DEVELOPMENT OF AN ANTIBIOTIC OPTIONS INDEX FOR ANTIBIOTIC RESISTANCE MONITORING

Taweesuk Manomayitthikan[1], Glenn N Borlace[2] and Nusaraporn Kessomboon[3]

[1]Department of Pharmacy, Queen Sirikit Heart Center of the Northeast, Faculty of Medicine; [2]Faculty of Pharmaceutical Science, [3]Department of Social and Administration Pharmacy, Faculty of Pharmaceutical Science, Khon Kaen University, Khon Kaen, Thailand

Abstract. Using antibiogram data to indicate the overall antibiotic resistance of a pathogen is complicated by the multiple antibiotic susceptibilities reported in the antibiogram. The objectives of this study were to develop and determine the benefits of an Antibiotic Options Index (AOI); an index that summarizes antibiotic susceptibility data for a pathogen by presenting it as the availability of antibiotic treatment options. The AOI was calculated using antibiogram data for the seven most commonly isolated pathogens from the National Antimicrobial Resistance Surveillance Center of Thailand between 1998 and 2014 and was classified as acceptable (AOI ≥ 0.8) or unacceptable (AOI < 0.8) based on the availability of treatment options. The AOI identified two problematic pathogens: *Acinetobacter baumannii* and methicillin-resistant *Staphylococcus aureus* (MRSA). For *A. baumannii*, the probability of having at least two viable antibiotic treatment options (AOI_{m2}) decreased from an acceptable level (0.93) in 1998 to an unacceptable level (0.53) in 2014 and for MRSA the AOI_{m2} decreased from an acceptable level (0.82) in 1998 to an unacceptable level (0.47) in 2014. By including the idea that the problem with increasing antibiotic resistance is a problem with treating infections, the AOI effectively compiles susceptibility data to present it as the probability of having effective antibiotic treatment. This index is calculated from widely available antibiogram data, making it more suitable to be used to monitor antibiotic resistance at the hospital, provincial and national levels.

Keywords: antibiotic options index, antibiogram, susceptibility, antibiotic resistance, monitoring

INTRODUCTION

Escalating antibiotic resistance rates affect health care systems around the world by increasing the length of hospital stays, health care costs, and mortality rates (Carmeli *et al*, 1999; Cosgrove, 2006; de Kraker *et al*, 2011). The World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) both recommend tracking bacterial resistance to help manage this antibiotic resistance crisis (Gu and Kaku, 2012; CDC, 2013). Managing the problem of antibiotic resis-

Correspondence: Taweesuk Manomayitthikan, Department of Pharmacy, Queen Sirikit Heart Center of the Northeast, Faculty of Medicine, Khon Kaen University, 123 Mitrapap Road, Amphoe Mueang, Khon Kaen, 40002, Thailand. Tel: +66 (0) 43 203 080; Fax: +66 (0) 43 203 018 E-mail: tawtan@kku.ac.th

tance requires cooperation from medical professionals, the lay public and policy makers. However, communication of antibiotic resistance to these groups has not been entirely successful. Antibiogram data is the most used information for monitoring and assessing antibiotic resistance. It gives a pathogen's antibiotic susceptibilities: the proportion of clinical isolates susceptible to that antibiotic. The problem with reporting a pathogen's antibiotic susceptibilities using an antibiogram is the complexity of the data. Susceptibility rates for a pathogen are reported individually, as shown in the following example: "The susceptibility rates for *Acinetobacter baumannii* to ceftazidime, ciprofloxacin, gentamicin, cefoperazone/sulbactam and imipenem were 30%, 29%, 34%, 41% and 32%, respectively". For monitoring purposes, reporting individual antibiotic susceptibility rates for a pathogen over multiple years creates an expanding set of numbers that can be difficult to interpret. Essentially, raw antibiogram data is unsuitable for communicating the extent of a pathogen's overall antibiotic resistance. In order to improve on this, we propose a new index called the Antibiotic Options Index (AOI) that summarizes the antibiotic susceptibilities for a pathogen by calculating the probability of having antibiotic options to treat that pathogen.

The AOI concept is based on the probability theory of multiple independent events (Taylor, 2013). In brief, if two events occur independently, then the probability of both events occurring simultaneously is the product of the two probabilities. This can be illustrated by calculating the outcomes and probabilities of two coins being flipped. When one coin is flipped, the result will be either a head or a tail and the probability of each is 0.5. If we flip two coins at the same time (two independent events), there are four possible outcomes and the probability of each outcome is the product of the two probabilities. For example, the probability of two heads occurring is 0.25 and is calculated by multiplying the probability of heads for Coin 1 (0.5) by the probability of heads for Coin 2 (0.5). The sum of the probabilities for all possible outcomes is equal to one. The outcomes and probabilities calculated for coin-flipping can be extended to antimicrobial susceptibility if we substitute susceptible or resistance for heads and tails. Here we describe how the susceptible and resistant proportions reported in an antibiogram can be used to design and implement the AOI.

MATERIALS AND METHODS

The AOI concept was reviewed by a panel of five experts (one infectious disease physician, two policymakers and two hospital executive officers) who proposed a five step AOI construction process. Step 1: identify which antibiotics are most frequently used to treat a pathogen. Step 2: select the antibiotic in each class with the lowest susceptible proportion to represent that class. Step 3: calculate antibiotic resistance proportions from antibiotic susceptible proportions. Step 4: generate possible outcomes and their probabilities from the susceptible and resistant proportions. Step 5: calculate the AOI. The AOI was then implemented using antibiogram data from the National Antimicrobial Resistance Surveillance Center of Thailand (National Antimicrobial Resistance Surveillance Center, 2014) during 1998-2014 for the seven most commonly isolated pathogens: *Acinetobacter baumannii*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA).

This study was approved by the Khon Kaen University Ethics Committee for Human Research (approval number HE581274).

RESULTS

Development of the AOI

The AOI was developed by applying the probability of multiple independent events (Taylor, 2013) to susceptibility or resistance to antibiotics. If events *A* and *B* occur independently, then $P(A \cap B) = P(A) \times P(B)$ where $P(A \cap B)$ is the probability of *A* and *B* happening simultaneously, $P(A)$ is the probability of event *A* happening and $P(B)$ is the probability of event *B* happening. In an antibiogram, antimicrobial susceptibility testing results can be considered to be either susceptible or resistant, intermediate susceptibility is assumed to be resistant. Therefore, the total number of possible outcomes for multiple antibiotics can be calculated by: 2^m where *m* is the number of antibiotics. For three antibiotics: Antibiotic 1 (*ATB1*), Antibiotic 2 (*ATB2*) and Antibiotic 3 (*ATB3*), there are eight susceptibility patterns (Fig 1). In Fig 1, the first pattern is *SSS*, which means the pathogen is susceptible to all three antibiotics (*ATB1*, *ATB2* and *ATB3*). The second pattern is *SSR*, which means the pathogen is susceptible to *ATB1* and *ATB2* and resistant to *ATB3*. The eighth pattern is *RRR*, which shows the pathogen is resistant to all three antibiotics.

To calculate an AOI, suppose the susceptible proportions of *ATB1*, *ATB2* and *ATB3* were 0.4, 0.3 and 0.2. The resistant proportions are calculated by subtracting the susceptible proportions from one. Thus, the resistant proportions for *ATB1*, *ATB2* and *ATB3* would be 0.6, 0.7 and 0.8, respectively. The probability of susceptibility pattern *i*, $P(A_i)$, can be calculated by multiplying the susceptibility proportions in pattern *i* together (Table 1). For example, the probability of susceptibility pattern 1, *P(SSS)*, comes from multiplying the susceptible proportions for *ATB1*, *ATB2* and *ATB3*: 0.4x0.3x0.2 = 0.024. The probability of susceptibility pattern 5, *P(RSS)*, comes from multiplying the resistant proportion of *ATB1* by the susceptible proportions for *ATB2* and *ATB3*: 0.6x0.3x0.2 = 0.036. The probabilities for other susceptibility patterns can be calculated similarly (Table 1). The AOI is the sum of the probabilities of the effective antibiotic treatment options, which includes susceptibility patterns that contain at least one susceptible result. In Table 1, the eligible susceptibility patterns are patterns 1 to 7, and the AOI is 0.664.

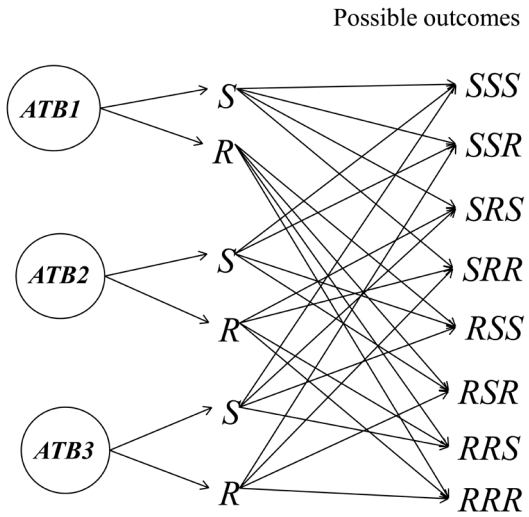

Fig 1–Possible outcomes from susceptibility results for three antibiotics. *ATB1*, Antibiotic 1; *ATB2*, Antibiotic 2; *ATB3*, Antibiotic 3; *S*, susceptible; R, resistant.

The AOI calculation from Table 1 can be expressed by the mathematical formula:

$$\mathrm{AOI}_{mk} = \sum_{i=1}^{2^m} P(A_i \mid B_i \geq k), A_i \in \Omega$$

where *m* is the number of antibiotics,

Table 1
The AOI calculation for three tested antibiotics.

Pattern No. (*i*)	Susceptibility pattern (A_i)	$P(A_i)$	$P(A_i \mid B_i \geq 1)$
1	*SSS*	0.4x0.3x0.2	0.024
2	*SSR*	0.4x0.3x0.8	0.096
3	*SRS*	0.4x0.7x0.2	0.056
4	*SRR*	0.4x0.7x0.8	0.224
5	*RSS*	0.6x0.3x0.2	0.036
6	*RSR*	0.6x0.3x0.8	0.114
7	*RRS*	0.6x0.7x0.2	0.084
8	*RRR*	0.6x0.7x0.8	Not eligible
		AOI	0.664

i, the pattern number; A_i, susceptibility pattern *i*; $P(A_i)$, the probability of A_i; B_i, the number of susceptible results in the susceptibility pattern *i*; $P(A_i \mid B_i \geq 1)$, the probability of susceptibility pattern *i* that contains at least one susceptible result.

k is the minimum number of susceptible results required to make a susceptibility pattern eligible for inclusion in the AOI calculation ($k = 1$ or 2, and $k \leq B_i$), *i* is the pattern number, A_i is the susceptibility pattern *i*, B_i is the number of susceptible results contained in the susceptibility pattern *i*. Ω is the set of susceptibility patterns derived from *m* antibiotics; $P(A_i)$ is the probability of susceptibility pattern *i* and $P(A_i \mid B_i \geq k)$ is the probability of susceptibility pattern *i* containing at least *k* susceptible results. The efficacy of the AOI is defined by two factors: the number of antibiotics (*m*) and the minimum number of susceptible results required (*k*).

Number of antibiotics (*m*)

The AOI has a value range from zero to one but if too many antibiotics are used to calculate the AOI, it reduces the sensitivity, with all of the resulting AOI values approaching one. To find the appropriate number of antibiotics (*m*) for the AOI calculation, we performed a sensitivity analysis (Fig 2) by varying susceptible proportions (0.2, 0.3, 0.5, 0.7 and 0.9) and the number of antibiotics ($m = 1$ to 10). Higher numbers of antibiotics or higher susceptibility rates resulted in AOIs that approach one (Fig 2). For seven or more antibiotics, calculated AIOs were less than one only for susceptibility rates less than 0.5 [Fig 2, S(0.3) and S(0.2)]. The AOI was *in*sensitive to susceptibility rates over 0.7 when more than five antibiotics were used [Fig 2, S(0.7)]. Therefore, five (or less) was determined to be the appropriate number of antibiotics to be used in the AOI calculation.

The minimum number of susceptible results required (*k*)

The minimum number of susceptible results is a key determinant of the efficacy of the AOI. At its most basic, the AOI_{m1} indicates the probability of having at least one suitable antibiotic choice to treat a pathogen. However, patients can have contraindications and clinical limitations such as adverse drug reactions that restrict the choice of antibiotics to use for therapy. In some situations, patients may also require a combination antibiotic regimen. In these

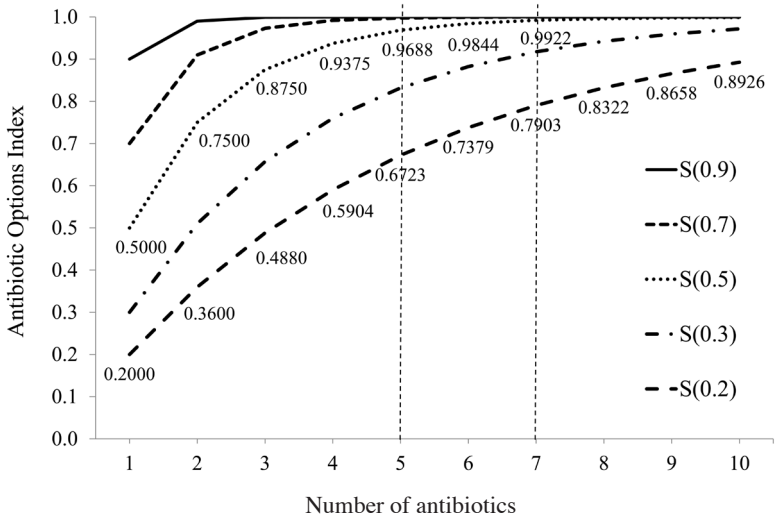

Fig 2–Sensitivity analysis of the number of antibiotics (*m*).

cases, an antibiotic susceptibility pattern with at least two susceptible results ensures that there will be sufficient treatment options. For these reasons, the AOI_{m2} is suggested as the more prudent indicator of the severity of antibiotic resistance.

Five-steps for AOI calculation

In order to illustrate the AOI calculation model, the five steps to determine the AOI for *A.baumannii* using 2014 NARST antibiogram data are presented.

Step 1. Identify which antibiotics are most frequently used to treat a pathogen. For *A. baumannii* infection, there are five antibiotic classes representing nine antibiotics: beta-lactams (ceftazidime and cefepime), beta-lactam/beta-lactamase inhibitor (cefoperazone/sulbactam), carbapenems (imipenem and meropenem), fluoroquinolones (ciprofloxacin and levofloxacin) and aminoglycosides (amikacin and gentamicin). The most frequently used antibiotics for the seven most commonly isolated pathogens (compiled from NARST data during 1998-2014) are presented in Table 2.

Step 2. Select the antibiotic in each class with the lowest susceptible proportion to represent that class. For *A. baumannii* in 2014, the representative susceptible proportions of beta-lactams, beta-lactam plus beta-lactamase inhibitor, carbapenems, fluoroquinolones and aminoglycosides were 0.30, 0.41, 0.30, 0.29 and 0.34, respectively.

Step 3. Calculate antibiotic resistant proportions from antibiotic susceptible proportions. The antibiotic resistant proportions for *A. baumannii* in 2014 were 0.70, 0.59, 0.70, 0.71 and 0.66 for beta-lactams, beta-lactam plus beta-lactamase inhibitor, carbapenems, fluoroquinolones and aminoglycosides, respectively.

Step 4. Generate the possible outcomes and their probabilities from the susceptible and resistant proportions. For five antibiotics (*m*), there are 32 possible susceptibility patterns, the probabilities of each susceptibility pattern are shown in Table 3.

Step 5. Calculate the AOI. The AOI_{m1} and AOI_{m2} were calculated by aggregating the susceptibility patterns that contain at least one (*k=1*) and two (*k=2*) susceptible results. The 2014 *A. baumannii* AOI_{51} and AOI_{52} were 0.86 and 0.53, respectively (Table 3).

Classification of the AOI

The five-person expert panel assembled to review the AOI concept determined that antibiotic susceptible

Table 2
Antibiotic agents used in the AOI calculating process.

Pathogens	Antibiotic classes								
	BL	BL+	CAR	FLQ	AMG	GCP	LIN	PHOS	SUL
A. baumannii	Ceft, Cefe	Cefo/Sul	Imi, Mer	Cip, Lev	Amk, Gen	-	-	-	-
E. coli	Cefu, Ceft, Cefe	Amp/Sul, Amo/Cla, Pip/Taz	Imi, Mer	Cip, Lev	Amk, Gen	-	-	-	-
K. pneumoniae	Cefu, Ceft, Cefe	Ampi/Sul, Amo/Cla, Pip/Taz	Imi, Mer	Cip, Lev	Amk, Gen	-	-	-	-
P. aeruginosa	Ceft, Cefe	Cefo/Sul, Pip/Taz	Imi, Mer	Cip, Lev	Amk, Gen	-	-	-	-
S. aureus	-	-	-	Cip, Lev	-	Van	Cli	Fos	Cot
MRSA	-	-	-	-	-	Van	-	Fos	-
S. pneumoniae	Pen	-	-	Lev	-	Van	Cli	-	Cot

BL, Beta-lactams; BL+, Beta-lactam/ beta-lactamase inhibitor; CAR, Carbapenems; FQL, Fluoroquinolones; AMG, Aminoglycosides; GCP, Glycopeptides; LIN, Lincosamides; PHOS, Phosphonics; SUL, Sulfonamides; Ceft, Ceftazidime; Cefe, Cefepime; Cefu, Cefuroxime; Amp/Sul, Ampicillin/Sulbactam; Amo/Cla, Amoxycillin/Clavulanic acid; Cefo/Sul, Cefoperazone/ Sulbactam; Pip/Taz, Piperacillin/ Tazobactam; Imi, Imipenem; Mer, Meropenem; Cip, Ciprofloxacin; Lev, Levofloxacin; Amk, Amikacin; Gen, Gentamicin; Van, Vancomycin; Cli, Clindamycin; Fos, Fosfomycin; Cot, Cotrimoxazole.

proportions should be more than 0.8 for effective empiric antibiotic treatment. Hence, the AOI was classified into two levels based on the availability of antimicrobial treatment options: acceptable level (AOI ≥ 0.8) and unacceptable level (AOI < 0.8). According to these criteria, in 2014 the AOI_{51} for *A. baumannii* (0.86) was acceptable but the AOI_{52} (0.53) was unacceptable (Table 3).

Implementation of the AOI using NARST antibiogram data

Yearly AOI_{m1} and AOI_{m2} values for the seven most commonly isolated pathogens in Thailand were calculated using 1998-2014 antibiogram data from NARST and are presented in Fig 3.

The AOI_{m1} identified no problematic pathogens; all pathogens were classified in the acceptable level. The AOI_{m1} values for six pathogens: *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *S. pneumoniae*, *S. aureus* and MRSA were over 0.95 throughout the study period. However, the AOI_{51} for *A. baumannii* was 0.99 in 1998 before separating from the other pathogens in 2002 and dropping to 0.89 in 2005 and 0.86 in 2014 (Fig 3, AOI_{m1}).

The AOI_{m2} identified two problematic pathogens: *A. baumannii* and MRSA. The AOI_{52} for *A. baumannii* dropped from an acceptable level in 1998 (0.93) to an unacceptable level in 2003 (0.79) and continued to decrease, reaching 0.53 in 2014. For MRSA, the AOI_{22} was classified as unacceptable in 1999 (0.79) and despite year-

Table 3
Calculation of the AOI of *A. baumannii*, 2014.

Pattern no.(i)	Susceptibility patterns(A_i)	$P(A_i \mid B_i \geq 1)$	$P(A_i \mid B_i \geq 2)$
1	*SSSSS*	0.0036	0.0036
2	*SSSSR*	0.0071	0.0071
3	*SSSRS*	0.0089	0.0089
4	*SSSRR*	0.0173	0.0173
5	*SSRSS*	0.0085	0.0085
6	*SSRSR*	0.0165	0.0165
7	*SSRRS*	0.0208	0.0208
8	*SSRRR*	0.0403	0.0403
9	*SRSSS*	0.0052	0.0052
10	*SRSSR*	0.0102	0.0102
11	*SRSRS*	0.0128	0.0128
12	*SRSRR*	0.0249	0.0249
13	*SRRSS*	0.0122	0.0122
14	*SRRSR*	0.0237	0.0237
15	*SRRRS*	0.0299	0.0299
16	*SRRRR*	0.0581	-
17	*RSSSS*	0.0085	0.0085
18	*RSSSR*	0.0165	0.0165
19	*RSSRS*	0.0208	0.0208
20	*RSSRR*	0.0403	0.0403
21	*RSRSS*	0.0198	0.0198
22	*RSRSR*	0.0385	0.0385
23	*RSRRS*	0.0485	0.0485
24	*RSRRR*	0.0941	-
25	*RRSSS*	0.0122	0.0122
26	*RRSSR*	0.0237	0.0237
27	*RRSRS*	0.0299	0.0299
28	*RRSRR*	0.0581	-
29	*RRRSS*	0.0285	0.0285
30	*RRRSR*	0.0553	-
31	*RRRRS*	0.0698	-
32	*RRRRR*	-	-
	Total	0.8645	0.5291

$P(A_i \mid B_i \geq 1)$ and $P(A_i \mid B_i \geq 2)$ are the probabilities of susceptibility patterns that contain at least one and two sensitive results, respectively.

on-year fluctuations in the AOI_{22} value, it remained at an unacceptable level and reached a low of 0.47 in 2014. Although never classified as unacceptable, the AOI_{52} for *E. coli* changed from 0.95 in 1998 to 0.81 in 2014. For the remaining pathogens, the AOI_{m2} stayed well within the acceptable level (>0.95) throughout the studied period. Interestingly, the AOI_{52} for *K. pneumoniae* started separating from *P.*

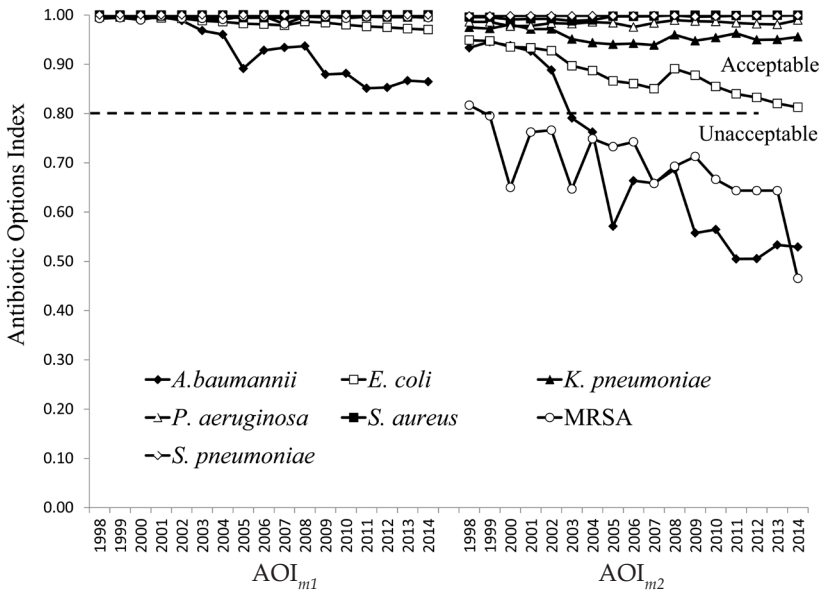

Fig 3–Identifying problematic pathogens from the profiles for AOI$_{m1}$ *vs* AOI$_{m2}$.

aeruginosa, S. aureus and *S. pneumoniae* in 2003 (0.95), but retained the same value in 2014 (0.95) (Fig 3, AOI$_{m2}$).

DISCUSSION

Due to the widespread availability of antibiogram data, the AOI represents an antibiotic resistance quantifying tool that can be used to summarize resistance for a given pathogen at multiple organizational levels. For Thailand, antibiotic susceptibility rates for all pathogens are available on the NARST website (National Antimicrobial Resistance Surveillance Center, 2014). The AOI for a pathogen can be calculated at the hospital level and the provincial or national level. The ease of gathering raw sensitivity data means the AOI can also be easily calculated and used to emerging drug-resistant pathogens such as extended spectrum beta-lactamase (ESBL) producing Enterobacteriaceae, multi-drug resistant (MDR), methicillin-resistant *S. aureus* (MRSA), vancomycin-resistant Enterococcus (VRE) and carbapenem-resistant Enterobacteriaceae (CRE), etc.

Of the seven most commonly isolated pathogens, *A. baumannii* showed the biggest reduction in AOI values during the study time period. The most dramatic changes in susceptibility for *A. baumannii* during this period were among the carbapenems (imipenem and meropenem) and cefoperazone/sulbactam (a beta-lactam plus beta-lactamase inhibitor drug). The sensitivity rates dropped from 98% in 1998 to 32% in 2014 for the carbapenems, and from 72% in 1998 to 41% in 2014 for cefoperazone/sulbactam. This dramatic decrease in sensitivity rates correlates well with previous reports indicating an overall increase in the use of carbapenems between 1996-2009 (Malathum, 2010; Malathum *et al*, 2011) and cefoperazone/sulbactam becoming the drug of choice for *A.baumannii* infection during 2000-2005 (Malathum *et al*, 2011). Decreasing antibiotic sensitivity rates for these key antibiotics were likely to result in increasing failure rates with antibiotic therapy for *A. baumannii* infection. Several studies in Thailand have shown an increase in mortality rates due to *A. baumannii* infection, from 30% in 2005 to 69% in 2012 (Anunnatsiri and Tonsawan, 2011; Santimaleeworagun *et al*, 2011; Chittawatanarat *et al*, 2014; Santimaleeworagun *et al*, 2014). The

AOI_{52} for *A. baumannii* showed steep declines during the years 2000-2005, before this increase in mortality. Further studies are needed to clarify any association between the AOI and clinical outcomes.

We believe the AOI offers an advantage over other tools for expressing antibiotic resistance due to its inclusion of various susceptibility results in a summary that describes the probability of having one or two viable treatment options. The AOI includes the idea that the problem with increasing antibiotic resistance is a problem with treating infections. This can help to communicate complex antibiotic resistance information to all of the groups that are required to cooperate in interventions to reduce the impact of the coming antibiotic resistance crisis. Classifying pathogens as acceptable or unacceptable according to the AOI is useful for identification of problematic pathogens. However, simply being able to report changes in the AOI over time means that trends can be spotted for pathogens that are not classified as unacceptable, as in the case with the AOI_{m2} for *E.coli*. Due to its scalability, the AOI is also suitable for monitoring antibiotic stewardship programs and the appropriateness of a hospital's antibiotic formulary list. For example, if the AOI of a pathogen in a hospital drops below 0.8 (unacceptable), the antibiotic list to treat this pathogen should be reviewed. In short, by summarizing complex resistance data in a single figure, the AOI is a tool that can improve the monitoring, assessing and communicating of antibiotic resistance.

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REFERENCES

Anunnatsiri S, Tonsawan P. Risk factors and clinical outcomes of multidrug-resistant *Acinetobacter baumannii* bacteremia at a university hospital in Thailand. *Southeast Asian J Trop Med Public Health* 2011; 42: 693-703.

Carmeli Y, Troillet N, Karchmer AW, Samore MH. Health and economic outcomes of antibiotic resistance in *Pseudomonas aeruginosa*. *Arch Intern Med* 1999; 159: 1127-32.

Centers for Disease Control and Prevention (CDC), US Department of Health and Human Services. Antibiotic resistance threats in the United States, 2013. Atlanta: CDC, 2013.

Chittawatanarat K, Jaipakdee W, Chotirosniramit N, Chandacham K, Jirapongcharoenlap T. Microbiology, resistance patterns, and risk factors of mortality in ventilator-associated bacterial pneumonia in a northern Thai tertiary-care university based general surgical intensive care unit. *Infect Drug Resist* 2014; 7: 203-10.

Cosgrove SE. The relationship between antimicrobial resistance and patient outcomes: mortality, length of hospital stay, and health care costs. *Clin Infect Dis* 2006; 42 (suppl 2): S82-9.

de Kraker MEA, Wolkewitz M, Davey PG, *et al*. Clinical impact of antimicrobial resistance in European Jan Hospitals: excess mortality and length of hospital stay related to methicillin-resistant *Staphylococcus aureus* bloodstream infections. *Antimicrob Agents Chemother* 2011; 55: 1598-605.

Gu Y, Kaku M. How can we fight against antimicrobial-resistant bacteria in the World Health Organization Western Pacific Region? *West Pac Surveill Resp J* 2012; 3: 40-2.

Malathum K. [Antibiotic resistance crisis and antibiotic use in Thailand]. *The Report of Situation of Drug System* 2010: 11-5.

Malathum K, Dejsirilert S, Thongmali O. Growing problem of multidrug-resistant *Acinetobacter baumannii* in Thailand. *Reg Health Forum* 2011; 15: 87-91.

National Antimicrobial Resistance Surveillance Center, Thailand (NARST). Antibiogram 2014. Nonthaburi: NARST, 2014. [Cited 2015 Jun 02]. Available from: http://narst.dmsc.moph.go.th/antibiograms.html

Santimaleeworagun W, Sumret W, Limsubjaroen K, *et al*. [Clinical outcomes and risk factors affecting 30-day mortality and treatment failure of patients infected with carbapenem-resistant *Acinetobacter baumannii* in a general hospital]. *Silpakorn Univ Sci Technol J* 2014; 8: 28-36.

Santimaleeworagun W, Wongpoowarak P, Chayakul P, Pattharachayakul S, Tansakul P, Garey KW. Clinical outcomes of patients infected with carbapenem-resistant *Acinetobacter baumannii* treated with single or combination antibiotic therapy. *J Med Assoc Thai* 2011; 94: 863-70.

Taylor S. Multiplication rule of probability. [online]. AlgebraLAB, 2013. [Cited 2015 Sep 02]. Available from: www.algebralab.org/lessons/lesson.aspx?file=Algebra_ProbabilityMultiplicationRule.xml