Systematic Literature Review on the Clinical and Economic Burdens of Antimicrobial Resistance in the Japanese Population

EPH230

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INTRODUCTION

Antimicrobial resistance (AMR) results in an increased risk of disease spread, severe illness, and death. Comprehensive evidence of clinical and economic burdens in AMR in Japan is limited.

OBJECTIVES

The aim of this study is to summarize existing research studies related to AMR-caused disease burden.

METHODS

This review was conducted in accordance with PRISMA guidelines. Studies published during 2012–2022 describing the Japanese adult population were included. The MEDLINE, Embase, Cochrane Library, and ICHUSHI databases were searched based on the inclusion/exclusion criteria. Outcomes were in-hospital death, hospitalization period, and direct medical costs. Studies with comparable control groups were assessed for differences in these outcomes.

Table 1: Eligibility criteria

Category	Inclusion criteria		Exclusion criteria
Population	• Adult patients (≥18 years of age) with at least one AMR infectious disease		• Healthy volunteers • <18 years of age • Animal/in vitro
Interventions/ comparators	• Any treatment		• No limitation
Outcomes	Clinical burden	• In-hospital mortality • Hospitalization period	• Any outcome other than clinical and economic burden
	Economic burden	• Direct medicals costs • Duration of antibiotics • Amount of antibiotics	
Study design	Interventional study	• Randomized control trials ➢ Randomized cross-over trials ➢ Cluster-randomized trials • Quasi-experimental studies ➢ Non-randomized controlled studies ➢ Before and after studies ➢ Interrupted time series	• Reviews, letters, comments, case reports, case series, and editorials • Systematic reviews
	Observational study	• Case-control studies • Cohort studies • Cross-sectional studies	
Language	• English language • Japanese language		• Any other language except English and Japanese
Countries	• Japan • Global studies with Japanese population		• Any other country except Japan
Publication type	• Full-text articles only		• Any other
Time limits	• Past 10 years for research articles		• Articles older than 2012

RESULTS

1. Study selection

Our searches initially identified 1,262 records, of which 56 unique studies from 57 publications were finally included following screening (Figure 1). Of the 56 observational studies, 35 were English and 21 were Japanese. 53 (94.6%) were cohort studies (Table 2). 22 studies (39.3%) reported outcomes in the AMR and non-AMR groups.

Figure 1: PRISMA flow diagram

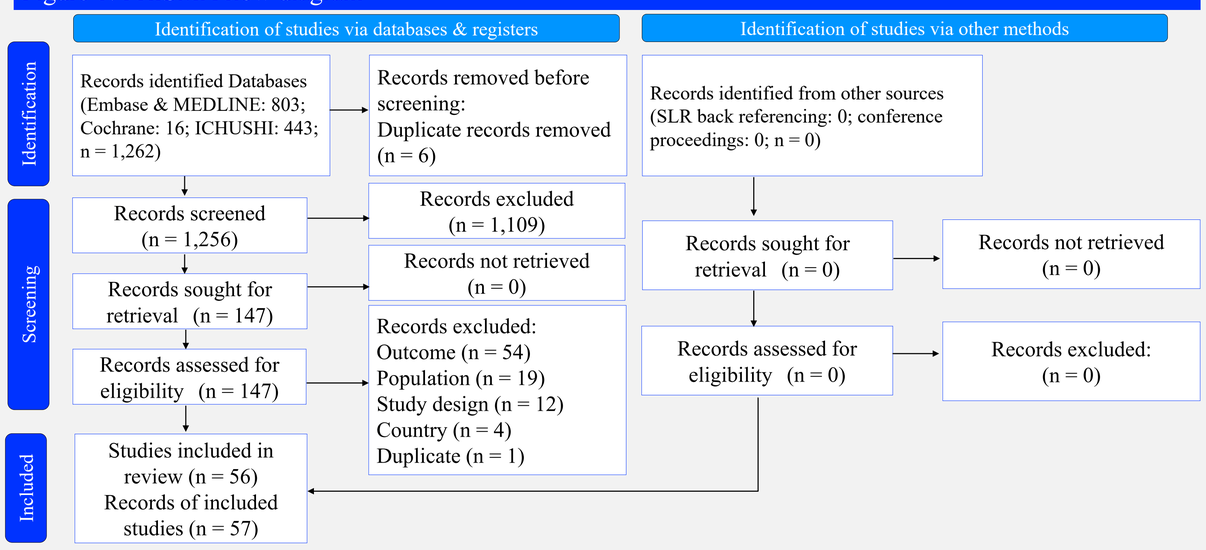
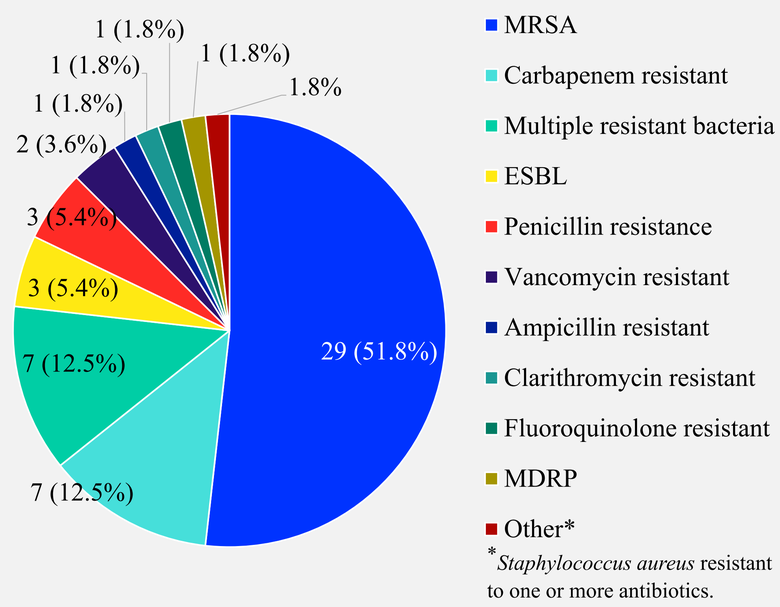


Table 2: Study characteristics

Parameter	N (%)	Parameter	N (%)
Analysis type (N = 56)		**Study setting (N = 56)**	
Propensity score matching	7 (12.5%)	Single-center	35 (62.5%)
IPTW	1 (1.8%)	Multicenter	19 (33.9%)
Without adjustment	48 (85.7%)	NR	2 (3.6%)
Study design (N = 56)		**Overall patient size (N = 56)**	
Cohort	53 (94.6%)	≤100	16 (28.6%)
Case-control	2 (3.6%)	101 to 200	13 (23.2%)
Cross-sectional	1 (1.8%)	201 to 300	3 (5.4%)
Study type (N = 56)		>300	21 (37.5%)
Single arm studies	34 (60.7%)	NR	3 (5.4%)
Studies with comparison arm	22 (39.3%)	**AMR patient size (N = 56)**	
Targeted infectious disease (N = 56)		≤100	28 (50.0%)
Multiple infection	23 (41.1%)	101 to 200	11 (19.6%)
Pneumonia	9 (16.1%)	201 to 300	3 (5.4%)
Urinary tract infection	2 (3.6%)	>300	12 (21.4%)
Vertebral osteomyelitis infection	1 (1.8%)	NR	2 (3.6%)
Bloodstream infection	14 (25.0%)	**Publication year (N = 56)**	
Surgical site infection	4 (7.1%)	2019-2022	17 (35.7%)
Sepsis	2 (3.6%)	2015-2018	16 (28.6%)
Invasive pneumococcal disease	1 (1.8%)	2012-2014	20 (35.7%)
Language (N = 56)			
Japanese	21 (37.5%)	English	35 (62.5%)

2. Pathogens

Figure 2: Antibiotics resistance (N=56)



Among all pathogens, MRSA was the most common (29 studies [51.8%]), followed by carbapenem-resistant bacteria (7 studies [12.5%]) and multiple resistant bacteria (7 studies [12.5%]). Among infections, bloodstream infections were the most common (14 studies [25.0%]), followed by pneumonia (9 studies [16.1%]), and surgical site infections (4 studies [7.1%]).

3. In-hospital mortality

In-hospital mortality rates for the AMR and non-AMR groups ranged from 10.5%–73.3% and 5.5%–45.0%, respectively.

Table 3a: In-hospital mortality with confounder adjustment

Author Year	AMR or Non-AMR: AMR	AMR or Non-AMR: Non-AMR	Study type	Confounder adjustment	In-hospital mortality: AMR	In-hospital mortality: Non-AMR
Imai 2022	Carbapenem resistant infection	Carbapenem susceptible infections	Retrospective cohort study	IPW	25.6%	23.8%
Sakamoto 2021	MRSA pneumonia	Non-MRSA pneumonia	Retrospective cohort study	Multivariable logistic regression analysis	31.2%	11.6%
Tsuzuki 2021	MRSA	MSSA	Retrospective cohort study	PS matching	36.7%	15.0%
Hayakawa 2020	Carbapenemase-producing *Enterobacteriaceae*	Non-Carbapenemase-producing *Enterobacteriaceae*	Prospective cohort study	IPW	10.5%	11.8%
Uematsu 2016	MRSA	Non-MRSA	Retrospective study	PS matching	22.6%	12.2%

Table 3b: In-hospital mortality without confounder adjustment

Author Year	AMR or Non-AMR: AMR	AMR or Non-AMR: Non-AMR	Study type	Confounder adjustment	In-hospital mortality: AMR	In-hospital mortality: Non-AMR
Umemura 2020	MRSA	MSSA	Prospective cohort study	NA	47.5%	30.5%
Tetsuka 2019	Carbapenemase-producing *Enterobacter cloacae* complex	Non-Carbapenemase-producing *Enterobacter cloacae* complex	Case-control study	NA	15.0%	11.0%
Uematsu 2018	MRSA	MSSA	Retrospective cohort study	NA	17.0%	13.0%
Uematsu 2017	MRSA	Non-MRSA	Retrospective study	NA	22.9%	6.26%
Shoji 2016	MRSA	MSSA	Retrospective study	NA	25.0%	5.5%
Hanaoka 2013	MDRP	Non-MDRP	Retrospective cohort study	NA	73.3%	45.0%

4. Direct medical costs

The median direct medical costs per patient for the AMR and non-AMR groups ranged from USD 6,681 to USD 22,263 and from USD 3,870 to USD 18,263, respectively, with the AMR group being higher.

Table 4: Direct medical costs

Author Year	AMR or Non-AMR: AMR	AMR or Non-AMR: Non-AMR	Study type	Confounder adjustment	Direct medical cost/ patient, USD Median (IQR): AMR	Direct medical cost/ patient, USD Median (IQR): Non-AMR	*P* Value
Imai 2022	Carbapenem resistant infections	Carbapenem susceptible infections	Retrospective cohort study	IPW	22,263 (13,763 – 40,398)	18,263 (11,867 – 28,264)	*P*=0.004
Tsuzuki 2021	MRSA	MSSA	Retrospective cohort study	PS matching	21,574 (15,043 – 39,247)	16,426 (11,406 – 26,552)	*P*=0.036
Uematsu 2016	MRSA	Non-MRSA	Retrospective study	PS matching	6,681 (4,591 – 11,128)	3,870 (2,577 – 6,287)	*P*<0.001

Conclusion

This study summarized the current evidence on AMR-caused disease burden in Japan. Because information is limited, further evidence generation is necessary for a better understanding of the disease burden effect of AMR in Japan.

Abbreviations: AMR, Antimicrobial resistance; ESBL, Extended-spectrum beta-lactamases; ICU, Intensive care unit; IPW, Inverse probability weight; MDRP, Multidrug-resistant *pseudomonas aeruginosa*; MRSA, Methicillin-resistant *staphylococcus aureus*; NR, Not reported; SD, Standard deviation; USD: United states dollars

Declaration of conflicting interests: The authors declare the following potential conflicts of interest with respect to the research and authorship: TM has been on the speakers' bureau for Pfizer Japan Inc., KYORIN Pharmaceutical Co., Ltd., and MSD K.K. AY and NY are full-time employees of Pfizer Japan Inc. HM and DA are employees of IQVIA Solutions Japan K.K., which received funding from Pfizer Japan Inc. to undertake the research outlined in this study.

Funding: This study was funded by Pfizer Japan Inc.

ISPOR Europe 2023, 12-15 November 2023, Copenhagen, Denmark