Global Prevalence of Colistin Resistance in Clinical Isolates of *Acinetobacter baumannii* A Systematic Review and Meta-Analysis

ali pormohammad (✉ pormohammadali@yahoo.com)

Naser Mohtavinejad

Tehran University

Pourya Gholizadeh

Tabriz

Masoud dadashi

Shahid Beheshti

Samira Karimaei

Tehran

Hossein Safari

Tehran University

Mohammad Azadbakht

Royan

Taher Azimi

Tehran university

Research article

Keywords: Prevalence, *Acinetobacter baumannii*, drug Resistance, Meta-Analysis

Posted Date: May 21st, 2019

DOI: <https://doi.org/10.21203/rs.2.9714/v1>

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Abstract

Introduction *Acinetobacter baumannii* antimicrobial resistance is a public health concern in developing and developed countries, especially in hospital setting. Understanding the antibiotic resistance profile can be helpful in providing better guidelines for prescription of appropriate antibiotics, reduction of antibiotic resistance, and introducing new and effective treatment options. **Method** Using the PRISMA guidelines, databases of PubMed, Embase, and Cochrane Library were searched systematically from January 1, 2000 to January 1, 2018. All statistical analyses were carried out via Comprehensive Meta-Analysis Software Version 2.0 (Biostat, Englewood, NJ). Depending on the heterogeneity test, either random or fix effect models were used for determining the pooled prevalence of drug resistance. **Result** A total of 150 studies were included from 41 countries of six different WHO regional offices worldwide. The highest and the lowest rate of resistance were observed for cefotaxim (99%, 95% CI: 95-99.9) in Africa and for colistin (1.1%, 95% CI: 0.3-4.5) in Western Pacific, respectively. Lebanon (17.5%, 95% CI: 16-19) and China (12%, 95% CI: 3.5-32.5) had the highest and Germany (0.2%, 95% CI: 0-2.5) had the lowest rate of resistance for colistin. **Conclusion** Our analysis showed that prevalence and rate of increased colistin resistance in South-East Asia and Eastern Mediterranean countries are higher than other regions of the world. Therefore, establishment of appropriate antibiotic usage guidelines should be essential in these countries.

Introduction

Acinetobacter species are important pathogens that are related with severe hospital-acquired infections (1). *Acinetobacter* species could create several types of infections such as secondary meningitis, bloodstream infection, and especially ventilator-associated pneumonia in the intensive care units (ICUs) (2-5). These bacterial strains, especially *Acinetobacter baumannii* (*A. baumannii*), have developed several strategies for resistance against a wide range of conditions including pH, salinity, and antimicrobial agents (6-8). Moreover, resistance to various categories of antibiotics including carbapenems has been revealed, too (9-12). Antimicrobial resistance (AMR) is a public health concern in developing and developed countries and increases the healthcare and hospitalization costs considerably in different parts of the world (13-15). According to the Centers for Disease Control and Prevention (CDC) reports, approximately two million people become infected with AMR microorganisms in the United States and nearly twenty three thousand Americans die yearly (16). The carbapenem resistant *A.baumannii* (CRAB) causes a great mortality rate between hospitalized patients, particularly in ICU (11). Over the last years, emerging of CRAB isolates has made polymyxin E (colistin) a significant and essential therapeutic choice for different infections (17, 18). The colistin has a significant activity against multi drug resistant (MDR) and extremely drug resistant (XDR) gram negative bacteria, especially *A.baumannii* (6, 19). Based on the several reports, it is estimated that more than fifty percent of all antibiotics prescribed by physicians are not needed (15). Furthermore, incorrect prescriptions and unsuitable consumption of colistin contribute to an increase in the colistin-resistant gram negative bacteria, particularly *A. baumannii* (5, 20). The pattern of AMR changes with time and between hospitals within a similar country and it also varies among WHO regional offices (15, 21). In addition, prevention, control, and treatment of infections caused by AMR *A.baumannii* could be challenging (22). Generally, understanding the AMR profile could be helpful in several procedures. Firstly, it can provide better guidelines for prescription of appropriate antibiotics and reduction of antibiotic resistance in microorganisms. Secondly, it can be helpful in introducing new and effective treatment options. Finally, understanding the AMR profile contributes to better prevention and control of infectious diseases (13). For this purpose, we conducted a systematic review and meta-analysis to investigate the prevalence of antibiotic resistance in *A.baumannii* isolates for the most usually prescribed antibiotics, especially colistin, for the patients in order to give an appropriate antibiotic resistance profile for *A.baumannii*. These data could be helpful in prevention and treatment of *A.baumannii* AMR isolates in different regions of the world.

Methods

Sources of information and Search Strategies

PubMed, Embase, and Cochrane Library were searched from January 1, 2000 to January 1, 2018 using the MeSH terms of "*Acinetobacter baumannii*", "*Acinetobacter*", "drug resistance" and "antimicrobial resistance". MeSH terms were combined with other words including "*A. baumannii*", "colistin resistance", "antibiotic(s)" and their synonyms. In addition, we searched related reviews and their references for relevant studies. We conducted our study according to PRISMA guideline (23).

Eligibility

Inclusion criteria

Three reviewers (MP, TA and AP) reviewed the titles and abstracts independently and chose those meeting the selection criteria for full-text evaluation. Discrepancies were discussed with a 4th reviewer (MD). All English language original articles that had reported the prevalence of colistin resistant *A. baumannii* clinical isolates with standard laboratory tests were included in the study. Studies were eligible if they had reported the prevalence of drug resistance in *A. baumannii* based on the standard tests guidelines such as Clinical and Laboratory Standards Institute (CLSI), European Committee on Antimicrobial Susceptibility Testing (EUCAST) or National Committee for Clinical Laboratory Standards (NCCLS) guidelines. Standard laboratory tests for antibiotic susceptibility tests in the included studies were as follows; disk diffusion method (DDM), minimum inhibitory concentration (MIC) or E-test and VITEK 2 system (bioMérieux). This study is aimed to investigate the prevalence of colistin resistant *A. baumannii* isolates in different regions of the world. Therefore, we just included studies that had reported colistin resistance prevalence. However, MDR and other antibiotic resistant *A. baumannii* are also reported in the current study. In this study, MDR was defined as resistance to three or more antimicrobial categories.

Exclusion criteria

The following articles were excluded: studies that did not report the sample size or had a sample size less than 10 (isolated *A. baumannii*); studies with inappropriate data, and studies that just reported antibiotic resistance in MDR or XDR isolates.

Data extraction and Data collection

The following data were extracted: name of the first author, enrolled study time, publication time, sample size, time and location of the study, numbers of isolated *A. baumannii*, and the number of colistin and other antibiotic resistance. Data were collected by three authors (MP, AP, TA), and there was a fourth author (MJN) who checked the accuracy of the extracted data.

Quality assessment

Quality assessment of the studies was performed by two reviewers independently according to the modified Critical Appraisal Checklist recommended by the Joanna Briggs Institute (24), and disagreements were resolved by consensus. We modified some of the checklist questions based on the aims of the study. The checklist is composed of seven questions (question four has two scores) that reviewers answered the questions for each study. The 'Yes' answer for each question received one score. Thus, final scores for each study could range from zero to eight (Table S1 in supplementary material).

Meta-Analysis Approach

All statistical analyses were carried out via Comprehensive Meta-Analysis Software Version 2.0 (Biostat, Englewood, NJ). Determination of heterogeneity among studies was undertaken using chi-squared test (Cochran's Q) to assess the appropriateness of pooling data. Depending on the heterogeneity test, either random or fix effect models were used for determining the pooled prevalence of drug resistance. Therefore, we used random effect model (M-H heterogeneity) for high heterogeneities ($I^2 > 50\%$) and Fix effect model for low heterogeneities ($I^2 < 50\%$) (25). Begg's and Egger's tests were used to assess the publication bias. The point estimates of effect size and prevalence and its 95% confidence interval (95% CI) were estimated for each study.

Result

Studies selection

A total of 27440 articles were found in the initial search, which 150 studies were included in the final analysis. Articles that were based on review or case reports, considered other antibiotic resistance prevalence rather than colistin, and reported antibiotic resistance just in MDR or XDR isolates were excluded from the study. Study selection process is shown in Fig 1, and characteristics of the selected articles are summarized in Table S1 (supplementary material). Included studies were from 41 different countries of six different WHO regional offices as following; eight articles from Africa, 20 from America, 47 from Eastern Mediterranean, 40 from Europe, 31 from South-East Asia, and 4 of them were from Western Pacific WHO regional offices. All included studies had used clinical samples for isolation of *A. baumannii*.

Prevalence of antibiotic resistance in *Acinetobacter baumannii* by WHO regional offices

Depending on the heterogeneity test results for different WHO regional offices, we used either random or fix effect models for determining the pooled prevalence of drug resistance. Therefore, random effect model was used for high heterogeneities ($I^2 > 50\%$) (M-H heterogeneity) and fix effect model was used for low heterogeneities ($I^2 < 50\%$). Pooled prevalence of antibiotic resistance in *A. baumannii* clinical isolates is shown in Table 1 by WHO regional offices. The highest and the lowest rate of resistance were observed for Cefotaxim (99%, 95% CI: 95-99.9) in Africa and for colistin (1.1%, 95% CI: 0.3-4.5) in Western Pacific, respectively.

Prevalence of Colistin resistance in *Acinetobacter baumannii* by countries

As presented in Table 2, Lebanon (17.5 %, 95% CI: 16-19) and China (12 %, 95% CI: 3.5-32.5) had the highest and Germany (0.2 %, 95% CI: 0-2.5) had the lowest rate of resistance for colistin among the 41 countries from different regions of the world.

Prevalence of Colistin resistance in *Acinetobacter baumannii* by different antibiotic susceptibility tests

Prevalence of antibiotic resistance in *A. baumannii* clinical isolates is shown in Table 3 by different antibiotic susceptibility tests. For detection of colistin resistance prevalence in *A. baumannii*, disc diffusion method showed a higher rate of resistance (5 %, 95% CI: 4-7) in comparison with the MIC (3 %, 95% CI: 2-4.5) and Vitek2 (2 %, 95% CI: 1-4) methods.

Time trend meta-analysis of colistin resistance in *Acinetobacter baumannii* by WHO regional offices

As time trend meta-analysis of colistin resistance is presented in Fig 2, there was no specific pattern of colistin resistance during 2000 to 2017. However, increased colistin resistance in different regions of the world is considerable. Totally, prevalence and rate of increased colistin resistance in South-East Asia and Eastern Mediterranean were higher than other regions of the world during 2000 to 2017.

Discussion

Globally, emergence of drug resistant *Acinetobacter* species, especially carbapenem resistance, MDR, and XDR *A. baumannii* has increased the mortality rate of hospitalized patients, particularly in ICU (1, 26). Therefore, understanding the antimicrobial resistance profile of *A. baumannii* is extremely essential for selection and prescription of appropriate antibiotics and reduction of antibiotic resistance in hospitalized patients. The global prevalence of antibiotic resistance, particularly colistin resistance in *A. baumannii* clinical isolates, was investigated in this systematic review and meta-analysis study from 2000 to 2017. To the best of our knowledge, the present study is the first comprehensive systematic review on the prevalence of *A. baumannii* antimicrobial resistance worldwide. Helping to the prescription of appropriate antibiotics, reduction of antibiotic resistance, prevention and control of infectious diseases are the main and significant goals of the study. Based on the European Centre for Disease Prevention (ECDC) reports, fifty percent of CRAB isolates were resistant to different categories of antibiotics (27). Also, resistance to various antibiotics such as carbapenems, fluoroquinolones, and aminoglycosides was very high in several European countries such as Poland (3). On the other hand, based on the European Antimicrobial Resistance Surveillance Network (EARS-Net) reports in 2013, the prevalence rate of MDR and XDR *A. baumannii* isolates increased progressively (28, 29). Moreover, according to a study carried out in Greece in 2011, the high percentage of *A. baumannii* isolates were MDR strains (21). In general, our meta-analysis study indicated that the overall estimate of MDR prevalence in the *A. baumannii* clinical isolates was 64% and 41% with DDM and MIC/E-test methods, respectively. Prevalence of MDR isolates is high, especially in some regions of the world such as Western Pacific (80%) and African (77.5 %) countries. Therefore, establishment of appropriate antibiotic usage guideline seems essential in these countries. Considering the increased prevalence of carbapenem resistance in *A. baumannii*, colistin has been used as an important and effective option for treatment of CRAB infections (3, 17). Based on the results of different studies, Carbapenems, sulbactam, tigecycline, and colistin have a significant activity against *A. baumannii* various infections (17, 30). Colistin therapy and increased consumption of this drug may cause several side effects such as nephrotoxicity and neurotoxicity (22). In our meta-analysis study, the prevalence of colistin resistance based on DDM, MIC/E-test, and Vitek2 methods in *A. baumannii* isolates was 5%, 3%, and 2%, respectively. Among 41 different countries publications included in the present study, the comprehensive analysis of colistin resistance rate showed that Germany and Lebanon had the lowest and the highest prevalence rate with 2% and 17.5 %, respectively. Considering the WHO regional offices, our time trend analysis showed an increase in the colistin resistance rate between 2004 until 2007 in developed countries such as European countries and a decrease in the colistin resistance rate between 2016 until 2017 in South-east Asia and American countries. Totally, there was no specific pattern for colistin resistance during 2000 to 2017. However, increased colistin resistance in different regions of the world is considerable.

The limited number or lack of studies from some regions of the world could be the main limitation for the current study. In spite of using meta-regression, subgroup, and sensitivity analyses to detect the sources of heterogeneity, publication bias and heterogeneity must be considered when interpreting the outcomes reported here.

Conclusion

Totally, our analysis showed that prevalence and rate of increased colistin resistance in South-East Asia and Eastern Mediterranean countries are higher than other regions of the world. Accordingly, there is no standard therapeutic recommendation for the management and controlling of MDR, XDR, and colistin-resistant *Acinetobacter* infections; therefore, similar to various published studies, we believe that combination therapy including colistin plus rifampicin, colistin plus vancomycin, colistin-carbapenem, trimethoprim-sulfamethoxazole with colistin or fosfomycin and aminoglycoside could have the highest synergistic effect against MDR and CRAB isolates compared to colistin alone (3, 11, 17, 22). Moreover, it has been revealed that combination therapy could reduce colistin toxicities related with overdose concentrations (22). More comparative studies are suggested to be done in order to understand the possible profits of combination therapies against monotherapy in treating MDR, XDR, and CRAB isolates.

Declarations

Acknowledgments

We appreciate Calgary University of Medical Sciences for the sincere cooperation with the research team.

Authors' contributions:

Study design: AP, MJN, TA.

Literature search, data collection, data analysis and data interpretation: AP, MJN, MD, TA, SK

Writing: AP, MJN, TA

Manuscript editing: AP, MJN, MA, TA, HS

Conflict of interest:

We declare that we have no conflicts of interest

Funding: no foundation source.

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Tables

Table1. Prevalence of antibiotic resistance in *Acinetobacter baumannii* clinical isolates by WHO Reginal Offices from 2000-2017.

WHO Regional Offices	America		Africa		Europe		Eastern Mediterranean		South- East Asia		Western Pacific	
<i>Antibiotic</i>	<i>Pooled prevalence</i> <i>[95% CI (%)]</i>	<i>N of study</i>	<i>Pooled prevalence</i> <i>[95% CI (%)]</i>	<i>N of study</i>	<i>Pooled prevalence</i> <i>[95% CI (%)]</i>	<i>N of study</i>	<i>Pooled prevalence</i> <i>[95% CI (%)]</i>	<i>N of study</i>	<i>Pooled prevalence</i> <i>[95% CI (%)]</i>	<i>N of study</i>	<i>Pooled prevalence</i> <i>[95% CI (%)]</i>	<i>N of study</i>
Colistin	3.2 (2-5.6)	20	2 (1-3.5)	9	1.8 (1-3)	45	4 (3-6)	58	6.7 (4.5-10)	35	1.1 (0.3-4.5)	4
MDR isolates	70 (43-89)	2	77.5 (74.5-80)	2	57 (38-74.5)	12	69.5 (52-82)	14	50 (26-74)	5	80 (69-87)	1
Ciprofloxacin	82 (71-90)	10	84 (46.5-96.5)	7	88 (83-92)	33	89 (84-92)	46	83 (67-92)	21	-	-
Aztreonam	92 (74-98)	5	99 (90-100)	1	95 (10-25)	9	95 (90-97)	22	90 (64-97)	5	-	-
Ceftazidime	76 (68-82)	12	90 (67-97)	8	92 (90-94)	28	93 (9)0-96	44	85 (70-93)	20	75 (37-93)	2
Cefepime	85 (75-92)	7	84 (47-97)	6	90 (53-94)	11	91 (86-94)	31	75 (54-89)	14	93 (85-97)	1
Amikacin	57 (48-66)	13	48 (28-69)	8	65 (0.2-16.5)	32	76 (71-81)	43	74 (62-83)	23	80 (70-87)	2
Ampicillin/ sulbactam	74 (63-83)	10	-	-	70 (50-90)	15	62 (53-70)	27	75 (55-88)	13	66 (40-84)	1
ceftriaxone	40 (2-95)	2	26 (18-37)	3	86 (60-96)	3	75 (57-87)	15	81 (49-95)	4	48 (33-62)	1
Cefotaxim	71 (10-98)	2	99 (95-99.9)	2	96 (91-98)	11	97 (95-99)	33	82 (72-89)	12	-	-
Meropenem	84 (75-90)	13	78 (61-90)	4	83 (76-89)	35	86 (81-90)	43	70 (44-87)	13	93 (50-99)	2
Ceftriaxone	93 (79-98)	7	94 (74-99)	2	87 (57-97)	6	97 (94-99)	24	85 (73-93)	7	88 (78-93)	1
Imipenem	71 (55-83)	11	65 (40-84)	8	79 (72-84)	35	81 (76-85)	54	69 (51-83)	22	80 (33-97)	3
Trimethopri/ sulfamethoxazole	78 (37-95)	43	70 (1.4-5)	5	83 (77-88)	22	83 (76-88)	23	80 (31-97)	6	44 (24-67)	1
Tetracycline	31.5 (3-87)	3	91 (89-93)	2	80 (66-90)	9	68 (60-76)	20	38 (18-67)	6	-	-
Gentamicin	81 (70-89)	11	53 (23-80)	6	75 (69-79)	26	82.5 (78-86)	42	85 (73-92)	18	39 (20-62)	1
Pip/tazobactam	74 (61-84)	9	69 (36-90)	6	87 (80-92)	26	91 (87-94)	28	74 (55-86)	19	33 (16-57)	1
Levofloxacin	78 (65-86)	9	94 (66-99)	1	77 (63-87)	9	87 (78-93)	25	90 (70-97)	5	81 (70-88)	1
Piperacillin	54 (49-58)	1	80 (44-95)	6	92 (85-96)	11	96 (94-97)	29	87 (74-94)	2	-	-
Tobramycin	62	7	42	4	49	15	68	30	76	5	-	-

	(51-73)		(38-44)		(36-63)		(64-73)		(58-88)			
Tigecycline	8	10	62	1	15	22	21	33	22	15	-	-
	(2-26)		(50-72)		(8.5-26)		(12-34)		(11-38)			

Table2. Prevalence of Colistin resistance in *Acinetobacter baumannii* clinical isolates by countries from 2000 to 2017.

Country	Study year/s	Study Number	Resistance (%)	95% CI (%)		resistance/ bacteria	I-squared
				Lower Limit	Upper Limit		
Syria	2012	1	6.9%	4.4%	10.7%	18 / 260	0.0
Algeria	2013	2	0.6%	0.1%	3.8%	0 / 184	0.0
Bangladesh	2013, 2016	2	2.7%	0.9%	7.9%	3 / 130	0.0
Bosnia	2014-2015	2	0.4%	0.1%	2.9%	0 / 311	0.0
Brazil	2016-2017	3	3.5%	1.5%	8.1%	211 / 14912	96.6
China	2015-2016	3	11.8%	3.6%	32.5%	62 / 395	75.3
Colombia	2015	1	3.1%	0.4%	19.1%	1 / 32	0.0
Croatia	2011	1	0.7%	0.0%	10.4%	0 / 69	0.0
Cuba	2012-21015	4	2.2%	0.9%	5.4%	14 / 757	55.4
Egypt	2014	2	5.0%	1.9%	12.6%	4 / 80	0.0
France	2016	1	1.0%	0.1%	14.3%	0 / 48	0.0
French Guiana	2016	1	4.3%	2.8%	6.7%	19 / 441	0.0
Germany	2012	1	0.2%	0.0%	2.5%	0 / 310	0.0
Greece	2012-2016	5	4.0%	1.0%	15.4%	53 / 2661	94.5
India	2013-2017	10	8.2%	3.0%	20.3%	233 / 2031	96.3
Iran	2011-2016	34	4.8%	3.0%	7.7%	289 / 3612	90.0
Iraq	2016	1	7.3%	3.5%	14.5%	7 / 96	0.0
Italy	2008-2015	3	1.4%	0.4%	5.7%	3 / 327	37.3
Jordan	2015	1	1.7%	0.4%	6.6%	2 / 116	0.0
Korea	2007-2017	12	7.8%	4.0%	14.7%	127 / 1047	86.0
Lebanon	2016	1	17.5%	16.2%	18.8%	585 / 3343	0.0
Libya	2015	1	2.9%	0.2%	33.6%	0 / 16	0.0
Maroc	2016	2	1.7%	1.0%	2.8%	15 / 882	0.0
Mexico	2016	1	1.5%	0.1%	20.1%	0 / 32	0.0
Nigeria	2016	1	4.2%	0.3%	42.5%	0 / 11	0.0
Pakistan	2014-2016	4	4.7%	0.3%	47.5%	54 / 945	97.6
Poland	2013-2016	4	0.9%	0.1%	9.6%	15 / 1154	86.6
Qatar	2016	1	0.9%	0.2%	3.4%	2 / 239	0.0
Russia	2012	1	0.5%	0.0%	7.6%	0 / 98	0.0
Saudi Arabia	2012-2016	11	1.9%	1.4%	2.6%	32 / 2124	0.0
Singapore	2006-2007	3	1.3%	0.3%	6.3%	0 / 123	0.0
South Africa	2015-2016	2	0.4%	0.1%	3.1%	0 / 227	0.0
Spain	2004-2016	6	5.9%	2.1%	15.9%	44 / 886	87.6
Switzerland	2013	1	0.7%	0.0%	10.4%	0 / 69	0.0
Taiwan	2013-2016	6	2.5%	0.3%	17.6%	34 / 591	92.4
Thailand	2008	1	2.0%	0.1%	25.1%	0 / 24	0.0
Tunisia	2013	2	0.5%	0.1%	3.7%	0 / 184	0.0
Turkey	2003-2016	19	1.4%	0.5%	3.7%	34 / 2894	84.8
UK	2002	1	2.3%	1.2%	4.1%	10 / 443	0.0
USA	2006-2016	11	3.4%	1.6%	7.3%	338 / 11195	97.3
Vietnam	2015	1	0.7%	0.0%	9.8%	0 / 74	0.0

Overall	2000-2017	170	11.2%	10.5%	12.0%	2209 / 53373	95.3
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Table3. Prevalence of antibiotic resistance in *Acinetobacter baumannii* clinical isolates by antibiotic susceptibility tests.

Methods	Disk diffusion				MIC/E-test				Vitek2			
<i>Antibiotic</i>	<i>Pooled prevalence (%)</i>	<i>n /N</i>	<i>N of study</i>	<i>I2 (%) P</i>	<i>Pooled prevalence (%)</i>	<i>n/N</i>	<i>N of study</i>	<i>I2 (%) P</i>	<i>Pooled prevalence (%)</i>	<i>n/N</i>	<i>N of study</i>	<i>I2 (%) P</i>
MDR isolates	64 (52-74)	2539/4249	25	< 0.001	41 (22-63)	1584/2566	7	< 0.001	90 (80-94)	5379/8203	4	< 0.001
Colistin	5 (4-7)	1196 / 11735	61	< 0.001	3 (2-4.5)	766 / 27052	77	< 0.001	2 (1-4)	247 / 14503	29	< 0.001
Ciprofloxacin	88 (84-91)	9989 / 11820	57	< 0.001	77 (69-84)	8088 / 10991	39	< 0.001	93 (89-95)	3574 / 3927	18	< 0.001
Cefepime	91 (87-94)	8178 / 9592	43	< 0.001	76 (68-84)	7711 / 10115	25	< 0.001	91 (85-95)	3460 / 3899	15	< 0.001
refampin	59 (43-73)	1009 / 2114	15	< 0.001	83 (60-94)	519 / 1063	11	< 0.001	64 (27-90)	102 / 149	2	< 0.001
Aztreonam	95 (91-97)	5370 / 5823	26	< 0.004	96 (89-98)	1695 / 2009	13	< 0.001	90 (43-99)	1275 / 1368	3	< 0.001
Ceftazidime	93 (90-95)	8825 / 10301	55	< 0.001	83 (77-87)	10050 / 12963	38	< 0.001	92 (89-95)	3634 / 3915	17	< 0.001
Ampicillin/ sulbactam	73 (65-80)	2865 / 3835	29	< 0.001	53 (42-65)	5511 / 8485	23	< 0.001	82 (61-93)	1884 / 3012	13	< 0.001
Cefotaxim	97 (94-98)	4420 / 4650	34	< 0.001	90 (83-95)	2038 / 2697	20	< 0.001	96 (88-98)	1176 / 1211	6	< 0.001
Meropenem	85 (81-89)	5455 / 6655	42	< 0.001	76 (69-82)	7903 / 12364	43	< 0.001	89 (80-94)	3290 / 4981	22	< 0.001
Ceftriaxone	96 (94-97)	3851 / 4019	31	< 0.001	78 (56-91)	5884 / 6788	8	< 0.001	92 (40-99)	582 / 977	3	< 0.001
Imipenem	78 (73-82)	9451 / 12340	59	< 0.001	67 (58-87)	7224 / 12112	49	< 0.001	88 (84-92)	4056 / 5056	22	< 0.001
Trimethopri/ sulfamethoxazole	83 (77-88)	6648 / 8411	31	< 0.001	76 (65-85)	4915 / 7208	16	< 0.001	82 (71-82)	2733 / 3426	10	< 0.001
Tetracycline	54.6 (37.3-71)	711/1192	13	< 0.001	53 (36-69.5)	861/2201	10	< 0.001	47 (25-70)	338/811	8	< 0.001
Gentamicin	81 (77-85)	8200 / 10497	49	< 0.001	77 (72-82)	7304 / 10357	35	< 0.001	74 (66-80)	3426 / 4826	16	< 0.001
Pip/tazobactam	87 (82-91)	8251 / 9982	41	< 0.001	76 (68-93)	8397 / 11229	31	1	88 (77-94)	2988 / 3571	13	< 0.001
Levofloxacin	87 (80-91)	3135 / 3634	20	< 0.001	79 (70-86)	8375 / 11138	21	< 0.001	87 (81-92)	792 / 931	5	< 0.001
Amikacin	73 (67-78)	8680 / 11975	58	< 0.001	62 (56-68)	7525 / 12589	46	< 0.001	73.5 (66-80)	2573 / 3620	14	< 0.001
Piperacillin	95 (91-97)	3770 / 4422	31	< 0.001	90 (83-94)	1478 / 1926	12	< 0.001	93 (78-98)	1526 / 1743	6	< 0.001
Tobramycin	65 (58-71)	3000 / 4976	31	< 0.001	60 (53-72)	5934 / 10130	22	< 0.001	53 (33-72)	1893 / 3226	8	< 0.001

Tigecycline	23 (14-35)	1150 / 3595	27 < 0.001	12 (6.5-24)	1054 / 5244	36 < 0.001	25 (14-40)	1184 / 3929	18 < 0.001
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Figures

Fig 1. Flow diagram of literature search and study selection.

Figure 1

Flow diagram of literature search and study selection

Figure 2

Time trend Meta-analysis, Colistin resistance in *Acinetobacter baumannii* clinical isolates by WHO Regional Offices from 2000 to 2017.

Supplementary Files

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