

3. There is lack of national monitoring programme. The existing programme in some countries may not be reliable and effective.

4. Legislative policy and regulation on AMU in livestock production are not well established. Even though legislative framework to control antibiotics exists, it may not be used properly or effectively.

5. Lack of measurements to ensure rational use of veterinary drugs especially at farm level is common.

6. Report of AMR in livestock and livestock products is rather scarce and not systematically recorded. There are insufficient antimicrobial susceptibility data analysis and dissemination.

7. Human resource and manpower, including trained-laboratory staff, are deficient. Employees usually have a full work load and are engaged in multiple roles. Assigned personnel may need further training.

8. Public education and awareness on public health risks of AMR are inadequate.

9. Financial resources, especially governmental funds, are not regularly available. Technology and facilities are limited.

10. There is no co-ordination among regulators, public health officials and relevant stakeholders.

11. Antibiotics can be easily accessed and obtained over counter. Veterinarian prescription is not needed when antibiotics are purchased.

12. Insufficient and poor veterinary services are common. Farm veterinarians are not aware of prudent use of antimicrobials in livestock production.

13. Scientific research on AMR is not common. There is a limited number of research on alternatives to antibiotics.

Major recommendations and conclusions

Based on this review, the collaboration on AMR monitoring and control among ASEAN countries is hampered by virtue of differences between perspectives, resources and programmes currently available in each country. Comprehensive approaches are necessary to develop and strengthen the control and monitoring programme in ASEAN nations. Regional cooperation on standardization and harmonization for AMR monitoring and control programme is imperative for future development and implementation of effective AMR control and prevention plan and long term development in the ASEAN region. Major recommendations are as follows:

1. Raise AMR to be a national issue that needs urgent attention by relevant authorities.

2. Educate and train laboratory staff on standardized antimicrobial susceptibility testing methods and AMR monitoring protocol and encourage the application of the standardized protocol in all laboratory units in the country.

3. Seek and support development of national monitoring programme and create a follow-up system to ensure the effectiveness and success of the programme.

4. Continue to advocate for fair and transparent legislative policy and regulation on veterinary drug use, AMR and AMU monitoring based on scientific evidence and risk assessment.

5. Support development of guidelines on rational use of veterinary drugs to ensure prudent and safe antimicrobial use in livestock.

6. Foster the AMR recording and reporting system and prompt dissemination of data to relevant departments.

7. Increase number of well trained laboratory staff and assign appropriate tasks to appropriate staff/worker to ensure full responsibilities and effectiveness.

8. Educate producers, veterinarians and nutritionists on prudent use of antimicrobials through workshops, seminars and other continuing education programmes.


10. Seek and support regular financial resources, technology and facilities that could be available from governmental and private sectors.

11. Foster a collaborative relationship and collaboration between regulators, public health officials and relevant stakeholders.

12. Advocate the requirement of prescription for veterinary drugs.

13. Increase number of veterinarians and veterinarian services in remote areas.

14. Initiate scientific investigations on AMR that expands from farm to fork. Seek and support innovative research on new technology for diagnosis and alternatives to antibiotics.

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บทคัดย่อ

ติดตามความเคลื่อนไหวของการดื้อยาในปศุสัตว์และผลิตภัณฑ์จากปศุสัตว์ในประเทศ

กลุ่มอาเซียน

อมรเทพ อาชวกุลเทพ1 Chung Ta Thi Kim2 Dethaloun Meunsene3 Didik Handijatno4 Hasliza Abu Hassim5 Hope R. G. Rovira6 Khin Sandar Myint7 Loinda R.Baldrias6 Meas Sothy8 Min Aung7 Nenny H. Wahyu4 Rortana Chea8 สุขฤทัย บุญมาไสว9 Soulasack Vannamahaxay3 สรรเพชญ อังกิติตระกูล10 Therese M. A. Collantes6 Tho Nguyen Van2 รุ่งทิพย์ ชวนชื่น12* แบคทีเรียดื้อยาโดยเฉพาะยิ่งแบคทีเรียที่ก่อโรคอาหารเป็นพิษได้อุบัติขึ้นทั่วโลกรวมทั้งประเทศในกลุ่มอาเซียน ส่งผลกระทบต่อเศรษฐกิจ สุขภาพและสังคม และการค้าระหว่างประเทศ สถานการณ์ได้รับความรู้สึกมากขึ้นเพราะแบคทีเรียที่เป็นอยู่ใหม่ๆที่จะต้องการติดตามอย่างใกล้ชิด ประกาศเศรษฐกิจอาเซียนทำให้เกิดความสัมพันธ์ระหว่างประเทศ โดยเน้นต้องเน้นการวางแผนป้องกันภัยการติดเชื้อ ประเทศไทยในกลุ่มอาเซียนต้องมีระบบการตรวจติดตามและดำเนินการควบคุมโรคที่สอดคล้องไปในทิศทางเดียวกันเพื่อให้การควบคุมและป้องกันเชื้อดื้อยาในภูมิภาคเป็นไปอย่างมีประสิทธิภาพ นอกจากนี้ยังต้องมีระบบการตรวจติดตามและควบคุมภัยการติดเชื้อในภูมิภาคที่สอดคล้องกับข้อตกลงเศรษฐกิจอาเซียนที่จะมีการจับมือระหว่างประเทศ คาดว่าในปี 2015 จะมีการจับมือระหว่างประเทศเพื่อจัดการกับภัยการติดเชื้อในภูมิภาคที่สอดคล้องกันทั้งในระดับประเทศและระดับภูมิภาคดังกล่าว การพัฒนาระบบการตรวจติดตามและควบคุมภัยการติดเชื้อในภูมิภาคในระดับภูมิภาคที่สอดคล้องกันทั้งในระดับประเทศและระดับภูมิภาคดังกล่าว การพัฒนาระบบการตรวจติดตามและควบคุมภัยการติดเชื้อในภูมิภาคในระดับภูมิภาคที่สอดคล้องกันทั้งในระดับประเทศและระดับภูมิภาค

คําสําคัญ: การดื้อยา อาเซียน ปศุสัตว์ ผลิตภัณฑ์จากปศุสัตว์

1คณะสัตวแพทยศาสตร์ มหาวิทยาลัยเกษตรศาสตร์ อ. ก่อมาิตย์ น. นครปฐม ประเทศไทย
2Faculty of Veterinary Medicine, Hanoi University of Agriculture, Hanoi, Vietnam
3Faculty of Agriculture, National University of Laos, Vientiane Capital, Lao PDR
4Faculty of Veterinary Medicine, Airlangga University, Surabaya, Indonesia
5Faculty of Veterinary Medicine, University Putra Malaysia, Selangor, Malaysia
6Department of Veterinary Paraclinical Sciences, College of Veterinary Medicine, University of the Philippines Los Banos, Laguna, Philippines
7Department of Animal Science, University of Veterinary Science, Nay Pyi Taw, Myanmar
8Division of Research and Extension, Royal University of Agriculture, Phnom Penh, Cambodia
9คณะสัตวแพทยศาสตร์ มหาวิทยาลัยมหิดล อ. ศาลายา น. นครปฐม ประเทศไทย
10คณะสัตวแพทยศาสตร์ มหาวิทยาลัยขอนแก่น อ. เมือง น. ขอนแก่น ประเทศไทย
11คณะสัตวแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่ อ. เมือง น. นครปฐม ประเทศไทย
12คณะสัตวแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย ปทุมวัน กรุงเทพฯ ประเทศไทย
*ผู้รับผิดชอบบทความ E-mail: rchuanchuen@yahoo.com