Original Article

Implementation of the World Health Organization's Global Antimicrobial Resistance Surveillance System (GLASS) for the Surveillance of Sputum Specimens Collected from Patients at Siriraj Hospital

Jitmuang A, MD[1], Naksanguan T, MD[2], Sirijatuphat R, MD[1], Supapueng O, PhD[3], Kiratisin P, MD[4], Thamlikitkul V, MD[1]

[1] Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[2] Buriram Hospital, Buriram, Thailand

[3] Department of Research and Development, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

[4] Department of Microbiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

Objective: To determine the feasibility and benefit of implementing the World Health Organization-recommended Global Antimicrobial Resistance Surveillance System (GLASS) for the surveillance of sputum specimens collected from patients at Siriraj Hospital.

Materials and Methods: All sputum specimens sent for culture between December 2016 and June 2017 at Siriraj Hospital were retrieved from the microbiology laboratory. A locally-developed web application program was used to transfer the sputum culture results into GLASS and to enter the clinical data of the patients with positive sputum cultures. The relevant clinical data of each patient with a positive sputum culture were collected, including the nature of the reported organisms, acquisition of infection, type and severity of infection, concordance of antibiotic treatment, outcomes of treatment, hospitalization cost, and in-hospital mortality. These data were extracted from the medical records and hospital database.

Results: Three hundred eighty-one patients with positive cultures for 1,050 bacterial isolates from 2,367 sputum specimens collected during the present study period were included. The most common isolated bacteria were *A. baumannii*, followed by *P. aeruginosa*, *S. maltophilia*, *K. pneumoniae*, and *S. aureus*. Among the 1,050 bacterial isolates, the rate of true infection was 58%, with *P. aeruginosa* and *A. baumannii*, the common causes of pneumonia. The rate of colonization was 42% with *A. baumannii* and *S. maltophilia*, the most common colonized bacteria. Most of the bacteria isolated from the sputum specimens were from patients who had hospital-associated infections (HAI, 70.1%), which the most common causative bacteria were *A. baumannii* (38.1%) and *P. aeruginosa* (34%); whereas methicillin-susceptible *S. aureus* (36.1%) and *K. pneumoniae* (29.1%) were observed in patients with community-associated infection (CAI). Among the patients with HAI, 60% had ventilator-associated pneumonia (VAP), particularly late-onset VAP (51.8%), and hospital-acquired pneumonia (HAP, 34%). The patients with HAI significantly had higher rates of sepsis ($p<0.001$) and of receiving non-concordant empirical antibiotics ($p<0.001$), more unfavorable outcomes ($p<0.001$), a longer length of hospital stay ($p<0.001$), and higher hospitalization costs ($p<0.001$) and higher in-hospital mortality ($p<0.001$) than those with CAI. For the antibiotic susceptibility profiles, *K. pneumoniae* colonization isolates were more resistant to antibiotics than the isolates causing true infections. Overall mortality of the patients with infections was 42.8%. In-hospital mortality of the patients with HAI, HAP, and late-onset VAP caused by antimicrobial resistant (AMR) bacteria was significantly higher than those with such infections caused by non-AMR bacteria.

Conclusion: GLASS provides more applicable and more reliable data for the AMR surveillance of sputum specimens than conventional laboratory-based surveillance in terms of the nature of the reported organisms, acquisition of infection, type and severity of infection, antibiotic susceptibility of isolated bacteria, concordance of antibiotic treatment, and the burden of respiratory tract infections. The information on HAP and VAP is useful for developing local clinical guidelines for choosing appropriate empirical antibiotics. However, GLASS has limitations in the AMR surveillance of sputum specimens from patients with CAP and it requires more time and resources than laboratory-based surveillance.

Keywords: Global antimicrobial resistance surveillance system, GLASS, Sputum specimens

Received 22 Jan 2020 | Revised 5 Feb 2020 | Accepted 7 Feb 2020

J Med Assoc Thai 2020;103(3):198-209
Website: http://www.jmatonline.com

Correspondence to:

Thamlikitkul V.

Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wang Lang Road, Bangkoknoi, Bangkok 10700, Thailand.

Phone: +66-2-4125994, **Fax**: +66-2-4125994

Email: visanu.tha@mahidol.ac.th

Antimicrobial resistance (AMR) has been dramatically increasing worldwide. In Thailand, the rate of new AMR infections is approximately 87,000 infections per year, which have further led to a combined additional length of hospitalization of

How to cite this article: Jitmuang A, Naksanguan T, Sirijatuphat R, Supapueng O, Kiratisin P, Thamlikitkul V. Implementation of the World Health Organization's Global Antimicrobial Resistance Surveillance System (GLASS) for the Surveillance of Sputum Specimens Collected from Patients at Siriraj Hospital. J Med Assoc Thai 2020;103:198-209.

three million days and 38,000 deaths[1]. Pneumonia is a principal cause of hospitalization and mortality in Thailand. Several bacteria that cause pneumonia are evolving resistance to the currently-used front-line antibiotics. *Streptococcus pneumoniae* resistant to penicillin and macrolide is a serious problem in many countries, including Singapore, Philippines, China, and Thailand[2]. In addition, the rate of AMR among bacteria causing hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP) is substantially rising in Thailand. Epidemiological studies of HAP and VAP in Thailand have revealed high rates of AMR organisms, such as carbapenem- or the extensively drug-resistant *Acinetobacter baumannii* in 83% to 95% of isolates, carbapenem-resistant *Pseudomonas aeruginosa* in 42% to 83% of isolates, and extended spectrum beta-lactamase-producing *Klebsiella pneumoniae* in 22% to 47% of isolates[3-5]. The overall mortality of patients with HAP or VAP was also found to be very high, up to 46%. AMR surveillance is highly crucial to determine the magnitude of AMR and to determine the appropriate antimicrobial treatment for patients with pneumonia. Conventional laboratory-based AMR surveillance systems based on local antibiograms has several limitations such as 1) the unknown nature of the reported organisms (true infection or colonization), 2) the indeterminate source of infection and acquisition (community- or healthcare-associated infection), and 3) duplication of the same organisms from the same episode of infection from the same patient. The conventional laboratory-based AMR surveillance system does not provide accurate information regarding the magnitude of AMR, and the data from such surveillance have limited value in generating a local guideline on choosing the appropriate antimicrobial treatment for specific sites of infection.

The Global Antimicrobial Resistance Surveillance System (GLASS), launched by the World Health Organization (WHO) in 2015, can evaluate priority clinical specimens, such as blood, urine, and feces, that are routinely sent for microbiological examinations[6]. GLASS is a case-based surveillance system comprising clinical, microbiological, and epidemiological data. The deduplication of microbiological data sets is also performed to prevent duplicate copies of repeated data[6]. The goal of GLASS is to collect valid data on AMR and use the data to aid developing local and national guidelines. This surveillance system is more complex and time-consuming but it can provide more reliable and less biased information than from conventional laboratory-based surveillance systems. The stepwise implementation of GLASS began at Siriraj Hospital in June 2016. The surveillance of blood culture specimens was performed first, followed by feces, urine, and sputum specimens. The surveillance of blood culture specimens using GLASS revealed it provided more benefits and was more applicable for monitoring the rate of AMR and for developing local guidelines for the antibiotic therapy of patients with bacteremia than the conventional laboratory-based surveillance system[7,8].

Although sputum specimens are not included in the priority clinical specimens according to the GLASS manual in early implementation, pneumonia is a common infection in both the community and hospital settings in Thailand, and AMR in the bacteria causing pneumonia has been increasing. The surveillance of sputum specimens using the GLASS methodology is challenging because many patients have an uncertain diagnosis of pneumonia based on the culture results from their sputum specimens, particularly patients with HAP and VAP. Furthermore, the organisms isolated from the sputum are often difficult to distinguish between true pathogens or respiratory colonization. The aim of the present study was to determine the feasibility and benefit of GLASS for the surveillance of sputum specimens collected from patients at Siriraj Hospital.

Materials and Methods

The present study protocol was approved by the Siriraj Institutional Review Board. All the sputum specimens sent for culture at the hospital microbiology laboratory between December 2016 and June 2017 were retrieved from the Department of Microbiology, and the sputum samples with positive cultures collected from 381 randomly selected patients were included. A locally-developed web application program (app) was developed and used to transfer the microbiological data of the sputum specimens provided by the microbiology laboratory and to enter the clinical data of the patients with positive sputum cultures. All the data were recorded by the investigators on the app installed in a personal tablet or smart phone under privacy protection. The data from the app comprised four parts. Part I comprises of the microbiology and demographic data of all the patients who had sputum specimens sent for culture. The results of the sputum cultures were transferred from the microbiology laboratory every day, and they were managed by trained back-office personnel before the results of the positive sputum culture specimens

were sent to the investigators. Part II comprises of the clinical data of the patients with a positive sputum culture, including the nature of the reported organisms (true infection or colonization), acquisition of infection (community-associated infection [CAI], or hospital-associated infection [HAI]), type of infection (community-acquired pneumonia [CAP], HAP, early- or late-onset VAP, or ventilator-associated tracheobronchitis [VAT]), severity of infection (sepsis or non-sepsis), empirical antibiotics, and specific antibiotics given to the patients with infections. All of these data were extracted from the medical records of the patients and/or the information from the responsible healthcare personnel. Part III comprises of the antibiotic susceptibility results of the isolated bacteria. These data were managed by the trained back-office personnel, who transferred the data from the laboratory. Part IV comprises of the data on the concordance of antimicrobial treatment according to the culture results, patients' outcomes at the end of treatment and at hospital discharge in terms of the length of hospital stay, hospitalization costs, and in-hospital mortality. These data were retrieved from the hospital database.

Definitions

Isolated bacteria were considered a true infection if the patient had clinical features of pneumonia compatible with the isolated bacteria and the responsible physician prescribed antibiotics to treat the recovered bacteria. The isolated bacteria were considered colonization if the patient had no clinical features of pneumonia or the clinical features resolved without antibiotic treatment or when they were left untreated with antibiotics.

Infection that occurred in a patient who was hospitalized for more than two days at Siriraj Hospital or at another hospital prior to admission to Siriraj Hospital, or in a patient who had healthcare-associated conditions, such as prior hospitalization within three months, prior to the use of antibiotics within 90 days, or when the patient was a resident of a long-term care facility, or receiving chronic hemodialysis was defined as HAI. Whereas pneumonia that occurred within two days of a patient being hospitalized at Siriraj Hospital and who had no previous healthcare-associated conditions and who had not been hospitalized prior to admission to Siriraj Hospital was defined as CAI[5,9,10].

CAP was defined as pneumonia with CAI criteria. HAP was defined as pneumonia with HAI criteria in a patient without mechanical ventilation.

VAP was defined as pneumonia that arises after 48 hours following mechanical ventilation, in which case it was categorized as early-onset VAP (pneumonia that occurred within four days after receiving endotracheal intubation) or late-onset VAP (pneumonia that occurred after four days after receiving endotracheal intubation). VAT was defined as lower respiratory tract HAI without changed in the chest radiograph[5,9,10].

Sepsis was defined as a life-threatening organ dysfunction due to pneumonia, such as altered mental status, a respiratory rate of more than 22 per minute, or systolic blood pressure of less than 100 mmHg[11].

Concordant antibiotic therapy meant at least one of the given antibiotics was active against the causative bacterial isolated, whereas non-concordant antibiotic treatment was when none of the given antibiotics had activity against the causative bacterial isolate.

Patients' outcomes at the end of antibiotic treatment were classified as 1) favorable response: a resolution of the clinical features, also as indicated by the laboratory results, including chest radiography at the end of antibiotic therapy, 2) superinfection: a new infection, such as pneumonia, due to new organism(s), or 3) death from pneumonia. In-hospital mortality was defined as death from any causes occurring during the hospital stay.

Antibiotic-resistant pneumonia was defined as pneumonia caused by one of the AMR organisms, such as enterobacteriaceae resistant to third-generation cephalosporins or carbapenems, piperacillin-tazobactam-resistant or carbapenem-resistant *P. aeruginosa*, carbapenem-resistant *A. baumannii*, and methicillin-resistant *Staphylococcus aureus* (MRSA).

Deduplication of the same bacteria isolated from the sputum cultures was performed for every episode of pneumonia. When the same isolates were recovered twice or more often in each episode of infection of the same patient, only one of the same bacteria with the identical antibiotic susceptibility profile was included.

Statistical analysis

The sample size of 381 patients was derived from an estimated prevalence of pneumonia of 30±2% in the patients who had positive sputum cultures with a type I error of 5% (2-sided). Data were presented herein as the number and percentage, mean, standard deviation, or median. Fisher's exact test or chi-square test was used to compare the categorical variables, and the t-test to compare quantitative variables. All the statistical analyses were performed using either

Table 1. Bacteria isolated from all the sputum specimens from all the admissions of all the included patients

Type of bacteria	Positive culture isolates (n=1,050) n (%)	Patients with positive culture (n=381)[a] n (%)
Bacteria		
Acinetobacter baumannii	255 (24.3)	140 (36.8)
Pseudomonas aeruginosa	222 (21.1)	118 (31.0)
Stenotrophomonas maltophilia	186 (17.7)	96 (25.2)
Klebsiella pneumoniae	140 (13.3)	96 (25.2)
Burkholderia cepacia	13 (1.2)	7 (1.8)
Enterobacter spp.	19 (1.8)	16 (4.2)
Escherichia coli	17 (1.6)	12 (3.2)
Gram-negative rods, NF	25 (2.4)	21 (5.5)
Haemophilus influenzae	15 (1.4)	14 (3.7)
Moraxella catarrhalis	15 (1.4)	13 (3.4)
Staphylococcus aureus	106 (10.1)	81 (21.3)
• MRSA	38 (3.6)	22 (5.8)
• MSSA	68 (6.5)	59 (15.5)
Streptococcus pneumoniae	6 (0.6)	6 (1.6)
Streptococcus agalactiae	5 (0.5)	5 (1.3)
Other gram-negative bacteria[b]	19 (1.8)	19 (5.0)
Other gram-positive bacteria[c]	7 (0.7)	7 (1.8)

MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *Staphylococcus aureus*; NF=non-fermenter

[a] Might have more than one positive culture specimen and polymicrobial bacteria

[b] Numbers of isolates: *Acinetobacter* spp. (5), *Aeromonas hydrophila* (3), *Cirobacter koseri* (1), *Pseudomonas* spp. (3), *Pasteurella* spp. (1), *Proteus mirabilis* (1), *Serratia marcescens* (4), *Providencia stuartii* (1)

[c] Numbers of isolates: *Nocardia* spp. (3), *Streptococcus* group G (2), *Streptococcus* group C (1), coagulase negative *Staphylococcus* spp. (1)

SPSS Statistics or Microsoft Excel. A p-value of less than 0.05 was considered statistically significant.

Results

Among the 381 included patients with positive sputum cultures collected between December 2016 and June 2017, there were 2,367 sputum specimens collected from 887 patients that recovered 1,050 bacterial isolates. All the included patients had 324 episodes of infections, where 281 patients (73.8%) had true infections, while 100 patients (26.2%) showed colonization with the bacteria isolated from their sputum specimens. The types of isolated bacteria are shown in Table 1. The most common isolated bacteria were *A. baumannii*, followed by *P. aeruginosa*, *Stenotrophomonas maltophilia*, *K. pneumoniae*, and *S. aureus*. The type of bacteria stratified by the proportion of infection and colonization for each organism per total isolate per patients showed a disparity among the causative and colonized bacterial isolates, as shown in Table 2. True infection was observed in 58% of the isolates, with *P. aeruginosa* was the most common bacteria causing infection, followed by *A. baumannii*, *K. pneumoniae*, *S. maltophilia*, and *S. aureus*. Colonization was observed in 42% of the isolates, with *A. baumannii* and *S. maltophilia* were the most common colonized bacteria.

Comparisons of the acquisition of infection between the patients with CAI and the patients with HAI are shown in Table 3. Most of the patients in both groups were elderly. Among the patients with CAI, the most common causative bacteria were methicillin-susceptible *S. aureus* or (MSSA), followed by *K. pneumoniae*, *Haemophilus influenzae*, and *P. aeruginosa*. Among the patients with HAI, the most common causative bacteria were *A. baumannii*, followed by *P. aeruginosa*, *K. pneumoniae*, and *S. maltophilia*. In the HAI group, 60% of the patients had VAP, particularly late-onset VAP. The patients with HAI significantly had a greater rate of sepsis or receiving non-concordant empirical antibiotic treatment and had more unfavorable outcomes at the end of treatment, fatality, and superinfection than those with CAI. The hospitalized patients with HAI were significantly associated with a longer length of hospital stay, greater hospitalization costs, and higher in-hospital mortality than those with CAI.

Comparisons of HAI classified as HAP, early- or late-onset VAP, and VAT are shown in Table 4. Late-onset VAP was the most common diagnosis, followed by HAP and early-onset VAP. In the HAI group, *A. baumannii* was significantly associated with VAP, whereas, there was no significant association among the other causative bacteria and types of HAI. Sepsis during HAI was more commonly observed in the patients with HAP and VAP than in the patients with VAT. The rates of concordant and non-concordant empirical antibiotic therapy were not significantly different among the different types of HAI. The patients with VAT showed a higher favorable clinical response and lower mortality at the end of treatment than those with other types of HAI. The patients with late-onset VAP showed a trend of increasing in-hospital mortality and were significantly associated with a longer hospital stay and higher hospitalization costs when compared with those with other types and sites of infections.

Table 2. Causative and colonized bacteria isolated from all the sputum specimens from all the admissions of all the included patients categorized by proportion of infection and colonization for each organism per total isolates/patients

Type of bacteria	Causative bacteria; n (%)		Colonized bacteria; n (%)	
	Isolates (n=609)	Patients (n=281)[a]	Isolates (n=441)	Patients (n=216)[a]
Bacteria, n (%)				
Pseudomonas aeruginosa	149/222 (67.1)	84/135 (61.9)	73/222 (32.9)	51/135 (37.8)
Acinetobacter baumannii	134/255 (52.5)	79/162 (48.8)	121/255 (47.5)	83/162 (51.2)
Klebsiella pneumoniae	100/140 (71.4)	72/103 (69.9)	40/140 (28.6)	31/103 (30.1)
Stenotrophomonas maltophilia	66/186 (35.5)	37/113 (32.7)	120/186 (64.5)	76/113 (67.3)
Burkholderia cepacia	10/13 (76.9)	6/8 (75.0)	3/13 (23.1)	2/8 (25.0)
Enterobacter spp.	12/19 (63.2)	11/17 (64.7)	7/19 (36.8)	6/17 (35.3)
Escherichia coli	9/17 (52.9)	7/13 (53.8)	8/17 (47.1)	6/13 (46.2)
Gram-negative rods, NF	12/25 (48.0)	10/21 (47.6)	13/25 (52.0)	11/21 (52.4)
Haemophilus influenzae	15/15 (100)	14/14 (100)	0 (0.0)	0 (0.0)
Moraxella catarrhalis	14/15 (93.3)	12/13 (92.3)	1/15 (6.7)	1/13 (7.7)
Staphylococcus aureus	66/106 (62.3)	51/84 (60.7)	40/106 (37.7)	33/84 (39.3)
• MRSA	21/38 (55.3)	11/24 (45.8)	17/38 (44.7)	13/24 (54.2)
• MSSA	45/68 (66.2)	40/60 (66.7)	23/68 (33.8)	20/60 (32.8)
Streptococcus pneumoniae	6/6 (100)	6/6 (100)	0 (0.0)	0 (0.0)
Streptococcus agalactiae	3/5 (60.0)	3/5 (60.0)	2/5 (40.0)	2/5 (40.0)
Other gram-negative bacteria[b]	10/19 (52.6)	10/19 (52.6)	9/19 (47.4)	9/19 (47.4)
Other gram-positive bacteria[c]	3/7 (42.8)	3/7 (42.8)	4/7 (57.2)	4/7 (57.2)

MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *Staphylococcus aureus*; NF=non-fermenter

[a] Might have more than one positive culture specimen and comprised of polymicrobial organisms

[b] Numbers of isolates: *Acinetobacter* spp. (5), *Aeromonas hydrophila* (3), *Cirobacter koseri* (1), *Pseudomonas* spp. (3), *Pasteurella* spp. (1), *Proteus mirabilis* (1), *Serratia marcescens* (4), *Providencia stuartii* (1)

[c] Numbers of isolates: *Nocardia* spp. (3), *Streptococcus* group G (2), *Streptococcus* group C (1), coagulase negative *Staphylococcus* spp. (1)

Comparisons of the pneumonia patients with and without sepsis revealed that sepsis significantly occurred in the patients with *A. baumannii* infections (p<0.001), patients with HAI (p<0.001), and patients with late-onset VAP (p<0.001), whereas it was less likely to occur in the patients with *H. influenzae* infections (p=0.003) and patients with CAI (p<0.001). The outcomes of the patients with sepsis in terms of mortality at the end of treatment (53.0% versus 8.8%, p<0.001), in-hospital mortality (66.3% versus 23.1%, p<0.001), and the median cost of hospitalization (US$ 14,581 versus US$ 9,458, p=0.007) were significantly worse than in those without sepsis. Comparisons of the patients who received concordant and non-concordant empirical antibiotics revealed that the patients with MSSA pneumonia (p=0.009) and patients with CAI (p<0.001) significantly received more concordant empirical antibiotic treatment, whereas pneumonia from *A. baumannii* (p=0.001), from *S. maltophilia* (p<0.001), and patients with HAI (p<0.001), especially late-onset VAP (p=0.012) significantly received more non-concordant empirical antibiotic treatment. The patients who received non-concordant empirical antibiotic treatment were significantly associated with more unfavorable outcomes at the end of treatment, including death (17.9% versus 34.3%, p=0.002) and superinfection (11.3% versus 22.0%, p=0.002), higher median hospitalization costs (US$ 9,466 versus US$ 15,534, p=0.005), and higher in-hospital mortality (30.1% versus 55.0%, p<0.001) than those who received concordant empirical antibiotics.

Antibiotic susceptibility profiles of the common bacterial isolates are shown in Table 5-8. Comparisons of the antibiotic susceptibility between the bacteria causing true infection and colonization are shown in Table 5. Colonized *K. pneumoniae* had a reduced susceptibility to several antimicrobial agents, including cephalosporins, carbapenems, and ciprofloxacin; whereas, the colonized *P. aeruginosa* had a reduced susceptibility to colistin when compared with such isolates causing true infections.

Table 3. Comparison of pneumonia patients with community-associated infection and hospital-associated infection

Characteristics	CAI (n=72)	HAI (n=197)	p-value	Both CAI & HAI (n=12)[a]
Age (years); median (range)	69 (0.1 to 90)	74 (1 to 97)	0.181	70 (27 to 91)
Male; n (%)	35 (48.6)	113 (57.4)	0.202	7 (58.3)
Bacteria; n (%)				
Acinetobacter baumannii	0 (0.0)	75 (38.1)	<0.001	4 (33.3)
Haemophilus influenzae	10 (13.9)	3 (1.5)	<0.001	1 (8.3)
Klebsiella pneumoniae	21 (29.2)	46 (23.4)	0.329	5 (41.7)
Moraxella catarrhalis	8 (11.1)	2 (1.0)	<0.001	2 (16.7)
Pseudomonas aeruginosa	9 (12.5)	67 (34.0)	0.001	8 (66.0)
Staphylococcus aureus	26 (36.1)	21 (10.7)	<0.001	4 (33.0)
• MRSA	0 (0.0)	10 (5.1)	0.067	1 (8.3)
• MSSA	26 (36.1)	11 (5.6)	<0.001	3 (25.0)
Streptococcus pneumoniae	6 (8.3)	0 (0.0)	<0.001	0 (0.0)
Stenotrophomona smaltophilia	1 (1.4)	34 (17.3)	0.001	2 (16.7)
Streptococcus agalactiae	3 (4.2)	0 (0.0)	0.019	0 (0.0)
Site and type of infections; n (%)				
Community-acquired pneumonia	72 (100)	-		12 (100)
Hospital-acquired pneumonia	-	67 (34.0)		4 (33.3)
Early-onset ventilator-associated pneumonia	-	18 (9.1)		1 (8.3)
Late-onset ventilator-associated pneumonia	-	102 (51.8)		7 (58.3)
Ventilator-associated tracheobronchitis	-	34 (17.3)		0 (0.0)
Sepsis; n (%)	11 (15.3)	83 (42.1)	<0.001	6 (50.0)
Empirical antibiotic treatment; n (%)				
Concordant antibiotic therapy	58 (80.6)	110 (55.8)	<0.001	8 (66.7)
Non-concordant antibiotic therapy	14 (19.4)	93 (47.2)	<0.001	6 (50.0)
Clinical response at end of treatment; n (%)				
Favorable response	60 (83.3)	122 (61.9)	0.001	8 (66.7)
Death	4 (5.6)	62 (31.5)	<0.001	3 (25.0)
Superinfection	5 (6.9)	37 (18.8)	0.018	7 (58.3)
Unknown	3 (4.2)	2 (1.0)	0.121	0 (0.0)
Hospitalized patients; median (range)	(n=47)	(n=187)		(n=11)
Length of hospital stay (days)	7 (1 to 85)	31 (1 to 414)	<0.001	33 (7 to 83)
Cost of hospitalization per patient (US$)	2,813 (154 to 18,353)	16,175 (395 to 503,046)	<0.001	9,474 (1,800 to 32,943)
In-hospital mortality; n (%)	6 (12.8)	86 (46.0)	<0.001	7 (63.6)

MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *Staphylococcus aureus*; CAI=community-associated infection; HAI=hospital-associated infection

[a] Patients who had multiple episodes on infections from CAI and HAI

A. baumannii, *S. maltophilia*, and MSSA had comparable antibiotic susceptibility rates between the colonization isolates and the true infection isolates. For the *A. baumannii* isolates, only colistin had a promising susceptibility rate for both colonization and true infection isolates. Fewer bacterial isolates associated with CAI were identified in the present study, as shown in Table 6. These were MSSA, *H. influenzae*, *Moraxella catarrhalis*, *P. aeruginosa*, and *S. pneumoniae*. *K. pneumoniae* isolated from CAI had reduced susceptibility to ceftazidime, cefotaxime, and ceftriaxone, but all the isolates were susceptible to carbapenems. Comparisons of the antibiotic susceptibility of the common bacteria causing CAI and HAI are shown in Table 7. *K. pneumoniae* isolated from the patients with CAI still had considerable

Table 4. Comparison of patients with hospital-acquired pneumonia, early- and late-onset ventilator-associated pneumonia, and ventilator-associated tracheobronchitis[a]

Characteristics	HAP (n=57)	Early-onset VAP (n=12)	Late-onset VAP (n=81)	VAT (n=25)	p-value
Age (years); median (range)	70 (18 to 95)	67 (6 to 90)	76 (1 to 97)	80 (28 to 88)	0.103
Male; n (%)	33 (57.9)	8 (66.7)	44 (54.3)	14 (56.0)	0.871
Isolated bacteria; n (%)					
Acinetobacter baumannii	12 (21.1)	3 (25.0)	41 (50.6)	7 (28.0)	0.002
Klebsiella pneumoniae	15 (26.3)	3 (25.0)	16 (19.8)	3 (12.0)	0.499
Pseudomonas aeruginosa	20 (35.1)	2 (16.7)	24 (29.6)	9 (36.0)	0.587
Staphylococcus aureus	5 (8.8)	2 (16.7)	6 (7.4)	2 (8.0)	0.652
• MRSA	1 (1.8)	1 (8.3)	3 (3.7)	0 (0.0)	0.459
• MSSA	4 (7.0)	1 (8.3)	3 (3.7)	2 (8.0)	0.557
Stenotrophomonas maltophilia	5 (8.8)	0 (0.0)	17 (21.0)	5 (20.0)	0.092
Sepsis; n (%)	25 (43.9)	5 (41.7)	35 (43.2)	3 (12.0)	0.031
Empirical antibiotic treatment; n (%)					
Concordant antibiotic therapy	34 (59.7)	8 (66.7)	45 (55.6)	12 (48.0)	0.682
Non-concordant antibiotic therapy	23 (40.4)	4 (33.3)	39 (48.2)	13 (52.0)	0.578
Clinical response at end of treatment; n (%)					
Favorable response	34 (59.7)	8 (66.7)	45 (55.6)	20 (80.0)	0.171
Death	20 (35.1)	4 (33.3)	25 (30.9)	1 (4.0)	0.030
Superinfection	3 (5.3)	0 (0.0)	21 (25.9)	5 (20.0)	0.003
Unknown	1 (1.8)	0 (0.0)	1 (1.2)	0 (0.0)	1.000
Hospitalized patients; median (range)	(n=51)	(n=12)	(n=78)	(n=25)	
Length of hospital stay (days)	19 (1 to 89)	11 (4 to 181)	42 (5 to 414)	38 (7 to 215)	<0.001
Cost of hospitalization per patient (US$)	6,001 (395 to 42,401)	8,490 (1,731 to 43,352)	28,173 (1,825 to 503,046)	17,192 (1,245 to 99,075)	<0.001
In-hospital mortality; n (%)	21 (41.2)	4 (33.3)	40 (51.3)	6 (24.0)	0.094

MRSA=methicillin-resistant *Staphylococcus aureus*; MSSA=methicillin-susceptible *Staphylococcus aureus*; HAP=hospital-acquired pneumonia; VAP=ventilator-associated pneumonia; VAT=ventilator-associated tracheobronchitis

[a] Patients who had multiple types of HAI were excluded

susceptibility to cefepime, piperacillin-tazobactam, ciprofloxacin, and carbapenems, whereas the isolates from the patients with HAI had remarkably lower susceptibility to such agents. Similarly, most of *P. aeruginosa* isolates from the patients with CAI were susceptible to all the anti-pseudomonal agents, whereas the isolates from the patients with HAI showed decreased susceptibility to almost all anti-pseudomonal agents, including carbapenems. Comparisons of the antibiotic susceptibility of the common bacterial isolates causing HAP and VAP are shown in Table 8. *A. baumannii* and *K. pneumoniae* isolated from VAP exhibited more resistance to several antibiotics than those isolated from HAP. For *A. baumannii* isolated from both groups, colistin was the single agent that showed the highest susceptibility rate. Interestingly, *K. pneumoniae* isolated from VAP showed a remarkably low susceptibility rate to cephalosporins, ciprofloxacin, piperacillin-tazobactm, and carbapenems. However, *K. pneumoniae* isolated from HAP still had a moderate to high susceptibility rate to carbapenems. *P. aeruginosa* isolated from HAP and VAP had a moderate susceptibility to anti-pseudomonal cephalosporins, piperacillin-tazobactam, and ciprofloxacin, whereas, the VAP isolates had a lower susceptibility rate to carbapenems. *S. maltophilia* isolated from VAP also had reduced susceptibility to levofloxacin.

Deduplication of all the isolated bacteria from the sputum specimens according to the criteria mentioned in the methods section revealed no significant differences in the antibiotic susceptibility profiles of the major isolated bacteria, namely: *A. baumannii*, *P. aeruginosa*, *K. pneumoniae*, and MRSA, when compared to those without deduplication of the isolated bacteria.

AMR bacteria considered a global threat by WHO[12] were also observed in the present study, including carbapenem-resistant *A. baumannii* (85.1%), extended-spectrum cephalosporin- and/or

Table 5. Antibiotic susceptibility of common causative bacteria and colonized bacteria

Organism	Types of infection	Total isolates	Percentage of antibiotic susceptibility profile																												
			Beta-lactams										Carbapenems			Polymyxins	Quinolones		Aminoglycosides			Glycopeptides		Miscellaneous							
			Amoxicillin/ clavulanic acid	Piperacillin/ tazobactam	Cefuroxime	Cefoperzaone/ sulbactam	Ceftazidime	Ceftriaxone	Cefepime	Oxacillin	Cefoxitin	Ertapenem	Meropenem	Imipenem	Doripenem	Colistin	Ciprofloxacin	Levofloxacin	Amikacin	Gentamicin	Netilmicin	Vancomycin	Linezolid	Clindamycin	Erythromycin	Chloramphenicol	TMP/SMX	Tetracycline	Minocycline	Tigecycline
A. baumannii	I	91		17		21	20	1	19				19	19		99	19		25	22							25			11
	C	93		23		31	28	0	27				26	27		98	29		36	33							36			20
P. aeruginosa	I	121		74			74		78				65	55	72	100	75		94	92	93									
	C	55		80			78		76				71	67	72	75	73		93	93	95									
K. pneumoniae	I	79	56	64	53		32	53	67		50	77	77	77	77		58		85	79	68					81	49	51		
	C	34	39	52	21		13	27	46		29	61	67	70	67		36		70	75	41					69	39	36		
S. maltophilia	I	44																80									96		96	
	C	82																83									93		99	
MSSA	I	43								100							98			100		100	100	95	95	98	100	72		
	C	20								100							85			95		100	100	90	85	95	100	60		

MSSA=methicillin-susceptible *Staphylococcus aureus*; C=colonization; I=infection; TMP/SMX=trimethoprim/sufamethpxazole

Table 6. Antibiotic susceptibility of common bacteria causing community-acquired pneumonia

Organism	Types of infection	Total isolates	Percentage of antibiotic susceptibility profile																										
			Beta-lactams										Carbapenems				Quinolones		Aminoglycosides			Glycopeptides		Miscellaneous					
			Penicillin	Ampicillin	Amoxicillin/ clavulanic acid	Piperacillin/ tazobactam	Cefuroxime	Cefotaxime	Ceftazidime	Ceftriaxone	Cefepime	Oxacillin	Ertapenem	Meropenem	Imipenem	Doripenem	Ciprofloxacin	Ofloxacin	Amikacin	Gentamicin	Netilmicin	Vancomycin	Linezolid	Clindamycin	Erythromycin	Chloramphenicol	TMP/SMX	Tetracycline
H. influenzae	CAP	15		40	100		100	100		100							100									80	47	67
M. catarhallis	CAP	15				100			100		100			100	100	100	100		100		100							
P. aeruginosa	CAP	11				100			100		100					100	100		100	100								
K. pneumoniae	CAP	25			88		84	67	63	84	92		100			100	92										89		
S. pneumoniae	CAP	6	100					100										100				100		100	50	33	83	50	33
MSSA	CAP	29										100					97			100		100		100	97	97	97	100	72

MSSA=methicillin-susceptible *Staphylococcus aureus*; CAP=community-acquired pneumonia; TMP/SMX=trimethoprim/sufamethpxazole

Table 7. Antibiotic susceptibility of common organisms causing community-associated infection and hospital-associated infection

Organism	Types of infection	Total isolates	Percentage of antibiotic susceptibility profile																								
			Beta-lactams										Carbapenems			Polymyxins	Quinolones	Aminoglycosides			Glycopeptides	Miscellaneous					
			Amoxicillin/clavulanic acid	Piperacillin/tazobactam	Cefuroxime	Cefotaxime	Ceftazidime	Ceftriaxone	Cefepime	Oxacillin	Cefoxitin	Ertapenem	Meropenem	Imipenem	Doripenem	Colistin	Ciprofloxacin	Amikacin	Gentamicin	Netilmicin	Vancomycin	Linezolid	Clindamycin	Erythromycin	Chloramphenicol	TMP/SMX	Tetracycline
P. aeruginosa	CAI	11		100			100		100				91	91	100		100	100	100	100							
	HAI	110		72			72		76				62	51	69	100	73	94	91	92							
K. pneumoniae	CAI	25	88	92	84	67	63	84	92		89	100	100	100	100		92	100	96	100				89	84	84
	HAI	54	41	52	38	17	23	38	55		36	66	67	67	67		43	78	70	59				78	32	35
MSSA	CAI	29								100							97		100		100	100	97	97	97	100	76
	HAI	14								100							100		100		100	100	93	93	100	100	64

MSSA=methicillin-susceptible *Staphylococcus aureus*; CAI=community-associated infection; HAI=hospital-associated infection; TMP/SMX=trimethoprim/sufamethpxazole

Table 8. Antibiotic susceptibility of common bacteria causing hospital-acquired pneumonia and ventilator-associated pneumonia

Organism	Types of infection	Total isolates	Percentage of antibiotic susceptibility profile																								
			Beta-lactams										Carbapenems			Polymyxins	Fluoroquinolone		Aminoglycosides			Miscellaneous					
			Amoxicillin/clavulanic acid	Piperacillin/tazobactam	Cefuroxime	Cefoperazone/sulbactam	Cefotaxime	Ceftazidime	Ceftriaxone	Cefepime	Cefoxitin	Ertapenem	Meropenem	Imipenem	Doripenem	Colistin	Ciprofloxacin	Levofloxacin	Amikacin	Gentamicin	Netilmicin	Chloramphenicol	Co-trimoxazole	Tetracycline	Minocycline	Tigecycline
A. baumannii	HAP	16		38		38		38	0	38			38	38		100	38		44	38			50			0
	VAP	66		11		14		12	2	12			12	12		98	12		18	15			20			14
K. pneumoniae	HAP	17	53	59	47		38	38	41	71	75	82	100	82	82		65		100	59	100	86	35	29		
	VAP	11	35	50	33		10	19	36	44	30	58	67	59	59		32		68	77	48	74	30	39		
P. aeruginosa	HAP	29		69				72		76			69	59	76	100	66		97	90	90					
	VAP	63		75				75		76			57	45	67	100	79		94	92	94					
S. maltophilia	HAP	5																100					100		100	
	VAP	22																76					93		97	

HAP=hospital-acquired pneumonia; VAP=ventilator-associated pneumonia

carbapenem-resistant Enterobacteriaceae (50.4%), piperacillin-tazobactam- or carbapenem-resistant *P. aeruginosa* (19.5%), and MRSA (32.0%). The overall mortality of the patients with infections was 42.8%. For in-hospital mortality stratified by the acquisition of infection and resistance profile, the mortality was significantly higher in the cases of pneumonia from HAI ($p<0.001$), particularly in HAP ($p=0.011$) and late-onset VAP ($p=0.015$), caused by AMR bacteria than those with such infections caused by non-AMR bacteria.

The projection of the annual burden of hospital-acquired lower respiratory tract infections from the 381 patients included in the present study revealed that the annual number of patients with hospital-acquired lower respiratory tract infections would be 920 patients, with 47,557 days of hospital stay and 423 deaths. The annual costs of hospitalization of these patients with hospital-acquired lower respiratory tract infections would be US $22.6 million.

Discussion

Although the surveillance of AMR should focus on the antibiotic susceptibility profiles of the isolated bacteria from sputum specimens, the present report analyzed and described much more information than only the reported antibiotic susceptibility profiles of the isolated bacteria from sputum specimens. The reason for performing such data analyses and the descriptions given in the additional information is that the present report contains the results from the implementation of GLASS, which is a new AMR surveillance system recommended by WHO. Some of the objectives of GLASS according to the manual for the early implementation of GLASS include, 1) collection, analysis, and reporting of harmonized data of infected patients, 2) estimation of the extent and burden of AMR, 3) informing the implementation of targeted prevention and control programs, 4) assessment of the impact of interventions, 5) promoting diagnostic stewardship for the responsible use of antimicrobial agents, and 6) ensuring the quality-assured, standardized identification of bacteria and antimicrobial susceptibility testing in patient management. It should be mentioned that the GLASS manual also reminds that nationally aggregated data may not provide the specific information required for decisions on treatment at the local level. Therefore, local data should be used as a basis for developing treatment guidelines whenever possible.

The present study implemented GLASS for sputum specimens at Siriraj Hospital even though sputum specimens are not included in the manual for the early implementation of GLASS. The authors did the present study the lower respiratory infections, especially HAP and VAP, are very common and important AMR infections in hospitalized patients at Siriraj Hospital[13,14].

The important findings of the present study were that only 58% of the isolated bacteria from the sputum specimens sent to the microbiology laboratory were really caused infections in 73.8% of the patients with positive sputum cultures. Therefore, healthcare personnel should be aware that antibiotics might not be necessary for nearly half of the positive sputum cultures or in nearly one-quarter of the patients with positive sputum cultures. The high prevalence of colonizing bacteria in nearly 50% of the isolates from the sputum cultures was similar to the observations from urine cultures[8].The aforementioned information emphasizes the importance of diagnostic stewardship and antibiotic stewardship in the patients who had their sputum specimens collected for culture. Most of the infections were severe HAI due to AMR bacteria, especially HAP and late-onset VAP. The patients with HAI, sepsis, infected with AMR bacteria, and receiving non-concordant antibiotic therapy had less favorable outcomes than those with CAI, no sepsis, infected with non-AMR bacteria, and receiving concordant antibiotic therapy.

Most of the included patients with positive sputum cultures were hospitalized patients. Consequently, the most common bacteria recovered from the sputum specimens of the patients were *A. baumannii*, *P. aeruginosa*, *S. maltophilia*, and *K. pneumoniae*. These common bacteria were also the common bacteria causing HAI, VAP, and VAP. Only colonized *K. pneumoniae* had reduced susceptibility to several antimicrobial agents, including cephalosporins, carbapenems, and ciprofloxacin, when compared with such isolates causing true infections.The antibiotic susceptibility profiles of colonized *A. baumannii*, *P. aeruginosa*, and *S. maltophilia* for the commonly used antibiotics were not significantly different from such isolates causing infections. The antibiotic susceptibility profiles of the deduplicate bacteria were not significantly different from the duplicate bacteria because most of the isolated bacteria were hospital-acquired isolates.

The present study revealed that *K. pneumoniae* and MSSA were more prevalent causative bacteria in the patients with CAP than *H. influenzae*, *M. catarrhalis*, and *S. pneumoniae*, and that some of the CAP cases were due to *P. aeruginosa*. The aforementioned

information on CAP is not in accordance with the reports on the epidemiology of CAP, which have stated that *S. pneumoniae*, *H. influenza*, and atypical pathogens, such as *Mycoplasma pneumoniae*, were the common pathogens causing CAP, whereas *K. pneumoniae*, MSSA and *P. aeruginosa* were very uncommon causes of CAP[2,15-17]. These findings could be explained by the fact that the present study started with the sputum samples sent to the microbiology laboratory for clinical purposes. Many cases of the patients with CAP were caused by non-bacteria or non-cultural bacteria, resulting in a negative culture of the sputum specimens. Moreover, many patients with CAP did not have sputum cultures done, especially those with mild severity pneumonia who received empiric antibiotic therapy without microbiological investigations, whereas only some of the patients with severe CAP were hospitalized and had sputum cultures done. Therefore, the data on the causative agents and antibiotic susceptibility of the isolated bacteria from the patients with CAP observed in the present study did not represent the true epidemiology of causative agents of CAP. This is one of limitations of GLASS, which is related to the case-findings based on clinical specimens sent routinely to laboratories for clinical purposes[6]; also, GLASS is inappropriate for the AMR surveillance of CAP and other infections with a similar nature, as mentioned earlier. The ideal AMR surveillance system is a case-based surveillance of clinical syndromes, which is a surveillance system based on patients in a defined population who present with signs and symptoms that meet the case definitions of the infection of interest. The results from such case-based surveillance of clinical syndromes would provide more precise data about the prevalence of the causative agents and the antibiotic susceptibility of the causative agents and the burden of AMR in the population. However, the case-based surveillance of clinical syndromes is extremely difficult and is not feasible to perform in practice, and it will consume much more resources than GLASS.

There are several limitations of the present study in addition to the issue of CAP as mentioned earlier. In some cases, multiple bacteria were isolated from the same sputum specimen of patients with infection and it was difficult to determine which one was the causative agent. In these cases, such isolated bacteria had to be assumed to be the causative agents. Some patients had both colonized bacteria and causative bacteria in the same sputum specimen or different specimens collected from the same episode of infection. The number of patients with CAP was small. The present study was conducted in a single large tertiary care university hospital for a limited period. Therefore, the study results might not be generalized to other healthcare facilities and the projected annual burden of hospital-acquired lower respiratory tract infections at Siriraj Hospital might be inaccurate.

Conclusion

GLASS is feasible to perform for sputum specimens and it provides more applicable and more reliable data for AMR of the sputum specimens in terms of the types and sites of infections, types and antibiotic susceptibility profiles of the bacteria in infected patients, and the burden of AMR in HAI. The information on HAP and VAP is useful for developing a local clinical guideline on choosing appropriate empirical antibiotics. However, GLASS has limitations in the AMR surveillance of sputum specimens from patients with CAP and it consumes more time and resources than the traditional laboratory-based surveillance system.

What is already known on this topic?

AMR surveillance of sputum samples is usually performed by a microbiology laboratory-based approach by collecting data on the types of organism and their antibiotic susceptibility profiles for all the isolated bacteria from adequately collected samples without clinical data and by removing the repeated isolates, resulting in inaccurate data that have less utility for developing antibiotic treatment guideline for the therapy of respiratory tract infections.

What this study adds?

The present study implemented the GLASS, recommended by the WHO, for sputum specimens collected from patients at Siriraj Hospital by combining the data from the microbiology laboratory with relevant clinical data of the patients with positive culture sputum samples, with the repeated isolates of bacteria from the same samples or patients removed. The study results revealed more valid information than those observed from the microbiology laboratory alone, which could be used for developing antibiotic treatment guidelines for the therapy of respiratory tract infections, and for estimating the burden of AMR in patients with respiratory tract infections.

Acknowledgement

The authors would like to thank Wiyada Arjratanakool, Nuttapong Srasrisom, Wanida Cheewathammarat, and Sukanya Chanboonchuay

for their assistance in managing the microbiology data. The authors also thank the Computer Unit and the Financial Department of Siriraj Hospital for providing data on some patients' outcomes and the cost of hospitalization.

Financial Support

The study was supported by the Health Systems Research Institute (Thailand) and the Faculty of Medicine Siriraj Hospital.

Conflicts of interest

The authors declare no conflict of interest.

References

1. Pumart P, Phodha T, Thamlikitkul V, Riewpaiboon A, Prakongsai P, Limwattananon S. Health and economic impacts of antimicrobial resistance in Thailand. J Health Syst Res 2012;6:352-60.
2. Song JH, Oh WS, Kang CI, Chung DR, Peck KR, Ko KS, et al. Epidemiology and clinical outcomes of community-acquired pneumonia in adult patients in Asian countries: a prospective study by the Asian network for surveillance of resistant pathogens. Int J Antimicrob Agents 2008;31:107-14.
3. Chawla R. Epidemiology, etiology, and diagnosis of hospital-acquired pneumonia and ventilator-associated pneumonia in Asian countries. Am J Infect Control 2008;36(4 Suppl):S93-100.
4. Reechaipichitkul W, Phondongnok S, Bourpoern J, Chaimanee P. Causative agents and resistance among hospital-acquired and ventilator-associated pneumonia patients at Srinagarind Hospital, northeastern Thailand. Southeast Asian J Trop Med Public Health 2013;44:490-502.
5. Werarak P, Kiratisin P, Thamlikitkul V. Hospital-acquired pneumonia and ventilator-associated pneumonia in adults at Siriraj Hospital: etiology, clinical outcomes, and impact of antimicrobial resistance. J Med Assoc Thai 2010;93 Suppl 1:S126-38.
6. Global Antimicrobial Resistance Surveillance System (GLASS). Manual for early implementation in humans. Geneva: World Health Organization; 2015.
7. Sirijatuphat R, Sripanidkulchai K, Boonyasiri A, Rattanaumpawan P, Supapueng O, Kiratisin P, et al. Implementation of global antimicrobial resistance surveillance system (GLASS) in patients with bacteremia. PLoS One 2018;13:e0190132.
8. Sirijatuphat R, Pongsuttiyakorn S, Supapueng O, Kiratisin P, Thamlikitkul V. Implementation of global antimicrobial resistance surveillance system (GLASS) in patients with bacteriuria. J Glob Antimicrob Resist 2019;20:60-7.
9. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Executive summary: Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis 2016;63:575-82.
10. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44 Suppl 2:S27-72.
11. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus definitions for sepsis and septic shock (Sepsis-3). JAMA 2016;315:801-10.
12. Willyard C. The drug-resistant bacteria that pose the greatest health threats. Nature 2017;543:15.
13. Rongrungruang Y, Sawanpanyalert N, Chomdacha P, Surasarang K, Wiruchkul N, Kachintorn K, et al. Health-care associated infections in Thailand 2011. J Med Assoc Thai 2013;96 Suppl 2:S117-23.
14. Danchaivijitr S, Judaeng T, Sripalakij S, Naksawas K, Plipat T. Prevalence of nosocomial infection in Thailand 2006. J Med Assoc Thai 2007;90:1524-9.
15. Reechaipichitkul W, Thavornpitak Y, Sutra S. Burden of adult pneumonia in Thailand: a nationwide hospital admission data 2010. J Med Assoc Thai 2014;97:283-92.
16. Self WH, Wunderink RG, Williams DJ, Zhu Y, Anderson EJ, Balk RA, et al. Staphylococcus aureus Community-acquired pneumonia: Prevalence, clinical characteristics, and outcomes. Clin Infect Dis 2016;63:300-9.
17. Arancibia F, Bauer TT, Ewig S, Mensa J, Gonzalez J, Niederman MS, et al. Community-acquired pneumonia due to gram-negative bacteria and Pseudomonas aeruginosa: incidence, risk, and prognosis. Arch Intern Med 2002;162:1849-58.