การระบุเชื้อก่อโรคที่มีปัญหาดื้อยาในประเทศไทยระหว่างปี พ.ศ. 2557 - 2561 โดยใช้ดัชนีทางเลือกยาปฏิชีวนะ

Identifying Problematic Pathogens in Thailand From 2014 to 2018 Using Antibiotic Options Index

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บทคัดย่อ

ความเป็นมา: *สถานการณ์การดื้อยาต้านจุลชีพของเชื้อก่อโรคชนิดหนึ่ง ๆ มักเกี่ยวข้องกับยาปฏิชีวนะหลายชนิดเสมอ ซึ่งยาปฏิชีวนะบางชนิดอาจมีความไวลดลง ในขณะที่ยาปฏิชีวนะชนิดอื่นอาจมีความไวเพิ่มขึ้น ทำให้ยากต่อการประเมินภาพรวมของสถานการณ์การดื้อยา ดัชนีทางเลือกยาปฏิชีวนะ (antibiotic options index, AOI) สามารถแสดงสถานการณ์นี้ในรูปแบบความน่าจะเป็นของการรักษาด้วยยาปฏิชีวนะ*

วัตถุประสงค์: *เพื่อระบุเชื้อก่อโรคที่เป็นปัญหาโดยใช้ดัชนีทางเลือกยาปฏิชีวนะจากเชื้อก่อโรคที่พบบ่อย 8 ชนิดที่แยกได้จากตัวอย่างเลือดในประเทศไทยระหว่างปี พ.ศ. 2557 - 2561*

วิธีวิจัย: *รวบรวมข้อมูลความไวต่อยาปฏิชีวนะของเชื้อก่อโรคทั้ง 8 ชนิดที่แยกได้จากตัวอย่างเลือด จาก*

Abstract

Background: *The antimicrobial resistance status of one pathogen is always involved with many antibiotics. Some antibiotics may have decreased susceptibility while increased susceptibility in others, making it difficult to quantify the overview of resistance situation. The antibiotic options index (AOI) can present this status as the probability of effective antibiotic treatment.*

Objectives: *This study aimed to identify problematic pathogens using the antibiotic options index among 8 commonly found pathogens isolated from blood specimens in Thailand from 2014 to 2018.*

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แอนติไบโอแกรมระหว่างปี พ.ศ. 2557 - 2561 ซึ่งเผยแพร่โดยเว็บไซต์ของศูนย์เฝ้าระวังการดื้อยาต้านจุลชีพแห่งชาติ หลังจากนั้นนำมาสร้างดัชนีทางเลือกยาปฏิชีวนะ ซึ่งแทนด้วยสัญลักษณ์ AOI_{m2} หมายถึงความน่าจะเป็นที่จะมียาปฏิชีวนะที่มีประสิทธิผลอย่างน้อย 2 ชนิดจากตัวเลือกยาปฏิชีวนะทั้งหมด m ชนิด ทั้งนี้ กำหนดให้เชื้อก่อโรคที่เป็นปัญหาคือ เชื้อก่อโรคที่มีค่า AOI_{m2} ของกลุ่มยาปฏิชีวนะหลัก (1^{o} AOI_{m2}) หรือกลุ่มยาปฏิชีวนะรอง (2^{o} AOI_{m2}) ต่ำกว่าร้อยละ 80

***ผลการวิจัย**: ระหว่างปี พ.ศ. 2557-2560 พบว่าเชื้อก่อโรคที่มีค่า 1^{o} AOI_{m2} ต่ำกว่าร้อยละ 80 มี 5 ชนิด ได้แก่ Acinetobacter baumannii, Escherichia coli, Klebsiella pneumoniae, Enterococcus faecium, และ Streptococcus pneumoniae ส่วนใน พ.ศ. 2561 มีเชื้อก่อโรคที่เป็นปัญหาเช่นเดียวกับปี พ.ศ. 2557-2560 ยกเว้น A. baumannii ช่วงระหว่างปี พ.ศ. 2557-2561 เชื้อก่อโรคที่มี 2^{o} AOI_{m2} ต่ำกว่าร้อยละ 80 มีเพียงชนิดเดียวคือ A. baumannii*

***สรุปผล**: เชื้อก่อโรคที่มีค่า 1^{o} AOI_{m2} ต่ำกว่าร้อยละ 80 มี 5 ชนิด ระหว่างปี พ.ศ. 2557 - 2560 และ 4 ชนิดในปี พ.ศ. 2561 ส่วนเชื้อก่อโรคที่มีค่า 2^{o} AOI_{m2} ต่ำกว่าร้อยละ 80 มีเพียงหนึ่งชนิดระหว่างปี พ.ศ. 2557 – 2561*

***Materials and Methods**: The antibiotic susceptibilities of the 8 commonly found pathogens isolated from blood specimens were collected from the national antibiogram 2014 - 2018 published by the NARST official website. The antibiotic options index was generated and presented as AOI_{m2}, which refers to the probability of having at least 2 effective antibiotics out of m antibiotic options. The AOI of the primary (1^{o} AOI_{m2}) or secondary antibiotic options (2^{o} AOI_{m2}) lower than 80% has been defined as a problematic pathogen.*

***Results**: During 2014 – 2017, 5 problematic pathogens had 1^{o} AOI_{m2} below 80% were Acinetobacter baumannii, Escherichia coli, Klebsiella pneumoniae, Enterococcus faecium, and Streptococcus pneumoniae; while in 2018, it had the same problematic pathogens as in 2014-2017 except A. baumannii. During 2014 – 2018, a problematic pathogen that had 2^{o} AOI_{m2} below 80% was A. baumannii.*

***Conclusions**: During 2014-2017 there were 5 problematic pathogens had 1^{o} AOI_{m2} below 80%, whereas there were 4 pathogens in 2018. One problematic pathogen that had 2^{o} AOI_{m2} below 80% was found during 2014 – 2018.*

คำสำคัญ: ดัชนีทางเลือกยาปฏิชีวนะ, การดื้อยาต้านจุลชีพ, เชื้อก่อโรคที่พบบ่อย, ประเทศไทย

Keyword: antibiotic options index, antimicrobial resistance, commonly found pathogens, problematic pathogen, Thailand

การอ้างอิงบทความ:

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Introduction

Antimicrobial resistance decreases the effectiveness of antibiotic treatment, leading to an increase in mortality rates, length of hospital stay, and associated healthcare costs.[1,2] Tackling the impact of emerging antimicrobial resistance requires several key strategies,[3] including optimizing antibiotic use,[4] preventing the spread of resistant strains,[5,6] supporting the creation of new drugs,[7] and increasing the efficiency of resistance status monitoring.[8,9] Managing antimicrobial resistance requires cooperation from all stakeholders, including government, private, and civil society sectors. Therefore, it is essential to communicate a simplified message regarding the antimicrobial resistance status. At present, the antimicrobial resistance situation is generally presented as the susceptibility to individual antibiotics. However, the antimicrobial resistance status always involves several antibiotics. It is difficult to quantify the overview of resistance status because some antibiotics show a decrease in susceptibility over time while others increase. The antibiotic options index (AOI) can solve this limitation by presenting the resistance situation as the probability of effective antibiotic treatment.[10]

Objectives

Our study aimed to use AOI to identify the problematic pathogens from eight commonly found pathogens isolated from blood specimens in Thailand during 2014 - 2018.

Materials and Methods

Data collection

Antibiotic susceptibilities of eight commonly found pathogens isolated from blood specimens were collected from the national antibiogram 2014 - 2018 published by the NARST official website.[11] Then AOI trends were generated for *Acinetobacter baumannii*, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterococcus faecium, Enterococcus faecalis, Staphylococcus aureus, and Streptococcus pneumoniae*. If susceptibility data is missing in some years, we substituted it with data of the new-nearest year. The Khon Kaen University Research Ethics Committee has confirmed that no ethical approval is required.

Antibiotic options index calculation

Antibiotic options index (AOI) calculation method was published in 2016, the reader can explore more detail from this article.[10] The AOI calculation in this study was performed by the AOI calculation program, which can request via e-mail: tawtan@kku.ac.th. AOI calculation is created based on the probabilistic theory of multiple independent events. In an antibiogram, antibiotic susceptibility testing results can be either susceptible (*S*) or resistant (*R*); intermediate susceptibility is assumed to be resistant. When two antibiotics are tested, there will be four possible susceptibility patterns: *SS*, *SR*, *RS*, or *RR.* The total number of possible susceptibility patterns from testing multiple antibiotics can be calculated by 2^m, where *m* is the number of antibiotics. For instance, if three antibiotics were tested, there would be eight possible susceptibility patterns, as shown in Table 1. According to the principle of independent events, one antibiotic susceptibility is assumed to be inde-

pendent of the other one. As a result, we can calculate the probability of a susceptibility pattern by multiplying possibility proportions altogether. As in Table 1, we assumed susceptible proportions of three antibiotics to be 0.3, 0.4, and 0.8. The resistant proportions can be calculated by subtracting the susceptible proportion from 1, which are 0.7, 0.6, and 0.2, respectively. Probability of susceptibility pattern 1 (*SSS*) is 0.096, come from 0.3 × 0.4 × 0.8. For the other patterns, do similarly. AOI presents as a probability of having antibiotic options that can effectively treat a given pathogen. At its most basic, the workable pattern should have at least one effective antibiotic (AOI_{m1}, the probability of at least one effective antibiotic out of *m* antibiotic options). The eligible patterns are the ones with at least one susceptible result, patterns 1 - 7. AOI_{31} can be calculated by aggregating eligible pattern's probabilities, which is 0.914 or 91.4% (Table 1). However, some patients may have clinical limitations, such as a severe drug allergy or a failure of responding to the drug, causing a restriction of antibiotic treatment choices. To ensure having sufficient treatment choices, we defined an eligible pattern as a pattern with at least two effective antibiotics. As a result, the patterns that meet the criteria are patterns 1 (*SSS*), 2 (*SSR*), 3 (*SRS*), and 5 (*RSS*). AOI_{32} is a sum of these probabilities, which is 0.488 or 48.8% (Table 1).

In conclusion, the antibiotic options index is denoted by AOI_{m2}, representing the treatment probability of at least *two* effective antibiotics out of *m* antibiotic options. Besides, we classified the severity of situation into three zones based on the AOI_{m2} value: safe zone ($AOI_{m2} \geq 90\%$), warning zone ($AOI_{m2} \geq 80\%$ and $< 90\%$), and unacceptable zone ($AOI_{m2} < 80\%$). AOI_{m2} of primary or secondary antibiotic options lower than 80% is determined as a problematic pathogen.

Antibiotic options

We classified antibiotic options into primary and secondary options by following the guidance of suggested groupings of antimicrobial

Table 1. Antibiotic Options Index (AOI) calculation for three antibiotics

Pattern no.	Susceptibility patterns	Probability for AOI_{31}	Probability for AOI_{32}
1	SSS	0.3 × 0.4 × 0.8 = 0.096	0.3 × 0.4 × 0.8 = 0.096
2	SSR	0.3 × 0.4 × 0.2 = 0.024	0.3 × 0.4 × 0.2 = 0.024
3	SRS	0.3 × 0.6 × 0.8 = 0.144	0.3 × 0.6 × 0.8 = 0.144
4	SRR	0.3 × 0.6 × 0.2 = 0.036	0.3 × 0.6 × 0.2 = 0.036
5	RSS	0.7 × 0.4 × 0.8 = 0.224	0.7 × 0.4 × 0.8 = 0.224
6	RSR	0.7 × 0.4 × 0.2 = 0.056	0.7 × 0.4 × 0.2 = 0.056
7	RRS	0.7 × 0.6 × 0.8 = 0.336	0.7 × 0.6 × 0.8 = 0.336
8	RRR	0.7 × 0.6 × 0.2 = 0.084	0.7 × 0.6 × 0.2 = 0.084
		AOI_{31} = 0.914	AOI_{32} = 0.488

agents for testing and reporting on organisms published by the Clinical and Laboratory Standard Institute (CLSI), 2018[12] as follows: 1) Primary antibiotic options were selected from group A antimicrobial agents, considered appropriate for routine reporting of results for the specific organism. 2) Secondary antibiotic options were chosen from group B and C antimicrobial agents, reserved for use when the organism is resistant or fails to respond to agents in group A. 3) The selected antibiotic options must be existing in the NARST's antibiogram to ensure that the susceptibility rates are available. 4) According to the probabilistic theory of multiple independent events, one antibiotic susceptibility result is assumed independent of another. Therefore, if more than one choice is in the same antibiotic class, we selected either one with the highest susceptibility rate to represent the class. The primary and secondary antibiotic options are shown in Table 2.

Results

National trends of the antibiotic options index during 2014 - 2018

During 2014 – 2017, we found that 1° AOI_{m2} identified five problematic pathogens including *A. baumannii, E. coli, K. pneumoniae, E. faecium, and S. pneumoniae*, whereas, in 2018, *A. baumannii* was not. When considered by 2° AOI_{m2}, only *A. baumannii* was a problematic pathogen during the study time (Table 3).

Acinetobacter baumannii

1° AOI_{52} (ampicillin-sulbactam, ceftazidime, gentamicin, levofloxacin, and imipenem) was 72.9% in 2014 stayed in the unacceptable zone, and 81.6% in 2018 was placed in the warning zone (Fig. 1). 2° AOI_{42} (amikacin, cefepime, cotrimoxazole, and piperacillin-tazobactam) was 58.5% in 2014 and 72.9% in 2018; both had stayed in the unacceptable zone. An uptrend of 1° AOI_{52} and 2° AOI_{42} during 2014 – 2018 resulted from all susceptibilities increasing. Primary option susceptibilities included ampicillin-sulbactam, ceftazidime, gentamicin, levofloxacin, and imipenem increased from 40.9% to 45.4%, 43.2% to 46.5%, 46.4% to 53.9%, 44.6% to 54.8%, and 44.8% to 50.2%, respectively. Secondary option susceptibilities included amikacin, cefepime, cotrimoxazole, and piperacillin-tazobactam raised from 53.3% to 60.1%; 42.0% to 50.6%; 36.8% to 54.3%; and 41.9% to 45.7%, respectively. In 2018, ranking from the highest antibiotic susceptibility were amikacin (60.1%), levofloxacin (54.8%), cotrimoxazole (54.3%), gentamicin (53.9%), cefepime (50.6%), imipenem (50.2%), ceftazidime (46.5%), piperacillin-tazobactam (45.7%) and ampicillin-sulbactam (45.4%) (Fig.1).

Escherichia coli

1° AOI_{32} (ampicillin, cefazolin, and gentamicin) was 33.1% in 2014, and 36.4% in 2018 both had stayed in the unacceptable zone (Fig. 2). 2° AOI_{62} (amikacin, ceftazidime, cotrimoxazole, levofloxacin, meropenem, and piperacillin-tazobactam) was 99.9% in 2014, and 2018 placed in the safe zone. In 2018, ranking from the highest antibiotic susceptibility were meropenem (98.6%), amikacin (98.3%), piperacillin-tazobactam (93.6%), ceftazidime (71.3%), gentamicin (70.7%), levofloxacin (59.2%), cotrimoxazole (45.9%), cefazolin (38.8%), and ampicillin (16.0%) (Fig.2).

Table 2 Primary and secondary antibiotic options for eight common pathogens

Pathogens	Primary antibiotic options	Secondary antibiotic options
Acinetobacter baumannii	Ampicillin-sulbactam, ceftazidime, gentamicin, fluoroquinolones[a], carbapenems[b].	Amikacin, cefepime, cotrimoxazole, piperacillin-tazobactam.
Escherichia coli	Ampicillin, cefazolin, gentamicin.	Amikacin, fluoroquinolones[a], carbapenems[b], beta-lactam plus beta-lactam inhibitor[c], cephalosporins[d], cotrimoxazole.
Klebsiella pneumoniae	Cefazolin, gentamicin.	Amikacin, fluoroquinolones[a], carbapenems[b], beta-lactam plus beta-lactam inhibitor[c], cephalosporins[d], cotrimoxazole.
Pseudomonas aeruginosa	Ceftazidime, gentamicin, piperacillin-tazobactam.	Amikacin, cefepime, fluoroquinolones[a], carbapenems[b].
Enterococcus faecalis	Ampicillin, gentamicin (120 mcg), vancomycin[e].	-
Enterococcus faecium	Ampicillin, gentamicin (120 mcg), vancomycin[e].	-
Staphylococcus aureus	Clindamycin, cotrimoxazole, erythromycin, cefoxitin (oxacillin).	Gentamicin, fluoroquinolones[a], tetracycline, vancomycin.
Streptococcus pneumoniae	Cotrimoxazole, erythromycin, penicillin.	Clindamycin, levofloxacin, tetracycline, vancomycin.

Note: [a] Fluoroquinolones: ciprofloxacin or levofloxacin; [b] Carbapenems: imipenem or meropenem; [c] Beta-lactam plus beta-lactam inhibitor: amoxicillin-clavulanate or ampicillin-sulbactam or piperacillin-tazobactam; [d] Cephalosporins: cefuroxime or ceftriaxone or ceftazidime or cefepime. If more than one choice is in the same class, we select either one with the highest susceptibility rate to represent the class. [e] For *E. faecalis* and *E. faecium*, ampicillin was merely an option in group A. As the AOI_{m2} principle needs at least two antibiotic choices; therefore, we included antibiotic choices in groups B and C as the primary option.

Klebsiella pneumoniae

1° AOI_{22} (cefazolin and gentamicin) was 50.0% in 2014, and 51.6% in 2018 both stayed in the unacceptable zone (Fig. 3). *K. pneumoniae* has intrinsic resistance to ampicillin; hence ampicillin cannot be used as the primary option. 2° AOI_{62} (amikacin, ceftazidime, cotrimoxazole, levofloxacin, meropenem, and piperacillin-tazobactam) was 99.9% both in 2014, and 2018 placed in the safe zone. In 2018, ranking from the highest antibiotic susceptibility were amikacin (94.0%), meropenem (89.6%), gentamicin (86.0%), levofloxacin (78.8%), piperacillin-tazobactam (77.4%), cefepime (70.6%), cotrimoxazole (66.8%), cefazolin (59.8%) (Fig.3).

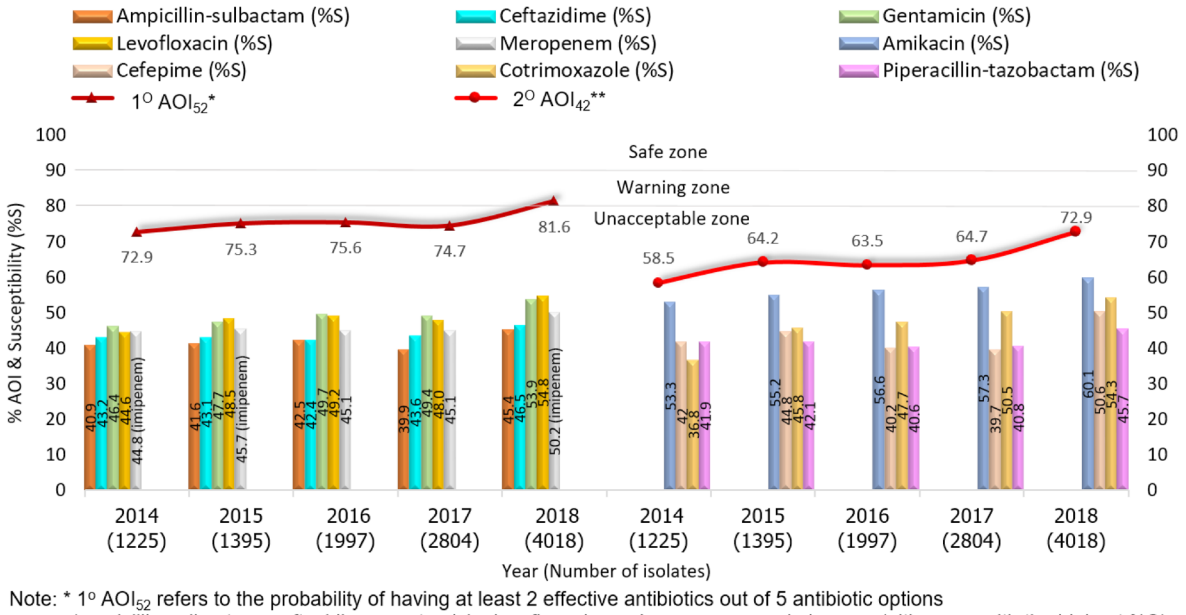
Pseudomonas aeruginosa

1° AOI_{32} (ceftazidime, gentamicin, and piperacillin-tazobactam) was 90.2% in 2014 and

Table 3 Problematic pathogens identified by 1° and 2° AOI_{m2} during 2014 - 2018

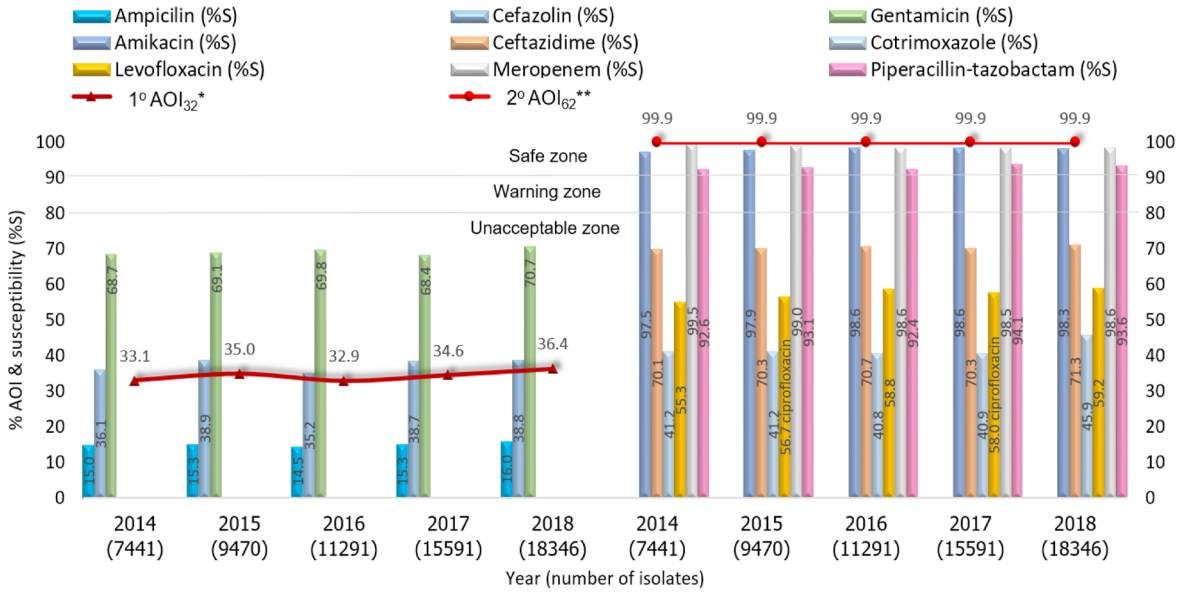
Pathogens	1° AOI_{m2}					2° AOI_{m2}				
	2014	2015	2016	2017	2018	2014	2015	2016	2017	2018
Acinetobacter baumannii	X	X	X	X	/	X	X	X	X	X
Escherichia coli	X	X	X	X	X	/	/	/	/	/
Klebsiella pneumoniae	X	X	X	X	X	/	/	/	/	/
Pseudomonas aeruginosa	/	/	/	/	/	/	/	/	/	/
Enterococcus faecalis	/	/	/	/	/	-	-	-	-	-
Enterococcus faecium	X	X	X	X	X	-	-	-	-	-
Staphylococcus aureus	/	/	/	/	/	/	/	/	/	/
Streptococcus pneumoniae	X	X	X	X	X	/	/	/	/	/

Note: X refers to AOI_{m2} lower than 80% identified as a problematic pathogen; / refers to AOI_{m2} more than 80%; - refers to the 2° AOI_{m2} were not calculated because there were a few antibiotic choices. We included all choices into the primary option.



Note: * 1º AOI_{52} refers to the probability of having at least 2 effective antibiotics out of 5 antibiotic options (ampicillin-sulbactam, ceftazidime, gentamicin, levofloxacin, and meropenem or imipenem (either one with the highest %S);
** 2º AOI_{42} the antibiotic options includes amikacin, cefepime, cotrimoxazole, and piperacillin-tazobactam.

Fig.1 1° and 2° AOI_{m2} for *Acinetobacter baumannii*, 2014 – 2018



Note: * 1° AOI_{32} refer to the probability of having at least 2 effective antibiotics out of 3 antibiotic options (ampicillin, cefazolin, and gentamicin); ** 2° AOI_{62} The 6 antibiotic options include amikacin, ceftazidime, cotrimoxazole, levofloxacin or ciprofloxacin (either one with the highest %S), meropenem, and piperacillin-tazobactam.

Fig.2 1° and 2° AOI_{m2} for *Escherichia coli*, 2014 – 2018

94.2% in 2018; both located in the safe zone (Fig. 4). 2° AOI_{42} (amikacin, cefepime, levofloxacin (in 2014) or ciprofloxacin (in 2018), and meropenem) was 98.3% in 2014 and 99.2% in 2018; both stayed in the safe zone. In 2018, ranking from the highest antibiotic susceptibility were amikacin (90.5%), ciprofloxacin (87.2%), piperacillin-tazobactam (86.1%), gentamicin (85.9%), cefepime (84.4%), ceftazidime (84.2%), meropenem (84.0%) (Fig.4).

Enterococcus faecalis

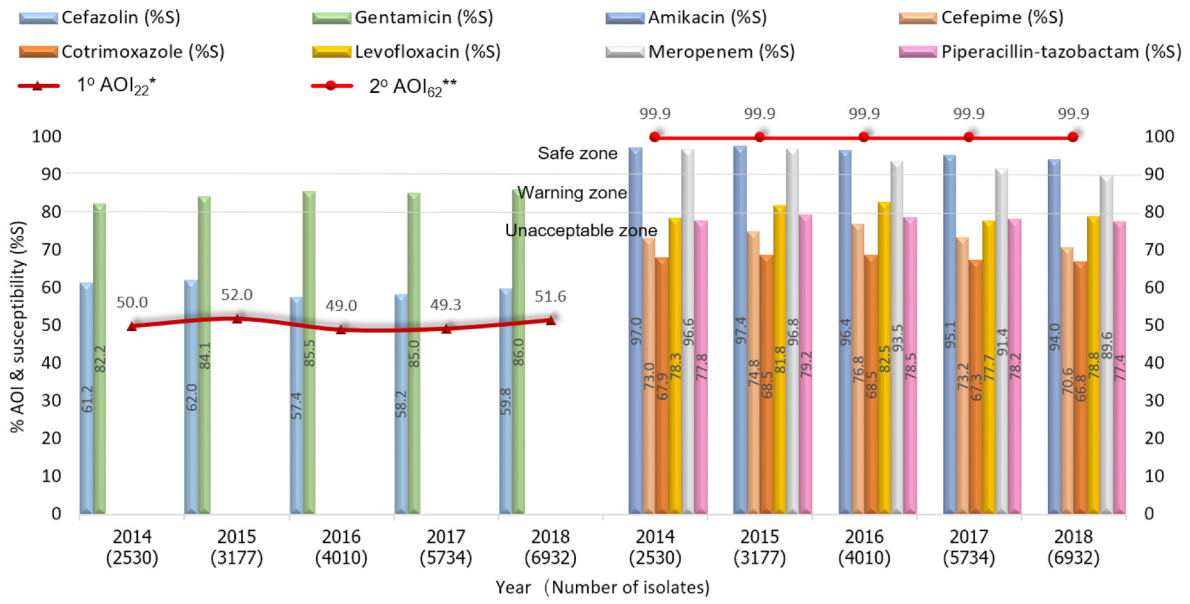
1° AOI_{32} (ampicillin, gentamicin 120 mcg, and vancomycin) was 93.9% in 2014 and 97.9% in 2018; both located in the safe zone (Fig.5). In 2018, ranking from the highest antibiotic susceptibility were vancomycin (97.8%), ampicillin (94.9%), and gentamicin 120 mcg (69.5%) (Fig.5).

Enterococcus faecium

1° AOI_{32} (ampicillin, gentamicin 120 mcg, and vancomycin) was 70.9% in 2014 and 69.1% in 2018; both located in the unacceptable zone (Fig. 5). In 2018, ranking from the highest antibiotic susceptibility were vancomycin (91.1%), gentamicin 120 mcg (70.1%), and ampicillin (16.3%) (Fig.5).

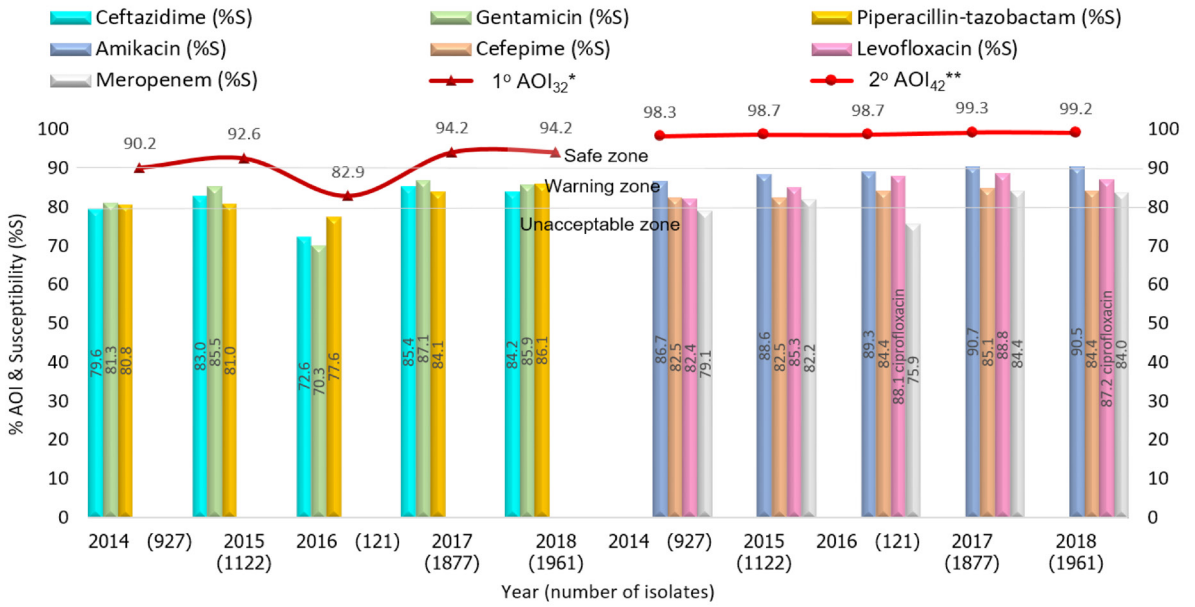
Staphylococcus aureus

1° AOI_{42} (cefoxitin, clindamycin, cotrimoxazole, and erythromycin) was 98.7% in 2014 and 99.7% in 2018; both located in the safe zone (Fig. 6). 2° AOI_{42} (gentamicin, levofloxacin, tetracycline, and vancomycin) was 97.6% in 2014 and 99.6% in 2018; both stayed in the safe zone. In 2018, seven antibiotic options that have susceptibility rates more than 80% were



Note: * 1º AOI_{22} refer to the probability of having at least 2 effective antibiotics out of 2 antibiotic options (cefazolin, and gentamicin); ** 2º AOI_{62} The antibiotic options include amikacin, ceftazidime, cotrimoxazole, levofloxacin, meropenem, and piperacillin-tazobactam.

Fig.3 1° and 2° AOI_{m2} for *Klebsiella pneumoniae*, 2014 – 2018



Note: * 1º AOI_{32} refer to the probability of having at least 2 effective antibiotics out of 3 antibiotic options (ceftazidime, gentamicin, and piperacillin-tazobactam); ** 2º AOI_{42} the antibiotic options include amikacin, cefepime, levofloxacin or ciprofloxacin (either one with the highest %S), and meropenem.

Fig.4 1° and 2° AOI_{m2} for *Pseudomonas aeruginosa*, 2014 – 2018

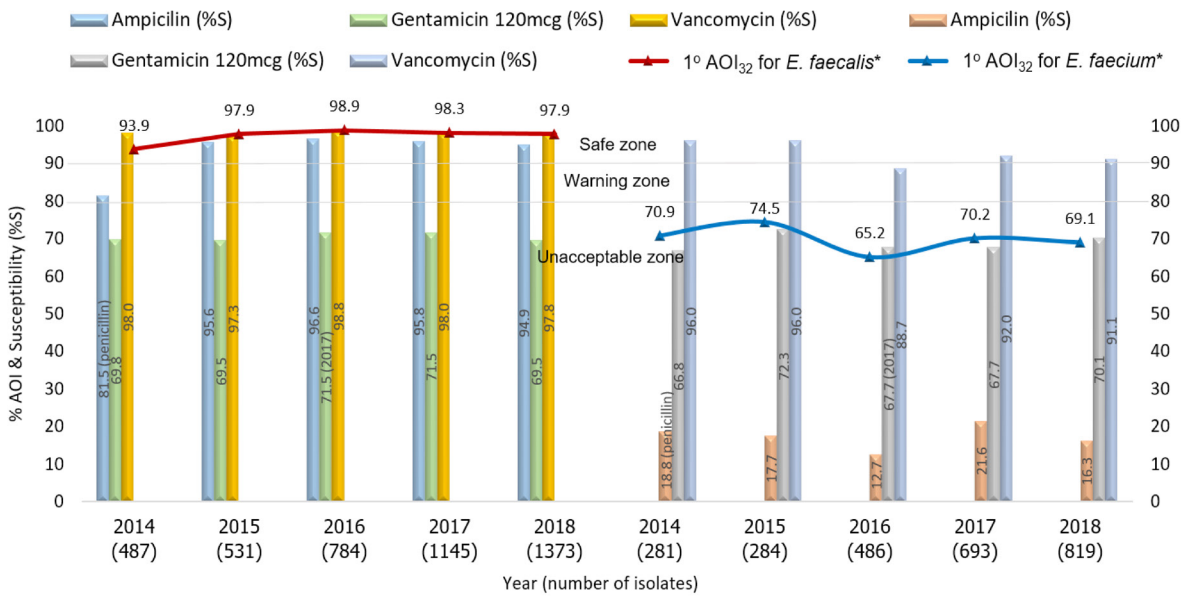
cefoxitin (91%), clindamycin (86.1%), cotrimoxazole (96.7%), erythromycin (82.5%), gentamicin (92.8%), levofloxacin (87.9), and vancomycin (99.7%). Tetracycline showed the lowest susceptibility rate of 63.5% (Fig.6).

Streptococcus pneumoniae

1° AOI_{32} (cotrimoxazole, erythromycin, and penicillin) was 74.8% in 2014 and 73.1% in 2018; both located in the unacceptable zone (Fig.7). 2° AOI_{42} (clindamycin, levofloxacin, tetracycline, and vancomycin) was 99.7% in 2014 and 99.4% in 2018; both stayed in the safe zone. In 2018, the susceptibilities ranked from the highest were vancomycin (99.8%), levofloxacin (98.3%), penicillin (74.0%), clindamycin (71.9%), erythromycin (68.9%), cotrimoxazole (54.2%), and tetracycline (28.6%) (Fig.7).

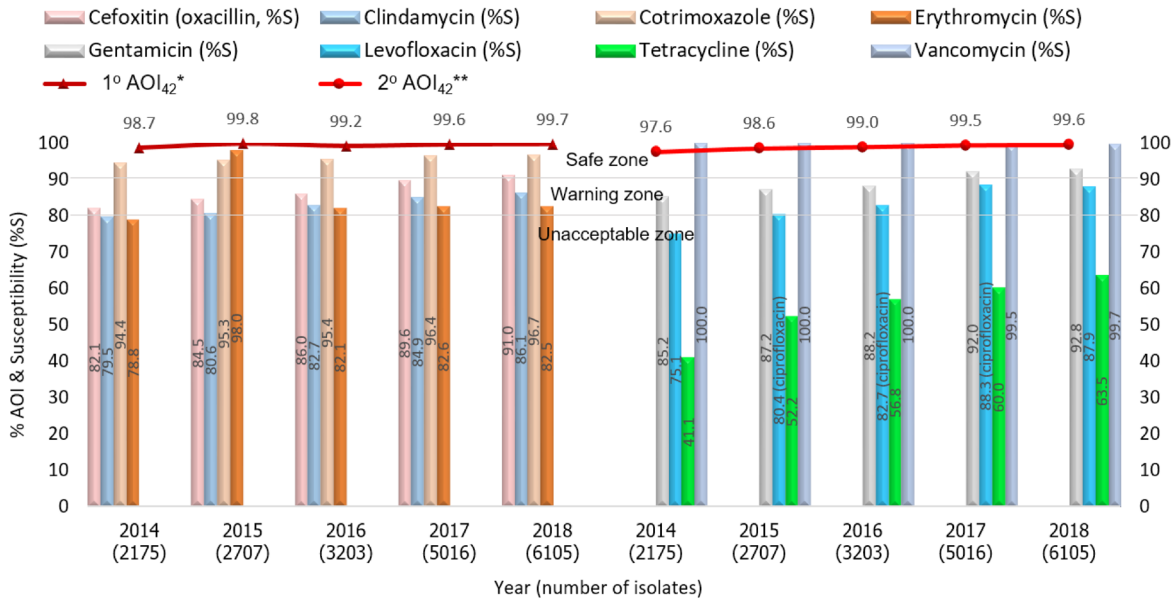
Discussion

The study results showed the problem of insufficient primary antibiotic options in five problematic pathogens including *A. baumannii, E. coli, K. pneumoniae, E. faecium, and S. pneumoniae*. However, these problems were alleviated with sufficient secondary antibiotic options, except for *A. baumannii* and *E. faecium*. 1° AOI_{32} of *A. baumannii* was under 80% during 2014 – 2017; however, it began moving a little above 80% in 2018 (81.6%). The problematic situation was 2° AOI_{42} which was under 80% through the study period (58.5% in 2014 to 72.9% in 2018) reflecting that there might not be enough secondary antibiotic options for the treatment of *A. baumannii* infection after primary options failed. Carbapenems had a high susceptibility



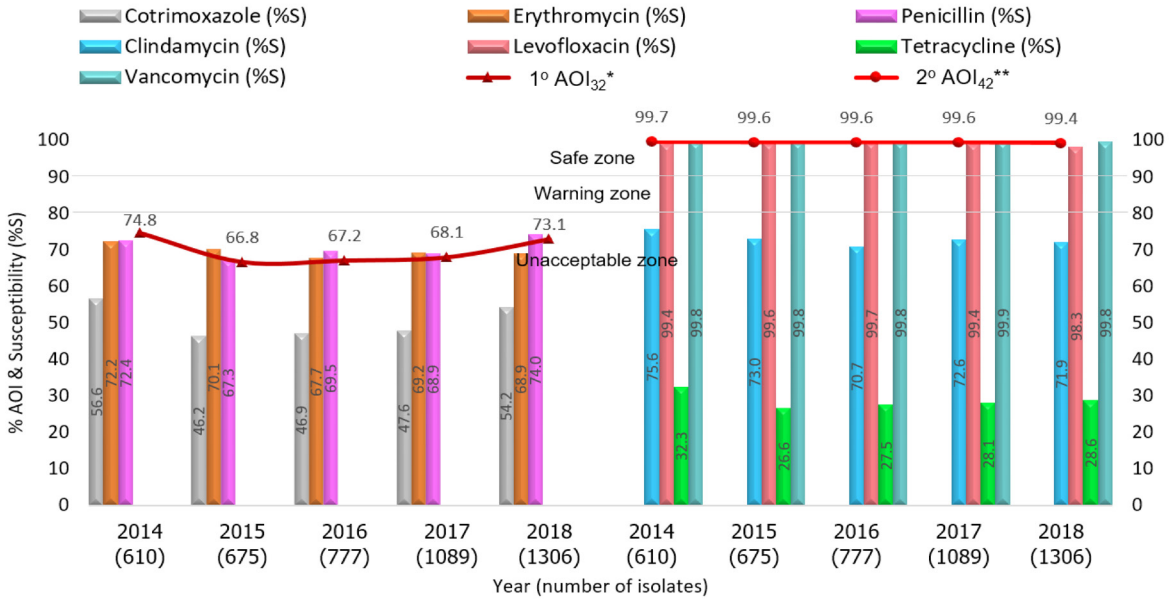
Note: * 1° AOI_{32} *E. faecalis* and *E. faecium* refer to the probability of having at least 2 effective antibiotics out of 3 antibiotic options (ampicillin, gentamicin 120 mcg, and vancomycin).

Fig.5 1° AOI_{m2} for *Enterococcus faecalis* and *Enterococcus faecium*, 2014 – 2018



Note: * 1º AOI_{42} refer to the probability of having at least 2 effective antibiotics out of 4 antibiotic options (cefoxitin (oxacillin), clindamycin, cotrimoxazole, and erythromycin); ** 2º AOI_{42} the antibiotic options include gentamicin, levofloxacin or ciprofloxacin (either one with the highest %S), tetracycline, and vancomycin.

Fig.6 1° and 2° AOI_{m2} for *Staphylococcus aureus*, 2014 – 2018



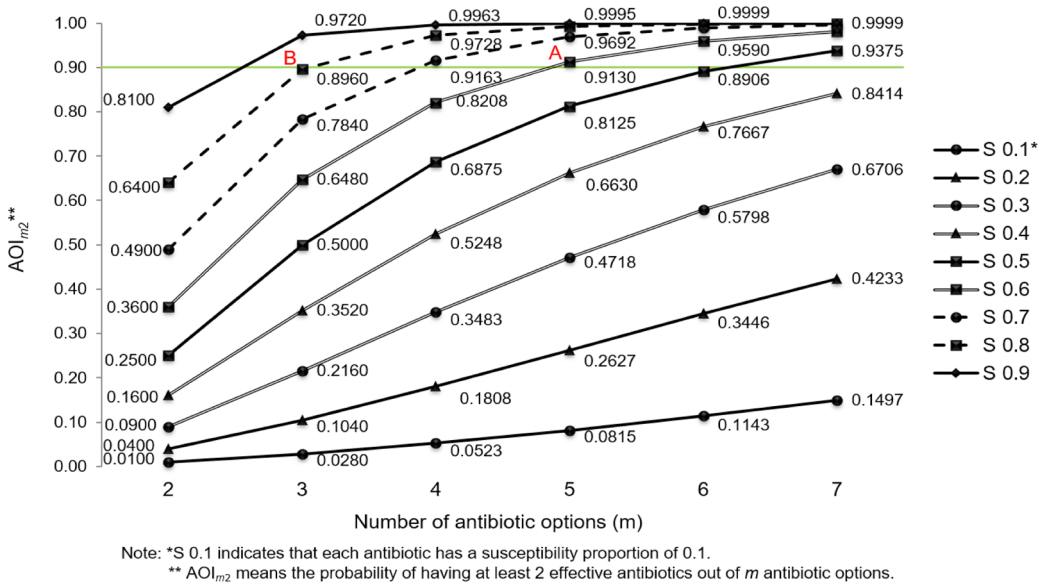
Note: * 1º AOI_{32} refer to the probability of having at least 2 effective antibiotics out of 3 antibiotic options (cotrimoxazole, erythromycin, and penicillin); ** 2º AOI_{42} the antibiotic options include clindamycin, levofloxacin, tetracycline, and vancomycin.

Fig.7 1° and 2° AOI_{m2} for *Streptococcus pneumoniae*, 2014 – 2018

(95%) for the treatment of *A. baumannii* infection since 2000 in Thailand.[13] The susceptibility continuously fell to around 50% during 2014 – 2018, as demonstrated in this study; these phenomena were possibly induced by a natural selective pressure related to the tremendous increased use of carbapenem.[14-16] In this study, since there were only three antibiotic options for *E. faecium*, they were classified as the primary options (not enough antibiotic choices to be classified as the secondary options). 1° AOI_{32} for *E. faecium* was lower than 80% (70.9 in 2014 and 69.1% in 2018). These presented a worrying situation when primary options failed.

AOI is associated with two key factors, the antibiotic susceptibility rate and the number of antibiotic options (Fig. 8). The more number of both factors, the more we gain AOI value. This knowledge point to the minimum requirement of antibiotic susceptibility relates to the number of antibiotic options. For instance, if there are five antibiotic options and the needed target of AOI_{52} is greater than 90%, each antibiotic's minimum required susceptibility proportion is 0.6 or 60%; these will provide AOI_{52} of 91.3% (Fig. 8, point A). Again, if there are three antibiotic options, each antibiotic's minimum required susceptibility proportion is 0.8 or 80%; these will provide AOI_{32} of 89.6% (Fig. 8, point B).

AOI represents an alternative way to present an overview of antibiotic resistance situations by summarizing a set of antibiotic susceptibilities into a definite index, presented as a percentage of treatment probability. Since the AOI calculation only requires the antibiotic susceptibility rates provided in an antibiogram, commonly available in most hospitals, the AOI can be generated and applied at multiple organizational levels, including local, regional, and national levels. We hope that the AOI will sim-



Note: *S 0.1 indicates that each antibiotic has a susceptibility proportion of 0.1.
** AOI_{m2} means the probability of having at least 2 effective antibiotics out of *m* antibiotic options.

Fig.8 Sensitivity analysis of the number of antibiotic options (*m*) and susceptibility proportions

plify the communication of antimicrobial resistance status, set a clear antibiotic susceptibility target, and help staff assesses an appropriate hospital antibiotic formulary.

Conclusion

There were five problematic pathogens with 1° AOI_{m2} below 80% during 2014 – 2017 and 4 in 2018. One problematic pathogen with 2° AOI_{m2} below 80% was found during 2014 – 2018. The index identifies the overview of the antimicrobial resistance situation involved with a set of antibiotics, presenting as the probability of effective antibiotic treatment. It is a promising alternative way to communicate and monitor the antimicrobial resistance situation.

Declarations

Funding:

No funding was obtained for this study.

Conflicts of Interest:

There are no potential conflicts of interest to declare.

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