Antimicrobial-resistant infections, and diagnostic and antimicrobial stewardship practices in inpatients in Indonesia



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Abstract

Antimicrobial-resistant (AMR) bacterial infection is a global threat to public health. Low and middle-income countries (LMICs), including Indonesia, is the hot spot of AMR infection. Understanding AMR situation, clinical diagnostic practices, and antimicrobial use practices in Indonesia could contribute to inform opportunities for intervention; including diagnostic stewardship programme and antimicrobial stewardship program (ASP). The objectives of my studies are to improve understanding of the epidemiology of AMR infections, clinical diagnostic practices and antibiotic use practices in Indonesian national referral hospital, and the current state of nation-wide ASP implementation in Indonesian hospitals before and during the COVID-19 pandemic.

Using routine microbiology and hospital admission databases of the Indonesian national referral hospital from 1 January 2019 to 31 December 2020, I evaluated proportion and incidence rate of AMR-bloodstream infections (BSIs), and blood culture utilization rate. I observed that in the Indonesian national referral hospital, the proportion of resistance for each bacterial pathogen was not different between COVID-19 and non-COVID-19 cases. The observed incidence rates of hospital-origin AMR-BSI increased in 2020, which was likely due to increased blood culture utilization.

I developed clinical diagnostic and antibiotic use practice parameters to monitor and evaluate hospital diagnostic and antimicrobial stewardship practices in resource-limited settings. Using data from routine microbiology, hospital admissions, and antimicrobial dispensing databases of the Indonesian national referral hospital spanning from 1 January 2019 to 31 December 2020, I assessed clinical diagnostic practices and antibiotic use practices. Specifically, I used Fine and Grey sub-distribution hazard models to evaluate the

time to mortality, time to blood culture sampling, and time to discontinuation of parenteral antibiotics, while accounting for competing risks for each outcome. I showed that the proportion of timely blood culture is low, and duration of parenteral antibiotics is long in both COVID-19 and non-COVID-19 patients.

I conducted the first nationwide assessment of the current state of hospital ASP implementation across all 34 provinces of Indonesia and estimated the impact of COVID-19 on ASPs at the sub-national level. Applying a mixed-method approach with an explanatory sequential design, I contextualized combined quantitative and qualitative data. Initially, ordinal regression models were used to estimate associations between ASP implementation scores and explanatory variables at both the hospital and district levels. Subsequently, practical thematic analysis was employed to delve deeper into the barriers and enablers of ASP implementation. By integrating the enablers and barriers identified from quantitative and qualitative findings using the System Engineering Initiative for Patient Safety (SEIPS) framework, I formulated recommended future actions.

This thesis describes works which generated data, provided evidence, and developed parameters of measuring hospital AMR infections, blood culture utilization, diagnostic practices, antibiotic use practices, and ASP implementation in Indonesia.

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All that I am and ever hope to be, I owe it all to Thee
Let me live my life, let it be pleasing Lord to Thee
And if I gain any praise, let it go to Calvary
To God be the glory, for the things He has done
~Andrae Crouch, 1971~

Statement of contributions

My supervisors, Direk Limmathurotsakul, Raph L. Hamers, Nicholas P. J. Day, and Catrin Moore provided scientific and methodological guidance throughout all stages of this work. Additional contributors for each chapter are listed below.

Chapter One

Michael W Gach, Gilbert Lazarus, Daniel Martin Simadibrata and Ralalicia Limato helped with data collection, verification, and statistical analysis.

Chapter Four

Ralacia Limato co-chaired the focus group discussion. Bachtiar Andy Musaffa helped with electronic form of self-assessment.

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List of abbreviations

3GCREC	3rd generation cephalosporin resistant- *E. coli*
3GCRKP	3rd generation cephalosporin resistant- *K. pneumoniae*
AMASS	AutoMated tool for Antimicrobial resistance Surveillance System
AMR	Antimicrobial-resistance
AMS	Antimicrobial stewardship
AMU	Antimicrobial use
aOR	Adjusted odds ratio
ARI	Acute respiratory infection
aSHR	Adjusted subdistribution-hazard ratio
ASP	Antibiotic Stewardship Programme
AST	Antibiotic susceptibility testing
AWaRe	Access, Watch, and Reserve
BSI	Bloodstream infection
CAI	Community-acquired infection
CAP	Community-acquired pneumonia
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
CLSI	Clinical and Laboratory Standards Institute
CMNH	Cipto Mangunkusumo National Hospital
CO	Community-origin
cOR	Crude odds ratio

CRACI	Carbapenem resistant- *Acinetobacter* spp.
CREC	Carbapenem resistant- *E. coli*
CRKP	Carbapenem resistant- *K. pneumoniae*
CSF	Cerebrospinal fluid
DALYs	Disability-adjusted life-years
DDD	Defined daily dose
DEFF	Design effect
DIY	Daerah Istimewa Yogyakarta
DOT	Duration of therapy
ECDC	European Centre for Disease Prevention and Control
ENT	Ear, nose, and throat
EUCAST	European Committee on Antimicrobial Susceptibility Testing
FGD	Focus group discussions
GLASS	Global Antimicrobial Resistance and Use Surveillance System
GLMM	Generalized linear mixed model
HAI	Healthcare-associated infections
HO	Hospital-origin
I	Interviewer
ICU	Intensive care unit
ID	Infectious disease
IPC	Infection prevention and control
IQR	Interquartile range
ISO	International Organization for Standardization
IT	Information technology
IV	Intravenous

J01A	Tetracyclines
J01B	Amphenicols
J01C	Beta-lactam antibacterials, penicillins
J01D	Other beta-lactam antibacterials
J01DE	4th-generation cephalosporins
J01DH	Carbapenems
J01E	Sulfonamides and trimethoprim
J01F	Macrolides, lincosamides and streptogramins
J01G	Aminoglycoside antibacterials
J01M	Quinolone antibacterials
J01R	Combinations of antibacterials
J01X	Other antibacterials
JKN	*Jaminan Kesehatan Nasional* (National health insurance)
LMICs	Low and middle-income countries
LRT	Lower respiratory tract
M	Male
MALDI-TOF MS	Matrix-assisted laser desorption/ionization coupled with time-of-flight mass spectrometer
MDR	Multidrug resistance
MICRO	Microbiology Investigation Criteria for Reporting Objectively
MoH	Ministry of Health
MRN	Medical record number
MRSA	Methicillin resistant- *Staphylococcus aureus*
NA	Not applicable/available
NS	Not specified

OB/GYN	Obstetrics and gynaecology
P&T	Pharmacy and therapeutics
P01A	Agents against amoebiasis and other protozoal diseases
PAMKI	*Perhimpunan Dokter Spesialis Mikrobiologi Klinik Indonesia*
PPS	Point prevelance survey
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
QA	Quality Assurance
SEIPS	System Engineering Initiative for Patient Safety
SOP	Standard operating procedure
STATA	Statistical software for data science
STI	Sexually transmitted infection
STROBE	Strengthening the Reporting of Observational studies in Epidemiology
TATFAR	Transatlantic Taskforce on Antimicrobial Resistance
UK	United Kingdom
UKCPAPIN	Pharmacy Infection Network of the UK Clinical Pharmacy Association
URR	Utilization rate ratio
US CDC	United States Centers for Disease Control and Prevention
USA	United State of America
UTI	Urinary tract infection
VINARES	Viet Nam Resistance
WHO	World Health Organization

Publication in relation to this thesis

Chapter 1

Gach MW, Lazarus G, Simadibrata DM, **Sinto R**, Saharman YR, Limato R, Nelwan EJ, van Doorn HR, Karuniawati A, Hamers RL. Antimicrobial resistance among common bacterial pathogens in Indonesia: a systematic review. The Lancet Regional Health - Southeast Asia. 2024;26:100414. doi:10.1016/j.lansea.2024.100414. eCollection 2024 Jul. PMID: 38778837; PMCID: PMC11109028.

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Chapter 2

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Chapter 4

Sinto R, Limato R, Radiani SP, Huda MN, Surendra H, Praptiwi AW, Herman Y, Musaffa BA, Lazarus G, Day NPJ, Limmathurotsakul D, Karuniawati A, Hamers RL. A nationwide mixed methods study of gaps and barriers to implementation of antimicrobial stewardship programs in hospitals in Indonesia. Journal of Hospital Infection. 2024 (published online ahead of print 18 October).
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Chapter 1
Introduction and Literature Reviews

1.1 Introduction

The burden of AMR (1-4) infections is high and expected to be high in LMICs. In 2021, 4.71 million deaths were associated with bacterial AMR, including 1.14 million deaths attributable to bacterial AMR (4). There is little information about AMR situation and related factors in Indonesia before and during the COVID-19 pandemic. In 2021, The Indonesian Society of Clinical Microbiology reported AMR prevalence estimates of 72% 3rd generation cephalosporin resistant- *K. pneumoniae* (3GCRKP), 69% carbapenem resistant *Acinetobacter baumanii,* and 62% 3rd generation cephalosporin resistant- *E. coli* (3GCREC) for key pathogens in hospitalized patients in Indonesia (5). The COVID-19 pandemic has potentially escalated AMR infections due to high antibiotic use, predominance of severe COVID-19 patients in intensive care unit (ICU) with multiple predispositions towards AMR infections and protracted hospital stay, overcrowding of patients, and limited guideline adherence (6-12).

There is a limited systematic surveillance networks evaluating the proportion and the incidence rate of AMR-BSIs in Indonesia. Indonesia reported the first AMR surveillance key indicators to the WHO Global Antimicrobial Resistance Surveillance System (GLASS) in 2021 and contributed to the WHO GLASS report in 2022; however, country specific data on incidence rate of AMR-BSI were not reported in the GLASS 2022 (13, 14).

There is little information on clinical diagnostic practices; including blood culture utilization rates, in Indonesia (15). Diagnostic stewardship could improve outcome for individual patients, deliver accurate representative surveillance data for treatment

recommendation and AMR infection control strategies (16-18). Blood culture is one of the most critical diagnostic tests to diagnose AMR infections (19, 20). Low blood culture utilization could lead to inappropriate estimation of proportion and incidence rates of AMR infections (21, 22). Therefore, it is crucially important to evaluate blood culture utilization alongside the AMR situation in Indonesia.

The pattern of antimicrobial use (AMU) per AWaRe (Access/Watch/Reserve) categories, antibiotic use practices (such as escalation and de-escalation), and antimicrobial stewardship (AMS) practice in Indonesia have not been reported (14, 23, 24). The WHO AWaRe categories provide a simple framework to group antibiotics into categories for stewardship and clear opportunity to help frame antibiotic policy (25). AMS have been shown to improve rational AMU and clinical outcomes in high-income settings (26-28). Antibiotic consumption was projected to increase in Indonesia between 2010 and 2030, and could lead to the increased AMR incidence rates (21, 30, 31). As part of its National Action Plan for AMR, the Ministry of Health (MoH) launched a standard that included having an ASP as a requirement for hospital accreditation (e.g antimicrobial prescribing guidelines, hospital antibiogram, and conducting periodic antibiotic audits) in 2018 (32), guidelines for hospital ASP implementation (e.g. for structure, tasks and evaluation procedures) in 2021 (33), a national practice guideline on antibiotic prescribing for common infections in 2021 (34). However, evidence is lacking on the current state of implementation of hospital ASPs in Indonesia (35).

I collaborated as a co-author in reporting systematic reviews on AMR among priority pathogens in Indonesia (36), AMU and appropriateness of antibiotic prescribing in Indonesia (24). I collected and verified studies, overseen the data collection and

verification, drafted, critically revised the reviews, accepted responsibility to submit for publication, and gave approval for the final version to be published.

1.2 Antimicrobial resistance among priority pathogens in Indonesia

National and global AMR surveillance systems are important to provide evidence for empiric treatment guidelines, estimate epidemiological burdens across time and space, and assess the impact of public health policies and interventions. However, despite progress, many LMICs have not been able to aggregate data to provide a representative country-level perspective. This systematic review aimed to aggregate all available AMR data in the human health sector published in the peer-reviewed literature in Indonesia since the year 2000, focusing on the twelve GLASS-specific bacterial pathogens, i.e. *Acinetobacter baumannii*, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Neisseria gonorrhoeae*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Salmonella enterica* serovar Typhi and Paratyphi A (typhoidal), *Salmonella spp.* (non-typhoidal), *Shigella spp.*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*, and the relevant pathogen-antimicrobial combinations, both for hospital and community settings.

1.2.1 Methods

1.2.1.1 Search strategy and selection criteria

We reported this systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020 guidelines. The detailed protocol has been registered in PROSPERO database (CRD42019155379). Five databases (PubMed, Embase, *Garba Rujukan Digital*, *Neliti* and *Jurnal Penelitian dan Pengembangan Pelayanan Kesehatan*) have been used to identify eligible articles, published since January 1, 2000 until May 25, 2023. The searches combined the terms

"Indonesia", "antimicrobial or antibiotic resistance", "susceptibility", "resistance", plus each of the bacterial pathogens included in the GLASS-AMR Manual 2.0 (**Table 1.1**) (37). Only peer-reviewed original articles published in English or Indonesian were included. We included reports on bacterial antibiotic susceptibility testing (AST) on isolates from human specimens collected in Indonesia (for both illness or carriage), and reporting on at least one GLASS bacterial pathogen. We excluded reports which (1) written as reviews, editorials, conference proceedings or individual case reports; (2) completed data collection before 2000; (3) did not report phenotypic AST data for at least one GLASS pathogen-antimicrobial combination; (4) had missing numerators/denominators of AST data that could not be calculated from raw data; (5) reported fewer than 10 isolates tested for AST; (6) did not separate Indonesian and non-Indonesian data. Two reviewers independently screened titles and abstracts of all articles, removed duplicate articles and/or datasets, and judged full-text articles for relevance and quality. A senior reviewer resolved any disagreements.

Table 1.1 Search strategy

Database	**Search keywords**
PubMed	(("indonesia"[MeSH Terms] OR "indonesia"[All Fields] OR "indonesia s"[All Fields] OR "indonesias"[All Fields]) AND ("drug resistance"[MeSH Terms] OR "antimicrobial resistance"[All Fields] OR "antibiotic resistance"[All Fields] OR "susceptibility"[All Fields] OR "resistance"[All Fields]) AND ("*Escherichia coli*"[MeSH Terms] OR "*Klebsiella*"[MeSH Terms] OR "Acinetobacter"[MeSH Terms] OR "Staphylococcus aureus"[MeSH Terms] OR "*Streptococcus pneumoniae*"[MeSH Terms] OR "Salmonella"[MeSH Terms] OR "Shigella"[MeSH Terms] OR "*Neisseria gonorrhoeae*"[MeSH Terms] OR "*Pseudomonas aeruginosa*"[MeSH Terms] OR "Neisseria meningitidis"[MeSH Terms] OR "*Haemophilus influenza*e"[MeSH Terms] OR "MRSA"[All Fields] OR "methicillin resistant- Staphylococcus aureus"[All Fields] OR "ESBL"[All Fields] OR "extended spectrum beta-lactamases"[All Fields])) AND (2000:2023[pdat])
Embase	#1. 'Indonesia'/exp #2. 'drug resistance'/exp #3. "antimicrobial resistance" OR "antibiotic resistance" OR "susceptibility" OR "resistance" #4. #2 OR #3

	#5. '*Escherichia coli*'/exp OR '*Escherichia coli*' OR '*Klebsiella*'/exp OR '*Klebsiella*' OR 'acinetobacter'/exp OR 'acinetobacter' OR '*Neisseria gonorrhoeae*'/exp OR '*Neisseria gonorrhoeae*' OR '*Pseudomonas aeruginosa*'/exp OR '*Pseudomonas aeruginosa*' OR 'salmonella'/exp OR 'salmonella' OR 'shigella'/exp OR 'shigella' OR 'staphylococcus aureus'/exp OR 'staphylococcus aureus' OR '*Streptococcus pneumoniae*'/exp OR '*Streptococcus pneumoniae*' OR 'neisseria meningitidis'/exp OR 'neisseria meningitidis' OR '*Haemophilus influenza*e'/exp OR '*Haemophilus influenza*e' #6. "MRSA" OR "methicillin resistant- Staphylococcus aureus" OR "ESBL" OR "extended spectrum beta-lactamases" #7. #5 OR #6 #8. #1 AND #4 AND #7 #9. #8 AND (2000:py OR 2001:py OR 2002:py OR 2003:py OR 2004:py OR 2005:py OR 2006:py OR 2007:py OR 2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py OR 2019:py OR 2020:py OR 2021:py OR 2022:py OR 2023:py)
Garba Rujukan Digital (GARUDA)	#1. antibiotic resistance, by title , from: 2000 , to: 2023 [66 hits] #2. antimicrobial resistance, by title , from: 2000 , to: 2023 [42 hits] #3. resistensi antibiotik, by title , from: 2000 , to: 2023 [119 hits] #4. resistensi antimikroba, by title , from: 2000 , to: 2023 [13 hits]
Neliti	#1. "antibiotic resistance" (filter: tanggal: 2000-2023) [133 hits] #2. "antimicrobial resistance" (filter: tanggal: 2000-2023) [133 hits] #3. "resistensi antibiotik" (filter: tanggal: 2000-2023) [120 hits] #4. "resistensi antimikroba" (filter: tanggal: 2000-2023) [380 hits]
Jurnal Penelitian dan Pengembangan Pelayanan Kesehatan	#1. antibiotic resistance [6 hits] #2. antimicrobial resistance [2 hit] #3. resistensi antibiotik [7 hits] #4. resistensi antimikroba [3 hit]

1.2.1.2 Risk of bias and quality assessment

Because the included studies were neither randomised controlled trials nor comparative studies, traditional methods for assessment of risk of bias were not applicable. To ensure quality, we excluded studies that did not report on an essential set of Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist core items (**Table 1.2**). We additionally recorded the quality of reporting for the 13 mandatory items of the Microbiology Investigation Criteria for Reporting Objectively (MICRO) checklist (**Table 1.3**) (38).

Table 1.2 Checklist of selected items from the STROBE statement

Section		**Item No**	**Recommendation**
Methods	Study design	4	Present key elements of study design
	Setting	5	Describe study's setting (hospital or community), geographic location, and period of data collection
Results	Descriptive data	14	Denominators and numerators of susceptible or non-susceptible samples (or can be calculated from data presented)
	Outcome data	15	*Cohort study*—Report numbers of outcome events or summary measures over time *Case-control study*—Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study*—Report numbers of outcome events or summary measures

Table 1.3 MICRO checklist of 13 mandatory items for reporting human clinical microbiological data in the 99 included studies

First author, Year of publication	1.Specimen type	2.Sampling period	3.Sampling strategy	5.Geographical setting	6.Clinical setting	8.Target organism identification	9.Antimicrobial susceptibility testing	11.AMR definitions	12.External QA	14.Duplicate and sequential isolates	15.Population	16.Denominators	18.Resistance proportions for single agent/class	Number of items missing in each study
Adhima, 2022 **(39)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Afifurrahman, 2014 **(40)**	●	●	●	●	●	●	○	○	○	○	○	●	●	5
Akbar, 2014 **(41)**	●	●	●	●	●	●	○	○	○	○	●	●	●	4
Amanda, 2020 **(42)**	●	●	●	●	●	●	●	●	○	○	●	●	●	2
Anggraini, 2022 **(43)**	●	●	●	●	●	●	●	●	○	○	○	●	●	3
Ariana, 2020 **(44)**	○	●	●	●	●	○	○	○	○	○	○	●	●	7
Artono, 2022 **(45)**	●	●	●	●	●	●	●	○	○	●	●	●	●	2
Azwar, 2012 **(46)**	●	●	●	●	●	○	○	○	○	○	●	●	●	5
Bukitwetan, 2007 **(47)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Chudlori, 2012 **(48)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Chung, 2011 **(49)**	●	●	●	●	●	●	●	●	○	○	●	●	●	2
Deurenberg, 2009 **(50)**	●	●	●	●	●	●	●	○	○	○	○	●	●	4
Devian, 2022 **(51)**	●	●	●	●	●	●	○	○	○	○	●	●	●	4
Donegan, 2006 **(52)**	●	●	●	●	●	●	●	●	○	○	●	●	●	2
Dwipoerwantoro, 2005 **(53)**	●	●	●	●	●	●	○	○	○	○	●	●	●	4
Fabian, 2020 **(54)**	○	●	○	●	○	○	○	●	○	○	○	●	●	8

First author, Year of publication	1.Specimen type	2.Sampling period	3.Sampling strategy	5.Geographical setting	6.Clinical setting	8.Target organism identification	9.Antimicrobial susceptibility testing	11.AMR definitions	12.External QA	14.Duplicate and sequential isolates	15.Population	16.Denominators	18.Resistance proportions for single agent/class	Number of items missing in each study
Farida, 2013 **(55)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Farida, 2014 **(56)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Fathin, 2022 **(57)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Firdiana, 2016 **(58)**	●	●	●	●	○	○	●	●	○	○	●	●	●	4
Hananta, 2016 **(59)**	●	●	●	●	●	●	●	●	●	○	●	●	●	1
Harimurti, 2016 **(60)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Harimurti, 2021 **(61)**	●	●	●	●	●	●	●	●	○	●	●	●	●	1
Harnanik, 2005 **(62)**	●	●	○	●	●	●	●	○	○	○	○	●	●	5
Herdiyanti, 2019 **(63)**	●	●	●	●	●	○	○	○	○	○	●	●	●	5
Herwana, 2010 **(64)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Hidayah, 2020 **(65)**	●	●	●	●	●	●	○	○	○	●	●	●	●	3
Indraningrat, 2022 **(66)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Indri, 2015 **(67)**	●	●	●	●	●	○	○	○	○	○	●	●	●	5
Indriatmi, 2019 **(68)**	●	●	●	●	●	●	●	●	○	○	●	●	●	2
Karmila, 2022 **(69)**	●	●	●	●	●	●	●	●	○	○	●	●	●	2
Kartasasmita, 2002**(70)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Khalilullah, 2011 **(71)**	●	●	●	●	●	●	●	○	○	○	○	●	●	3
Kitagawa, 2018 **(72)**	●	●	●	●	●	●	●	○	○	○	●	●	●	4

First author, Year of publication	1.Specimen type	2.Sampling period	3.Sampling strategy	5.Geographical setting	6.Clinical setting	8.Target organism identification	9.Antimicrobial susceptibility testing	11.AMR definitions	12.External QA	14.Duplicate and sequential isolates	15.Population	16.Denominators	18.Resistance proportions for single agent/class	Number of items missing in each study
Lestari, 2008 **(73)**	●	●	●	●	●	●	●	○	○	○	○	●	●	4
Lestari, 2010 **(74)**	●	●	●	●	●	●	●	●	○	○	●	●	●	2
Lestari, 2013 **(75)**	●	●	●	●	●	○	○	○	○	○	○	●	●	6
Lugito, 2017 **(76)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Mayasari, 2017 **(77)**	●	●	○	●	●	●	○	○	○	○	●	●	●	5
Meriyani, 2021 **(78)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Meta, 2014 **(79)**	●	●	●	●	●	●	○	○	○	○	●	●	●	4
Moehario, 2009 **(80)**	●	●	●	●	●	○	●	○	○	○	●	●	●	4
Moehario, 2020 **(81)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Muktiarti, 2021 **(82)**	●	●	●	●	○	●	●	●	○	●	○	●	●	3
Murni, 2016 **(83)**	●	●	●	●	●	●	●	●	○	●	●	●	●	1
Nathania, 2022 **(84)**	●	●	○	●	○	●	●	○	○	○	○	●	●	6
Nirwati, 2018 **(85)**	●	●	○	●	●	●	●	○	○	○	●	●	●	4
Nirwati, 2019 **(86)**	●	●	○	●	●	●	●	●	○	○	●	●	●	3
Nur, 2016 **(87)**	●	●	●	●	●	●	●	●	○	○	●	●	●	2
Oyofo, 2002 **(88)**	●	●	●	●	●	●	○	○	○	○	●	●	●	4
Parut, 2015 **(89)**	●	●	●	●	●	●	●	●	○	○	●	●	●	2
Patilaya, 2019 **(90)**	●	●	○	●	○	●	●	●	○	○	○	●	●	5

First author, Year of publication	1.Specimen type	2.Sampling period	3.Sampling strategy	5.Geographical setting	6.Clinical setting	8.Target organism identification	9.Antimicrobial susceptibility testing	11.AMR definitions	12.External QA	14.Duplicate and sequential isolates	15.Population	16.Denominators	18.Resistance proportions for single agent/class	Number of items missing in each study
Pelegrin, 2020 **(91)**	●	●	●	●	●	●	●	○	○	○	○	●	●	4
Permana, 2022 **(92)**	●	●	●	●	●	●	●	○	○	●	●	●	●	2
Prabowo, 2012 **(93)**	●	●	○	●	●	●	●	○	○	○	●	●	●	4
Punjabi, 2013 **(94)**	●	●	●	●	●	●	●	○	●	●	●	●	●	1
Purba, 2019 **(95)**	●	●	●	●	●	○	○	●	○	○	●	●	●	4
Puspandari, 2016 **(96)**	●	○	●	●	●	●	●	●	○	○	●	●	●	3
Rachman, 2016 **(97)**	●	●	●	●	●	○	○	○	○	○	○	●	●	6
Radji, 2011 **(98)**	●	●	●	●	●	○	●	○	○	○	○	●	●	5
Radji, 2014 **(99)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Rahman, 2015 **(100)**	●	●	●	●	●	●	○	○	○	○	○	●	●	5
Ramdhani, 2022 **(101)**	○	●	○	●	●	●	●	●	○	○	○	●	●	5
Rosana, 2020a **(102)**	●	●	●	●	●	●	●	○	○	●	●	●	●	2
Rosana, 2020b **(103)**	●	●	●	●	●	●	●	○	○	○	○	●	●	4
Rosyid, 2021 **(104)**	●	●	●	●	●	○	●	●	○	●	●	●	●	2
Safari, 2014 **(105)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Safari, 2015 **(106)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Safari, 2020 **(107)**	●	●	●	●	○	●	●	○	○	○	●	●	●	4
Safari, 2022a **(108)**	●	●	●	●	●	●	●	○	○	○	○	●	●	4

First author, Year of publication	1.Specimen type	2.Sampling period	3.Sampling strategy	5.Geographical setting	6.Clinical setting	8.Target organism identification	9.Antimicrobial susceptibility testing	11.AMR definitions	12.External QA	14.Duplicate and sequential isolates	15.Population	16.Denominators	18.Resistance proportions for single agent/class	Number of items missing in each study
Safari, 2022b **(109)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Sahara, 2023 **(110)**	●	●	●	●	●	●	●	○	○	○	○	●	●	4
Saharman, 2018 **(111)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Saharman, 2019 **(112)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Saharman, 2020 **(113)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Said, 2017 **(114)**	●	●	●	●	●	●	●	●	○	○	○	●	●	3
Salsabila, 2021 **(115)**	●	●	○	●	●	●	●	●	○	●	●	●	●	2
Santoso, 2022 **(116)**	●	●	●	●	●	●	●	●	○	●	●	●	●	1
Saputro, 2013 **(117)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Sari, 2015 **(118)**	●	●	○	●	●	○	○	○	○	○	●	●	●	6
Sari, 2017 **(119)**	●	●	●	●	●	○	○	○	○	○	●	●	●	5
Setyati, 2012 **(120)**	●	●	●	●	●	●	●	○	○	○	○	●	●	4
Sholeh, 2020 **(121)**	●	●	●	●	●	●	●	○	○	●	●	●	●	2
Sinto, 2022 **(122)**	●	●	●	●	●	●	●	●	●	●	●	●	●	0
Soedarmono, 2022 **(123)**	●	●	●	●	●	●	●	○	○	○	●	●	●	3
Subagdja, 2022 **(124)**	○	●	●	●	●	●	●	○	○	○	●	●	●	4
Sugianli, 2017 **(125)**	●	●	●	●	●	●	●	●	●	○	●	●	●	1
Suranadi, 2021 **(126)**	●	●	●	●	●	●	●	○	○	●	●	●	●	2

First author, Year of publication	1.Specimen type	2.Sampling period	3.Sampling strategy	5.Geographical setting	6.Clinical setting	8.Target organism identification	9.Antimicrobial susceptibility testing	11.AMR definitions	12.External QA	14.Duplicate and sequential isolates	15.Population	16.Denominators	18.Resistance proportions for single agent/class	Number of items missing in each study
Sutrisna, 2006 **(127)**	●	●	●	●	●	●	●	○	○	○	○	●	●	4
Tan, 2021 **(128)**	●	●	●	●	●	●	●	○	○	●	●	●	●	2
Tandiono, 2022 **(129)**	●	●	●	●	●	○	●	●	○	○	●	●	●	3
Tauran, 2022 **(130)**	●	●	●	●	●	●	●	●	○	●	●	●	●	1
Tjaniadi, 2003 **(131)**	●	●	●	●	●	●	●	●	○	●	●	●	●	1
Tjoa, 2013 **(132)**	●	●	●	●	●	●	●	○	○	○	○	●	●	4
Wang, 2011 **(133)**	●	●	●	●	●	○	●	●	○	○	○	●	●	4
Wardhana, 2017 **(134)**	●	●	●	●	●	○	○	○	○	○	●	●	●	5
Wijaksana, 2019 **(135)**	●	●	●	●	●	○	○	○	○	○	●	●	●	5
Wikaningtyas, 2015 **(136)**	●	●	●	●	●	○	●	○	○	○	○	●	●	5
Yanagi, 2009 **(137)**	●	●	●	●	●	●	●	●	○	○	○	●	●	3
Number of studies with item missing	4	1	11	0	6	19	21	68	95	82	27	0	0	-
% of studies with item missing	4.0 %	1.0%	11.1%	0.0%	6.1%	19.2%	21.2%	68.7%	96.0%	82.8%	27.3%	0.0%	0.0%	-

Abbreviations: AMR, antimicrobial resistance; MICRO, Microbiology Investigation Criteria for Reporting Objectively; QA, quality assurance.

1.2.1.3 Data extraction

Two reviewers extracted data onto a predefined extraction form. We extracted and tabulated data on general article information (first author, year of publication), and author-reported summary estimates (not individual-level data) of the AST results for relevant pathogen-antimicrobial combinations (GLASS and additional clinically relevant combinations) (**Table 1.4**), specimen type (e.g. blood, urine, stool), study population (health status, age group, sex), health care setting (hospital or community), geographic location, period of data collection, and laboratory method information. Studies were classified as community setting if they were performed in communities, primary care, and outpatient clinics. Studies were classified as hospital setting if they were performed among mixed or unspecified inpatients and outpatients. For hospital-setting studies, as per GLASS, we defined community acquired infection (CAI) for patients in the hospital less (or more) than the first two calendar days of admission when the first specimen culture positive for a pathogen were taken, with calendar day one equal to the day of admission. Author-reported AST interpretative criteria were extracted (e.g. Clinical and Laboratory Standards Institute [CLSI], European Committee on Antimicrobial Susceptibility Testing [EUCAST]). When reported, we considered intermediate susceptibility as resistant. When applicable, we calculated resistance proportions as the inverse of susceptibility. Where AST results were given for more than one for a class of antibiotic (e.g. third-generation cephalosporins, fluoroquinolones, group 2 carbapenems [doripenem, imipenem, meropenem]), the highest individual-antibiotic resistance proportion was selected to represent class resistance, except for the aminoglycosides since gentamicin, amikacin and tobramycin show markedly different resistance patterns. Resistance of *S. aureus* to cefoxitin, methicillin and/or oxacillin was considered methicillin resistant- *S. aureus* (MRSA).

Table 1.4 Pathogen-antimicrobial combinations included in the review

Antibiotics		*A. baumannii*	*E. coli*	*H. influenzae*	*K. pneumoniae*	*N. gonorrhoeae*	*N. meningitidis*	*P. aeruginosa*	*Salmonella* spp.	*Salmonella enterica serovar* Typhi and Paratyphi A	*Shigella* spp.	*S. aureus*	*S. pneumoniae*
Aminoglycosides	Amikacin	●○	●○		●○			●○					
	Gentamicin	●○	●○		●○	●○		●○					
	Tobramycin							●○					
Carbapenems	Doripenem	●○	●○		●○			●○	●○				●
	Ertapenem		●○		●○				●○				
	Imipenem	●○	●○		●○			●○	●○				●○
	Meropenem	●○	●○		●○			●○	●○				●○
Second generation cephalosporins	Cefoxitin											●○	
Third-generation cephalosporins	Ceftriaxone		●○	●○	●○	●○	●		●○	●○	●○		●○
	Ceftazidime		●○		●○			●○	●○	●○	●		
	Cefotaxime		●○	●○	●○	●	●		●○	●○	●○		●○
	Cefixime					●○							
Fourth-generation cephalosporins	Cefepime		●○		●○								
Fluoroquinolones	Ciprof-loxacin		●○		●○	●○	●	●○	●○	●○	●○		
	Levof-loxacin		●○	●○	●○		●	●○	●○	●○	●		
	Moxif-loxacin		●○		●○				●	●○	●		
Macrolides	Azithro-mycin					●○				●	●○		
	Erythro-mycin											●○	●○

Antibiotics		*A. baumannii*	*E. coli*	*H. influenzae*	*K. pneumoniae*	*N. gonorrhoeae*	*N. meningitidis*	*P. aeruginosa*	*Salmonella* spp.	*Salmonella enterica serovar* Typhi and Paratyphi A	*Shigella* spp.	*S. aureus*	*S. pneumoniae*
Penicillin	Amoxicillin-clavulanic- acid			●○									
	Ampicillin		●○	●○						●○			
	Oxacillin											●○	●○
	Penicillin G					●○	●						●○
	Mecillinam		●		●								
	Piperacillin/Tazobactam							●○					
Polymyxin	Colistin	●○	●○		●○			●○					
Sulfonamides	Co-trimoxazole		●○	●○	●○				●○	●○	●○		●○
Tetracyclines	Tigecycline	●○											
	Minocycline	●											
Others	Chloram-phenicol									●○			
	Clindamycin											●○	
	Fosfomycin		●○		●○								
	Nitrofu-rantoin		●○										
	Rifampicin						●						
	Spectino-mycin					●○							
	Vancomycin											●○	

Pathogen-antimicrobial combinations: ● Included in GLASS-AMR 2.0 manual; ● Additional combinations included in the review; ○ Data available in the studies included in the review

1.2.1.4 Statistical analysis

We considered quantitative meta-analysis inappropriate because of a paucity of data and substantial heterogeneity in study design, populations studied, period of data collection, and type of specimens collected. We reported the weighted mean proportion of resistant isolates for hospital and community settings, calculated by adding the number of resistant isolates divided by the total number of isolates that underwent AST for each included study. We calculated 95% confidence intervals using the Clopper-Pearson exact method when the number of studies for a pathogen-antimicrobial combination was more than one. In addition, when sufficient data were available, we analysed AMR time trends for bacterial pathogens and antimicrobial combinations, aggregated per 6-year intervals from 2000 to 2023. Data management was performed using Microsoft Excel® for Microsoft 365 MSO (Microsoft Corp., Redmond, WA) and visualisations using GraphPad Prism version 9.5.0 (GraphPad Software, Boston, MA).

1.2.2 Results

1.2.2.1 Study characteristics

The search strategy gave 1,829 hits. After removed duplicate articles, screened title and abstract, 264 articles remained. After full-text screening and quality assessment, 99 (37.5%) reports were included (**Figure 1.1**). We summarized characteristics of included studies in **Table 1.5** and **Table 1.6.** Most studies were conducted in hospital settings (70.7%, 70/99), 24 (24.2%) studies in community settings, and five (5.1%) in both. Of the 70 hospital-based reports, only nine specified isolates associated with HAIs and three with CAIs. Most studies originated from Java Island (74.7%, 74/99). 37 reports (37.4%) included only adults, 24 (24.2%) both adults and children, 19 (19.2%) only children, and 19 (19.2%) did not specify age groups.

Figure 1.1 PRISMA flow diagram. Reproduced from (36)

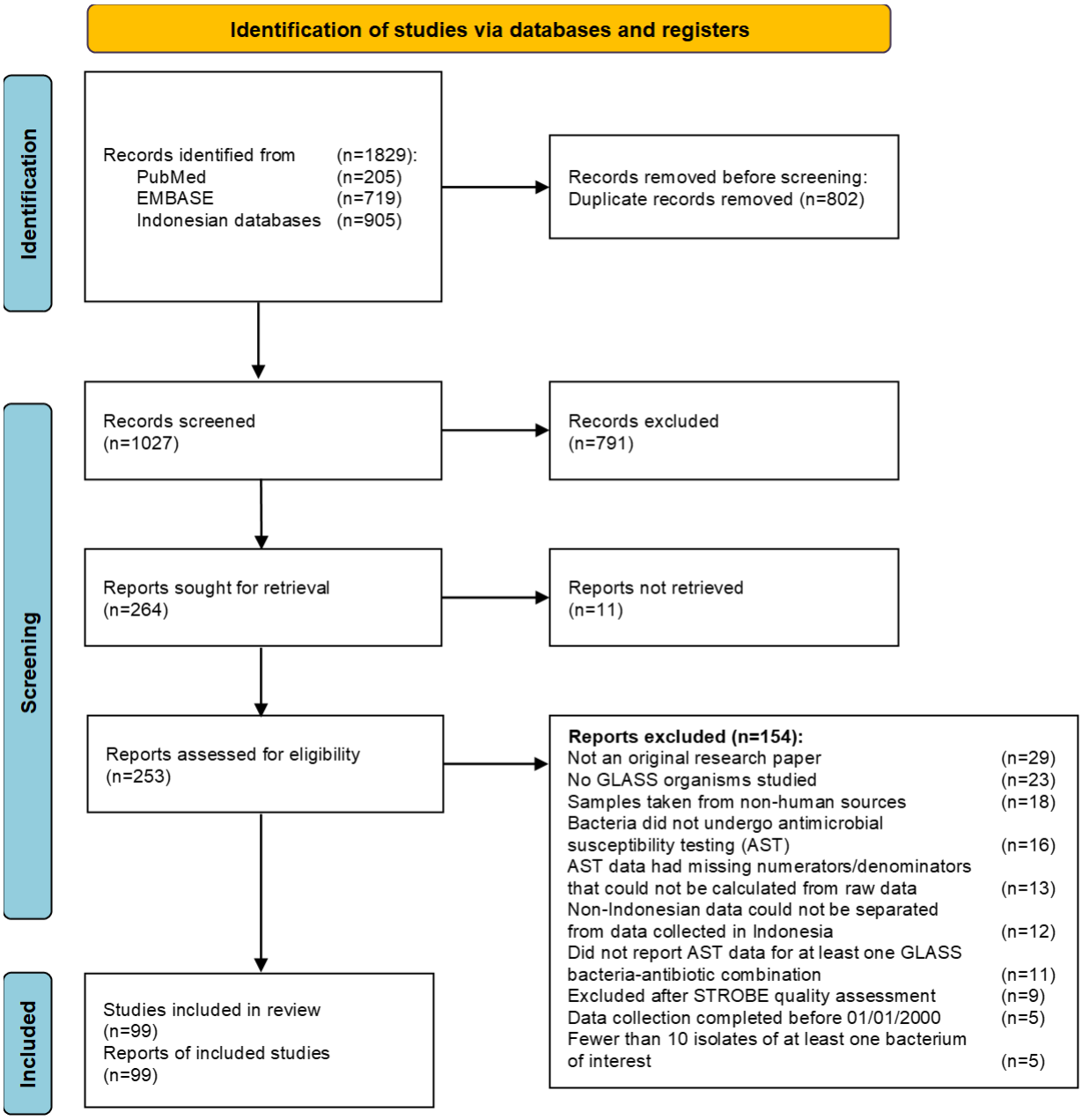


Table 1.5 Characteristics of included reports

Total reports	**N=99**	**%**
GLASS bacterial pathogens		
Klebsiella pneumoniae	41	41.4%
Escherichia coli	40	40.4%
Pseudomonas aeruginosa	31	31.3%
Acinetobacter baumannii	26	26.3%
Staphylococcus aureus	25	25.3%
Streptococcus pneumoniae	18	18.2%
Salmonella enterica serovar Typhi/Paratyphi A	7	7.1%
Neisseria gonorrhoeae	6	6.1%
Shigella spp.	5	5.1%
Haemophilus influenzae	3	3.0%
Salmonella spp.	3	3.0%
Neisseria meningitidis	0	0.0%
Specimen type		
Blood	31	31.3%
Lower respiratory tract	28	28.3%
Urine	24	24.2%
Stool/rectal swab	9	9.1%
Urethral, cervical, rectal, pharyngeal swabs	6	6.1%
Cerebrospinal fluid	3	3.0%
Other[a]	46	46.5%
Phenotypic AST method		
Diffusion methods	59	59.6%
Automated system (Phoenix, Vitek)	26	26.3%
Dilution methods (micro-, macro-, agar dilution)	13	13.1%
MALDI-TOF MS	4	4.0%
E-test	3	3.0%
Chromogenic agar	1	1.0%
Not specified	15	15.2%
AST interpretative criteria		
CLSI	58	58.6%
EUCAST	9	9.1%
Not specified	32	32.3%
Study design		
Cross-sectional	51	51.5%
Retrospective	36	36.4%
Prospective	12	12.1%
Geographical location[b]		
Java	74	74.7%
Sumatra	19	19.2%
Bali	9	9.1%
Kalimantan	6	6.1%
Sulawesi	4	4.0%

Total reports	**N=99**	**%**
Papua	1	1.0%
Study setting		
Hospitals	70	70.7%
Communities	24	24.2%
Mixed	5	5.1%
Year of publication		
2018-2023	46	46.5%
2012-2017	35	35.4%
2006-2011	13	13.1%
2000-2005	5	5.1%
Patient age groups		
Adults	37	37.4%
Adults and children	24	24.2%
Children	19	19.2%
Not specified	19	19.2%
Patient sex		
Females and males	60	60.6%
Female only	5	5.1%
Not specified	34	34.3%

Total N for some characteristics is greater than N=99 because some reports were included in more than category, i.e. for GLASS bacterial pathogens (43 reports), specimen type (22), phenotypic AST method (18), geographic location (7), and AST interpretative criteria (3).

[a]Other specimen types include pus (14 studies, 14.1%), nasopharyngeal swabs (13 studies, 13.1%), wound/ulcer swabs (9 studies, 9.1%), throat swab (6 studies, 6.1%), tissue samples (4 studies, 4.0%), nasal swabs (3 studies, 3.0%), pleural fluid (3 studies, 3.0%), middle ear fluid (1 study, 1.0%), ear swab (1 study, 1.0%), vaginal swab (1 study, 1.0%), and unspecified (2 study, 2.0%). One study may list multiple other specimen types.

[b]There were no reports originating from Maluku or Nusa Tenggara.

Abbreviations: AST, antimicrobial susceptibility testing; CLSI, Clinical and Laboratory Standards Institute; EUCAST, European Committee on Antimicrobial Susceptibility Testing; GLASS, Global Antimicrobial Resistance and Use Surveillance System; MALDI-TOF MS, matrix-assisted laser desorption/ionization coupled with time-of-flight mass spectrometer

Table 1.6 Summary of individual reports included in the review

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
Adhima, 2022 **(39)**	Retrospective	Hospital	2019	Surabaya	Adults and children	M+F	UTI	Urine	*A. baumannii* (5) *E. coli* (40) *K. pneumoniae* (12) *P. aeruginosa* (14) *S. aureus* (3) *S. pneumoniae* (138)	Automated system (Phoenix, Vitek), microdilution Reported MIC	CLSI (NS)
Afifurrahman, 2014 **(40)**	Cross-sectional	Hospital	2012-2013	Palembang	NS	NS	NS	Blood, exudative/ transudative fluids, lower respiratory tract, pus, urine, swabs, others	*S. aureus* (1118)	NS	NS
Akbar, 2014 **(40)**	Retrospective	Hospital	2018	Pekanbaru	Adults	M+F	Diabetic ulcers	Wound swab	*A. baumannii* (8) *K. pneumoniae* (138) *E. coli* (4) *P. aeruginosa* (138)	NS	NS
Amanda, 2021 **(42)**	Cross-Sectional	Hospital	2018-2019	Jakarta	Adults	M+F	CAP	Lower respiratory tract	*S. pneumoniae* (14)	Microdilution Reported MIC	CLSI (M100-S29)
Anggraini, 2022 **(43)**	Cross-sectional	Hospital	2015-2019	Riau	Children	NS	Patients in neonatal ICU with a bacterial infection	Blood, lower respiratory tract, pus, urine, and others	*A. baumannii* (1263)	Automated system (Vitek 2)	NS

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
Ariana, 2020 **(44)**	Retrospective	Hospital	2018	Surabaya	NS	NS	UTI	NS	*E. coli* (149)	NS	NS
Artono, 2022 **(45)**	Retrospective	Hospital	2019-2020	Surabaya	Adults and children	M+F	Chronic suppurative otitis media patients who had undergone mastoidectomy	Ear swab	*E. coli* (138) *P. aeruginosa* (15)	Disc diffusion	CLSI (NS)
Azwar, 2012 **(46)**	Cross-sectional	Hospital	2010	Aceh	NS	NS	Chronic cough	Lower respiratory tract	*K. pneumoniae* (11) *P. aeruginosa* (5) *S. aureus* (9)	NS	NS
Bukitwetan, 2007 **(47)**	Cross-sectional	Community	2003-2005	Jakarta	Children	NS	Diarrhoea	Stool/rectal swab	*Salmonella* spp. (56)	Disc diffusion	CLSI (M02-A6, M100-S11)
Chudlori, 2012 **(48)**	Retrospective	Hospital	2012	Surakarta	Adults and children	M+F	NS	Pus	*S. aureus* (138)	Disc diffusion	CLSI (NS)
Chung, 2011 **(49)**	Prospective	Hospital	2008-2009	Jakarta, Surabaya, Semarang	Adults	M+F	Hospital-acquired or ventilator-acquired pneumonia	Blood, tracheal or bronchial aspirates, sputum	*K. pneumoniae (4)*	Microdilution	CLSI
Deurenberg, 2009 **(50)**	Cross-sectional	Community	2006	Yogyakarta	NS	M+F	Patients in ENT outpatient clinic	Nasal swabs	*S. aureus* (62)	Microdilution	CLSI (M100-S12)

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
Devian, 2022 **(51)**	Retrospective	Hospital	2021	Bali	Adults and children	M+F	Patients in ICU receiving ventilator treatment	Lower respiratory tract, blood	*A. baumannii* (37) *K. pneumoniae* (31) *P. aeruginosa* (41)	NS	CLSI (NS)
Donegan, 2006 **(52)**	Cross-sectional	Community	2004	Bali	Adults	F	Female sex workers attending STI clinic	Urethral, cervical, pharyngeal and rectal swabs	*N. gonorrhoeae* (147)	Agar dilution, disc diffusion Reported MIC	CLSI (M07-A10, M100-S15)
Dwipoerwantoro, 2005 **(52)**	Cross-sectional	Hospital	2001-2002	Jakarta	Children	M+F	Dysentry	Stool/rectal swab	*Shigella* spp. (24)	Chromogenic agar	NS
Fabian, 2020 **(54)**	Retrospective	Hospital	2016	Surabaya	Adults and children	NS	NS	Blood	*A. baumannii* (164) *P. aeruginosa* (63)	NS	NS
Farida, 2013 **(55)**	Cross-sectional	Community	2010	Semarang	Adults and children	M+F	Population-based survey, among healthy persons	Nasopharyngeal swab	*K. pneumoniae* (54)	Automated system (Vitek 2)	NS
Farida, 2014 **(56)**	Cross-sectional	Community	2010	Semarang	Adults and children	M+F	Population-based survey among healthy persons	Nasopharyngeal swab	*S. pneumoniae* (142)	Disc diffusion, E-test	EUCAST (v2.0)
Fathin, 2022 **(57)**	Retrospective	Hospital	2017-2018	Medan	Adults and children	M+F	Pneumonia	Lower respiratory tract	*A. baumannii* (10) *E. coli* (138) *K. pneumoniae* (13)	NS	NS

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
									P. aeruginosa (138)		
Firdiana, 2016 **(58)**	Cross-sectional	Community	2016	Semarang	Adults	F	Female sex workers with endocervical discharge	Urethral, cervical, pharyngeal and rectal swabs	*N. gonorrhoeae* (26)	Disc diffusion	NS
Hananta, 2016 **(59)**	Cross-sectional	Community	2014	Bali, Jakarta, Yogyakarta	Adults	M+ F+ Transwomen	Persons attending STI services	Urethral, cervical, pharyngeal and rectal swabs	*N. gonorrhoeae* (79)	Disc diffusion, E-test Reported MIC	EUCAST (v3.1)
Harimurti, 2016 **(60)**	Cross-sectional	Community	2012	Jakarta	Adults	M+ F	People living with HIV	Nasopharyngeal swab	*S. pneumoniae* (138)	Disc diffusion	CLSI (M100-S16)
Harimurti, 2021 **(139)**	Prospective	Community	2015	Banda Aceh, Banjarmasin, Bekasi, Gorontalo, Jakarta, Makassar, Medan, Palangkaraya, Surabaya	NS	M+ F	Pre-travel screening before Hajj	Nasopharyngeal swab	*S. pneumoniae* (70)	Disc diffusion	CLSI (M100-S26)
Harnanik, 2005 **(62)**	Cross-sectional	Hospital	2005	Yogyakarta	NS	NS	NS	Urine	*E. coli* (138)	Disc diffusion	NS
Herdiyanti, 2019 **(63)**	Retrospective	Hospital	2017	Surabaya	Adults	M+ F	UTI	Urine	*E. coli* (127) *K. pneumoniae* (36)	NS	NS

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
Herwana, 2010 **(64)**	Cross-sectional	Community	2005-2007	Jakarta	Children	NS	Diarrhoea	Stool/rectal swab	*Shigella* spp. (57)	Disc diffusion	CLSI (M100-S11)
Hidayah, 2020 **(65)**	Cross-sectional	Hospital	2017	Bojonegoro	Adults	M+F	Hospitalised patients (internal medicine and surgery)	Rectal swab	*E. coli* (80)	Disc diffusion	NS
Indraningrat, 2022 **(66)**	Retrospective	Hospital	2018	Bali	Adults and children	M+F	NS	Blood, lower respiratory tract, pus, urine, and others	*A. baumannii* (5) *E. coli* (15) *K. pneumoniae* (8) *S. aureus* (8)	NS	NS
Indri, 2015 **(67)**	Cross-sectional	Hospital	2012	Palembang	Children	M+F	UTI	Urine	*E. coli* (118) *K. pneumonia* (56) *P. aeruginosa* (35) *S. aureus* (65)	NS	NS
Indriatmi, 2019 **(68)**	Cross-sectional	Community	2018	Jakarta	Adults	M+F	Persons attending sexual health clinic	Urethral, cervical, pharyngeal and rectal swabs	*N. gonorrhoeae* (35)	Automated system (Vitek 2), disc diffusion	CLSI (M100-S27)
Karmila, 2020 **(69)**	Retrospective	Hospital	2016-2018	Palembang	Children	M+F	Neonates with clinical sepsis	Blood	*S. aureus* (5)	Automated system (Vitek 2)	CLSI (M100-S24)
Kartasasmita, 2002 **(70)**	Cross-sectional	Community	1999-2000	Bandung	Children	M+F	Pneumonia	Nasopharyngeal swab	*S. pneumoniae* (120)	Disc diffusion	NS
Khalilullah, 2011 **(71)**	Cross-sectional	Hospital	2010	Aceh	NS	NS	UTI	Urine	*A. baumannii* (15) *E. coli* (37)	Disc diffusion	CLSI (NS)

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
									K. pneumoniae (33) *P. aeruginosa* (12) *S. aureus* (4)		
Kitagawa, 2018 **(72)**	Retrospective	Hospital	2014	Surabaya	Adults and children	NS	UTI	Urine	*E. coli* (214) *K. pneumoniae* (76) *P. aeruginosa* (27)	Disc diffusion	CLSI (M02-A7)
Lestari, 2008 **(73)**	Cross-sectional	Hospital and community	2001-2002	Semarang and Surabaya	NS	NS	Screening of patients admitted to or discharged from hospital, their relatives, and patients visiting primary health centres	Rectal swab	*E. coli* (3284)	Disc diffusion	CLSI (M02-A7)
Lestari, 2010 **(74)**	Cross-sectional	Hospital and community	2001-2002	Surabaya and Semarang	Adults and children	M+F	Screening of patients admitted to or discharged from hospital, their relatives, and patients visiting	Nasal swab	*S. aureus* (361)	Disc diffusion	CLSI (M02-A7)

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
							primary health centres				
Lestari, 2013 **(75)**	Cross-sectional	Hospital	2011	Jakarta	NS	M+F	Patients in ICU	Blood and lower respiratory tract	*A. baumannii* (138) *E. coli* (3) *K. pneumoniae* (9) *P. aeruginosa* (19)	NS	NS
Lugito, 2017 **(76)**	Retrospective	Hospital	2011-2015	Banten	Adults and children	M+F	NS	Blood	*Salmonella enterica serovar* Typhi/Paratyphi *A.*(168)	Agar dilution, automated system (Vitek 2) Reported MIC	CLSI (M100-S23)
Mayasari, 2017 **(77)**	Retrospective	Hospital	2017	Banjarmasin	Adults	M+F	NS	Lower respiratory tract and pleural fluid	*K. pneumoniae* (25)	Agar dilution, automated system (Vitek 2)	NS
Meriyani, 2021 **(78)**	Retrospective	Hospital	2017-2019	Bali	Adults and children	M+F	Patients in ICU	Blood, lower respiratory tract, pus, and urine	*A. baumannii* (106) *E. coli* (40) *K. pneumoniae* (68) *P. aeruginosa* (33)	Disc diffusion	CLSI (NS)
Meta, 2014 **(79)**	Cross-sectional	Hospital	2013-2014	Pekanbaru	Adults	M+F	Diabetic ulcers	Wound swab	*S. aureus* (138)	NS	NS
Moehario, 2009 **(80)**	Cross-sectional	Hospital	2002-2008	Jakarta	NS	M+F	Patients in ICU or internal medicine ward	Blood	*E. coli* (29) *K. pneumoniae* (67) *Salmonella enterica serovar* Typhi/Paratyphi A (35)	Disc diffusion	CLSI (NS)

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
									P. aeruginosa (90)		
Moehario, 2020 **(81)**	Retrospective	Hospital	2015-2018	Jakarta	Adults	M+F	Hospitalised and ICU patients	Blood, lower respiratory tract, urine, throat swab, pus	*A. baumannii* (44)	Disc diffusion	CLSI (M100-S28)
Muktiarti, 2021 **(82)**	Prospective	Community	2013	Jakarta	Children	NS	People living with HIV on antiretroviral therapy	Nasopharyngeal swab	*S. pneumoniae* (27)	Disc diffusion	CLSI (M100-S29)
Murni, 2016 **(83)**	Prospective	Hospital	2010-2013	Yogyakarta	Children	M+F	Hospitalised with suspicion of nosocomial bloodstream infection	Blood	*E. coli* (138) *K. pneumoniae* (9) *P. aeruginosa* (93)	Disc diffusion	CLSI (M100-S21)
Nathania, 2022 **(84)**	Retrospective	Hospital	2015-2021	Jakarta	NS	NS	Typhoid fever	NS	*Salmonella enterica serovar* Typhi/Paratyphi A (28)	Disc diffusion	CLSI (M100-S21, M100-S30), EUCAST (v12.0)
Nirwati, 2018 **(85)**	Cross-sectional	Hospital	2016-2017	Klaten	Adults and children	M+F	Hospitalised Patients	Blood, lower respiratory tract, pus, wound swab, and others	*A. baumannii* (80)	Disc diffusion	CLSI (M100-S25)
Nirwati, 2019 **(86)**	Retrospective	Hospital	2017-2018	Klaten	Adults and children	M+F	Hospitalised Patients	Blood, lower respiratory tract, pus, stool, urine, and others	*K. pneumoniae* (167)	Disc diffusion	CLSI (M100-S25)

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
Nur, 2016 **(87)**	Cross-sectional	Hospital	2015	Aceh	Adults	M+F	Diabetic foot ulcers	Foot ulcer swab and pus	*E. coli* (24) *Shigella* spp. (39)	Disc diffusion	CLSI (M100-S25)
Oyofo, 2002 **(88)**	Cross-sectional	Hospital	1999-2000	Bali, Batam, Jakarta, Makassar, Medan, Padang, Pontianak	Adults and children	M+F	Diarrhoea	Stool/rectal swab	*Salmonella* spp. (158) *Shigella* spp. (277)	Disc diffusion	NS
Parut, 2015 **(89)**	Cross-sectional	Hospital	2014	Surabaya	Adults	F	Pregnant women with asymptomatic bacteriuria	Urine	*E. coli* (5) *K. pneumoniae* (138)	Disc diffusion	CLSI (M31-A2)
Patilaya, 2019 **(90)**	Cross-sectional	Hospital	2016	Klaten	NS	NS	Post-surgical patients	Pus	*K. pneumoniae* (138)	Disc diffusion	CLSI (M100S)
Pelegrin, 2019 **(91)**	Prospective	Hospital	2013	Jakarta	Adults	NS	ICU patients	Blood, lower respiratory tract, rectal swab, throat swab, tissue swab, urine, wound swab	*P. aeruginosa* (107)	Automated system (Vitek 2) Reported MIC	EUCAST (v8.1)
Permana, 2022 **(92)**	Cross-sectional	Hospital	2020	Bandung	Adults	M+F	Diabetic foot infection	Wound	*A. baumannii* (8) *E. coli* (7) *K. pneumoniae* (13) *S. aureus* (138)	Automated system (Vitek 2)	NS
Prabowo, 2012 **(93)**	Cross-sectional	Hospital	2011	Yogyakarta	Adults	M+F	UTI	Urine	*E. coli* (18)	Disc diffusion	CLSI (NS)

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
									Salmonella enterica serovar Typhi/Paratyphi A (138)		
Punjabi, 2013 **(94)**	Prospective	Community	2001-2003	Jakarta	All	M+F	Diarrhoea or fever	Blood	*Salmonella enterica serovar* Typhi/Paratyphi A (262)	Disc diffusion	NS
Purba, 2019 **(95)**	Retrospective	Hospital	2014-2016	Surabaya	Adults	M+F	CAP	Blood and lower respiratory tract	*A. baumannii* (27) *E. coli* (10) *K. pneumoniae* (25) *P. aeruginosa* (19) *S.aureus* (9) *S. pneumoniae* (26)	Disc diffusion	CLSI (NS)
Puspandari, 2016 **(96)**	Retrospective	Community	2016	Jakarta	Adults	F	Female sex workers	Urethral, cervical, pharyngeal and rectal swabs	*N. gonorrhoeae* (179)	Automated system (Vitek 2), disc diffusion	CLSI (M100-S25)
Rachman, 2016 **(97)**	Cross-sectional	Hospital	2015	Banjarmasin	NS	NS	Diabetic mellitus with UTI	Urine	*E. coli* (17) *P. aeruginosa* (3)	Disc diffusion	NS
Radji, 2011 **(98)**	Cross-sectional	Hospital	2009-2010	Jakarta	NS	NS	Patients in ICU treated receiving antibiotics	Blood, peritoneal fluid, respiratory tract, urine, and wound	*E. coli* (13) *K. pneumoniae* (38) *P. aeruginosa* (66)	Disc diffusion	CLSI (M100-S16)
Radji, 2014 **(99)**	Retrospective	Hospital	2012	Jakarta	Adults	M+F	Patients hospitalized with diabetic foot	Foot ulcer samples	*E. coli (138)* *S. aureus* (35)	Disc diffusion	CLSI (M100-S16)

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
Rahman, 2015 **(100)**	Retrospective	Hospital	2014	Riau	NS	NS	Patients in ICU	Blood, lower respiratory tract	*A. baumannii* (59)	Automated system (Vitek 2)	NS
Ramdhani, 2022 **(101)**	Retrospective	Hospital	2017	Tasikmalaya	Adults	NS	Acute respiratory tract infection	Throat swab	*H. influenzae* (77)	Disc diffusion	NS
Rosana, 2020a**(103)**	Cross-sectional	Community	2015-2017	Jakarta	Adults and children	F	Pregnant women with no symptoms of UTI	Urine	*E. coli* (138) *K. pneumoniae* (15)	Automated system (Vitek)	CLSI (M100-S25)
Rosana, 2020b **(102)**	Cross-sectional	Hospital and community	2014-2015	Jakarta	NS	NS	UTI	Urine	*E. coli* (138) *K. pneumoniae* (11)	Automated system (Vitek 2)	CLSI (NS)
Rosyid, 2021 **(104)**	Cross-sectional	Community	2019	Surabaya	Adults	M+F	Lower respiratory tract infection	Lower respiratory tract	*A. baumannii* (4) *K. pneumoniae* (138) *P. aeruginosa* (8) *S. aureus* (11) *S. pneumoniae* (3)	Automated system (Vitek 2), microdilution Reported MIC	CLSI (NS)
Safari, 2014 **(105)**	Cross-sectional	Community	2012	Jakarta	Children	M+F	Screening of people living with HIV	Nasopharyngeal swab	*S. pneumoniae* (42)	Disc diffusion	CLSI (M100-S17)
Safari, 2015 **(106)**	Cross-sectional	Community	2011	Jakarta	Adults	M+F	Screening at routine clinics	Nasopharyngeal swab	*S. aureus* (42) *S. pneumoniae* (4)	Disc diffusion	CLSI (M100-S17)

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
Safari, 2020 **(107)**	Retrospective	Hospital	2012	Jakarta	Adults and children	NS	People living with HIV	Nasopharyngeal swab	*H. influenzae* (34)	Disc diffusion	CLSI (NS)
Safari, 2022a **(108)**	Retrospective	Hospital	2017	Bali	Adults and children	NS	Fever and upper respiratory tract symptoms	Nasopharyngeal swab	*S. pneumoniae* (37)	Disc diffusion	CLSI (M100-S29)
Safari, 2022b **(109)**	Cross-sectional	Community	2018-2019	Banyumas	Children	NS	Acute otitis media	Nasopharyngeal swab	*H. influenzae* (85)	Microdilution Reported MIC	CLSI (M100-S29)
Sahara, 2023 **(110)**	Retrospective	Hospital	2018	Lampung	NS	NS	Hospitalised patients	Blood, urine, pus, sputum, bodily fluids, swabs	*E. coli* (138)	Disc diffusion Automated system (Vitek 2)	CLSI (M100-S20)
Saharman, 2018 **(111)**	Prospective	Hospital	2013-2014	Jakarta	Adults	M+F	Patients in ICU	Stool/rectal swabs, throat swabs	*A. baumannii* (325)	Automated system (Vitek 2) Reported MIC	EUCAST (v3.1)
Saharman, 2019 **(112)**	Prospective	Hospital	2013-2014	Jakarta	Adults	M+F	Patients in ICU	Stool/rectal swabs, throat swabs	*P. aeruginosa* (281)	Automated system (Vitek 2) Reported MIC	EUCAST (v3.1)
Saharman, 2020 **(113)**	Prospective	Hospital	2013-2014	Jakarta	Adults	M+F	Patients in ICU	Stool/rectal swabs, throat swabs	*K. pneumoniae* (370)	Automated system (Vitek 2)	EUCAST (v3.1)

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
										Reported MIC	
Said, 2017 **(114)**	Cross-sectional	Hospital	2014	Jakarta	Adults	M+F	Various, including tuberculosis and pneumonia	Lower respiratory tract	*S. pneumoniae* (13)	Disc diffusion Reported MIC	CLSI (M100-S25)
Salsabila, 2021 **(115)**	Cross-sectional	Community	2019	Kotabaru	Children	M+F	Screening at community health services	Nasopharyngeal swab	*S. pneumoniae* (85)	Disc diffusion, microdilution Reported MIC	CLSI (M100-S29)
Santoso, 2022 **(116)**	Retrospective	Hospital	2021-2022	Bandung	Adults	M+F	COVID-19 with secondary pulmonary bacterial infection	Lower respiratory tract	*A. baumannii* (58) *K. pneumoniae* (36) *P. aeruginosa* (138) *S. aureus* (5)	Automated system (Vitek 2)	CLSI (M60-Ed2, M100-S30)
Saputro, 2013 **(117)**	Cross-sectional	Community	2013	Semarang	Children	M+F	Pneumonia	Nasopharyngeal swab	*S. pneumoniae* (23)	Disc diffusion	CLSI (M100-S22)
Sari, 2015 **(119)**	Retrospective	Hospital	2013	Palembang	Children	M+F	Patients in neonatal ICU with a bacterial infection	Blood, lower respiratory tract, urine	*E. coli* (9) *K. pneumoniae* (12) *P. aeruginosa* (9) *S. aureus* (7)	NS	NS
Sari, 2017 **(118)**	Cross-sectional	Hospital	2014-2015	Central Java	Children	M+F	Patients in neonatal ICU with a	Blood	*A. baumannii* (21) *K. pneumoniae* (49) *P. aeruginosa* (31)	Agar dilution, automated system	NS

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
							bacterial infection			(Vitek 2), disc diffusion Reported MIC	
Setyati, 2012 **(120)**	Retrospective	Hospital	2011	Yogyakarta	Children	NS	Patients in pediatric ICU with pneumonia	Blood and tracheal aspirate	*E. coli* (3) *K. pneumoniae* (15) *P. aeruginosa* (37) *S. aureus* (138)	Disc diffusion	NS
Sholeh, 2020 **(121)**	Cross-sectional	Hospital	2017	Surabaya	Adults and children	M+F	Patients in ICU or infectious diseases ward	Rectal swab	*E. coli* (64)	Disc diffusion	CLSI (M100-S26)
Sinto, 2022 **(122)**	Retrospective	Hospital and community	2019-2020	Jakarta	Adults and children	M+F	Hospitalised Patients	Blood	*E. coli* (230) *K. pneumoniae* (408) *P. aeruginosa* (157) *Salmonella* spp. (33) *S. aureus* (216) *S. pneumoniae* (3)	Automated system (Vitek 2), disc diffusion	CLSI (M39-A4)
Soedarmono, 2022 **(123)**	Prospective	Hospital	2013-2016	Bandung, Denpasar, Jakarta, Makassar, Semarang, Surabaya, Yogyakarta	Adults and children	M+F	Fever	Blood	*E. coli* (14) *K. pneumoniae* (5) *P. aeruginosa* (138) *Salmonella enterica serovar* Typhi/Paratyphi A (51) *S. aureus* (10)	Automated system (Phoenix, Vitek 2)	NS

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
									S. pneumoniae (138)		
Subagdja, 2022 **(124)**	Retrospective	Hospital	2020-2021	Bandung	Adults	M+F	COVID-19	Blood, lower respiratory tract, pus, and urine	*A. baumannii* (134) *E. coli* (69) *K. pneumoniae* (148) *P. aeruginosa* (65) *S. aureus* (15)	Automated system (Vitek 2)	CLSI (M100-S30)
Sugianli, 2017 **(125)**	Cross-sectional	Hospital and community	2014-2015	Bandung and Medan	Adults	M	UTI	Urine	*E. coli* (521) *K. pneumonia* (136)	Disc diffusion	CLSI (M02-A11), EUCAST (NS)
Suranadi, 2021 **(126)**	Prospective	Hospital	2018-2021	Bali	Adults	M+F	Patients in ICU and high care unit	Blood, lower respiratory tract, pleural fluid, pus, tissue swab, urine, wound swab	*P. aeruginosa* (14)	Automated system (Vitek 2)	CLSI (M100-S22)
Sutrisna, 2006 **(127)**	Cross-sectional	Community	2004	Papua, Surabaya	Adults	M+F	Sex workers	Urethral, cervical, pharyngeal and rectal swabs	*N. gonorrhoeae* (163)	Dilution methods	NS
Tan, 2021 **(128)**	Prospective	Hospital	2019-2020	Surabaya	Adults	M+F	Hospitalised people living with HIV	Blood and lower respiratory tract	*A. baumannii* (4) *E. coli* (5) *K. pneumoniae* (14) *P. aeruginosa* (4) *S. aureus* (4) *Salmonella* spp. (138)	NS	NS

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
Tandiono, 2022 **(129)**	Retrospective	Hospital	2019-2020	Tangerang	Adults and children	M+F	Patients in ICU	Blood, CSF, lower respiratory tract, pus, stool, urine, and others	*E. coli* (89)	Automated system (Vitek 2)	NS
Tauran, 2022 **(130)**	Retrospective	Hospital and community	2015-2018	Makassar	Adults and children	M+F	Hospitalised patients	Blood	*E. coli* (104) *K. pneumoniae* (171) *P. aeruginosa* (68) *S. aureus* (245)	Automated system (Vitek 2), disc diffusion	CLSI (NS)
Tjaniadi, 2003 **(131)**	Cross-sectional	Hospital	1995-2001	Batam, Denpasar, Jakarta, Makassar, Medan, Padang, Pontianak,	Adults and children	M+F	Diarrhoea	Stool/rectal swab	*Shigella* spp. (767)	Disc diffusion	CLSI (M02-A6)
Tjoa, 2013 **(132)**	Cross-sectional	Hospital	2010-2011	Jakarta	Children	NS	Sepsis and other neonates in ICU	Blood, skin swabs	*A. baumannii (17)*	Disc diffusion	CLSI
Wang, 2011 **(133)**	Cross-sectional	Hospital	2009-2010	Semarang	Adults	NS	CAP	Blood, lower respiratory tract, middle ear fluid, nasopharyngeal swabs, and pleural fluid	*K. pneumoniae* (41) *S. pneumoniae* (55)	Microdilution Reported MIC	CLSI (M45-H, M100-S20)
Wardhana, 2017 **(134)**	Retrospective	Hospital	2016	Jakarta	Adults and children	M+F	Burns	Lower respiratory tract, blood, tissue,	*A. baumannii* (10) *K. pneumoniae* (15) *P. aeruginosa* (11)	NS	NS

First author, Year of publication	Study design	Setting	Year of data collection	Location	Age group	Sex	Syndrome/ Population	Specimen type	GLASS organisms included (N isolates)	Antibiotic sensitivity testing	
										Phenotypic methods	Interpretative criteria (version)
								wound swab and urine			
Wijaksana, 2019 **(135)**	Retrospective	Hospital	2017	Riau	Adults	M+F	Patients in ICU with sepsis	Lower respiratory tract, blood, urine, CSF	*A. baumannii* (14) *E. coli* (5) *K. pneumoniae* (9) *P. aeruginosa* (138)	E-test	NS
Wikaningtyas, 2015 **(136)**	Cross-sectional	Hospital	2012	Bandung	NS	M+F	Patients in ICU	Lower respiratory tract and others	*A. baumannii* (12) *E. coli* (36) *K. pneumoniae* (10) *S. aureus* (11)	Disc diffusion	NS
Yanagi, 2009 **(137)**	Retrospective	Hospital	2006	Surabaya	NS	NS	Enteric fever	Blood and stool	*Salmonella enterica serovar* Typhi/Paratyphi A (17)	Disc diffusion	CLSI (M100-S18)

Abbreviations: CAP, Community-acquired pneumonia; CLSI, Clinical and Laboratory Standards Institute; ENT, ear, nose, and throat; EUCAST, European Committee on Antimicrobial Susceptibility Testing; F, female; ICU, intensive care unit; M, male; NS, not specified; STI, sexually transmitted infection; UTI, urinary tract infection

We included 18,231 bacterial isolates in the review, including 12,361 from hospitals and 5,870 from community settings (GLASS priority specimen types are summarised in **Table 1.7**). The reported bacterial pathogens were *Klebsiella pneumoniae* (41 reports, 2340 isolates), *Escherichia coli* (40 reports, 5475 isolates), *Pseudomonas aeruginosa* (31 reports, 1498 isolates), *Acinetobacter baumannii* (26 reports, 2700 isolates), *Staphylococcus aureus* (25 reports, 2613 isolates), *Streptococcus pneumoniae* (18 reports, 799 isolates), *Salmonella enterica serovar* Typhi and Paratyphi A (7 reports, 562 isolates), *N. gonorrhoeae* (6 reports, 629 isolates), *Shigella* spp. (5 reports, 1164 isolates), *Salmonella* spp. (non-typhoidal) (3 reports, 259 isolates), and *Haemophilus influenzae* (3 reports, 192 isolates). There were no reports describing *Neisseria meningitidis* (**Figure 1.2**). AST was mostly performed by disc diffusion method (59 reports). Minimum inhibitory concentrations were only reported in 14 reports (14.1%). AST interpretative criteria used were stated in 67 reports (67.7%), including CLSI (58 reports) and EUCAST (9 reports). 13 reports did not report the specific edition used. Genotypic methods were additionally used for confirmatory testing in 22 reports, including PCR (18 reports), multilocus sequence typing (4 reports), and next-generation sequencing (1 report).

We reviewed implementation of the 13 MICRO mandatory items. Of 99 reports, 54 (54.5%) missed 3-4 items, with a median of 3 (range 1-8) missing items. The most frequently missing mandatory items were external QA (item #12, 95 reports, 95.7%), duplicate and sequential isolates (item #14, 82 reports, 82.8%) and AMR definitions (item #11, 68 reports, 68.7%) (**Table 1.3**).

Table 1.7 Summary of number of bacterial isolates and specimen types included in the review for each GLASS pathogen

Micro-organism	Number of studies	Number of isolates															
		Hospital								Community							
		Blood	CSF	LRT	Stool	Urethral, cervical, pharyngeal and rectal swabs	Urine	Other*	Total	Blood	CSF	LRT	Stool	Urethral, cervical, pharyngeal and rectal swabs	Urine	Other *	Total
A. baumannii	26	446	0	69				2128	2643	53	0	4				0	57
E. coli	40	276	0	15			837	1417	2545	123	0	0			307	2500	2930
H. influenzae	3	0	0	0				107	107	0	0	0				85	85
K. pneumoniae	41	651	0	101			331	1010	2093	97	0	16			80	54	247
P. aeruginosa	31	442	0	109				879	1430	60	0	8				0	68
N. meningitidis	0	0	0					0	0	0	0					0	0
N. gonorrhoeae	6					0		0	0					629		0	629
Salmonella **spp. (non-typhoidal)**	3	18			158			0	176	27			56			0	83
Salmonella enterica serovar **Typhi and Paratyphi A**	8	254			0			46	300	262			0			0	262
Shigella **spp.**	5				1068			39	1107				57			0	57
S. aureus	25	562	0	343				892	1797	132	0	11				673	816
S. pneumoniae	18	5	0	27				131	163	0	0	3				633	636

Specimen types were classified according to the GLASS priority specimen type categories. *Other: pus, other sources of swab (including conjunctival, nasal, wound swab)

Abbreviations: CSF, cerebrospinal fluid; LRT, lower respiratory tract

Figure 1.2 Number of reports and bacterial isolated included for each GLASS bacterial pathogen. Reproduced from (36)

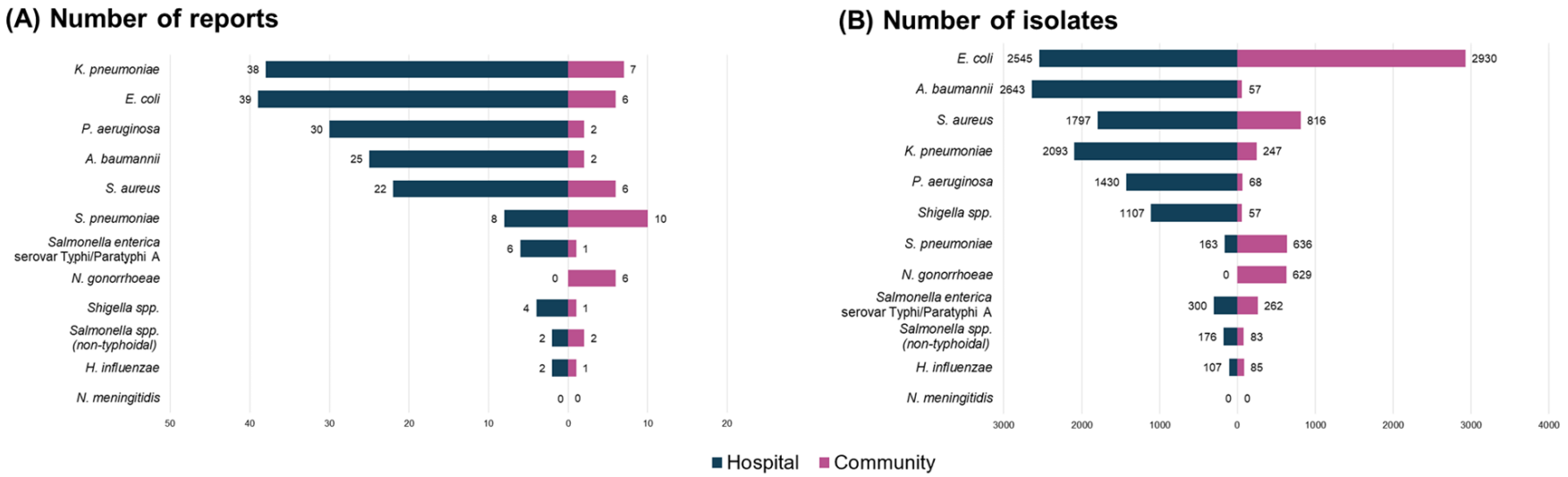


Figure shows tornado plots of (A) the number of included reports that described resistance data for each of the GLASS bacterial pathogens (99 overall; 70 from hospitals, 24 from communities, 5 from both); and (B) the number of included bacterial isolates for each of the GLASS bacterial pathogens (18231 overall; 12361 from hospitals and 5870 from communities), stratified by hospitals and communities. Data are sorted in descending order of number of total reports and isolates in hospitals and communities.

1.2.2.2 Proportions of resistance for each of the pathogen-antimicrobial combinations

Klebsiella pneumoniae

41 reports described 2,340 isolates, including 38 hospital reports (2,093 isolates) and 7 community reports (247 isolates). In hospitals, the proportion of resistant bacterial isolates was 71.8% (95%CI 69.3-74.3; 944/1,314) for 3GC; 31.5% (26.8-36.5; 116/368) for carbapenems; 55.6% (52.7-58.5; 657/1,181) for fluoroquinolones; 51.5% (48.9-54.1; 768/1,491) for gentamicin; 19.7% (17.9-21.7; 330/1,672) for amikacin; 54.8% (51.6-57.8; 558/1019) for co-trimoxazole; 17.6% (13.5-22.5; 52/295) for fosfomycin; and 88.5% (76.6-95.6; 46/52) of those tested for colistin **(Figure 1.3** and **Table 1.8)**. Across the ten hospital reports that distinguished Healthcare-associated infections (HAI) and/or CAI, the resistance proportion was 84.1% (80.6-87.1; 427/508) and 47.4% (36.0-59.1; 37/78) for 3GC; 36.2% (32.1-40.4; 237/757) and 26.3% (13.4-43.1; 10/38) for carbapenems; 70.9% (66.1-75.3; 280/395) and 30.9% (20.2-43.3; 21/68) for fluoroquinolones; 66.0% (61.7-70.0; 343/520) and 18.5% (5/27) for gentamicin; 36.2% (32.1-40.4; 191/528) and 7.4% (19/27) for amikacin; and 54.5% (48.0-60.8; 134/246) and 22.2% (6/27) for co-trimoxazole. Time series showed that, compared to previous years (2012-2017), recent (2018-2023) resistance proportions increased for carbapenems (38.7% [33.1-44.5] vs 28.2% [25.2-31.3], fluoroquinolones (60.4% [56.7-63.9] vs 43.8% [38.0-49.8]) and amikacin (23.9% [21.2-26.7] vs 15.9% [13.0-19.0]); decreased for 3GC (68.4% [64.6-72.0] vs 83.2% [79.8-86.3]), cefepime (56.8% [53.1-60.4] vs 82.0% [77.4-86.0]) and co-trimoxazole (50.2% [46.3-54.1] vs 63.8% [58.5-68.8%]); and was stable for gentamicin (49.8% [46.4-53.2] vs 55.6% [51.0-60.1]) and fosfomycin (0.0% [0.0-60.2] vs 20.2% [15.3-25.8]) (**Figures 1.4 and 1.6**). In communities, the proportion of resistant bacterial isolates was 53.6% (95%CI 45.7-61.3; 90/168) for 3GC; 27.8% (17.9-39.6; 20/72) for carbapenems; 52.5% (43.9-61.0; 73/139) for fluoroquinolones; 50.9% (41.3-60.5; 57/112)

for cefepime; 36.2% (28.2-44.8; 50/138) for gentamicin; 15.2% (9.1-23.2; 17/112) for amikacin; 33.7% (23.7-44.9; 28/83) for co-trimoxazole; and 10.0% (2.1-26.5; 3/30) for fosfomycin. Across the seven studies that reported on the resistance mechanisms for *K. pneumoniae*, the proportion of extended-spectrum beta-lactamase (ESBL) producing isolates ranged between 31.8% and 77.6% (weighted mean proportion 50.9% [95%CI 45.5-56.2]; 179/352).

Figure 1.3 Weighted mean proportions of resistant bacterial isolates for each GLASS pathogen-antimicrobial combination in hospital and community settings. Reproduced from (36)

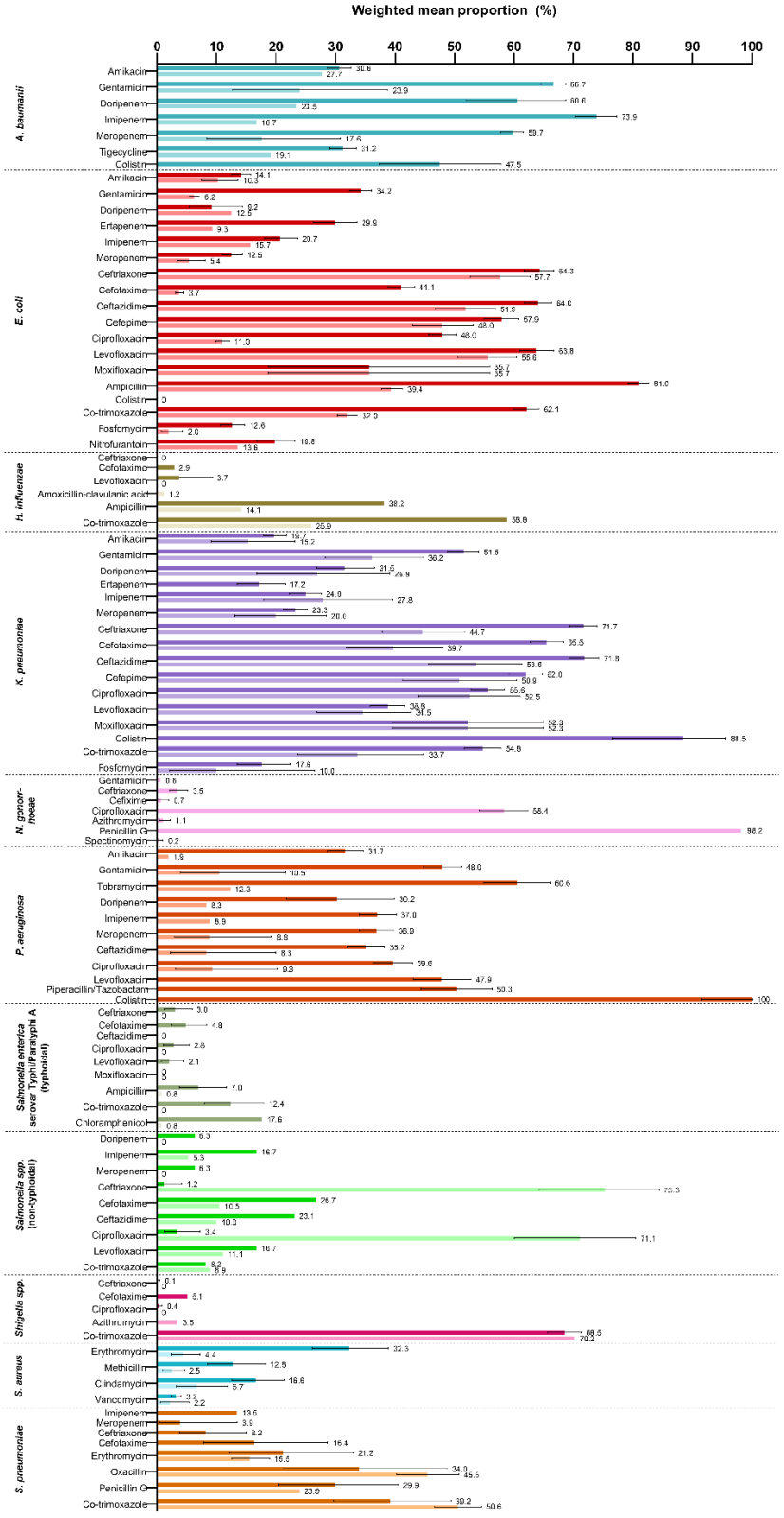


Figure shows bar charts of weighted mean proportions of AMR for all pathogen-antimicrobial combinations in hospitals (dark color) and communities (light color). 95% confidence intervals were estimated using Clopper-Pearson exact method (where the number of studies was greater than one).

Table 1.8 Numbers and proportions of resistant isolates for *Klebsiella pneumoniae*-antimicrobial combinations

Antibiotics	Hospitals					Communities				
	Blood	**Urine**	**Lower respiratory tract**	**Other**	**Total**	**Blood**	**Urine**	**Lower respiratory tract**	**Other**	**Total**
Aminoglycosides										
Amikacin	193/610 (31.6%; 28.0-35.5) [6]	34/265 (12.8%; 9.1-17.5) [5]	13/174 (7.5%; 4.0-12.4) [4]	90/623 (14.4%; 11.8-17.5) [16]	330/1672 (19.7%; 17.9-21.7) [30]	5/32 (15.6%) [1]	0/19 (0.0%) [1]		12/61 (19.7%) [1]	17/112 (15.2%; 9.1-23.2) [3]
Gentamicin	407/602 (67.6%; 63.7-71.3) [6]	102/206 (49.5%; 42.5-56.5) [4]	39/90 (43.3%; 32.9-54.2) [4]	220/593 (37.1%; 33.2-41.1) [14]	768/1491 (51.5%; 48.9-54.1) [27]	21/32 (65.6%) [1]	3/34 (8.8%; 1.9-23.7) [2]	0/16 (0.0%) [1]	26/56 (46.4%) [1]	50/138 (36.2%; 28.2-44.8) [5]
Carbapenems	34.5% (30.1-39.1) [2]	37.6% (31.3-44.2) [4]	19.3% (11.7-29.1) [4]	23.9% (20.2-28.0) [9]	31.5% (26.8-36.5) [4]	29.6% [1]	0.0% [1]	6.3% (2.9-11.5) [3]	26.9% [1]	27.8% (17.9-39.6) [2]
Doripenem	111/343 (32.4%; 27.4-37.6) [2]			5/25 (20.0%; 6.8-40.7) [2]	116/368 (31.5%; 26.8-36.5) [4]	8/27 (29.6%) [1]			10/40 (25.0%) [1]	18/67 (26.9%; 16.8-39.1) [2]
Ertapenem	8/80 (10.0%; 4.4-18.8) [2]	25/85 (29.4%) [1]	17/77 (22.1%; 13.4-33.0) [3]	13/124 (10.5%; 5.7-17.3) [4]	63/366 (17.2%; 13.5-21.5) [10]					
Imipenem	141/434 (32.5%; 28.1-37.1) [5]	9/144 (6.3%; 2.9-11.5) [3]	2/13 (15.4%) [1]	118/493 (23.9%; 20.2-28.0) [9]	270/1084 (24.9%; 22.4-27.6) [17]	8/27 (29.6%) [1]			12/45 (26.7%) [1]	20/72 (27.8%; 17.9-39.6) [2]
Meropenem	155/449 (34.5%; 30.1-39.1) [2]	86/229 (37.6%; 31.3-44.2) [4]	17/88 (19.3%; 11.7-29.1) [4]	149/983 (15.2%; 13.0-17.6) [16]	407/1749 (23.3%; 21.3-25.3) [26]	8/32 (25.0%) [1]	0/15 (0.0%) [1]	1/16 (6.3%) [1]	14/52 (26.9%) [1]	23/115 (20.0%; 13.1-28.5) [4]
Third-generation cephalosporins	87.0% (83.6-89.8) [5]	90.3% (85.9-93.7) [3]	67.8% (57.1-77.2) [4]	52.4% (47.4-57.4) [12]	71.8% (69.3-74.3) [26]	70.7% (59.6-80.3) [2]	67.9% [1]	6.3% [1]	1.9% [1]	53.6% (45.7-61.3) [5]

Antibiotics	Hospitals					Communities				
	Blood	**Urine**	**Lower respiratory tract**	**Other**	**Total**	**Blood**	**Urine**	**Lower respiratory tract**	**Other**	**Total**
Ceftriaxone	497/586 (84.8%; 81.6-87.6) [6]	224/248 (90.3%; 85.9-93.7) [3]	61/90 (67.8%; 57.1-77.2) [4]	308/596 (51.7%; 47.6-55.8) [14]	1090/1520 (71.7%; 69.4-74.0) [26]	54/82 (65.9%; 54.6-76.0) [2]	38/56 (67.9%) [1]	0/16 (0.0%) [1]	1/54 (1.9%) [1]	93/208 (44.7%; 37.8-51.7) [5]
Cefotaxime	387/518 (74.7%; 70.7-78.4) [6]	123/177 (69.5%; 62.1-76.2) [4]	46/75 (61.3%; 49.4-72.4) [4]	206/393 (52.4%; 47.4-57.4) [12]	762/1163 (65.5%; 62.7-68.3) [25]	58/82 (70.7%; 59.6-80.3) [2]	1/15 (6.7%) [1]		1/54 (1.9%) [1]	60/151 (39.7%; 31.9-48.0) [4]
Ceftazidime	420/483 (87.0%; 83.6-89.8) [5]	263/304 (86.5%; 82.2-90.1) [4]	56/99 (56.6%; 46.2-66.5) [5]	205/428 (47.9%; 43.1-52.7) [13]	944/1314 (71.8%; 69.3-74.3) [26]	52/81 (64.2%; 52.8-74.6) [2]	37/71 (52.1%; 39.9-64.1) [2]	1/16 (6.3%) [1]		90/168 (53.6%; 45.7-61.3) [5]
Fourth-generation cephalosporins										
Cefepime	302/388 (77.8%; 73.4-81.9) [5]	174/192 (90.6%; 85.6-94.3) [2]	44/90 (48.9%; 38.2-59.7) [4]	220/523 (42.1%; 37.8-46.4) [11]	740/1193 (62.0%; 59.2-64.8) [21]	24/41 (58.5%) [1]	33/71 (46.5%; 34.5-58.7) [2]			57/112 (50.9%; 41.3-60.5) [3]
Fluoroquinolones	60.0% (55.5-64.5) [6]	76.9% (68.7-83.9) [3]	55.8% (41.3-69.5) [2]	52.3% (39.5-64.9) [2]	55.6% (52.7-58.5) [27]	67.3% [1]	50.7% (38.6-62.8) [2]	12.5% [1]		52.5% (43.9-61.0) [4]
Ciprofloxacin	284/473 (60.0%; 55.5-64.5) [6]	100/130 (76.9%; 68.7-83.9) [3]	44/90 (48.9%; 38.2-59.7) [4]	229/488 (46.9%; 42.4-51.5) [15]	657/1181 (55.6%; 52.7-58.5) [27]	35/52 (67.3%) [1]	36/71 (50.7%; 38.6-62.8) [2]	2/16 (12.5%) [1]		73/139 (52.5%; 43.9-61.0) [4]
Levofloxacin	195/530 (36.8%; 32.7-41.1) [4]	94/173 (54.3%; 46.6-61.9) [3]	29/52 (55.8%; 41.3-69.5) [2]	115/362 (31.8%; 27.0-36.8) [10]	433/1117 (38.8%; 35.9-41.7) [19]	19/77 (24.7%; 15.6-35.8) [2]	32/71 (45.1%; 33.2-57.3) [2]			51/148 (34.5%; 26.8-42.7) [4]
Moxifloxacin				34/65 (52.3%; 39.5-64.9) [2]	34/65 (52.3%; 39.5-64.9) [2]					

Antibiotics	Hospitals					Communities				
	Blood	**Urine**	**Lower respiratory tract**	**Other**	**Total**	**Blood**	**Urine**	**Lower respiratory tract**	**Other**	**Total**
Polymyxin										
Colistin				46/52 (88.5%; 76.6-95.6) [3]	46/52 (88.5%; 76.6-95.6) [3]					
Sulfonamides										
Co-trimoxazole	146/257 (56.8%; 50.5-63.0) [3]	126/156 (80.8%; 73.7-86.6) [5]	36/77 (46.8%; 35.3-58.5) [3]	250/529 (47.3%; 42.9-51.6) [12]	558/1019 (54.8%; 51.6-57.8) [23]		12/43 (27.9%; 15.3-43.7) [3]	1/16 (6.3%) [1]	15/24 (62.5%) [1]	28/83 (33.7%; 23.7-44.9) [5]
Other antibiotics										
Fosfomycin	2/51 (3.9%; 0.5-13.5) [2]	43/168 (25.6%; 19.2-32.9) [4]	1/13 (7.7%) [1]	6/63 (9.5%; 3.6-19.6) [4]	52/295 (17.6%; 13.5-22.5) [10]		3/30 (10.0%; 2.1-26.5) [2]			3/30 (10.0%; 2.1-26.5) [2]

The data are presented as: number of resistant isolates (numerator)/ number of total isolates (denominator) (weighted mean proportion; 95%CI) [N studies]. 95% confidence intervals were estimated using Clopper-Pearson exact method where the number of studies was greater than one.

Figure 1.4 Time trends in the weighted mean proportions of AMR for selected Gram-negative GLASS pathogens in hospitals. Reproduced from (36)

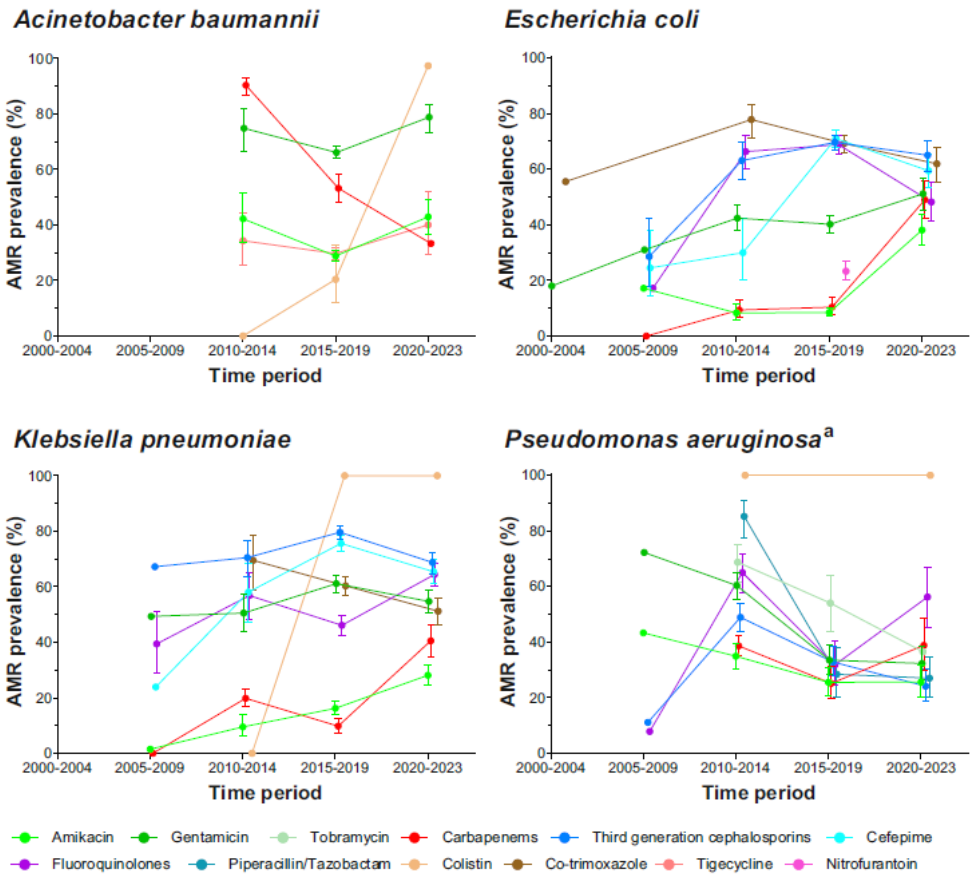
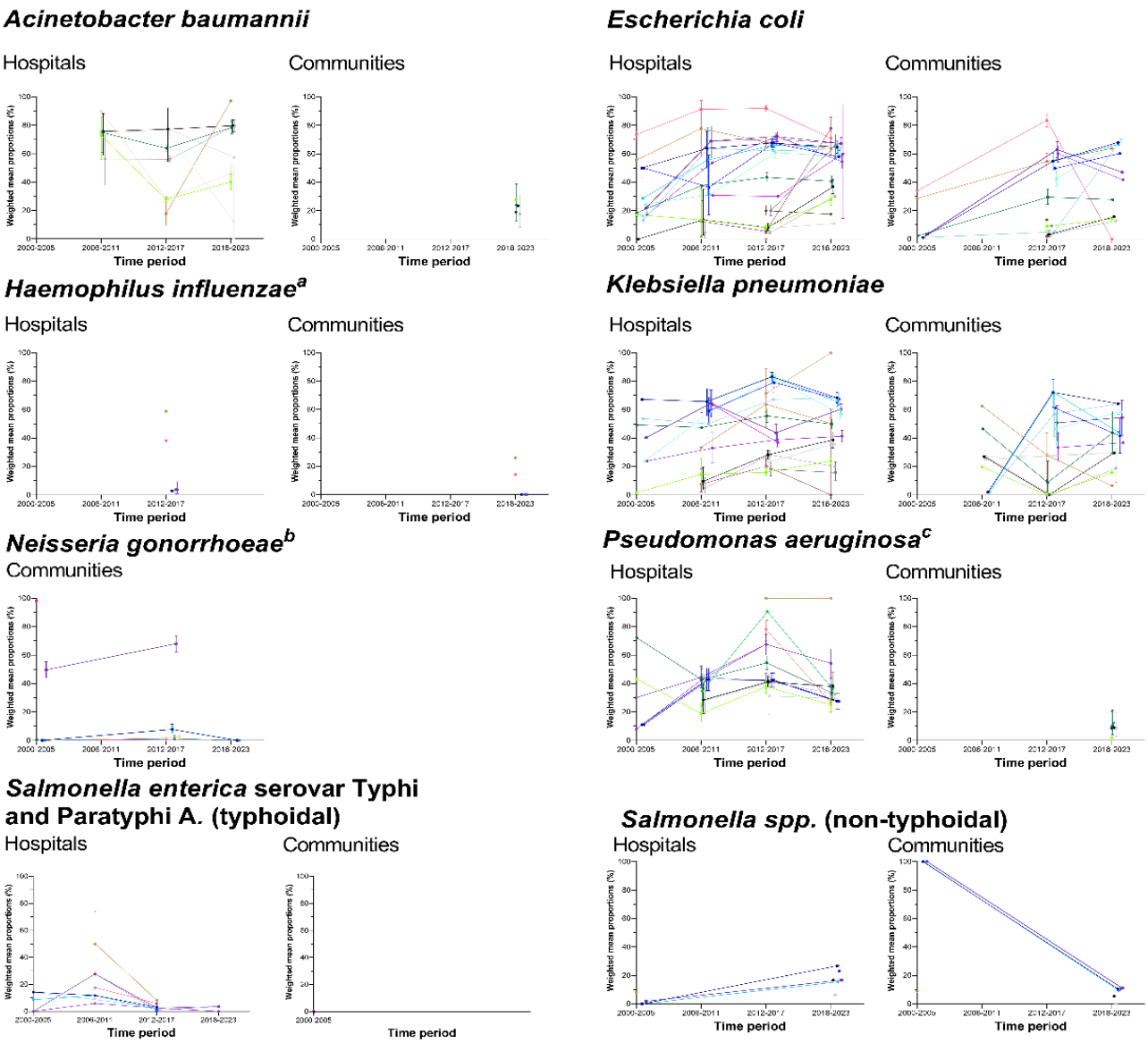


Figure shows connected scatter plots of time trends in the weighted mean proportions of AMR for Gram-negative GLASS pathogens in hospitals. Pathogens for which insufficient time trend data were available are not shown (see data supplement). The period of data collection was categorized into 6-year intervals from 2000 to 2023. For studies that collected data for two years, the latest year was used as the year of data collection. For studies that collected data for more than two years, the median of the period of data collection (rounded to the nearest integer) was used as the year of data collection. 95% confidence intervals were estimated using Clopper-Pearson exact method (where the number of studies was greater than one).

[a]The estimate for third-generation cephalosporins was based on ceftazidime only

Figure 1.5 Time trends in the weighted mean proportions of AMR for all GLASS pathogen-antimicrobial combinations in hospitals and community settings. Reproduced from (36)



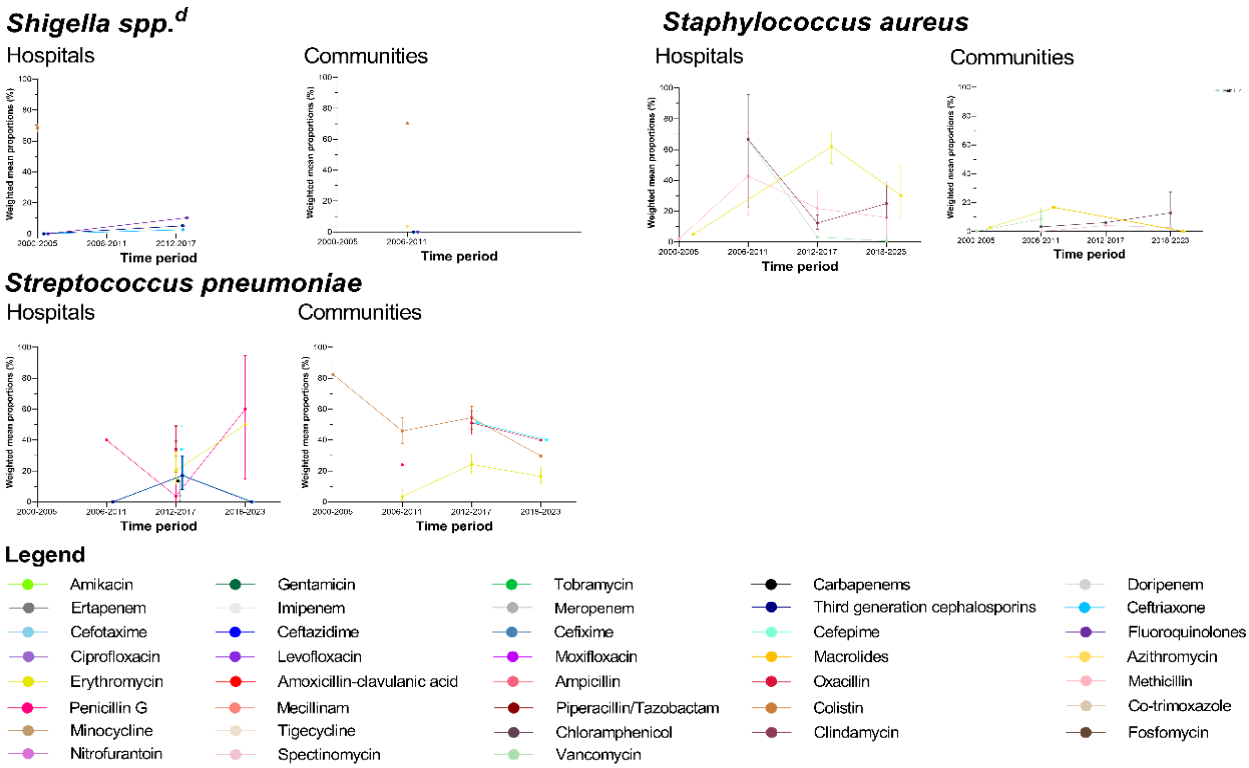


Figure shows connected scatter plots of time trends in the weighted mean proportions of AMR for all relevant pathogen-antimicrobial combinations. The period of data collection was categorized into 6-year intervals from 2000 to 2023. For studies that collected data for two years, the latest year was used as the year of data collection. For studies that collected data for more than two years, the median of the period of data collection (rounded to the nearest integer) was used as the year of data collection. 95% confidence intervals were estimated using Clopper-Pearson exact method (where the number of studies was greater than one).

[a]The estimate for fluoroquinolones is derived only from levofloxacin.
[b]The estimate for fluoroquinolones is derived only from ciprofloxacin.
[c]The estimate for third-generation cephalosporins is derived only from ceftazidime.
[d]The estimate for fluoroquinolones is derived only from ciprofloxacin.

Escherichia coli

40 reports described 5475 isolates, including 39 hospital reports (2545 isolates) and 6 community reports (2930 isolates). In hospitals, the proportion of resistant bacterial isolates was 64.3% (95%CI 61.8-66.7; 975/1517) for 3GC; 20.7% (18.1-23.6%; 180/868) for carbapenems; 63.8% (60.9-66.7; 691/1083) for fluoroquinolones; 34.2% (32.3-36.1; 832/2431) for gentamicin; 14.1% (12.5-15.7; 259/1841) for amikacin; 81.0% (79.2-82.7; 1618/1997) for ampicillin; 62.1% (59.9-64.2; 1213/1954) for co-trimoxazole; 19.8% (16.8-23.2; 125/630) for nitrofurantoin; 12.6% (10.7-14.8; 125/1030) for fosfomycin; 0.0% (0/4) for colistin (**Figure 1.3** and **Table 1.9**). Across the six hospital reports that distinguished HAI and/or CAI, the resistance proportion was 75.6% (70.0-80.6; 204/270) and 30.0% (3/10) for 3GC; 14.1% (9.3-20.3; 24/170) and 20.0% (2/10) for carbapenems; 66.5% (59.7-72.9; 139/209) and 40.0% (4/10) for fluoroquinolones; 43.7% (37.0-50.6; 94/215) and 10.0% (1/10) for gentamicin; 10.6% (7.2-14.7; 30/284) and 20.0% (2/10) for amikacin, and 67.4% (56.8-76.8; 62/92) and 30.0% (3/10) for co-trimoxazole. Time series showed that, compared to previous years (2012-2017), recent (2018-2023) resistance proportions increased for carbapenems (36.8% [32.0-41.9] vs 8.1% [5.8-11.1]) and amikacin (27.6% [23.9-31.6] vs 8.1% [6.6-9.8]); decreased for ampicillin (70.9% [65.7-75.7] vs 92.0% [89.9-93.8]); and was stable for 3GC (64.8% [60.5-68.9] vs 67.6% [64.7-70.3]), cefepime (58.4% [53.9-62.9] vs 60.8% [56.9-64.7]), fluoroquinolones (67.2% [62.6-71.6] vs 72.2% [68.5-75.6]), gentamicin (40.7% [36.7-44.7] vs 43.5% [40.3-46.7], and co-trimoxazole (63.6% [59.1-68.0] vs 68.1% [64.4-72.6]) (**Figure 1.4 and 1.5**). In communities, the proportion of resistant bacterial isolates was 57.7% (95%CI 52.6-62.7; 222/385) for 3GC; 15.7% (15/83) for carbapenems; 48.0% (42.9-53.2; 181/377) for cefepime; 55.6% (50.5-60.5, 220/396) for fluoroquinolones; 6.2% (5.4-7.2; 181/2913) for gentamicin; 10.3% (7.5-

13.7; 41/397) for amikacin; 39.4% (37.6-41.3; 1109/2813) for ampicillin; 32.0% (30.3-33.7; 913/2854) for co-trimoxazole; 13.6% (38/280) for nitrofurantoin; and 2.0% (0.8-4.4; 6/294) for fosfomycin. Across the five studies that reported on the resistance mechanisms for *E. coli*, the proportion of ESBL-producing isolates ranged between 3.8% and 62.3% (weighted mean proportion 48.0% [95%CI 42.9-53.0]; 189/394).

Table 1.9 Numbers and proportions of resistant isolates for *Escherichia coli*-antimicrobial combinations

Antibiotics	Hospitals					Communities			
	Blood	Urine	Lower respiratory tract	Other	Total	Blood	Urine	Other	Total
Aminoglycosides									
Amikacin	32/249 (12.9%; 9.0-17.7) [4]	62/740 (8.4%; 6.5-10.6) [5]	1/5 (20.0%; 0.5-71.6) [2]	164/847 (19.4%; 16.8-22.2) [20]	259/1841 (14.1%; 12.5-15.7) [31]	15/117 (12.8%; 7.4-20.3) [2]	26/280 (9.3%) [1]		41/397 (10.3%; 7.5-13.7) [3]
Gentamicin	103/244 (42.2%; 35.9-48.7) [4]	310/685 (45.3%; 41.5-49.1) [7]	1/5 (20.0%; 0.5-71.6) [2]	418/1497 (27.9%; 25.7-30.3) [17]	832/2431 (34.2%; 32.3-36.1) [30]	31/113 (27.4%; 19.5-36.6) [2]	89/300 (29.7%; 24.6-35.2) [2]	61/2500 (2.4%) [1]	181/2913 (6.2%; 5.4-7.2) [5]
Carbapenems	14.1% (9.3-20.3) [3]	8.2% (5.7-11.4) [4]	100.0% [1]	40.3% (34.8-46.1) [10]	20.7% (18.1-23.6) [18]	15.7% [1]	3.3% (1.6-6.0) [2]		15.7% [1]
Doripenem	13/148 (8.8%; 4.8-14.6) [2]			4/36 (11.1%; 3.1-26.1) [2]	17/184 (9.2%; 5.5-14.4) [4]	10/80 (12.5%) [1]			10/80 (12.5%) [1]
Ertapenem	1/22 (4.5%) [1]	68/242 (28.1%; 22.5-34.2) [2]		121/372 (32.5%; 27.8-37.5) [8]	190/636 (29.9%; 26.3-33.6) [11]		26/280 (9.3%) [1]		26/280 (9.3%) [1]
Imipenem	24/170 (14.1%; 9.3-20.3) [3]	32/390 (8.2%; 5.7-11.4) [4]	1/3 (33.3%) [1]	123/305 (40.3%; 34.8-46.1) [10]	180/868 (20.7%; 18.1-23.6) [18]	13/83 (15.7%) [1]			13/83 (15.7%) [1]
Meropenem	24/221 (10.9%; 7.1-15.7) [3]	14/463 (3.0%; 1.7-5.0) [5]	2/2 (100.0%) [1]	141/761 (18.5%; 15.8-21.5) [18]	181/1447 (12.5%; 10.8-14.3) [27]	12/105 (11.4%; 6.0-19.1) [2]	10/300 (3.3%; 1.6-6.0) [2]		22/405 (5.4%; 3.4-8.1) [4]
Third-generation cephalosporins	79.9% (73.7-85.2) [4]	77.1% (73.7-80.3) [5]	100.0% [1]	56.4% (52.9-59.8) [19]	64.3% (61.8-66.7) [30]	68.0% [1]	55.0% [1]	1.2% [1]	57.7% (52.6-62.7) [3]

Antibiotics	Hospitals					Communities			
	Blood	Urine	Lower respiratory tract	Other	Total	Blood	Urine	Other	Total
Ceftriaxone	181/246 (73.6%; 67.6-79.0) [5]	322/435 (74.0%; 69.6-78.1) [5]	2/2 (100.0%) [1]	470/834 (56.4%; 52.9-59.8) [19]	975/1517 (64.3%; 61.8-66.7) [30]	68/105 (64.8%; 54.8-73.8) [2]	154/280 (55.0%) [1]		222/385 (57.7%; 52.6-62.7) [3]
Cefotaxime	153/209 (73.2%; 66.7-79.1) [4]	218/311 (70.1%; 64.7-75.1) [4]	4/5 (80.0%; 28.4-99.5) [2]	405/1374 (29.5%; 27.1-32.0) [19]	780/1899 (41.1%; 38.9-43.3) [29]	66/97 (68.0%) [1]	1/20 (5.0%) [1]	31/2500 (1.2%) [1]	98/2617 (3.7%; 3.1-4.5) [3]
Ceftazidime	163/204 (79.9%; 73.7-85.2) [4]	495/642 (77.1%; 73.7-80.3) [5]	2/3 (66.7%) [1]	397/802 (49.5%; 46.0-53.0) [17]	1057/1651 (64.0%; 61.7-66.3) [27]	56/95 (58.9%; 48.4-68.9) [2]	149/300 (49.7%; 43.9-55.5) [2]		205/395 (51.9%; 46.8-56.9) [4]
Fourth-generation Cephalosporins									
Cefepime	84/136 (61.8%; 53.0-70.0) [3]	228/301 (75.7%; 70.5-80.5) [3]	2/5 (40.0%; 5.3-85.3) [2]	360/722 (49.9%; 46.2-53.6) [13]	674/1164 (57.9%; 55.0-60.8) [21]	54/77 (70.1%) [1]	127/300 (42.3%; 36.7-48.1) [2]		181/377 (48.0%; 42.9-53.2) [3]
Fluoroquinolones	61.1% (53.5-68.4) [4]	79.4% (74.7-83.6) [4]	0.0% [1]	56.5% (51.2-61.7) [11]	63.8% (60.9-66.7) [19]	47.1% [1]	63.0% (57.3-68.5) [2]	3.3% [1]	55.6% (50.5-60.5) [3]
Ciprofloxacin	107/175 (61.1%; 53.5-68.4) [4]	266/335 (79.4%; 74.7-83.6) [4]		506/1322 (38.3%; 35.6-41.0) [19]	879/1832 (48.0%; 45.7-50.3) [27]	48/102 (47.1%) [1]	189/300 (63.0%; 57.3-68.5) [2]	82/2500 (3.3%) [1]	319/2902 (11.0%; 9.9-12.2) [4]
Levofloxacin	123/210 (58.6%; 51.6-65.3) [3]	365/512 (71.3%; 67.2-75.2) [4]	0/2 (0.0%) [1]	203/359 (56.5%; 51.2-61.7) [11]	691/1083 (63.8%; 60.9-66.7) [19]	40/96 (41.7%) [1]	180/300 (60.0%; 54.2-65.6) [2]		220/396 (55.6%; 50.5-60.5) [3]
Moxifloxacin				10/28 (35.7%; 18.6-55.9) [5]	10/28 (35.7%; 18.6-55.9) [5]				
Penicillins									

Antibiotics	Hospitals					Communities			
	Blood	Urine	Lower respiratory tract	Other	Total	Blood	Urine	Other	Total
Ampicillin	85/88 (96.6%) [1]	519/547 (94.9%; 92.7-96.6) [6]	5/5 (100.0%; 47.8-100.0) [2]	1009/1357 (74.4%; 71.9-76.7) [14]	1618/1997 (81.0%; 79.2-82.7) [23]	12/14 (85.7%; 57.2-98.2) [2]	248/299 (82.9%; 78.2-87.0) [2]	849/2500 (34.0%) [1]	1109/2813 (39.4%; 37.6-41.3) [5]
Polymyxin									
Colistin				0/4 (0.0%) [1]	0/4 (0.0%) [1]				
Sulfonamides									
Co-trimoxazole	57/83 (68.7%; 57.6-78.4) [2]	322/430 (74.9%; 70.5-78.9) [6]	2/3 (66.7%) [1]	832/1438 (57.9%; 55.3-60.4) [15]	1213/1954 (62.1%; 59.9-64.2) [24]	30/47 (63.8%) [1]	168/307 (54.7%; 49.0-60.4) [3]	715/2500 (28.6%) [1]	913/2854 (32.0%; 30.3-33.7) [5]
Other antibiotics									
Fosfomycin		37/511 (7.2%; 5.1-9.8) [4]	1/3 (33.3%) [1]	92/516 (17.8%; 14.6-21.4) [9]	130/1030 (12.6%; 10.7-14.8) [14]		6/294 (2.0%; 0.8-4.4) [2]		6/294 (2.0%; 0.8-4.4) [2]
Nitrofurantoin		89/368 (24.2%; 19.9-28.9) [2]		36/262 (13.7%; 9.8-18.5) [3]	125/630 (19.8%; 16.8-23.2) [5]		38/280 (13.6%) [1]		38/280 (13.6%) [1]

The data are presented as: number of resistant isolates (numerator)/number of total isolates (denominator) (weighted mean proportion; 95%CI) [N studies]. 95% confidence intervals were estimated using Clopper-Pearson exact method where the number of studies was greater than one.

Pseudomonas aeruginosa

31 reports described 1498 isolates, including 30 hospital reports (1430 isolates) and 2 community reports (68 isolates). In hospitals, the proportion of resistant bacterial isolates was 35.2% (95%CI 32.1-38.3; 322/916) for ceftazidime; 50.3% (44.4-56.3; 145/288) for piperacillin/tazobactam; 37.0% (34.0-40.2; 360/972) for carbapenems; 47.9 (43.0-52.8%; 202/422) for fluoroquinolones; 48.0% (44.9-51.2; 468/974) for gentamicin; 31.7% (28.8-34.7; 311/982) for amikacin, 60.6% (54.9-66.1; 186/307) for tobramycin; and 100% (91.6-100.0; 42/42) for those tested for colistin (**Figure 1.3** and **Table 1.10**). Across the six hospital reports that distinguished HAI and/or CAI, the resistance proportion was 28.7% (21.4-36.8; 41/143) and 15.8% (3/19) for ceftazidime; 62.5% (10/16) and 52.6% (10/19) for piperacillin/tazobactam; 33.5% (29.1-38.1; 148/442) and 36.8% (7/19) for carbapenems; 51.4% (39.4-63.1; 38/74) and 63.2% (12/19) for fluoroquinolones; 29.5% (22.7-37.1; 49/166) and 31.6% (6/19) for gentamicin; and 24.9% (18.5-32.1; 42/169) and 26.3% (5/19) for amikacin. Time series showed that, compared to previous years (2012-2017), recent (2018-2023) resistance proportions decreased for ceftazidime (27.4% [22.1-33.3] vs 42.4% [37.6-47.4%]), piperacillin/tazobactam (26.5% [19.7-34.1] vs 78.2% [70.2-84.9]), gentamicin (33.5% [28.0-39.3] vs 54.6% [49.8-59.4]) and amikacin (25.1% [20.0-30.7] vs 37.7 [33.2-42.3]); and was stable for carbapenems (38.0% [28.8-47.8] vs 41.2% [37.1-45.3]) and fluoroquinolones (54.2% [43.7-64.4] vs 67.6% [60.1-74.6]). There were insufficient data to interpret time trends for tobramycin (**Figure 1.4** and **1.5**). In communities, the proportion of resistant bacterial isolates was 8.9% (3/36) for carbapenems; 8.3% (95%CI 2.3-20.0; 4/48) for ceftazidime; 9.3% (3.1-20.3; 5/54) for fluoroquinolones; 10.5% (4.0-21.5; 6/57) for gentamicin; 1.9% (1/54) for amikacin; and 12.3% (7/57) for tobramycin.

Table 1.10 Numbers and proportions of resistant isolates for *Pseudomonas aeruginosa*-antimicrobial combinations

Antibiotics	Hospitals				Communities		
	Blood	Lower respiratory tract	Other	Total	Blood	Lower respiratory tract	Total
Aminoglycosides							
Amikacin	122/444 (27.5%; 23.4-31.9) [7]	43/104 (41.3%; 31.8-51.4) [5]	146/434 (33.6%; 29.2-38.3) [15]	311/982 (31.7%; 28.8-34.7) [24]	1/54 (1.9%) [1]		1/54 (1.9%) [1]
Gentamicin	204/442 (46.2%; 41.4-50.9) [7]	49/104 (47.1%; 37.2-57.2) [5]	215/428 (50.2%; 45.4-55.1) [17]	468/974 (48.0%; 44.9-51.2) [26]	6/49 (12.2%) [1]	0/8 (0.0%) [1]	6/57 (10.5%; 4.0-21.5) [2]
Tobramycin	72/143 (50.3%; 41.9-58.8) [3]	24/39 (61.5%; 44.6-76.6) [2]	90/125 (72.0%; 63.3-79.7) [3]	186/307 (60.6%; 54.9-66.1) [5]	7/57 (12.3%) [1]		7/57 (12.3%) [1]
Carbapenems	25.3% (16.9-35.2) [2]	70.7% (54.5-83.9) [2]	72.7% [1]	37.0% (34.0-40.2) [19]	10.2% [1]	0.0% [1]	8.9% [1]
Doripenem	24/95 (25.3%; 16.9-35.2) [2]		8/11 (72.7%) [1]	32/106 (30.2%; 21.7-39.9) [3]	3/36 (8.3%) [1]		3/36 (8.3%) [1]
Imipenem	67/308 (21.8%; 17.3-26.8) [6]	29/41 (70.7%; 54.5-83.9) [2]	264/623 (42.4%; 38.5-46.4) [14]	360/972 (37.0%; 34.0-40.2) [19]	4/45 (8.9%) [1]		4/45 (8.9%) [1]
Meropenem	56/236 (23.7%; 18.5-29.7) [4]	50/86 (58.1%; 47.0-68.7) [5]	292/758 (38.5%; 35.0-42.1) [15]	398/1080 (36.9%; 34.0-39.8) [23]	5/49 (10.2%) [1]	0/8 (0.0%) [1]	5/57 (8.8%; 2.9-19.3) [2]
Third-generation cephalosporins	21.0% (17.2-25.2) [7]	50.0% (40.0-60.0) [5]	46.3% (41.3-51.4) [13]	35.2% (32.1-38.3) [22]	10.0% [1]	0.0% [1]	8.3% (2.3-20.0) [2]
Ceftazidime	88/419 (21.0%; 17.2-25.2) [7]	52/104 (50.0%; 40.0-60.0) [5]	182/393 (46.3%; 41.3-51.4) [13]	322/916 (35.2%; 32.1-38.3) [22]	4/40 (10.0%) [1]	0/8 (0.0%) [1]	4/48 (8.3%; 2.3-20.0) [2]
Fluoroquinolones	23.1% (18.8-27.9) [6]	59.0% (47.7-69.7) [4]	59.6% (52.8-66.2) [9]	47.9% (43.0-52.8) [14]	2.2% [1]	50.0% [1]	9.3% (3.1-20.3) [2]
Ciprofloxacin	80/346 (23.1%; 18.8-27.9) [6]	49/104 (47.1%; 37.2-57.2) [5]	216/421 (51.3%; 46.4-56.2) [15]	345/871 (39.6%; 36.3-42.9) [23]	1/46 (2.2%) [1]	4/8 (50.0%) [1]	5/54 (9.3%; 3.1-20.3) [2]

Levofloxacin	23/121 (19.0%; 12.4-27.1) [2]	49/83 (59.0%; 47.7-69.7) [4]	130/218 (59.6%; 52.8-66.2) [9]	202/422 (47.9%; 43.0-52.8) [14]			
Penicillins							
Piperacillin/Tazobactam		43/77 (55.8%; 44.1-67.2) [3]	102/211 (48.3%; 41.4-55.3) [8]	145/288 (50.3%; 44.4-56.3) [10]			
Polymyxin							
Colistin		41/41 (100.0%) [1]	1/1 (100.0%) [1]	42/42 (100.0%; 91.6-100.0) [2]			

The data are presented as: number of resistant isolates (numerator)/ number of total isolates (denominator) (weighted mean proportion; 95%CI) [N studies]. 95% confidence intervals were estimated using Clopper-Pearson exact method where the number of studies was greater than one.

Acinetobacter baumannii

26 reports described 2700 isolates, including 25 hospital reports (2643 isolates) and 2 community reports (57 isolates). In hospitals, the proportion of resistant bacterial isolates was 73.9% (95%CI 70.3-77.3; 471/637) for carbapenems; 66.7% (64.6-68.7; 1378/2066) for gentamicin; 30.6% (28.6-32.6; 642/2099) for amikacin; 31.2% (29.0-33.5; 521/1671) for tigecycline and 47.5% (37.3-57.8; 47/99) for colistin (**Figure 1.3** and **Table 1.11**). Among the five hospital reports that distinguished HAI and/or CAI, the resistance proportion was 92.8% (89.8-95.1; 371/400) and 50.0% (14/28) for carbapenems; 85.3% (75.3-92.4; 64/75) and 21.4% (6/28) gentamicin; and 49.3% (37.6-61.1; 37/75) and 17.9% (5/28) for amikacin. Time series showed that, compared to previous years (2012-2017), recent (2018-2023) resistance proportions increased for gentamicin (78.5% [73.9-82.6] vs 63.8% [61.4-66.1]), amikacin (40.1% [35.0-45.4] vs 27.7% [25.5-29.8] and tigecycline (45.8% [38.6-53.2] vs 28.5% [26.2-30.9]), and was stable for carbapenems (79.8% [75.3-83.8] vs 77.3% [54.6-92.2]) (**Figure 1.4** and **1.5**). In communities, the proportion of resistant bacteria was 23.5% (8/34) for carbapenems; 23.9% (95%CI 12.6-38.8; 11/46) for gentamicin; 27.7% (13/47) for amikacin; and 19.1% (9/47) for tigecycline.

Table 1.11 Numbers and proportions of resistant isolates for *Acinetobacter baumannii*-antimicrobial combinations

Antibiotics	Hospitals				Communities		
	Blood	**Lower respiratory tract**	**Other**	**Total**	**Blood**	**Lower respiratory tract**	**Total**
Aminoglycosides							
Amikacin	119/250 (47.6%; 41.3-54.0) [4]	27/69 (39.1%; 27.6-51.6) [3]	496/1780 (27.9%; 25.8-30.0) [16]	642/2099 (30.6%; 28.6-32.6) [23]	13/47 (27.7%) [1]		13/47 (27.7%) [1]
Gentamicin	180/250 (72.0%; 66.0-77.5) [4]	50/69 (72.5%; 60.4-82.5) [3]	1148/1747 (65.7%; 63.4-67.9) [16]	1378/2066 (66.7%; 64.6-68.7) [23]	11/42 (26.2%) [1]	0/4 (0.0%) [1]	11/46 (23.9%; 12.6-38.8) [2]
Carbapenems	57.5% [1]	76.8% (65.1-86.1) [3]	85.4% (81.8-88.5) [9]	73.9% (70.3-77.3) [12]	23.5% [1]	0.0% [1]	23.5% [1]
Doripenem	69/120 (57.5%) [1]		17/22 (77.3%; 54.6-92.2) [2]	86/142 (60.6%; 52.0-68.7) [3]	8/34 (23.5%) [1]		8/34 (23.5%) [1]
Imipenem	84/184 (45.7%; 38.3-53.1) [3]		387/453 (85.4%; 81.8-88.5) [9]	471/637 (73.9%; 70.3-77.3) [12]	6/36 (16.7%) [1]		6/36 (16.7%) [1]
Meropenem	120/246 (48.8%; 42.4-55.2) [4]	53/69 (76.8%; 65.1-86.1) [3]	1270/2103 (60.4%; 58.3-62.5) [18]	1443/2418 (59.7%; 57.7-61.6) [25]	9/47 (19.1%) [1]	0/4 (0.0%) [1]	9/51 (17.6%; 8.4-30.9) [2]
Tetracycline							
Tigecycline	12/79 (15.2%; 8.1-25.0) [2]	30/69 (43.5%; 31.6-56.0) [3]	479/1523 (31.5%; 29.1-33.8) [11]	521/1671 (31.2%; 29.0-33.5) [16]	9/47 (19.1%) [1]		9/47 (19.1%) [1]
Polymyxin							
Colistin			47/99 (47.5%; 37.3-57.8) [4]	47/99 (47.5%; 37.3-57.8) [4]			

The data are presented as: number of resistant isolates (numerator)/ number of total isolates (denominator) (weighted mean proportion; 95%CI) [N studies]. 95% confidence intervals were estimated using Clopper-Pearson exact method where the number of studies was greater than one.

Staphylococcus aureus

25 reports described 2613 isolates, including 22 hospital reports (1797 isolates) and 6 community reports (816 isolates). In hospitals, the proportion of resistant bacterial isolates was 12.8% (95%CI 8.5-18.3; 25/195) for methicillin; 3.2% (2.4-4.1; 51/1612) for vancomycin; 16.6% (12.5-21.4; 48/289) for clindamycin; and 32.3% (26.1-38.9; 71/220) for erythromycin (**Figure 1.3** and **Table 1.12).** Among the five hospital reports that distinguished HAI and/or CAI, the resistance proportion was unknown (no HAI data) and 62.5% (5/8) for methicillin; 7.4% (4.8-10.8; 24/324) and 0.0% (0/9) for vancomycin; 14.6% (10.4-19.6; 36/247) and unknown (no CAI data) for clindamycin; and 40.0% (2/3) and unknown (no CAI data) for erythromycin. Time series showed that, compared to previous years (2012-2017), recent (2018-2023) resistance proportions decreased for erythromycin (30.0% [14.7-49.4] vs 62.0% [51.2-71.9]), and was stable for methicillin (15.8% [3.4-39.6] vs 21.9% [12.5-34.0]), clindamycin (25.0% [15.5-36.6] vs 12.3% [8.2-17.5]), and vancomycin (0.7% [0.0-3.6] vs 3.2% [2.3-4.2]) (**Figure 1.4 and 1.5**). In communities, the proportion of resistant bacterial isolates was 2.5% (95%CI 1.1-4.6; 9/367) for methicillin; 2.2% (0.6-5.4; 4/185) for vancomycin; 6.7% (3.2-11.9%; 10/150) for clindamycin; and 4.4% (2.4-7.3; 14/317) for erythromycin.

Table 1.12 Numbers and proportions of resistant isolates for *Staphylococcus aureus*-antimicrobial combinations

Antibiotics	Hospitals				Communities			
	Blood	Lower respiratory tract	Other	Total	Blood	Lower respiratory tract	Other	Total
Macrolides								
Erythromycin		2/5 (40.0%) [1]	69/215 (32.1%; 25.9-38.8) [7]	71/220 (32.3%; 26.1-38.9) [8]		0/11 (0.0%) [1]	14/306 (4.6%; 2.5-7.6) [2]	14/317 (4.4%; 2.4-7.3) [3]
Penicillins								
Methicillin[a]	1/7 (14.3%) [1]	6/10 (60.0%; 26.2-87.8) [2]	18/178 (10.1%; 6.1-15.5) [9]	25/195 (12.8%; 8.5-18.3) [12]			9/367 (2.5%; 1.1-4.6) [3]	9/367 (2.5%; 1.1-4.6) [3]
Other antibiotics								
Clindamycin	34/242 (14.0%; 9.9-19.1) [2]	3/7 (42.9%; 9.9-81.6) [2]	11/40 (27.5%; 14.6-43.9) [5]	48/289 (16.6%; 12.5-21.4) [9]	8/77 (10.4%; 4.6-19.4) [2]	0/11 (0.0%) [1]	2/62 (3.2%) [1]	10/150 (6.7%; 3.2-11.9) [4]
Vancomycin	29/539 (5.4%; 3.6-7.6) [3]	5/334 (1.5%; 0.5-3.5) [3]	17/739 (2.3%; 1.3-3.7) [12]	51/1612 (3.2%; 2.4-4.1) [16]	4/123 (3.3%; 0.9-8.1) [2]		0/62 (0.0%) [1]	4/185 (2.2%; 0.6-5.4) [3]

The data are presented as: number of resistant isolates (numerator)/ number of total isolates (denominator) (weighted mean proportion; 95%CI) [N studies]. 95% confidence intervals were estimated using Clopper-Pearson exact method where the number of studies was greater than one. [a]Resistance to methicillin detected using either cefoxitin or oxacillin

Streptococcus pneumoniae

18 reports described 799 isolates, including 8 hospital reports (163 isolates) and 10 community reports (636 isolates). In hospitals, the proportion of resistant bacterial isolates was 29.9% (95%CI 20.5-40.6; 26/87) for penicillin G; 16.4% (7.8-28.8; 9/55) for 3GC; 39.2% (29.7-49.4; 40/102) for co-trimoxazole; 21.2% (12.1-33.0; 14/66) for erythromycin; and 13.5% (5/37) for carbapenems (**Figure 1.3** and **Table 1.13**). Across the three hospital reports that distinguished HAI and/or CAI, the resistance proportion was 66.7% (2/3) and 40.0% (22/55) for penicillin G; 24.3% (9/37) and unknown (no CAI data) for co-trimoxazole; unknown (no HAI data) and 9.8% (4.6-17.8%; 9/92) for 3GC; and unknown (no HAI data) and 15.6% (5/32) for carbapenems. Time series showed that, compared to previous years (2012-2017), recent (2018-2023) resistance proportions were increased for penicillin G (60.0% [14.7-94.7] vs 3.7% [0.1-19.0]) (**Figure 1.4 and 1.5**). In communities, the proportion of resistant bacterial isolates was 23.9% (34/142) for penicillin G; 50.6% (46.6-54.5; 320/633) for co-trimoxazole; and 15.5% (12.5-18.9; 80/516) for erythromycin.

Table 1.13 Numbers and proportions of resistant isolates for *Streptococcus pneumoniae*-antimicrobial combinations

Antibiotics	Hospitals				Communities		
	Blood	**Lower respiratory tract**	**Other**	**Total**	**Lower respiratory tract**	**Other**	**Total**
Carbapenems		0.0% [1]	13.5% [1]	13.5% [1]			
Imipenem			5/37 (13.5%) [1]	5/37 (13.5%) [1]			
Meropenem		0/14 (0.0%) [1]	2/37 (5.4%) [1]	2/51 (3.9%; 0.5-13.5) [2]			
Third-generation cephalosporins	50.0% [1]	7.1% [1]	23.1% (11.1-39.3) [2]	16.4% (7.8-28.8) [4]			
Ceftriaxone	1/2 (50.0%) [1]	1/14 (7.1%) [1]	7/94 (7.4%; 3.0-14.7) [3]	9/110 (8.2%; 3.8-15.0) [5]			
Cefotaxime	0/2 (0.0%) [1]	0/14 (0.0%) [1]	9/39 (23.1%; 11.1-39.3) [2]	9/55 (16.4%; 7.8-28.8) [4]			
Macrolides							
Erythromycin		3/27 (11.1%; 2.4-29.2) [2]	11/39 (28.2%; 15.0-44.9) [2]	14/66 (21.2%; 12.1-33.0) [4]	0/3 (0.0%) [1]	80/513 (15.6%; 12.6-19.0) [8]	80/516 (15.5%; 12.5-18.9) [9]
Penicillins							
Oxacillin		1/13 (7.7%) [1]	16/37 (43.2%) [1]	17/50 (34.0%; 21.2-48.8) [2]		167/367 (45.5%; 40.3-50.8) [6]	167/367 (45.5%; 40.3-50.8) [6]
Penicillin G	2/3 (66.7%) [1]	1/27 (3.7%; 0.1-19.0) [2]	23/57 (40.4%; 27.6-54.2) [2]	26/87 (29.9%; 20.5-40.6) [5]		34/142 (23.9%) [1]	34/142 (23.9%) [1]
Sulfonamides							
Co-trimoxazole	1/1 (100.0%) [1]	7/27 (25.9%; 11.1-46.3) [2]	32/74 (43.2%; 31.8-55.3) [2]	40/102 (39.2%; 29.7-49.4) [5]		320/633 (50.6%; 46.6-54.5) [9]	320/633 (50.6%; 46.6-54.5) [9]

The data are presented as: number of resistant isolates (numerator)/ number of total isolates (denominator) (weighted mean proportion; 95%CI) [N studies]. 95% confidence intervals were estimated using Clopper-Pearson exact method where the number of studies was greater than one.

***Salmonella enterica serovar* Typhi and Paratyphi A (typhoidal)**

7 reports described 562 isolates, including 6 hospital reports (300 isolates) and 1 community report (262 isolates). In hospitals, the proportion of resistant bacterial isolates was 2.8% (95%CI 1.2-5.4; 8/287) for fluoroquinolones; 12.4% (8.0-18.0; 23/186) for co-trimoxazole; 4.8% (2.4-8.4; 11/230) for 3GC; 7.0% (3.8-11.7; 13/185) for ampicillin; and 17.6% (3/17) for chloramphenicol (**Figure 1.3** and **Table 1.14**). In communities, the proportion of resistant bacterial isolates was 0.0% for fluoroquinolones, 3GC and co-trimoxazole (each 0/262) and 0.8% for ampicillin and chloramphenicol (both 2/262).

Neisseria gonorrhoeae

6 reports described 629 isolates, all in communities. The proportion of resistant bacterial isolates was 58.4% (95%CI 54.3-62.4; 347/594) for fluoroquinolones; 3.5% (2.2-5.2; 22/629) for 3GC; 98.2% (160/163) for penicillin G, 1.1% (0.4-2.3; 6/568) for azithromycin; and 0.2% (0.0-1.1; 1/489) for spectinomycin (**Figure 1.3** and **Table 1.15**).

***Shigella* spp.**

5 reports described 1164 isolates, including 4 hospital reports (1107 isolates) and 1 community report (57 isolates). All reports were published more than 5 years ago. In hospitals, the proportion of resistant bacterial isolates was 0.4% (95%CI 0.1-0.9; 4/1107) for fluoroquinolone; 5.1% (2/39) for 3GC; and 68.5% (65.7-71.3; 732/1068) for co-trimoxazole (**Figure 1.3** and **Table 1.16**). In communities, the proportion of resistant bacterial isolates was 0.0% (both 0/57) for fluoroquinolones and 3GC; 70.2% (40/57) for co-trimoxazole; and 3.5% (2/57) for azithromycin (2/57).

Table 1.14 Numbers and proportions of resistant isolates for *Salmonella enterica serovar* Typhi and Paratyphi A (typoidal)-antimicrobial combinations

Antibiotics	Hospitals			Communities	
	Blood	Other	Total	Blood	Total
Third-generation cephalosporins	4.8% (2.4-8.4) [3]	11.8% [1]	4.8% (2.4-8.4) [3]	0.0% [1]	0.0% [1]
Ceftriaxone	6/247 (2.4%; 0.9-5.2) [3]	2/17 (11.8%) [1]	8/264 (3.0%; 1.3-5.9) [4]	0/262 (0.0%) [1]	0/262 (0.0%) [1]
Cefotaxime	11/230 (4.8%; 2.4-8.4) [3]		11/230 (4.8%; 2.4-8.4) [3]		
Ceftazidime	0/50 (0.0%) [1]		0/50 (0.0%) [1]		
Fluoroquinolones	2.1% (0.7-4.8) [3]	13.0% (4.9-26.3) [3]	2.8% (1.2-5.4) [6]	0.0% [1]	0.0% [1]
Ciprofloxacin	2/241 (0.8%; 0.1-3.0) [3]	6/46 (13.0%; 4.9-26.3) [3]	8/287 (2.8%; 1.2-5.4) [6]	0/262 (0.0%) [1]	0/262 (0.0%) [1]
Levofloxacin	5/239 (2.1%; 0.7-4.8) [3]	1/45 (2.2%; 0.1-11.8) [2]	6/284 (2.1%; 0.8-4.5) [5]		
Moxifloxacin		0/28 (0.0%) [1]	0/28 (0.0%) [1]		
Penicillins					
Ampicillin	10/168 (6.0%) [1]	3/17 (17.6%) [1]	13/185 (7.0%; 3.8-11.7) [2]	2/262 (0.8%) [1]	2/262 (0.8%) [1]
Sulfonamides					
Co-trimoxazole	14/168 (8.3%) [1]	9/18 (50.0%; 26.0-74.0) [2]	23/186 (12.4%; 8.0-18.0) [3]	0/262 (0.0%) [1]	0/262 (0.0%) [1]
Other antibiotics					
Chloramphenicol		3/17 (17.6%) [1]	3/17 (17.6%) [1]	2/262 (0.8%) [1]	2/262 (0.8%) [1]

The data are presented as: number of resistant isolates (numerator)/ number of total isolates (denominator) (weighted mean proportion; 95%CI) [N studies]. 95% confidence intervals were estimated using Clopper-Pearson exact method where the number of studies was greater than one

Table 1.15 Numbers and proportions of resistant isolates for *Neisseria gonorrhoeae*-antimicrobial combinations

Antibiotics	Communities	
	Urethral, cervical, pharyngeal and rectal swabs	Total
Aminoglycosides		
Gentamicin	1/163 (0.6%) [1]	1/163 (0.6%) [1]
Third-generation cephalosporins	3.5% (2.2-5.2) [6]	3.5% (2.2-5.2) [6]
Ceftriaxone	22/629 (3.5%; 2.2-5.2) [6]	22/629 (3.5%; 2.2-5.2) [6]
Cefixime	3/440 (0.7%; 0.1-2.0) [4]	3/440 (0.7%; 0.1-2.0) [4]
Fluoroquinolones	58.4% (54.3-62.4) [5]	58.4% (54.3-62.4) [5]
Ciprofloxacin	347/594 (58.4%; 54.3-62.4) [5]	347/594 (58.4%; 54.3-62.4) [5]
Macrolides		
Azithromycin	6/568 (1.1%; 0.4-2.3) [4]	6/568 (1.1%; 0.4-2.3) [4]
Penicillins		
Penicillin G	160/163 (98.2%) [1]	160/163 (98.2%) [1]
Other antibiotics		
Spectinomycin	1/489 (0.2%; 0.0-1.1) [3]	1/489 (0.2%; 0.0-1.1) [3]

The data are presented as: number of resistant isolates (numerator)/ number of total isolates (denominator) (weighted mean proportion; 95%CI) [N studies]. 95% confidence intervals were estimated using Clopper-Pearson exact method where the number of studies was greater than one.

Table 1.16 Numbers and proportions of resistant isolates for *Shigella* spp.-antimicrobial combinations

Antibiotics	Hospitals			Communities	
	Stool[a]	Other	Total	Stool[a]	Total
Third-generation cephalosporins	0.0% (0.0-0.3) [3]	5.1% [1]	5.1% [1]	0.0% [1]	0.0% [1]
Ceftriaxone	0/1068 (0.0%; 0.0-0.3) [3]	1/39 (2.6%) [1]	1/1107 (0.1%; 0.0-0.5) [4]	0/57 (0.0%) [1]	0/57 (0.0%) [1]
Cefotaxime		2/39 (5.1%) [1]	2/39 (5.1%) [1]		
Fluoroquinolones	0.0% (0.0-0.3) [3]	10.3% [1]	0.4% (0.1-0.9) [4]	0.0% [1]	0.0% [1]
Ciprofloxacin	0/1068 (0.0%; 0.0-0.3) [3]	4/39 (10.3%) [1]	4/1107 (0.4%; 0.1-0.9) [4]	0/57 (0.0%) [1]	0/57 (0.0%) [1]
Macrolides					
Azithromycin				2/57 (3.5%) [1]	2/57 (3.5%) [1]
Sulfonamides					
Co-trimoxazole	732/1068 (68.5%; 65.7-71.3) [3]		732/1068 (68.5%; 65.7-71.3) [3]	40/57 (70.2%) [1]	40/57 (70.2%) [1]

The data are presented as: number of resistant isolates (numerator)/ number of total isolates (denominator) (weighted mean proportion; 95%CI) [N studies]. 95% confidence intervals were estimated using Clopper-Pearson exact method where the number of studies was greater than one. [a]Stool specimens include rectal swabs.

Haemophilus influenzae

3 reports described 192 isolates, including 2 hospital reports (107 isolates) and 1 community report (85 isolates). In hospitals, the proportion of resistant bacterial isolates was 38.2% (13/34) for ampicillin; 2.9% (1/34) for 3GC; 3.7% (95%CI 1.0-9.3; 4/107) for fluoroquinolones; and 58.8% (20/34) for co-trimoxazole (**Figure 1.3** and **Table 1.17**). In communities, the proportion of resistant bacterial isolates was 14.1% (12/85) for ampicillin; 0.0% (both 0/85) for 3GC and fluoroquinolones; 25.9% (22/85) for co-trimoxazole; and 1.2% (1/85) for amoxicillin-clavulanic acid.

***Salmonella* spp. (non-typhoidal)**

3 reports described 259 isolates, including 2 reports (176 isolates) in hospitals and 2 reports (83 isolates) in communities. In hospitals, the proportion of resistant bacterial isolates was 16.7% (3/18) for fluoroquinolones; 26.7% (4/15) for 3GC; 16.7% (2/12) for carbapenems; and 8.2% (13/158) for co-trimoxazole (**Figure 1.3** and **Table 1.18**). In communities, the proportion of resistant bacterial isolates was 71.1% (95%CI 60.1-80.5; 59/83) for fluoroquinolones; 75.3% (64.2-84.4; 58/77) for 3GC; 5.3% (1/19) for carbapenems; and 8.9% (5/56) for co-trimoxazole.

Table 1.17 Numbers and proportions of resistant isolates for *Haemophilus influenza*e-antimicrobial combinations

Antibiotics	Hospitals		Communities	
	Other	Total	Other	Total
Third-generation cephalosporins	2.9% [1]	2.9% [1]	0.0% [1]	0.0% [1]
Ceftriaxone			0/85 (0.0%) [1]	0/85 (0.0%) [1]
Cefotaxime	1/34 (2.9%) [1]	1/34 (2.9%) [1]		
Fluoroquinolones	3.7% (1.0-9.3) [2]	3.7% (1.0-9.3) [2]	0.0% [1]	0.0% [1]
Levofloxacin	4/107 (3.7%; 1.0-9.3) [2]	4/107 (3.7%; 1.0-9.3) [2]	0/85 (0.0%) [1]	0/85 (0.0%) [1]
Penicillins				
Amoxicillin-clavulanic acid			1/85 (1.2%) [1]	1/85 (1.2%) [1]
Ampicillin	13/34 (38.2%) [1]	13/34 (38.2%) [1]	12/85 (14.1%) [1]	12/85 (14.1%) [1]
Sulfonamides				
Co-trimoxazole	20/34 (58.8%) [1]	20/34 (58.8%) [1]	16/85 (18.8%) [1]	22/85 (25.9%) [1]

The data are presented as: number of resistant isolates (numerator)/ number of total isolates (denominator) (weighted mean proportion; 95%CI) [N studies]. 95% confidence intervals were estimated using Clopper-Pearson exact method where the number of studies was greater than one.

Table 1.18 Numbers and proportions of resistant isolates for *Salmonella* spp. (non-typhoidal)-antimicrobial combinations

Antibiotics	Hospitals			Communities		
	Blood	**Stool[a]**	**Total**	**Blood**	**Stool[a]**	**Total**
Carbapenems	16.7% [1]		16.7% [1]	5.3% [1]		5.3% [1]
Doripenem	1/16 (6.3%) [1]		1/16 (6.3%) [1]	0/19 (0.0%) [1]		0/19 (0.0%) [1]
Imipenem	2/12 (16.7%) [1]		2/12 (16.7%) [1]	1/19 (5.3%) [1]		1/19 (5.3%) [1]
Meropenem	1/16 (6.3%) [1]		1/16 (6.3%) [1]	0/24 (0.0%) [1]		0/24 (0.0%) [1]
Third-generation cephalosporins	26.7% [1]	0.0% [1]	26.7% [1]	10.5% [1]	100.0% [1]	75.3% (64.2-84.4) [2]
Ceftriaxone	2/13 (15.4%) [1]	0/158 (0.0%) [1]	2/171 (1.2%; 0.1-4.2) [2]	2/21 (9.5%) [1]	56/56 (100.0%) [1]	58/77 (75.3%; 64.2-84.4) [2]
Cefotaxime	4/15 (26.7%) [1]		4/15 (26.7%) [1]	2/19 (10.5%) [1]		2/19 (10.5%) [1]
Ceftazidime	3/13 (23.1%) [1]		3/13 (23.1%) [1]	2/20 (10.0%) [1]		2/20 (10.0%) [1]
Fluoroquinolones	16.7% [1]	1.9% [1]	16.7% [1]	11.1% [1]	100.0% [1]	71.1% (60.1-80.5) [2]
Ciprofloxacin	3/18 (16.7%) [1]	3/158 (1.9%) [1]	6/176 (3.4%; 1.3-7.3) [2]	3/27 (11.1%) [1]	56/56 (100.0%) [1]	59/83 (71.1%; 60.1-80.5) [2]
Levofloxacin	3/18 (16.7%) [1]		3/18 (16.7%) [1]	3/27 (11.1%) [1]		3/27 (11.1%) [1]
Sulfonamides						
Co-trimoxazole		13/158 (8.2%) [1]	13/158 (8.2%) [1]		5/56 (8.9%) [1]	5/56 (8.9%) [1]

The data are presented as: number of resistant isolates (numerator)/ number of total isolates (denominator) (weighted mean proportion; 95%CI) [N studies]. 95% confidence intervals were estimated using Clopper-Pearson exact method where the number of studies was greater than one. [a]Stool specimens include rectal swabs.

Neisseria meningitidis

None of the included reports reported resistance data for *N. meningitidis*.

The resistance estimates for common bacterial pathogens to many of the most accessible and widely used antibiotics in Indonesian hospitalised populations were among the highest reported for the Southeast Asia region (14, 140-143) and, for comparison, were higher than reported for the European Union (144). These findings largely corroborate previous reports on culture data from routine clinical practice in sentinel Indonesian hospitals in 2021, which were not included in this review (**Table 1.19**) (5, 14).

Table 1.19 A comparison between Indonesia, other Southeast Asian countries and the European Union of AMR prevalence estimates for key pathogen-antimicrobial combinations in hospitalized populations

	Indonesia			**Malaysia**	**Philippines**	**Thailand**	**Vietnam**	**European Union**
Country income level	Upper-middle			Upper-middle	Lower-middle	Upper-middle	Lower-middle	High
Population size (in million)[b]	275.5			33.9	115.6	71.7	98.2	448.0
AMR data source[c]	Systematic review (2000-2023)	GLASS (2021) (14)	Indonesian Society for Clinical Microbiology (PAMKI) report (2021) (5)	National Antibiotic Resistance Surveillance report (2021) (140)	AMR Surveillance Program report (2022) (141)	GLASS (2021) (14)	VINARES network (2016-2017) (142)	ECDC report (2021) (144)
3GC resistant- *E. coli*	64%	70%	62%	21%	42%	35%	66%	14%
Carbapenem resistant- *E. coli*	21%	15%	15%	1%	9%	1.6%	11%	0.2%
3GC resistant- *K. pneumoniae*	72%	79%	72%	25%	46%	39%	53%	34%
Carbapenem resistant- *K. pneumoniae*	32%	17%	30%	6%	16%	12%	27%	12%
Ceftazidime resistant- *P. aeruginosa*	35%	NA	34%	8%	15%	17%	46%	16%
Carbapenem resistant- *P. aeruginosa*	37%	NA	38%	9%	15%	18%	45%	18%
Carbapenem resistant- *A. baumannii*	74%	89%	69%	69%	53%	49%	79%	40%
Penicillin resistant- *S. pneumoniae*	30%	20%	NS	3%	16%	38%	58%	16%
Methicillin resistant- *S. aureus*	13%	40%	39%	7%	33%	25%	73%	16%

[a]World Bank Group country classification by income level 2022
[b]Data from World Bank group (https://data.worldbank.org/indicator/SP.POP.TOTL?locations=MY-TH-VN-PH-EU-ID&name_desc=false)
[c]Data shown in table are based on the most recent available data sources.

Abbreviations: 3GC, third generation cephalosporins; ECDC, European Centre for Disease Prevention and Control; GLASS, WHO Global Antimicrobial Resistance Surveillance System; NS, not available; PAMKI, Perhimpunan Dokter Spesialis Mikrobiologi Klinik Indonesia; VINARES, Viet Nam Resistance.

This review found that in hospital settings, around 21% of *E. coli* isolates, 32% of *K. pneumoniae* isolates and 37% of *P. aeruginosa* and 74% of *A. baumannii* isolates were resistant to carbapenems. Moreover, the rising resistance levels to carbapenems in *K. pneumoniae* and *E. coli* over time means that the management of severe infections associated with *Enterobacterales* is increasingly dependent on more expensive and less readily available antibiotics.

The systematic review was limited by substantial variability in populations, methodology and laboratory methods, reporting methods between studies. Studies were overrepresent hospitals that have microbiological laboratory capacity, served complex patient populations with high antibiotic exposure and therefore a higher risk of a drug-resistant infection with unknown blood culture sampling rates; Thus, this may overestimated AMR prevalence. Furthermore, there is unknown data of COVID-19 pandemic impact in AMR in the Indonesia.

1.3 Antimicrobial use and appropriateness of antibiotic prescribing in Indonesia

Representative contemporary data on antibiotic use are lacking, although anecdotal data suggest antibiotic overuse in the healthcare system, widespread over-the-counter use in communities, and high rates of AMR mostly among common Gram-negative bacteria. A comprehensive review on antibiotic use in human health in Indonesia has not been conducted.

1.3.1 Methods

1.3.1.1 Search strategy and selection criteria

We reported this systematic review according to the PRISMA 2020 guidelines (143). The detailed protocol has been registered in the PROSPERO database (CRD42019134641). Five databases (PubMed, EMBASE, Google Scholar, *Garba Rujukan Digital* and *Neliti*) have been used to identify eligible articles, published since 1 January 2000 until 1 June 2021. The searched combined the terms Indonesia, antibiotic, antimicrobial, consumption, prescription, dispensing and stewardship (**Table 1.20)**. The review was limited to antibacterials for systematic human use (J01 category in WHO ATC/DDD index). Only peer-reviewed original articles published in English or Indonesian were included.

Table 1.20 Search strategy

Database	Keywords
PubMed	("Anti-Bacterial Agents"[Mesh] OR "Antibiotic Prophylaxis"[Mesh]) OR ((“anti-bacterial”[tiab] OR “antibiotic”[tiab] OR “antimicrobial”[tiab]) AND (“use”[tiab] OR “usage”[tiab] OR “prescription*”[tiab] OR “prescribing”[tiab] OR “consumption”[tiab] OR “dispensing”[tiab] OR “stewardship”[tiab])) AND ("Indonesia"[tiab] OR "Indonesia"[MeSH])
EMBASE	(((antibiotic or antimicrobial or antibacterial) and (us* or consum* or prescri* or dispensi* or stewardship) and indonesia) not animal not environment not plant not cancer not chemotherapy not carriage not etiology not susceptib* not molecular not vaccine not probiotic).ti,ab.
Google Scholar	indonesia antibiotic|antimicrobial use|usage|prescription|prescribing|consumption|dispensing|stewardship -animal -environment -plant -cancer -chemotherapy -carriage -etiology -susceptible -susceptibility -molecular -vaccine -probiotic
Neliti	(antibiotik)
Garba Rujukan Digital (Garuda)	antibiotik (in title)

Original papers were included if reporting on one or more domains of:

1. Antibiotic consumption: estimates of antibiotic (J01 drug) use in adults expressed as Defined Daily Dose (DDD) normalized to 100 patient-days (for inpatients) or inhabitant-days (for outpatients) (or with alternative units of measure that could be converted). DDD is defined as the assumed average maintenance drug dose per day for its main indication in adults as established by the WHO Collaborating Centre for Drug Statistics and Methodology. For this review, we extracted data on the top-3 antibiotics in each study, then we ranked top-15 antibiotics with the highest DDDs. We grouped them according to the WHO AWaRe (Access, Watch, and Reserve) classification (145). We decided post-hoc to exclude paediatric studies because all studies incorrectly used DDD instead of days of therapy (DOT), as advised by WHO (dose recommendations may differ based on age and weight) (146).
2. Appropriateness of antibiotic prescribing: [a] drug prescription audits using Gyssens method, i.e., an expert panel of at least two reviewers retrospectively evaluates each antibiotic prescription (based on available clinical and microbiological data in the medical record and local guidelines) by sequentially categorizing six indicators: (vi) insufficient data; (v) antibiotic is not indicated; (iv) alternative antibiotic is available that is (iv-a) more effective, (iv-b) less toxic, (iv-c) less costly, (iv-d) has narrower spectrum; inappropriate duration, (iii-a) either too long, (iii-b) or too short; incorrect (ii-a) dose, (ii-b) interval, (ii-c) route; (i) incorrect timing; and (0) appropriate use; [b] studies that assessed antibiotic prescriptions according to named reference guideline(s), based on the following eight pre-defined indicators: no contra-indication or allergy label, indication, drug choice, dose, frequency, duration, route of administration, and overall rational use. We included in this category point prevalence surveys (e.g., Global-PPS, WHO).

We excluded non-human studies; describing or comparing the effectiveness, cost, quality and/or molecular profiles of antibiotics; exclusively targeting particular diagnoses and its treatment; and studies of which the full text could not be accessed. All steps in this systematic literature search were conducted using Mendeley reference management software. Two reviewers independently screened titles and abstracts of all articles, removed duplicate articles and/or datasets and judged full-text articles for relevance and quality. A senior researcher resolved any disagreements.

1.3.1.2 Risk of bias and quality assessment

Because the included studies were neither randomised controlled studies nor comparative studies, traditional methods for assessment of risk of bias were not applicable. To ensure quality, we excluded studies that did not report an essential set of STROBE checklist core items (147), or did not fulfil additional criteria (**Table 1.21**).

Table 1.21 Quality assessment criteria for study inclusion

No	Items	Antibiotic consumption	Antibiotic appropriateness
	STROBE checklist core items		
1	Presents key elements of study design early in the paper (item 4)	●	●
2	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection (item 5)	●	●
3	Give the eligibility criteria, and the sources and methods of selection of participants (item 6)	●	●
4	For each variable of interest, give sources of data and details of methods of assessment (measurement) (item 8)	●	●
5	Explain how the study size was arrived at (item 10)	●	●
6	Report numbers of individuals at each stage of study—e.g., numbers potentially eligible, examined for eligibility, confirmed eligible,	●	●

No	Items	Antibiotic consumption	Antibiotic appropriateness
	included in the study, completing follow-up, and analysed (item 13)		
7	Give characteristics of study participants (e.g., demographic, clinical, social) and information on exposures and potential confounders (item 14)	●	●
	Additional theme-specific items		
8	Minimum study sample size	50	50
9	DDD method correctly applied [a]	●	
10	Gyssens flowchart method correctly applied (including evaluation by at least 2 independent expert reviewers) [b]		●
11	Reference prescribing guidelines specified		●
12	Survey questionnaire/questions available in paper		●
13	Information that is crucial for data interpretation is missing or conflicting	●	●

Abbreviations: DDD, defined daily dose; [a] Definitions and general considerations available from: https://www.whocc.no/ddd/definition_and_general_considera/; [b] Gyssens IC, Antimicrob Chemother 1992:30:724–7; Van Der Meer JWM, Clin Mircobial Infect 2001;suppl6:12–5.

1.3.1.3 Data extraction

Two reviewers extracted data onto a predefined extraction form. We extracted and tabulated data on general article information (first author, year of publication), study design, location, population, health care setting, year of study, study sample size, indicators, interventions, outcome measures and effects, and emerging themes, as appropriate and relevant, based on the author-reported summary estimates (not individual patient-level data).

1.3.1.4 Statistical analysis

Because of the likeliness of unexplained heterogeneity, data on antibiotic consumption and appropriateness of antibiotic prescribing were pooled using a random-effects model meta-analysis (148). Data on antibiotic consumption were pooled with meta-analyses of rates

using the generic inverse variance method, with DDD/100 patient-days as the rate and sample sizes as the denominator. Data on the appropriateness of antibiotic prescribing (each for Gyssens method and reference guidelines) were pooled with meta-analyses of proportions using the generalized linear mixed model (GLMM) with the logit transformation to retain studies with extreme proportions (149). Heterogeneity was assessed using I^2 statistic (low <25%, moderate 25-49%, substantial 50-74%, or high 75-100%) and chi-squared test ($p<0.10$). When two or more studies involved overlapping populations, data synthesis was prioritised to studies with larger sample sizes. Subgroup analyses were then performed by dichotomising the studies based on health care setting (primary vs secondary/tertiary), study location (Java vs non-Java), year of study (before vs after 2016), AWaRe classification (access vs watch antibiotics) (for DDD only), and age groups (adults vs children) (for appropriateness only). We also performed a leave-one-out sensitivity analysis (for DDD and Gyssens) and by replicating the analysis using other transformations (i.e., Freeman-Tukey double arcsine, arcsine, inverse-variance logit, log transformations) and without transformation (for Gyssens only) to assess the robustness of the findings. All meta-analyses were performed in R version 4.1.0 using the additional *meta* (4.18-2), *metafor* (3.0-2), and *forestplot* packages (1.10.1). When appropriate ($k\geq10$), publication bias assessments were performed visually by using funnel plots and quantitatively by using Egger's tests with a significance level set at 10%. The funnel plots were generated by plotting the inverse square root of study sizes against the effect estimates due to the expected variability of study sizes and the fact that conventional funnel plots may be inaccurate in assessing potential publication bias in meta-analyses of proportions (150).

1.3.2 Results

1.3.2.1 Study characteristics

The search strategy gave 9323 hits. After duplicate removal, title and abstract screening and duplicate removal, 551 articles remained. After full-text screening and quality assessment, 67 (12.2%) reports were included (**Figure 1.6**). We summarized characteristics of included studies in **Tables 1.22** and **1.23**. Most studies had an observational design (91.0%, 61/67), and were conducted in hospital settings (83.6%, 56/67), in the public sector (70.6%, 48/68), in Java (67.1%, 45/67), and during the last ten years (97.0%, 65/67).

Figure 1.6 Flow diagram. Reproduced from (24)

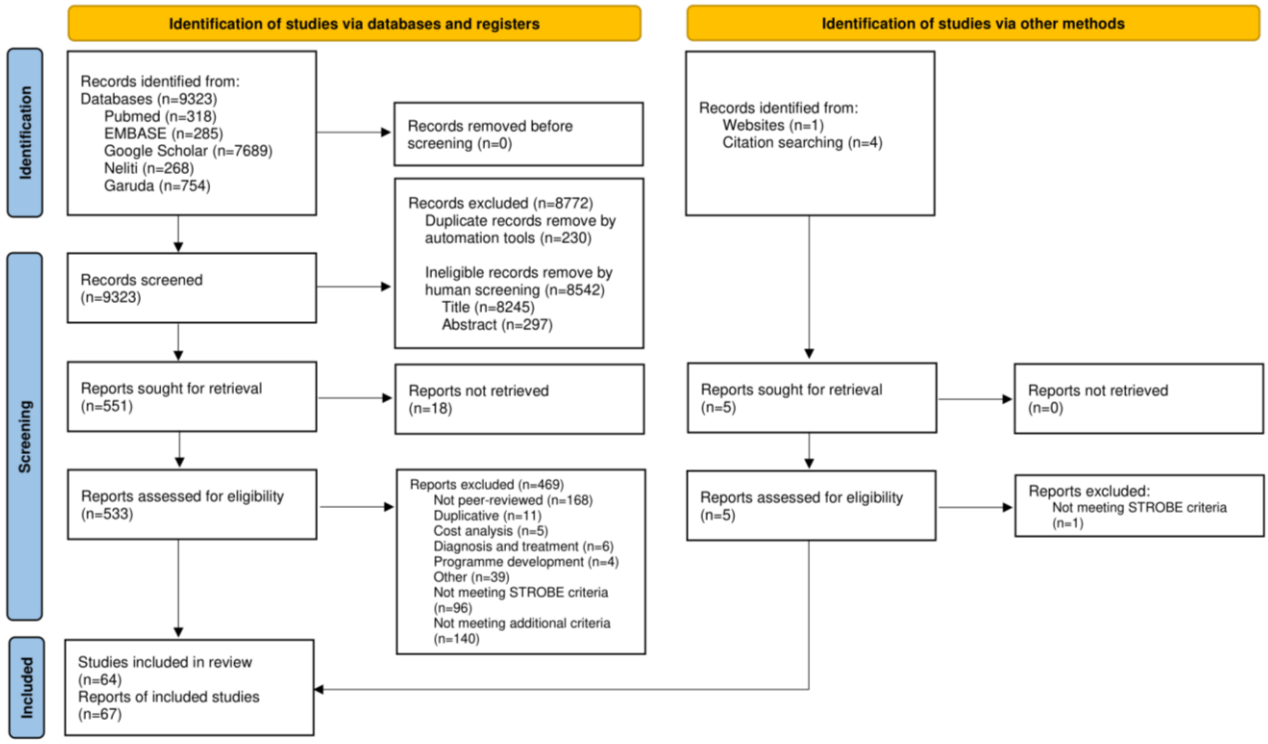


Table 1.22 Characteristics of included reports

Total reports	**N**	**%**
	67	
Domains	**69**	
Antibiotic consumption	20	29.0
Appropriateness of antibiotic prescribing	49	71.0
Gyssens method	18	26.1
Reference guidelines	31	44.9

Total reports	**N**	**%**
	67	
Study design	**67**	
Observational	61	91.0
Pre-post design	6	9.0
Study population	**67**	
Inpatients	56	83.6
Outpatients	11	16.4
Study location	**67**	
Java	45	67.1
Sumatra	12	17.9
Papua and Nusa Tenggara	4	6.0
Sulawesi	2	3.0
Kalimantan	4	6.0
Bali	0	0
Year of study	**67**	
2016-2021	30	44.8
2011-2015	35	52.2
2000-2010	2	3.0
Health care level	**67**	
Primary	17	25.4
Secondary/tertiary	47	70.1
No information provided	3	4.5
Health care sector	**68**	
Public	48	70.6
Private	17	25.0
No information provided	3	4.4

Total N for some characteristics are greater than N=67 because some reports were included in more than category, i.e. for domain (2 reports), and health care sector

Table 1.23 Characteristics of included studies

Table 1.23.a. Antibiotic consumption (20 studies)

No	Author	Year of publication	Year of Study	City, province	Island	Healthcare level	Healthcare sector	Age groups	Study population	No. of population	Study design
1	Andriani (151)	2020	2018-2019	Jambi, Jambi	Sumatra	Primary	Public	Adults	Outpatients	462	Cross-sectional
2	Dirga (152)*	2021	2017	Lampung, Lampung	Sumatra	Secondary	Public	Adults	Internal medicine inpatients	164	Cross-sectional
3	Hadi (153)*	2008	2003-2004	Surabaya, East Java	Java	Tertiary	Public	Adults	Fever inpatients (pre-intervention)	212	Quasi-experimental
4	Herawati (154)	2019	2016	Surabaya, East Java	Java	Secondary	Private	Adults	Surgery inpatients	343	Cross-sectional
5	Kartika (155)*	2019	2018	Semarang, Central Java	Java	Secondary	Public	Adults	Internal medicine inpatients (pre-intervention)	50	Quasi-experimental
6	Kusuma (156)	2016	2013	Banyumas, Central Java	Java	Secondary	Public	Adults	Ob/Gyn inpatients	247	Cross-sectional
7	Mahmudah (157)	2016	2013	Bandung, West Java	Java	Secondary	Private	Adults	Digestive surgery inpatients	208	Cross-sectional
8	Massey (158)	2021	2019	Mataram, West Nusa Tenggara	Nusa Tenggara	Secondary	Public	Adults	Surgery inpatients	323	Cross-sectional
9	Muliani (159)	2021	2019	Surabaya, East Java	Java	Secondary	Private	Adults	Surgery inpatients	164	Cross-sectional
10	Narulita (160)*	2020	2018-2019	Pamekasan, East Java	Java	Secondary	Public	Adults	Surgery inpatients (pre-intervention)	200	Quasi-experimental
11	Perdaka (161)	2020	2017-2018	Jambi, Jambi	Sumatra	Primary	Public	Adults	Outpatients	1255	Cross-sectional
12	Pradipta (162)	2015	2008-2010	Bandung, West Java	Java	Primary	Public	Adults	Outpatients	5,178,106	Cross-sectional
13	Pratama (163)	2019	2016-2017	Surabaya, East Java	Java	Secondary	Public	Adults	Surgery inpatients	463	Cross-sectional
14	Ayunda (164)	2021	2016-2018	Yogyakarta, DIY	Java	Secondary	Private	Adults	Adult inpatients with pneumonia	251	Cross-sectional
15	Rachmawati (165)	2020	2017	Pasuruan, East Java	Java	Secondary	Public	Adults	Internal medicine inpatients	973	Cross-sectional
16	Sholih (166)	2019	2018	Karawang, West Java	Java	Primary	Public	Adults	Inpatients	81	Cross-sectional

No	Author	Year of publication	Year of Study	City, province	Island	Healthcare level	Healthcare sector	Age groups	Study population	No. of population	Study design
17	Susanto (167)	2019	2017-2018	Pekanbaru, Riau	Sumatra	Secondary	Private	Adults	Inpatients (pre-intervention)	5,319	Quasi-experimental
18	Trisia (168)	2020	2017-2018	Jambi, Jambi	Sumatra	Primary	Public	Adults	Outpatients	4,053	Cross-sectional
19	Wikantiananda (169)	2019	2016	(City NA), West Java	Java	Tertiary	Public	Adults	Intensive Care Unit inpatients	57	Cross-sectional
20	Yulia (170)	2017	2016	Surabaya, East Java	Java	Secondary	Private	Adults	Inpatients	695	Cross-sectional

*Studies included in multiple domains.
Abbreviations: NA, not applicable/available; DIY, Daerah Istimewa Yogyakarta; Ob/Gyn, obstetrics and gynaecology

Table 1.23.b. Prescribing appropriateness (49 studies)

No	First author	Year of publication	Year of study	City, Province	Island	Health care level	Healthcare sector	Age groups	Study population	No. of prescription[a]	Study design
Gyssens method											
1	Adani (171)	2015	2014	Semarang, Central Java	Java	Primary	Public	Children	Paediatric inpatients	173	Cross-sectional
2	Aljufri (172)	2021	2017-2019	Semarang, Central Java	Java	Tertiary	Public	Adults	Inpatients with pneumonia	98	Cross-sectional
3	Anggraini (173)	2018	2014	Pontianak, West Kalimantan	Kalimantan	Primary	Public	Mixed	Typhoid inpatients	62	Cross-sectional
4	Hanifah (174)	2018	2017	Semarang, Central Java	Java	Secondary	Private	Mixed	Typhoid inpatients	98	Cross-sectional
5	Hardiana (175)	2021	2019	Jakarta, DKI Jakarta	Java	Tertiary	Public	Adults	Inpatients with pneumonia	88	Cross-sectional
6	Ibrahim (176)	2020	2019	Surabaya, East Java	Java	Tertiary	Public	Adults	Inpatients with infection	84	Cross-sectional
7	Inez (177)	2019	2018	Tanjungpura, West Kalimantan	Kalimantan	Secondary	Public	Children	Inpatients	63	Quasi-experimental

No	First author	Year of publication	Year of study	City, Province	Island	Health care level	Healthcare sector	Age groups	Study population	No. of prescription[a]	Study design
8	Kartika (155)*	2019	2018	Semarang, Central Java	Java	Secondary	Public	Adults	Internal medicine inpatients	50	Quasi-experimental
9	Maakh (178)	2019	2018	Atambua, East Nusa Tenggara	Nusa Tenggara	Secondary	Public	Adults	Ob/Gyn inpatients	100	Cross-sectional
10	Magdalena (179)	2018	2017	Pekanbaru, Riau	Sumatra	Secondary	Private	Adults	ICU and medical ward inpatients	877	Cross-sectional
11	Muthoharoh (180)	2018	2017	Pekalongan, Central Java	Java	Secondary	Public	Mixed	Surgical inpatients	100	Cross-sectional
12	Purwaningsih (181)	2015	2014-2015	Semarang, Central Java	Java	Secondary	Private	Children	Inpatients	385	Cross-sectional
13	Rosdiana (182)*	2018	2016	Pekanbaru, Riau	Sumatra	Secondary	Public	Adults	Inpatients	92	Quasi-experimental
14	Setiawan (183)	2018	2016	Surabaya, East Java	Java	Tertiary	Public	Adults	ICU inpatients	110	Cross-sectional
15	Sumiwi (184)	2014	2013	Bandung, West Java	Java	NA	NA	Adults	Digestive surgery inpatients	344	Cross-sectional
16	Sutrisno (185)	2013	2011-2012	Yogyakarta, DIY DIY	Java	Tertiary	Public	Adults	Pneumonia inpatients	57	Cross-sectional
17	Waridiarto (186)	2015	2015	Semarang, Central Java	Java	Tertiary	Public	Adults	Orthopaedic inpatients	150	Cross-sectional
18	Yoanitha (187)	2018	2016	Bandung, West Java	Java	Tertiary	Public	Adults	Ob/Gyn inpatients	236	Cross-sectional
Reference guidelines											
1	Andrajati (188)	2016	2012	Depok, West Java	Java	Primary	Public	Mixed	Outpatients with various indications	392	Cross-sectional
2	Anggraini (189)	2020	2013	Jakarta, DKI Jakarta	Java	NA	Public	Adults	Pre-surgical inpatients	837	Cross-sectional
3	Bakhtiar (190)	2019	2018	Sorong, West Papua	Papua	Secondary	Public	Adults	Post-surgical inpatients	83	Cross-sectional
4	Benua (191)	2019	2018	Poso, Central Sulawesi	Sulawesi	Primary	Public	Mixed	Acute respiratory infection outpatients	126	Cross-sectional
5	Bestari (192)	2017	2016	(City NA), Central Java	Java	Tertiary	Public	Children	Paediatric pneumonia inpatients	90	Cross-sectional

No	First author	Year of publication	Year of study	City, Province	Island	Health care level	Healthcare sector	Age groups	Study population	No. of prescription[a]	Study design
6	Dania (193)	2016	2014	Yogyakarta, DIY	Java	Secondary	Private	Adults	Ob/Gyn inpatients receiving prophylaxis and therapeutic antibiotics	59	Cross-sectional
7	Dewi (194)	2018	2017	Jakarta, DKI Jakarta	Java	Tertiary	Public	Adults	ICU inpatients with sepsis or septic shock	60	Cross-sectional
8	Dewi (195)	2020	2018	Jambi, Jambi	Sumatra	Primary	Public	Children	Acute respiratory infection outpatients	51	Cross-sectional
9	Dewi (196)	2020	2019	Jambi, Jambi	Sumatra	Primary	Public	Children	Acute respiratory infection outpatients	70	Cross-sectional
10	Dirga (152)*	2021	2017	Lampung, Lampung	Sumatra	Secondary	Public	Adults	Internal medicine inpatients	168	Cross-sectional
11	Elvina (197)	2017	2016	Jakarta, DKI Jakarta	Java	NA	NA	Adults	Inpatients with pneumonia	96	Cross-sectional
12	Fakhrunnisa (198)	2020	2018	Tegal, Central Java	Java	Primary	Public	Mixed	Acute respiratory infection outpatients	632	Cross-sectional
13	Fithria (199)	2015	2013	Semarang, Central Java	Java	Secondary	Private	Children	Inpatients with acute diarrhoea	54	Cross-sectional
14	Grassella (200)	2019	2018	Pontianak, West Kalimantan	Kalimantan	Secondary	Public	Children	Acute respiratory infection outpatients	340	Cross-sectional
15	Harartasyahrani (201)	2021	2020	Prabumulih, South Sumatra	Sumatra	Secondary	Private	Adults	Surgery inpatients	119	Cross-sectional
16	Hasyul (202)	2019	2017	Garut, West Java	Java	Primary	Public	Mixed	Typhoid outpatients	705	Cross-sectional
17	Herlina (203)	2021	2017	Mataram, West Nusa Tenggara	Nusa Tenggara	Secondary	Public	Adults	Urinary tract infection inpatients	105	Cross-sectional
18	Islam (204)	2017	2014	Jakarta, DKI Jakarta	Java	Secondary	Public	Adults	Pneumonia inpatients	139	Cross-sectional
19	Jamiati (205)	2019	2017	Gayo Lues, Aceh	Sumatra	Primary	Public	Mixed	Outpatients	86	Cross-sectional
20	Kaparang (206)	2014	2013	Manado, North Sulawesi	Sulawesi	Tertiary	Public	Children	Pneumonia inpatients	112	Cross-sectional
21	Kurniawati (207)	2021	2019	Yogyakarta, DIY	Java	Secondary	NA	Adults	Urinary tract infection inpatients	61	Cross-sectional

No	First author	Year of publication	Year of study	City, Province	Island	Health care level	Healthcare sector	Age groups	Study population	No. of prescription [a]	Study design
22	Limato (208)	2021	2019	Jakarta, DKI Jakarta	Java	Secondary, Tertiary	Public, Private	Mixed	Inpatients receiving systemic antimicrobials	915	Cross-sectional
23	Nawakasari (209)	2019	2017	Klaten, Central Java	Java	Tertiary	Public	Adults	Urinary tract infection inpatients	76	Cross-sectional
24	Nyoman (210)	2017	2015	Bandung, West Java	Java	Primary	Private	Children	Acute respiratory infection outpatients	425	Cross-sectional
25	Octavia (211)	2019	2018	Lamongan, East Java	Java	Secondary	Private	Adults	Ob/Gyn inpatients (prophylaxis)	54	Cross-sectional
26	Ofisya (212)	2020	2019	Pontianak, West Kalimantan	Kalimantan	Secondary	Public	Mixed	Pneumonia inpatients	86	Cross-sectional
27	Oktaviani (213)	2015	2014-2015	(City NA), Riau	Sumatra	Secondary	Public	Adults	Ob/Gyn inpatients (prophylaxis)	140	Cross-sectional
28	Ovikariani (214)	2019	2019	Semarang, Central Java	Java	Primary	Public	Mixed	Pneumonia outpatients	79	Cross-sectional
29	Rusdiana (215)	2016	2014	Tangerang, West Java	Java	Secondary	Private	Adults	Ob/Gyn inpatients (prophylaxis)	256	Cross-sectional
30	Sugiarti (216)	2015	2014	Malang, East Java	Java	Primary	Public	Children	Acute respiratory infection outpatients	120	Cross-sectional
31	Zazuli (217)	2015	2009	Bandung, West Java	Java	Secondary	Private	Adults	Pre- and post-surgical inpatients	1290	Cross-sectional

*Studies included in multiple domains. [a] For reference guidelines, we reported as total number of prescriptions the highest number reported in a given domain; if no number of prescriptions was reported, we reported total number of patients.

Abbreviations: NA, not applicable/available; DIY, Daerah Istimewa Yogyakarta; Ob/Gyn, obstetrics and gynaecology.

1.3.2.2 Antibiotic consumption

We found 20 reports (5193626 patients) reported data on antibiotic consumption (152-170). Most of the studies were conducted in secondary/tertiary care (16 reports, 76.2%), in Java (14 reports, 66.7%), and between 2016-2021 (17 reports, 81.0%; **Table 1.24**). The pooled estimate of overall antibiotic consumption was 110.1 DDD per 100 patient-days (95% confidence interval [CI] 98.5-121.6; I^2=100%; **Figure 1.7**), with ceftriaxone as the highest consumed antibiotic (60.2 DDD per 100 patient-days [95%CI 34.2-86.1]), followed by ampicillin (28.0 DDD per 100 patient-days [95%CI 0.00-82.8]) and levofloxacin (21.4 DDD per 100 patient-days [95%CI 15.4-27.3]; **Figure 1.8**). Sensitivity analysis found that the pooled estimate was not dominated by a single report (**Figure 1.9**).

We performed subgroup analyses (**Figure 1.8**) and showed higher antibiotic consumption in secondary/tertiary care (134.1 DDD per 100 patient-days [95%CI 88.7-179.6]) than primary care (37.8 DDD per 100 patient-days [95%CI 25.9-49.8]), and in recent years (2016-2021: 123.8 DDD per 100 patient-days [95%CI 100.2-147.3]) than previous years (2000-2015: 55.2 DDD per 100 patient-days [95%CI 18.5-91.9]), but there were no significant differences between Java (114 DDD per 100 patient-days [95%CI 70.7-158.0]) and outside of Java (100.0 [95%CI 68.7-131.3]). Reporting bias or true heterogeneity in antibiotic consumption patterns between studies, hospitals and/or geographic areas was shown by the asymmetrical funnel plot (**Figure 1.10**) and Egger's p=0.047.

Table 1.24 Summary of studies on antibiotic consumption based on DDD

First author	Year of publication	Location	Health care level	Study population	No. of patients	Total antibiotics	Access Antibiotics							Watch Antibiotics							
							Chloramphenicol	Amoxicillin	Ampicillin	Cefazolin	Cefadroxil	Gentamicin	Metronidazole	Cefotaxime	Ceftriaxone	Cefixime	Cefoperazone	Meropenem	Azithromycin	Ciprofloxacin	Levofloxacin
Secondary/tertiary care																					
Dirga (152)	2021	Lampung	Secondary	Internal medicine inpatients	164	116.3	-	-	-	-	-	0.5	22.4	3.9	62.3	1.8	1.5	0.4	3.9	1.5	11.7
Hadi (153)	2008	Surabaya	Tertiary	Fever inpatients (pre-intervention)	212	99.8	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Herawati (154)	2019	Surabaya	Tertiary	Surgery inpatients	343	30.4	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kartika (155)	2019	Semarang	Secondary	Internal medicine inpatients (pre-intervention)	50	103.7	-	0.0	-	-	-	0.7	0.0	3.8	45.9	1.9	-	-	3.2	20.8	27.4
Kusuma (156)	2016	Banyumas	Secondary/ Tertiary	Ob/Gyn inpatients	247	77.7	-	22.7	56.0	1.0	10.7	-	-	6.0	2.3	-	6.0	-	-	-	-
Mahmudah (157)	2016	Bandung	Tertiary	Digestive surgery inpatients	208	18.0	-	-	-	0.0	0.1	0.0	4.6	0.3	8.8	1.1	0.1	0.4	-	0.7	0.1
Massey (158)	2021	Mataram	Secondary	Surgery inpatients	323	414.7	-	9.0	-	-	2.0	-	3.1	23.7	258.6	45.5	2.1	-	-	2.0	16.1
Muliani (159)	2021	Surabaya	Secondary	Surgery inpatients	164	144.3	-	0.7	-	5.1	-	0.2	12.2	0.1	75.6	-	-	20.9	-	-	0.8

First author	Year of publication	Location	Health care level	Study population	No. of patients	Total antibiotics	Access Antibiotics							Watch Antibiotics							
							Chloramphenicol	Amoxicillin	Ampicillin	Cefazolin	Cefadroxil	Gentamicin	Metronidazole	Cefotaxime	Ceftriaxone	Cefixime	Cefoperazone	Meropenem	Azithromycin	Ciprofloxacin	Levofloxacin
Narulita (160)	2020	Pamekasan	Secondary	Surgery inpatients (pre-intervention)	200	197.4	-	-	-	-	-	1.7	12.7	0.1	160.2	-	0.2	1.1	-	17.3	0.1
Pratama (163)	2019	Surabaya	Secondary	Surgery inpatients	463	102.9	-	-	-	11.3	-	1.9	27.3	2.3	53.9	-	-	3.3	-	-	1.1
Ayunda (164)	2021	Yogyakarta	Secondary	Inpatients with pneumonia	251	43.8	-	-	-	-	-	0.4	-	0.1	19.5	2.8	-	0.3	1.3	0.3	4.0
Rachmawati (165)	2020	Pasuruan	Secondary	Internal medicine inpatients	973	75.3	-	0.3	0.1	0.0	4.2	0.1	9.7	2.3	27.8	5.3	-	2.6	0.3	8.4	3.6
Susanto (167)	2019	Pekanbaru	Secondary	Inpatients (pre-intervention)	5319	49.5	-	0.8	-	1.4	-	0.0	-	0.8	14.8	-	1.0	3.4	-	0.6	13.6
Wikantiananda (169)	2019	West Java province	Tertiary	ICU inpatients	57	296.8	-	-	-	3.8	-	2.6	17.0	2.9	30.6	-	-	49.9	-	3.4	143.2
Yulia (170)	2017	Surabaya	Secondary	Hospital-wide inpatients	695	241.3	-	20.6	-	-	-	-	7.1	-	79.2	38.1	-	21.9	-	9.0	34.5
Primary health care																					
Andriani (151)	2020	Jambi	Primary	Out-patients	462	6.9	0.0	4.0	-	-	0.6	-	-	-	-	-	-	-	-	1.9	-
Perdaka (161)	2020	Jambi	Primary	Out-patients	1,255	6.4	0.1	4.6	-	-	0.1	-	-	-	-	-	-	-	-	1.5	-

First author	Year of publication	Location	Health care level	Study population	No. of patients	Total antibiotics	Access Antibiotics							Watch Antibiotics							
							Chloramphenicol	Amoxicillin	Ampicillin	Cefazolin	Cefadroxil	Gentamicin	Metronidazole	Cefotaxime	Ceftriaxone	Cefixime	Cefoperazone	Meropenem	Azithromycin	Ciprofloxacin	Levofloxacin
Pradipta (162)	2015	Bandung	Primary	Out-patients	5,178,106	25.3	0.4	16.8	-	-	-	-	-	-	-	-	-	-	-	1.6	-
Sholih (166)	2019	Karawang	Primary	Inpatients	81	144.5	17.1	65.8	-	-	-	-	-	-	2.7	-	45.9	-	-	12.3	-
Trisia (168)	2020	Jambi	Primary	Out-patients	4,053	6.1	-	3.9	-	-	0.6	-	-	-	-	-	-	-	-	1.1	-

The table summarizes 20 studies on antibiotic consumption, expressed as (or converted to) DDD per 100 patient-days, overall and/or for individual antibiotics, and divided by primary versus secondary/tertiary settings. We listed the 15 antibiotics that were ranked as the top-3 most frequently used antibiotics in at least 2 studies, grouped by Access and Watch. The ATC/DDD versions used in the studied were 2003 (Hadi 2008), 2011 (Dirga 2021, Pradipta 2015, Sholih 2019), 2013 (Kusuma 2016, Trisia 2020), 2017 (Herawati 2019, Narulita 2020), 2018 (Perdaka 2020, Rachmawati 2020), 2019 (Andriani 2020) or not reported (Kartika 2019, Pratama 2019, Mahmudah 2016, Massey 2021, Muliani 2021, Ayunda 2021, Susanto 2019, Wikantiananda 2019, Yulia 2017).

Abbreviations: -, not available; ICU, intensive care unit; Ob/Gyn, Obstetrics and gynaecology

Figure 1.7 Forest plot of 20 reports on the DDD of total antibiotic use. Reproduced from (24)

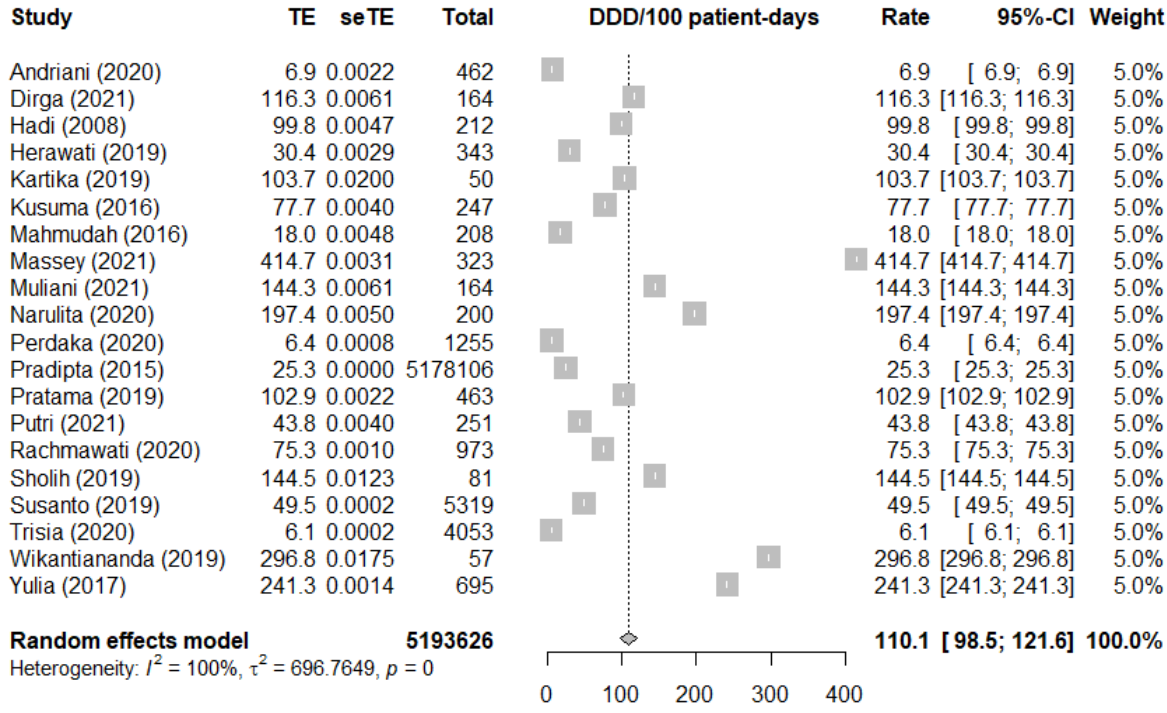
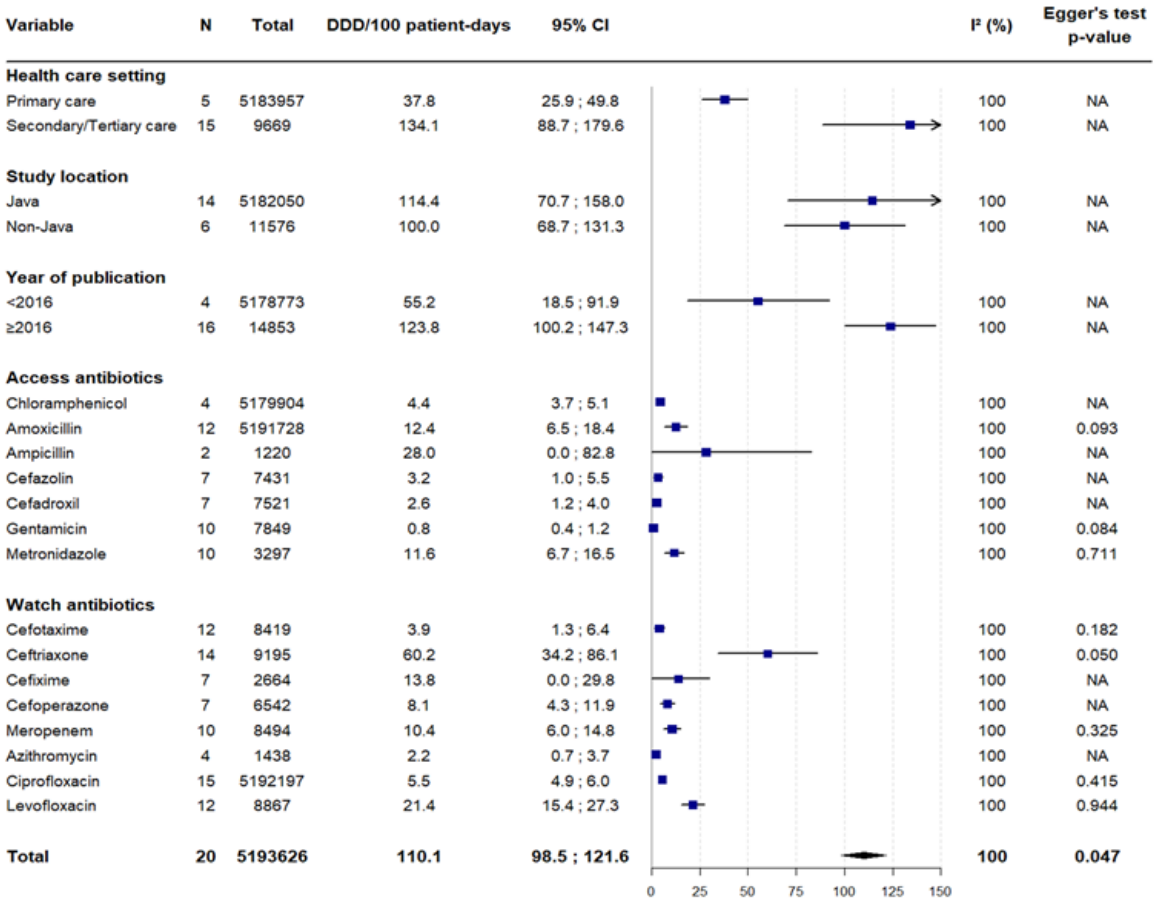


Figure 1.8 Summary forest plot reports on antibiotic consumption. Reproduced from (24)



The figure summarizes 20 reports in the domain antibiotic consumption, expressed as DDD/100 patient-days, for the top-15 antibiotics. Egger's tests to assess publication bias could only be performed for the primary analysis and the individual AWaRe antibiotics.
Abbreviations: CI, confidence interval; DDD, defined daily dose; NA, not applicable.

Figure 1.9 Results of leave-one-out sensitivity analysis for meta-analysis of the DDD of total antibiotic use. Reproduced from (24)

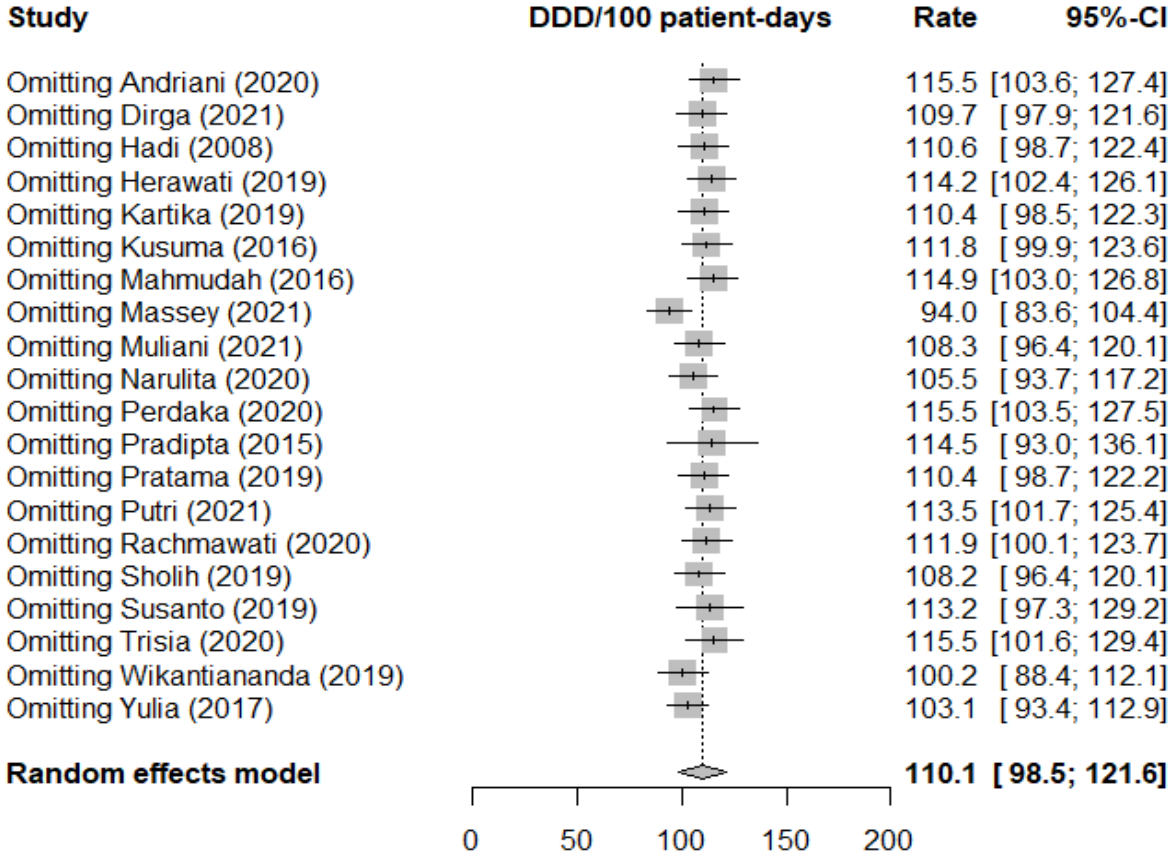
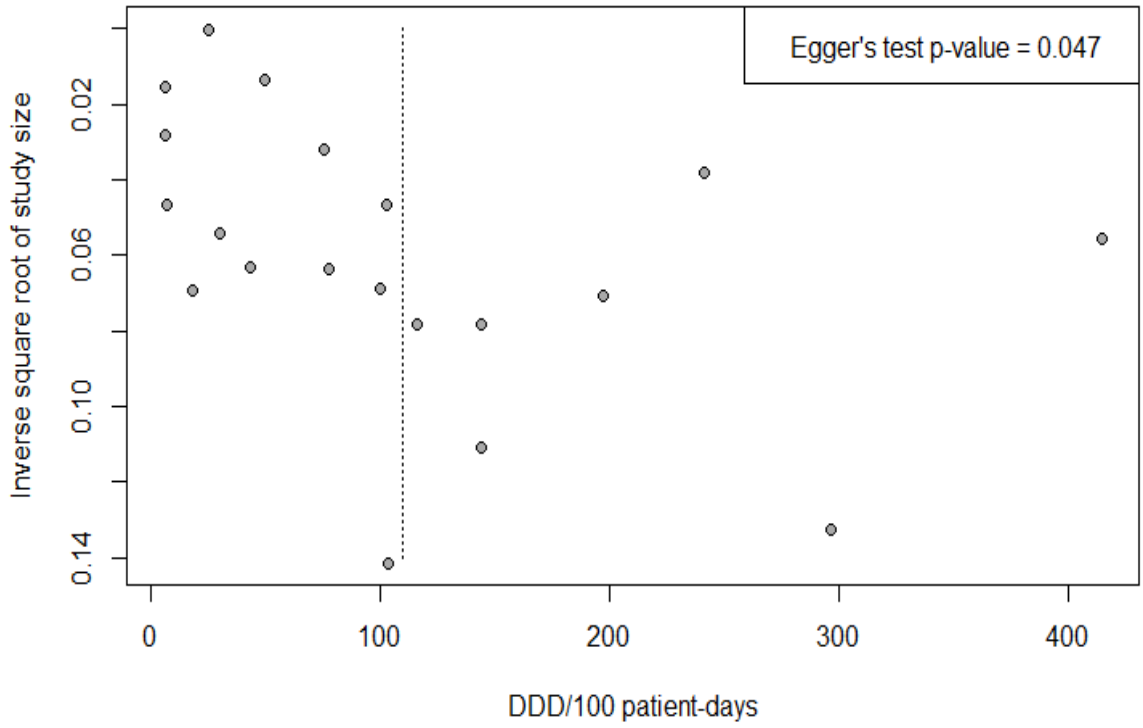


Figure 1.10 Funnel plot indicating evidence of publication bias (as shown by asymmetry) for meta-analysis of the DDD of total antibiotic use. Reproduced from (24)



1.3.2.3 Appropriateness of antibiotic prescribing

A total of 49 reports reported data on the appropriateness of antibiotic prescribing, of which 18 (3,167 prescriptions) used Gyssens method and 31 (7,826 prescriptions) used reference guidelines. Most were conducted in secondary/tertiary care (37 reports, 74.0%), in Java (33 reports, 66.0%), and in adults (29 reports, 58.0%) (**Table 1.25-1.26**).

Table 1.25. Summary of studies on appropriateness of antibiotic prescribing (according to Gyssesns method)

First author	Year of study	Location	Healthcare level	Study population	No. of prescriptions	Classification												
						iv	**v**	**iv**				**iii**		**ii**			**i**	**Appropriate**
								iva	**ivb**	**ivc**	**ivd**	**iiia**	**iiib**	**Iia**	**iib**	**iic**		
Secondary/ tertiary healthcare																		
Aljufri (172)	2017-2019	Semarang	Tertiary	Pneumonia inpatients	98	0.0	0.0	5.1	0.0	-	0.0	0.0	0.0	1.02	5.1	0.0	0.0	88.8
Hanifah (174)	2017	Semarang	Secondary	Typhoid inpatients	98	0.0	0.0	25.5	0.0	15.3	0.0	0.0	11.2	22.4	5.1	0.0	0.0	20.4
Hardiana (175)	2019	Jakarta	Tertiary	Pneumonia inpatients	88	0.0	0.0	7.9	0.0	2.3	0.0	5.7	10.2	0.0	0.0	0.0	0.0	73.9
Ibrahim (176)	2019	Surabaya	Tertiary	Inpatients with infection	84	36.9	11.9	6.0	0.0	0.0	0.0	0.0	0.0	0.0	1.2	0.0	0.0	44.1
Inez (177)	2018	Tanjungpura	Secondary	Paediatric inpatients	63	4.8	82.5	11.1	0.0	0.0	0.0	0.0	1.6	0.0	0.0	0.0	0.0	0.0
Kartika (155)	2018	Semarang	Secondary	Internal medicine inpatients (pre-intervention)	50	0.0	46	12	2.0	0.0	2.0	0.0	2.0	6.0	0.0	2.0	0.0	28.0
Maakh (178)	2018	Atambua	Secondary	Ob/gyn inpatients	100	9.0	7.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	84.0
Magdalena (179)	2017	Pekanbaru	Secondary	ICU inpatients	307	0.0	2.6	6.5	0.0	0.0	4.9	10.1	1.6	3.9	2.6	0.0	0.0	67.8
				Medical ward inpatients	570	0.0	5.3	9.1	0.0	0.0	5.4	4.2	1.8	3.7	1.8	1.4	0.0	67.4
Muthoharoh (180)	2017	Pekalongan	Secondary	Surgical inpatients	100	0.0	13.0	73.0	0.0	1.0	0.0	3.0	0.0	0.0	0.0	0.0	0.0	10.0
Purwaningsih (181)	2014-2015	Semarang	Secondary	Paediatric inpatients	385	-	8.6	22.1	0.0	20.0	1.6	0.0	0.0	44.4	37.7	0.0	0.0	23.9

First author	Year of study	Location	Healthcare level	Study population	No. of prescriptions	Classification												
						iv	**v**	**iv**				**iii**		**ii**			**i**	**Appropriate**
								iva	**ivb**	**ivc**	**ivd**	**iiia**	**iiib**	**Iia**	**iib**	**iic**		
Rosdiana (182)	2016	Pekanbaru	Secondary	Inpatients (pre-intervention)	92	0.0	27.2	35.9	0.0	2.2	0.0	0.0	0.0	1.1	0.0	0.0	0.0	33.7
Setiawan (183)	2016	Surabaya	Tertiary	ICU inpatients	110	31.8	7.3	-	-	-	-	-	-	-	-	-	-	52.7
Sumiwi (184)	2013	Bandung	Secondary	Digestive surgery inpatients	344	-	35.2	57.8	0.0	0.0	0.0	2.0	0.30	1.5	0.3	0.0	0.0	2.9
Sutrisno (185)	2011-2012	Yogyakarta	Tertiary	Pneumonia inpatients	57	0.0	2.0	5.9	0.0	1.0	0.0	7.9	6.9	2.0	6.9	17.8	-	49.5
Waridiarto (186)	2015	Semarang	Tertiary	Orthopaedic inpatients	150	1.3	42	0.0	0.0	0.0	8.0	3.3	0.0	0.0	0.0	0.0	-	45.3
Yoanitha (187)	2016	Bandung	Tertiary	Ob/gyn inpatients	236	0.0	40.3	-	-	-	-	0.0	0.0	0.0	0.0	0.0	0.0	22.0
Primary healthcare																		
Adani (171)	2014	Semarang	Primary	Paediatric inpatients	173	0.0	62.4	1.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	5.2	-	30.6
Anggraini (173)	2014	Pontianak	Primary	Typhoid inpatients	62	0.0	4.8	3.2	0.0	0.0	0.0	0.0	16.1	0.0	0.0	0.0	6.5	69.4

The table summarizes 18 studies on the appropriateness of antibiotic based on the Gyssens method. Gyssens evaluates the quality of each antibiotic prescription by sequentially categorizing 6 indicators from vi to i**:** vi=insufficient data; v=antibiotic is not indicated; iv=alternative antibiotic is available that is more effective (iva), less toxic (ivb), less costly (ivc); has narrower spectrum (ivd); iii=inappropriate duration: too long (iiia) or too short (iiib); ii=incorrect: dose (iia), interval (iib), route (iic); i=incorrect timing

Abbreviations: -, not available; ICU, intensive care unit; Ob/Gyn, Obstetrics and gynaecology.

Table 1.26. Summary of studies on appropriateness of antibiotic prescribing (according to reference guidelines)

First author	Year of study	Location	Health care level	Study population	No. of prescriptions	Appropriate (%)								Reference guidelines
						No contra-indication/ allergy label	**Indication**	**Drug choice**	**Dose**	**Dosing frequency**	**Duration**	**Administration route**	**Overall rational Use**	
Secondary/tertiary health care														
Anggraini (189)	2020	Jakarta	Secondary	Pre-surgical inpatients	837	-	-	0.5	0. 5	-	-	0.5	0.0	IN
Bakhtiar (190)	2018	Sorong	Secondary	Post-surgical inpatients	83	94	100	100	100	-	92.8	100	79.5[a]	IN
Bestari (192)	2016	Central Java	Tertiary	Paediatric pneumonia inpatients	90	100	100	72.2	9.2	-	-	-	8.9	NH
Dania (193)	2014	Yogyakarta	Secondary	Ob/gyn inpatients (therapy)	59	-	-	-	-	-	100	-	-	IHB
Dewi (194)	2017	Jakarta	Tertiary	Adult ICU inpatients with sepsis or septic shock	60	-	-	66.7	48.3	-	-	-	-	I
Dirga (152)	2017	Lampung	Secondary	Internal medicine inpatients	168	100	98.8	89.3	52.9	-	-	-	-	INBH
Elvina (197)	2016	Jakarta	Secondary	Adult inpatients with pneumonia	96	-	-	86.5	91.7	-	74	-	-	INB
Fithria (199)	2013	Semarang	Secondary	Paediatric inpatients with acute diarrhoea	54	-	-	0	-	-	-	-	-	IB
Grassella (200)	2018	Pontianak	Secondary	Paediatric ARI outpatients	340	99.7	91.7	72.9	72.6	96.5	56.8	100	-	NBW
Harartasyahrani (201)	2020	Prabumulih	Secondary	Pre-surgical inpatients	119	-	-	92.4	86.4	7.3	40	100	6.7	IN
Herlina (203)	2017	Mataram	Secondary	UTI inpatients	105	-	-	100	100	99.1	88.6	-	-	I
Islam (204)	2014	Jakarta	Tertiary	Pneumonia inpatients	139	-	-	5.7	88.5	-	60.4	-	-	INB W
Kaparang (206)	2013	Manado	Tertiary	Paediatric pneumonia inpatients	112	100	100	100	91.1	-	88.4	-	-	NHB
Kurniawati (207)	2019	Yogyakarta	Secondary	UTI inpatients	61	-	-	100	88.5	98.4	88.5	100	-	IB

Limato (208)	2019	Jakarta	Secondary, Tertiary	Hospital-wide inpatients	915	-	-	52.2	-	-	-	-	-	HN
Nawakasari (209)	2017	Klaten	Tertiary	UTI inpatients	76	100	100	96.1	27.6	-	-	-	-	INBH
Octavia (211)	2018	Lamongan	Secondary	Ob/gyn inpatients (prophylaxis)	54	-	-	98.1	100	100	-	100	-	I
Ofisya (212)	2019	Pontianak	Secondary	Pneumonia inpatients	86	-	100	93	68.6	-	62.8	-	-	IN
Oktaviani (213)	2014-2015	Riau	Secondary	Ob/gyn inpatients (prophylaxis)	140	-	-	34.3	65.7	100	72.9	100	-	INB
Rusdiana (215)	2014	Tangerang	Secondary	Ob/gyn inpatients (prophylaxis)	256	-	-	0.0	7.8	0	-	100	-	B
Zazuli (217)	2009	Bandung	Secondary	Pre- and post-surgical inpatients	1290	-	99.6	-	97.2	-	-	-	-	IB
Primary health care														
Andrajati (188)	2012	Depok	Primary	Outpatients with various indications	392	-	-	87.2	-	98.2	59.4	-	43.9	N
Benua (191)	2018	Poso	Primary	ARI outpatients	126	-	100	-	80.9	80.9	100	100	-	N
Dewi (194)	2018	Jambi	Primary	Paediatric ARI outpatients	70	98.5	100	54.2	-	48.5	1.4	-	-	N
Dewi (196)	2019	Jambi	Primary	Toddler ARI outpatients	51	100	100	-	100	-	0	-	-	N
Fakhrunnisa (198)	2018	Tegal	Primary	ARI outpatients	632	-	-	78.0	90.5	98.2	33.7	-	1.7	N
Hasyul (202)	2017	Garut	Primary	Typhoid outpatients	705	-	96.9	58.3	63.3	-	49.8	-	-	N
Jamiati (205)	2017	Aceh	Primary	Outpatients	86	-	54.6	-	60.5	83.7	26.7	-	-	N
Nyoman (210)	2015	Bandung	Primary	Paediatric ARI outpatients	425	-	100	96.5	42.2	-	52.8	-	-	I
Ovikariani (214)	2019	Semarang	Primary	ARI outpatients	79	100	23.0	23.0	82.3	-	-	-	-	N
Sugiarti (216)	2014	Malang	Primary	Paediatric ARI outpatients	120	-	24.2	100	8.9	-	-	-	-	N

The table summarizes 31 studies on appropriateness of antibiotic prescribing, based on antibiotic prescribing reference guidelines (as provided in the article), divided by primary and secondary/tertiary care settings. Appropriateness is defined by the following indicators: indication, drug choice, dose, frequency/interval, duration, and route of administration. An antibiotic prescription was classified as rational use if all indicators were scored as compliant with the reference guideline by the authors.

Abbreviations: ARI, acute respiratory infection; -, not available; UTI, urinary tract infection; ICU, intensive care unit; Ob/Gyn, obstetrics and gynaecology; I, international; N, national; H, hospital; B, book; W, website

The pooled estimate for the appropriateness of antibiotic prescribing was 35.3% (95%CI 20.7-53.4%; I^2=97.2%) (**Figure 1.11**) based on the Gyssens method. Confidence analysis showed that the overall estimate was not dominated by a single study (**Figure 1.12**) and was similar between approximation methods (**Figure 1.13**). The funnel plot was fairly symmetrical (Egger's p=0.108; **Figure 1.14**), indicating low risk of bias from small-study effects. Subgroup analyses showed higher appropriateness of antibiotic prescribing in adults (43.1% [95%CI 25.9-62.2%] than in children (8.4% [95%CI 0.6-57.9%]), but there were no significant differences between primary care 49.4% [95% CI 23.7-75.4%]) vs secondary/tertiary care (32.3% [95%CI 17.9-51.0%]), Java (31.4% [95%CI 18.8-47.6%]) vs elsewhere (38.1% [95%CI 6.2-85.0%], and recent years (2016-2021: 39.1% [95%CI 19.4-63.0%] vs previous years (2000-2015: 26.1% [95%CI 12.4-47.1%] (**Figure 1.15 (A)**).

Most individual indicators of appropriateness scored excellent (>80%), except for duration (65.8% [95%CI 38.6-85.5%]) (**Figure 1.15 (B)**) and overall rational antibiotic use (8.0% [95%CI 1.0-43.6%]) based on reference guidelines. Between-study heterogeneity was substantial (75-100%) for all indicators, except for administration route (I^2=0%, p>0.999) and no contraindication/allergy label (I^2=6.4%, p=0.382). Possible small-study effects were found for indication and duration (Egger's test p=0.092 and p=0.074, respectively). Subgroup analysis showed higher appropriateness of duration in secondary/tertiary care (80.0% [95%CI 66.0-89.2%]) than primary care (34.5% [95%CI 4.3-86.1%]), and in adults (83.2% [95%CI 65.3-92.9%] than children (17.9% [95%CI 1.2-79.4%]; **Figure 1.16**), and higher appropriateness of drug choice, dosing, and overall rational use outside of Java (95.2% [95%CI 73.9-99.3%], 90.0% [95%CI 71.1-97.1%], and 34.5% [95%CI 3.1-89.8%] than in Java (70.0% [95%CI 23.2-94.7%], 67.2% [95%CI 32.3-89.8%), and 3.3% [95%CI 0.3-32.0%]; **Figure 1.17-1.19,** respectively) –although the latter differences were not

statistically significant. There were no significant differences for no contraindication/allergy label, indication, dosing frequency, or administration route (**Figure 1.20-1.23**).

Figure 1.11 Forest plot showing results of meta-analysis on the overall appropriateness of antibiotic prescribing according to Gyssens method (18 reports). Reproduced from (24)

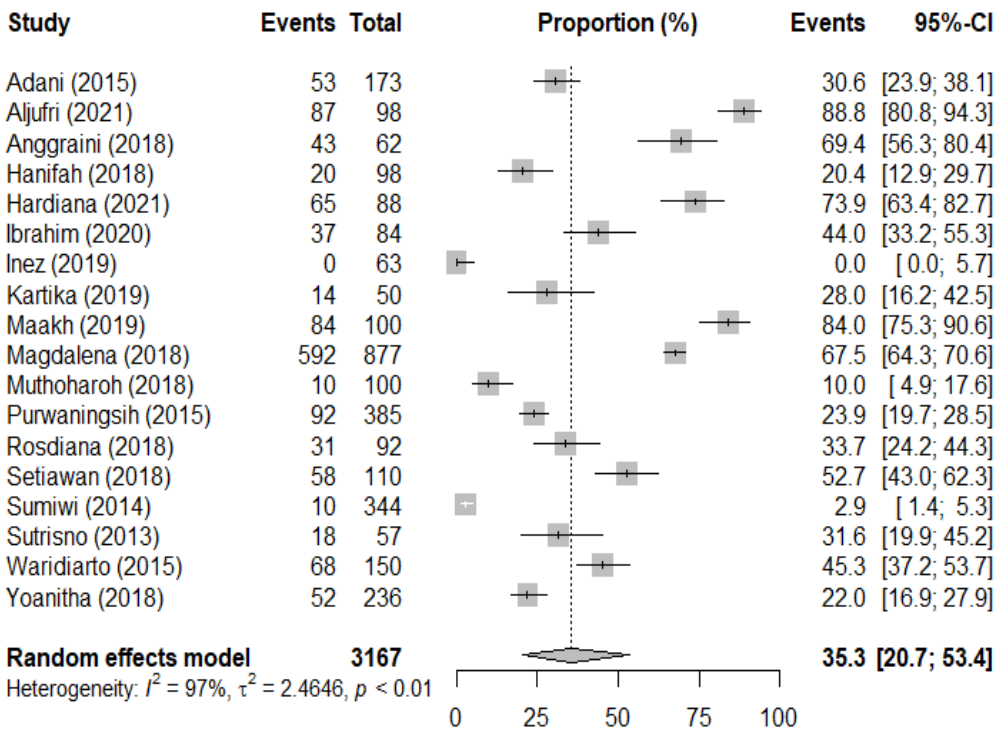


Figure 1.12 Results of leave-one-out sensitivity analysis for meta-analysis on the overall appropriateness of antibiotic prescribing according to Gyssens method. Reproduced from (24)

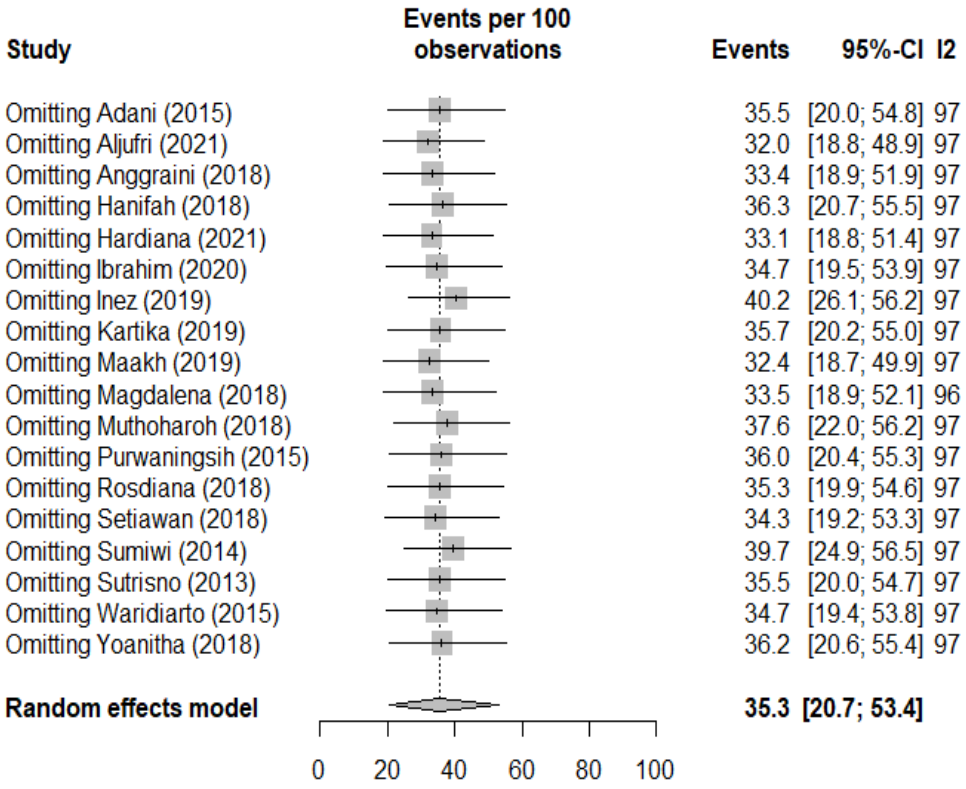


Figure 1.13 Results of sensitivity analysis for meta-analysis on the overall appropriateness of antibiotic prescribing according to Gyssens method by using alternative methods other than GLMM method. Reproduced from (24)

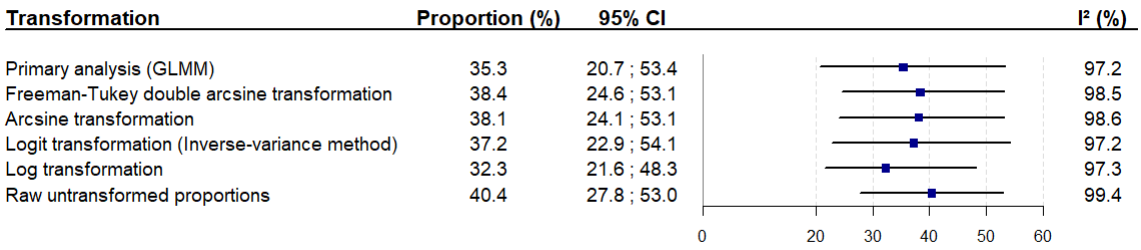


Figure 1.14 Funnel plot for the meta-analysis on the overall appropriateness of antibiotic prescribing according to Gyssens method. The relatively symmetrical funnel plot and the non-significant Egger's test indicate that no publication bias is detected. Reproduced from (24)

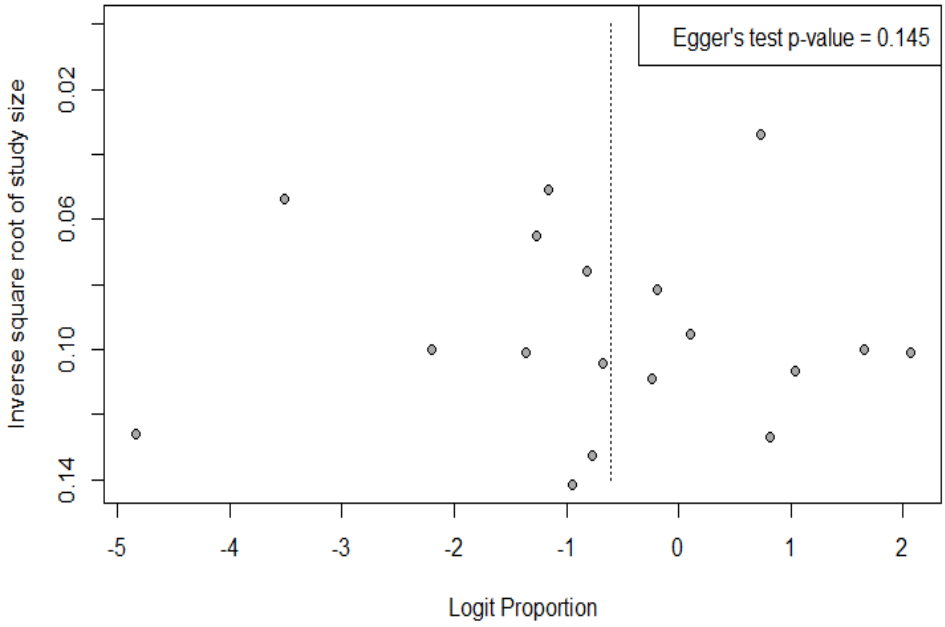
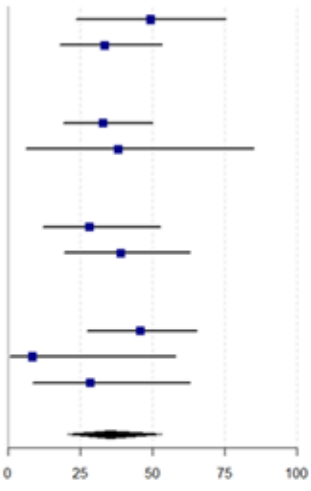


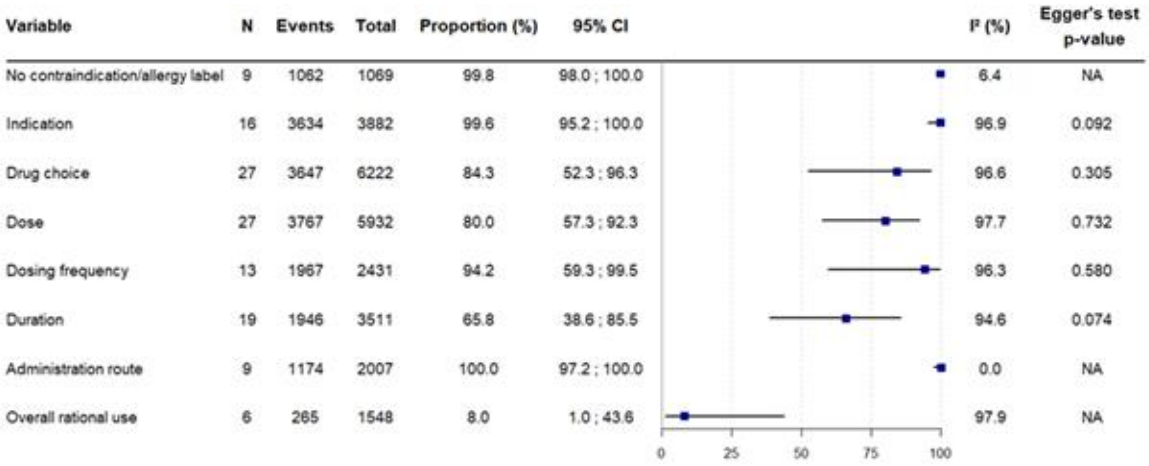
Figure 1.15 Summary forest plot on prescribing appropriateness. Reproduced from (24)
(A) Overall appropriateness of antibiotic prescribing based on Gyssens method (18 reports)

Variable	N	Events	Total	Proportion (%)	95% CI	I^2 (%)	Egger's test p-value
Health care setting							
Primary care	2	96	235	49.4	23.7 ; 75.4	96.1	NA
Secondary/Tertiary care	16	1238	2932	33.5	18.1 ; 53.4	97.4	NA
Study location							
Java	13	584	1973	32.9	19.2 ; 50.2	95.9	NA
Non-Java	5	750	1194	38.1	6.2 ; 85.0	92.2	NA
Year of publication							
<2016	6	284	1171	28.1	12.1 ; 52.6	96.1	NA
≥2016	12	1050	1996	39.1	19.4 ; 63.0	96.8	NA
Age groups							
Adults	12	1116	2286	45.9	27.5 ; 65.5	97.2	NA
Children	3	145	621	8.4	0.6 ; 57.9	28.7	NA
Mixed	3	73	260	28.5	8.5 ; 63.1	96.5	NA
Total	**18**	**1334**	**3167**	**35.3**	**20.7 ; 53.4**	**97.2**	**0.145**



The figure summarizes 49 reports in the domain prescribing appropriateness based on Gyssens method (A) or reference guidelines (B). Indicators (B) were reported by different numbers of studies. Egger's test to assess publication bias in Gyssens method (A) could only be performed for the primary analysis.
Abbreviations: CI, confidence interval; NA, not applicable.

(B) Overall appropriateness of antibiotic prescribing based on reference guidelines (30 reports)



The figure summarizes 49 reports in the domain prescribing appropriateness based on Gyssens method (A) or references guidelines (B). Indicators (B) were reported by different numbers of studies. Egger's test to assess publication bias in Gyssens method (A) could only be performed for the primary analysis.
Abbreviations: CI, confidence interval; NA, not applicable.

Figure 1.16 Summary forest plot of 19 reports on the appropriateness of antibiotic prescribing according to the "duration" indicator in the reference guidelines. Reproduced from (24)

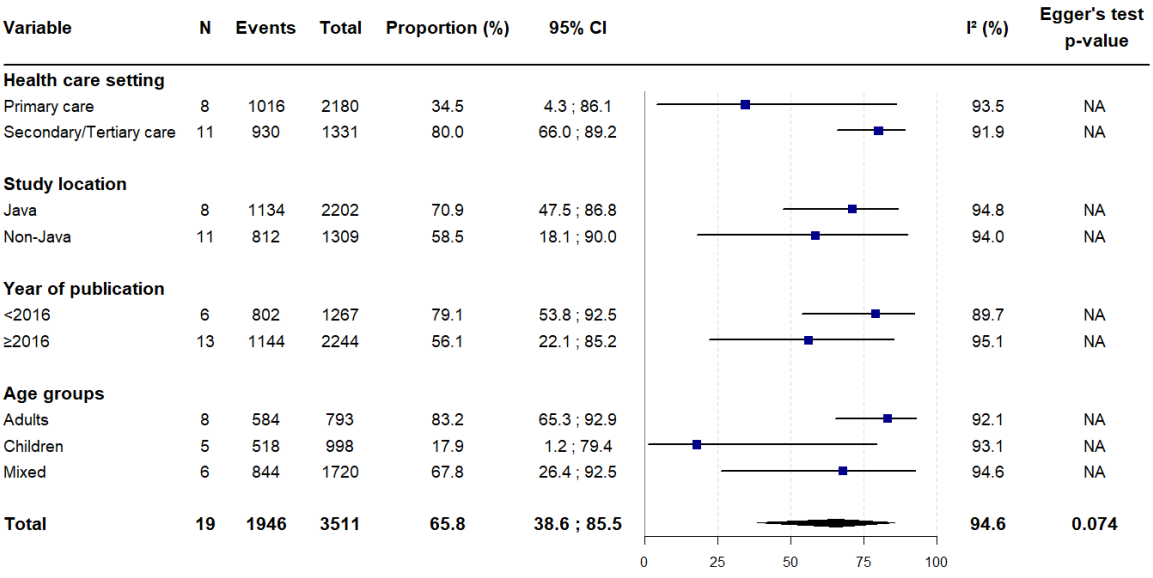


Figure 1.17 Summary forest plot of 27 reports on the appropriateness of antibiotic prescribing according to the "drug choice" indicator in the reference guidelines. Reproduced from (24)

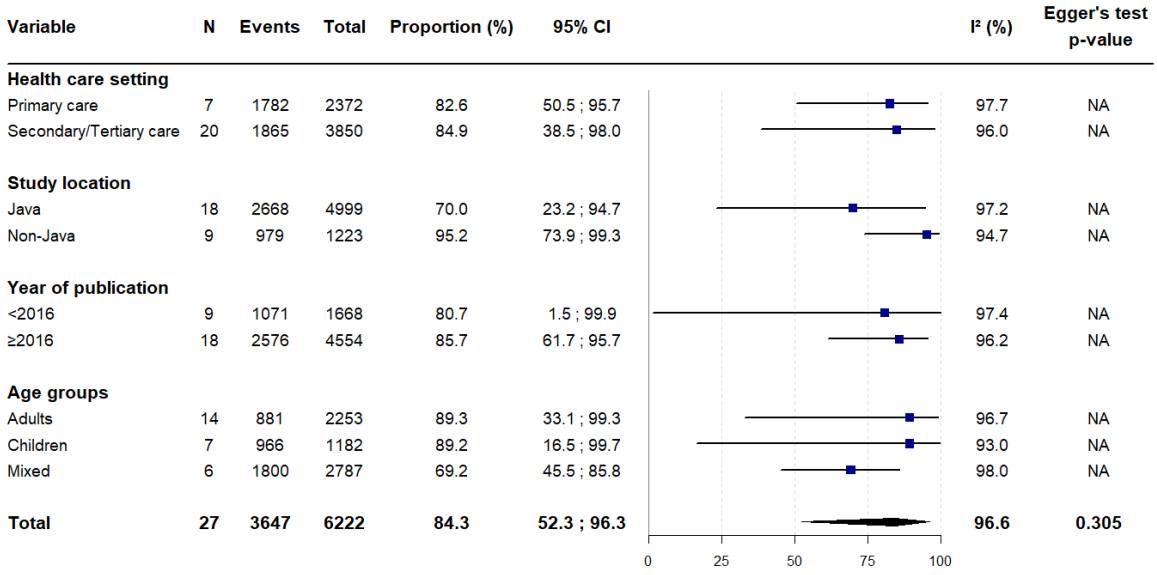


Figure 1.18 Summary forest plot of 27 reports on the appropriateness of antibiotic prescribing according to the "dose" indicator in the reference guidelines. Reproduced from (24)

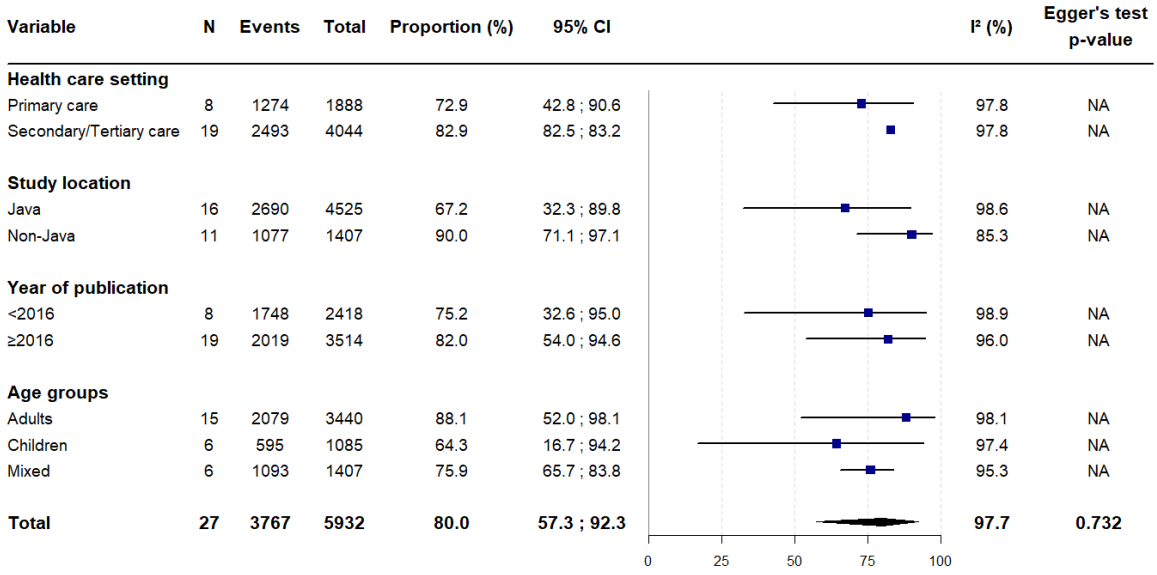
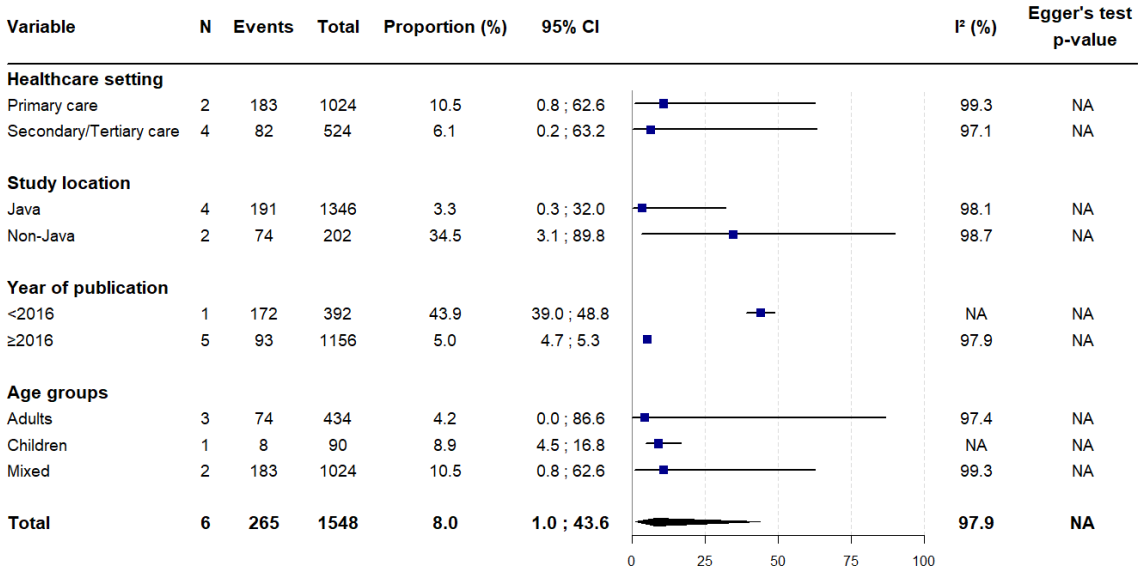
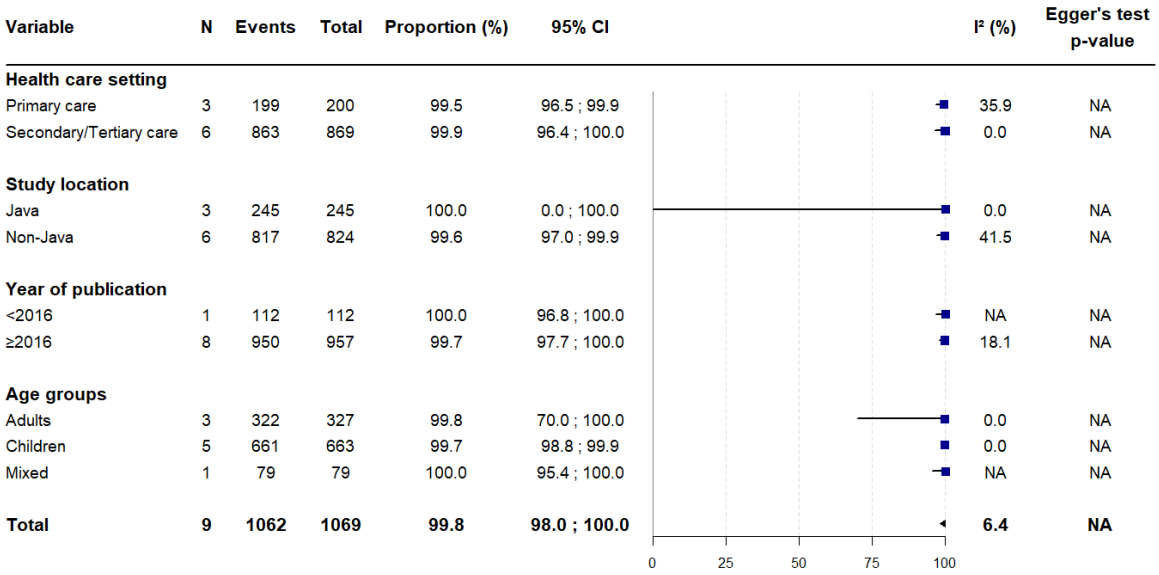


Figure 1.19 Summary forest plot of 6 reports on the appropriateness of antibiotic prescribing according to the "overall rational use" indicator in the reference guidelines. Reproduced from (24)



Variable	N	Events	Total	Proportion (%)	95% CI	I² (%)	Egger's test p-value
Healthcare setting							
Primary care	2	183	1024	10.5	0.8 ; 62.6	99.3	NA
Secondary/Tertiary care	4	82	524	6.1	0.2 ; 63.2	97.1	NA
Study location							
Java	4	191	1346	3.3	0.3 ; 32.0	98.1	NA
Non-Java	2	74	202	34.5	3.1 ; 89.8	98.7	NA
Year of publication							
<2016	1	172	392	43.9	39.0 ; 48.8	NA	NA
≥2016	5	93	1156	5.0	4.7 ; 5.3	97.9	NA
Age groups							
Adults	3	74	434	4.2	0.0 ; 86.6	97.4	NA
Children	1	8	90	8.9	4.5 ; 16.8	NA	NA
Mixed	2	183	1024	10.5	0.8 ; 62.6	99.3	NA
Total	**6**	**265**	**1548**	**8.0**	**1.0 ; 43.6**	**97.9**	**NA**

Figure 1.20 Summary forest plot of 9 reports on the appropriateness of antibiotic prescribing according to the "no contraindication/allergy label" indicator in the reference guidelines. Reproduced from (24)



Variable	N	Events	Total	Proportion (%)	95% CI	I² (%)	Egger's test p-value
Health care setting							
Primary care	3	199	200	99.5	96.5 ; 99.9	35.9	NA
Secondary/Tertiary care	6	863	869	99.9	96.4 ; 100.0	0.0	NA
Study location							
Java	3	245	245	100.0	0.0 ; 100.0	0.0	NA
Non-Java	6	817	824	99.6	97.0 ; 99.9	41.5	NA
Year of publication							
<2016	1	112	112	100.0	96.8 ; 100.0	NA	NA
≥2016	8	950	957	99.7	97.7 ; 100.0	18.1	NA
Age groups							
Adults	3	322	327	99.8	70.0 ; 100.0	0.0	NA
Children	5	661	663	99.7	98.8 ; 99.9	0.0	NA
Mixed	1	79	79	100.0	95.4 ; 100.0	NA	NA
Total	**9**	**1062**	**1069**	**99.8**	**98.0 ; 100.0**	**6.4**	**NA**

Figure 1.21 Summary forest plot of 16 reports on the appropriateness of antibiotic prescribing according to the "indicators" indicator in the reference guidelines. Reproduced from (24)

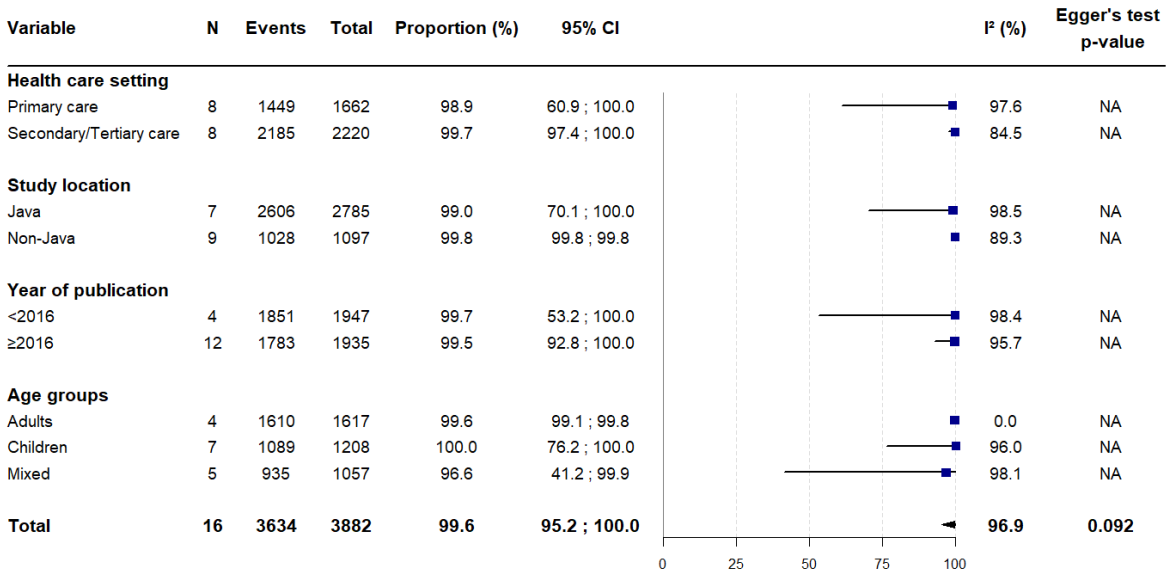


Figure 1.22 Summary forest plot of 13 reports on the appropriateness of antibiotic prescribing according to the "dosing frequency" indicator in the reference guidelines. Reproduced from (24)

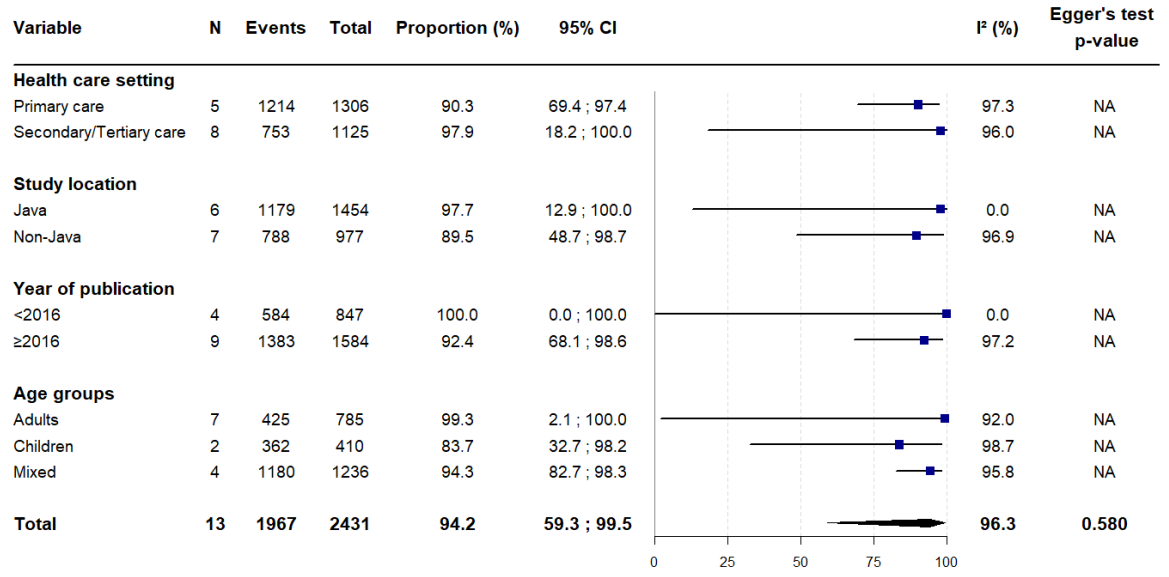
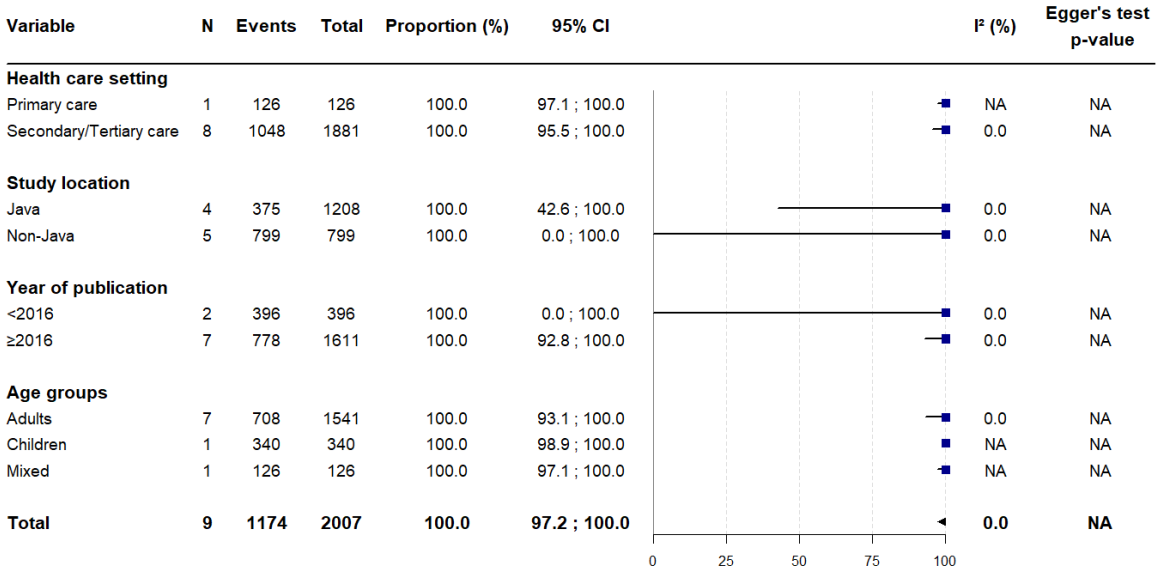


Figure 1.23 Summary forest plot of 9 reports on the appropriateness of antibiotic prescribing according to the "administration route" indicator in the reference guidelines. Reproduced from (24)



This systematic review is limited by the ability to draw firm conclusions on the contemporary nationwide antibiotic use situation in Indonesia due to heterogeneity of data and study methodology. Publications were predominantly from Java Island. Pooled inpatient and outpatient antibiotic use were used for capturing a nationwide antibiotic use in Indonesia, although this method could create bias due to heterogeneity of infection severity between patient in the different study populations. In addition, there is unknown data of COVID-19 pandemic impact in the antimicrobial use and appropriateness of antibiotic prescribing in Indonesia.

1.4 Thesis outline

The focus of this DPhil thesis is the epidemiology of hospital AMR infections, blood culture utilization, diagnostic and antibiotic use practices, ASP implementation in Indonesia, and the impact of the COVID-19 pandemic on the epidemiology. In particular, the specific objectives are to (1) evaluate epidemiology of AMR BSI, blood culture

utilization; (2) develop and evaluate clinical diagnostic practices and antibiotic use practices parameters; (3) assess the current state of nation-wide ASP implementation, and identify barriers and enablers of ASP implementation in Indonesian hospitals at the hospital-, district-, and province-level.

Specific objective 1 (Chapter 2): to evaluate epidemiology of AMR BSI, blood culture utilization, and the impact of the COVID-19 pandemic on the AMR BSI and blood culture utilization in the Indonesian national referral hospital.

I conducted a two-years retrospective surveillance study on AMR BSI and blood culture utilization in the Indonesian national referral hospital. Data on blood culture, included the medical record number (MRN), admission date, specimen type, specimen date, culture and AST result were collected from the Hospital Information System Management. Hospital admission data included MRN, admission date, discharge date and healthcare reimbursement program were collected from the routine in-patient electronic records. Analyses were performed to evaluate blood culture utilization and epidemiology of AMR BSI in the Indonesian national referral hospital before and during the COVID-19 pandemic. The blood culture utilization rate, proportion and incidence of resistance were calculated. Poisson regression models were used to assess changes in rate over time.

Specific objective 2 (Chapter 3): to evaluate clinical diagnostic practices and antibiotic use practices, and the impact of the COVID-19 pandemic on those practices in the Indonesian national referral hospital.

I developed clinical diagnostic and antibiotic use practice parameters intended for use in resource-limited settings to monitor and evaluate hospital diagnostic and antimicrobial stewardship efforts. The aims are to improve monitoring on outcome of hospital

stewardships programmes (e.g. increase in specimens submitted for bacterial culture according to standard operating procedures (SOPs) and DDDs per 1,000 patient-days) and patient outcome (e.g. in-hospital mortality), in addition to measurement on processes of hospital stewardship progammes (e.g., presence of SOPs and how many medical charts are reviewed). I used Fine and Grey subdistribution hazard model to evaluate two years diagnostic practices and antibiotic use practices in the Indonesian national referral hospital.

Specific objective 3 (Chapter 4): to assess the current state of nation-wide ASP implementation in Indonesian hospitals, and the impact of the COVID-19 pandemic on the ASP elements implementation.

I conducted a cross-sectional, online, self-administered questionnaire-based survey, using a data collection instrument which I developed based on six core elements of ASP and additional items on the influence of COVID-19, among hospitals across all 34 provinces in Indonesia. I supplemented this survey with focus group discussions (FGDs) among hospital ASP leaders and team members representing different hospital types, stages of ASP implementation and resource availability. The aims are to assess the current ASP implementation in Indonesian hospitals, the impact of COVID-19 pandemic on ASP programmes in Indonesian hospitals and to identify barriers and enablers of ASP implementation in Indonesian hospitals at the national and province-level. A mixed-method approach with explanatory sequential design to contextualize combined quantitative and qualitative data was used. First, I used ordinal regression models to estimate associations between the ASP implementation score and explanatory variables at the hospital and district levels. Subsequently, I used practical thematic analysis to further explore the barriers and enablers of ASP implementation. I integrated the enablers and barriers to ASP

implementation identified from the quantitative and qualitative findings using the SEIPS framework, and formulated recommended future actions.

Conclusions (Chapter 5): Discussions, implications, and future research directions

I summarized the main findings and discussed how overall findings contribute to the growing literature on the epidemiology of hospital AMR infections, blood culture utilization, diagnostic and antibiotic use practices, ASP implementation in Indonesia. I also discussed the implication of the available evidence for health policy and the potential directions for future work.

Chapter 2
Blood Culture Utilization and Epidemiology of Antimicrobial-Resistant Bloodstream Infections before and during the COVID-19 Pandemic in the Indonesian National Referral Hospital

2.1 Abstract

Background

There is a lack of data on blood culture utilization and AMR infections in LMICs. In addition, there has been a concern for increasing AMR infections among COVID-19 cases in LMICs. I investigated epidemiology of AMR BSI before and during the COVID-19 pandemic in the Indonesian national referral hospital.

Methods

I evaluated blood culture utilization rate, and proportion and incidence rate of AMR-BSI caused by WHO-defined priority bacteria using routine hospital databases from 2019 to 2020. I classified a patient as a COVID-19 case if their SARS-CoV-2 RT-PCR result was positive. I defined the proportion of resistance as the ratio of the number of patients having a positive blood culture for a WHO global priority resistant pathogen per the total number of patients having a positive blood culture for the given pathogen. I used Poisson regression models to assess changes in rate over time.

Results

Of 60,228 in-hospital patients, 8,175 had at least one blood culture taken (total 17,819 blood cultures), giving a blood culture utilization rate of 30.6 per 1,000 patient-days. A total of 1,311 patients were COVID-19 cases. Blood culture utilization rate had been

increasing before and during the COVID-19 pandemic (utilization rate ratio 1.02 per month; 95%CI 1.01-1.02, p<0.001), and was higher among COVID-19 cases than non-COVID-19 cases (43.5 vs. 30.2 per 1,000 patient-days, p<0.001). The most common pathogens identified were *K. pneumoniae* (23.3%), *Acinetobacter* spp. (13.9%) and *E. coli* (13.1%). The proportion of resistance for each bacterial pathogen was similar between COVID-19 and non-COVID-19 cases (all p>0.10). Incidence rate of hospital-origin AMR-BSI increased from 130.1 cases per 100,000 patient-days in 2019 to 165.5 in 2020 (incidence rate ratio 1.016 per month, 95%CI:1.016-1.017, p<0.001), and was not associated with COVID-19 infection (p=0.96).

Conclusions

In my setting, AMR-BSI incidence and etiology were similar between COVID-19 and non-COVID-19 cases. Incidence rates of hospital-origin AMR-BSI increased in 2020, which was likely due to increased blood culture utilization. I recommend increasing blood culture utilization and generating AMR surveillance reports in LMICs to inform local health care providers and policy makers.

2.2 Introduction

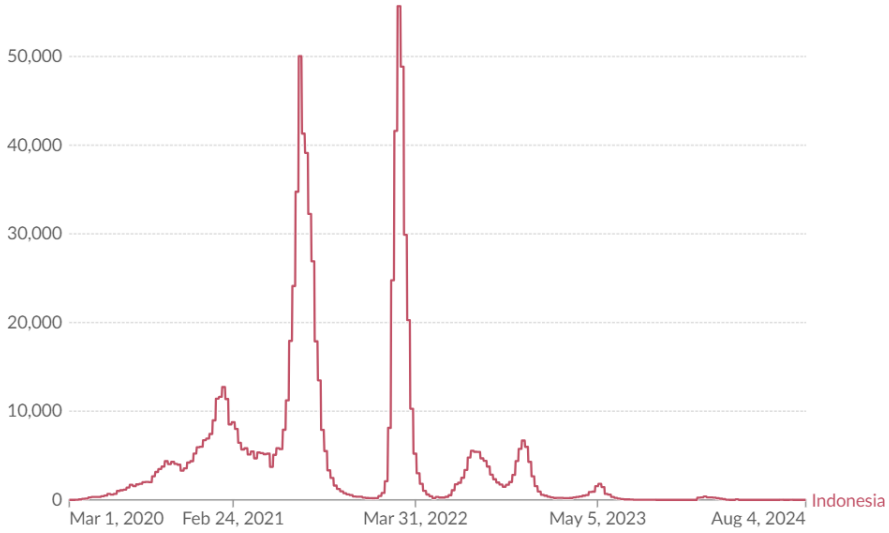
AMR bacterial infections pose a global health problem, with a disproportionate impact in LMICs (2, 3). The COVID-19 pandemic has potentially escalated this problem due to increased use of antibiotics in patients hospitalized with COVID-19 and increased opportunities for hospital-acquired infections that are resistant among patients admitted with COVID-19, particularly with large patient numbers and overcrowded hospitals (6-12).

Microbiology laboratories with blood culture facility hold a critical function of diagnosing the bacterial etiology of infection and monitoring the AMR situation. The Surviving Sepsis Campaign International Guidelines recommend performing blood culture before starting antimicrobial therapy in patients presenting with sepsis (218). Blood culture can be used to identify pathogenic organisms causing either community or hospital-acquired BSI; hence, blood culture results can guide definitive antimicrobial choices for each individual patient. In addition, antibiogram and surveillance reports can be used to monitor the epidemiology of AMR infections, guide empirical antimicrobial choices to population, identify practice that worsen AMR, detect outbreak, enable emergency preparedness, and risk assessment (World Health Organization [WHO], 219).

There is a lack of systematic surveillance networks evaluating blood culture utilization and burden of AMR infections in LMICs, including Indonesia. Indonesia is a lower-middle-income country in Southeast Asia with the world's fourth largest population. A range of complex factors, e.g. limited laboratory infrastructure and limited specialized health care practitioners, lack of regulations on antimicrobial use and high burden of infectious diseases have hampered the implementation of the Indonesian National Action Plan for AMR (220-222). Indonesia first reported AMR surveillance key indicators to the WHO GLASS in 2021 (13). The blood culture utilization in Indonesia is lower than Thailand (9% patients sampled for blood cultures out of all inpatients in Makassar versus 21% in Thailand in 2015) (223), which could lead to an underestimation of incidence rates and an overestimation of the proportion of AMR infection as has been modelled previously (224). Thus, it is crucial to evaluate blood culture utilization rate together with the trend of AMR infections, particularly in LMICs (224).

Indonesia has been highly impacted by the COVID-19 pandemic. Following the first two confirmed cases of SARS-CoV-2 infection in Indonesia on March 2nd 2020, there was a rapid increase with three pandemic waves of COVID-19 patients reaching 5.8 million confirmed cases and 1506,000 deaths countrywide at March 2022 (**Figure 2.1**) (225). Here, I evaluated blood culture utilization and epidemiology of AMR-BSIs in the Indonesian national referral hospital before and during the COVID-19 pandemic.

Figure 2.1 Daily new confirmed cases of COVID-19 in Indonesia. Reproduced from (226)



2.3 Methods

2.3.1 Study design, setting and population

I conducted a retrospective hospital-wide surveillance study on inpatients in the Cipto Mangunkusumo National Hospital, the Indonesian national referral hospital in Jakarta, Indonesia, from 1 January 2019 to 31 December 2020.

2.3.2 Data collection

I used routine databases of hospital admission and microbiology of the Indonesian national referral hospital. At the hospital, blood culture collection was determined by attending physicians based on the national standard practice, i.e. blood culture recommended to be collected in sepsis patient prior to intravenous antibiotic administration (227). Blood cultures were routinely performed at the microbiology laboratory of the Department of Clinical Pathology (International Organization for Standardization [ISO] 15189, ISO 17205 and Joint Committee International accredited). A BacT/ALERT 3D automated microbial detection system machine was used. Isolated bacteria were identified using conventional bacterial identification methods and Vitek®2 (bioMerieux, Inc. Durham, USA). AST was performed using the Kirby-Bauer disc diffusion method according to Clinical and Laboratory Standards Institute guidelines (228). I obtained blood culture and hospital admission data through the Hospital Information System Management.

2.3.3 Definitions

I defined the blood culture utilization rate is as the ratio of the number of blood cultures per 1,000 patient-days (224). I defined blood culture contamination as the isolation of one or more common commensal organisms listed on National Healthcare Safety Network the Centers for Disease Control and Prevention (CDC) list 2022 in only one set of blood culture or one of a series of two or more blood culture (229). I defined the blood culture contamination rate as the ratio of the number of blood culture contamination per number of total blood cultures (230).

I used the definitions of infection origin as proposed by World Health Organization (WHO) GLASS. For deduplication purposes, I included only the first isolate per patient, per pathogen, per study period in the analyses (231).

My target pathogens were 12 bacteria species in the WHO global priority pathogens list 2017 (232). I defined the parameters of resistance in **Table 2.1**. Moreover, as proposed by the WHO GLASS (231), I also estimated the incidence rate of AMR BSI per 100,000 tested patients as described previously (224).

Table 2.1 Definition of parameters of AMR

Parameter of AMR	Definition
Proportion of resistance	Ratio of the number of patients having a positive blood culture for a WHO global priority resistant pathogen per the total number of patients having a positive blood culture for the given pathogen (233).
Incidence rate of community-origin AMR BSI	Ratio of the number of patients with community-origin AMR BSI per 1,000 admissions (37).
Incidence rate of hospital-origin AMR BSI	Ratio of the number of patients with hospital-origin AMR BSI for each pathogen and antibiotic per 100,000 bed-days at risk of hospital-acquired infection. Patients were considered at risk of hospital-acquired infection after they stayed in the hospital for more than 2 calendar days (37).
Patients tested for community-origin BSI	Patients with the first blood culture performed within the first two calendar days of admissions during the reporting period (37).
Patients tested for hospital-origin BSI	Patients with the first blood culture performed after the first two calendar days of admissions during the reporting period (37).

Footnote: AMR = antimicrobial resistance, BSI = bloodstream infection. The denominator to calculate incidence rate of community-origin and hospital-origin AMR BSI were determined based on risk of acquiring community-origin (i.e. admission) and hospital-origin (i.e. patient-days) AMR BSI.

I classified a patient as a COVID-19 case if their SARS-CoV-2 RT-PCR result was positive at any point during the admission period. The year 2019 and 2020 was regarded as before and during the COVID-19 pandemic, respectively.

2.3.4 Ethics

The Faculty of Medicine Universitas Indonesia Ethics Committee (KET-115/UN2.F1/ETIK/PPM.00.02/2021) and Oxford Tropical Research Ethics Committee (Reference: 503-22) approved the study. The requirement for patient consent was waived as this was a secondary analysis of anonymised routine surveillance data. Permission was obtained from the hospital's Innovation and Intellectual Property Directorate to use the routine hospital database for this study.

2.3.5 Data analysis

I used Pearson's chi-squared test and Fisher's Exact test to compare categorical variables between groups. I used Kruskal Wallis to compare continuous variables between groups.

I compared the blood culture utilization rate, contamination rate, proportion of isolated pathogens, and proportions and incidence rates of AMR BSI between COVID-19 and non-COVID-19 cases and between patients admitted in 2019 and 2020. I used Poisson regression models to assess changes in rate per month over time. I performed all data analyses using the Statistical software for data science (STATA) version 15.1 (StataCorp, College Station, TX, USA). I visualized figures with GraphPad Prism version 8.3.0 (La Jolla, California, USA). I also generated an overall AMR surveillance report using AutoMated tool for Antimicrobial resistance Surveillance System (AMASS) (233).

2.4 Results

2.4.1 Baseline characteristics

Of 91,960 admissions (from 60,228 patients) admitted during the study period, 1,373 (from 1,311 patients) were COVID-19 cases (**Figure 2.1** and **Table 2.1**). In 2019, prior to the

COVID-19 pandemic, the number of hospital admissions per month was relatively stable with a mean of 4,085 (range 3,374-4,818; **Figure 2.1**). At the start of the COVID-19 pandemic, the number of hospital admissions per month decreased sharply from 4,162 in March 2020 to 2,514 in April 2020 (39% decrease). The proportion of COVID-19 admissions per total admissions increased from 0.7% (31 admissions) in March 2020 and reached the highest to 9.7% (393 admissions) in December 2020. Overall, the total numbers of admissions per year was higher in 2019 at 49,014 (of 31,903 patients) than in 2020 at 42,946 (of 28,325 patients) (12% difference; **Table 2.1**).

2.4.2 Blood culture utilization

Of 60,228 patients, 8,175 had at least one blood culture taken (total 17,819 blood cultures). Total patient-days during the study period were 583,248, giving a blood culture utilization rate of 30.6 per 1,000 patient-days. 2,735 patients had at least two blood cultures sampled within a single admission, and the median duration between the first and second blood culture was 5 calendar days (inter quartile range [IQR] 3-8 calendar days).

The blood culture utilization rate showed an increasing trend over 2019, before the COVID-19 pandemic, from 16.7 per 1,000 patient-days in January 2019 to 28.1 in December 2019 (utilization rate ratio [URR] 1.02 per month; 95% Confidence Interval (CI) 1.01-1.02, $p<0.001$, **Figure 2.2B**). This increasing trend continued throughout 2020 (URR 1.02 per month; 95% CI 1.01-1.02, $p<0.001$).

Figure 2.2 Flow diagram. Reproduced from (122)

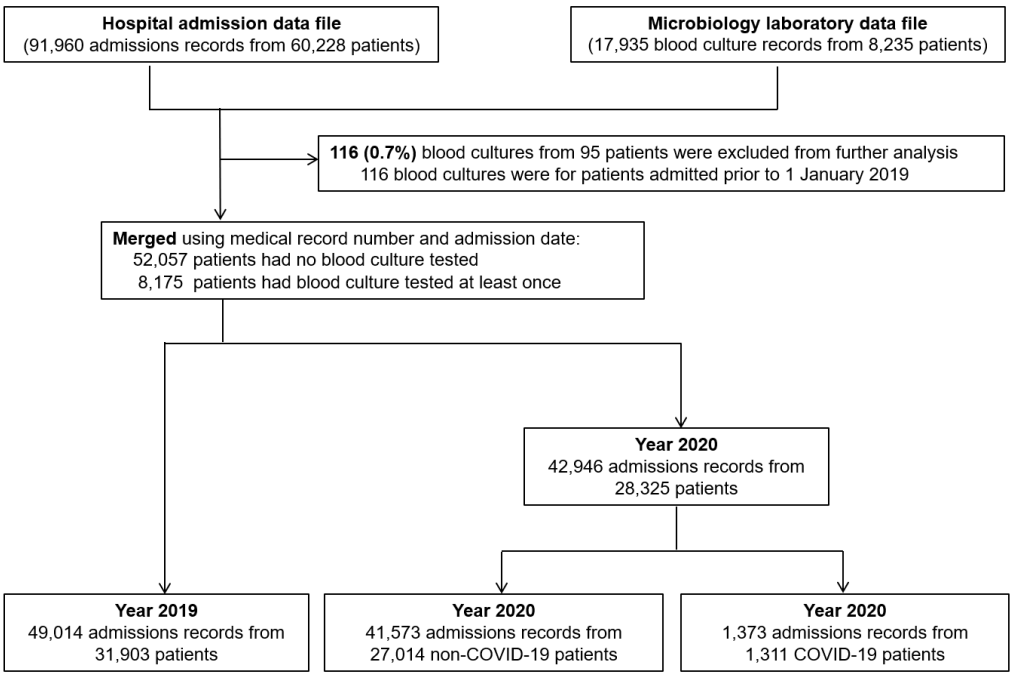


Table 2.2 Baseline characteristics by year and by COVID-19 status

Parameters	Year 2019	Year 2020	P values	Non-COVID-19 cases	COVID-19 cases*	P values
Total number of admissions	49,014	42,946	-	90,587	1,373	-
Total number of inpatients (de-duplicated)	31,903	28,325	-	58,917	1,311	-
Number of patient-days	308,926	274,322	-	571,707	11,541	-
Number of blood culture specimens received	8,155	9,664	-	17,286	533	-
Number of blood culture positive for any organism	1,589	2,025	-	3,513	101	-
Blood culture positivity rate**	19.5%	20.9%	0.02	20.3%	18.9%	0.44
Number of blood culture positive for commensal bacteria***	438	570	-	977	32	-
Blood culture contamination rate****	5.4%	5.9%	0.13	5.7%	6.0%	0.73
Number of patients sampled for blood cultures (de-duplicated)	4,026	4,501	-	7,973	348	-
Prevalence of patients sampled for blood cultures among all inpatients	12.6%	15.9%	<0.001	13.5%	26.5%	<0.001
Average number of blood culture specimens sampled per admission	1.6	1.7	-	1.7	1.5	-
Total number of admissions that had at least two blood culture specimens sampled (%)	2,472 (5.0%)	2,889 (6.7%)	<0.001	5,174 (5.7%)	187 (13.6%)	<0.001
Median duration between the first and second blood culture specimen (days, IQR)*****	5 (3-9)	5 (3-8)	0.52	5 (3-8)	4 (2-7)	0.57

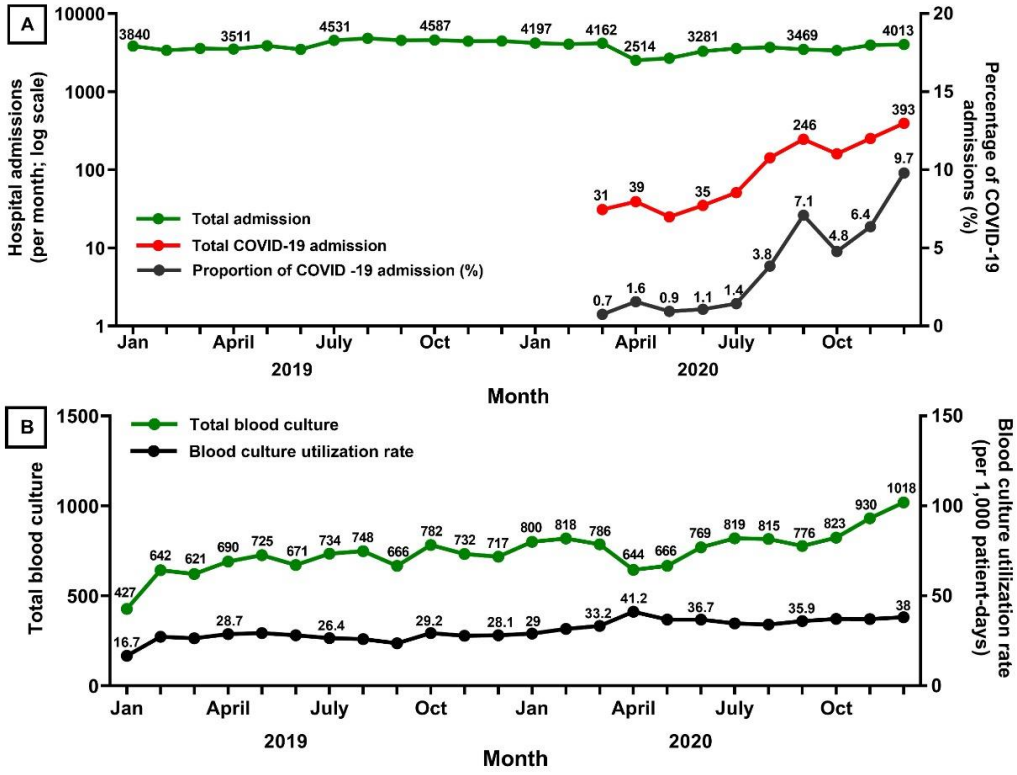
Footnote: BSI = bloodstream infection ***** All COVID-19 cases were in 2020. ** Blood culture positivity rate: number of blood culture positive for any organism/ number of blood culture specimens received. *** Commensal bacteria included coagulase-negative *Staphylococci, viridans group Streptococci, Propionibacterium acnes, Corynebacterium* spp., and *Bacillus* spp. **** Blood culture contamination rate: number of blood culture positive for commensal bacteria/ number of blood culture specimens received. ***** Among admissions that had at least two blood culture specimens sampled.

Table 2.3 Blood culture utilization rate by year and by COVID-19 status

Parameters	Year 2019	Year 2020	P values	Non-COVID-19 cases	COVID-19 cases*	P values
Blood culture utilization rate (per 1,000 patient-days)	26.4	35.1	<0.001	30.2	43.5	<0.001
Blood culture utilization for community-origin BSI						
Prevalence of blood culture specimens being collected within the first 2 calendar days of hospital admission	34.3% (2,801/8,155)	31.9% (3,087/9,664)	0.01	32.7% (5,650/17,286)	45.0% (240/533)	<0.001
Number of patients tested for community-origin BSI (de-duplicated) **	1,747	2,481	-	4,458	176	-
Blood culture utilization for hospital-origin BSI						
Prevalence of blood culture specimens being collected after the first 2 calendar days of hospital admission	65.7% (5,354/8,155)	68.1% (6,577/9,664)	0.01	67.3% (11,636/17,286)	55.0% (293/533)	<0.001
Number of patients tested for hospital-origin BSI (de-duplicated) **	2,556	2,385	-	4,175`	176	-

Footnote: BSI = bloodstream infection ***** All COVID-19 cases were in 2020. ** Patients tested for community-origin BSI are defined as patients with the first blood culture performed within the first two calendar days of admissions during the reporting period. Patients tested for hospital-origin BSI are defined as patients with the first blood culture performed after the first two calendar days of admissions during the reporting period.

Figure 2.3 Numbers of patient admissions (A) and blood cultures (B) among inpatients from 2019 to 2020. Reproduced from (122)



The blood culture utilization rate was higher among COVID-19 cases compared to non-COVID-19 cases (43.5 vs. 30.2 per 1,000 patient-days; p<0.001; **Table 2.1**). In a multivariable Poisson regression model, the blood culture utilization rate was independently associated with time (adjusted URR [aURR]: 1.02 per month, 95% CI 1.01-1.02, p<0.001) and COVID-19 cases (aURR 1.19, 95% CI 1.09-1.30, p<0.001).

2.4.3 Isolated organisms

Of 17,819 blood cultures, 1,008 were positive for commensal bacteria, giving a blood culture contamination rate of 5.6% during the study period. Of 8,175 patients who had at least one blood culture taken, 1,895 (23.1%) had at least one blood culture positive for one or more pathogenic organisms.

Among patients with BSI, 1,342 (70.8%) were Gram-negative bacteria, 296 (15.6%) were Gram-positive bacteria, 205 (10.8%) were fungi and 52 (2.8%) were polymicrobial infections (**Table 2.2** and **2.3**). The most common pathogens identified were *K. pneumoniae* (23.3%; n=442), *Acinetobacter* spp. (13.9%; n=263), *E. coli* (13.1%; n=249), *S. aureus* (11.6%; n=219) and *P. aeruginosa* (8.6%; n=163).

The proportion of isolated pathogens among BSI patients was moderately different between 2019 and 2020 (**Table 2.2**). The isolated pathogens were not different between COVID-19 and non-COVID-19 cases (all p>0.05), except that the proportion of *Enterococcus faecalis* was lower in non-COVID-19 than COVID-19 cases (3.0% vs. 10.4% p=0.01).

Table 2.3 Pathogenic organisms isolated from 1,895 patients with BSIs at Cipto Mangunkusumo National Hospital (CMNH), Indonesia, between 2019 and 2020*

Pathogens	Year 2019 (N=828)	Year 2020 (N=1067)	P values	Non COVID-19 cases (N=1838)	COVID-19 cases** (N=57)	P values
Gram negative bacteria						
E. coli	115 (13.9%)	115 (10.7%)	0.04	221 (12%)	9 (15.8%)	0.39
K. pneumonia	201 (24.3%)	207 (19.4%)	0.01	398 (21.7%)	10(17.5%)	0.45
Klebsiella spp.	16 (1.9%)	18 (1.7%)	0.69	32 (1.7%)	2 (3.5%)	0.32
Proteus spp.	7 (0.9%)	12 (1.1%)	0.54	19 (1%)	0 (0%)	0.44
Salmonella spp.	21 (2.5%)	12 (1.1%)	0.02	33 (1.8%)	0 (0%)	0.62
S. enterica	3 (0.4%)	1 (0.1%)	0.32	4 (0.2%)	0 (0%)	>0.99
S. enterica serovar Typhi	2 (0.2%)	4 (0.4%)	0.70	5 (0.3%)	1 (1.8%)	0.05
Shigella spp.	1 (0.1%)	0 (0%)	0.43	1 (0.1%)	0 (0%)	>0.99
P. aeruginosa	59 (7.1%)	98 (9.2%)	0.10	152 (8.3%)	5 (8.8%)	0.89
Pseudomonas spp.	1 (0.1%)	3 (0.3%)	0.63	4 (0.2%)	0 (0%)	>0.99
Acinetobacter spp.	102 (12.3%)	151 (14.1%)	0.24	245 (13.3%)	8 (14%)	0.87
Aeromonas spp.	5 (0.6%)	5 (0.5%)	0.75	10 (0.5%)	0 (0%)	>0.99
B. cepacian	6 (0.8%)	7 (0.7%)	0.85	13 (0.7%)	0 (0%)	>0.99
Citrobacter spp.	4 (0.5%)	3 (0.3%)	0.70	7 (0.4%)	0 (0%)	>0.99
Serratia spp.	11 (1.3%)	6 (0.6%)	0.07	17 (0.9%)	0 (0%)	>0.99
Other Gram-negative	63 (7.6%)	83 (7.7%)	0.89	143 (7.8%)	3 (5.3%)	0.48
Gram positive bacteria						
S. aureus	88 (10.6%)	128 (12%)	0.35	213 (11.6%)	3 (5.3%)	0.13
S. pneumoniae	2 (0.2%)	1 (0.1%)	0.58	2 (0.1%)	1 (1.8%)	0.08
S. pyogenes	2 (0.2%)	2 (0.2%)	>0.99	4 (0.2%)	0 (0%)	>0.99
E. faecium	6 (0.8%)	5 (0.5%)	0.54	11 (0.6%)	0 (0%)	>0.99
E. faecalis	22 (2.7%)	39 (3.6%)	0.22	55 (3.0%)	6 (10.4%)	0.01
L. garvieae	0 (0%)	1 (0.1%)	>0.99	1 (0.1%)	0 (0%)	>0.99
Fungi						
Candida albicans	7 (0.9%)	30 (2.8%)	0.01	34 (1.8%)	3 (5.3%)	0.67
Non-albicans *Candida spp*	53 (6.4%)	110 (10.3%)	0.01	157 (8.5%)	6 (10.5%)	0.59
Cryptococcus spp.	2 (0.2%)	0 (0%)	0.19	2 (0.1%)	0 (0%)	>0.99
Other fungi	0 (0%)	3 (0.3%)	0.26	3 (0.3%)	0 (0%)	>0.99
Polymicrobial	29 (3.5%)	23 (2.2%)	0.07	52 (2.8%)	0 (0%)	0.40

Footnote: BSI = bloodstream infection * Only the first pathogenic isolate per patient during the study period was included. ****** All COVID-19 cases were in 2020. *** Three most common polymicrobial infections were *E. coli* + *K. pneumoniae* (10 patients), *K. pneumoniae* + Other Gram-negative bacteria (10 patients), *Acinetobacter* spp. + *K. pneumoniae* (7 patients).

Table 2.4 Polymicrobial pathogenic organisms isolated from 52 patients with BSIs at CMNH, Indonesia, between 2019 and 2020

Pathogens	Year 2019 (N=29)	Year 2020 (N=23)	Non COVID-19 cases (N=52)	COVID-19 cases* (N=0)	Community-origin BSI (N=14)	Hospital-origin BSI (N=38)
Acinetobacter sp. + *K. pneumoniae*	2	5	7	0	1	6
Acinetobacter spp. + *P. aeruginosa*	1	1	2	0	0	2
Acinetobacter spp. + *S. aureus*	0	1	1	0	0	1
Citrobacter spp. + *E. coli*	0	1	1	0	1	0
E. coli + *K. pneumoniae*	7	3	10	0	4	6
E. coli + *Klebsiella* spp.	2	0	2	0	2	0
E. coli + *Proteus* spp.	1	1	2	0	2	0
E. coli + *P. aeruginosa*	1	0	1	0	0	1
E. coli + *Salmonella* sp.	1	0	1	0	1	0
E. coli + Other Gram-negative bacteria	2	0	2	0	0	2
E. faecium + *K. pneumoniae*	1	0	1	0	0	1
E. faecalis + *S. aureus*	0	2	2	0	0	2
E. faecalis + Other Gram-negative bacteria	1	0	1	0	0	1
K. pneumoniae + *P. aeruginosa*	2	0	2	0	0	2
K. pneumoniae + *Proteus* spp.	1	1	2	0	1	1
K. pneumoniae + *Serratia* spp.	1	0	1	0	0	1
K. pneumoniae + Non-albicans *Candida*	1	0	1	0	0	1
K. pneumoniae + Other Gram-negative bacteria	2	8	10	0	2	8
Klebsiella spp. + *S. enterica*	1	0	1	0	0	1
Klebsiella spp. + Other	1	0	1	0	0	1
P. aeruginosa + Other Gram-negative bacteria	1	0	1	0	0	1

Community-origin and hospital-origin BSI are defined as proposed by WHO GLASS (231).
***** All COVID-19 cases were in 2020.

The most common pathogens identified as the cause of community-origin BSI was *E. coli* (20%; n=103/515), followed by *S. aureus* (16.9%; n=87/515) and *K. pneumoniae* (11.1%; n=57/515), while the most common pathogens identified as the cause of hospital-origin BSI was *K. pneumoniae* (25.4%; n=351/1,380), followed by *Acinetobacter* spp. (14%; n=193/1,380) and non-albicans *Candida* (10.7%; n=16/1,380) (**Table 2.3** and **2.4**).

2.4.4 Proportion of AMR BSI

Of 442 patients with BSI caused by *K. pneumoniae*, 371 (83.9%) were 3GCRKP and 160 (36.2%) were carbapenem resistant- *K. pneumoniae* (CRKP) (**Table 2.3**). Of 249 patients with BSI caused by *E. coli*, 187 (76.1%) were 3GCREC and 34 (13.6%) were carbapenem resistant- *E. coli* (CREC). All CREC and CRKP were also resistant to 3rd generation cephalosporin. The proportion of carbapenem resistant- *Acinetobacter* spp. (CRACI) was 46.8% (123/263).

The proportion of AMR for each priority pathogen was not different between 2019 and 2020 (all p>0.10), and between COVID-19 and non-COVID-19 cases (all p>0.10; **Table 2.5**). However, the proportion of AMR for each priority pathogen were different between community-origin BSI and hospital-origin BSI (**Table 2.6**). For example, the proportion of 3GCRKP (61.5% vs. 87.8%, p<0.001), 3GCREC (67.8% vs. 77.6%, p=0.02) and CRACI (16.4% vs. 56.9%, p<0.001) were lower among community-origin BSI compared to those of hospital-origin BSI. **Table 2.7** provides additional details on proportion of AMR stratified by infection origin (community-origin vs. hospital-origin) and COVID-19 status. The overall AMR surveillance report is provided in Appendix 1.

2.4.5 Incidence rates of AMR BSI

The incidence rate of community-origin AMR BSI per 1,000 admissions was not significantly different between year 2019 and 2020 (1.6 to 1.6 per 1,000 admissions, p=0.97; Table 2.8), while the incidence rate of hospital-origin AMR BSI per 100,000 patient-days in 2020 (165.5 per 100,000 patient-days at risk) was higher than 2019 (130.1 per 100,000 patient-days at risk) (p=0.003). No specific outbreaks of AMR BSI were observed during the study period.

The incidence rate of community-origin AMR BSI per 1,000 admissions was not different between COVID-19 and non-COVID-19 cases during 2019 and 2020 (1.5 vs. 1.6, p>0.99). The incidence rate of hospital-origin AMR BSI per 100,000 patient-days at risk was also not different between COVID-19 and non-COVID-19 cases (143.7 vs. 146.9, p=0.96).

I observed that the incidence rate of community-origin AMR BSI per 100,000 tested patients was higher in 2019 compared to 2020 (4350.3 vs. 2,700.5 per 100,000 tested patients, p=0.004), while incidence rate of hospital-origin AMR BSI per 100,000 tested patients was lower in 2019 (11,071.9 vs. 13,501.1 per 100,000 tested patients, p=0.01; Table 4). I found that incidence rate of community-origin AMR BSI and of hospital-origin AMR BSI per 100,000 tested patients was not significantly different between non-COVID-19 and COVID-19 cases (p=0.11 and p=0.07, respectively).

Table 2.5 Pathogenic organisms isolated from 1,895 patients with bloodstream infections at CMNH, Indonesia, between 2019 and 2020*

Pathogens	Community-origin BSI (N=515)	Hospital-origin BSI (N=1380)	P value
Gram negative bacteria			
E. coli	103 (20%)	127 (9.2%)	< 0.001
K. pneumonia	57 (11.1%)	351 (25.4%)	< 0.001
Klebsiella spp.	10 (1.9%)	24 (1.7%)	0.76
Proteus spp.	5 (1%)	14 (1%)	0.93
Salmonella sp.	18 (3.5%)	15 (1.1%)	< 0.001
Non-Typhi *S. enterica*	2 (0.4%)	2 (0.1%)	0.29
S. enterica serotype Typhi	6 (1.2%)	0 (0%)	< 0.001
Shigella sp.	1 (0.2%)	0 (0%)	0.27
P. aeruginosa	62 (12%)	95 (6.9%)	< 0.001
Pseudomonas spp.	1 (0.2%)	3 (0.2%)	> 0.99
Acinetobacter spp.	60 (11.7%)	193 (14%)	0.18
Aeromonas spp.	3 (0.6%)	7 (0.5%)	0.73
B. cepacian	4 (0.8%)	9 (0.7%)	0.75
Citrobacter spp.	0 (0%)	7 (0.5%)	0.20
Serratia spp.	2 (0.4%)	15 (1.1%)	0.39
Other Gram-negative bacteria	39 (7.6%)	107 (7.8%)	0.89
Gram positive bacteria			
S. aureus	87 (16.9%)	129 (9.4%)	< 0.001
S. pneumoniae	3 (0.6%)	0 (0%)	0.02
S. pyogenes	4 (0.8%)	0 (0%)	0.01
E. faecium	1 (0.2%)	10 (0.7%)	0.30
E. faecalis	15 (2.9%)	46 (3.3%)	0.64
L. garvieae	0 (0%)	1 (0.1%)	> 0.99
Fungi			
C. albicans	2 (0.4%)	35 (2.5%)	0.01
Non-albicans *Candida*	16 (3.1%)	147 (10.7%)	< 0.001
Cryptococcus spp.	0 (0%)	2 (0.1%)	> 0.99
Other fungi	0 (0%)	3 (0.2%)	0.56
Polymicrobial infections**	14 (2.7%)	38 (2.8%)	0.96

BSI = bloodstream infection * Only the first pathogenic isolate per patient during the study period was included. ** Three most common polymicrobial infections were *E. coli* + *K. pneumoniae* (10 patients), *Klebsiella pneumoniae* + Other Gram-negative bacteria (10 patients), *Acinetobacter* sp. + *Klebsiella pneumoniae* (7 patients). Polymicrobial infections was described in Table 2.3.

Table 2.6 Proportion of WHO global priority AMR pathogens causing bloodstream infection

Priority AMR pathogens *	Year 2019	Year 2020	P values	Non COVID-19 cases	COVID-19 cases**	P values
Carbapenem resistant *Acinetobacter* spp.	46% (48/105)	48.7% (77/158)	0.56	48.2% (123/255)	25% (2/8)	0.29
Carbapenem resistant *P. aeruginosa*	27% (17/64)	24.2% (24/99)	0.74	26% (41/158)	0% (0/5)	0.33
Carbapenem resistant *** *K. pneumoniae*	34% (75/218)	38% (85/224)	0.44	35.9% (155/432)	50% (5/10)	0.51
3rd Cephalosporin resistant *** *K. pneumoniae*	85.3% (186/218)	82.5% (185/224)	0.43	83.8% (362/432)	90% (9/10)	>0.99
Carbapenem resistant *** *E. coli*	16.3% (21/129)	10.8% (13/120)	0.21	13% (31/240)	34% (3/9)	0.11
3rd Cephalosporin resistant *** *E. coli*	76% (98/129)	74.2% (89/120)	0.74	75% (180/240)	77.8% (7/9)	>0.99
Vancomycin resistant *E. faecium*	0% (0/7)	20% (1/5)	0.42	8.3% (1/12)	0% (0/0)	
Methicillin resistant *S. aureus*	3.4% (3/88)	9.2% (12/131)	0.11	6.9% (15/216)	0% (0/3)	>0.99
Fluoroquinolone resistant *Salmonella* spp.	17.9% (5/28)	5.9% (1/17)	0.38	13.3% (6/45)	0% (0/0)	>0.99
Fluoroquinolone resistant *Shigella* spp.	100% (1/1)	0% (0/0)		100% (1/1)	0% (0/0)	
Penicillin resistant S. *pneumoniae*	50% (1/2)	0% (0/1)	>0.99	50% (1/2)	0% (0/1)	>0.99
Overall****	55.9% (359/642)	51.5% (389/755)	0.10	53.6% (730/1361)	50% (18/36)	0.67

Footnote: CO = community-origin. HO = hospital-origin. CO and HO are defined as proposed by WHO GLASS.(231) * Only the first pathogenic isolate per patient during the study period was included. ****** All COVID-19 cases were in 2020. *** All carbapenem resistant- *E. coli* and *K. pneumoniae* were also resistant to 3rd cephalosporin cephalosporin. **** Among patients with blood culture positive for *Acinetobacter* spp., *P. aeruginosa, K. pneumoniae, E. coli, E. faecium, S. aureus, Salmonella spp., Shigella spp.* or S. *pneumoniae*

Table 2.7 Prevalence of WHO global priority AMR pathogens causing BSIs stratified by infection origin

Priority AMR pathogens *	**Community-origin**	**Hospital-origin**	**P values**
Carbapenem resistant- *Acinetobacter* spp.	16.4% (10/61)	56.9% (115/202)	< 0.001
Carbapenem resistant- *P. aeruginosa*	11.3% (7/62)	33.7% (34/101)	< 0.001
Carbapenem resistant- *** *K. pneumoniae*	21.5% (14/65)	38.7% (146/377)	0.01
3rd Cephalosporin resistant- *** *K. pneumoniae*	61.5% (40/65)	87.8% (331/377)	< 0.001
Carbapenem resistant- *** *E. coli*	11.6% (13/112)	15.3% (21/137)	0.40
3rd Cephalosporin resistant- *** *E. coli*	67.8% (76/112)	77.6% (111/137)	0.02
Vancomycin resistant- *E. faecium*	0% (0/1)	9.1% (1/11)	>0.99
Methicillin resistant- *S. aureus*	5.8% (5/87)	7.6% (10/132)	0.60
Fluoroquinolone resistant- *Salmonella* spp.	11.1% (3/27)	16.7% (3/18)	0.67
Fluoroquinolone resistant- *Shigella* spp.	100% (1/1)	0% (0/0)	
Penicillin resistant- S. *pneumoniae*	33.3% (1/3)	0% (0/0)	
Overall****	34.1% (143/419)	61.8% (605/978)	<0.001

CO = community-origin. HO = hospital-origin. CO and HO are defined as proposed by WHO GLASS.(231) * Only the first pathogenic isolate per patient during the study period was included. ****** All COVID-19 cases were in 2020. *** All carbapenem resistant- *E. coli* and *K. pneumoniae* were also resistant to 3rd cephalosporin. **** Among patients with blood culture positive for *Acinetobacter* spp., *P. aeruginosa*, *K. pneumoniae, E. coli, E. faecium, S. aureus, Salmonella spp*, *Shigella* spp. or S. *pneumoniae*

Table 2.8 Proportion of WHO global priority AMR pathogens causing BSIs stratified by infection origin and COVID-19 status

Priority AMR pathogens *	**Community-origin**			**Hospital-origin**		
	Non-COVID-19 cases	**COVID-19 cases**	**P values**	**Non-COVID-19 cases**	**COVID-19 cases**	**P values**
Carbapenem resistant *Acinetobacter* spp.	17% (10/59)	0% (0/2)	>0.99	57.6% (113/196)	33.3% (2/6)	0.41
Carbapenem resistant *P. aeruginosa*	12% (7/58)	0% (0/4)	>0.99	43% (43/100)	0% (0/1)	>0.99
Carbapenem resistant *** *K. pneumoniae*	21,8% (14/64)	0% (0/1)	>0.99	38% (141/372)	55.5% (5/9)	0.23
3rd Cephalosporin resistant *** *K. pneumoniae*	62.5% (40/64)	0% (0/1)	0.38	86.5% (322/372)	100% (9/9)	0.61
Carbapenem resistant *** *E. coli*	10,4% (11/106)	33.3% (2/6)	0.14	15% (20/134)	33.3% (1/3)	0.4
3rd Cephalosporin resistant *** *E. coli*	67% (71/106)	83.3% (5/6)	0.66	81.3% (109/134)	66.6% (2/3)	0.45
Vancomycin resistant *E. faecium*	0% (0/1)	- (0/0)	-	9% (1/11)	- (0/0)	-
Methicillin resistant *S. aureus*	5.8% (5/86)	0% (0/1)	>0.99	7.7% (10/130)	0% (0/2)	>0.99
Fluoroquinolone resistant *Salmonella* spp.	11.1% (3/27)	0% (0/1)	>0.99	16.6% (3/18)	- (0/0)	-
Fluoroquinolone resistant *Shigella* spp.	100% (1/1)	- (0/0)	-	- (0/0)	- (0/0)	-
Penicillin resistant S. *pneumoniae*	50% (1/2)	0% (0/1)	>0.99	- (0/0)	- (0/0)	-
Overall****	35% (138/404)	33.3% (5/15)	0.95	61.8% (592/957)	62% (13/21)	0.99

CO = community-origin. HO = hospital-origin. CO and HO are defined as proposed by WHO GLASS.(231) * Only the first pathogenic isolate per patient during the study period was included. ****** All COVID-19 cases were in 2020. *** All carbapenem resistant- *E. coli* and *K. pneumoniae* were also resistant to 3rd cephalosporin. **** Among patients with blood culture positive for *Acinetobacter* spp., *P. aeruginosa*, *K. pneumoniae, E. coli, E. faecium, S. aureus, Salmonella* spp., *Shigella* spp. or *S. pneumoniae*

Table 2.9 Incidence rate of WHO global priority AMR pathogens causing BSIs

	Year 2019	Year 2020	P values	Non COVID-19 cases	COVID-19 cases**	P values
Incidence rate of community-origin BSI caused by WHO global priority AMR pathogens						
per 1,000 admissions	1.6 (76/49,014)	1.6 (67/42,946)	0.97	1.6 (141/90,587)	1.5 (2/1,373)	> 0.99
per 100,000 patients tested for community-origin BSI*	4,350.3 (76/1,747)	2,700.5 (67/2,481)	0.004	3,162.8 (141/4,458)	1,136.3 (2/176)	0.11
Incidence rate of hospital-origin BSI caused by WHO global priority AMR pathogens						
per 1,000 admissions at risk of hospital-origin BSI*	8.5 (283/33,226)	10.9 (322/29,510)	0.003	9.5 (589/61,758)	14.6 (16/1,089)	0.10
per 100,000 patient-days at risk of hospital-origin BSI*	130.1 (283/217,398)	165.5 (322/194,486)	0.003	146.9 (589/400,750)	143.7 (16/11,134)	0.96
per 100,000 patients tested for hospital-origin BSI*	11,071.9 (283/2,556)	13,501.1 (322/2,385)	0.01	14,107.7 (589/4,175)	9,090.9 (16/176)	0.07

Footnote: BSI = bloodstream infection ***** Patients tested for community-origin BSI are defined as patients with the first blood culture performed within the first two calendar days of admissions during the reporting period. Patients were considered at risk of hospital-origin BSI after they stayed in the hospital for more than 2 days. Patients tested for hospital-origin BSI are defined as patients with the first blood culture performed after the first two calendar days of admissions during the reporting period ****** All COVID-19 cases were in 2020.

2.5 Discussion

This study illustrates that the use of readily available electronic hospital databases could provide robust and useful information on blood culture utilization and burden of AMR infections before and during the COVID-19 pandemic in LMICs. Although several reports have recently described an increase in AMR infections among COVID-19 cases (234, 235), I did not observe a difference of AMR BSI between COVID-19 and non-COVID-19 cases during the same time period in our setting. Strikingly, our study showed that the blood culture utilization rate had been increasing at the hospital before the COVID-19 pandemic (in 2019) and during the pandemic (in 2020), and, furthermore, that it was higher in COVID-19 cases than non-COVID-19 cases.

I did not observe a clear difference in the proportion and incidence rate of AMR infections between COVID-19 and non-COVID-19 cases, which is consistent with a study from Singapore (236). Improved infection prevention control in hospitals and communities, and reduced mobilization in community could hypothetically explain the unclear difference in the proportion and incidence rate of AMR infections between COVID-19 and non-COVID-19 cases (237). Nonetheless, studies from China (238), India (235), Italy (239), Taiwan (234), reported an increase in the proportion or incidence rates of AMR infections in COVID-19 patients. Multiple possible reasons for an increase include the high antibiotic use, predominance of severe COVID-19 patients in ICU with multiple predisposition towards AMR infections and protracted hospital stay, overcrowding of patients, and limited guideline adherence (8-12). Therefore, appropriate antimicrobial prescribing, accurate diagnosis and appropriate infection prevention control are crucial for both COVID-19 and non-COVID-19 patients.

The observed increase in the incidence rate of hospital-origin AMR BSI during the COVID-19 pandemic is most likely due to the increase in blood culture utilization rate. A simulation study showed that observed incidence rate of AMR BSI (per 100,000 patient-days) could considerably increase if a hospital improves their blood culture utilization rate even if there are no changes in true susceptibility profiles of pathogenic organisms and in true infection rates in that environment over time (224). I did not observe changes in proportion of AMR BSI and specific outbreaks of AMR infections during the study period, as was noticed by Hospital Infection Prevention Control Committee.

The observed increase in blood culture utilization rate before and during the COVID-19 pandemic could be due to several reasons. Before the COVID-19 pandemic, a new national clinical practice guideline on sepsis was launched with recommendation to take blood cultures prior to empirical antibiotic (227). Nonetheless, despite improvements, the blood culture utilization rate in non-COVID-19 cases was still lower than those reported in Thailand and many other high-income countries (e.g. 307.7, 86.5, 65.4 per 1,000 patient-days in United States, France and United Kingdom, respectively) (223, 240, 241). Direct comparison of the rate with other LMICs could not be performed due to limited existing publication (1). The low culture rate could be explained by lack of physician awareness of the sepsis guidelines, misperceptions that blood culture will add health care cost, among other factors (242). Previous studies have reported contrasting findings on blood culture utilization in COVID-19 patients (235, 243, 244). The increase in blood culture utilization among COVID-19 cases in the study hospital is probably because the national referral hospital manages mostly COVID-19 patients with comorbidities and severe conditions. Given these are very sick people empirical antibiotic treatment is commonly recommended

(245). However, a recent meta-analysis has concluded that antibiotics are heavily overused in COVID-19 cases (246).

Local reporting on the hospital AMR epidemiology allows us to understand the local situation and support local actions. The top three pathogens causing BSIs are similar with findings in other countries in the region (13, 247). However, I did not observe higher rate of *S. aureus* co-infection in COVID-19 patients, contrary to several reports from past viral and COVID-19 pandemic worldwide (248). I observed high rate of community origin BSI caused by *P. aeruginosa* and low rate of community origin BSI caused by *S. pneumoniae*. In addition, my analysis shows BSI cases with *Salmonella enterica serovar* Typhi, *Shigella* spp., and *Burkholderia pseudomallei*. Those pathogens are the cause of typhoid, shigellosis and melioidosis, respectively, and are notifiable pathogens in many countries (249, 250). This information can support the decision making of the Ministry of Health in Indonesia, where a system of notifiable pathogens is not officially established. Our study also found that 8.6% of hospital-acquired BSI was caused by non-albicans *Candida* spp. There is limited information of fungal infections, particularly of non-albicans *Candida* infections, as the cause of BSI in LMICs (251-254). The relatively high proportion of fungemia in this data, compared with 1.1% in Thailand (253), could be due the complex, immunocompromised patient populations, with common invasive procedures and high antibiotic use, all of which are risk factors of invasive candidiasis (12, 255). Available data worldwide suggest increasing incidence of fungemia caused by non-albicans *Candida* species (251, 256, 257) together with increasing resistance. I reported our findings to the hospital Infection and Antimicrobial Resistance Control Committee, and these are used to support local guidelines for the prevention and treatment of hospital acquired invasive fungal infections (258).

2.6 Limitations

This study has some limitations. First, I could not determine whether a blood culture was taken before or after failure of empirical treatment as there was a low adherence to take blood culture prior to antibiotic treatment. Some patients might also be treated with parenteral antibiotics without blood culture taken. Addition of clinical and patient data to the laboratory-based surveillances could improve data representativeness in the future (259, 260). Second, the AMR surveillance reports should not be used to guide empirical antibiotics without careful consideration. Hospitals in LMICs with a low blood culture utilization rate should use AMR surveillance reports stratified by exposure to an empirical antibiotic at the study hospital to guide choice of first-line empiric antimicrobial therapy rather than the total antibiogram (224). Third, although large, this study may lack power to observe a difference in AMR BSI between COVID-19 and non-COVID-19 cases. In addition, the study was conducted using data on early COVID-19 pandemic, i.e year 2020; Thus, it may not be generalizable to other periods of COVID-19 pandemic. Fourth, I used calendar days of admission as a surrogate for defining origin of infection and data of patient transfers were not available. Therefore, a proportion of community-origin BSIs reported could be hospital-origin BSIs transferring from other hospitals. Fifth, I modelled blood culture utilization rate linearly. The rate could be modelled in other ways using nonlinear modelling. Lastly, the findings may not be generalizable to all other hospitals or the country at large.

2.7 Implications

I recommend increasing blood culture utilization among patients who were indicated for test and generating AMR surveillance reports in LMICs to inform local health care

providers and policy makers. Applied in this report, I recommend stratified report of parameters of AMR surveillance (proportions and incidence rates of AMR infections) based on origin of infection. AMR surveillance report should include report on blood culture utilization rate for a better interpretation of parameters of AMR surveillance.

2.8 Conclusions

In the Indonesian national referral hospital, AMR-BSI incidence and etiology were not different between COVID-19 and non-COVID-19 cases. Incidence rates of hospital-origin AMR BSI increased in 2020, which was likely due to increased blood culture utilization.

Chapter 3
Diagnostic and antibiotic use practices among COVID-19 and non-COVID-19 patients in the Indonesian National Referral Hospital

3.1 Abstract

Background

Little is known about diagnostic and antibiotic use practices in LMICs before and during COVID-19 pandemic. This information is crucial for monitoring and evaluation of diagnostic and antimicrobial stewardships in healthcare facilities.

Methods

I linked and analyzed routine databases of hospital admission, microbiology laboratory and drug dispensing of Indonesian National Referral Hospital from 2019 to 2020. I classified patients as COVID-19 cases if their SARS-CoV-2 RT-PCR result were positive. I used blood culture practices and time to discontinuation of parenteral antibiotics among inpatients who received a parenteral antibiotic for at least four consecutive days to assess diagnostic and antibiotic use practices, respectively. I used Fine and Grey subdistribution hazard model.

Results

Of 1,311 COVID-19 and 58,917 non-COVID-19 inpatients, 333 (25.4%) and 18,837 (32.0%) received a parenteral antibiotic for at least four consecutive days. Proportion of patients having blood culture taken within ±1 calendar day of parenteral antibiotics being started was higher in COVID-19 than in non-COVID-19 patients (21.0% [70/333] vs. 18.7% [3,529/18,837]; $p<0.001$). Cumulative incidence of having a blood culture taken

within 28 days was higher in COVID-19 than in non-COVID-19 patients (44.7% [149/333] vs. 33.2% [6,254/18,837]; adjusted subdistribution-hazard ratio [aSHR] 1.71, 95% confidence interval [CI] 1.47-1.99, p<0.001). The median time to discontinuation of parenteral antibiotics was longer in COVID-19 than in non-COVID-19 patients (13 days vs. 8 days; aSHR 0.73, 95%Cl 0.65-0.83, p<0.001).

Conclusions

Routine electronic data could be used to inform diagnostic and antibiotic use practices in LMICs. In Indonesia, the proportion of timely blood culture is low in both COVID-19 and non-COVID-19 patients, and duration of parenteral antibiotics is longer in COVID-19 patients. Improving diagnostic and antimicrobial stewardship is critically needed.

3.2 Introduction

AMR bacterial infection is a global threat to public health (2). LMICs, including Indonesia, are considered hotspots of AMR, driven by the lack of laboratory support for infectious disease diagnosis and high levels of inappropriate antibiotic use in hospitals (261, 262).

Diagnostic and AMS are increasingly implemented in LMICs (16, 28, 263). Although processes of the stewardship programmes (e.g., presence of standard operating procedures [SOPs] and how many patient medical charts are reviewed) are frequently monitored and reported, outcomes of those stewardship programmes (e.g. increase in specimens submitted for bacterial culture according to SOPs and DDDs per 1,000 patient-days) or patient outcomes (e.g. in-hospital mortality) are rarely monitored and reported. This is because measuring and analyzing diagnostic and antibiotic use practices overtime are labor-intensive and prohibitively costly.

I aimed to analyze drug dispensing data, and evaluate diagnostic and antibiotic use practices in the Indonesian national referral hospital before and during the COVID-19 pandemic.

3.3 Methods

3.3.1 Study design, setting and population

I conducted a retrospective hospital-wide longitudinal surveillance study using routine electronic data on all patients hospitalized at CMNH, the national referral hospital in Jakarta, Indonesia, from 1 January 2019 to 31 December 2020.

3.3.2 Data collection

I used the routine hospital databases containing hospital admission, laboratory microbiology and drug dispensing data. The hospital admission data collected included MRN, sex, age, admission and discharge date. The microbiology laboratory data collected included MRN, admission date, specimen type, specimen collection date, culture result using conventional bacterial identification methods and Vitek®2 (bioMerieux, Inc. Durham, USA), antibiotic susceptibility profile according to Clinical and Laboratory Standards Institute guidelines, and result report date. The drug dispensing data collected included MRN, admission date, drug name, route of drug administration, the dosage regimen, drug start date and stop date. I used the MRN and admission date to link the three databases together. I accessed data on 1 March 2021.

3.3.3 Definitions

3.3.3.1 Severe infection

I defined patients with severe infection using the criteria modified from the United States CDC (264). I evaluated patients who received a parenteral antibiotic for at least four consecutive days as a surrogate for severe infection, with the first calendar equal to the start date of parenteral antibiotics. I also included patients who died, were discharged to a hospice or transferred to other hospital before completing four consecutive days of parenteral antibiotics and had parenteral antibiotics continuously until the day prior to death, hospice discharge or transfer (224).

3.3.3.2 Diagnostic practices

To measure diagnostic practices, I estimated (a) the proportion of patients with blood culture taken within $\pm$1 calendar day of parenteral antibiotics being started, (b) the proportion of patients with blood culture taken within 28 days of parenteral antibiotics being started, and (c) the median blood culture turnaround-time (16, 28, 224) (**Table 3.1**).

Table 3.1 Definition of parameters of diagnostic practices

Parameter of diagnosis practices	Definition
Proportion of patients with blood culture taken within $\pm$1 calendar day of parenteral antibiotics being started	Ratio of the number of patients with severe infection where blood cultures were taken from one calendar day before to one calendar day after starting parenteral antibiotics, and the total number of patients with severe infection.
Proportion of patients with blood culture taken within 28 days of parenteral antibiotics being started	Ratio of the number of patients with severe infection where blood cultures were taken from one calendar day before to 28 calendar days after starting parenteral antibiotics, and the total number of patients with severe infection.
Blood culture turnaround-time	Time interval between blood culture taken from patients and blood culture results positive for organisms reported by laboratory (16).

I used the proportion of patients having blood culture taken within ±1 calendar day of parenteral antibiotics being started to measure the compliance with the recommendations that blood specimens should be taken before starting antimicrobial therapy in patients with suspected sepsis and septic shock if no substantial delay in the start of antimicrobials occurs (i.e. <45 min) and that if the antibiotic is administered first, the blood specimens should be collected for culture within 24 hours (218).

3.3.3.3 Antibiotic use practices

To measure antibiotic use practices, I estimated (a) the proportion of antibiotic use based on the AWaRe system (28), (b) median time to discontinuation of parenteral antibiotics (28), (c) the proportion of patients with narrow-spectrum parenteral antibiotics (antibiotics within the Access and Watch category without anti-MRSA/ antipseudomonal activity) within 2 calendar days following blood culture report among those who had a blood culture positive for 3GCSEC or 3GCSKP and remained on a parenteral antibiotic on the day that the blood culture results were reported (265), and (d) the proportion of patients with parenteral antibiotic discontinuation within 2 calendar days following blood culture report among those who had blood culture results negative for organisms and remained on a parenteral antibiotic on the day that the blood culture results were reported (266).

I measured antibiotic use among inpatients in terms of DDD per 1,000 inpatient-days. I defined DDD as the assumed average maintenance dose per day for a drug used for its main indication in adults as specified by WHO (267). I defined pharmacological subgroups of antibacterials for systemic use according to group based on the Anatomical Therapeutic Chemical classification system, including tetracyclines (J01A), amphenicols (J01B), beta-lactam antibacterials, penicillins (J01C), other beta-lactam antibacterials (J01D),

sulfonamides and trimethoprim (J01E), macrolides, lincosamides and streptogramins (J01F), aminoglycoside antibacterials (J01G), quinolone antibacterials (J01M), combinations of antibacterials (J01R), other antibacterials (J01X), agents against amoebiasis and other protozoal diseases (P01A).

I also assessed the change of parenteral antibiotic among patients with severe infection within 28 days. I categorized parenteral antibiotic use on each calendar day as escalation, de-escalation, change to other antibiotics with similar spectrum, no change from the previous antibiotic or stop. I defined antibiotic escalation as (a) adding a new parenteral antibiotic, (b) changing parenteral antibiotic with an increase in AWaRe categories, or (c) changing parenteral antibiotic within the Watch category but from those without anti-MRSA activity and without antipseudomonal activity to those with anti-MRSA activity (e.g. vancomycin) or antipseudomonal activity (e.g. antipseudomonal cephalosporin, antipseudomonal penicillin and carbapenems) compared to the previous day. I defined de-escalation as the inverse of these. I defined change to other antibiotics with similar spectrum as changing parenteral antibiotics to other parenteral antibiotics within similar AWaRe categories, and with similar anti-MRSA activity and antipseudomonal activity for parenteral antibiotics within the Watch category compared to the previous day. I defined no change as continuation of current parenteral antibiotics, while stop as discontinuation of parenteral antibiotics (266, 268-271). I also evaluated initial parenteral antibiotics. Parenteral antibiotics being prescribed within the first calendar day that a parenteral antibiotic was started were regarded as initial parenteral antibiotics (272, 273).

3.3.4 Ethics

The Faculty of Medicine Universitas Indonesia Ethics Committee (KET-115/UN2.F1/ETIK/PPM.00.02/2021) and Oxford Tropical Research Ethics Committee approved the study (503-22). The requirement for individual patient consent was waived. Additional permission was obtained from the Innovation and Intellectual Property Directorate CMNH, to use the routine hospital databases for research.

3.3.5 Data analysis

I used Pearson's chi-squared test or Fisher's Exact test to compare categorical variables between groups when appropriate. I used Mann-Whitney test to compare continuous variables between groups. I compared time to mortality, having blood culture taken and discontinuation of parenteral antibiotics within 28 days between groups by using Fine and Grey models to account for competing risks (274, 275). Mortality included in-hospital mortality and discharge to a hospice. I considered discharge to home as a competing risk for mortality. I considered mortality, discharge to home and discontinuation of parenteral antibiotics as competing risks for having blood culture taken. For patients who had parenteral antibiotics up to the calendar date that they were discharged home, all parenteral antibiotics were considered discontinued on the discharge date. I consider mortality as a competing risk for discontinuation of parenteral antibiotics. I performed all data analyses using the STATA version 15.1 (StataCorp, College Station, TX, USA). I visualized data using the GraphPad Prism version 8.3.0 (La Jolla, California, USA) and SankeyMATIC (https://sankeymatic.com/).

3.4 Results

3.4.1 Baseline characteristics

Of 91,960 admissions (from 60,228 patients) admitted from 1 January 2019 to 31 December 2020, 35,766 (38.9%) admissions received at least one antibiotic (**Figure 3.1** and **Table 3.2**).

Figure 3.1 Flow Diagram. Reproduced from (276)

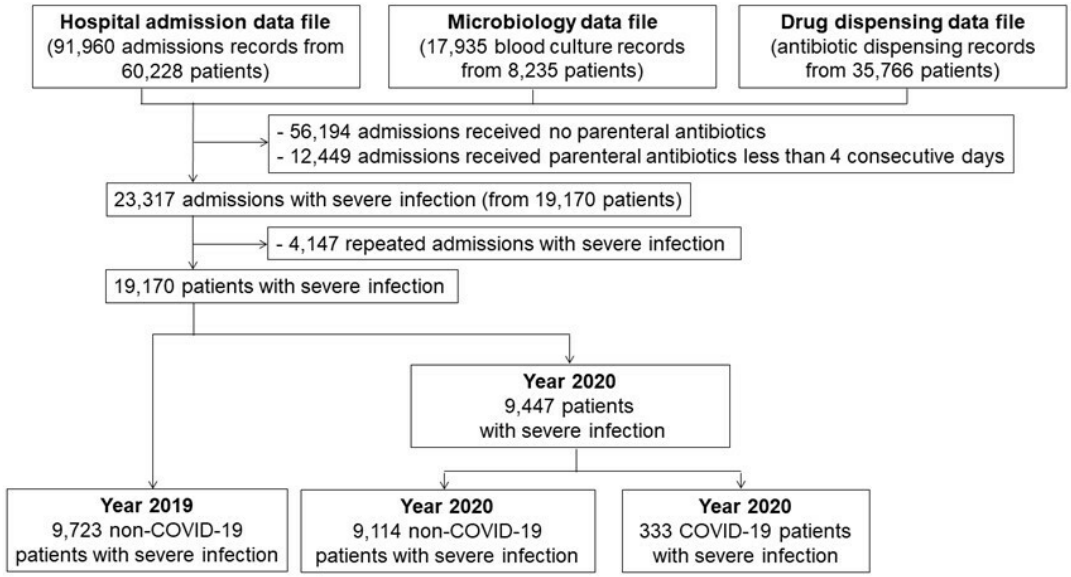


Table 3.2 Baseline characteristics of all patients hospitalized at the Indonesian national referral hospital, Jakarta, Indonesia from 1 January 2019 to 31 December 2020.

Parameters	**Total**	**COVID-19**	**Non-COVID-19**	**P values**
Total number of admissions	91,960	1,373	90,587	
Total number of inpatients (de-duplicated)	60,228	1,311	58,917	
Number of patient-days	583,248	11,541	571,707	
Median age (years old, IQR)*	39 (17-55)	41 (26-57)	39 (17-55)	0.47
Sex*				
Female	32,167 (53.4%)	646 (49.5%)	31,521 (53.5%)	0.002
Male	28,061 (46.6%)	665 (50.7%)	27,396 (46.5%)	
Payor**				
Universal health coverage	77,149 (83.9%)	1,373 (100%)	75,776 (83.6%)	<0.001
Private insurance	2,071 (2.3%)	-	2,071 (2.3%)	
Self-paid	12,740 (13.8%)	-	12,740 (7.59%)	
Number of admissions with at least one dose of parenteral antibiotic**	35,766	599	35,167	
Proportion of admissions with at least one dose of parenteral antibiotic**	38.9% (35,766/91,960)	43.6% (599/1,373)	38.8% (35,167/90,587)	<0.001
Number of admissions with severe infection***	23,317	336	22,981	
Number of patients with severe infection***	19,170	333	18,837	
Proportion of patients with severe infection***	31.8% (19,170/60,288)	25.4% (333/1,311)	31.9% (18,837/58,917)	<0.001
Total antibiotic consumption (DDD per 1,000 patient-days)**	624.1	1,502.8	606.3	
Access category	182.4 (29.3%)	82.2 (5.5%)	184.4 (30.4%)	<0.001

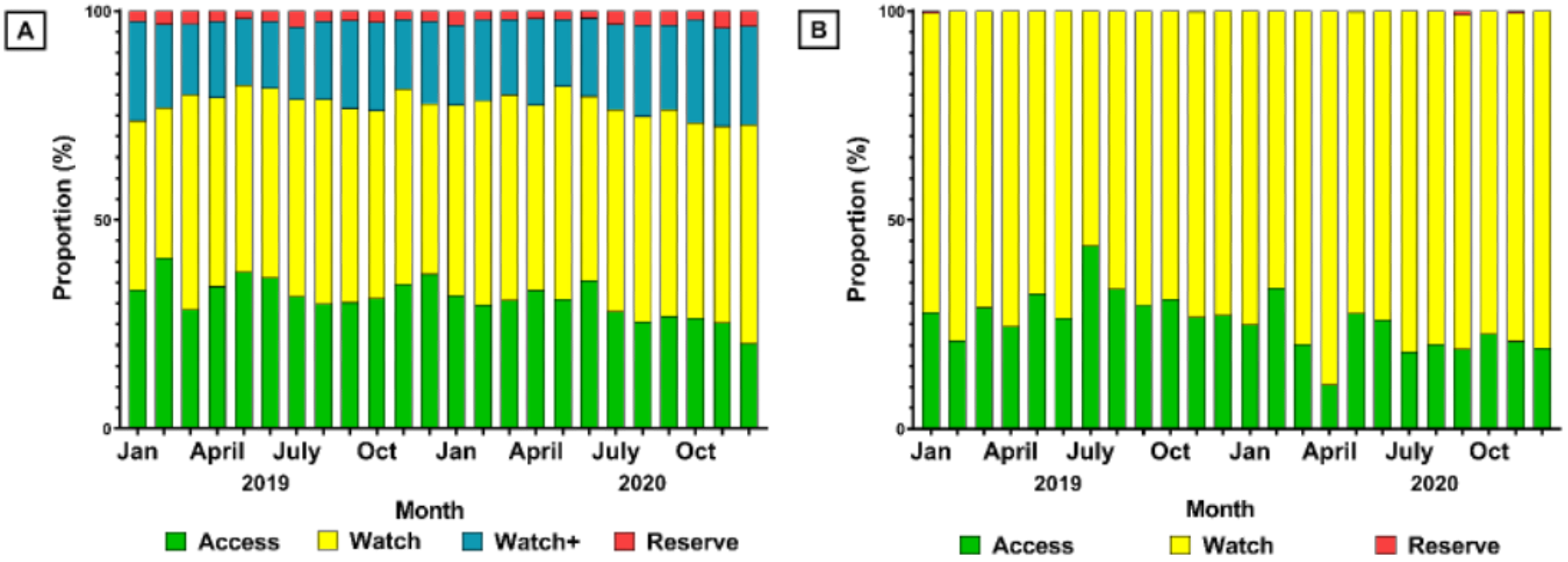
Watch category	429.3 (68.7%)	1,395.5 (92.6%)	409.8 (67.6%)	
Reserve category	12.4 (2.0%)	25.1 (1.9%)	12.1 (2.0%)	

*per patients **per admissions ***Severe infection is defined by four consecutive days of parenteral antibiotics, or died, were discharged to a hospice or transferred to other hospital before completing four consecutive days of antibiotics and had antibiotics continuously until the day prior to death, a hospice discharge or transfer

Total consumption of antibiotics among inpatients was 624.1 DDD per 1,000 inpatient-days, of which 77.6% (484.3 DDD per 1,000 inpatient-days) and 22.3% (139.8 DDD per 1,000 inpatient-days) were parenteral and oral antibiotics, respectively. Overall, 29.3% (182.4 DDD per 1,000 inpatient-days), 68.7% (429.3 DDD per 1,000 inpatient-days) and 2.0% (12.4 DDD per 1,000 inpatient-days) were classified as Access, Watch and Reserve categories, respectively (**Figure 3.2**).

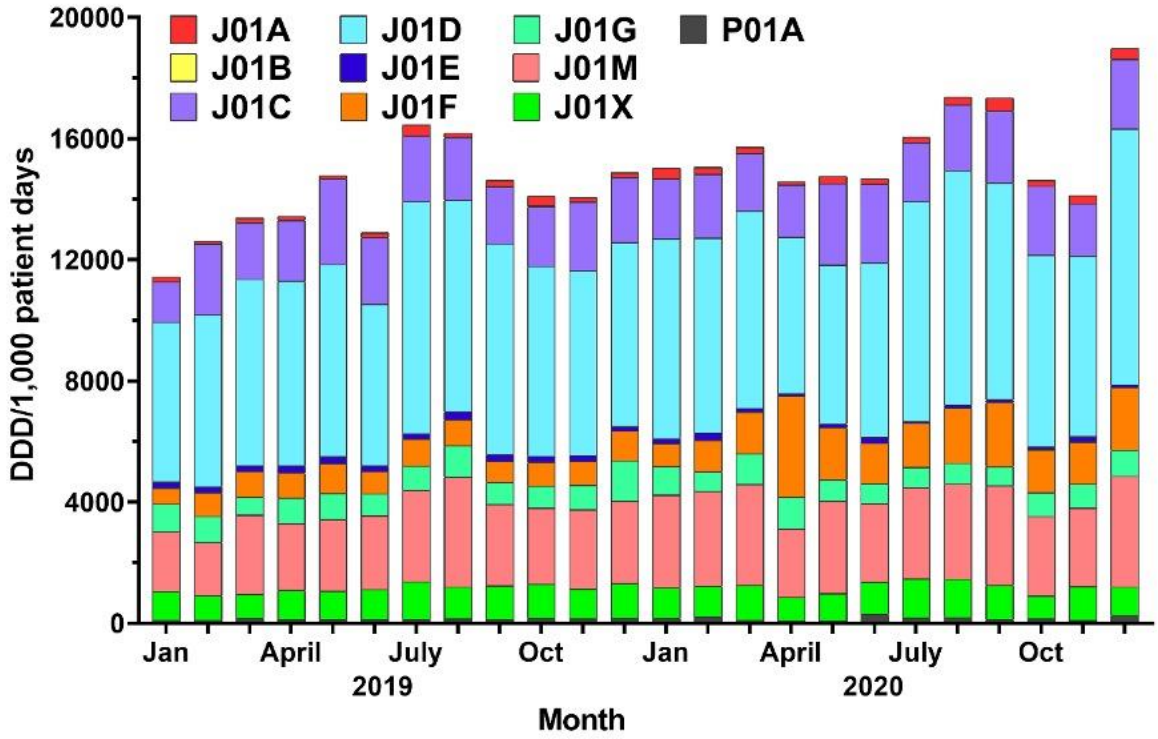
Of all parenteral antibiotic consumption among inpatients (484.3 DDD per 1,000 inpatient-days), 46.9% (227.1 DDD per 1,000 inpatient-days) were other beta-lactam antibacterials (J01D), 20.2% (97.8 DDD per 1,000 inpatient-days) were quinolone antibacterials (J01M), and 15.4% (74.6 DDD per 1,000 inpatient-days) were penicillins (J01C) (**Figure 3.3**). Of all other beta-lactam antibacterials (J01D) consumption (227.1 DDD per 1,000 inpatient-days), 65.0% (147.6 DDD per 1,000 inpatient-days) were 3rd-generation cephalosporins (J01DD), 21.7% (49.3 DDD per 1,000 inpatient-days) were carbapenems (J01DH), and 8.0% (18.2 DDD per 1,000 inpatient-days) were 4th-generation cephalosporins (J01DE).

Figure 3.2 Proportional consumption of (A) parenteral and (B) oral antibiotics by AWaRe categorization among all admissions (n=91,960) of all inpatients (n=60,228) between 2019 and 2020. Reproduced from (276)



Footnote: For this figure, antibiotics in the Watch category was divided to Watch and Watch+. Watch+ category comprises antibiotics in the Watch category with anti-MRSA activity (e.g. vancomycin) or antipseudomonal activity (e.g. antipseudomonal cephalosporin, antipseudomonal penicillin and carbapenems).

Figure 3.3 Consumption of parenteral antibiotics (DDD per 1,000 patient days) by pharmacological subgroups among all admissions (n=91,960) of all inpatients (n=60,228) between 2019 and 2020. Reproduced from (276)



Footnote: J01A: tetracyclines; J01B: amphenicols; J01C: beta-lactam antibacterials, penicillins; J01D: other beta-lactam antibacterials; J01E: sulfonamides and trimethoprim; J01F: macrolides, lincosamides and streptogramins; J01G: aminoglycoside antibacterials; J01M: quinolone antibacterials; J01R: combinations of antibacterials; J01X: other antibacterials, P01A: agents against amoebiasis and other protozoal diseases

Of 91,960 admissions (60,228 patients), 1,373 (from 1,311 patients) were COVID-19 cases. Total antibiotic consumption was 1,502.8 and 606.3 DDD per 1,000 inpatient-days in COVID-19 and non-COVID-19 patients, respectively (**Table 3.2**).

Of 60,228 patients, 19,170 (31.8%) received at least four consecutive days of parenteral antibiotics, were classified as patients with severe infection, and the first admission per patient which fulfilled the criteria of severe infection were included for further analysis.

3.4.2 Patients with severe infection

Among 19,170 patients with severe infection, 333 (1.7%) were COVID-19 patients and 18,837 (98.3%) were non-COVID-19 patients (**Table 3.3**). The median age was higher in COVID-19 patients than non-COVID-19 patients (47 vs. 39 years, p<0.001). The sex distribution was not different between the two groups (p=0.23).

Table 3.3 Characteristics of 19,170 patients with severe infection

Parameters	**COVID-19 patients with severe infection (n=333)**	**Non-COVID-19 patients with severe infection (n=18,837)**	**P values**
Median age (years old, IQR)	47 (IQR 25-62, range 0-93)	39 (IQR 15-56, range 0-95)	<0.001
Sex			
Female	156 (46.8%)	9,445 (50.1%)	0.23
Male	177 (53.2%)	9,392 (49.9%)	
Median duration of hospital stay (days)	8 (IQR 4-16, range 1-90)	8 (IQR 4-15, range 1-119)	0.08
Time when a parenteral antibiotic was started [a]			
1-2 calendar day after admission	207 (62.2%)	13,137 (69.7%)	<0.001
3-7 calendar day after admission	97 (29.1%)	3,840 (20.4%)	
> 7 days after admission	29 (8.7%)	1,860 (9.9%)	
Number of parenteral antibiotics received on the day that a parenteral antibiotic was started (%)			
1	255 (76.6%)	14,091 (74.8%)	0.66
2	72 (21.6%)	4,451 (23.6%)	
≥3	6 (1.8%)	295 (1.6%)	
Total antibiotic consumption (DDD per 1,000 patient-days) [b]	1656.4	807.6	
Access category	153.9 (9.3%)	263.8 (32.7%)	<0.001
Watch category	1427.3 (86.2%)	520.3 (64.4%)	
Reserve category	75.2 (4.5%)	23.5 (2.9%)	
28-day mortality [c]	95 (28.5%)	4,485 (23.8%)	0.02

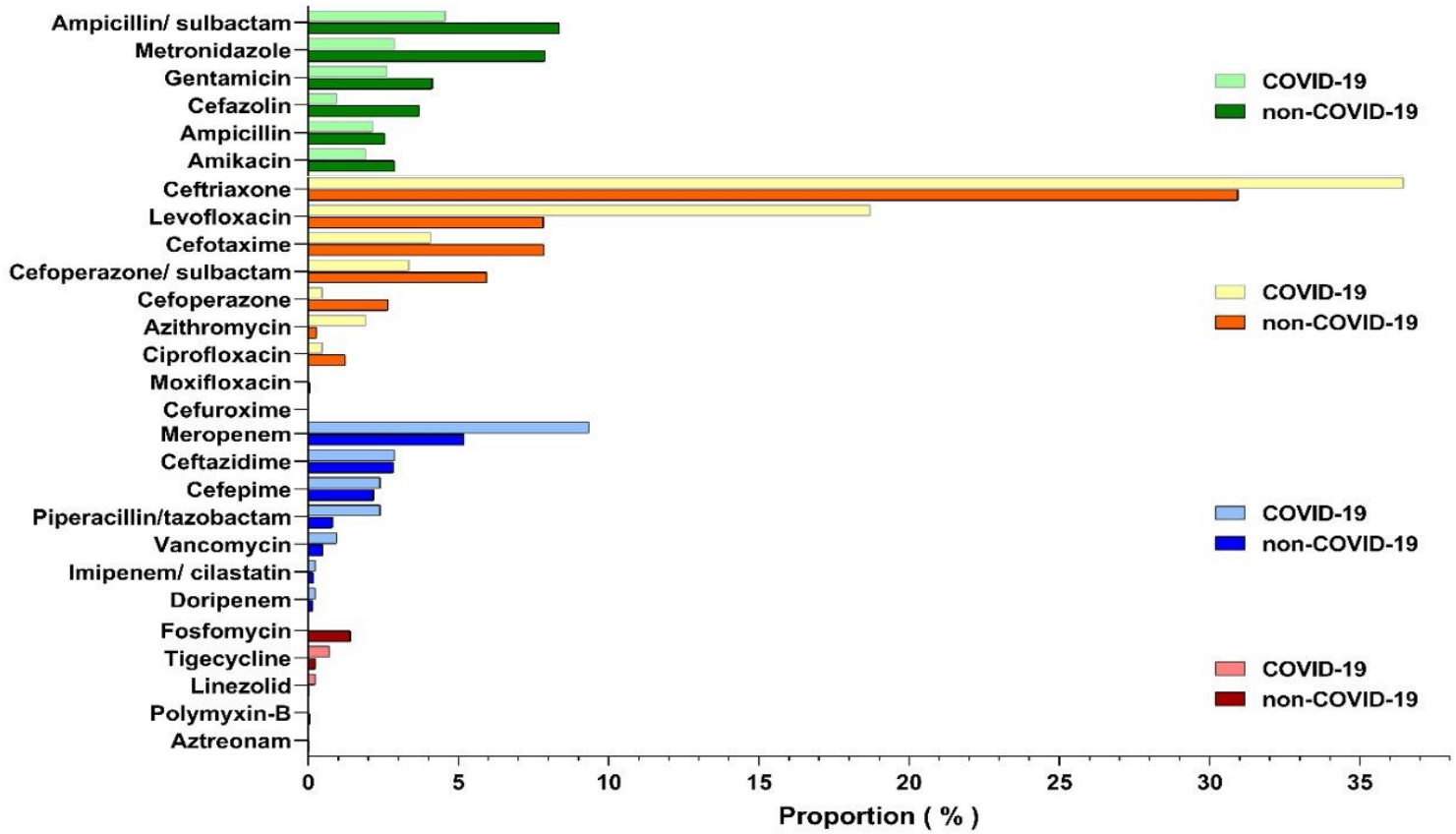
Footnote: Only the first admission per patient which fulfilled the criteria of severe infection were included. Patients with severe infection are defined as those who received a parenteral antibiotic for at least four consecutive days. Patients who died, were discharged to a hospice or transferred to other hospital before completing four consecutive days of parenteral antibiotics and had parenteral antibiotics continuously until the day prior to death, hospice discharge or transfer were also included as patients with severe infection [a] Time was measured when a parenteral antibiotic was started and continued for at least four consecutive days. The day of admission was equal to 1 calendar day after admission. [b] Total antibiotic consumption was estimated from the day of parenteral antibiotics being started to the discharge date. [c] 28-day mortality included in-hospital mortality and discharged to a hospice within 28 days of parenteral antibiotics being started.

The proportion of parenteral antibiotics consumption under Watch and Reserve category was significantly higher in COVID-19 patients than non-COVID-19 patients (86.2% vs. 64.4% and 4.5% vs. 2.9%, respectively; p<0.001; **Table 3.3**). The proportion of patients

being prescribed one, two or at least three initial parenteral antibiotics within the first calendar days of parenteral antibiotics being started was not different between two groups (p=0.66) (**Table 3.2**). Ceftriaxone (36.9% [123/333]), levofloxacin (18.9% [63/333]) and meropenem (9.3% [31/333]) were commonly used as the initial antibiotics in COVID-19 patients, while ceftriaxone (30.9% [582/18,837]), ampicillin/sulbactam (8.5% [160/18,837]) and metronidazole (7.8% [147/18,837]) were commonly prescribed as the initial antibiotics in non-COVID-19 patients (**Figure 3.4**).

The 28-day mortality among 19,170 patients with severe infection was 23.9% (**Table 3.3** and **3.4**). Using Fine and Grey model, I found that the risk of mortality was higher in COVID-19 patients than non-COVID-19 patients (28.5% vs. 23.8%, aSHR 1.29; 95%CI 1.04-1.58, p=0.02; **Table 3.4** and **Figure 3.5 (A)**).

Figure 3.4 Distribution of initial antibiotic among 19,170 patients with severe infection. Reproduced from (276)



Footnote: Parenteral antibiotics being prescribed within the first calendar day that a parenteral antibiotic was started were regarded as initial parenteral antibiotics. Patients who received a parenteral antibiotic for at least four consecutive days was used as a surrogate for severe infection, with the first calendar equal to the start date of parenteral antibiotics. Patients who died, were discharged to a hospice or transferred to other hospital before completing four consecutive days of parenteral antibiotics and had parenteral antibiotics continuously until the day prior to death, hospice discharge or transfer were also included as patients with severe infection.

Table 3.4 Mortality, proportion of having blood culture sampled and median time to parenteral antibiotics discontinuation of patients with severe infection within 28 days after parenteral antibiotics being started, stratified by variables and COVID-19 status

Variables	**28-day mortality (%) [a]**		**Proportion of having blood culture sampled (%)**		**Median time to discontinuation of parenteral antibiotics (IQR)**	
	COVID-19	**Non-COVID-19**	**COVID-19**	**Non-COVID-19**	**COVID-19**	**Non-COVID-19**
Sex						
Female	37/156 (23.7%)	2231/9445 (23.6%)	64/156 (41.0%)	2941/9445 (31.1%)	6 (5-11)	5 (5-9)
Male	58/177 (32.8%)	2254/9392 (24.0%)	85/177 (48.0%)	3313/9392 (35.3%)	6 (5-12)	6 (5-10)
Age (years old)						
<1	0/6 (0%)	380/1844 (20.6%)	4/6 (66.7%)	1479/1844 (80.2%)	7 (5-28)	8 (5-18)
1-4	6/19 (31.6%)	255/1332 (19.1%)	16/19 (84.2%)	771/1332 (57.9%)	5 (5-8)	6 (5-11)
5-14	9/29 (31.0%)	281/1455 (19.3%)	26/29 (89.7%)	758/1455 (52.1%)	7 (5-14)	5 (5-9)
15-24	5/25 (20.0%)	386/1616 (23.9%)	19/25 (76.0%)	463/1616 (28.7%)	7 (5-20)	5 (5-8)
25-34	6/38 (15.9%)	465/2057 (22.6%)	11/38 (28.9%)	339/2057 (16.5%)	5 (4-8)	5 (5-7)
35-44	8/38 (21.1%)	607/2486 (24.4%)	11/38 (28.9%)	506/2486 (20.4%)	5 (4-8)	5 (5-8)
45-54	12/50 (24%)	698/2787 (25.0%)	22/50 (44.0%)	672/2787 (24.1%)	7 (5-13)	5 (5-9)
55-64	18/63 (28.6%)	731/2866 (25.5%)	16/63 (25.4%)	707/2866 (24.7%)	6 (4-11)	6 (5-10)
≥ 65	31/65 (47.7%)	682/2394 (28.5%)	24/65 (36.9%)	559/2394 (23.4%)	6 (5-13)	6 (5-10)
Admission year						
2019	-	2282/9433 (24.2%)	-	3113/9433 (33.0%)	-	5 (5-10)
2020	95/333 (28.5%)	2203/9404 (23.4%)	149/333 (44.7%)	3141/9404 (33.4%)	6 (5-11)	5 (5-9)

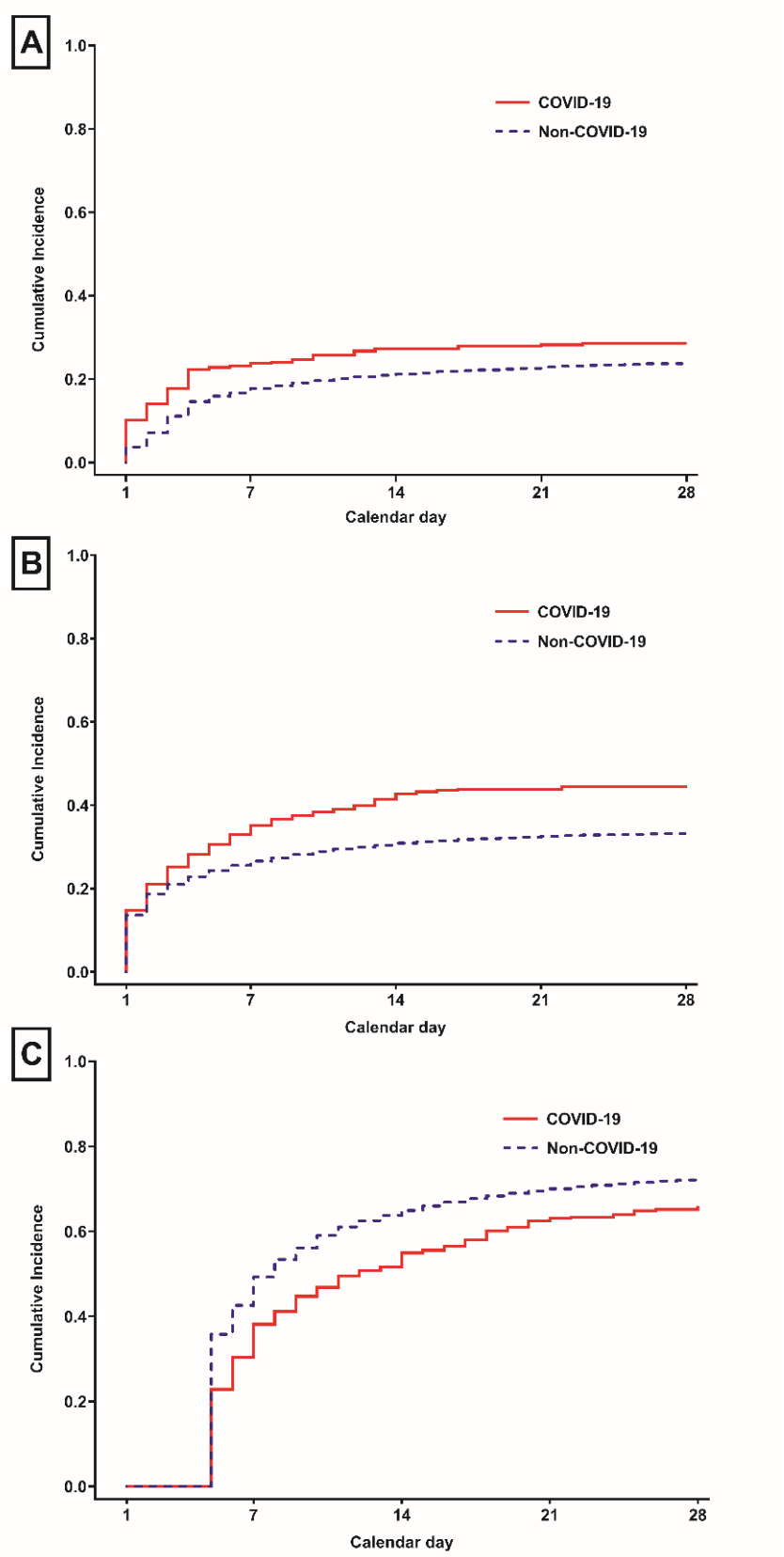
[a] Mortality included in-hospital mortality and discharged to a hospice

Table 3.5 Multivariable analyses for time to mortality, having blood culture sampled and discontinuation of parenteral antibiotics among 19,170 patients with severe infection

Variables	Mortality [a]		Having blood culture sampled [b]		Discontinuation of parenteral antibiotics [c]	
	Adjusted SHR	**P values**	**Adjusted SHR**	**P values**	**Adjusted SHR**	**P values**
COVID-19 status						
Non-COVID-19	Reference		Reference		Reference	
COVID-19	1.29 (1.04-1.58)	0.02	1.71 (1.47-1.99)	<0.001	0.73 (0.65-0.83)	<0.001
Sex						
Female	Reference		Reference		Reference	
Male	1.02 (0.97-1.09)	0.38	1.04 (0.99-1.09)	<0.001	0.92 (0.89-0.94)	<0.001
Age (years old)						
<1	1.09 (0.93-1.28)	<0.001	7.54 (6.73-8.45)	<0.001	0.84 (0.79-0.89)	0.72
1-4	1.01 (0.84-1.20)		4.54 (4.01-5.14)		0.88 (0.82-0.95)	
5-14	1.07 (0.92-1.25)		3.98 (3.52-4.51)		0.94 (0.87-1.00)	
15-24	1.26 (1.07-1.48)		1.90 (1.65-2.17)		0.88 (0.82-0.94)	
25-34	Reference		Reference		Reference	
35-44	1.24 (1.07-1.41)		1.25 (1.09-1.43)		0.99 (0.93-1.05)	
45-54	1.23 (1.07-1.41)		1.51 (1.33-1.71)		0.94 (0.89-1.00)	
55-64	1.22 (1.06-1.40)		1.51 (1.33-1.72)		0.90 (0.85-0.95)	
≥65	1.30 (1.13-1.49)		1.44 (1.26-1.64)		0.87 (0.82-0.92)	
Admission year						
2019	Reference		Reference		Reference	
2020	0.96 (0.91-1.02)	0.18	1.06 (1.01-1.11)	0.02	0.94 (0.92-0.97)	<0.001

Footnote: SHR = sub-distribution hazard ratio. Fine and Grey sub-distribution hazard models were used. [a] Mortality included in-hospital mortality and discharged to a hospice. Discharged home from the hospital was considered as a competing risk for mortality. [b] In-hospital mortality, discharged to a hospice and discontinuation of parenteral antibiotics were considered as a competing risk for having blood culture sampled. Blood culture sampled on -1 calendar day when a parenteral antibiotic was started was included in the model as sampled on the calendar day when a parenteral antibiotic was started. [c] In-hospital mortality and discharged to a hospice were considered as a competing risk for discontinuation of parenteral antibiotics.

Figure 3.5 Cumulative incidence of (A) mortality, (B) having blood culture sampled, and (C) discontinuation of parenteral antibiotics among 19,170 patients with severe infection. Reproduced from (276)



3.4.3 Blood culture practices

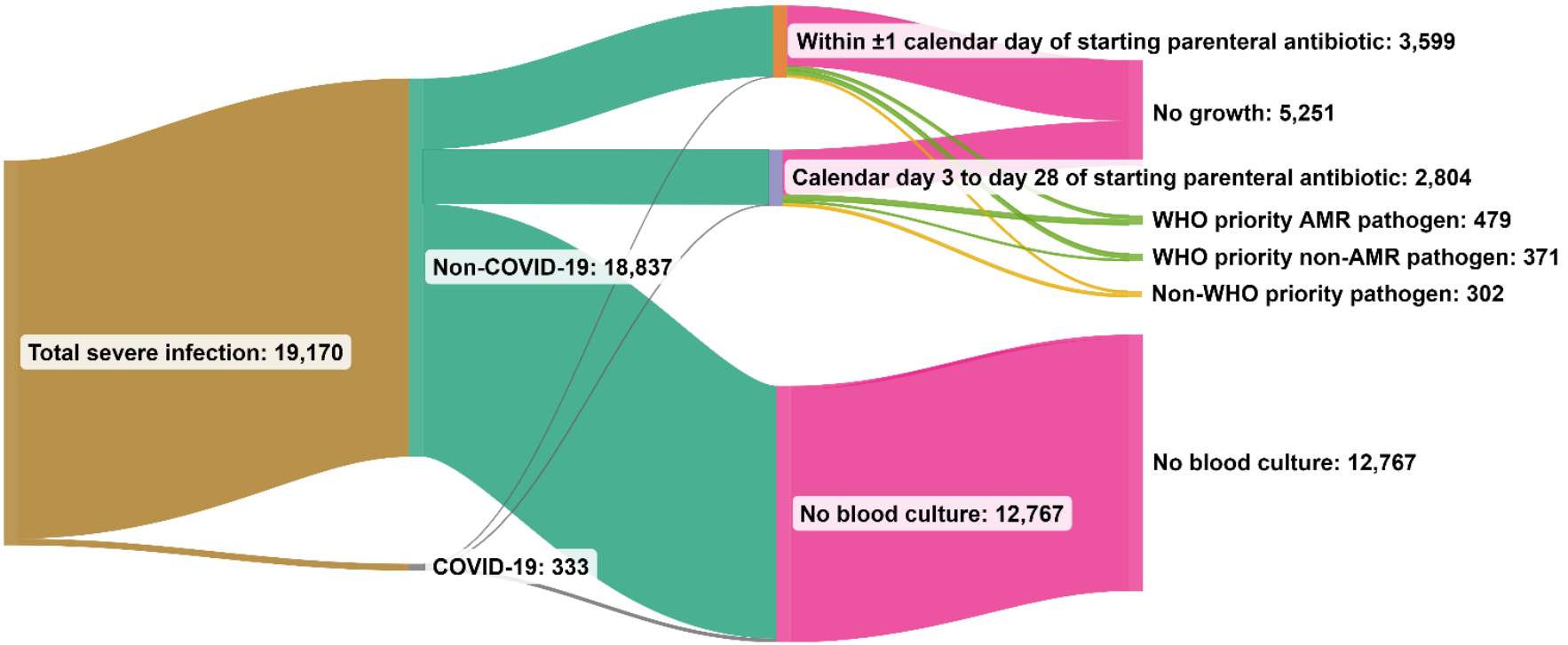
Of 19,170 patients with severe infection, 3,599 (18.8%) had blood culture taken within ±1 calendar day of parenteral antibiotics being started (**Table 3.6** and **Figure 3.6**). The proportion was higher in COVID-19 than in non-COVID-19 patients (21.0% [70/333] vs. 18.7% [3,529/18,837]; p<0.001).

Table 3.6 Parameters for clinical diagnostic practices and antibiotic use practices among 19,170 patients with severe infection

Parameters	**COVID-19 patients with severe infection (n=333)**	**Non-COVID-19 patients with severe infection (n=18,837)**	**P values**
Parameters for clinical diagnostic practices			
Proportion of patients with blood culture taken within ±1 calendar day of parenteral antibiotic being started	21.0% (70/333)	18.7% (3,529/18,837)	<0.001
Proportion of patients with blood culture taken from calendar day 3 to day 28 of parenteral antibiotic being started	31.8% (106/333)	21.3% (4,012/18,837)	<0.001
Proportion of patients with at least one blood culture taken within 28 calendar days of parenteral antibiotic being started	44.7% (149/333)	33.2% (6,254/18,837)	<0.001
Median blood culture turn-around time (days, IQR, n)	4 (4-5, n=34)	4 (4-5, n=1,593)	0.69
Parameters for antibiotic use practices			
Proportion of patients with narrow-spectrum parenteral antibiotic within 2 calendar days following blood culture report among those who had a blood culture positive for 3GCSEC or 3GCSKP and remained on a parenteral antibiotic on the day that blood culture results were reported	0% (0/1)	38.4% (20/52)	0.43
Proportion of patient with parenteral antibiotic discontinuation within 2 calendar following blood culture report among those who had a negative blood culture and remained on a parenteral antibiotic on the day that blood culture results were reported	19.4% (7/36)	26.8% (616/2,298)	0.32

Footnote: 3GCSEC=3rd generation cephalosporin sensitive *E. coli*, 3GCSKP=3rd generation cephalosporin sensitive *K. pneumoniae*, Narrow-spectrum parenteral antibiotics are defined as antibiotics within the Access and Watch category without anti-MRSA or antipseudomonal activity

Figure 3.6 Sankey diagram showing first blood culture test and blood culture result among 19,170 patients with severe infection. Reproduced from (276)



The proportion of patients having blood culture taken within 28 days after parenteral antibiotics being started was 33.4%. Using Fine and Grey model, I found that having blood culture taken within 28 days was higher in COVID-19 than non-COVID-19 patients (44.7% vs. 33.2%; aSHR 1.71; 95%CI 1.47-1.99, p<0.001; **Table 3.5**) and in those admitted in 2020 than those admitted in 2019 (aSHR 1.06; 95%CI 1.01-1.11, p=0.02). **Figure 3.5 (B)** shows that, of COVID-19 and non-COVID-19 patients, 21.0% and 18.7% had the first blood culture taken on ±1 calendar day of parenteral antibiotics being started and the other 23.7% and 14.5% gradually had the first blood culture taken between calendar day 2 and 14 of parenteral antibiotics being started, respectively.

The median blood culture turn-around time was not different between the two groups (4 vs. 4 days; p=0.69).

3.4.4 Antibiotic use practices

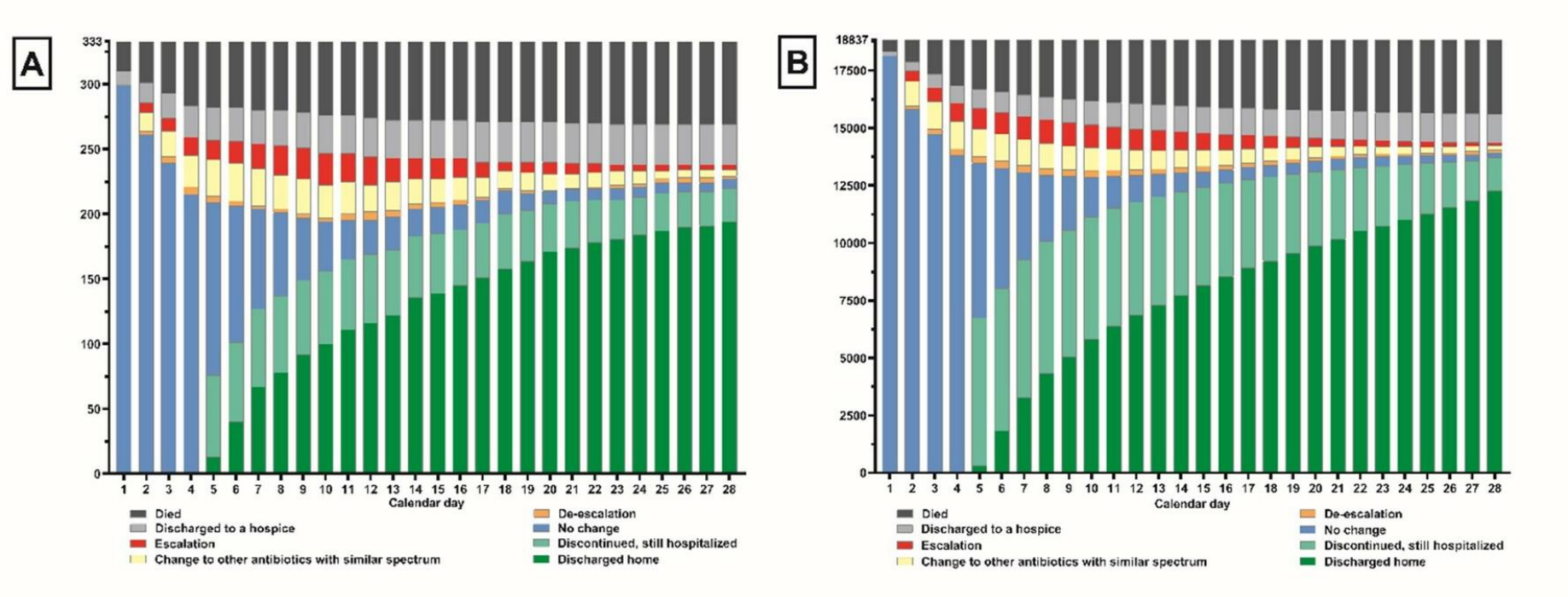
Figure 3.7 shows escalation, change, de-escalation and discontinuation of parenteral antibiotics compared to the parenteral antibiotics the patients received the day before. Of 19,170 patients with severe infection, 2,466 (12.9%) had parenteral antibiotics escalated, 3,267 (17.0%) changed to other antibiotics with similar spectrum, and 1,001 (5.2%) de-escalated at least once within 28 days after parenteral antibiotics being started. **Figure 3.8** shows the proportion of the dispensed parenteral antibiotics categorized by AWaRe classification over 28 calendar days.

Of 19,170 patients with severe infection, 72.7% had parenteral antibiotics discontinued within 28 days (**Figure 3.5 (C)**). The median time to discontinuation of parenteral antibiotics was longer in COVID-19 than non-COVID-19 patients (13 days vs. 8 days;

aSHR 0.64; 95%CI 0.55-0.75, p<0.001; **Table 3.5** and **Figure 3.5 (C)**), and in those admitted in 2020 than those admitted in 2019 (aSHR 0.94; 95%CI 0.92-0.97, p<0.001).

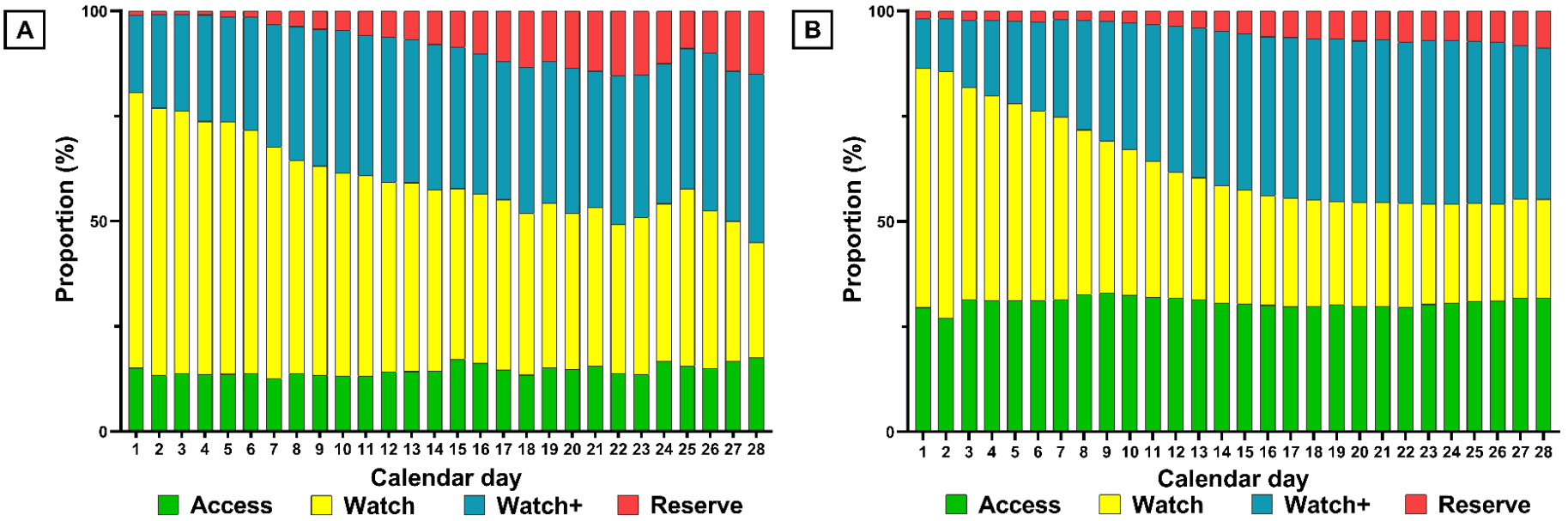
Of 53 patients with severe infection who had a blood culture positive for 3GCSEC or 3GCSKP and remained on a parenteral antibiotic on the day that blood culture results were reported, 20 (37.7%) had narrow-spectrum parenteral antibiotic within 2 calendar days following blood culture report. The proportion was not different between the two groups (p=0.43). Of 2,344 patients with severe infection who had blood culture results negative for any organisms and remained on a parenteral antibiotic on the day that blood culture results were reported, 623 (26.6%) had parenteral antibiotics discontinued within 2 calendar days following blood culture report. This proportion was not different between the two groups (p=0.32).

Figure 3.7 Antibiotic stewardship among (A) 333 COVID-19 patients and (B) 18,837 non-COVID-19 patients with severe infection. Reproduced from (276)



Footnote: "Antibiotic escalation" is defined as (a) adding a new antibiotic, (b) changing antibiotics to other antibiotics with an increase in Access, Watch and Reserve categories, or (c) changing antibiotics in the Watch category without anti-MRSA activity and antipseudomonal activity to other antibiotics within the Watch category with anti-MRSA activity (e.g. vancomycin) or antipseudomonal activity (e.g. antipseudomonal cephalosporin, antipseudomonal penicillin and carbapenems) compared to the parenteral antibiotics received on the day before. "Antibiotic de-escalation" is defined as the inverse of these. "Change to other antibiotics with similar spectrum" is defined as changing antibiotics to other antibiotics within similar Access, Watch and Reserve categories, and with similar anti-MRSA activity and antipseudomonal activity for antibiotics within the Watch category. Only parenteral antibiotics were included in the analysis.

Figure 3.8 Proportional consumption of parenteral antibiotics given to (A) 333 COVID-19 patients and (B) 18,837 non-COVID-19 patients with severe infection by AWaRe categorization over 28 calendar days. Reproduced from (276)



Footnote: For this figure, I divided antibiotics in the Watch category to Watch and Watch+. Watch+ category comprises antibiotics in Watch category with anti-MRSA activity (e.g. vancomycin) or antipseudomonal activity (e.g. antipseudomonal cephalosporin, antipseudomonal penicillin and carbapenems.

3.5 Discussion

This study demonstrates that the routine electronic hospital databases could be used to monitor and report outcomes of diagnostic and ASPs in hospitals in LMICs. In the study hospital, I found that the proportion of timely blood culture was low in inpatients, and duration of parenteral antibiotics was longer in COVID-19 patients. Most of the parenteral antibiotics used for inpatients were from the Watch Category. After adjusting for COVID-19 patients, I found that the blood culture practice minimally improved in year 2020 compared to 2019; however, the time to discontinuation of parenteral antibiotics was longer in 2020 compared to 2019. I shared these findings with the AMS committee of the hospital, highlighting the urgency of improving both diagnostic and ASPs in the study hospital.

The proportion of patient with severe infection having blood culture sampled within ±1 calendar day of parenteral antibiotics being started was lower than those reported in other high-income countries (277, 278) and in Thailand (224). Furthermore, I observed a high proportion of patients with severe infection having the first blood culture taken from calendar day 2 to 14 after the start of parenteral antibiotic administration. This shows that delayed blood culture is not uncommon in the study hospital, although there is an increasing trend of blood culture utilization during the study period (122). This is of concern as underutilization and delayed blood culture can have a negative impact on individual patient management (16) and can overestimate proportions and underestimate incidence rates of AMR infections in the cumulative antibiograms (224, 279).

The better blood culture practice among COVID-19 patients compared to non-COVID-19 patients is encouraging. This could be because the study hospital, which is the national referral hospital, manages COVID-19 patients with comorbidities and severe clinical

presentations. Additionally, in COVID-19 patients, clinicians tend to consult infectious diseases physicians and sampled blood culture prior to parenteral antibiotic administration more frequently (122). This improvement should be strengthened further until all sepsis patients have blood culture sampled within ±1 calendar day of parenteral antimicrobial therapy being started (280).

I observed a longer median blood culture turn-around time compared to those reported in high-income countries, i.e. 2-3 days (281-283). The blood culture turn-around time is critical for gaining the maximum benefits of blood culture as a guidance for clinicians in deciding rational antibiotic prescriptions, reduce length of hospitalization and increase patient survival (16, 242, 284-287). Efforts to shorten blood culture turn-around time by improvement of internal laboratory workflows (e.g., work shifts and laboratory staffing) should be commenced (16, 242, 283, 288).

I observed the longer median time to discontinuation of parenteral antibiotics in inpatients compared to those recommended in the guidelines (i.e. 5-8 days) (218). The longer time to discontinuation parenteral antibiotics and higher use of Watch and Reserve antibiotics in COVID-19 patients could be due to the fear of high mortality in the early COVID-19 pandemic, in addition to the clinical profile of patients managed in our hospital (15). Previous studies reported an overuse of antibiotics amongst COVID-19 hospitalized patients. Azithromycin, a Watch antibiotic, was initially promoted as a potential COVID-19 regimen due to its antiviral and anti-inflammatory properties, although this was not supported by further studies (289). Furthermore, there might be a false belief of antibiotic use as medical prophylaxis to reduce secondary bacterial infections (290-293). These

highlight the need to improve clinician adherence to the well-developed evidence-based antibiotic guidelines (292, 293).

I observed that a de-escalation practice is uncommon in the study hospital using multiple parameters, similar to reports from other LMICs (294). The common barrier to de-escalation following blood culture positive for monomicrobial narrow-spectrum antibiotic susceptible Enterobacterales could be the fear that patients may deteriorate if the broad-spectrum antibiotic is de-escalated (265). The low proportion of antibiotic discontinuation following negative blood culture could reflect the physician lack of trust in negative results (268). These data highlight the necessity to emphasize consideration of de-escalation following positive blood culture with drug sensitive pathogens and discontinuation following negative blood culture in patients with positive treatment response as an opportunity to reduce the overuse of broad-spectrum antibiotics (266, 268, 295).

3.6 Limitations

This study has several limitations. First, I could not exclude patients who had parenteral antibiotics for surgical prophylaxis for at least four consecutive days and analyze data for each clinical syndrome, including diagnosis and reason of admission, due to data limitation. Second, parameters used for evaluating practices are not free from bias, although they have been frequently used in previous studies. Third, use of routine data could not determine whether the practice in every single patient was appropriate or inappropriate. However, the analysis of routine data can represent the overall practice at the study hospital. Lastly, the findings may not be generalizable to all hospitals in LMICs.

3.7 Implications

Improving diagnostic and antimicrobial stewardship is critically needed. I recommend hospitals in LMICs to perform routine monitoring and improvement of diagnostic and antimicrobial stewardship.

3.8 Conclusion

In the Indonesian referral hospital, the proportion of timely blood culture is low, and duration of parenteral antibiotics is long in both COVID-19 and non-COVID-19 patients.

Chapter 4
A nationwide mixed-methods study of gaps and barriers to implementation of antimicrobial stewardship programs in hospitals in Indonesia

4.1 Abstract

Background

There is an urgent need to understand the implementation barriers of ASP in low- and middle-income countries.

Methods

I conducted a mixed-methods study in public and private hospitals across all provinces in Indonesia (March-December 2023). I used a self-assessment questionnaire with a scoring system, and multilevel ordinal regression to assess associations with hospital and district-level characteristics. FGD with hospital stakeholders examined barriers and enablers. I applied a patient safety framework to integrate results.

Results

575 (19%) of 3026 hospitals completed the self-assessment, of whom 516 (89.7%) had a formal ASP (median 4 [IQR1-5] years), and 14 participated in FGD. The median overall ASP development score was 48.4% (35.9-62.5%), classifying 41 (8.0%) hospitals as inadequate (0-25%), 237 (45.9%) as basic (26-50%), 179 (34.7%) as intermediate (51-75%) and 59 (11.4%) as advanced (76-100%). Scores were highest for hospital leadership support (83.4% [66.7-100%]), followed by ASP team and infectious disease training (66.7% [55.6-77.8%]); education (50% [0.0-75.0%]); ASP interventions (43.8% [18.7-68.7%]); hospital infrastructure (42.9% [14.3-71.4%]); and monitoring, reporting and

feedback (40.9% [27.3-54.5%]). A higher ASP development score was associated with higher hospital tiered level, longer ASP duration, and higher district-level public health development index and gross domestic expenditure, but not with hospital ownership or geographic region. FGDs highlighted barriers related to hospital leadership support, staff technical and behavioural skills, cross-disciplinary collaboration, fear of loss of prescriber autonomy, microbiology and information technology (IT) support, and hospital accreditation.

Conclusions

Identified implementation barriers can inform actions for context-specific, sustainable improvement of ASPs.

4.2 Introduction

Southeast Asia is a region of great importance in the development and spread of AMR-bacteria (2, 31) due to the widespread and unregulated use of antimicrobial agents, little access to high-quality routine antibiotics, poor infection prevention and control (IPC), amongst other factors, i.e. limited access to safe drinking water, effective sanitation, and vaccination, and use of antibiotics in livestock production (2, 31, 296-298).

ASP has been defined as a set of coordinated interventions designed to measure and improve the appropriate use of antibiotic agents. Implementation of ASPs in hospitals is an essential component of AMR prevention and control efforts and has improved patient outcomes and reduce adverse events, although most available evidence comes from high-income countries (299-301).

Indonesia is a populous (275 million) middle-income country, with widely varying socio-economic and health indicators, and a decentralized public healthcare system, alongside a substantial private health sector (302). Antimicrobial consumption is high and poorly regulated, and an estimated 34,530-133,753 people died because of bacterial AMR in 2019 (24, 303). As part of its National Action Plan for AMR, the Ministry of Health (MoH) launched an accreditation standard that included ASP in 2018 (304), and guidelines for ASP implementation (305) and antibiotic prescribing (306) in 2021.

There is a need to better understand the key organizational and behavioral challenges to effective ASP implementation. Previous study in limited number of hospital in Jakarta, the Indonesian capital city, concluded main barriers to ASP implementation, including (1) Ineffective implementation of mandatory ASP under hospital accreditation; (2) Priorities to generate profits and interprofessional relationships between doctors and hospital managers or ASP leaders; (3) Cost-prohibitive bacterial culture testing and thresholds of national health insurance coverage; (4) Unreliable infrastructures (32). These barriers have not been evaluated nationwide with diverse hospital characteristics. I conducted a nationwide mixed-methods evaluation of hospital ASPs. I first aggregated hospital self-assessment scores, then assessed associated hospital and district-level factors, and, lastly, examined barriers and enablers through FGDs with hospital stakeholders. My analysis also incorporated impacts of the COVID-19 pandemic.

4.3 Methods

4.3.1 Study design

This nationwide mixed-methods study involved an ASP self-assessment that scored the ASP development level in each participant hospital (March-July 2023), followed by FGDs

with ASP stakeholders in selected hospitals (August-December 2023). I integrated the quantitative and qualitative findings applying the SEIPS framework (33), a comprehensive outlook that considers both the people working within the system, the wider socio-technical influences on their environment, and the tools and tasks required to deliver high-quality care. I finally formulated future recommended actions.

The Faculty of Medicine Universitas Indonesia Ethics Committee (KET-1189/UN2.F1/ETIK/PPM.00.02/2022) and Oxford Tropical Research Ethics Committee (554-22) approved the study. FGD participants provided written consent. The study was endorsed by the MoH, and all hospital directors gave their written permission. This study is reported as per the Strengthening the Reporting of Observational Studies in Epidemiology guideline (**Table 4.1**).

Table 4.1 STROBE checklist

	Item no	Recommendation	Page
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	162
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	162
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	164
Objectives	3	State specific objectives, including any prespecified hypotheses	164
Methods			
Study design	4	Present key elements of study design early in the paper	164
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	164
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants	164
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	174-175
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	172-174
Bias	9	Describe any efforts to address potential sources of bias	174
Study size	10	Explain how the study size was arrived at	170-171
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	174
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	174
		(b) Describe any methods used to examine subgroups	174
		(c) Explain how missing data were addressed	NA
		(d) If applicable, describe analytical methods taking account of sampling strategy	174
		(e) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	176
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	Fig 4.1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 4.5
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	195
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	196-197
		(b) Report category boundaries when continuous variables were categorized	196-197
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and sensitivity analyses	196-197
Discussion			
Key results	18	Summarize key results with reference to study objectives	228
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	227

	Item no	Recommendation	Page
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	228
Generalizability	21	Discuss the generalizability (external validity) of the study results	225
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

4.3.2 Self-assessment survey procedures

Eligible hospitals were all 3026 (1092 public and 1934 private) MoH-registered general and specialised, public and private hospitals across all tiered levels hospitals in all 34 provinces (as per September 2022). MoH designates hospital tiered levels based on number of inpatients beds and specialists in internal medicine, obstetrics-gynecology, pediatrics and surgery) as type A (≥251 beds, ≥6 specialists), B (201-250 beds, ≥3 specialists), C (101-200 beds, ≥2 specialists), or D (51-100 beds, ≥1 specialist) (34). I excluded hospitals that were not in operation, not able or willing to participate, and/or uncontactable.

4.3.3 Sample size calculation

Hospitals are the main unit of measurement. The sample size calculation is aimed to ensure representativeness of acute care hospitals in each province and total inpatient beds. I used a systematic sampling design to achieve representative samples for each province and nationwide. I adopted the hospital systematic sampling approach developed as part of the European Centre for Disease Prevention and Control point prevalence survey of healthcare-associated infections and antimicrobial use in European acute care hospitals. I calculated the sample size to estimate an anticipated prevalence (ASP hospital checklist score) and precision at the province level. The number of hospitals to be included depends on the expected design effect and on the average hospital size in each province (270).

Underlying assumptions:

1. Because of lacking data, I assumed prevalence and precision of the results similar for all provinces.
2. Prevalence estimation: Based on these preliminary data from comparable settings, I conservatively chose a 50% outcome prevalence for this study (i.e., to maximize the sample size).
3. Precision assumption: ±4%
4. Design effect: The selected hospitals can be considered as clusters of patients of the total acute care hospital patient population. Therefore, a correction for cluster surveys (design effect) must be applied when calculating the sample size. The design effect (DEFF) of a statistic is the ratio of actual variance for a given sample design over the variance if the patients were selected randomly (i.e., from all, or a much larger number of hospitals). The higher the design effect, the more patients must be included in the sample to estimate the same prevalence with the same precision. The design effect increases with the size of the clusters (average hospital size) and with the magnitude (%) of the outcome under study (ASP hospital checklist score). Given that national data are lacking on point prevalence surveys or ASP, we estimated DEFF for different hospital size categories on the basis of data from ECDC point prevalence survey (**Table 4.2**). The DEFF is incorporated for each province after estimating the average hospital size per province utilizing Ministry of Health hospital administrative data. DEFF was based on Average Hospital Size as a function of cluster size (average number of inpatient beds of acute care hospitals).

Table 4.2 DEFF based on average hospital size

Average hospital size	DEFF
0-49	1.8
50-79	2.6
80-109	2.7
110-139	4.1
140-179	5.7
180-229	5.7
230-299	6.0
300-379	6.8
380-529	8.0
530+	10.5

Table 4.3 estimates the number of hospitals needed to estimate ASP performance of 50% (46-54%), with DEFF depending on average hospital size by province, and survey sampling steps.

4.3.4 Hospital sampling steps

The stages of the sampling plan are explained below:

Systematic Sampling Procedures

Before the hospital selection process, I sorted the hospitals according to:

1. Number of inpatient beds, to ensure that hospitals of different sizes are represented in exactly the same way in the sample as in the national/regional population of hospitals;
2. Hospital level/tier (A, B, C, D), to ensure representativeness of the different levels of hospitals; and
3. Ownership status (public/private), to ensure representativeness of the health sectors.

Selection of Hospitals

To ensure proportional and representative selection of hospitals, I followed the following procedure:

1. I obtained a list of all registered hospitals in each province. The list included information on the total number of beds, hospital level and ownership status (public vs private).
2. I sorted the list in ascending order based on number of inpatient beds, level and ownership status.
3. I obtained the number of hospitals to be sampled per province based on above tables.
4. I determined a sampling interval by dividing the total number of hospitals by the number to be sampled (i.e. sampling interval k). The total number of the sample was based on the final list of hospitals obtained from the MoH.
5. I generated a random number between 1 and k (designated i), using excel =RAND() function to start the sampling.
6. Round 1: from the random start, every k^{th} hospital was selected from the list, thus selecting the i^{th} hospital, i^{th}+k hospital, the i^{th}+2k hospital, etc.
7. Substitution of selected hospitals was required in case of refusal/inability to participate. Substitution procedures was as follows:

   (i) Round 2: I selected the next hospital on the list (i^{th}+1 hospital, i^{th}+k+1 hospital, i^{th}+2k+1 hospital etc.) to replace the first selected hospital which did not respond to the round 1 survey;

   (ii) Round 3: I selected the next hospital on the list (i^{th}+2 hospital, i^{th}+k+2 hospital, i^{th}+2k+2 hospital etc.) to replace the first selected hospital which did not respond to the round 2 survey;

   (iii) Round 4: I invited all remaining hospitals.

Table 4.3 Representative hospital sampling strategy and sample size calculation

Province	No of hospitals in 2022[1]	No of bed in 2022	Average hospital size	Estimated DEFF	Recommended sample size	Total no. of hospital sampled per province	% Public	No. of hospitals sampled per province	
								Public	Private
Aceh	72	9787	134	4.1	2319	17	45%	8	9
North Sumatra	202	24674	118	4.1	2403	20	25%	5	15
West Sumatra	76	7912	98	2.7	1507	15	43%	6	9
Riau	76	8701	114	4.1	2302	20	30%	6	14
Jambi	40	4949	124	4.1	2195	18	48%	9	9
South Sumatra	86	10138	118	2.7	1530	13	46%	6	7
Bengkulu	26	2682	107	2.7	1325	12	66%	8	4
Lampung	83	8950	110	4.1	2307	21	27%	6	15
Bangka Belitung Islands	27	2674	99	2.7	1324	13	50%	6	7
Riau Islands	37	5105	142	5.7	3062	22	50%	11	11
DKI Jakarta	192	26161	133	4.1	2406	18	30%	5	13
West Java	392	53742	136	4.1	2434	18	20%	4	14
Central Java	331	46607	140	5.7	3378	24	25%	6	18
DI Yogyakarta	80	7762	95	2.7	1505	16	22%	4	12
East Java	404	51706	124	4.1	2433	19	30%	5	14
Banten	124	14496	116	4.1	2363	20	15%	3	17
Bali	74	8914	124	4.1	2306	19	31%	6	13
West Nusa Tenggara	43	5650	135	4.1	2225	16	50%	8	8
East Nusa Tenggara	55	5854	105	2.7	1470	14	57%	8	6
West Kalimantan	53	6450	119	4.1	2252	18	56%	10	8
Central Kalimantan	30	4056	131	4.1	2144	16	74%	12	4
South Kalimantan	53	6680	126	4.1	2258	18	43%	8	10
East Kalimantan	59	6937	118	4.1	2265	19	46%	9	10
North Kalimantan	13	1205	93	2.7	1082	11	82%	9	2
North Sulawesi	53	7163	135	4.1	2271	16	55%	9	7
Central Sulawesi	39	5230	134	4.1	2208	16	74%	12	4
South Sulawesi	118	16850	139	4.1	2377	17	50%	9	8
Southeast Sulawesi	36	4049	107	2.7	1412	13	52%	7	6
Gorontalo	19	2372	125	4.1	1965	16	74%	12	4
West Sulawesi	12	1478	106	2.7	1153	11	63%	7	4
Maluku	32	3850	104	2.7	1402	12	76%	9	3

Province	No of hospitals in 2022[1]	No of bed in 2022	Average hospital size	Estimated DEFF	Recommended sample size	Total no. of hospital sampled per province	% Public	No. of hospitals sampled per province	
								Public	Private
North Maluku	20	1790	81	2.7	1214	15	77%	12	3
West Papua	23	2166	83	2.7	1269	15	77%	12	3
Papua	46	5002	102	2.7	1447	14	78%	11	3
Total	**3026**	**381742**	**3975**	**3.7**	**67513**	**562**	**47.8%**	**268**	**294**

Footnotes: The selected hospitals can be considered as clusters of patients of the general hospital patient population. Therefore, a correction for cluster surveys (design effect) has to be applied when calculating the sample size. With cluster sampling approach, the total sample number was calculated factoring in the design effect per province to obtain the effective sample size as described in the formula below:

$$ss = DEFF \times N \times p \times (1-p) \times \frac{Z^2 \times (N-1) + (p \times (1-p))}{c^2}$$

where:
DEFF = adapted from the DEFF obtained in previous ECDC Point Prevalence Survey
N = *N* is the size of population in each province, based on *Potensi Desa* data 2018
P = base proportion for indicators of interest, set to 50%
Z = Z-score value 95% confidence interval, which is 1.96
C = margin of error, which is set at 4%

I lead multidisciplinary experts (infectious disease specialists, clinical microbiologist, epidemiologist, health system researcher) in the development of the self-assessment questionnaire based on existing questionnaires, and covered six ASP domains (i.e. hospital leadership support; ASP team and infectious disease training; hospital infrastructure; ASP interventions; ASP monitoring and reporting, and education) (28, 305, 307, 308) (64 Yes/No items) plus COVID-19 impacts (309, 310) (45 Yes/No or Likert-scale items) (**Table 4.4**).

The survey instrument was adapted from (i) the Indonesian MOH national ASP programme guideline (2021), which has been adapted from the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR) set of core and supplementary indicators for hospital ASPs (2015), covering hospital leadership support; ASP team and infectious disease training; hospital infrastructures; ASP interventions; monitoring and reporting of ASPs; and AMR/ASP education. Additional items were added from (ii) the US CDC core elements of hospital ASPs (2019) and (iii) WHO guideline ASPs in health facilities in low- and middle-income countries (2019). Relevant hospital-level items that focus on the influence of COVID-19 on ASP activities; human resources; and the changes in treatment guidelines and implementation were adopted from (iv) the COVID-19 Survey from The Pharmacy Infection Network (PIN) of the United Kingdom Clinical Pharmacy Association (UKCPAPIN), and (v) the WHO AMR Surveillance and Quality Assessment Collaborating Centres Network. The final 109-item questionnaire was piloted in 10 hospitals to improve clarity and flow, and took about 60 minutes to complete.

The self-assessment was electronically delivered to each hospital with an invitation letter from MoH, and completed by the ASP team. The research team checked data reliability by

repeating the self-assessment in a telephone interview in a 10% sample of participant hospitals (expressed as percentage agreement and Cohen's kappa).

I collected district-level human development and health-system capacity indicators from relevant government sources (**Table 4.5**).

4.3.5 Focus group discussions

For the FGDs, I developed an interview guide based on the ASP domains (28, 305, 307, 308) and the previous study findings (32). To obtain different perspectives, I purposively selected a varied sample of 14 hospitals based on ownership, tiered level, and geographical region. I conducted the FGDs by videoconference. Each FGD included 6-7 people (i.e. ASP leader, clinician, pharmacist, microbiology staff, IPC staff, and hospital manager). The FGDs were conducted iteratively, with follow-up questions in line with participant responses. The FGDs were conducted in Indonesian, audio-recorded, verbatim-transcribed, and then translated to English. The FGDs lasted between 50-110 minutes (average 80 minutes).

Table 4.4 Source of items included in the ASP self-assessment questionnaire

	Hospital leadership support	ASP team and ID training	Hospital infrastructure	ASP interventions	Monitoring, reporting and feedback	Education	IPC	Total
Core questionnaire								
MoH ASP checklist[1]	2	9	6	12	12	2	-	43
WHO LMIC AMS checklist[2]	2	-	-	1	2	-	-	5
US CDC AMS core elements[3]	-	2	-	2	5	1	-	10
Self-developed items	-	-	1	1	3	1	-	6
COVID-19 impacts questionnaire								
UKCPAPIN[4]	-	-	-	2	1	1	-	4
WHO AMR Surveillance and Quality Assessment Collaborating Centres Network[5]	-	-	11	-	5	-	-	16
Self-developed items	1	6	1	6	4	-	7	25
TOTAL	**5**	**17**	**19**	**24**	**32**	**5**	**7**	**109**

1. Ministry of Health ASP checklist (adapted from the Transatlantic Taskforce on Antimicrobial Resistance ASP checklist)
2. US Centers for Disease Control and Prevention core elements of hospital ASP 2019
3. WHO ASP in health facilities in LMICs 2019
4. WHO AMR Surveillance and Quality Assessment Collaborating Centres Network. Questionnaire of impact of the COVID-19 pandemic on antimicrobial stewardship
5. Pharmacy Infection Network of the UK Clinical Pharmacy Association (UKCPAPIN). Assessment checklist on impact of COVID-19 on antimicrobial stewardship activities/programs in the United Kingdom

Abbreviations: AMR, antimicrobial resistance; AMS, antimicrobial stewardship; ASP, antimicrobial stewardship program; ID, infectious diseases; IPC, infection prevention and control; LMIC, low- and middle-income countries; MoH, Ministry of Health; TATFAR, Transatlantic Taskforce on Antimicrobial Resistance; UKCPAPIN, Pharmacy Infection Network of the UK Clinical Pharmacy Association; US CDC, United States Centers for Disease Control and Prevention; WHO, World Health Organization.

Table 4.5 Data source of hospital and district-level factors

Variable	Date	Data source	Available from
Hospital accreditation status	1 July 2023	Indonesian Commission on Hospital Accreditation. Hasil akreditasi: rumah sakit terakreditasi 2023	https://kars.or.id/ (accessed on 1 July 2023)
District-level doctors, midwives, primary health centers and hospitals per 100 000 population	1 September 2022	Directorate of Health Quality Service, Ministry of Health	
District-level public health development index, health insurance coverage	2018	Ministry of Health, The National Research Institute of Department of Health. 2018 Public Health Development Index	http://ejournal2.litbang.kemkes.go.id/index.php/lpb/article/view/3537 (accessed on 1 July 2023) (accessed on 1 July 2023)
District-level human development index, life expectancy birth (years), average duration of formal education	2022	Statistics Indonesia. Human Development Index 2023	https://www.bps.go.id/en/publication/2023/05/16/ef80bec78ab91cb5b703b943/human-development-index-2022.html (accessed on 1 July 2023)
District-level per-capita domestic expenditure	2022	Statistics Indonesia. Gross Regional Domestic Product of Regencies/Municipalities in Indonesia 2018-2022	https://www.bps.go.id/id/publication/2023/06/14/99ca8a81cd97e69dc04a31bc/produk-domestik-regional-bruto-kabupaten-kota-di-indonesia-2018-2022.html] (accessed on 1 July 2023)

4.3.6 Data analysis

I maintained hospital anonymity during analysis and reporting. I analyzed self-assessment results using descriptive and regression statistics. I calculated the percentage of participant hospitals selecting each answer choice using the total number of responding hospitals as the denominator. I summed total percentage scores overall and per ASP domain. ASP development was based on the total scores classified as inadequate (0-25%); basic (26-50%); intermediate (51-75%); or advanced (76-100%). I used multilevel ordinal regression, with province as a random-effect variable to adjust for clustering of observations within provinces, to estimate associations between total ASP scores (overall and per domain) and independent variables at the hospital and district level. I categorized district-level data into quartiles (i.e., lowest, low-middle, middle-high, and highest). Given the hierarchical data

structure I applied multilevel modelling to adjust for clustering of observations within districts and/or provinces. The null model analysis, wherein no predictor was added, revealed that province and district level accounted for 17% and 0%, respectively, of the variance for overall ASP implementation score (likelihood ratio test p=0.004), and the final model therefore only included province as the random-effect variable. Using predictive approach with variables at the hospital and district level as the predictors of total ASP scores (overall and per domain), I forwarded each independent variable with a $p<0.20$ in the univariable model to the multivariable model. Final model selection was informed by likelihood ratio test. I analyzed data with Stata v15.1 (StataCorp, TX) and visualized with GraphPad Prism v8.3.0 (La Jolla, CA). I performed thematic analysis of the FGD data (311). Together with two other researchers, I openly coded and analysed data using both an inductive and a deductive approach to develop a preliminary coding dictionary that was refined as more transcripts were analyzed. To ensure consistency and reliability, we read the transcripts and field notes and met weekly to discuss the codes and agree on the themes generated.

4.4 Results

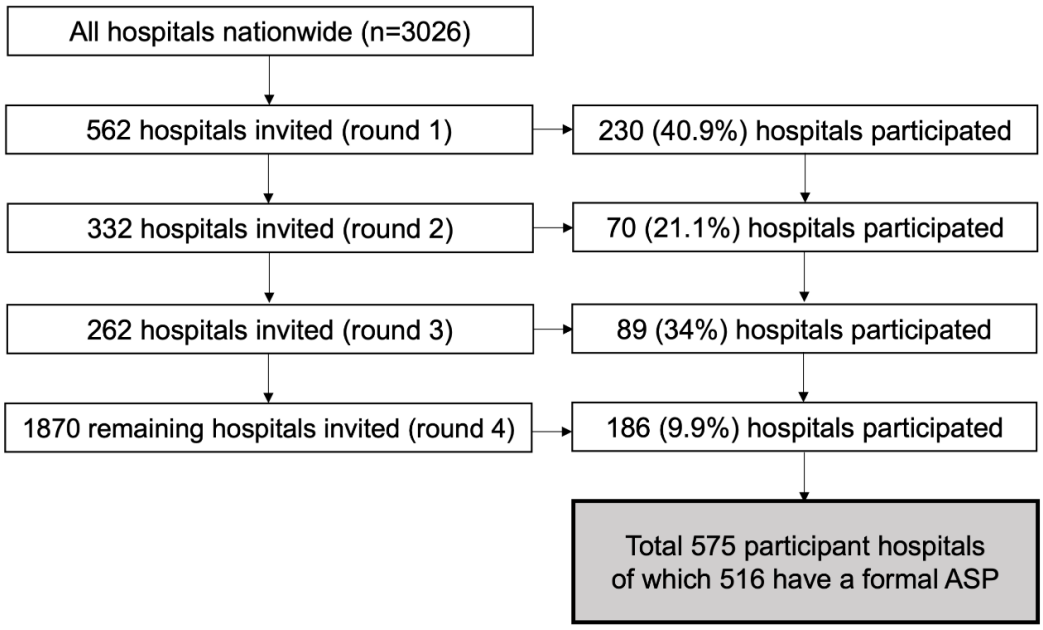
4.4.1 Participant characteristics

562, 332, and 262 hospitals were invited to the self-assessment in the round 1, 2, and 3, respectively. Due to limited hospital response in those 3 rounds, we invited 1870 remaining hospital in the last round. 575 (19.0%) of 3026 hospitals completed the self-assessment **(Figure 4.1)**, with the highest response rate in type A hospitals, accredited hospitals, the public sector, and the geographic regions of Bali, Kalimantan and Java **(Figure 4.2, Tables 4.6-4.9)**. 323 (56.2%) of participant hospitals were situated in Java island, where 50% of all hospitals are located. Compared to the telephone interview in a 10% sample of

participant hospitals, self-assessment data were reliable (Cohen's kappa 0.91 overall and ≥0.83 for each item, indicating near-perfect agreement) (**Table 4.10**). **Table 4.6** summarizes hospital characteristics. 516 (89.7%) of 575 hospitals had a formal ASP, with a median duration of 4 (interquartile range [IQR] 1-5) years, which were included in further analysis **(Figure 4.1)**.

I conducted FGDs at 14 hospitals involving 82 individual participants (15 ASP team leaders, 13 physicians, 9 microbiology staff, 13 pharmacists, 26 IPC staff, 6 managers) (**Table 4.11**). The following main themes emerged from the FGDs: health system and external environment; hospital leadership; ASP team and roles; hospital infrastructure; organization and culture; and COVID-19 pandemic (**Table 4.12**).

Figure 4.1 Flow diagram of the ASP self-assessment



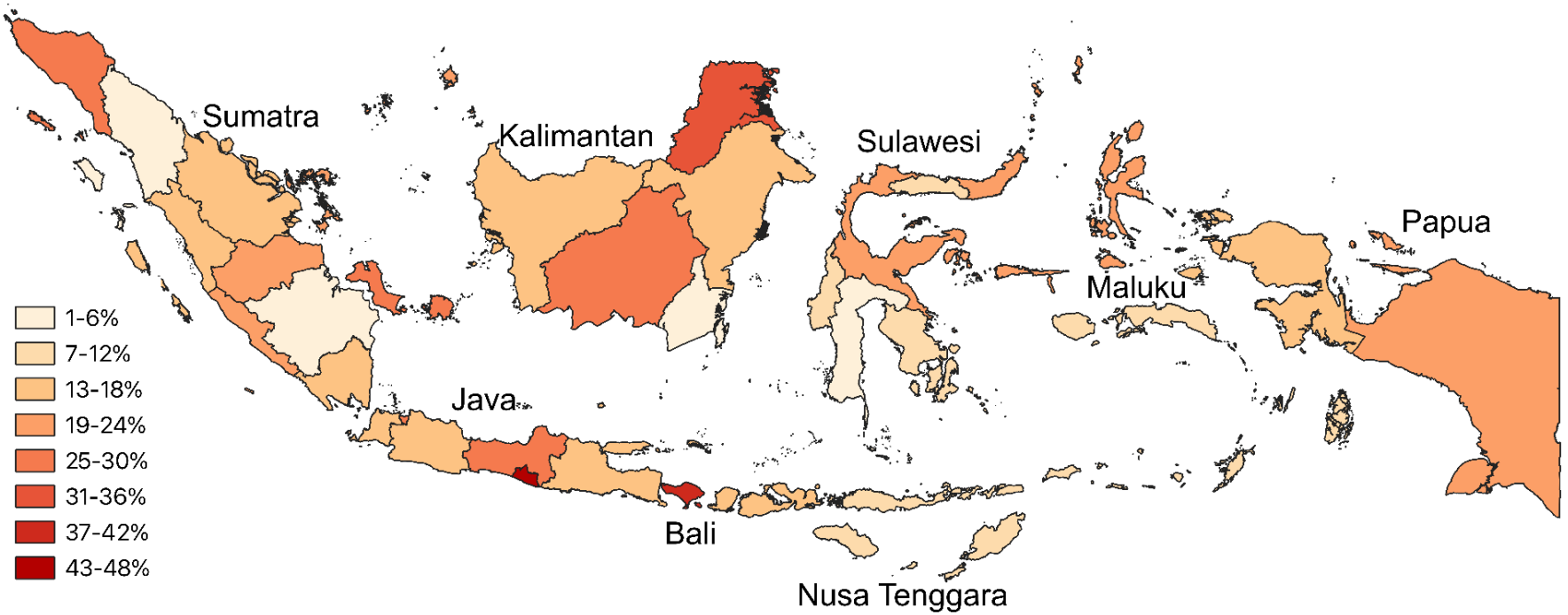
The ASP self-assessment survey adopted a systematic hospital sampling approach to achieve a representative sample for each province, with a target sample size of 562 hospitals. Survey rounds 2, 3 and 4 invited substitutions for non-respondent hospitals, according to a prespecified procedure. See Table 2 for further details.

Abbreviations: ASP, antimicrobial stewardship program

Figure 4.2 Geographic distribution of the participant hospitals
(A) Number of participant hospitals per province



(B) Participant hospitals as a percentage of the total number of hospitals per province



Geographical map of Indonesia showing hospitals that participated in the ASP self-assessment across all 34 provinces

Table 4.6 Characteristics of participant hospitals

Characteristic	All hospitals nationwide (n=3026)	Participant hospitals in self-assessment (n=575)	Participant hospitals in self-assessment with ASP (n=516)	Participant hospitals in FGD[e] (n=14)
Hospital level[a]				
A	65 (2.2%)	36 (6.3%)	36 (7%)	1 (7.1%)
B	442 (14.6%)	123 (21.4%)	123 (23.8%)	4 (28.6%)
C	1608 (53.1%)	299 (52%)	262 (50.8%)	5 (35.7%)
D	911 (30.1%)	117 (20.4%)	95 (18.4%)	4 (28.6%)
Hospital size[b]				
<101	1555 (51.4%)	230 (40%)	192 (37.2%)	4 (28.6%)
101-250	1171 (38.7%)	260 (45.2%)	239 (46.3%)	6 (42.8%)
>250	300 (9.9%)	85 (14.8%)	85 (16.5%)	4 (28.6%)
Hospital ownership				
Private	1934 (63.9%)	332 (57.7%)	299 (57.9%)	7 (50.0%)
Public	1092 (36.1%)	243 (42.3%)	217 (42.1%)	7 (50.0%)
Hospital accreditation[c]				
Accredited	1147 (37.9%)	301 (52.3%)	285 (55.2%)	11 (78.6%)
Not accredited	1879 (62.1%)	274 (47.7%)	231 (44.8%)	3 (21.4%)
National health insurance service provider[d]				
Yes	2613 (86.3%)	523 (91.0%)	473 (91.7%)	11 (78.6%)
No	413 (13.7%)	52 (9.0%)	43 (8.3%)	3 (21.4%)
Geographic region				
Java	1523 (50.3%)	323 (56.2%)	305 (59.1%)	2 (14.3%)
Sumatra	725 (24%)	110 (19.1%)	91 (17.6%)	2 (14.3%)
Sulawesi	277 (9.2%)	33 (5.7%)	27 (5.2%)	1 (7.1%)
Kalimantan	208 (6.9%)	46 (8%)	38 (7.4%)	1 (7.1%)
Nusa Tenggara	98 (3.24%)	13 (2.3%)	13 (2.5%)	3 (21.4%)
Bali	74 (2.5%)	30 (5.2%)	28 (5.4%)	2 (14.3%)
Papua	69 (9.2%)	13 (2.3%)	9 (1.7%)	1 (7.1%)
Maluku	52 (1.7%)	7 (1.2%)	5 (1.0%)	2 (14.3%)

[a] Ministry of Health defines hospital tiered levels based on number of inpatients beds and specialists as type A (≥251 beds and ≥6 specialists), B (201-250 beds and ≥3 specialists), C (101-200 beds and ≥2 specialists), or D (51-100 beds and ≥1 specialist)

[b] Hospital size was based on number of inpatient beds at the time of the self-assessment.

[c] By the Indonesian Hospital Accreditation Commission (*Komisi Akreditasi Rumah Sakit*) at time of the self-assessment

[d] Hospital providing patient services under the national health insurance (*Jaminan Kesehatan Nasional*)

[e] Further details of the hospital and individual participants selected for FDGs are provided in Table 6.

Abbreviations: ASP, antimicrobial stewardship program; FGD, focus group discussion.

Table 4.7 Response rate in ASP self-assessment

Characteristic	All invited hospitals	Participant hospitals in self-assessment	Participation %
Nationwide	3026	575	19.0%
Hospital level			
A	65	36	55.4%
B	442	123	27.8%
C	1608	299	18.6%
D	911	117	12.8%
Hospital size			
>250	300	85	28.3%
101-250	1171	260	22.2%
<101	1555	230	14.8%
Hospital ownership			
Public	1092	243	22.3%
Private	1934	332	17.2%
Hospital accreditation			
Accredited	1147	301	26.2%
Not accredited	1879	274	14.6%
National health insurance service provider			
Yes	2613	523	20.0%
No	413	52	12.6%
Geographic region			
Bali	74	30	40.5%
Kalimantan	208	46	22.1%
Java	1523	323	21.2%
Papua	69	13	18.8%
Sumatra	725	110	15.2%
Maluku	52	7	13.5%
Nusa Tenggara	98	13	13.3%
Sulawesi	277	33	11.9%
Province			
DI Yogyakarta	80	35	43.8%
Bali	74	30	40.5%
South Kalimantan	53	18	34.0%
North Kalimantan	13	4	30.8%
Aceh	72	21	29.2%
DKI Jakarta	192	55	28.6%
South Sumatra	86	13	28.3%
Central Kalimantan	30	8	26.7%
Bangka Belitung Islands	27	7	25.9%
Central Java	331	85	25.7%
North Sulawesi	53	12	22.6%
Jambi	40	9	22.5%
West Papua	23	5	21.7%
Riau Islands	37	8	21.6%
Central Sulawesi	39	8	20.5%
North Maluku	20	4	20.0%
Bengkulu	26	5	19.2%
East Java	404	73	18.1%
Banten	124	22	17.7%
Papua	46	8	17.4%
West Nusa Tenggara	43	7	16.3%
Riau	76	12	15.8%
East Kalimantan	59	9	15.3%
Lampung	83	12	14.5%

Characteristic	All invited hospitals	Participant hospitals in self-assessment	Participation %
West Java	392	53	13.5%
West Kalimantan	53	7	13.2%
West Sumatra	76	10	13.2%
Southeast Sulawesi	36	4	11.1%
East Nusa Tenggara	55	6	10.9%
Gorontalo	19	2	10.5%
Maluku	32	3	9.4%
West Sulawesi	12	1	8.3%
North Sumatra	202	13	6.4%

Table 4.8 Hospital responses to the ASP self-assessment by hospital level and ownership

Item	All participant hospitals with ASP (n=516)	Hospital level				Hospital ownership	
		Type A (n=36)	Type B (n=123)	Type C (n=262)	Type D (n=95)	Public (n=217)	Private (n=299)
ASP hospital leadership support							
There is formal statement of support from hospital leadership for ASP	504 (97.7%)	36 (100.0%)	121 (98.4%)	258 (98.5%)	89 (93.7%)	213 (98.2%)	291 (97.3%)
There is allocated financial support for AMS activities	429 (83.1%)	34 (94.4%)	111 (90.2%)	215 (82.1%)	69 (72.6%)	182 (83.9%)	247 (82.6%)
The management has formally identified ASP as a priority objective and included it in its key performance indicators	311 (60.3%)	20 (55.6%)	78 (63.4%)	156 (59.5%)	57 (60.0%)	109 (50.2%)	202 (67.6%)
There is a health-care facility ASP action plan, which is updated regularly as required.	428 (83.9%)	30 (83.3%)	110 (89.4%)	217 (82.8%)	71 (74.7%)	179 (82.5%)	249 (83.3%)
ASP team and infectious disease training							
AMS committee/team have sufficient time for stewardship activities	406 (78.7%)	26 (72.2%)	98 (79.7%)	208 (79.4%)	74 (77.9%)	162 (74.7%)	244 (81.6%)
AMS activities are integrated into other quality improvement and patient safety efforts	428 (83.9%)	30 (83.3%)	110 (89.4%)	217(82.8%)	71 (74.7%)	179 (82.5%)	249 (83.3%)
There is a physician (or other) leader for ASP activities	487 (94.4%)	36 (100.0%)	119 (96.7%)	246 (93.9%)	86 (90.5%)	208 (95.9%)	279 (93.3%)
If 'Yes', leader has specialized infectious disease training	300 (58.1%)	29 (80.6%)	94 (76.4%)	144 (55.0%)	33 (34.7%)	133 (61.3%)	167 (55.9%)
There is a pharmacist working on ASP activities	505 (97.9%)	36 (100.0%)	122 (99.2%)	257 (98.1%)	90 (94.7%)	212 (97.7%)	293 (98.0%)
If 'Yes', pharmacist has specialized infectious disease training	244 (47.3%)	27 (75.0%)	83 (67.5%)	113 (43.1%)	21 (22.1%)	109 (50.2%)	135 (45.2%)
There is an infection prevention and control staff contributing to optimizing antibiotic use	462 (89.5%)	36 (100.0%)	111 (90.2%)	235 (89.7%)	80 (84.2%)	190 (87.6%)	272 (91.0%)
There is a microbiologist contributing to optimizing antibiotic use	186 (36.1%)	27 (75.0%)	80 (65.0%)	63 (24.1%)	16 (16.8%)	95 (43.8%)	91 (30.4%)
There is a clinical pharmacologist contributing to optimizing antibiotic use	74 (14,3%)	11 (30.6%)	26 (21.1%)	26 (9.9%)	11 (11.6%)	37 (17.1%)	37 (12.4%)
There is a nurse contributing to optimizing antibiotic use	446 (86.4%)	32 (88.9%)	114 (92.7%)	223 (85.1%)	77 (81.1%)	186 (85.7%)	260 (87.0%)
There is IT staff contributing to optimizing antibiotic use	277 (53.7%)	23 (63.9%)	68 (55.3%)	133 (50.8%)	53 (55.8%)	100 (46.1%)	177 (59.2%)
Hospital infrastructure							
There is an in-house microbiology laboratory or access to clinical microbiology service	240 (45.5%)	29 (80.6%)	98 (79.7%)	93 (35.5%)	20 (21.1%)	110 (50.7%)	130 (43.5%)
If 'Yes', microbiology service makes use of rapid diagnostic reporting	139 (26.9%)	21 (58.3%)	73 (59.3%)	39 (14.9%)	6 (6.3%)	71 (32.7%)	68 (22.7%)
If 'Yes', microbiology service uses selective antibiotic susceptibility reporting	151 (29.3%)	23 (63.9%)	77 (62.6%)	46 (17.6%)	5 (5.3%)	75 (34.6%)	76 (25.4%)
Prescribers can obtain the appropriate antibiotics in a timely manner	322 (62.4%)	27 (75.0%)	97 (78.9%)	145 (55.3%)	53 (55.8%)	133 (61.3%)	189 (63.2%)
Hospital has the IT capabilities to collect and analyze ASP data	209 (40.5%)	20 (55.6%)	62 (50.4%)	96 (36.6%)	31 (32.6%)	74 (34.1%)	135 (45.2%)
Hospital uses electronic medical records	255 (49.4%)	24 (67.7%)	80 (65.0%)	118 (45.0%)	33 (34.7%)	101 (46.5%)	154 (51.5%)

Item	All participant hospitals with ASP (n=516)	Hospital level				Hospital ownership	
		Type A (n=36)	Type B (n=123)	Type C (n=262)	Type D (n=95)	Public (n=217)	Private (n=299)
Hospital uses electronic prescriptions	257 (49.8%)	23 (63.9%)	83 (67.5%)	117 (44.7%)	34 (35.8%)	84 (38.7%)	173 (57.9%)
ASP interventions							
Watch and Reserve group antimicrobials require pre-authorization before or 24 hours of administration	221 (42.8%)	26 (72.2%)	70 (56.9%)	102 (38.9%)	23 (24.2%)	102 (47.0%)	119 (39.8%)
AMS team conducts prospective review and feedback before or 24 hours of antimicrobials administration	189 (36.6%)	19 (52.8%)	57 (46.3%)	93 (35.5%)	20 (21.1%)	81 (37.3%)	108 (36.1%)
Hospital uses computerized decision support systems in antibiotic prescribing	121 (23.5%)	14 (38.9%)	46 (37.4%)	45 (17.2%)	16 (16.8%)	44 (20.3%)	77 (25.8%)
Hospital has facility-specific antibiotic treatment guidelines for commonly treated infections	323 (62.6%)	28 (77.8%)	85 (69.1%)	160 (61.2%)	50 (52.6%)	149 (68.7%)	174 (58.2%)
If 'Yes', guidelines for community-acquired pneumonia	233 (45.2%)	24 (66.7%)	70 (56.9%)	116 (44.3%)	23 (24.2%)	109 (50.2%)	124 (41.5%)
If 'Yes', guidelines for hospital-acquired/ventilator-associated pneumonia	185 (35.9%)	23 (63.9%)	59 (48.0%)	87 (33.2%)	16 (16.8%)	47 (40.1%)	98 (32.8%)
If 'Yes', guidelines for skin and soft tissue infections	234 (45.3%)	22 (61.1%)	69 (56.1%)	114 (43.5%)	29 (30.5%)	101 (46.5%)	133 (44.5%)
If 'Yes', guidelines for sepsis	249 (48.3%)	23 (63.9%)	70 (56.9%)	120 (45.8%)	36 (38.0%)	114 (52.5%)	135 (45.2%)
If 'Yes', guidelines for urinary tract infections	229 (44.4%)	23 (63.9%)	70 (56.9%)	103 (39.3%)	33 (34.7%)	111 (51.2%)	118 (39.5%)
If 'Yes', guidelines for intra-abdominal infections	185 (35.9%)	19 (52.8%)	61 (50.0%)	86 (32.8%)	19 (20.0%)	92 (42.4%)	93 (31.1%)
Hospital has guidelines for the de-escalation of broad-spectrum antibiotics	273 (52.9%)	22 (61.1%)	82 (66.7%)	133 (50.8%)	36 (37.9%)	107 (49.3%)	166 (55.5%)
Hospital has guidelines for IV-to-oral conversion of antibiotics	264 (51.2%)	22 (61.1%)	73 (59.3%)	132 (50.4%)	37 (38.9%)	107 (49.3%)	157 (52.5%)
Hospital guidelines readily available at the point of care	206 (39.9%)	18 (50%)	63 (51.2%)	100 (38.2%)	25 (26.3%)	70 (32.3)	136 (45.5%)
AS team conducts regular ward rounds	207 (40.1%)	22 (61.1%)	60 (48.8%)	100 (38.2%)	25 (26.3%)	79 (36.4%)	128 (42.8%)
Facility has a policy that requires prescribers to document dose, duration and indication for all antibiotic prescriptions	371 (71.9%)	29 (80.6%)	93 (75.6%)	189 (72.1%)	60 (62.5%)	164 (75.6%)	207 (69.2%)
Facility has a formal procedure for all prescribers to conduct daily reviews of antibiotic selection until a definitive diagnosis and treatment duration are established	261 (50.6%)	24 (66.7%)	68 (55.3%)	131 (50.0%)	38 (40.0%)	103 (47.5%)	158 (52.8%)
Monitoring reporting and feedback							
Hospital performs audits of the targeted antimicrobial consumption based on quantitative and qualitative analysis							
DDD	246 (47.7%)	28 (77.8%)	77 (62.6%)	106 (40.5%)	35 (36.8%)	120 (55.3%)	126 (42.1%)
DOT	185 (35.9%)	19 (52.8%)	63 (51.2%)	77 (29.4%)	26 (27.7%)	79 (36.4%)	106 (35.5%)
PPS (point prevalence survey)	190 (36.8%)	11 (30.6%)	54 (43.9%)	95 (36.3%)	30 (31.6%)	62 (28.6%)	128 (42.8%)
Gyssens (qualitative analysis of antibiotic use)	190 (36.8%)	26 (72.2%)	62 (50.4%)	78 (29.8%)	24 (25.3%)	103 (47.5%)	87 (29.0%)
Hospital monitors the antimicrobial procurement and financing	359 (69.6%)	29 (80.6%)	90 (73.2%)	178 (67.9%)	62 (65.3%)	143 (65.9%)	216 (72.2%)
Hospital monitors compliance with clinical practice guidelines	354 (68.6%)	27 (75.0%)	87 (70.7%)	177 (67.6%)	63 (66.3%)	141 (65.0%)	213 (71.2%)

Item	All participant hospitals with ASP (n=516)	Hospital level				Hospital ownership	
		Type A (n=36)	Type B (n=123)	Type C (n=262)	Type D (n=95)	Public (n=217)	Private (n=299)
Results of prospective reviews fed back directly to the responsible physician	266 (51.5%)	23 (63.9%)	68 (55.3%)	132 (50.4%)	43 (45.3%)	111 (51.2%)	155 (51.8%)
Hospital regularly publishes the microbe patterns and the outcomes associated with ASP activities	180 (34.9%)	23 (63.9%)	69 (56.1%)	72 (27.5%)	16 (16.8%)	75 (34.6%)	105 (35.1%)
Hospital has antibiogram report	211 (40.9%)	24 (66.7%)	82 (66.7%)	87 (33.2%)	18 (18.9%)	93 (42.9%)	118 (39.5%)
If 'Yes', the antibiogram updated every at least once a year	166 (32.2%)	23 (63.9%)	70 (56.9%)	61 (23.3%)	12 (12.6%)	79 (36.4%)	87 (29.1%)
If 'Yes', the antibiogram easily accessible	156 (30.2%)	17 (47.2%)	65 (52.8%)	61 (23.3%)	13 (13.7%)	62 (28.6%)	94 (31.4%)
If 'Yes', antibiogram specific by unit	146 (28.3%)	26 (72.2%)	54 (43.9%)	55 (21.0%)	11 (11.6%)	65 (30.0%)	81 (27.1%)
Hospital monitors prospective audit and feedback interventions	96 (18.6%)	9 (25.0%)	26 (21.1%)	46 (17.6%)	15 (15.8%)	51 (23.5%)	45 (15.1%)
Hospital monitors preauthorization interventions	224 (43.4%)	18 (50.0%)	59 (48.0%)	103 (39.3%)	44 (46.3%)	98 (45.2%)	126 (42.1%)
Hospital routinely monitors adherence to documentation policy (dose, duration and indication)	316 (61.2%)	24 (66.7%)	83 (67.5%)	152 (58.0%)	57 (60.0%)	135 (62.2%)	181 (60.5%)
Hospital tracks *Clostridioides difficile* infection in the context of antibiotic use	177 (34.3%)	9 (25.0%)	47 (38.2%)	82 (31.3%)	39 (41.1%)	66 (30.4%)	111 (37.1%)
Hospital monitors patient length of stay	329 (63.8%)	26 (72.2%)	83 (67.5%)	165 (63.0%)	55 (57.9%)	141 (65.0%)	188 (63.0%)
Hospital monitors patient mortality	266 (51.5%)	22 (61.1%)	66 (53.6%)	133 (50.8%)	45 (47.4%)	113 (52.1%)	153 (51.2%)
Hospital monitors the cost effectiveness of the ASP	259 (50.2%)	20 (55.6%)	66 (53.6%)	127 (48.5%)	46 (48.4%)	118 (54.4%)	141 (47.2%)
Hospital reports on antibiotic susceptibility rates and key findings are shared with prescribers along with specific action points	151 (29.3%)	15 (41.7%)	38 (30.9%)	70 (26.7%)	28 (29.5%)	71 (32.7%)	80 (26.8%)
Findings from audits/reviews of the quality/appropriateness of antibiotic use are communicated directly to prescribers along with specific action points	155 (30.0%)	13 (36.1%)	37 (30.1%)	79 (30.2%)	26 (27.4%)	69 (31.8%)	86 (28.8%)
ASP tracks antibiotic use by submitting to the MoH	176 (34.1%)	15 (41.7%)	49 (39.8%)	86 (32.8%)	26 (9.9%)	81 (37.3%)	95 (31.8%)
Education							
Hospital provides educational and training activities for physicians and other staff involved to promote the rational use of antimicrobials	318 (61.6%)	22 (61.1%)	76 (61.8%)	161 (61.5%)	59 (62.1%)	136 (62.7%)	182 (60.9%)
If 'Yes', the activity is mandatory and certified	230 (44.6%)	14 (38.9%)	51 (41.5%)	118 (45.0%)	47 (49.5%)	102 (47.0%)	128 (42.8%)
ASP provides education to prescribers as part of the prospective audit and feedback process	183 (35.5%)	17 (47.2%)	49 (39.8%)	88 (33.6%)	29 (30.5%)	82 (37.8%)	101 (33.8%)
The AS team/committee provides trainings on skills to run an ASP	210 (40.7%)	13 (36.1%)	53 (43.1%)	102 (38.9%)	42 (44.2%)	85 (39.2%)	125 (41.8%)

Abbreviations: AMS, Antimicrobial stewardship; ASP, Antimicrobial stewardship program; IV, intravenous; IT, information technology; MoH, Ministry of Health.

Table 4.9 Hospital responses to the ASP self-assessment by geographic region

Item	All participant hospitals with ASP (n=516)	Geographic region							
		Java (n=305)	Sumatra (n=91)	Bali (n=28)	Nusa Tenggara (n=13)	Kalimantan (n=38)	Sulawesi (n=27)	Maluku (n=5)	Papua (n=9)
ASP hospital leadership support									
There is formal statement of support from hospital leadership for ASP	504 (97.7%)	300 (98.4%)	88 (96.7%)	27 (96.4%)	11 (84.6%)	38 (100%)	27 (100%)	4 (80.0%)	9 (100%)
There is allocated financial support for ASP activities	429 (83.1%)	266 (87.2%)	71 (78.0%)	21 (75%)	10 (76.9%)	32 (84.2%)	21 (77.8%)	3 (60.0%)	5 (55.6%)
The management has formally identified ASP as a priority objective and included it in its key performance indicators	311 (60.3%)	190 (62.3%)	53 (58.2%)	18 (64.3%)	12 (92.3%)	15 (39.5%)	17 (63.0%)	3 (60.0%)	3 (33.3%)
There is a health-care facility ASP action plan, which is updated regularly as required.	428 (83.9%)	259 (84.9%)	71 (78.0%)	24 (85.7%)	11 (84.6%)	31 (81.6%)	22 (81.5%)	4 (80.0%)	6 (66.7%)
ASP team and infectious disease training									
AMS committee/team have sufficient time for stewardship activities	406 (78.7%)	237 (77.7%)	72 (79.1%)	22 (78.6%)	12 (92.3%)	30 (79.0%)	23 (85.2%)	3 (60.0%)	7 (77.8)
AMS activities are integrated into other quality improvement and patient safety efforts	428 (83.9%)	259 (8.9%)	71 (78.0%)	24 (85.7%)	11 (84.6%)	31 (81.6%)	22 (81.5%)	4 (80.0%)	6 (66.7%)
There is a physician (or other) leader for ASP activities	487 (94.4%)	289 (94.8%)	81 (89.0%)	28 (100%)	12 (92.3%)	38 (100%)	27 (100%)	4 (80.0%)	8 (88.9%)
If 'Yes', leader has specialized infectious disease training	300 (58.1%)	191 (62.6%)	42 (46.2%)	14 (50.0%)	10 (76.9%)	22 (57.9%)	18 (66.7%)	0 (0.0%)	3 (33.3%)
There is a pharmacist working on ASP activities	505 (97.9%)	299 (98.0%)	89 (97.8%)	28 (100%)	12 (92.3%)	38 (100%)	27 (100%)	4 (80.0%)	8 (88.9%)
If 'Yes', pharmacist has specialized infectious disease training	244 (47.3%)	162 (53.1%)	34 (37.4%)	10 (35.7%)	7 (53.9%)	15 (39.5%)	12 (44.4%)	1 (20.0%)	3 (33.3%)
There is an infection prevention and control staff contributing to optimizing antibiotic use	462 (89.5%)	281 (92.1%)	75 (82.4%)	27 (96.4%)	11 (84.6%)	33 (86.8%)	26 (96.3%)	2 (40.0%)	7 (77.8%)
There is a microbiologist contributing to optimizing antibiotic use	186 (36.1%)	116 (38.0%)	30 (33.0%)	10 (35.7%)	5 (38.5%)	13 (34.2%)	9 (33.3%)	2 (40.0%)	1 (11.1%)
There is a clinical pharmacologist contributing to optimizing antibiotic use	74 (14.3%)	53 (17.4%)	12 (13.2%)	0 (0.0%)	2 (15.4%)	2 (5.3%)	4 (14.8%)	1 (20.0%)	0 (0.0%)
There is a nurse contributing to optimizing antibiotic use	446 (86.4%)	275 (90.2%)	72 (79.1%)	25 (89.3%)	10 (76.9%)	32 (84.2%)	24 (88.9%)	2 (40.0%)	6 (66.7%)
There is IT staff contributing to optimizing antibiotic use	277 (53.7%)	178 (58.4%)	48 (52.8%)	11 (39.3%)	5 (38.5%)	15 (39.5%)	15 (55.6%)	1 (20.0%)	4 (44.4%)
Hospital infrastructure									
There is an in-house microbiology laboratory or access to clinical microbiology service	240 (45.5%)	157 (51.5%)	36 (39.6%)	10 (35.7%)	7 (53.8%)	15 (39.5%)	12 (44.4%)	2 (40.0%)	1 (11.1%)
If 'Yes', microbiology service makes use of rapid diagnostic reporting	139 (26.9%)	96 (31.5%)	20 (22.0%)	3 (10.7%)	5 (38.5%)	8 (21.1%)	6 (22.2%)	1 (20.0%)	0 (0.0%)
If 'Yes', microbiology service uses selective antibiotic susceptibility reporting	151 (29.3%)	104 (34.1%)	21 (23.1%)	4 (14.3%)	5 (38.5%%)	8 (21.1%)	8 (29.6%)	1 (20.0%)	0 (0.0%)
Prescribers can obtain the appropriate antibiotics in a timely manner	322 (62.4%)	200 (65.6%)	558 (63.7%)	17 (60.7%)	7 (53.9%)	17 (44.7%)	19 (70.4%)	3 (60.0%)	1 (11.1%)
Hospital has the IT capabilities to collect and analyze ASP data	209 (40.5%)	131 (43.0%)	35 (38.5%)	7 (25.0%)	7 (53.9%)	16 (42.1%)	10 (37.0%)	1 (20.0%)	2 (22.2%)
Hospital uses electronic medical records	255 (49.4%)	161 (53.8%)	43 (47.3%)	13 (46.4%)	6 (46.2%)	16 (42.1%)	12 (44.4%)	2 (40.0%)	2 (22.2%)

Item	All participant hospitals with ASP (n=516)	Geographic region							
		Java (n=305)	Sumatra (n=91)	Bali (n=28)	Nusa Tenggara (n=13)	Kalimantan (n=38)	Sulawesi (n=27)	Maluku (n=5)	Papua (n=9)
Hospital uses electronic prescriptions	257 (49.8%)	172 (56.4%)	40 (44.0%)	12 (42.9%)	5 (38.5%)	14 (36.8%)	11 (40.7%)	2 (40.0%)	1 (11.1%)
ASP interventions									
Watch and Reserve group antimicrobials require pre-authorization before or 24 hours of administration	221 (42.8%)	141 (46.2%)	38 (41.8%)	12 (42.9%)	4 (30.8%)	12 (31.6%)	10 (37.0%)	2 (40.0%)	2 (22.2%)
ASP team conducts prospective review and feedback before or 24 hours of antimicrobials administration	189 (36.6%)	127 (41.6%)	32 (35.2%)	9 (32.1%)	2 (15.4%)	11 (28.9%)	6 (22.2%)	1 (20.0%)	1 (11.1%)
Hospital uses computerized decision support systems in antibiotic prescribing	121 (23.5%)	82 (26.9%)	19 (20.9%)	5 (17.9%)	0 (0.0%)	8 (21.1%)	7 (25.9%)	0 (0.0%)	0 (0.0%)
Hospital has facility-specific antibiotic treatment guidelines for commonly treated infections	323 (62.6%)	190 (62.3%)	63 (69.2%)	16 (57.1%)	5 (38.5%)	26 (68.4%)	16 (59.3%)	3 (60.0%)	4 (44.4%)
If 'Yes', guidelines for community-acquired pneumonia	233 (45.2%)	135 (44.3%)	49 (53.9%)	11 (39.3%)	3 (23.1%)	18 (47.4%)	12 (44.4%)	2 (40.0%	3 (33.3%)
If 'Yes', guidelines for hospital-acquired/ventilator-associated pneumonia	185 (35.9%)	107 (35.1%)	38 (41.8%)	12 (42.9%)	3 (23.1%)	12 (31.6%)	9 (33.3%)	3 (60.0%)	1 (11.1%)
If 'Yes', guidelines for skin and soft tissue infections	234 (45.3%)	134 (43.9%)	47 (51.7%)	13 (46.4%)	5 (38.5%%)	17 (44.7%)	12 (44.4%	3 (60.0%)	3 (33.3%)
If 'Yes', guidelines for sepsis	249 (48.3%)	145 (47.5%)	50 (55.0%)	13 (46.4%)	4 (30.8%)	19 (50.0%)	12 (44.4%)	3 (60.0%)	4 (33.3%)
If 'Yes', guidelines for urinary tract infections	229 (44.4%)	128 (42.0%)	47 (51.7%)	13 (46.4%)	4 (30.8%)	19 (50.0%)	13 (48.2%)	3 (60.0%)	2 (22.2%)
If 'Yes', guidelines for intra-abdominal infections	185 (35.9%)	102 (33.4%)	42 (46.2%)	11 (39.3%)	3 (23.1%)	11 (29.0%)	11 (40.7%)	2 (40.0%)	3 (33.3%)
Hospital has guidelines for the de-escalation of broad-spectrum antibiotics	273 (52.9%)	184 (60.3%)	36 (39.6%)	16 (57.1%)	7 (53.9%)	16 (42.1%)	10 (37.0%)	1 (20.0%)	3 (33.3%)
Hospital has guidelines for IV-to-oral conversion of antibiotics	264 (51.2%)	161 (52.8%)	52 (57.1%)	16 (57.1%)	7 (53.9%)	12 (31.6%)	12 (44.4%)	1 (20.0%)	3 (33.3%)
Hospital guidelines readily available at the point of care	206 (39.9%)	136 (44.6%)	38 (41.8%)	10 (35.7%)	5 (38.5%)	6 (15.8%)	8 (29.6%)	2 (40.0%)	1 (11.1%)
ASP team conducts regular ward rounds	207 (40.1%)	139 (45.6%)	30 (33.0%)	12 (42.9%)	5 (38.5%)	9 (23.7%)	10 (37.0%)	1 (20.0%)	1 (11.1%)
Facility has a policy that requires prescribers to document dose, duration and indication for all antibiotic prescriptions	371 (71.9%)	214 (70.2%)	67 (73.6%)	22 (78.6%)	9 (69.2%)	29 (76.3%)	19 (70.4%)	4 (80.0%)	7 (77.8%)
Facility has a formal procedure for all prescribers to conduct daily reviews of antibiotic selection until a definitive diagnosis and treatment duration are established	261 (50.6%)	172 (56.4%)	42 (46.2%)	16 (57.1%)	6 (46.2%)	11 (29.0%)	11 (40.7%)	1 (20.0%)	2 (22.2%)
Monitoring reporting and feedback									
Hospital performs audits of the targeted antimicrobial consumption based on quantitative and qualitative analysis									
DDD	246 (47.7%)	157 (51.5%)	42 (46.2%)	15 (53.6%)	5 (38.5%)	16 (42.1%)	8 (29.6%)	1 (20.0%)	2 (22.2%)
DOT	185 (35.9%)	114 (37.4%)	35 (38.5%)	11 (39.3%)	4 (30.8%)	11 (29.0%)	10 (37.0%)	0 (0.0%)	0 (0.0%)
PPS	190 (36.8%)	132 (43.3%)	26 (28.6%)	10 (35.7%)	6 (46.2%)	8 (21.1%)	6 (22.2%)	1 (20.0%)	1 (11.1%)
Gyssens (qualitative analysis of antibiotic use)	190 (36.8%)	124 (40.7%)	31 (34.1%)	10 (35.7%)	4 (30.8%)	11 (28.9%)	8 (29.6%)	1 (20.0%)	1 (11.1%)
Hospital monitors the antimicrobial procurement and financing	359 (69.6%)	223 (73.1%)	56 (61.5%)	21 (75.0%)	7 (53.9%)	25 (65.8%)	19 (70.4%)	4 (80.0%)	4 (44.4%)
Hospital monitors compliance with clinical practice guidelines	354 (68.6%)	217 (71.2%)	61 (67.0%)	19 (67.9%)	8 (61.5%)	29 (76.3%)	16 (59.3%)	2 (40.0%)	2 (22.2%)
Results of prospective reviews fed back directly to the responsible physician	266 (51.5%)	169 (55.4)	46 (50.6%)	14 (50.0%)	6 (46.2%)	19 (50.0%)	10 (37.0%)	1 (20.0%)	1 (11.1%)
Hospital regularly publishes the microbe patterns and the outcomes associated with ASP activities	180 (34.9%)	122 (40.0%)	27 (29.7%)	11 (39.3%)	5 (38.5%)	9 (23.7%)	6 (22.2%)	0 (0.0%)	0 (0.0%)

Item	All participant hospitals with ASP (n=516)	Geographic region							
		Java (n=305)	Sumatra (n=91)	Bali (n=28)	Nusa Tenggara (n=13)	Kalimantan (n=38)	Sulawesi (n=27)	Maluku (n=5)	Papua (n=9)
Hospital has antibiogram report	211 (40.9%)	150 (49.2%)	28 (30.8%)	10 (35.7%)	7 (53.8%)	10 (26.3%)	6 (22.2%)	0 (0.0%)	0 (0.0%)
If 'Yes', the antibiogram updated every at least once a year	166 (32.2%)	112 (36.7%)	24 (26.4%)	10 (35.7%)	5 (38.5%)	10 (26.3%)	5 (18.5%)	0 (0.0%)	0 (0.0%)
If 'Yes', the antibiogram easily accessible	156 (30.2%)	110 (36.1%)	23 (25.3%)	6 (21.4%)	6 (46.2%)	7 (18.4%)	4 (14.8%)	0 (0.0%)	0 (0.0%)
If 'Yes', antibiogram specific by unit	146 (28.3%)	96 (31.5%)	24 (26.4%)	4 (14.3%)	6 (46.2%)	9 (23.7%)	5 (18.5%)	1 (20.0%)	1 (11.1%)
Hospital monitors prospective audit and feedback interventions	96 (18.6%)	52 (17.1%)	22 (24.2%)	5 (17.9%%)	3 (23.1%)	8 (21.1%)	4 (14.8%)	0 (0.0%)	2 (22.2%)
Hospital monitors preauthorization interventions	224 (43.4%)	134 (44.0%)	37 (41.0%)	13 (46.4%)	6 (46.2%)	20 (52.6%)	10 (37.0%)	1 (20.0%)	5 (55.6%)
Hospital routinely monitors adherence to documentation policy (dose, duration and indication)	316 (61.2%)	191 (62.6%)	52 (57.1%)	19 (67.9%)	7 (53.8%)	24 (63.2%)	17 (63.0%)	2 (40.0%)	4 (44.4%)
Hospital tracks *Clostridioides difficile* infection in the context of antibiotic use	177 (34.3%)	137 (44.9%)	18 (19.8%)	6 (21.4%)	5 (38.5%)	4 (10.5%)	4 (14.8%)	1 (20.0%)	2 (22.2%)
Hospital monitors patient length of stay	329 (63.8%)	194 (63.6%)	63 (69.2%)	17 (60.7%)	6 (46.2%)	21 (55.3%)	19 (70.4%)	3 (60.0%)	6 (66.7%)
Hospital monitors patient mortality	266 (51.5%)	145 (47.5%)	50 (55.0%)	15 (53.6%)	7 (53.8%)	22 (57.9%)	17 (63.0%)	3 (60.0%)	7 (77.8%)
Hospital monitors the cost effectiveness of the ASP	259 (50.2%)	147 (48.2%)	45 (49.5%)	18 (64.3%)	5 (38.5%)	22 (57.9%)	14 (51.9%)	4 (80.0%)	4 (44.4%)
Hospital reports on antibiotic susceptibility rates and key findings are shared with prescribers along with specific action points	151 (29.3%)	87 (28.5%)	23 (25.3%)	11 (39.3%)	6 (46.2%)	12 (31.6%)	11 (40.7%)	0 (0.0%	1 (11.1%)
Findings from audits/reviews of the quality/appropriateness of antibiotic use are communicated directly to prescribers along with specific action points	155 (30.0%)	91 (29.8%)	25 (27.5%)	10 (35.7%)	7 (53.8%)	12 (31.6%)	10 (37.0%)	0 (0.0%)	0 (0.0%)
ASP tracks antibiotic use by submitting to the MOH	176 (34.1%)	103 (33.8%)	31 (34.1%)	13 (46.4%)	4 (30.8%)	13 (34.2%)	10 (37.0%)	2 (40.0%)	0 (0.0%)
Education									
Hospital provides educational and training activities for physicians and other staff involved to promote the rational use of antimicrobials	318 (61.6%)	190 (62.3%)	51 (56.0%)	22 (78.6%)	7 (53.8%)	23 (60.5%)	16 (59.3%)	4 (80.0%)	5 (55.6%)
If 'Yes', the activity is mandatory and certified	230 (44.6%)	135 (44.3%)	40 (44.0%)	16 (57.1%)	5 (38.5%)	17 (44.7%)	11 (40.7%)	3 (60.0%)	3 (33.3%)
ASP provides education to prescribers as part of the prospective audit and feedback process	183 (35.5)	105 (34.4%)	34 (37.4%)	13 (46.4%)	6 (46.2%)	15 (39.5%)	8 (29.6%)	1 (20.0%)	1 (11.1%)

Abbreviations: AMS, Antimicrobial stewardship ; ASP, Antimicrobial stewardship program; IV, intravenous; IT, information technology; MoH, Ministry of Health

Table 4.10 Reliability of the responses in ASP self-assessment

	Item	YES/YES (TP)	NO/NO (TN)	YES/NO (FP)	NO/YES (312)	Agreement (%)	Cohen's Kappa (95%CI)
	All 14 core elements	447	461	281	267	95.9	0.91 (0.88-0.94)
C1	There is formal statement of support from hospital leadership of ASP	51	1	0	0	100	1.0 (1.0-1.0)
C2	There is allocated financial support for ASP activities	42	8	1	1	96.2	0.87 (0.68-1.0)
C3	There is a physician (or other) leader for ASP activities	50	2	0	0	100	1.0 (1.0-1.0)
C4	There is a pharmacist working on ASP activities	51	1	0	0	100	1.0 (1.0-1.0)
C5	There is an infection prevention and control staff contributing to optimizing antibiotic use	46	5	0	1	98.1	0.90 (0.70-1.0)
C6	There is a microbiologist contributing to optimizing antibiotic use	17	32	1	2	94.2	0.87 (0.73-1.0)
C7	There is an in-house microbiology laboratory or access to clinical microbiology service	21	28	1	2	94.2	0.88 (0.75-1.0)
C8	Watch and Reserve group antimicrobials require pre-authorization before 24 hours of administration	22	26	0	4	92.3	0.85 (0.70-0.99)
C9	ASP team conducts prospective review ad feedback before or 24 hours of antimicrobials administration	15	33	1	3	92.3	0.83 (0.66-0.99)
C10	Hospital has facility-specific antibiotic treatment guidelines for commonly treated infections	35	14	1	2	94.2	0.86 (0.70-1.0)
	Hospital performs audits of the targeted antimicrobial consumption based on quantitative and qualitative analysis						
C11	DDD (defined daily dose)	29	21	1	1	96.2	0.92 (0.80-1.0)
C12	Gyssens (qualitative analysis of antibiotic use)	25	24	0	3	94.2	0.89 (0.76-1.0)
C13	Hospital regularly publishes the microbe patterns and the outcomes associated with AS activities	14	3	1	2	94.2	0.86 (0.71-1.0)
C14	Hospital has antibiogram report	21	29	1	1	96.2	0.92 (0.81-1.0)

The research team checked self-assessment data reliability by repeating 14 core questions in a telephone interview in a random sample of 10% (n=52) of participant hospitals, stratified by hospital tiered level, ownership, and geographic regions.

Cohen's Kappa was calculated as {2 x (TP x TN-FN x FP)}tab / {(TP+FP) x (FP+TN) + (TP+FN) x (FN+TN)}. Kappa is interpreted as follows: values ≤0-0.20 indicate none to slight (0.01-0.20) agreement; 0.21-0.40 fair agreement; 0.41-0.60 moderate agreement; 0.61-0.80 substantial agreement; and 0.81-1.00 near perfect agreement.

Abbreviations: AS, antimicrobial stewardship; ASP, antimicrobial stewardship program; CI, confidence interval; TP, true-positive; TN, true-negative; FP, false-positive; FN, false-negative

Table 4.11 Characteristics of participant hospitals in focus group discussions

FGD code	Hospital level[a]	Hospital size[b]	Hospital ownership	Accreditation status[c]	National health insurance service provider[d]	Geographical region	ASP implementation score	Number of participants						
								Total	ASP leader	Pharmacist	Clinical microbiologist/ pathologist[e]	IPC staff	Clinician	Hospital manager
1	A	320	Public	Accredited	Yes	Sumatra	61	4	1	1	-	1	-	-
2	D	77	Private	Not accredited	No	Java	51	6	1	1	-	2	1	1
3	B	254	Public	Accredited	Yes	Bali	56	6	1	1	1	2	1	-
4	C	160	Pubic	Accredited	Yes	Maluku	33	6	1	1	-	3	1	-
5	B	320	Public	Accredited	Yes	Sumatra	62	6	2	1	1	1	1	-
6	C	200	Private	Accredited	Yes	Java	39	2	1	-	-	-	1	-
7	B	202	Private	Accredited	Yes	Sulawesi	31	8	1	1	1	2	1	2
8	C	125	Private	Accredited	No	Bali	29	7	1	1	2	2	1	-
9	C	133	Private	Accredited	Yes	Papua	20	5	1	1	-	2	-	1
10	D	51	Public	Accredited	Yes	Kalimantan	26	6	1	1	1	2	-	1
11	D	51	Private	Not accredited	Yes	Nusa Tenggara	34	5	1	-	-	3	1	-
12	C	136	Private	Not accredited	No	Nusa Tenggara	18	6	1	1	1	2	-	1
13	D	64	Public	Accredited	Yes	Maluku	18	9	1	2	1	1	4	-
14	B	272	Pubic	Accredited	Yes	Nusa Tenggara	47	6	1	1	1	2	1	-
							TOTAL	**82**	**15**	**13**	**9**	**25**	**13**	**6**

[a]MoH designates hospital tiers based on number of inpatients beds and specialists as type A (≥251 beds and ≥6 specialists), B (201-250 beds and ≥ specialists), C (101-200 beds and ≥2 specialists), or D (51-100 beds and ≥1 specialist).
[b]Hospital size was based on the reported number of inpatient beds at the time of the survey.
[c]Accreditation by the Indonesian Commission on Accreditation of Hospitals (*Komite Akreditasi Rumah Sakit*).
[d]Hospital providing patient services under the national health insurance.
[e]Including clinical microbiologist/pathologist and/or laboratory staff trained to deliver microbiology services.
Abbreviations: ASP, antimicrobial stewardship program; FGD, focus group discussion; IPC, infection prevention and control.

Table 4.12 Summary of enablers and barriers to hospital ASP implementation, with indicative quotes, identified during the focus group discussions with ASP stakeholders

Health system and external environment	
Enablers	
Hospital accreditation	*"So, ASP was started in 2018. The reason behind the ASP initiation was because our hospital was undergoing hospital accreditation. One of the accreditation requirements we must meet is the availability of ASP."* (FGD8, ASP leader/clinician) *"…the current ASP was established in 2022. Before that, it had been running since this hospital was first operated [in 2008]. However, due to the limited number of pharmacists, it disappeared. In 2022, due to the 2023 accreditation, it was re-established."* (FGD11, ASP leader/clinical pharmacist)
National guideline on hospital ASP	*"In 2021, the Ministry of Health (MoH) released regulation no. 28 on hospital ASP guideline. So, we use that guideline to measure antibiotic use using Gyssens [method] as a benchmark."* (FGD4, ASP leader, clinician)
Guidelines from professional organizations	*"The College of Obstetrics and Gynecology is very supportive of ASP implementation. Its guidelines have determined that for clean contaminated surgery, first-generation cephalosporins are the antibiotic prophylaxis of choice."* (FGD3, ASP leader/clinical microbiologist)
Reporting to the MoH	*"...we have reported the quality of antibiotic use to the department of quality of service at our hospital. Antibiotic use outputs are integrated into the quality indicators report that we send to the MoH every month."* (FGD13, ASP team member/clinical pharmacist)
Barriers	
Lack of feedback to hospitals	*"We send culture and ASP reports to the MoH every year. Our hospital complies with this requirement because we need it for the accreditation. Because of this, our mindset is set towards 'we have to do this (ASP) because of the accreditation.' However, there is no feedback yet from the MoH; meanwhile we have been working so hard on the reports… I hope that hospital ASP is not limited to the MoH regulation, but the MoH also do the monitoring and evaluation. So, there will be a reward and punishment. So far, we haven't received it."* (FGD6, ASP team member/clinician) *"Until now there has been no feedback, but we keep sending the reports… We send the ASP report annually together with the bacterial profile and antibiotic resistance patterns."* (FGD14, clinical pharmacist/ASP team member)
Hospital ASP is no longer a national program	*"ASP used to be a national program. Now, it is [a program] under pharmacy. So, our perspectives about the program (ASP) is different that it becomes less [important]. If possible, make ASP as a national program again."* (FGD6, ASP team member/clinician)
Hospital leadership	
Enablers	
Written leadership support	*"The stewardship team was established based on the decree by the hospital director. We then started working, from creating policies and then guidelines for antibiotic use."* (FGD8, ASP leader/clinician)
Key performance indicators	*"The hospital director included ASP [target outputs] in the quality assessment, as part of quality improvement and patient safety. The director monitors the ASP report... If we were late to report, we are reprimanded by the director"* (FGD5, ASP leader/clinician) *"Regarding microbiology services, we serve 24 hours because we have targets that are included in our unit [performance] indicators, for example, turnaround time for blood and non-blood specimens… We [clinical pathologists] also work 24 hours for providing expertise assessment… I and the other clinical pathologist specialists share a schedule"* (FGD14, IPC leader/clinical pathologist)
Address friction	*"We know that our colleagues, the specialists, furthermore the sub-specialists, they are very, very difficult to intervene. However, we are supported by the hospital director... Some time ago, someone was adamant. I felt like I couldn't handle the disagreement. So, I report it to the director. She said, "if it is too difficult, let me handle it".* (FGD1, ASP leader/clinician)
Dedicated budget	*"We don't' manage the 'fresh' money allocated for ASP… The one who manages it is the general department of the hospital. We don't receive money, we receive goods. The budget exists as a basis for procurement. We propose the budget we need, but it is managed by the general department of the hospital."* (FGD14, ASP leader/clinician) *"We make a work plan and budgeting. We plan this year and propose what we are going to do next year and make a budget."* (FGD9, ASP leader/clinician)
Barriers	

Low prioritization of ASP	*"In my opinion, the management perceived ASP is not something important… I have repeatedly asked for a dissemination meeting related to our antibiotic guidelines. However, it was difficult to be held."* (FGD2, ASP leader/clinician)
AMS team and roles	
Enablers	
Training for the ASP team	*"The training costs are allocated. Not long ago, there was a training for pharmacists in Surabaya. If I'm not mistaken, we applied for it in a short period of time, and it was approved."* (FGD9, ASP leader/clinician) *"This year, we have two trainings: offline and online. We proposed some names, and they (hospital management) approved it. That includes the budget."* (FGD14, ASP leader/clinician)
Collaboration with the IPC committee	*"I, as part of the IPC team, supervise the administration of antibiotics. We make sure that the prophylactic antibiotics are 100% in accordance with the guidelines, for example, in C-section cases. Following, we then carry out monitoring and evaluation with the stewardship team related to the implementation of policies and guidelines for the use of prophylactic antibiotics."* (FGD10, IPC staff) *"Related to coordination between IPC and ASP, we have an IPC information system that contains a list of all patients with 7 days follow-up. The administered antibiotics are recorded, so we can monitor whether this patient has been using antibiotics for 3 to 5 days. If we still find signs of infection during the morning report update, we immediately report it and coordinate with the ward nurses and doctor in charge."* (FGD7, IPC staff) *"In this hospital, the role of the IPC is huge because antibiotic use is one of the five main IPC programs. Therefore, we are involved in the ASP."* (FGD13, IPC staff)
The role of pharmacy and therapeutics (P&T) committee in monitoring antibiotic use	*"The P&T is indeed has a central role in antibiotic use monitoring. P&T committee had been around for a long time before the antibiotic stewardship team to monitor the antibiotic use. So, if our antibiotic use is not in line with the guidelines, even since the patients are still in the emergency room, the P&T committee reprimands us. Now, the authority is gradually transferred to the ASP team."* (FGD4, clinician/IPC staff)
Barriers	
Additional workload with no incentives and limited dedicated time for ASP	*"All of us has a main job, but here (ASP), we do double job, even triple job… We don't have one staff assigned only to work for ASP. It is the same story as our nurses in the wards who collect the ASP data."* (FGD5, ASP leader/clinician) *"Apart from our main duties as clinicians, there is no budget allocated for incentives for staff working for ASP."* (FGD2, ASP leader/clinician) *"I suggest that there will be compensation [for antibiotic approval] because it is the same as patient consultation at the on-site practice. Therefore, we can receive [ASP] consultation at any time.* (FGD1, ASP leader/clinician,)
Staff turnover	I: *"What are the factors that cause the previous ASP was not running?"* P: *"All of the ASP team personals are not working in this hospital anymore."* (FGD13, ASP leader/clinician)
Part-time employment	*"Here, the ASP leader does not stand by at this hospital. That is also an obstacle for us to communicate... there has not been a follow-up yet."* (FGD12, clinical pharmacist/ASP secretary) *"Doctor X (ASP leader) only comes to this hospital once a month."* (FGD12, laboratory staff)
Limited knowledge and skills in antibiotic use monitoring	I: *"Why has the DDD not been evaluated yet?"* P: *"… but I'm confused about where to start."* (FGD12, clinical pharmacist)
Hospital infrastructure	
Enablers	
Electronic information system helps ASP monitoring	*"This hospital has been using electronic medical records, so I can easily monitor antibiotic use in the wards."* (FGD3, ASP leader/clinical microbiologist) *"Patients with Reserve antibiotic prescriptions are visited by a clinical pharmacist. This data is recorded in the integrated patient progress note in the electronic medical records… Since the first day of antibiotic administration, the plan is to do evaluation on the fifth day, as recommended by the ASP team. On the fifth day, we do assessments to see if there is any improvement in patient condition. We then ask [the doctor in-charge] whether the antibiotic, e.g., meropenem, will be discontinued or de-escalated."* (FGD3, clinical pharmacist/ASP team member)
Electronic information system facilitates automatic stop order	*"In the past we used manual health records, but now an electronic system. A warning will appear in the electronic health records as a reminder. If you click it, you can see the automatic stop order."* (FGD14, clinical pharmacist/ASP team member)

	"If an antibiotic has been prescribed for 5 days, pharmacist will click the automatic stop order and there will be a warning on the screen. The pharmacist will confirm it with the doctor in-charge to stop or continue the prescription… If there is no response from the doctor in-charge, the antibiotic will be stopped by the pharmacist." (FGD14, clinician/ASP team member)
Barriers	
Microbiology facilities are unavailable in type C and D hospitals	*"Currently, we don't have microbiology facilities, so we cannot do culture testing. So, we send the culture examination to a private laboratory, but the problem is cost, and usually patients refuse to pay."* (FGD13, laboratory staff) I: *"Is there any specimens have been taken to be sent to the laboratory of the other hospitals or regional government laboratory for culture testing?"* P: *"We have never done it, because for the entire province, there is no culture testing services available yet."* (FGD4, ASP leader/clinician)
No or limited referral system for culture testing due to geography	*"From this hospital [in Tidore island], you have to take a speedboat for approximately 40 minutes, then travel overland for approximately 4 hours to reach Tobelo (another island where a microbiology laboratory has just built but not operated yet)... Our district is located in an island, separated by the sea, so the access is quite difficult."* (FGD4, IPC staff/clinical pathologist) *"The sampling can be done here. Officers from a private laboratory are in this area. However, the samples then must be sent to Ternate and then to Jakarta. So, it takes a long time to get the culture results."* (FGD13, ASP leader/clinician)
Long turnaround time of culture testing from sampling to reporting	*"In terms of access to culture testing, we have it. The laboratory can process the sample based on our requests, including blood, urine, etc. ... However, it still takes us 6 to 7 days before the culture results are released."* (FGD1, clinician/IPC staff) *"… once when labkesda (regional government laboratory) still received blood samples, it took 2-3 weeks to get the results."* (FGD9, ASP leader/clinician)
Organization and culture	
Enablers	
Collaborative ASP approaches	*"The way we handle friction in antibiotic pre-authorization is by inviting the clinician who requests the antibiotics. We hold a group discussion. I invite all relevant departments because I don't want this to become a personal problem... This is not a problem between the ASP team and the clinicians, but also a hospital problem related to patient service and holistic patient care. We invite the hospital management, the medical service team, patient service manager, and people from the pharmacy, and laboratory."* (FGD14, ASP leader/clinician)
Cost saving perspectives	*"We are a private hospital. So, we aim for cost effectiveness, and one of them is related to antibiotics. We see ASP as a way for us to do so."* (FGD7, hospital manager) *"Related to JKN scheme, in this hospital, based on the instruction from the director, we strictly use antibiotics listed in the national formulary. Prescriptions outside the national formulary are not approved if there are drugs in its list that work the same way. This is important for quality control and cost effectiveness. With the right antibiotic choice, it is expected that patients will have fewer days of treatment and can recover quickly. So, the cost of treatment does not exceed the package, and if possible lower than the cost of the package."* (FGD3, clinical pharmacist/ASP team member)
Barriers	
Prescribers' autonomy	*"In private hospitals, doctors in-charge (specialists) have the highest authority… They have significant roles to play, especially when they 'supply' patients to the hospital. They are like little kings."* (FGD2, ASP leader/clinician)
Hierarchy in the medical profession	*"Seniority and hierarchy are still strong. Our challenge is there. Our approach from junior to senior doctors is [limited to] providing suggestions."* (FGD7, hospital manager) *"Because for us, for example, the pharmacists, it is quite difficult for them to deal with the specialists due to their limited knowledge."* (FGD9, hospital director)
COVID-19 pandemic	
Enablers	
Improved diagnostic capacity	*"During the COVID-19 era, we got additions in terms of diagnostic equipment, including PCR… The diagnostic capacity of our team increases, and the tests using PCR can get prompt results. For the morning samples, we can get the results by evening."* (FGD1, IPC staff/clinician) *"In terms of COVID-19, especially for internal medicine patients, now we have CRP test."* (FGD5, ASP leader/clinician)
Improved IPC compliance	*"During COVID-19, besides the increased need of personal protective equipment, there was also an increased awareness of hand rub and isolation procedures."* (FGD7, IPC staff)

Barriers	
Re-allocation of human resources and time	*"Definitely we lacked staff during COVID-19. They were re-allocated to deliver services in the new COVID wing."* (FGD5, ASP leader/clinician) *"The implementation of ASP was greatly decreased because most of our human resources were work from home at that time."* (FGD8, ASP leader/clinician)
Antimicrobial pre-authorization was on hold	*"At that time (during COVID-19), ASP was not running. So, there were no antibiotic restrictions such as pre-authorization for the use of the Reserve antibiotics. Apart from not having the time to run the program, we also concerned that it could delay the treatment."* (FGD3, clinical pharmacist/ASP team member)
Liberal antibiotic prescribing	*"At that time, we were sent guidelines that were changed for six times. The initial guidelines stated that [for COVID-19 patients], azithromycin should be prescribed. During hospitalization, if I'm not mistaken, the antibiotic choice was levofloxacin. Because of that, we immediately prescribed it. If you look at it now, those treatments were inaccurate because you also have to consider the clinical presentation… At that time, we (clinicians) were a bit misaligned with ASP because prescribing antibiotics without any basis. However, it was an emergency situation, and we are given guidelines, so we complied with the guidelines."* (FGD3, clinician)

Abbreviations: ASP, antibiotic stewardship program; CRP, c-reactive protein; DDD, defined daily dose; FGD, focus group discussion; JKN (*Jaminan Kesehatan Nasional*), national health insurance; I, interviewer; IPC, infection prevention and control; MoH, Ministry of Health; P, participant; P&T committee, pharmacy and therapeutics committee.

4.4.2 ASP self-assessment scores

Across all 516 participant hospitals with an ASP, the total percentage score for overall ASP development was median 48.4% (IQR35.9-62.5%) (31 [IQR23-40] of 64 points) (**Table 4.13, Figure 4.3**), classifying 41 (8.0%) as inadequate, 237 (45.9%) as basic, 179 (34.7%) as intermediate and 59 (11.4%) as advanced. In multivariable analysis, higher overall ASP development scores were associated with hospital level (A or B, versus D), ASP duration (>5 versus ≤2 years), district-level public health development index (highest, upper-middle or lower-middle, versus lowest quartile), and district-level gross domestic expenditure (highest or upper-middle, versus lowest quartile), but not with hospital ownership or geographic region (**Figure 4, Table 4.14-4.15, appendix 3-4**). ASP domain-specific percentage scores were highest for hospital leadership support (83.4% [66.7-100%]), followed by ASP team and infectious disease training (66.7% [55.6-77.8%]); education (50% [0.0-75.0%]); ASP interventions (43.8% [18.7-68.7%]); hospital infrastructure (42.9% [14.3-71.4%]); and monitoring, reporting and feedback (40.9% [27.3-54.5%]) (**Figure 4.5, Table 4.13**).

Table 4.13 Summary of ASP self-assessment scores

	Total	P	Hospital leadership support	P	ASP team and ID training	P	Hospital infra-structure	P	ASP interventions	P	Monitoring, reporting, feedback	P	Education	P
Maximum score	64		6		9		7		16		22		4	
Median score	31 (23-40)		5 (4-6)		6 (5-7)		3 (1-5)		7 (3-11)		9 (6-12)		2 (0-3)	
Percentage score (median, range)	48.4% (35.9-62.5)		83.4% (66.7-100)		66.7% (55.6-77.8)		42.9% (14.3-71.4)		43.8% (18.7-68.7%)		40.9% (27.3-54.5%)		50.0% (0.0-75.0%)	
Hospital level[a]		<0.001												
A	40 (32.5-51.5)		6 (4.5-6)	0.153	7 (6-8)	<0.001	5 (3-7)	<0.001	11.5 (6.5-14.5)	<0.001	12 (8.5-17)	<0.001	2 (0.5-3)	0.966
B	39 (31-48)		6 (5-6)		7 (6-8)		5 (3.5-6)		9 (5.5-13.5)		11 (7-15)		2 (0-3)	
C	30 (23-36)		5 (4-6)		6 (4-7)		2 (1-4)		7 (2-11)		8 (5-11)		2 (0-3)	
D	26 (20-31)		5 (3.5-6)		5 (4-6)		2 (1-3)		5 (1.5-8)		7 (5-10.5)		2 (0-3)	
Hospital size[b]		<0.001												
>250	37 (27-48)		5 (5-6)	0.930	7 (6-8)	<0.001	4 (2-6)	<0.001	9 (4-13)	0.003	12 (6-15)	0.001	2 (0-3)	0.760
101-250	32 (24-40)		5 (4-6)		6 (5-7)		3 (1-5)		7 (3-11)		9 (5-12)		2 (0-3)	
<101	28 (22-38)		5 (4-6)		5 (4-6)		2 (1-4)		6.5 (2-10)		8 (5-11.5)		2 (0-3)	
Hospital ownership		0.559												
Public	32.5 (23-40)		5 (4-6)	0.008	6 (5-7)	0.338	3 (1-5)	0.529	8 (3-12)	0.381	9 (5-13)	0.336	2 (0-3)	0.581
Private	31 (24-39)		6 (5-6)		6 (5-7)		3 (1-5)		7 (3-11)		9 (6-12)		2 (0-3)	
Hospital accreditation[c]		<0.001												
Accredited	33 (25-42)		6 (5-6)	0.004	6 (4-7)	0.001	3 (2-5)	<0.001	8 (4-12)	0.005	10 (6-13)	0.001	2 (0-3)	0.928
Not accredited	29 (22-36)		5 (4-7)		6 (4-7)		2 (1-4)		7 (2-10)		8 (5-12)		2 (0-3)	
National health insurance		0.748												

	Total	P	Hospital leadership support	P	ASP team and ID training	P	Hospital infra-structure	P	ASP interventions	P	Monitoring, reporting, feedback	P	Education	P
service provider														
Yes	32 (23-40)		5 (4-6)	0.340	6 (5-7)	0.734	3 (1-5)	0.006	7 (3-11)	0.515	9 (6-12)	0.917	2 (0-3)	0.104
No	30 (25-43.5)		6 (5-6)		6 (5-7)		4 (2-6)		8 (3-9)		8 (5-14)		2 (1-3)	
ASP duration (years)														
>5	36 (28-47)	<0.001	6 (5-6)	0.001	7 (6-8)	<0.001	4 (2-6)	<0.001	8 (5-13)	0.004	11 (7-15)	<0.001	2 (0-3)	0.246
2-5	31 (24-39)		6 (4-6)		5.5 (5-7)		3 (1-4)		7 (3-11)		9 (6-12)		2 (0-3)	
<2	28 (21-36)		5 (4-6)		6 (4-7)		2 (1-4)		7 (2-11)		8 (5-11)		2 (0-3)	
Geographic region														
Java	32 (25-41)	0.007	6 (5-6)	0.156	6 (5-7)	0.004	4 (2-5)	<0.001	8 (3-11)	0.303	11 (6-13)	0.005	2 (0-3)	0.430
Sumatra	32 (21.5-41.5)		5 (4-6)		5 (4-7)		2 (1-4)		8 (2-12)		9 (5-14)		2 (0-3)	
Bali	31.5 (24.5-39)		5 (4-6)		5 (4-7)		2 (1-3.5)		7 (3.5-11)		10 (5.5-13)		2 (1-4)	
Nusa Tenggara	32 (29-34)		6 (5-6)		6 (5-7)		4 (2-5)		3 (2-9)		11(7-12)		2 (0-3)	
Kalimantan	28 (23-36)		5 (4-6)		5 (4-6)		2 (1-3)		6 (2-9)		9 (6-11)		2 (0-2)	
Sulawesi	32 (22.5-33)		6 (5-6)		6 (5-7)		2 (1-4.5)		8 (1.5-10.5)		7 (5-11.5)		1 (0-3)	
Maluku	27 (18-33)		5 (4-6)		4 (2-4)		1 (1-4)		8 (2-9)		5 (4-7)		2 (1-3)	
Papua	23 (12-25)		4 (3-5)		5 (4-6)		0 (0-1)		2 (1-5)		4 (3-6)		1 (0-2)	

Table shows the hospital ASP self-assessment scores, expressed as median score with interquartile range, overall and per relevant hospital subcategories. Maximum overall and domain-specific scores are shown in each column heading.

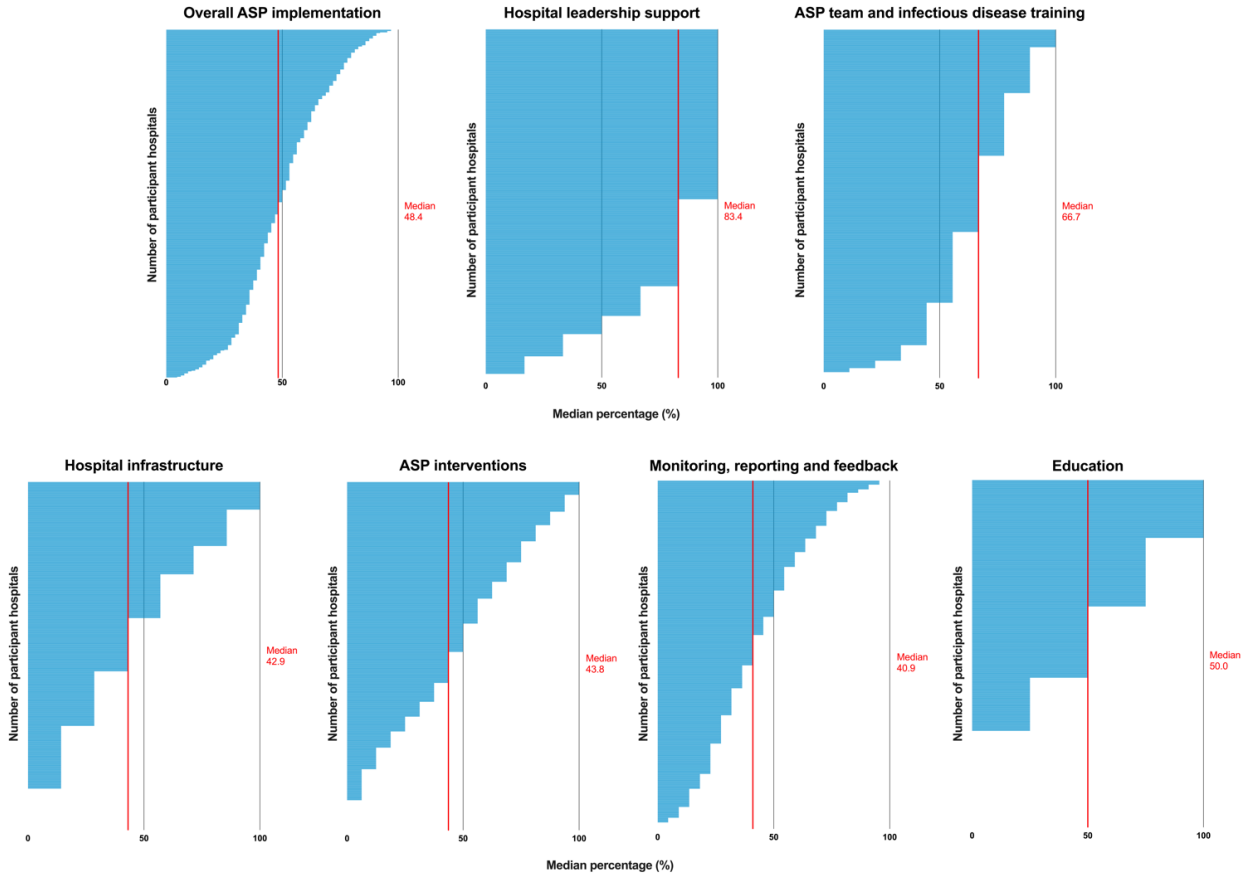
[a]MoH designates hospital tiers based on number of inpatients beds and specialists as type A (≥251 beds and ≥6 specialists), B (201-250 beds and ≥3 specialists), C (101-200 beds and ≥2 specialists), or D (51-100 beds and ≥1 specialist).

[b]Hospital size was based on number of inpatient beds at the time of the survey (from the Ministry of Health).

[c]Accreditation by the Indonesian Commission on Accreditation of Hospitals (*Komite Akreditasi Rumah Sakit).*

Abbreviations: ASP, antimicrobial stewardship program; ID, infectious disease.

Figure 4.3 Distribution of overall and per-domain ASP implementation score



Bar charts showing the distribution of the percentage scores in the ASP self-assessment (overall and domain-specific) among the 516 participant hospitals with a formal ASP. Abbreviations: ASP, antimicrobial stewardship program.

Figure 4.4 Multivariable analysis of hospital and district-level factors associated with ASP self-assessment scores

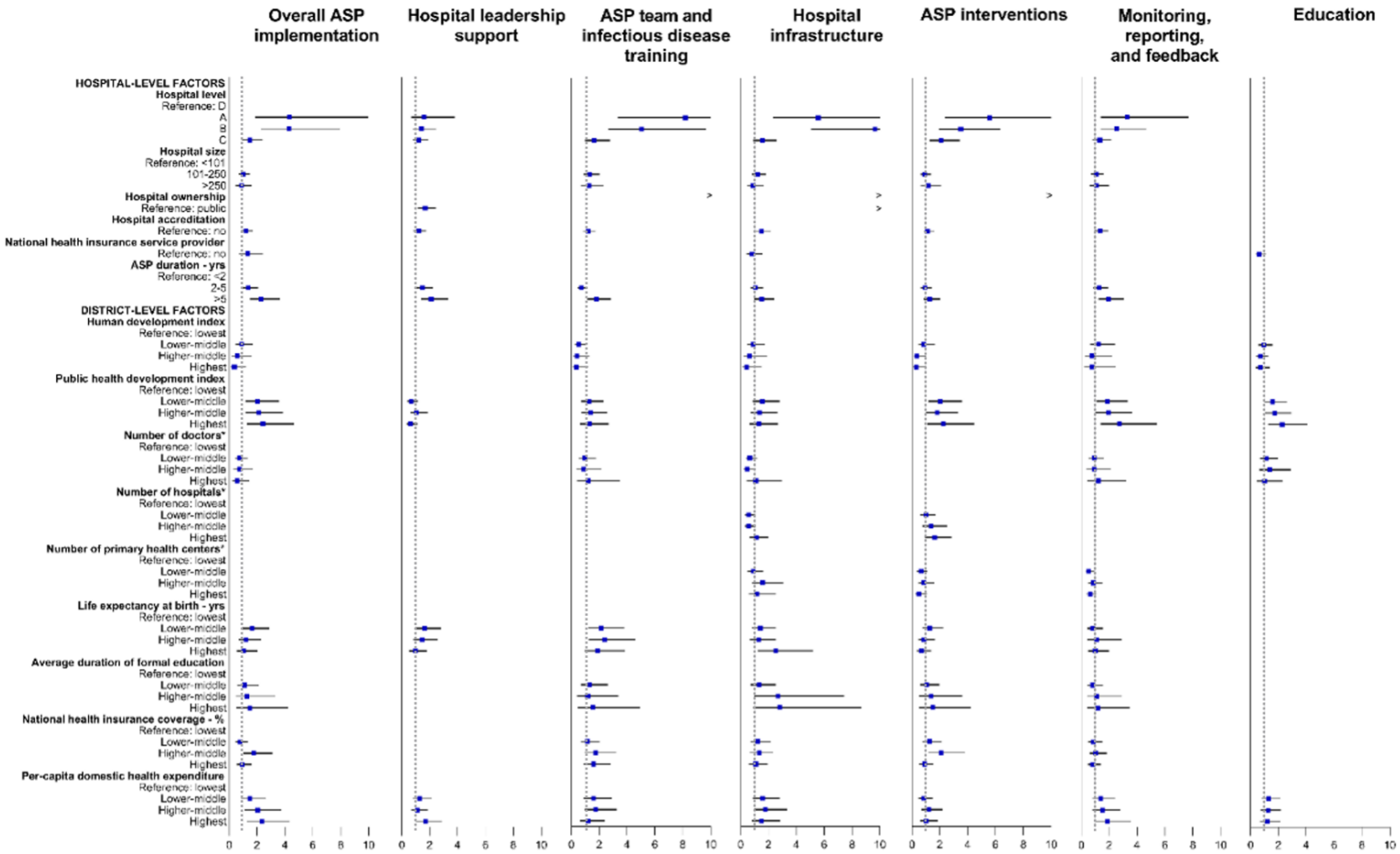


Figure shows results of multilevel ordinal regression to estimate associations between total ASP scores (overall and per domain) and independent variables at the hospital and district level. Province was included as the random-effect variable to adjust for clustering of observations within provinces. District-level data were categorized into quartiles (i.e., lowest, low-middle, middle-high, and highest). Each independent variable with a $p<0.20$ in the univariable model was forwarded to the multivariable model. Final model selection was based on forward selection informed by likelihood ratio test. Independent variables geographic region and district-level midwives per 100 000 population were examined in univariable models and were not associated. See table S10 for further details on the regression models.
*Per 100 000 population.

Abbreviations: ASP, antimicrobial stewardship program

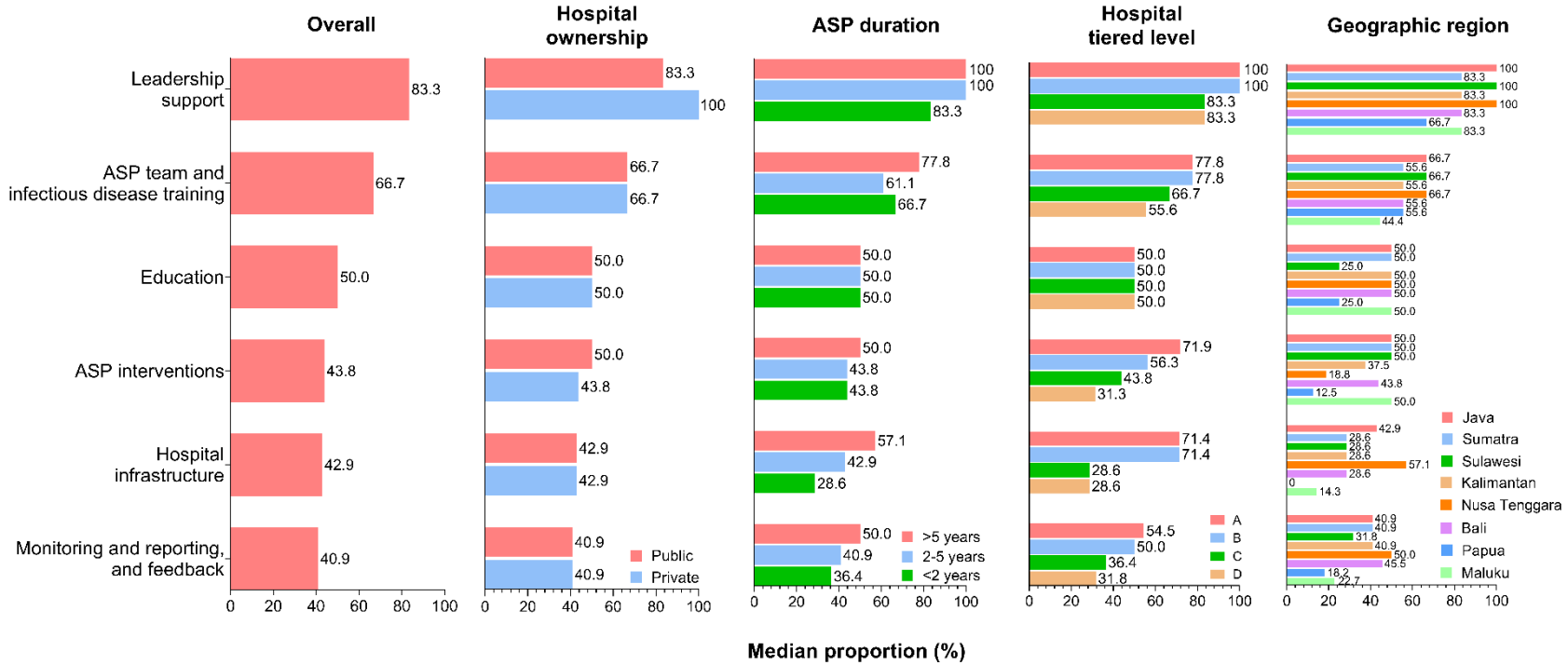
Table 4.14 Summary of hospital and district-level factors associated with ASP self-assessment scores

	Overall ASP implementation	**Hospital leadership support**	**ASP team and infectious disease training**	**Hospital infrastructure**	**ASP interventions**	**Monitoring, reporting, and feedback**	**Education**
Hospital level	√		√	√	√	√	
Hospital ownership		√					
Hospital accreditation				√			
ASP duration (years)	√	√	√			√	
District-level public health development index	√					√	√
District-level life expectancy birth (years)				√			
District-level per-capita domestic health expenditure	√	√				√	

Table shows a summary of the associations identified by the multilevel ordinal regression models between total ASP scores (overall and per domain) and independent variables at the hospital and district level. A tick (√) symbol indicates statistically significant associations in multivariable analysis. The results of the individual regression models are shown in Tables 4.12-4.13.

Abbreviations: ASP, antimicrobial stewardship program.

Figure 4.5 ASP implementation scores across all participant hospitals



Bar chart showing the aggregated scores of the ASP self-assessment survey in all 516 participant hospitals with a formal ASP, expressed as median percentage overall score and domain-specific scores

4.4.3 Hospital leadership support

Formal hospital leadership support through a written document and dedicated funding for AMS activities (e.g. ASP-related training) were in place in 97.7% (504/516) and 83.1% (429/516) of hospitals, respectively. In multivariable analysis, higher leadership support scores were associated with private hospitals (versus public), ASP duration, and district-level gross domestic expenditure, but not with hospital level or geographic region. Hospital leadership promoted ASP development by allocating budget, establishing key performance indicators, and addressing friction between prescribers and the ASP team.

4.4.4 ASP team and infectious disease training

AS activities were led by a physician in 94.4% (487/516) of hospitals, and involved a pharmacist, IPC staff and clinical microbiologist/pathologist in 97.9% (505/516), 89.5% (462/516) and 36.1% (186/516) of hospitals, respectively. In multivariable analysis, higher ASP team and infectious disease training scores were associated with hospital level and ASP duration, but not with hospital ownership.

Collaboration between the ASP team and pre-existing IPC program and/or the pharmacy and therapeutics committee was perceived as promoting ASP implementation. High staff turnover across ASP roles was perceived as a barrier to ASP sustainability. AMS activities incurred substantial additional workload, without financial incentives, which limited the dedicated time available.

> *"All of us have a main job, but here [ASP], we do a double job, even a triple job. We don't even have one staff assigned to work for the ASP. It is the same story for our ward nurses who collect ASP data."* (FGD5, ASP leader/clinician)

Hospitals in remote locations encountered additional challenges related to the part-time or intermittent availability of crucial ASP team members, such as a clinical microbiologist/pathologist.

4.4.5 Hospital infrastructure

Overall, 45.5% (240/516) of hospitals had access to a microbiology service, ranging from 80.6% (29/36) of type A to 21.1% (20/95) of type D hospitals. In multivariable analysis, higher hospital infrastructure scores were associated with hospital level, accreditation and district-level life expectancy, but not with hospital ownership.

Some hospitals with on-site microbiology reported long turn-around times of culture results.

> *"We have access to culture testing. However, it still takes 6 to 7 days before the results are released."* (FGD1, clinician/IPC staff)

Hospitals in remote settings in eastern Indonesia, specifically Maluku, East Nusa Tenggara and Papua, reported limited access to microbiology, including slow and costly specimen referral to a main island, such as Java or Sulawesi.

> *"From this hospital, you must take a speedboat for approximately 40 minutes, then travel overland for approximately 4 hours to reach the city."* (FGD2, IPC staff/clinical pathologist)

Many hospitals reported a lack of IT support (59.5%, 209/516) to collect and analyze AS-relevant data. Hospital information systems could offer opportunities for ASP including electronic prescribing, automatic stop orders and tracking of antibiotic use for surveillance.

4.4.6 ASP interventions

Pre-authorization of Watch and Reserve antimicrobials, prospective review and feedback before antimicrobial administration, and regular AMS ward rounds were done in 42.8% (221/516), 36.6% (189/516) and 40.1% (207/516) of hospitals, respectively. Hospital-specific treatment guidelines for common infections were available in 62.6% (323/516) of hospitals. In multivariable analysis, higher ASP intervention scores were associated with hospital level, but not with hospital ownership or geographic region.

FGD participants reported that antibiotic pre-authorization was effective in reducing irrational antibiotic prescribing and improving guideline adherence, provided that the ASP team actively engaged all stakeholders in addressing friction with prescribers.

> *"The way we handle friction in antibiotic pre-authorization is by inviting the prescribing clinician. We hold a group discussion, involving the hospital management, medical service team, patient service manager, pharmacy and laboratory."* (FGD14, ASP leader/clinician)

FGD participants from both public and private hospitals agreed that effective AS strategies could reduce expenses.

The FGDs revealed that hierarchical relationships and the fear of loss of prescribers' autonomy, especially in private hospitals, continue to hinder multidisciplinary work:

> *"Seniority and hierarchy are still strong. Our approach is that junior doctors only provide suggestions to the senior doctors."* (FGD7, hospital manager)

"In private hospitals, specialists have the highest authority, especially those who 'supply' the hospitals with patients. They are like kings." (FGD2, ASP leader/clinician)

4.4.7 Monitoring, reporting and feedback

Antibiotic consumption was monitored in 47.7% (246/516; Defined Daily Dose) and 35.9% (185/516; Duration of Treatment) of hospitals. Surveys or audits of antibiotic prescribing had been performed in 36.8% (190/516) of hospitals; 81.6% (155/190) of those communicated survey results directly to prescribers with specific action points. Availability of an institutional antibiogram was reported by 40.9% (211/516) of hospitals. In multivariable analysis, higher monitoring, reporting, and feedback scores were associated with hospital level, ASP duration, district-level public health development index, district-level gross domestic expenditure, but not with hospital ownership. In some hospitals, mandatory monthly reporting of antibiotic use quality indicators to MoH was only partially done or not at all, due to the additional workload.

4.4.8 Education

AMS-related education/training for clinical staff had been provided in 61.6% (318/516) of hospitals. In multivariable analysis, higher education scores were associated with district-level public health development index, but not with hospital level, ownership or geographic region. Hospital management generally supported AMS-related trainings. Participants highlighted specific knowledge needs, including how to use AMS metrics to achieve behavior change.

4.4.9 External environment

Implementation of national ASP guidelines and antibiotic prescribing guidelines from professional societies were mentioned as important enablers. Participants agreed that including ASP in the national hospital accreditation standard, could be the most important factor to advance ASP implementation.

> *"The reason behind the ASP initiation in 2018 was because our hospital was undergoing hospital accreditation. One of the requirements was that we must establish an ASP."* (FGD8, ASP leader/clinician)

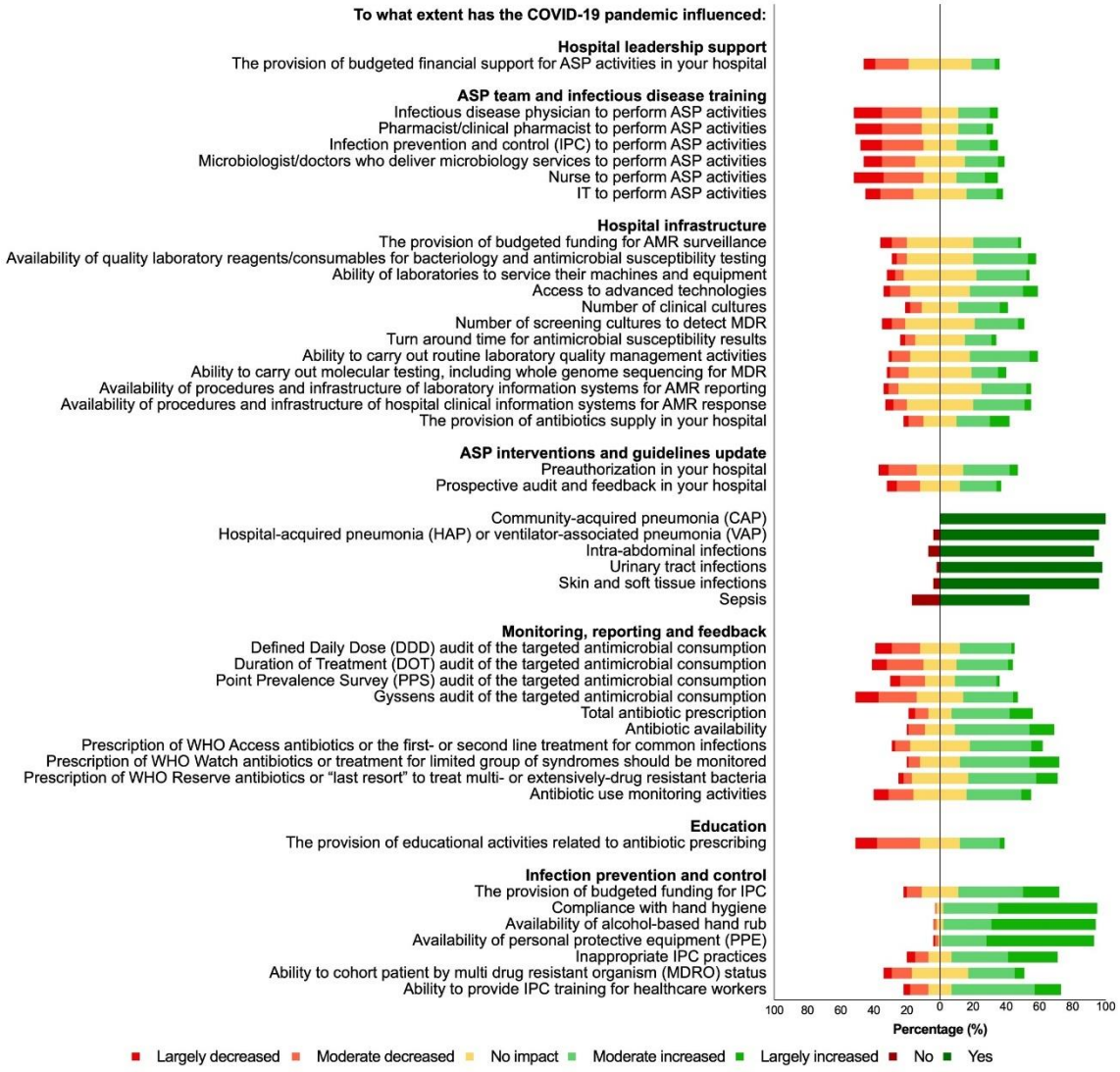
However, due to a simplification of the national hospital accreditation standard by MOH in 2022, ASP is no longer compulsory to achieve accreditation, which resulted in reduced prioritization and motivation to implement ASP.

4.4.10 COVID-19 impacts

During COVID-19, many AMS activities were limited or on hold due to re-allocation of human and financial resources. There was reduced availability of pharmacists, infectious disease physicians and IPC staff for AMS activities. Antibiotic consumption increased overall, backed up by COVID-19 treatment guidelines. By contrast, improvements during COVID-19 included increased bacterial culture use; updated treatment guidelines for common infections; enhanced analysis and reporting of antibiotic consumption data; and improved IPC practices, especially the use of alcohol-based hand rub, personal protective equipment and hand hygiene (**Figure 4.6**).

Table 4.15 integrates all the identified barriers and enablers of ASP implementation in a framework.

Figure 4.6 Bar chart of COVID-19 impacts on ASP implementation



Bar chart showing hospital responses to the 41 COVID-19 items included in the ASP self-assessment.
The questionnaire was programmed in such a manner that some of the COVID-19-related items were asked as a follow-up to a related core item that was responded "Yes", which explains the varying denominators; for example: "Does your hospital allocate any budgeted financial support for ASP activities?" (item# A1.2), if answered "Yes" was followed by "To what extent has the COVID-19 pandemic influenced the provision of budgeted financial support for ASP activities in your hospital? (item# B1.1). For readability, the bar charts do not include "Don't know" responses. "No" and "Yes" responses were required for 6 questions on the availability of updated hospital guidelines during COVID-19 pandemic. The underlying data (n, %) are summarised in Appendix 5.

Abbreviations: AMR, antimicrobial resistance; ASP, antimicrobial stewardship program; IPC, infection prevention and control; IT, information technology MDR, multidrug resistance; WHO, World Health Organizations.

Table 4.15 Summary of barriers to and enablers of ASP in Indonesian hospitals

	Barriers	**Enablers**
Organization	Lack of formal hospital leadership support, limited understanding by hospital leaders of relevance of ASP	Written formal leadership support
	Lack of designated ASP leader	Designated ASP leader
	Lack of dedicated budget for AMS activities and staff	Dedicated budget for AMS activities and staff
	Lack of dedicated time for ASP	Key performance indicators for ASP
	Type of hospital, especially in level C and D hospitals and remote settings	Hospital leaders engage in ASP (e.g. supports discussion around antibiotic practice changes, and addresses friction with prescribers)
	Hierarchical relationships	Potential for cost savings from effective AS strategies
	Frequent staff turnover	ASP development included in national standard for hospital accreditation
	Excessive workload	
	Lack of staff compensation/incentive model	
	Restriction in national formulary and reimbursement as part of national health insurance	
Individuals	Hierarchical relationships	Physician as designated ASP leader
	Irrational antibiotic prescribing practices, including non-adherence to antibiotic guidelines	Multidisciplinary work routines
	Fear of loss of prescribers' autonomy, especially in private hospitals	ASP team engage all relevant stakeholders in addressing friction with prescribers
	Limited awareness of local AMR data	ASP team engage in communicating antibiotic use survey/audit results to prescribers with specific action points
	Limited adoption of AMS principles	
	Limited knowledge of AMS metrics and how to use these to change behavior	
Tasks	Excessive workload	Build ASP with IPC program and/or pharmacy and therapeutics committee
	Inability to monitor antibiotic use data on a regular basis	Daily ward rounds by infectious disease consultant, microbiologist and/or pharmacist
	Part-time or intermittent availability of key ASP team members	
	Microbiology laboratory has long turn-around-times of bacterial culture results	
	Complex sample logistics for bacterial cultures in remote settings	
	Limited training in quality improvement implementation	
	Inefficient processes for approval of bacterial cultures and restricted antimicrobials	
	Lack of reliable and timely microbiological laboratory services, especially in level C and D hospitals and in remote settings	Electronic prescriptions and automatic stop orders

	Barriers	Enablers
Tools and information technology	Lack of IT support to collect and analyze ASP-relevant data	Electronic medical record to allow efficient tracking of antimicrobial resistance/antibiotic use data
	Limited opportunities for AMS training	Microbiology results integrated in electronic medical record
	Lack of hospital treatment guidelines for common infections	Training in quality improvement, patient safety and how to change behavior
External environment	Limited guidance from public authorities on initiatives to improve antibiotic use, ASP implementation, etc.	COVID-19 pandemic (e.g. improved IPC)
	Lack of feedback from MOH on annual hospital reports on antibiotic use and resistance	Reporting antibiotic use and consumption data to public authorities
	COVID-19 pandemic (e.g. re-allocation of staff and resources)	Implementation of national ASP guidelines
	Low district-level public health development index	Implementation of antibiotic prescribing guidelines from professional societies
	Low district-level per-capita domestic health expenditure	Include ASP in national standard for hospital accreditation
	Restriction in national formulary and reimbursement as part of national health insurance	

Integration of barriers and enablers of ASP identified from the quantitative and qualitative study data using the Systems Engineering Initiative for Patient Safety Framework. Abbreviations: AMR, antimicrobial resistance; AMS, antimicrobial stewardship; ASP, antimicrobial stewardship program; IPC, infection prevention and control; IT, information technology.

4.5 Discussion

This is the first comprehensive nationwide evaluation of the current ASP structures, activities, and key barriers and enablers of ASP implementation in Indonesian hospitals. 10% of participant hospitals had not yet initiated an ASP; and of those who had a formal ASP, about half (54%) had only reached an inadequate or basic level of development. I identified substantial gaps across the ASP domains, especially regarding education, ASP interventions, hospital infrastructure, and monitoring, reporting and feedback. Progress was particularly limited in the lower hospital tiers (type C and D) and in those districts that had the lowest public health development index and gross domestic expenditure. ASP development was most advanced in hospitals that had operated their ASP for a longer time and, overall, was similar between government and private hospitals. The study findings add additional insights to our previous qualitative study among hospital and national AMS stakeholders, mainly in Jakarta, that concluded that significant progress and sustainability of ASP has been challenged by lack of sustainable support from hospital management, limited national health insurance cover for bacterial cultures, and limited functionality of enabling infrastructures, such as microbiology laboratories and surgical facilities, profit generation and interprofessional dynamics (32).

Hospital accreditation by the Indonesian Commission on Hospital Accreditation, was cited as one of the most fundamental enablers for ASP development (304). Due to changing government priorities, however, since 2022, ASP implementation is no longer compulsory for hospitals to acquire national accreditation (313), which has led to deprioritization and demotivation among hospital managers and ASP teams. There is a need for more robust national and sub-national regulations to help prioritize ASPs, set minimum requirements, and develop rigorous structures to evaluate progress on reaching improvement targets (e.g.,

quality of prescribing, incident AMR infections) (305). This also requires better reimbursement models to incentivize ASP development in Indonesia, and other LMICs (314).

Strong hospital leadership support was identified as critical, not only for allocating resources for ASP structures and activities, but also for establishing key performance indicators, enforcing compliance with hospital-specific clinical practice guidelines, as well as addressing friction between ASP team members and prescribers. This aligns with findings in various settings, that identified the presence of an accountable and supportive governance structure as an important enabler (315-317).

The findings further highlighted that cultural determinants remain an important obstacle to the multidisciplinary approaches needed to improve rational antibiotic use, and the need for addressing counterproductive hierarchical relationships among health care workers (e.g., prescribers versus ASP clinician, pharmacist, nurse) and developing cohesive work routines across disciplines with shared responsibilities. There is an urgent need for culture-resonant strategies to strengthen both technical (e.g., consequences of antibiotic over-use, best treatment practices) and AMS-related behavioral skills (e.g., effective communication, teamwork and quality improvement), which are a prerequisite for any ASP (318, 319). Educational initiatives, mostly in high-income settings, that incorporated both technical and behavioral aspects using patient safety as a framework, have been successful in improving antibiotic prescribing (318-320). Furthermore, excessive workload and lack of appropriate financial compensation posed additional barriers, which echoes earlier reports related to IPC program implementation (321).

Robust microbiology services, a basic pillar for diagnostic stewardship (322), are underdeveloped in Indonesia; a survey in 2022 found that only 11% of hospitals had an in-house microbiology laboratory (323), is lower than reported for Thailand (55.9% in 2022) (324) and Vietnam (50.7% in 2018) (325). Consequently, blood culture utilisation rates have been very low in Indonesia (reported at 30.6 per 1,000 patient-days (122), compared to 82 per 1,000 patient-days in Thailand (224). The gaps in microbiology were most evident in the lower tier (type C and D) hospitals (comprising 83% of all hospitals), particularly in remote and underdeveloped islands. MoH, with support from international donors, are making investments to further strengthen the microbiological laboratory capacity (323). Furthermore, MoH will launch a national electronic medical record to be rolled out to all registered health facilities (326) will create important opportunities for enhanced AS activities such as electronic prescribing and ASP-related data aggregation and reporting.

The COVID-19 pandemic has exposed structural vulnerabilities in national health systems in Indonesia and other LMICs (246), resulted in a drastic reduction in AS activities because of re-allocation of funding and staff to COVID-19-related priorities, and antibiotic consumption increased following COVID-19 treatment guidelines (246), as reported in other settings (310). However, its positive impacts, such as improved bacterial culture (276) and IPC practices, have contributed to strengthening ASP structures (327).

4.6 Limitations

This study has some limitations. First, I have made deliberate efforts to achieve a hospital study sample that was representative of the distribution of hospital types across the major islands and all provinces in terms of ownership, tiered level and size. The geographical

representation of hospitals across the major islands was fairly balanced (based on total number of hospitals and study participation rates). Nonetheless, substantial non-participation could have introduced selection bias, and hospital participation was higher for some regions and the upper-level hospitals, with potential of over-representation of hospitals with more resources (e.g. microbiology laboratory) and more advanced ASP development. Second, the ASP self-assessment relied on self-report, which has potential for social desirability and recall bias, although the high data reliability observed during the quality control process suggested that this effect may have been limited. Third, the qualitative data collected through the FGDs have potential for subjectivity as it relied on the perceptions and experience from both the researchers and participants. Lastly, the study design was unable to robustly assess stewardship outcome indicators, such as prevalence of rational antibiotic use and antibiotic resistance.

4.7 Implications

Future actions on (1) organization and hospital support, (2) individuals, tasks and culture, (3) tools and technology, (4) external environment to implement effective and sustainable ASPs in Indonesia are needed.

In the organization and hospital support domain, I recommended to (1) improve engagement of hospital leadership in antimicrobial stewardship activities; (2) set ASP as a hospital priority, with relevant key performance indicators and financial support; (3) ensure minimum staffing requirements, ensure ASP members have dedicated time and incentives to operate an ASP.

In the individuals, tasks and culture domain, I recommended to (1) identify key areas for improving antimicrobial use locally; (2) develop and disseminate hospital-specific guidelines for antimicrobial use for common infections; (3) improve processes for tracking and monitoring antimicrobial use and resistance data; (4) improve access to antimicrobial stewardship-related training, including quality improvement and behaviour change, for pharmacists, physicians and nurses; (5) engage frontline healthcare workers in AS activities (e.g., provide feedback on inappropriate use, share AMS-related data) and create a learning healthcare system; promote multidisciplinary teamwork between ASP team, prescribers, IPC program and Pharmacy and Therapeutics committee.

In tools and technology domain, I recommended to (1) build network referral system of laboratory to enable reliable and timely microbiology services, including in lower tier (type C and D) hospitals as well as in remote settings; (2) improve information technology access to support AS activities (e.g., for antibiotic use tracking); (3) leverage the government-initiated national electronic medical record to include functionality to facilitate electronic prescribing, automatic stop order, remote pre-authorization, and integration of microbiology lab results.

External to hospital, I recommended to (1) include ASP development in the national standard for hospital accreditation; (2) expand implementation resources for ASPs (e.g., guidance on ASP implementation strategies, educational resources about inappropriate antibiotic use); (3) develop efficient systems for local and national level reporting of antimicrobial use/resistance data and feedback on activities and measurable activities and outcomes.

4.8. Conclusion

I identified globally-relevant as well as context-specific gaps and barriers to robust and sustainable ASP implementation in public and private hospitals in Indonesia. Several barriers can be feasibly addressed in the short term (e.g., education, hospital administrators' engagement, and making a business case for ASP), whereas additional barriers will require longer-term efforts and investments (e.g., improving microbiology and IT resources, staff compensation, cross-disciplinary collaborations, and ASP re-inclusion in hospital accreditation).

Chapter 5
Conclusions

This chapter begins with an overview of the main findings, summarizing their contributions to the expanding literature on the epidemiology of hospital AMR infections, blood culture utilization, diagnostic and antibiotic use practices, and ASP implementation in Indonesia. Additionally, it discusses the implications of the available evidence for health policy and suggests potential directions for future research.

5.1 An overview of the key findings

The overall aim of the research performed in this thesis is to improve the understanding of the epidemiology of AMR infections and ASP implementation in Indonesia. Specifically, I (1) evaluated epidemiology of AMR BSI, blood culture utilization; (2) developed and evaluated clinical diagnostic practices and antibiotic use practices parameters; (3) assessed the current state of nation-wide ASP implementation, and identified barriers and enablers of ASP implementation in Indonesian hospitals at the hospital, provincial, and national level.

I observed high proportion of AMR BSI, low blood culture utilization, high antibiotic use from the Watch Category, blood culture sampled and a longer duration of parenteral antibiotics, low proportion of patients having BC within $\pm$1 calendar day of starting parenteral antibiotic and long duration of parenteral antibiotics in Indonesian national referral hospital. I identified context-specific gaps and barriers to robust and sustainable ASP implementation in public and private hospitals in Indonesia.

5.1.1 Epidemiology of AMR BSI and blood culture utilization

The two-year retrospective surveillance study on AMR-BSI and blood culture utilization in the Indonesian national referral hospital indicated a blood culture utilization rate of 30.6 per 1,000 patient-days. Notably, the utilization rate had been increasing both before and during the COVID-19 pandemic, with higher rates observed among COVID-19 cases compared to non-COVID-19 cases. Gram-negative pathogens were the most identified pathogens. The proportion of resistance for each bacterial pathogen was similar between COVID-19 and non-COVID-19 cases. Interestingly, the incidence rate of hospital-origin AMR-BSI increased in 2020 and was not associated with COVID-19 infection.

This pioneering study in Indonesia represents the first utilization and systematic analysis of local data on AMR epidemiology to comprehend the local situation both before and during the COVID-19 pandemic. The findings outlined in Chapter 2 demonstrate that the utilization of readily available electronic hospital databases can yield robust and valuable insights into blood culture utilization and the burden of AMR infections in LMICs, particularly during times of crisis such as the COVID-19 pandemic.

5.1.2 Clinical diagnostic practices and antibiotic use practices

The second angle that this thesis investigated are clinical diagnostic and antibiotic use practices in the Indonesian national referral hospital. To measure diagnostic practices, I estimated (a) the proportion of patients with blood culture taken within $\pm$1 calendar day of parenteral antibiotics being started, (b) the proportion of patients with blood culture taken within 28 days of parenteral antibiotics being started, and (c) the median blood culture turnaround-time. To measure antibiotic use practices, I estimated (a) the proportion of antibiotic use based on the AWaRe system (Access, Watch and Reserve), (b) median time

to discontinuation of parenteral antibiotic, (c) the proportion of patients with narrow-spectrum parenteral antibiotics (antibiotics within the Access and Watch category without anti- MRSA/ antipseudomonal activity) within 2 calendar days following blood culture report among those who had a blood culture positive for 3GCSEC or 3GCSKP and remained on a parenteral antibiotic on the day that the blood culture results were reported, and (d) the proportion of patients with parenteral antibiotic discontinuation within 2 calendar days following blood culture report among those who had blood culture results negative for organisms and remained on a parenteral antibiotic on the day that the blood culture results were reported.

I found that the proportion of timely blood culture was low in inpatients, and duration of parenteral antibiotics was longer in COVID-19 patients. Most of the parenteral antibiotics used for inpatients were from the Watch Category. After adjusting for COVID-19 patients, I found that the blood culture practice minimally improved in 2020 compared to 2019; however, the time to discontinuation of parenteral antibiotics was longer in 2020 compared to 2019.

This first study in Indonesia represents the first utilization and systematic analysis of local data on hospital admission, laboratory microbiology and drug dispensing data to monitor and report outcomes of diagnostic and ASPs both before and during the COVID-19 pandemic. The findings outlined in Chapter 3 demonstrate that the utilization of readily available electronic hospital databases can yield robust and valuable insights into routine monitoring and improvement of diagnostic and antimicrobial stewardship.

5.1.3 Indonesian nation-wide ASP implementation

Finally, this thesis includes a nationwide robust assessment of ASP implementation. I found 10% of participant hospitals had not yet initiated an ASP; and of those who had a formal ASP, 54% had only reached an inadequate or basic ASP development level. I identified substantial gaps across the ASP domains, especially regarding education, ASP interventions, hospital infrastructure, and monitoring, reporting and feedback. Progress was particularly limited in the lower hospital tiers (type C and D) and in those districts that had the lowest public health development index and gross domestic expenditure. ASP development was most advanced in hospitals that had operated their ASP for a longer time and, overall, was similar for government and private hospitals. The findings identified globally relevant and context-specific enablers and barriers to ASP implementation in Indonesia. I summarized the findings applying the Systems Engineering Initiative for Patient Safety Framework into organization, individuals, tasks, tools and information technology, external environment domains.

5.2 Implications to healthcare policy

The research presented in this thesis underscores the urgent threat posed by AMR infections and identifies significant gaps in data, resources, and practices essential for designing strategies to mitigate their impact in Indonesia. Recommendations are provided to enhance diagnostic and antimicrobial stewardship practices.

Chapter 2 emphasizes the importance of increasing blood culture utilization and generating AMR surveillance reports in LMICs to inform local healthcare providers and policymakers. I recommend the implementation of stratified reports detailing parameters of AMR surveillance, such as proportions and incidence rates of AMR infections, based on the

origin of infection. Additionally, I propose the inclusion of blood culture utilization rates in AMR surveillance reports to facilitate a more comprehensive interpretation of AMR surveillance parameters.

Chapter 3 illustrates the recommendations to measure clinical diagnostic and antibiotic use practices using the developed parameters. I recommend using the results of this measurement to critically plan actions to improve diagnostic and antibiotic stewardships in the hospital.

Based on findings on chapter 4, I recommend future actions for implementing effective and sustainable ASP in Indonesian hospitals in 4 domains, i.e. (1) organization and hospital support; (2) individuals, tasks and culture; (3) tools and technology; (4) external environment.

5.3 Future research areas

Referring to the WHO global research agenda for AMR in human health year 2023 (328), I elaborate several future research areas. An extension of this retrospective surveillance study is to estimate the excess of mortality, disability-adjusted life-years (DALYs), length of stay, cost of hospitalization attributable to AMR infections using patients without infection as the comparator and associated with AMR infections using patients with susceptible infection as the comparator. This can be done by collecting retrospective hospital admission, clinical, microbiology and antibiotic use data; some of which has been collected and analyzed in this thesis. Expansion to more comprehensive surveillance on pathogens resistance to the new antibiotic and genomic surveillance for AMR should be started. The protocol could be implemented in a wide range of hospitals in Indonesia and

into subcategories of infectious syndrome based on location of infection to produce more nationally extensive and representative data. The national data will fill the gap on the sparsity of data from many LMICs, including Indonesia, on the distribution of pathogens by infectious syndrome, the prevalence of resistance for key pathogen–drug combinations, and the impact involving AMR infections. The findings could strengthen the Indonesian national action plan aimed at reducing and managing AMR infections.

Future studies on outcome of strengthening ASP implementation in both technical (best practice for management of common syndrome), behavioural (teamwork, effective communication) and infrastructure aspects on improvement of clinical diagnosis and antibiotic use practice parameters, proportion of resistance for bacterial pathogen, hospitalization cost among hospitals of similar bed count and over time are needed to provide an understanding on the extent of ASP as an effort in tackling global health crisis. An extension of the mixed methods study on gaps and barriers of ASP implementation in lower-level hospitals in Indonesia, including in hospitals which have not implemented ASP, would inform the context-specific intervention, and support a more precise recommended actions for sustainable improvement. This extension study needs to explore other dimensions of the AMR problem in Indonesia, i.e. insufficient access to supporting tests to confirm the diagnosis of infection, and antibiotics, which kill more people than AMR.

5.4 Conclusions

This thesis evaluated data, provided evidence, and developed concept of measuring hospital AMR infections, blood culture utilization, diagnostic and antibiotic use practices, ASP implementation in Indonesia. Data and evidence generated from this thesis can inform the

better interpretation of parameters of AMR surveillance, diagnostic and antibiotic use practices, and formulation of appropriate approaches for sustainable improvement of ASP practices.

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Appendix

Appendix 1. AMR Surveillance Report

Antimicrobial Resistance (AMR) Surveillance Report

Hospital name: RSUPN Dr. Cipto Mangunkusumo
Country name: Indonesia

Data from:
01 Jan 2019 to 31 Dec 2020

Contact person: Robert Sinto
Contact address: Department of Internal Medicine, RSUPN Dr. Cipto Mangunkusumo
Contact email: robert.sinto01@ui.ac.id

Generated on: 26 Jan 2022

Generated by

AutoMated tool for Antimicrobial resistance Surveillance System (AMASS)
Version 1.1 (released on January 12, 2021)

The AMASS application is available under the Creative Commons Attribution 4.0 International Public License (CC BY 4.0). The application can be downloaded at: http://www.amass.website

The AMASS application used microbiology_data and hospital_admission_data files that are stored in the same folder as the application (AMASS.bat) to generate this report.

The goal of the AMASS application is to enable hospitals with microbiology data available in electronic formats to analyze their own data and generate AMR surveillance reports promptly. If hospital admission date data are available, the reports will additionally be stratified by infection origin (community–origin or hospital–origin). If mortality data (such as patient discharge outcome data) are available, a report on mortality involving AMR infection will be added.

This automatically generated report has limitations, and requires users to understand those limitations and use the summary data in the report with careful interpretation.

A valid report could have local implications and much wider benefits if shared with national and international organizations.

This automatically generated report is under the jurisdiction of the hospital to copy, redistribute, and share with any individual or organization.

This automatically generated report contains no patient identifier, similar to standard reports on cumulative antimicrobial susceptibility.

For any query on AMASS, please contact:
Cherry Lim (cherry@tropmedres.ac) and
Direk Limmathurotsakul (direk@tropmedres.ac)

Suggested title for citation:
Antimicrobial resistance surveillance report, RSUPN Dr. Cipto Mangunkusumo, Indonesia, NA to NA.

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Introduction

Antimicrobial resistance (AMR) is a global health crisis [1]. The report by Lord Jim O'Neill estimated that 700,000 global deaths could be attributable to AMR in 2015, and projected that the annual death toll could reach 10 million by 2050 [1]. However, data of AMR surveillance from low and middle–income countries (LMICs) are scarce [1,2], and data of mortality associated with AMR infections are rarely available. A recent study estimated that 19,000 deaths are attributable to AMR infections in Thailand annually, using routinely available microbiological and hospital databases [3]. The study also proposed that hospitals in LMICs should utilize routinely available microbiological and hospital admission databases to generate reports on AMR surveillance systematically [3].

Reports on AMR surveillance can have a wide range of benefits [2]; including

- characterization of the frequency of resistance and organisms in different facilities and regions;
- prospective and retrospective information on emerging public health threats;
- evaluation and optimization of local and national standard treatment guidelines;
- evaluation of the impact of interventions beyond antimicrobial guidelines that aim to reduce AMR; and
- data sharing with national and international organizations to support decisions on resource allocation for interventions against AMR and to inform the implementation of action plans at national and global levels.

When reporting AMR surveillance results, it is generally recommended that (a) duplicate results of bacterial isolates are removed, and (b) reports are stratified by infection origin (community–origin or hospital–origin), if possible [2]. Many hospitals in LMICs lack time and resources needed to analyze the data (particularly to deduplicate data and to generate tables and figures), write the reports, and to release the data or reports [4].

AutoMated tool for Antimicrobial resistance Surveillance System (AMASS) was developed as an offline, open–access and easy–to–use application that allows a hospital to perform data analysis independently and generate isolate–based and sample–based surveillance reports stratified by infection origin from routinely collected electronic databases. The application was built in R, which is a free software environment. The application has been placed within a user–friendly interface that only requires the user to double–click on the application icon. The AMASS application can be downloaded at:
http://www.amass.website

Please note that the AMASS application and the automatically–generated report have limitations, and require readers to understand those limitations and review the reports and summary data carefully. We encourage the user of the AMASS application to perform manual validation (such as printing and listing isolates of the species to cross check with the reports), as recommended by Clinical and Laboratory Standards Insitute (CLSI) [5] and European Antimicrobial Resistance Surveillance Network (EUCAST) [6,7]. Moreover, it is important to note that the AMASS is an add–on automatized report generating tool and does not replace WHONET, Laboratory Information System (LIS), quality assurance programme, or antimicrobial surveillance systems (including the WHO GLASS).

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Section [1]: Data overview

Introduction
An overview of the data detected by the AMASS application is generated by default. The summary is based on the raw data files saved within the same folder as the application file (AMASS.bat).

Please review and validate this section carefully before proceeds to the next section.

Results
The microbiology_data file (stored in the same folder as the application file) had:

17901 specimen data records with collection dates ranging from
01 Jan 2019 to ***31 Dec 2020***

The hospital_admission_data file (stored in the same folder as the application file) had:

91960 admission data records with hospital admission dates ranging from
NA to ***NA***

Notes:
[1] If the periods of the data in microbiology_data and hospital_admission_data files are not similar, the automatically–generated report should be interpreted with caution. The AMASS generates the reports based on the available data.

Reporting period by months:
Data was stratified by month to assist detection of missing data, and verification of whether the month distribution of data records in microbiology_data file and hospital_admission_data file reflected the microbiology culture frequency and admission rate of the hospital, respectively. For example if the number of specimens in the microbiology_data file reported below is lower than what is expected, please check the raw data file and data dictionary files.

Month	Number of specimen data records in microbiology_data file	Number of admission data records in hospital_admission_data file
January	*1235*	*8037*
February	*1465*	*7431*
March	*1414*	*7730*
April	*1339*	*6025*
May	*1400*	*6551*
June	*1443*	*6761*
July	*1561*	*8098*
August	*1571*	*8518*
September	*1448*	*8007*
October	*1612*	*7947*
November	*1670*	*8381*
December	*1743*	*8474*
Total:	*17901*	*91960*

Note:
[1] Additional general demographic data will be made available in the next version of the AMASS application.

Section [2]: Isolate–based surveillance report

Introduction
An isolate–based surveillance report is generated by default, even if the hospital_ admission_data file is unavailable. This is to enable hospitals with only microbiology data available to utilize the de–duplication and report generation functions of AMASS.
This report is without stratification by origin of infection.

The report generated by the AMASS application version 1.1 includes only blood samples. The next version of AMASS will include other specimen types, including cerebrospinal fluid (CSF), urine, stool, and other specimens.

Organisms under this survey:

- *Staphylococcus aureus*
- *Enterococcus* spp.
- *Streptococcus pneumoniae*
- *Salmonella* spp.
- *Escherichia coli*
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Acinetobacter* spp.

Results
The microbiology_data file had:

Sample collection dates ranged from ***01 Jan 2019*** to ***31 Dec 2020***
Number of records of blood specimens collected within the above date range:
17901 blood specimens records

*Number of records of blood specimens with *negative culture (no growth):*
14205 blood specimens records
Number of records of blood specimens with culture positive for a microorganism:
3696 blood specimens records

Number of records of blood specimens with culture positive for organism under this survey:
2030 blood specimens records

The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period as described in the method. The number of patients with positive samples is as follows:

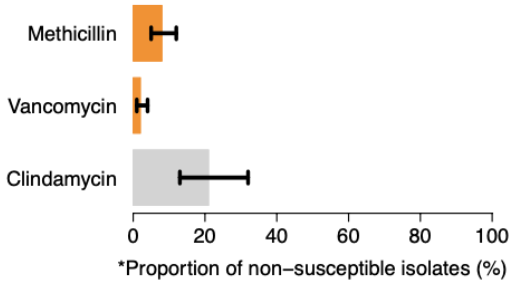
Organism	Number of records of blood specimens culture positive for the organism	**Number of patients with blood culture positive for the organism (de–duplicated)
Staphylococcus aureus	***293***	***212***
***Enterococcus* spp.**	***90***	***74***
Streptococcus pneumoniae	***3***	***3***
***Salmonella* spp.**	***49***	***45***
Escherichia coli	***288***	***248***
Klebsiella pneumoniae	***738***	***441***
Pseudomonas aeruginosa	***208***	***160***
***Acinetobacter* spp.**	***361***	***249***
Total:	***2030***	***1432***

*The negative culture included data values specified as 'no growth' in the dictionary_for_ microbiology_data file (details on data dictionary files are in the method section) to represent specimens with negative culture for any microorganism.
**Only the first isolate for each patient per specimen type, per pathogen, and per evaluation period was included in the analysis.

The following figures and tables show the proportion of patients with blood culture positive for antimicrobial non–susceptible isolates.

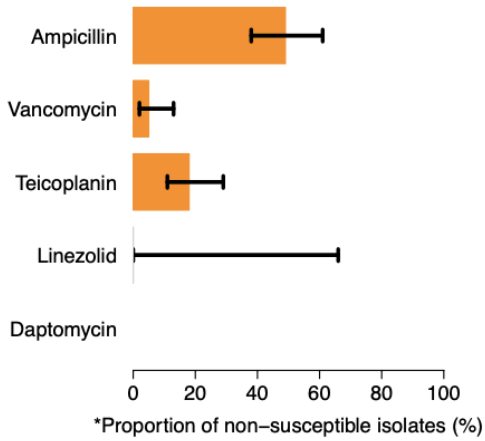
Section [2]: Isolate–based surveillance report

Blood: ***Staphylococcus aureus*** ***(No. of patients = 212)***



Antibiotic agent	% NS (n)	95% CI
Methicillin	8% (16/209)	5%–12%
Vancomycin	2% (3/193)	1%–4%
Clindamycin	21% (15/70)	13%–32%

Blood: ***Enterococcus* spp.** ***(No. of patients = 74)***

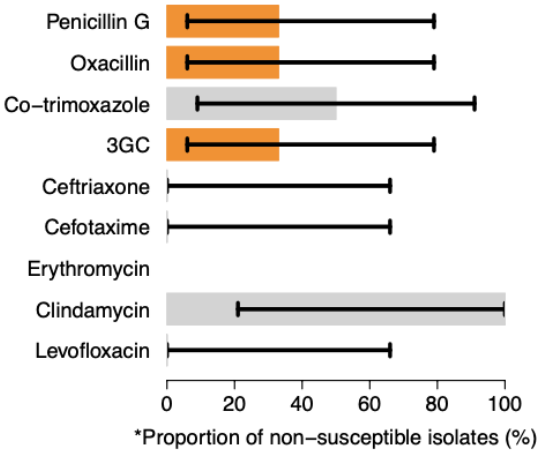


Antibiotic agent	% NS (n)	95% CI
Ampicillin	49% (35/71)	38%–61%
Vancomycin	5% (3/61)	2%–13%
Teicoplanin	18% (12/67)	11%–29%
Linezolid	0% (0/2)	0%–66%
Daptomycin	NA	–

*Proportion of non–susceptible isolates (% NS) represents the number of patients with blood culture positive for non–susceptible isolates (numerator) over the total number of patients with blood culture positive for the organism and the organism was tested for susceptibility against the antibiotic (denominator). The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period. Grey bars indicate that testing with the antibiotic occurred for less than 70% of the total number of patients with blood culture positive for the organism.
CI = confidence interval; NA = Not available/reported/tested; Methicillin: methicillin, oxacillin, or cefoxitin

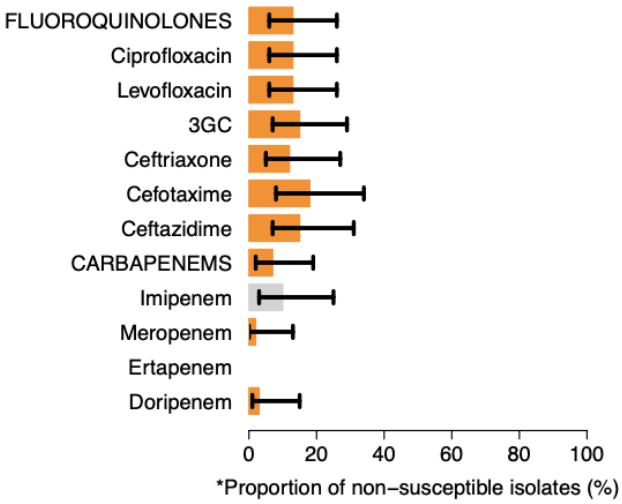
Section [2]: Isolate–based surveillance report

Blood: *Streptococcus pneumoniae* (No. of patients = 3)



Antibiotic agent	% NS (n)	95% CI
Penicillin G	33% (1/3)	6%–79%
Oxacillin	33% (1/3)	6%–79%
Co–trimoxazole	50% (1/2)	9%–91%
3GC	33% (1/3)	6%–79%
Ceftriaxone	0% (0/2)	0%–66%
Cefotaxime	0% (0/2)	0%–66%
Erythromycin	NA	–
Clindamycin	100% (1/1)	21%–100%
Levofloxacin	0% (0/2)	0%–66%

Blood: *Salmonella* spp. (No. of patients = 45)

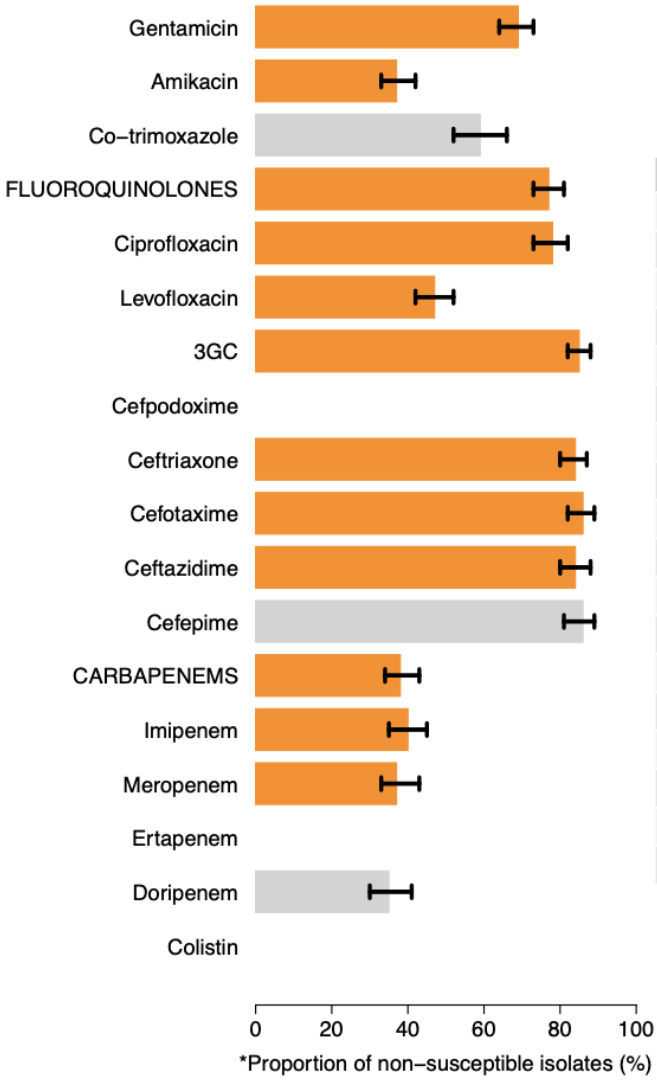


Antibiotic agent	% NS (n)	95% CI
FLUOROQUINOLONES	13% (6/45)	6%–26%
Ciprofloxacin	13% (6/45)	6%–26%
Levofloxacin	13% (6/45)	6%–26%
3GC	15% (6/40)	7%–29%
Ceftriaxone	12% (4/34)	5%–27%
Cefotaxime	18% (6/34)	8%–34%
Ceftazidime	15% (5/33)	7%–31%
CARBAPENEMS	7% (3/43)	2%–19%
Imipenem	10% (3/31)	3%–25%
Meropenem	2% (1/40)	0%–13%
Ertapenem	NA	–
Doripenem	3% (1/35)	1%–15%

*Proportion of non–susceptible isolates (% NS) represents the number of patients with blood culture positive for non–susceptible isolates (numerator) over the total number of patients with blood culture positive for the organism and the organism was tested for susceptibility against the antibiotic (denominator). The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period. Grey bars indicate that testing with the antibiotic occurred for less than 70% of the total number of blood culture positive for the organism.
CI = confidence interval; NA = Not available/reported/tested; 3GC = 3rd–generation cephalosporin;
FLUOROQUINOLONES: ciprofloxacin or levofloxacin; CARBAPENEMS: imipenem, meropenem, ertapenem or doripenem

Section [2]: Isolate–based surveillance report

Blood: ***Klebsiella pneumoniae*** ***(No. of patients = 441)***



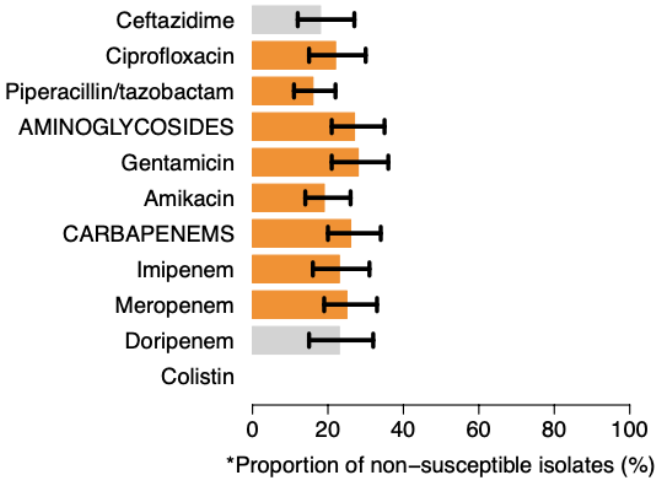
Antibiotic agent	% NS (n)	95% CI
Gentamicin	69% (268/388)	64%–73%
Amikacin	37% (150/402)	33%–42%
Co–trimoxazole	59% (115/194)	52%–66%
FLUOROQUINOLONES	77% (291/376)	73%–81%
Ciprofloxacin	78% (279/358)	73%–82%
Levofloxacin	47% (165/351)	42%–52%
3GC	85% (371/434)	82%–88%
Cefpodoxime	NA	–
Ceftriaxone	84% (310/369)	80%–87%
Cefotaxime	86% (287/334)	82%–89%
Ceftazidime	84% (277/330)	80%–88%
Cefepime	86% (240/280)	81%–89%
CARBAPENEMS	38% (160/419)	34%–43%
Imipenem	40% (126/315)	35%–45%
Meropenem	37% (134/358)	33%–43%
Ertapenem	NA	–
Doripenem	35% (99/284)	30%–41%
Colistin	NA	–

*Proportion of non–susceptible isolates (% NS) represents the number of patients with blood culture positive for non–susceptible isolates (numerator) over the total number of patients with blood culture positive for the organism and the organism was tested for susceptibility against the antibiotic (denominator). The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period. Grey bars indicate that testing with the antibiotic occurred for less than 70% of the total number of blood culture positive for the organism.
CI = confidence interval; NA = Not available/reported/tested; 3GC = 3rd–generation cephalosporin; FLUOROQUINOLONES: ciprofloxacin or levofloxacin; CARBAPENEMS: imipenem, meropenem, ertapenem or doripenem

Section [2]: Isolate–based surveillance report

Blood: *Pseudomonas aeruginosa*

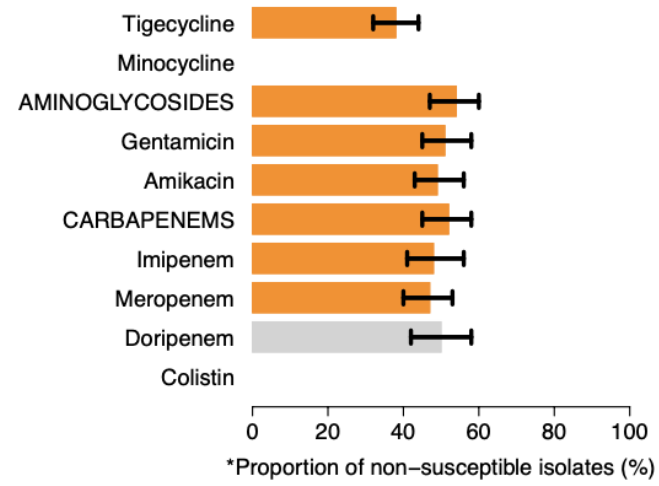
(No. of patients = 160)



Antibiotic agent	% NS (n)	95% CI
Ceftazidime	18% (19/105)	12%–27%
Ciprofloxacin	22% (27/125)	15%–30%
Piperacillin/tazobactam	16% (23/147)	11%–22%
AMINOGLYCOSIDES	27% (42/153)	21%–35%
Gentamicin	28% (38/136)	21%–36%
Amikacin	19% (28/145)	14%–26%
CARBAPENEMS	26% (40/153)	20%–34%
Imipenem	23% (28/122)	16%–31%
Meropenem	25% (33/131)	19%–33%
Doripenem	23% (22/97)	15%–32%
Colistin	NA	–

Blood: *Acinetobacter* spp.

(No. of patients = 249)



Antibiotic agent	% NS (n)	95% CI
Tigecycline	38% (83/220)	32%–44%
Minocycline	NA	–
AMINOGLYCOSIDES	54% (125/232)	47%–60%
Gentamicin	51% (107/208)	45%–58%
Amikacin	49% (108/219)	43%–56%
CARBAPENEMS	52% (120/233)	45%–58%
Imipenem	48% (85/176)	41%–56%
Meropenem	47% (94/202)	40%–53%
Doripenem	50% (77/154)	42%–58%
Colistin	NA	–

*Proportion of non–susceptible isolates (% NS) represents the number of patients with blood culture positive for non–susceptible isolates (numerator) over the total number of patients with blood culture positive for the organism and the organism was tested for susceptibility against the antibiotic (denominator). The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period. Grey bars indicate that testing with the antibiotic occurred for less than 70% of the total number of blood culture positive for the organism.
CI = confidence interval; NA = Not available/reported/tested; AMINOGLYCOSIDES: either gentamicin or amikacin; CARBAPENEMS: imipenem, meropenem, ertapenem or doripenem

Section [3]: Isolate–based surveillance report with stratification by infection origin

Introduction

An isolate–based surveillance report with stratification by origin of infection is generated only if admission date data are available in the raw data file(s) with the appropriate specification in the data dictionaries.

Stratification by origin of infection is used as a proxy to define where the bloodstream infection (BSI) was contracted (hospital versus community).

The definitions of infection origin proposed by the WHO GLASS are used. In brief, community–origin BSI is defined as patients in the hospital for less than or equal to two calendar days when the first specimen culture postive for the pathogen was taken. Hospital–origin BSI is defined as patients admitted for more than two calendar days when the first specimen culture positive for the pathogen was taken.

Results:

The data included in the analysis to generate the report had:

Sample collection dates ranged from ***01 Jan 2019*** to ***31 Dec 2020***

**Number of patients with blood culture positive for pathogen under the survey:*

1432 patients

***Number of patients with community–origin BSI:*

418 patients

***Number of patients with hospital–origin BSI:*

1014 patients

****Number of patients with unknown infection of origin status:*

0 patients

Organism	Number of patients with blood culture positive for the organism	Community –origin**	Hospital –origin**	Unknown origin***
Staphylococcus aureus	***212***	***82***	***130***	***0***
***Enterococcus* spp.**	***74***	***17***	***57***	***0***
Streptococcus pneumoniae	***3***	***3***	***0***	***0***
***Salmonella* spp.**	***45***	***27***	***18***	***0***
Escherichia coli	***248***	***111***	***137***	***0***
Klebsiella pneumoniae	***441***	***65***	***376***	***0***
Pseudomonas aeruginosa	***160***	***60***	***100***	***0***
***Acinetobacter* spp.**	***249***	***53***	***196***	***0***
Total:	**1432**	***418***	***1014***	***0***

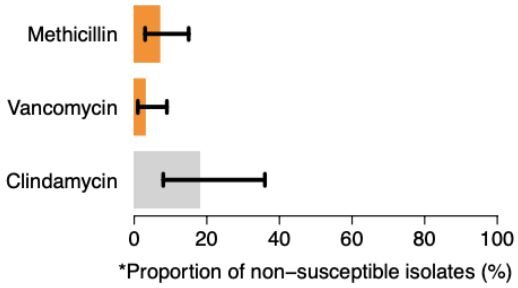
Note:
NA= Not applicable (hospital admission date or infection origin data are not available)

*Only the first isolate for each patient per specimen type per pathogen under the reporting period is included in the analysis. Please refer to Section [2] for details on how this number was calculated from the raw microbiology_data file.
**The definitions of infection origin proposed by the WHO GLASS is used. In brief, community–origin BSI was defined as patients in the hospital for less than or equal to two calendar days when the first blood culture positive for the pathogen was taken. Hospital–origin BSI was defined as patients admitted for more than two calendar days when the first specimen culture positive for the pathogen was taken.
Please refer to the 'Methods' section for more details on the definitions used.
***Unknown origin could be because admission date data are not available or the patient was not hospitalised.

The following figures and tables below show the proportion of patients with blood culture positive for antimicrobial non–susceptible isolates stratified by infection of origin.

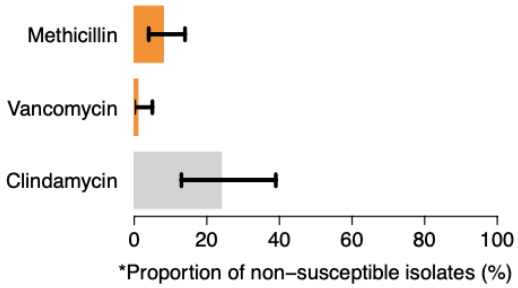
Section [3]: Isolate–based surveillance report with stratification by infection origin

Blood: ***Staphylococcus aureus*** **Community–origin** ***(No. of patients = 82)***



Antibiotic agent	% NS (n)	95% CI
Methicillin	7% (6/82)	3%–15%
Vancomycin	3% (2/74)	1%–9%
Clindamycin	18% (5/28)	8%–36%

Blood: ***Staphylococcus aureus*** **Hospital–origin** ***(No. of patients = 130)***

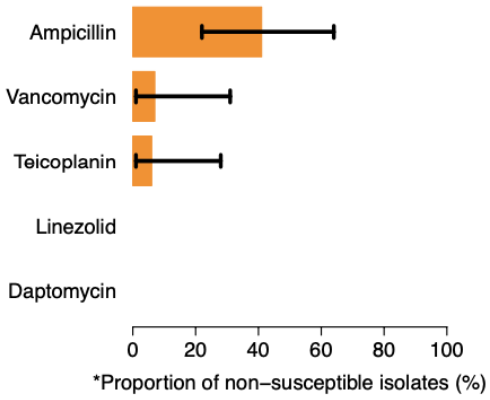


Antibiotic agent	% NS (n)	95% CI
Methicillin	8% (10/127)	4%–14%
Vancomycin	1% (1/119)	0%–5%
Clindamycin	24% (10/42)	13%–39%

*Proportion of non–susceptible isolates (% NS) represents the number of patients with blood culture positive for non–susceptible isolates (numerator) over the total number of patients with blood culture positive for the organism and the organism was tested for susceptibility against the antibiotic (denominator). The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period. Grey bars indicate that testing with the antibiotic occurred for less than 70% of the total number of patients with blood culture positive for the organism.
CI = confidence interval; NA = Not available/reported/tested; Methicillin: methicillin, oxacillin, or cefoxitin

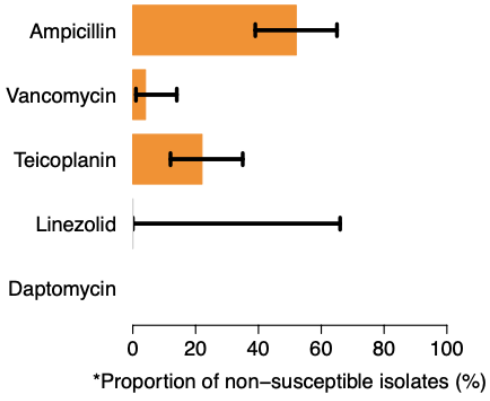
Section [3]: Isolate–based surveillance report with stratification by infection origin

Blood: ***Enterococcus*** **spp.** **Community–origin** ***(No. of patients = 17)***



Antibiotic agent	% NS (n)	95% CI
Ampicillin	41% (7/17)	22%–64%
Vancomycin	7% (1/14)	1%–31%
Teicoplanin	6% (1/16)	1%–28%
Linezolid	NA	–
Daptomycin	NA	–

Blood: ***Enterococcus*** **spp.** **Hospital–origin** ***(No. of patients = 57)***

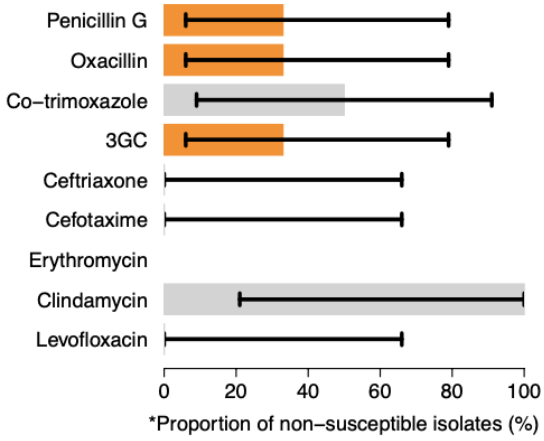


Antibiotic agent	% NS (n)	95% CI
Ampicillin	52% (28/54)	39%–65%
Vancomycin	4% (2/47)	1%–14%
Teicoplanin	22% (11/51)	12%–35%
Linezolid	0% (0/2)	0%–66%
Daptomycin	NA	–

*Proportion of non–susceptible isolates (% NS) represents the number of patients with blood culture positive for non–susceptible isolates (numerator) over the total number of patients with blood culture positive for the organism and the organism was tested for susceptibility against the antibiotic (denominator). The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period. Grey bars indicate that testing with the antibiotic occurred for less than 70% of the total number of patients with blood culture positive for the organism.
CI = confidence interval; NA = Not available/reported/tested; Methicillin: methicillin, oxacillin, or cefoxitin

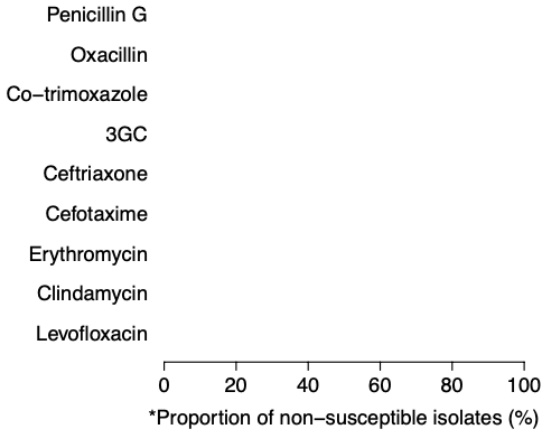
Section [3]: Isolate–based surveillance report with stratification by infection origin

Blood: ***Streptococcus pneumoniae*** **Community–origin** ***(No. of patients = 3)***



Antibiotic agent	% NS (n)	95% CI
Penicillin G	33% (1/3)	6%–79%
Oxacillin	33% (1/3)	6%–79%
Co–trimoxazole	50% (1/2)	9%–91%
3GC	33% (1/3)	6%–79%
Ceftriaxone	0% (0/2)	0%–66%
Cefotaxime	0% (0/2)	0%–66%
Erythromycin	NA	–
Clindamycin	100% (1/1)	21%–100%
Levofloxacin	0% (0/2)	0%–66%

Blood: ***Streptococcus pneumoniae*** **Hospital–origin** ***(No. of patients = 0)***

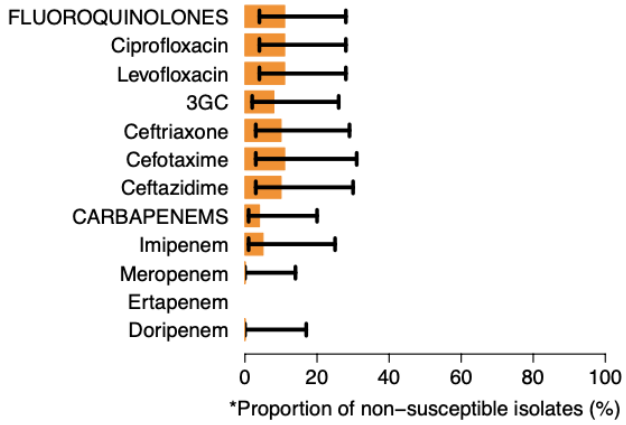


Antibiotic agent	% NS (n)	95% CI
Penicillin G	NA	–
Oxacillin	NA	–
Co–trimoxazole	NA	–
3GC	NA	–
Ceftriaxone	NA	–
Cefotaxime	NA	–
Erythromycin	NA	–
Clindamycin	NA	–
Levofloxacin	NA	–

*Proportion of non–susceptible isolates (% NS) represents the number of patients with blood culture positive for non–susceptible isolates (numerator) over the total number of patients with blood culture positive for the organism and the organism was tested for susceptibility against the antibiotic (denominator). The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period. Grey bars indicate that testing with the antibiotic occurred for less than 70% of the total number of blood culture positive for the organism.
CI = confidence interval; NA = Not available/reported/tested; 3GC = 3rd–generation cephalosporin; FLUOROQUINOLONES: ciprofloxacin or levofloxacin; CARBAPENEMS: imipenem, meropenem, ertapenem or doripenem

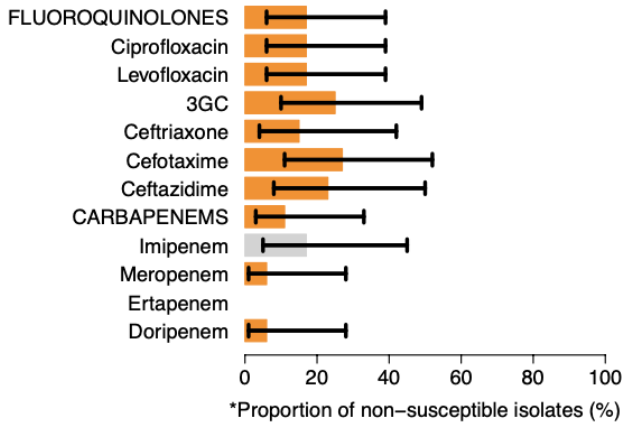
Section [3]: Isolate–based surveillance report with stratification by infection origin

Blood: *Salmonella* spp. **Community–origin *(No. of patients = 27)***



Antibiotic agent	% NS (n)	95% CI
FLUOROQUINOLONES	11% (3/27)	4%–28%
Ciprofloxacin	11% (3/27)	4%–28%
Levofloxacin	11% (3/27)	4%–28%
3GC	8% (2/24)	2%–26%
Ceftriaxone	10% (2/21)	3%–29%
Cefotaxime	11% (2/19)	3%–31%
Ceftazidime	10% (2/20)	3%–30%
CARBAPENEMS	4% (1/25)	1%–20%
Imipenem	5% (1/19)	1%–25%
Meropenem	0% (0/24)	0%–14%
Ertapenem	NA	–
Doripenem	0% (0/19)	0%–17%

Blood: *Salmonella* spp. **Hospital–origin *(No. of patients = 18)***

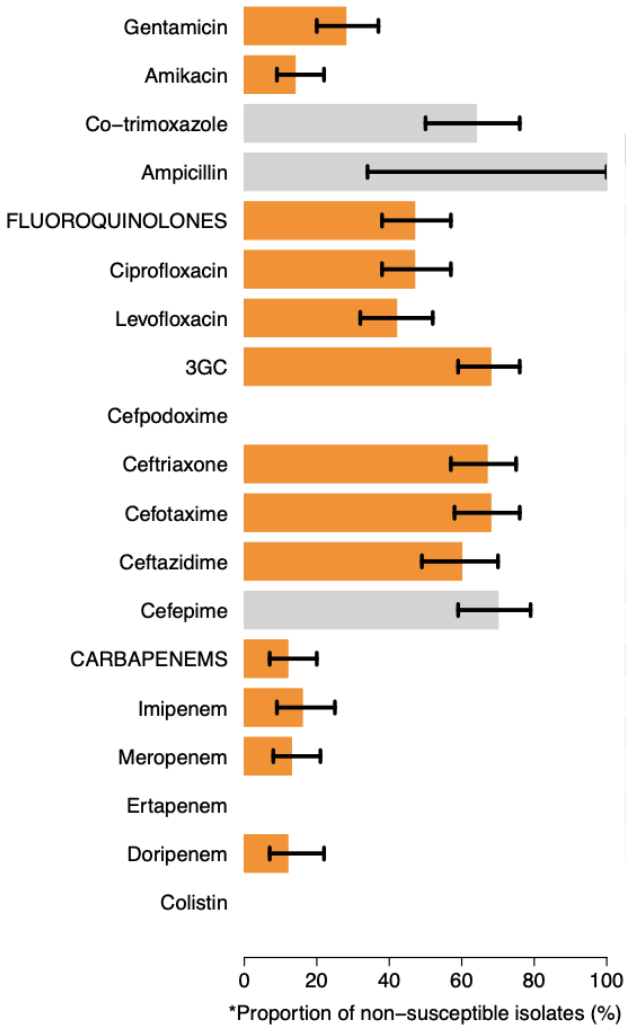


Antibiotic agent	% NS (n)	95% CI
FLUOROQUINOLONES	17% (3/18)	6%–39%
Ciprofloxacin	17% (3/18)	6%–39%
Levofloxacin	17% (3/18)	6%–39%
3GC	25% (4/16)	10%–49%
Ceftriaxone	15% (2/13)	4%–42%
Cefotaxime	27% (4/15)	11%–52%
Ceftazidime	23% (3/13)	8%–50%
CARBAPENEMS	11% (2/18)	3%–33%
Imipenem	17% (2/12)	5%–45%
Meropenem	6% (1/16)	1%–28%
Ertapenem	NA	–
Doripenem	6% (1/16)	1%–28%

*Proportion of non–susceptible isolates (% NS) represents the number of patients with blood culture positive for non–susceptible isolates (numerator) over the total number of patients with blood culture positive for the organism and the organism was tested for susceptibility against the antibiotic (denominator). The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period. Grey bars indicate that testing with the antibiotic occurred for less than 70% of the total number of blood culture positive for the organism.
CI = confidence interval; NA = Not available/reported/tested; 3GC = 3rd–generation cephalosporin; FLUOROQUINOLONES: ciprofloxacin or levofloxacin; CARBAPENEMS: imipenem, meropenem, ertapenem or doripenem

Section [3]: Isolate–based surveillance report with stratification by infection origin

Blood: ***Escherichia coli*** **Community–origin** ***(No. of patients = 111)***

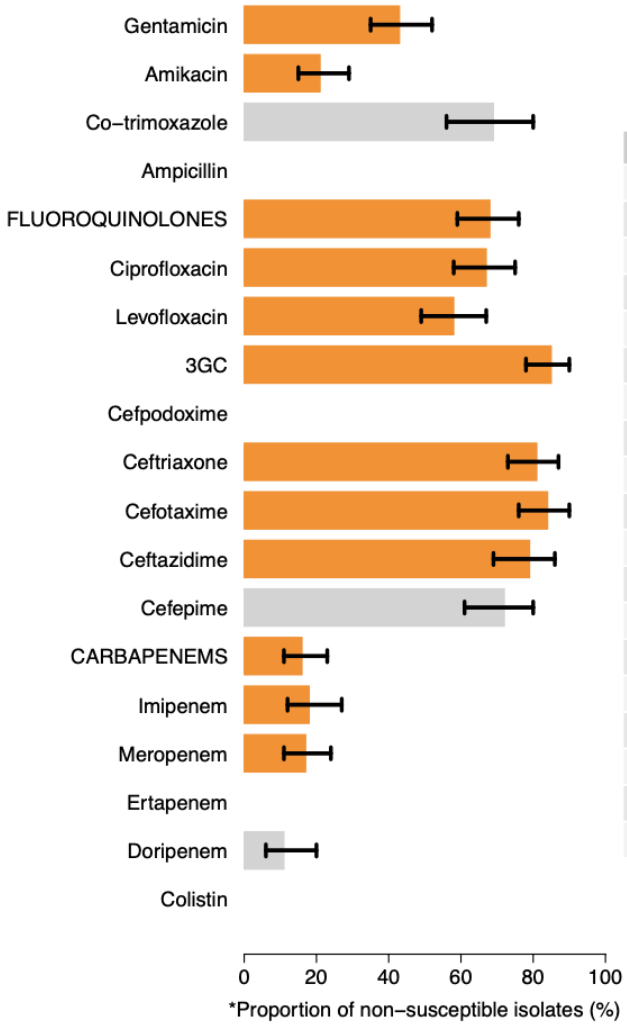


Antibiotic agent	% NS (n)	95% CI
Gentamicin	28% (28/101)	20%–37%
Amikacin	14% (15/105)	9%–22%
Co–trimoxazole	64% (30/47)	50%–76%
Ampicillin	100% (2/2)	34%–100%
FLUOROQUINOLONES	47% (49/104)	38%–57%
Ciprofloxacin	47% (48/102)	38%–57%
Levofloxacin	42% (40/96)	32%–52%
3GC	68% (76/111)	59%–76%
Cefpodoxime	NA	–
Ceftriaxone	67% (62/93)	57%–75%
Cefotaxime	68% (66/97)	58%–76%
Ceftazidime	60% (50/83)	49%–70%
Cefepime	70% (54/77)	59%–79%
CARBAPENEMS	12% (13/107)	7%–20%
Imipenem	16% (13/83)	9%–25%
Meropenem	13% (12/93)	8%–21%
Ertapenem	NA	–
Doripenem	12% (10/80)	7%–22%
Colistin	NA	–

*Proportion of non–susceptible isolates (% NS) represents the number of patients with blood culture positive for non–susceptible isolates (numerator) over the total number of patients with blood culture positive for the organism and the organism was tested for susceptibility against the antibiotic (denominator). The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period. Grey bars indicate that testing with the antibiotic occurred for less than 70% of the total number of blood culture positive for the organism.
CI = confidence interval; NA = Not available/reported/tested; 3GC = 3rd–generation cephalosporin; FLUOROQUINOLONES: ciprofloxacin or levofloxacin; CARBAPENEMS: imipenem, meropenem, ertapenem or doripenem

Section [3]: Isolate–based surveillance report with stratification by infection origin

Blood: ***Escherichia coli*** **Hospital–origin** ***(No. of patients = 137)***

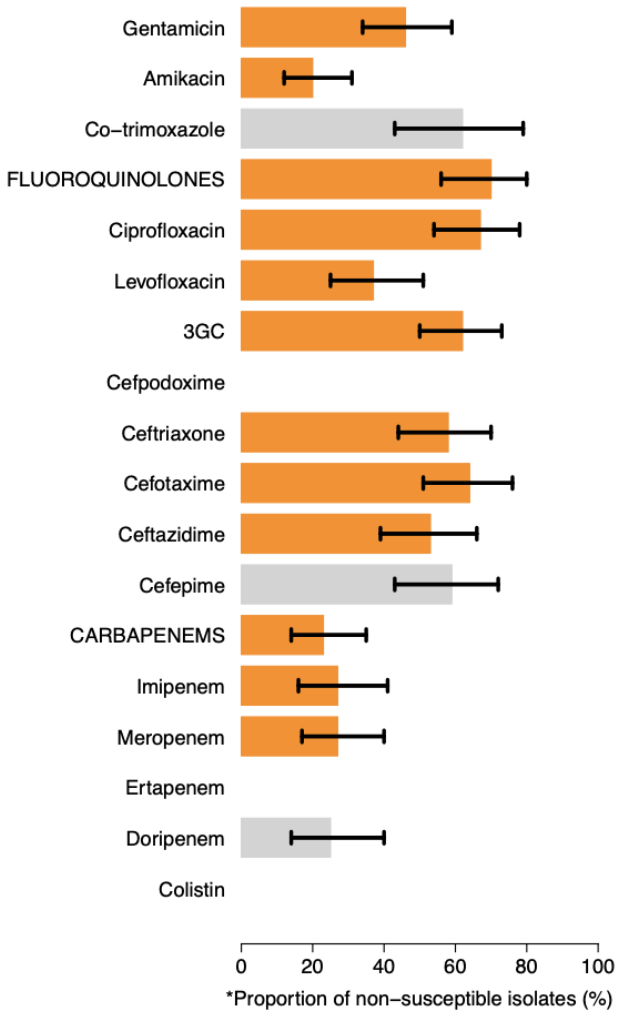


Antibiotic agent	% NS (n)	95% CI
Gentamicin	43% (52/120)	35%–52%
Amikacin	21% (26/125)	15%–29%
Co–trimoxazole	69% (38/55)	56%–80%
Ampicillin	NA	–
FLUOROQUINOLONES	68% (81/119)	59%–76%
Ciprofloxacin	67% (78/117)	58%–75%
Levofloxacin	58% (63/108)	49%–67%
3GC	85% (111/131)	78%–90%
Cefpodoxime	NA	–
Ceftriaxone	81% (91/112)	73%–87%
Cefotaxime	84% (89/106)	76%–90%
Ceftazidime	79% (77/98)	69%–86%
Cefepime	72% (61/85)	61%–80%
CARBAPENEMS	16% (21/132)	11%–23%
Imipenem	18% (19/103)	12%–27%
Meropenem	17% (19/115)	11%–24%
Ertapenem	NA	–
Doripenem	11% (9/82)	6%–20%
Colistin	NA	–

*Proportion of non–susceptible isolates (% NS) represents the number of patients with blood culture positive for non–susceptible isolates (numerator) over the total number of patients with blood culture positive for the organism and the organism was tested for susceptibility against the antibiotic (denominator). The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period. Grey bars indicate that testing with the antibiotic occurred for less than 70% of the total number of blood culture positive for the organism.
CI = confidence interval; NA = Not available/reported/tested; 3GC = 3rd–generation cephalosporin; FLUOROQUINOLONES: ciprofloxacin or levofloxacin; CARBAPENEMS: imipenem, meropenem, ertapenem or doripenem

Section [3]: Isolate–based surveillance report with stratification by infection origin

Blood: ***Klebsiella pneumoniae*** **Community–origin** ***(No. of patients = 65)***

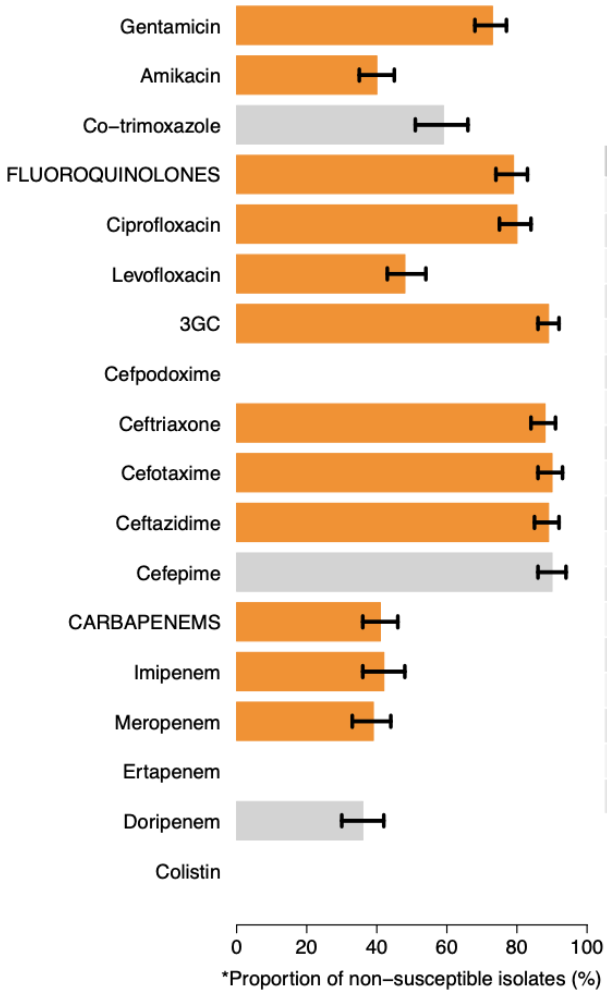


Antibiotic agent	% NS (n)	95% CI
Gentamicin	46% (26/56)	34%–59%
Amikacin	20% (12/61)	12%–31%
Co–trimoxazole	62% (15/24)	43%–79%
FLUOROQUINOLONES	70% (37/53)	56%–80%
Ciprofloxacin	67% (35/52)	54%–78%
Levofloxacin	37% (18/49)	25%–51%
3GC	62% (40/64)	50%–73%
Cefpodoxime	NA	–
Ceftriaxone	58% (30/52)	44%–70%
Cefotaxime	64% (34/53)	51%–76%
Ceftazidime	53% (26/49)	39%–66%
Cefepime	59% (24/41)	43%–72%
CARBAPENEMS	23% (14/61)	14%–35%
Imipenem	27% (12/45)	16%–41%
Meropenem	27% (14/52)	17%–40%
Ertapenem	NA	–
Doripenem	25% (10/40)	14%–40%
Colistin	NA	–

*Proportion of non–susceptible isolates (% NS) represents the number of patients with blood culture positive for non–susceptible isolates (numerator) over the total number of patients with blood culture positive for the organism and the organism was tested for susceptibility against the antibiotic (denominator). The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period. Grey bars indicate that testing with the antibiotic occurred for less than 70% of the total number of blood culture positive for the organism.
CI = confidence interval; NA = Not available/reported/tested; 3GC = 3rd–generation cephalosporin; FLUOROQUINOLONES: ciprofloxacin or levofloxacin; CARBAPENEMS: imipenem, meropenem, ertapenem or doripenem

Section [3]: Isolate–based surveillance report with stratification by infection origin

Blood: ***Klebsiella pneumoniae*** **Hospital–origin** ***(No. of patients = 376)***

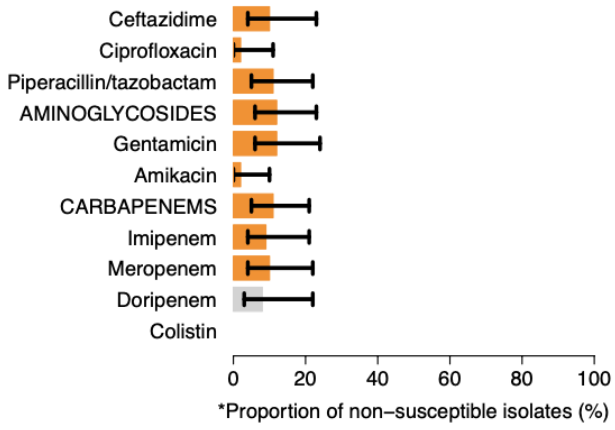


Antibiotic agent	% NS (n)	95% CI
Gentamicin	73% (242/332)	68%–77%
Amikacin	40% (136/341)	35%–45%
Co–trimoxazole	59% (100/170)	51%–66%
FLUOROQUINOLONES	79% (254/323)	74%–83%
Ciprofloxacin	80% (244/306)	75%–84%
Levofloxacin	48% (146/302)	43%–54%
3GC	89% (331/370)	86%–92%
Cefpodoxime	NA	–
Ceftriaxone	88% (280/317)	84%–91%
Cefotaxime	90% (252/280)	86%–93%
Ceftazidime	89% (251/281)	85%–92%
Cefepime	90% (216/239)	86%–94%
CARBAPENEMS	41% (145/358)	36%–46%
Imipenem	42% (113/271)	36%–48%
Meropenem	39% (119/307)	33%–44%
Ertapenem	NA	–
Doripenem	36% (87/243)	30%–42%
Colistin	NA	–

*Proportion of non–susceptible isolates (% NS) represents the number of patients with blood culture positive for non–susceptible isolates (numerator) over the total number of patients with blood culture positive for the organism and the organism was tested for susceptibility against the antibiotic (denominator). The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period. Grey bars indicate that testing with the antibiotic occurred for less than 70% of the total number of blood culture positive for the organism.
CI = confidence interval; NA = Not available/reported/tested; 3GC = 3rd–generation cephalosporin; FLUOROQUINOLONES: ciprofloxacin or levofloxacin; CARBAPENEMS: imipenem, meropenem, ertapenem or doripenem

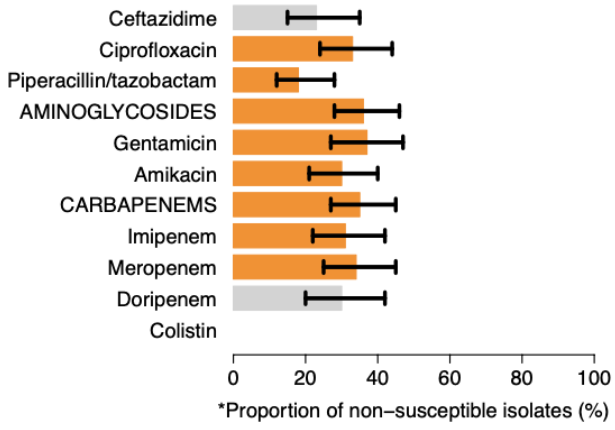
Section [3]: Isolate–based surveillance report with stratification by infection origin

Blood: ***Pseudomonas aeruginosa*** **Community–origin** ***(No. of patients = 60)***



Antibiotic agent	% NS (n)	95% CI
Ceftazidime	10% (4/40)	4%–23%
Ciprofloxacin	2% (1/46)	0%–11%
Piperacillin/tazobactam	11% (6/55)	5%–22%
AMINOGLYCOSIDES	12% (7/57)	6%–23%
Gentamicin	12% (6/49)	6%–24%
Amikacin	2% (1/54)	0%–10%
CARBAPENEMS	11% (6/57)	5%–21%
Imipenem	9% (4/45)	4%–21%
Meropenem	10% (5/49)	4%–22%
Doripenem	8% (3/36)	3%–22%
Colistin	NA	–

Blood: ***Pseudomonas aeruginosa*** **Hospital–origin** ***(No. of patients = 100)***

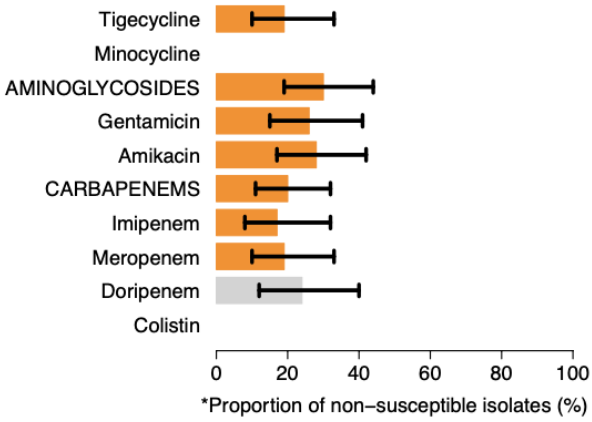


Antibiotic agent	% NS (n)	95% CI
Ceftazidime	23% (15/65)	15%–35%
Ciprofloxacin	33% (26/79)	24%–44%
Piperacillin/tazobactam	18% (17/92)	12%–28%
AMINOGLYCOSIDES	36% (35/96)	28%–46%
Gentamicin	37% (32/87)	27%–47%
Amikacin	30% (27/91)	21%–40%
CARBAPENEMS	35% (34/96)	27%–45%
Imipenem	31% (24/77)	22%–42%
Meropenem	34% (28/82)	25%–45%
Doripenem	30% (18/61)	20%–42%
Colistin	NA	–

*Proportion of non–susceptible isolates (% NS) represents the number of patients with blood culture positive for non–susceptible isolates (numerator) over the total number of patients with blood culture positive for the organism and the organism was tested for susceptibility against the antibiotic (denominator). The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period. Grey bars indicate that testing with the antibiotic occurred for less than 70% of the total number of blood culture positive for the organism.
CI = confidence interval; NA = Not available/reported/tested; AMINOGLYCOSIDES: either gentamicin or amikacin; CARBAPENEMS: imipenem, meropenem, ertapenem or doripenem

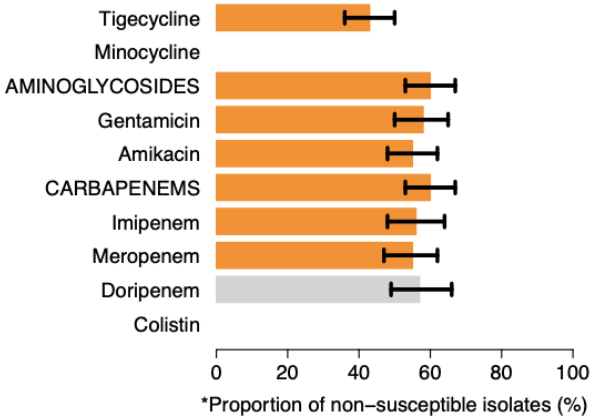
Section [3]: Isolate–based surveillance report with stratification by infection origin

Blood: ***Acinetobacter*** **spp.** **Community–origin** ***(No. of patients = 53)***



Antibiotic agent	% NS (n)	95% CI
Tigecycline	19% (9/47)	10%–33%
Minocycline	NA	–
AMINOGLYCOSIDES	30% (15/50)	19%–44%
Gentamicin	26% (11/42)	15%–41%
Amikacin	28% (13/47)	17%–42%
CARBAPENEMS	20% (10/51)	11%–32%
Imipenem	17% (6/36)	8%–32%
Meropenem	19% (9/47)	10%–33%
Doripenem	24% (8/34)	12%–40%
Colistin	NA	–

Blood: ***Acinetobacter*** **spp.** **Hospital–origin** ***(No. of patients = 196)***



Antibiotic agent	% NS (n)	95% CI
Tigecycline	43% (74/173)	36%–50%
Minocycline	NA	–
AMINOGLYCOSIDES	60% (110/182)	53%–67%
Gentamicin	58% (96/166)	50%–65%
Amikacin	55% (95/172)	48%–62%
CARBAPENEMS	60% (110/182)	53%–67%
Imipenem	56% (79/140)	48%–64%
Meropenem	55% (84/154)	47%–62%
Doripenem	57% (69/120)	49%–66%
Colistin	NA	–

*Proportion of non–susceptible isolates (% NS) represents the number of patients with blood culture positive for non–susceptible isolates (numerator) over the total number of patients with blood culture positive for the organism and the organism was tested for susceptibility against the antibiotic (denominator). The AMASS application de–duplicated the data by including only the first isolate per patient per specimen type per evaluation period. Grey bars indicate that testing with the antibiotic occurred for less than 70% of the total number of blood culture positive for the organism.
CI = confidence interval; NA = Not available/reported/tested; AMINOGLYCOSIDES: either gentamicin or amikacin; CARBAPENEMS: imipenem, meropenem, ertapenem or doripenem

Section [4]: Sample–based surveillance report

Introduction
A sample–based surveillance report is generated if data of culture negative is available.

The sample–based approach involves the collection of data on all blood samples taken for microbiological testing and includes information on the number of positive blood samples for a specific specimen type (both pathogens under the survey and other bacteria) as well as number of negative (no microbial growth) samples. After removal of duplicate results and assuming that routine blood culture testing is applied systematically, we can use the number of tested patients as a proxy for a number of patients with new cases of bloodstream infection (BSI).

Results:
The microbiology_data file had:

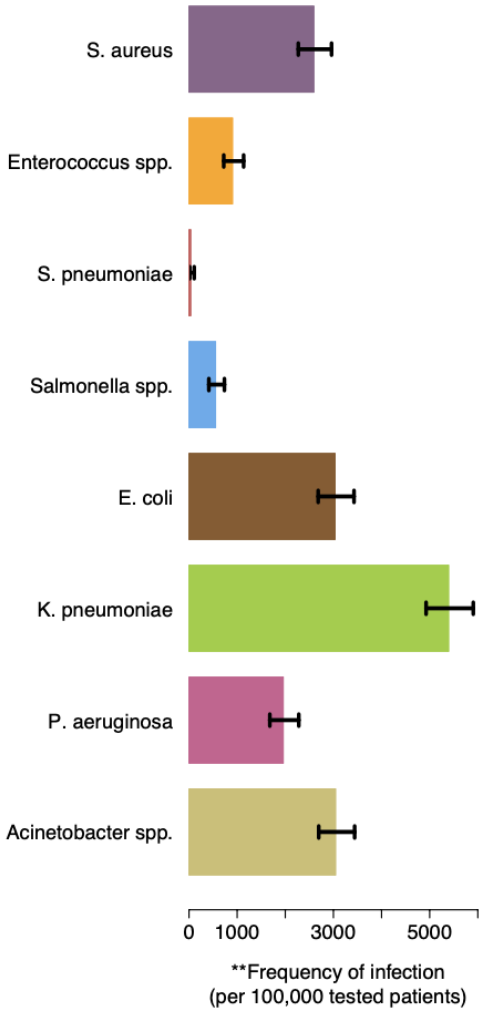
Specimen collection dates ranged from ***01 Jan 2019 to 31 Dec 2020***
Number of records on blood specimen collected within the above date range:
17901 blood specimen records
**Number of patients sampled for blood culture within the above date range:*
8175 patients sampled for blood culture

Note:
*Number of patients sampled for blood culture is used as denominator to estimate the frequency of infections per 100,000 tested patients

The following figures show the frequncy of infections for patients with blood culture tested.

Section [4]: Sample–based surveillance report

Blood: *Pathogens under this surveillance ***(No. of patients = 8175)***

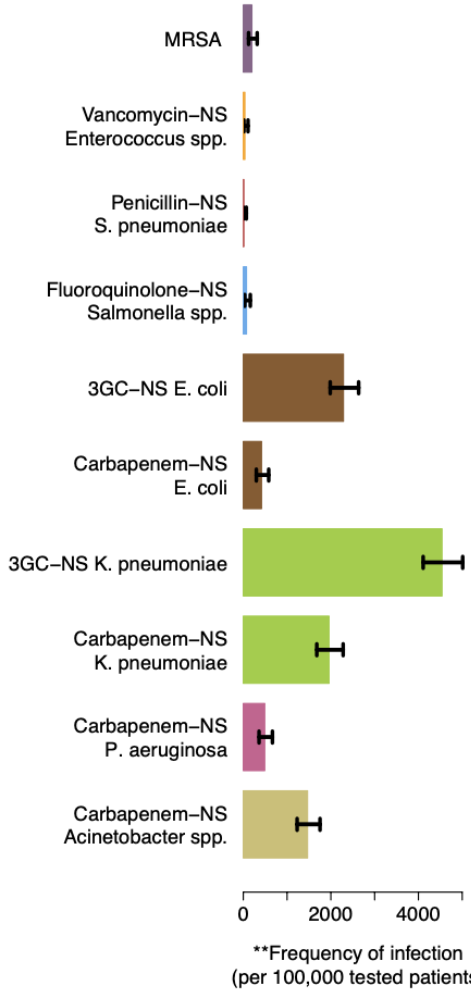


Organisms	**Frequency (95% CI)
S. aureus	2594 (2271–2961)
Enterococcus spp.	906 (722–1135)
S. pneumoniae	37 (13–108)
Salmonella spp.	551 (412–736)
E. coli	3034 (2684–3429)
K. pneumoniae	5395 (4926–5906)
P. aeruginosa	1958 (1679–2281)
Acinetobacter spp.	3046 (2695–3442)

*We apologise that the bacteria name in the table and in the figure are not written in italic. This is because of the R command we used. We will improve this in the next version.
**Frequency of infection per 100,000 tested patients represents the number of patients with blood culture positive for a pathogen (numerator) over the total number of tested patients (denominator). The AMASS application de–duplicates the data by included only the first isolate of each patient per specimen type per reporting period.
CI = confidence interval; NS = non–susceptible; NA = Not available/reported/tested; 3GC = 3rd–generation cephalosporin

Section [4]: Sample–based surveillance report

Blood: ***AMR pathogens under this surveillance** ***(No. of patients = 8175)***



Organism	**Frequency (95% CI)
MRSA	196 (121–318)
Vancomycin–NS Enterococcus spp.	37 (13–108)
Penicillin–NS S. pneumoniae	13 (3–70)
Fluoroquinolone–NS Salmonella spp.	74 (34–161)
3GC–NS E. coli	2288 (1986–2635)
Carbapenem–NS E. coli	416 (298–581)
3GC–NS K. pneumoniae	4539 (4108–5012)
Carbapenem–NS K. pneumoniae	1958 (1679–2281)
Carbapenem–NS P. aeruginosa	490 (360–666)
Carbapenem–NS Acinetobacter spp.	1468 (1230–1753)

*We apologise that the bacteria name in the table and in the figure are not written in italic. This is because of the R command we used. We will improve this in the next version.
**Frequency of infection per 100,000 tested patients represents the number of patients with blood culture positive for a pathogen (numerator) over the total number of tested patients (denominator). The AMASS application de–duplicates the data by included only the first isolate of each patient per specimen type per reporting period.
CI = confidence interval; NS = non–susceptible; NA = Not available/reported/tested; 3GC = 3rd–generation cephalosporin

Section [5]: Sample–based surveillance report with stratification by infection origin

Introduction

A sample–based surveillance report with stratification by origin of infection is generated only if data of culture negative is available and admission date or a variable containing the classification is available in the raw data file with the appropriate specification in the data dictionaries.

Results:

The data included in the analysis had:

Specimen collection dates ranged from ***01 Jan 2019 to 31 Dec 2020***

Number of records on blood specimen collected within the above date range:

17901 blood specimen records

Number of patients sampled for blood culture within the above date range:

8175 patients sampled for blood culture

4128 *patients had at least one admission having the first blood culture drawn within first 2 calendar days of hospital admission.*

This parameter is used as a denominators for frequency of community–origin bacteraemia (per 100,000 patients tested for blood culture on admission).

4736 *patients had at least one admission having the first blood culture drawn after 2 calendar days of hospital admission.*

This parameter is used as a denominators for frequency of hospital–origin bacteraemia (per 100,000 patients tested for blood culture for HAI).

0 *patients had a blood drawn for culture and with unknown origin of infection. Validation of this statistics is highly recommended.*

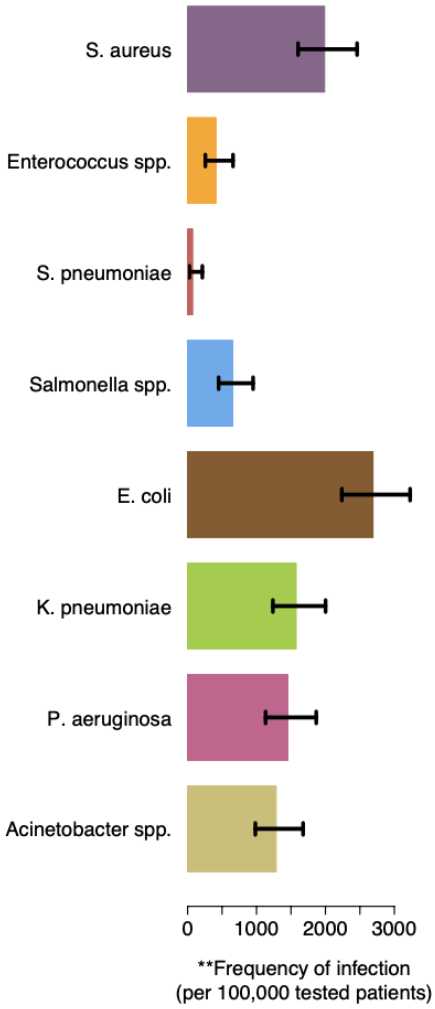
Note:

689 *patients had more than one admissions, of which at least one admission had the first blood culture drawn within the first 2 calendar days of hospital admission AND at least one admission had the first blood culture drawn after 2 calendar days of hospital admission.*

The following figures show the frequency of infections for patients with blood culture tested and stratified by infection origin, under this surveillance.

Section [5]: Sample–based surveillance report with stratification by infection origin

Blood: ***Pathogens** **Community–origin** ***(No. of patients = 4128)***

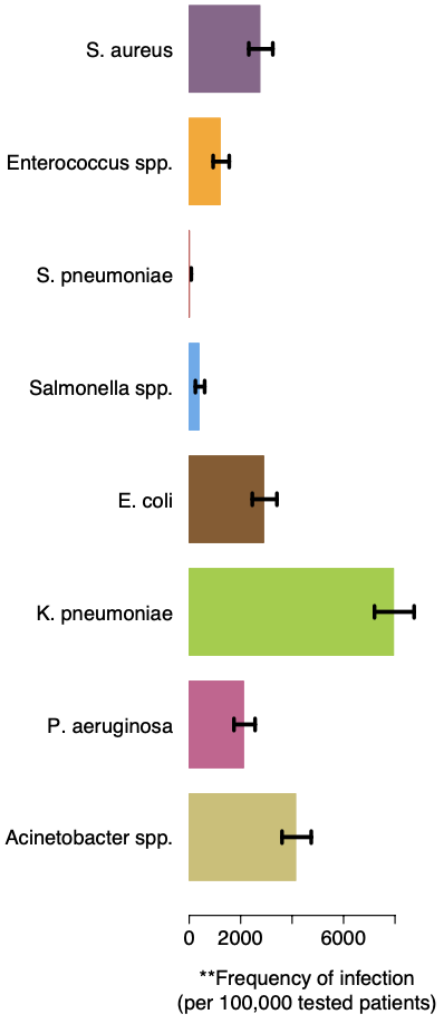


Organism	**Frequency (95% CI)
S. aureus	1987 (1604–2459)
Enterococcus spp.	412 (258–659)
S. pneumoniae	73 (25–214)
Salmonella spp.	655 (450–950)
E. coli	2689 (2238–3229)
K. pneumoniae	1575 (1238–2002)
P. aeruginosa	1454 (1131–1867)
Acinetobacter spp.	1284 (983–1676)

*We apologise that the bacteria name in the table and in the figure are not written in italic. This is because of the R command we used. We will improve this in the next version.
**Frequency of infection per 100,000 tested patients on admission represents the number of patients with blood culture positive for a pathogen (numerator) over the total number of tested population on admission (denominator). The AMASS application de–duplicates the data by included only the first isolate of each patient per specimen type per reporting period.
CI = confidence interval; NS = non–susceptible; NA = Not available/reported/tested; 3GC = 3rd–generation cephalosporin

Section [5]: Sample–based surveillance report with stratification by infection origin

Blood: ***Pathogens** **Hospital–origin** ***(No. of patients = 4736)***

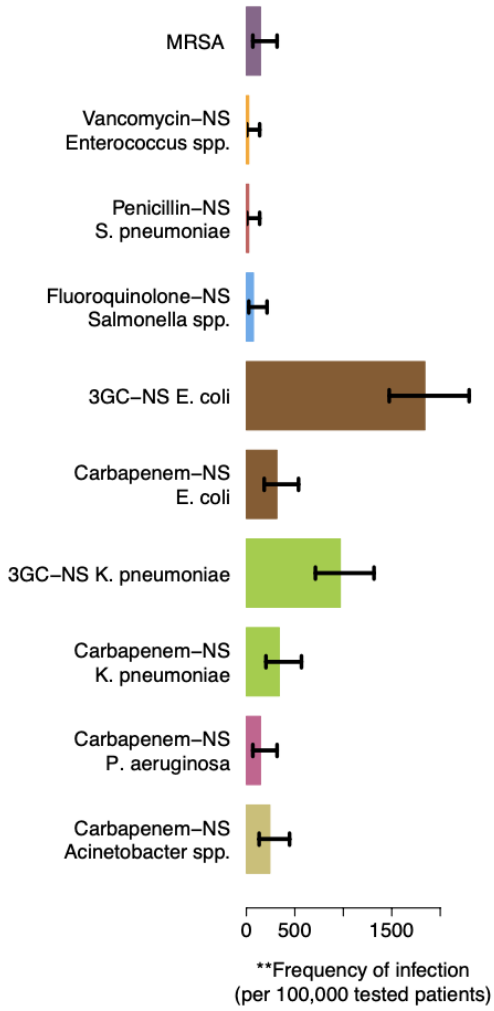


Organism	**Frequency (95% CI)
S. aureus	2745 (2317–3250)
Enterococcus spp.	1204 (931–1557)
S. pneumoniae	0 (0–82)
Salmonella spp.	381 (241–601)
E. coli	2893 (2453–3410)
K. pneumoniae	7940 (7203–8744)
P. aeruginosa	2112 (1740–2562)
Acinetobacter spp.	4139 (3608–4744)

*We apologise that the bacteria name in the table and in the figure are not written in italic. This is because of the R command we used. We will improve this in the next version.
**Frequency of infection per 100,000 tested population at risk of HAI represents the number of patients with blood culture positive for a pathogen (numerator) over the total number of tested population at risk of HAI (denominator). The AMASS application de–duplicates the data by included only the first isolate of each patient per specimen type per reporting period.
CI = confidence interval; NS = non–susceptible; NA = Not available/reported/tested; 3GC = 3rd–generation cephalosporin

Section [5]: Sample–based surveillance report with stratification by infection origin

Blood: ***AMR pathogens** **Community–origin** ***(No. of patients = 4128)***

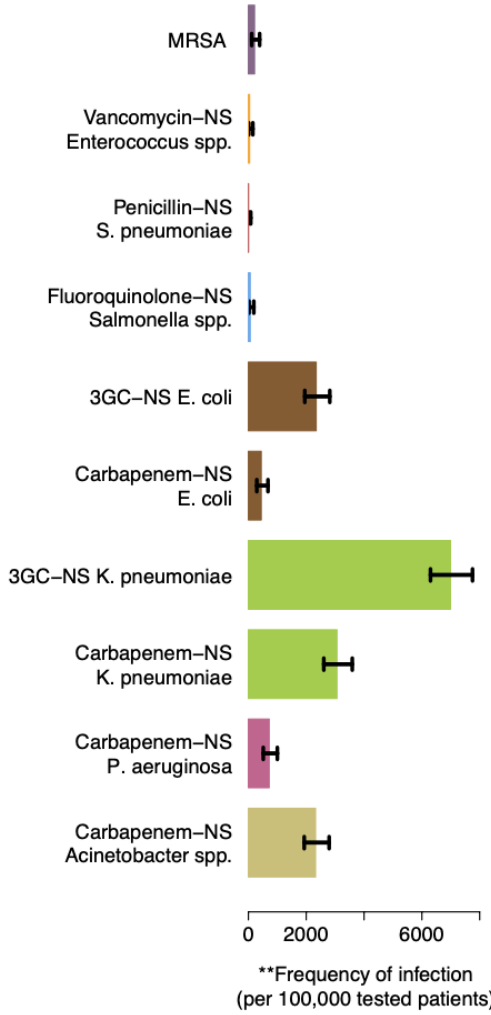


Organism	**Frequency (95% CI)
MRSA	146 (67–317)
Vancomycin–NS Enterococcus spp.	25 (5–138)
Penicillin–NS S. pneumoniae	25 (5–138)
Fluoroquinolone–NS Salmonella spp.	73 (25–214)
3GC–NS E. coli	1842 (1474–2299)
Carbapenem–NS E. coli	315 (185–539)
3GC–NS K. pneumoniae	969 (713–1317)
Carbapenem–NS K. pneumoniae	340 (203–569)
Carbapenem–NS P. aeruginosa	146 (67–317)
Carbapenem–NS Acinetobacter spp.	243 (132–446)

*We apologise that the bacteria name in the table and in the figure are not written in italic. This is because of the R command we used. We will improve this in the next version.
**Frequency of infection per 100,000 tested patients represents the number of patients with blood culture positive for a pathogen (numerator) over the total number of tested patients (denominator). The AMASS application de–duplicates the data by included only the first isolate of each patient per specimen type per reporting period.
CI = confidence interval; NS = non–susceptible; NA = Not available/reported/tested; 3GC = 3rd–generation cephalosporin

Section [5]: Sample–based surveillance report with stratification by infection origin

Blood: ***AMR pathogens** **Hospital–origin** ***(No. of patients = 4736)***



Organism	**Frequency (95% CI)
MRSA	212 (115–389)
Vancomycin–NS Enterococcus spp.	43 (12–154)
Penicillin–NS S. pneumoniae	0 (0–82)
Fluoroquinolone–NS Salmonella spp.	64 (22–187)
3GC–NS E. coli	2344 (1950–2815)
Carbapenem–NS E. coli	444 (291–677)
3GC–NS K. pneumoniae	6990 (6298–7751)
Carbapenem–NS K. pneumoniae	3062 (2608–3592)
Carbapenem–NS P. aeruginosa	718 (515–1002)
Carbapenem–NS Acinetobacter spp.	2323 (1931–2792)

*We apologise that the bacteria name in the table and in the figure are not written in italic. This is because of the R command we used. We will improve this in the next version.
**Frequency of infection per 100,000 tested patients represents the number of patients with blood culture positive for a pathogen (numerator) over the total number of tested patients (denominator). The AMASS application de–duplicates the data by included only the first isolate of each patient per specimen type per reporting period.
CI = confidence interval; NS = non–susceptible; NA = Not available/reported/tested; 3GC = 3rd–generation cephalosporin

Report [6] Mortality in AMR antimicrobial–susceptible infections

Not applicable because hospital_admission_data.csv file is not available, or in–hospital outcome (in hospital_admission_data.csv file) is not available.

Methods used by the AMASS application

Data source:
For each run (double–click on AMASS.bat file), the AMASS application used the microbiology data file (microbiology_data) and the hospital admission data file (hospital_admission_data) that were stored in the same folder as the application file. Hence, if the user would like to update, correct, revise or change the data, the data files in the folder should be updated before the AMASS.bat file is double–clicked again. A new report based on the updated data would then be generated.

Requirements:
– Computer with Microsoft Windows 7 or 10
AMASS may work in other versions of Microsoft Windows and other operating systems. However, thorough testing and adjustment have not been performed.
– AMASS.zip package file
The AMASS application is to be downloaded from http://www.amass.website, and unzipped to generate an AMASS folder that could be stored under any folder in the computer. The AMASS folder contains 4 files (AMASS.bat, z_Rcode.R, dictionary_for_microbiology_data.xlsx, and dictionary_for_hospital_admission_data.xlsx), and 5 folders (Variables, Rprogram, Example_Dataset_1_WHONET, Example_Dataset_2, and ResultData).
– Microbiology data file (microbiology_data in .csv or .xlsx file format)
The user needs to obtain microbiology data, and then copy & paste this data file into the same folder as the AMASS.bat file.
– [Optional] Hospital admission data file (hospital_admission_data)
If available, the user could obtain hospital admission data, and then copy & paste this data file into the same folder as the AMASS.bat file.

Not required:
– Internet to run AMASS application
The AMASS application will run offline. No data are transferred while the application is running and reports are being generated; the reports are in PDF format (do not contain any patient identifier) and can be shared under the user's jurisdiction.
– R
The download package (AMASS.zip) included R portable and R libraries that the AMASS application requires. The user does not need to install any programme before using the AMASS. The user also does not have to uninstall R prgramme if the computer already has the R prgramme installed. The user does not need to know how to use R prgramme.

For example:
If variable name for 'hospital number' is written as 'hn' in the raw data file, the user would need to add 'hn' in the cell next to 'hospital_number'. If data value for blood specimens is defined by 'Blood–Hemoculture' in the raw data file, then the user would need to add 'Blood–Hemoculture' in the cell next to 'blood_specimen'.

Dictionary file (dictionary_for_microbiology_data.xlsx) may show up as in the table below:

Variable names used in AMASS	**Variable names used in your microbiology data file**	**Requirements**
Don't change values in this column, but you can add rows with similar values if you need	Change values in this column to represent how variable names are written in your raw microbiology data file	
hospital_number		Required
Values described in AMASS	**Values used in your microbiology data file**	**Requirements**
blood_specimen		Required

Please fill in your variable names as follows:

Variable names used in AMASS	**Variable names used in your microbiology data file**	**Requirements**
Don't change values in this column, but you can add rows with similar values if you need	Change values in this column to represent how variable names are written in your raw microbiology data file	
hospital_number	hn	Required
Values described in AMASS	**Values used in your microbiology data file**	**Requirements**
blood_specimen	Blood–Hemoculture	Required

Then, save the file. For every time the user double–clicked AMASS.bat, the application would know that the variable named 'hn' is similar to 'hospital_number' and represents the patient identifier in the analysis.

Organisms included in this report:

– *Staphylococcus aureus*
– *Enterococcus* spp.
– *Streptococcus pneumoniae*
– *Salmonella* spp.
– *Escherichia coli*
– *Klebsiella pneumoniae*
– *Pseudomonas aeruginosa*
– *Acinetobacter* spp.

The eight organisms and antibiotics included in the report were selected based on the global priority list of antibiotic resistant bacteria and Global Antimicrobial Resistance Surveillance System (GLASS) of WHO [1,2].

Definitions:

The definitions of infection origin proposed by the WHO GLASS was used [1]. In brief, community–origin bloodstream infection (BSI) was defined for patients in the hospital within the first two calendar days of admission when the first blood culture positive specimens were taken. Hospital–origin BSI was defined for patients in the hospital longer than the first calendar days of admission when the first blood culture positive specimens were taken. In cases when the user had additional data on infection origin defined by infection control team or based on referral data, the user could edit the data dictionary file (variable name 'infection_origin') and the AMASS application would use the data of that variable to stratify the data by origin of infection instead of the above definition. However, in cases when data on infection origin were not available (as in many hospitals in LMICs), the above definition would be calculated based on admission date and specimen collection date (with cutoff of 2 calendar days) and used to classify infections as community–origin or hospital–origin.

De–duplication:

When more than one blood culture was collected during patient management, duplicated findings of the same patient were excluded (de–duplicated). Only one result was reported for each patient per sample type (blood) and surveyed organisms (listed above). For example, if two blood cultures from the same patient had *E. coli*, only the first would be included in the report. If there was growth of *E. coli* in one blood culture and of *K. pneumoniae* in the other blood culture, then both results would be reported. One would be for the report on *E. coli* and the other one would be for the report on *K. pneumoniae.*

References:

[1] World Health Organization (2018) Global Antimicrobial Resistance Surveillance System (GLASS) Report. Early implantation 2016–2017. http://apps.who.int/iris/bitstream/handle/10665/259744/9789241513449–eng.pdf. (accessed on 3 Dec 2018)

[2] World Health Organization (2017) Global priority list of antibiotic–resistant bacteria to guide research, discovery, and development of new antibiotics. https://www.who.int/medicines/publications/WHO–PPL–Short_Summary_25Feb–ET_NM_WHO.pdf. (accessed on 3 Dec 2018)

Investigator team

The AMASS application is being developed by Cherry Lim, Clare Ling, Elizabeth Ashley, Paul Turner, Rahul Batra, Rogier van Doorn, Soawapak Hinjoy, Sopon Iamsirithaworn, Susanna Dunachie, Tri Wangrangsimakul, Viriya Hantrakun, William Schilling, John Stelling, Jonathan Edgeworth, Guy Thwaites, Nicholas PJ Day, Ben Cooper and Direk Limmathurotskul.

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Appendix 2. Hospital Checklist

Hospital Antibiotic Stewardship Programme (ASP) Assessment Checklist

Your hospital has been selected to take part in a survey that aims to assess the current state of the antibiotic stewardship programmes (ASP) in hospitals across Indonesia. The survey aims to assess which aspects of ASP are already in place to ensure optimal antibiotic prescribing in your hospital and which areas still need to be improved. The survey will also assess the specific challenges experienced during the COVID-19 pandemic.

This study has been endorsed by the *Komite Pengendalian Resistensi Antimikroba* (KPRA), MoH, and is executed by researchers from the Medical Faculty of University of Indonesia and Oxford University Clinical Research Unit Indonesia, both in Jakarta. Through this survey we hope to learn and contribute to strenghtening ASP in Indonesian hospitals.

We kindly request that the leader of the ASP team/committee is responsible for the completion of this survey, with consultation of the other members of the hospital ASP team/committee as needed.

You are kindly requested to complete the questionnaire by ticking the appropriate boxes. All items are formulated as either Yes/No or multiple choice (5-point Likert scale) questions. The survey includes a total of 107 question and its completion will take about 30-60 minutes of your time.

The results of the survey will be fed back to the participant hospitals in a written report and a feedback session. That session will be accredited with medical education credits (SKP).

If you have any question or concern about the study, please contact principal investigator dr. Robert Sinto, Sp.PD, K-PTI (0815-8835432).

Instructions:

- The survey shall be completed by the ASP team leader, in consultation with the relevant ASP team members.
- Please complete the survey at your earliest convenience, but no later than two weeks after receipt.
- For each question, please tick ☑ ONE answer that reflects the **ACTUAL situation** in your hospital, and **not the expected or desired** one.
- Please try to answer all questions and provide comments so we can obtain a good understanding of your needs, any gaps, which will inform how to design strategies for support or advocacy.

If you have any question or encounter any technical problems while completing the survey, please contact:

Name: _____
Email: _____
Phone: _____

Thank you for your contribution:
Fakultas Kedokteran Universitas Indonesia
In collaboration with National *Komite Pengendalian Resistensi Antimikroba* (KPRA), Ministry of Health Republic of Indonesia and OUCRU ID.

General information

1. In what province is your hospital located? (*Dropdown option of 34 provinces*)
2. Your hospital name (*free text*) _____
3. Type of hospital based on service management
   - □ Public
   - □ Private
4. Type of hospital based on medical facility and resources
   - □ A
   - □ B
   - □ C
   - □ D
5. Does your hospital provide health services under JKN scheme (BPJS Kesehatan)?
   - □ Yes
   - □ No
6. Total number of inpatient beds at time of survey (*as reported to the national/provincial/ district government*) _____
7. Total number of COVID beds at time of survey (if available) _____
8. Year of starting ASP in your hospital (based on hospital official letter) (*free text*) _____
9. Who is completing the survey? (*free text*)

Name: _____

Position/role:

□ Chair of hospital ASP committee/ team
□ Member of hospital ASP committee/ team
□ Other _____

Phone number: _____

Email: _____

STRUCTURE OF THE SURVEY QUESTIONNAIRE

Section	No of questions	Theme
PART A	Antimicrobial Stewardship Programme	
A1	6	Hospital leadership support
A2	9	ASP team and infectious disease training
A3	7	Hospital infrastructures
A4	16	Interventions
A5	19	Monitoring, reporting, and feedback
A6	5	Education
A7	0	Infection prevention and control
Total	**62**	
PART B	The influence of COVID-19 on ASP programme implementation	
B1	1	Hospital leadership support
B2	6	ASP team and infectious disease training
B3	12	Hospital infrastructures
B4	8	Interventions
B5	10	Monitoring, reporting, and feedback
B6	1	Education
B7	7	Infection prevention and control
Total	**45**	

PART A: ANTIMICROBIAL STEWARDSHIP PROGRAMME

Source	No	Antimicrobial Stewardship Elements	Yes	No	Comments
HOSPITAL LEADERSHIP SUPPORT					
MoH [C1]	A1.1	Does your hospital have a formal statement of support from hospital leadership that supports ASP activities to improve antibiotic use? (e.g., hospital leadership decision letter regarding the control of antimicrobial use, the implementation of ASP activities, etc.)	☐	☐	
MoH [C2]	A1.2	Does your hospital allocate any budgeted financial support for ASP activities (e.g., fund support for operational, ASP training and education, service improvement of clinical microbiology, and the provision of information technology microbiology and information technology [IT] services)?	☐	☐	
WHO LMICs [1]	A1.3	The management has formally identified ASP as a priority objective for the hospital and included it in its key performance indicators.	☐	☐	
WHO LMICs [2]	A1.4	A health-care facility ASP action plan is endorsed that prioritizes activities and measures progress and accountability for ensuring appropriate antibiotic use, based on existing national or international guidelines and/or an existing national strategy. The ASP action plan is updated regularly as required.	☐	☐	
CDC Core Elements [Leadership 5]	A1.5	Does your facility leadership ensure that ASP committee/team have sufficient time to contribute to stewardship activities?	☐	☐	
CDC Core Elements [Leadership 6]	A1.6	Does hospital leadership ensure that antibiotic stewardship activities are integrated into other quality improvement and patient safety efforts, such as sepsis management and diagnostic stewardship?	☐	☐	
ASP TEAM AND INFECTIOUS DISEASE TRAINING					
MoH [C3]	A2.1	Does your hospital have a physician (or other) leader responsible for ASP activities?	☐	☐	
MoH [S1]	A2.2	If you answer 'Yes' to the MoH [C3], does this leader have specialized infectious disease training?	☐	☐	
MoH [C4]	A2.3	Does your hospital have a pharmacist working on ASP activities?	☐	☐	
MoH [S2]	A2.4	If you answer 'Yes' to the MoH [C4], is the pharmacist a clinical pharmacist or does this pharmacist have specialized infectious disease training?	☐	☐	
MoH		Do any of the following staff work with physicians or pharmacists to optimize antibiotic use?			
MoH [C5]	A2.5	Infection prevention and control staff	☐	☐	
MoH [C6]	A2.6	Microbiologist/doctors who deliver microbiology services	☐	☐	
MoH [S3]	A2.7	Doctors who deliver clinical pharmacology services	☐	☐	
MoH [S4]	A2.8	Nurse	☐	☐	
MoH [S5]	A2.9	IT staff	☐	☐	
HOSPITAL INFRASTRUCTURE					
Microbiology laboratory					
MoH [C13]	A3.1	Does your hospital have an in-house microbiology laboratory or have access to a reliable and timely clinical microbiology service?	☐	☐	

Source	No	Antimicrobial Stewardship Elements	Yes	No	Comments
MoH [S25]	A3.2	If you answer 'Yes' for MoH [C13], does your microbiology service make use of rapid diagnostic reporting?	☐	☐	
MoH [S26]	A3.3	If you answer 'Yes' for MoH [C13], does your microbiology service use selective antibiotic susceptibility reporting?	☐	☐	
Pharmacy					
SELF DVLP	A3.4	Can prescribers obtain the appropriate antibiotics in a timely manner in your hospital? *Appropriate antibiotics* mean antibiotics based on culture and susceptibility result, or antibiotic guidelines. *Timely manner* means appropriate with recommended time for antibiotic initiation time according to existing guidelines and subsequent time on scheduled interval.	☐	☐	
Information and Technology (IT)					
MoH [S22]	A3.5	Does your hospital have the IT capabilities to collect and analyse ASP data?	☐	☐	
MoH [S23]	A3.6	Does your hospital use electronic medical records?	☐	☐	
MoH [S21]	A3.7	Does your hospital use electronic prescriptions?	☐	☐	
ASP PROGRAM INTERVENTIONS					
MoH [C7]	A4.1	Do watch and reserve group antimicrobials at your hospital require pre-authorization before administration to the patient, or within 24 hours of administering the antimicrobial to the patient?	☐	☐	
MoH [C8]	A4.2	Does the ASP team conduct prospective review and feedback before antimicrobials are administered to patients, or within 24 hours after antimicrobials are administered to patients?	☐	☐	
MoH [S6]	A4.3	Does your hospital use computerized decision support systems in relation to antibiotic prescribing?	☐	☐	
MoH [C9]	A4.4	Does your hospital have facility-specific antibiotic treatment guidelines for commonly treated infections? If you answered 'Yes', do you have facility-specific antibiotic treatment guidelines for these following infections:	☐	☐	
MoH [S7]	A4.5	Community-acquired pneumonia (CAP)?	☐	☐	
MoH [S8]	A4.6	Hospital-acquired pneumonia (329) /ventilator-associated pneumonia (VAP)?	☐	☐	
MoH [S9]	A4.7	Skin and soft tissue infections?	☐	☐	
MoH [S10]	A4.8	Sepsis?	☐	☐	
MoH [S11]	A4.9	Urinary tract infections?	☐	☐	
MoH [S12]	A4.10	Intra-abdominal infections?	☐	☐	
MoH [S13]	A4.11	Does your hospital have guidelines for the de-escalation of broad-spectrum antibiotics, including carbapenems?	☐	☐	
MoH [S14]	A4.12	Does your hospital have guidelines for IV-to-oral conversion of antibiotics?	☐	☐	
MoH [S15]	A4.13	If you answered 'Yes' to any of questions MoH [S7-14], are hospital guidelines readily available at the point of care?	☐	☐	
WHO LMICs [13]	A4.14	The ASP team conduct regular ward rounds (in one or more wards) and other ASP interventions in select facility departments (one or more) identified in the health-care facility ASP action plan.	☐	☐	
CDC Core Elements [Action 6]	A4.15	Does your facility have a policy that requires prescribers to document in the medical record or during order entry a	☐	☐	

Source	No	Antimicrobial Stewardship Elements	Yes	No	Comments
		dose, duration and indication for all antibiotic prescriptions?			
CDC Core Elements [Action 7]	A4.16	Does your facility have a formal procedure for all prescribers to conduct daily reviews of antibiotic selection until a definitive diagnosis and treatment duration are established (i.e., time out)?	☐	☐	
ASP MONITORING AND REPORTING, AND FEEDBACK					
MoH [C10]	A5.1	Does your hospital perform audits of the targeted antimicrobial consumption based on quantitative and qualitative analysis?			
		DDD (defined daily dose, i.e. assumed average maintenance dose per day for a drug used for its main indication in adults)	☐	☐	
		DOT (duration of treatment)	☐	☐	
		PPS (point prevalence survey, i.e. survey collects information on prescribing practices of antibiotics and other information relevant to treatment and management of infectious diseases in hospitalized patients, and complements surveillance of antimicrobial consumption)	☐	☐	
		Gyssens (qualitative analysis of antibiotic use)	☐	☐	
MoH [S16]	A5.2	Does your hospital monitor the antimicrobial procurement and financing?	☐	☐	
MoH [S17]	A5.3	Does your hospital monitor compliance with clinical practice guidelines (PPK)?	☐	☐	
MoH [S18]	A5.4	Are the results of prospective reviews fed back directly to the responsible physician (DPJP)?	☐	☐	
MoH [C11]	A5.5	Does your hospital regularly publish the microbe patterns, and the outcomes associated with ASP activities?	☐	☐	
MoH [C12]	A5.6	Do you have a hospital antibiogram report?	☐	☐	
MoH [S19]	A5.7	If you answer 'Yes' for MoH [C12], is the antibiogram updated every at least once a year?	☐	☐	
MoH [S20]	A5.8	If you answer 'Yes' for MoH [C12], is the antibiogram easily accessible?	☐	☐	
MoH [S21]	A5.9	If you answer 'Yes' for MoH [C12], is there an antibiogram specific by unit?	☐	☐	
CDC Core Elements [Tracking 2]	A5.10	Does your hospital monitor prospective audit and feedback interventions by tracking the types of interventions and acceptance of recommendations?	☐	☐	
CDC Core Elements [Tracking 3]	A5.11	Does your hospital monitor preauthorization interventions by tracking which agents are being requested for which conditions?	☐	☐	
CDC Core Elements [Tracking 5]	A5.12	Does your hospital routinely monitor adherence to a documentation policy (dose, duration and indication)?	☐	☐	
CDC Core Elements [Tracking 10]	A5.13	Does your hospital track CDI (*Clostridioides difficile* infection) in the context of antibiotic use?	☐	☐	
SELF DVLP	A5.14	Does your hospital monitor patient clinical outcome: length of stay			
SELF DVLP	A5.15	Does your hospital monitor patient clinical outcome: mortality			
SELF DVLP	A5.16	Does your hospital monitor the cost effectiveness of the programme (e.g., antibiotic purchase)			

Source	No	Antimicrobial Stewardship Elements	Yes	No	Comments
WHO LMICs [Reporting 26]	A5.17	The hospital reports on antibiotic susceptibility rates are reviewed, and analyses and key findings are shared with prescribers along with specific action points.	☐	☐	
WHO LMICs [Reporting 27]	A5.18	Findings from audits/reviews of the quality/appropriateness of antibiotic use are communicated directly to prescribers along with specific action points.	☐	☐	
CDC Core Elements [Tracking 1]	A5.19	Does your hospital ASP programme track antibiotic use by submitting to the National KPRA?	☐	☐	
EDUCATION					
MoH [S26]	A6.1	Does your hospital provide educational and training activities for physicians and other staff involved to promote the wise use of antimicrobials?	☐	☐	
MoH [S27]	A6.2	If the answer to MoH S27 is 'Yes', is the activity mandatory and is training certified?	☐	☐	
CDC Core Elements	A6.3	Does your stewardship program provide education to prescribers as part of the prospective audit and feedback process (real-time discussion between ASP team and the prescriber, sometimes called “handshake stewardship”)	☐	☐	
SELF DEVLP	A6.4	Has the ASP team/committee in your hospital provided trainings on skills to run an ASP programme? For example, knowledge and skills related to programme management, developing feasible/context specific interventions, assess the programme indicators (process, output, outcome), and develop an action plan.	☐	☐	

Source	No	THE IMPACT OF COVID-19 PANDEMIC ON ANTIMICROBIAL STEWARDSHIP ELEMENTS	Large increase	Moderate increase	No impact	Moderate decrease	Large decrease	Do not know	Not applicable (this element did not exist before the COVID-19 pandemic)
HOSPITAL LEADERSHIP SUPPORT									
COVID SELF DVLP	B1.1	To what extent has the COVID-19 pandemic influenced the provision of budgeted financial support for ASP activities in your hospital?	☐	☐	☐	☐	☐	☐	☐
ASP TEAM AND INFECTIOUS DISEASE TRAINING									
		To what extent has the COVID-19 pandemic influenced the following staff's availability to perform ASP activities (e.g., antibiotic review, monitoring antibiotic use, consultation related to culture and susceptibility test result)?							
COVID SELF DVLP	B2.1	Infectious disease physician	☐	☐	☐	☐	☐	☐	☐
	B2.2	Pharmacist/clinical pharmacist	☐	☐	☐	☐	☐	☐	☐
	B2.3	Infection prevention and control staff							
	B2.4	Microbiologist/ doctors who deliver microbiology services	☐	☐	☐	☐	☐	☐	☐
	B2.5	Nurse	☐	☐	☐	☐	☐	☐	☐
	B2.6	IT staff	☐	☐	☐	☐	☐	☐	☐
HOSPITAL INFRASTRUCTURE									
		To what extent has the COVID-19 pandemic influenced:							
COVID WHO	B3.1	The provision of budgeted funding for AMR surveillance	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B3.2	Availability of quality laboratory reagents/consumables for bacteriology and antimicrobial susceptibility testing	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B3.3	Ability of laboratories to service their machines and equipment, e.g. repairs, compliance and updates	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B3.4	Access to advanced technologies e.g. molecular testing for MDR organisms	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B3.5	Number of clinical cultures i.e., workload of routine microbiology	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B3.6	Number of screening cultures (i.e. culture perform routinely in asymptomatic patient) to detect MDR	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B3.7	Turn around time for antimicrobial susceptibility results	☐	☐	☐	☐	☐	☐	☐

COVID WHO	B3.8	Ability to carry out routine laboratory quality management activities?	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B3.9	Ability to carry out molecular testing, including whole genome sequencing for MDR	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B3.10	Availability of procedures and infrastructure of *laboratory* information systems for AMR reporting	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B3.11	Availability of procedures and infrastructure of *hospital clinical* information systems for AMR response	☐	☐	☐	☐	☐	☐	☐
COVID SELF DVLP	B3.12	To what extent has the COVID-19 pandemic influenced the provision of antibiotics supply in your hospital?	☐	☐	☐	☐	☐	☐	☐
INTERVENTIONS									
COVID SELF DVLP	B4.1	To what extent has the COVID-19 pandemic influenced the implementation of preauthorization in your hospital?	☐	☐	☐	☐	☐	☐	☐
COVID SELF DVLP	B4.2	To what extent has the COVID-19 pandemic influenced the implementation of prospective audit and feedback in your hospital?	☐	☐	☐	☐	☐	☐	☐
COVID UKCAC PIN	B4.3	Have your hospital updated hospital guideline for community-acquired pneumonia? ☐ Yes ☐ No							
COVID UKCAC PIN	B4.4	Have your hospital updated hospital guideline for hospital-acquired pneumonia/ventilator-associated pneumonia? ☐ Yes ☐ No							
COVID SELF DVLP	B4.5	Have your hospital updated hospital guideline for intra-abdominal infections? ☐ Yes ☐ No							
COVID SELF DVLP	B4.6	Have your hospital updated hospital guideline for urinary tract infections? ☐ Yes ☐ No							
COVID	B4.7	Have your hospital updated hospital guideline for skin and soft tissue infections?							

SELF DVLP		☐ Yes ☐ No							
COVID SELF DVLP	B4.8	Have your hospital updated hospital guideline for sepsis? ☐ Yes ☐ No							
MONITORING, REPORTING, AND FEEDBACK									
		To what extent has the COVID-19 pandemic influenced/had impact on these following audits of the targeted antimicrobial consumption based on quantitative and qualitative analysis?							
COVID SELF DVLP	B5.1	DDD (defined daily dose, i.e. assumed average maintenance dose per day for a drug used for its main indication in adults)	☐	☐	☐	☐	☐	☐	☐
COVID SELF DVLP	B5.2	DOT (duration of treatment)	☐	☐	☐	☐	☐	☐	☐
COVID UKCAC PIN	B5.3	PPS (point prevalence survey, i.e. survey collects information on prescribing practices of antibiotics and other information relevant to treatment and management of infectious diseases in hospitalized patients, and complements surveillance of antimicrobial consumption)	☐	☐	☐	☐	☐	☐	☐
COVID SELF DVLP	B5.4	Gyssens (qualitative analysis of antibiotic use)	☐	☐	☐	☐	☐	☐	☐
		To what extent has the COVID-19 pandemic had an impact to the following antibiotic use?							
COVID WHO	B5.5	Total antibiotic prescription	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B5.6	Antibiotic availability i.e., antibiotic supply chain	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B5.7	Prescription of WHO Access antibiotics or the first- or second-line treatment for common infections, e.g., amoxicillin, gentamycin, metronidazole, cefadroxil, cefazolin.	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B5.8	Prescription of WHO Watch antibiotics or treatment for limited group of syndromes, should be monitored, e.g.,	☐	☐	☐	☐	☐	☐	☐

		azithromycin, ceftriaxone, cefixime, amikacin, levofloxacin, fosfomycin.							
COVID WHO	B5.9	Prescription of WHO Reserve antibiotics or "last resort" to treat multi- or extensively-drug resistant bacteria, e.g., carbapenems, vancomycin, cefepime, piperacillin-tazobactam.	☐	☐	☐	☐	☐	☐	☐
COVID SELF DVLP	B5.10	Comments related to antibiotic use monitoring activities during COVID pandemic (*free text*)							
EDUCATION									
COVID UKCAC PIN	B6.1	Does COVID-19 pandemic have an impact on the provision of educational activities related to optimizing antibiotic prescribing?	☐	☐	☐	☐	☐	☐	☐
INFECTION PREVENTION AND CONTROL									
		Do you think there has been an impact on infection prevention and control (IPC) as a result of COVID-19 in terms of							
COVID SELF DVLP	B7.1	The provision of budgeted funding for infection prevention and control (IPC)							
COVID WHO	B7.2	Compliance with hand hygiene, e.g., 5 moments of hand hygiene	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B7.3	Availability of alcohol-based hand rub	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B7.4	Availability of personal protective equipment (PPE) e.g., mask, respirator, gown, gloves	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B7.5	Inappropriate infection prevention and control (IPC) practices e.g., double or triple gowning/gloving, performing hand hygiene over gloved hands	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B7.6	Ability to cohort patient by multi drug resistant organism (MDRO) status	☐	☐	☐	☐	☐	☐	☐
COVID WHO	B7.7	Ability to provide infection prevention and control (IPC) training for healthcare workers	☐	☐	☐	☐	☐	☐	☐

Appendix 3. Analysis of hospital and district-level factors associated with ASP self-assessment scores for overall ASP implementation, hospital leadership support, ASP team and infectious diseases training, and hospital infrastructure

Characteristic	Overall ASP implementation				Hospital leadership support				ASP team and infectious disease training				Hospital infrastructure			
	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P
Hospital level																
A	7.29 (3.54-15.01)		4.32 (1.85-10.08)		1.48 (0.71-3.07)		1.61 (0.68-3.79)		13.22 (6.22-28.12)		8.19 (3.34-20.12)		11.10 (5.22-23.60)		5.57 (2.31-13.45)	
B	5.95 (3.56-9.93)		4.29 (2.31-7.95)		1.70 (1.02-2.83)		1.40 (0.80-2.45)		7.25 (4.22-12.46)		5.06 (2.65-9.67)		14.17 (8.14-24.67)		9.65 (5.05-18.45)	
C	1.74 (1.13-2.67)		1.48 (0.92-2.40)		1.24 (0.80-1.92)		1.21 (0.77-1.92)		1.83 (1.14-2.93)		1.63 (0.97-2.76)		1.99 (1.26-3.13)		1.55 (0.93-2.57)	
D	ref	<0.001	ref	<0.001	ref	0.195	ref	0.319	ref	<0.001	ref	<0.001	ref	<0.001	ref	<0.001
Hospital size																
<101	ref	<0.001	ref	0.894	ref	0.976	-	-	ref	<0.001	ref	0.279	ref	<0.001	ref	0.817
101-250	1.60 (1.10-2.22)		1.00 (0.67-1.50)		1.00 (0.70-1.30)		-	-	1.92 (1.34-2.77)		1.34 (0.89-2.04)		1.77 (1.24-2.52)		1.21 (0.80-1.83)	
>250	3.17 (1.96-0.12)		0.88 (0.48-1.59)		1.05 (0.65-1.70)		-	-	4.24 (2.60-6.93)		1.25 (0.68-2.29)		3.68 (2.24-6.06)		0.88 (0.47-1.65)	
Hospital ownership																
Private	0.88 (0.63-1.22)	0.436	-	-	1.58 (1.14-2.20)	0.006	1.67 (1.14-2.43)		0.78 (0.56-1.09)	0.148	-	-	1.01 (0.73-1.41)	0.944	-	-
Public	ref		-	-	ref		ref	0.007	ref		-	-	ref		-	-
Hospital accreditation																
Not accredited	ref		ref	0.254	ref		ref	0.258	ref		ref	0.295	ref		ref	0.024
Accredited	1.77 (1.29-2.43)	<0.001	1.22 (0.87-1.72)		1.47 (1.06-2.05)	0.021	1.23 (0.86-1.77)		1.65 (1.19-2.28)	0.003	1.21 (0.85-1.73)		1.86 (1.34-2.58)	<0.001	1.51 (1.06-2.16)	
National health insurance service provider																
No	ref		-	-	ref		-	-	ref		-	-	ref		ref	
Yes	1.05 (0.58-1.86)	0.880	-	-	0.76 (0.42-1.37)	0.356	-	-	0.96 (0.53-1.73)	0.891	-	-	0.60 (0.34-1.06)	0.077	0.83 (0.44-1.56)	0.563
ASP duration (years)																
<2	ref	<0.001	ref	0.001	ref	0.002	ref	0.001	ref	<0.001	ref	0.024	ref	<0.001	ref	0.061

Characteristic	Overall ASP implementation				Hospital leadership support				ASP team and infectious disease training				Hospital infrastructure			
	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P
2-5	1.47 (1.01-2.13)		1.38 (0.93-2.06)		1.44 (0.98-2.12)		1.50 (1.01-2.25)		0.88 (0.60-1.30)		0.72 (0.47-1.09)		1.24 (0.85-1.81)		1.07 (0.70-1.62)	
>5	3.21 (2.15-4.80)		2.31 (1.47-3.65)		2.03 (1.35-3.04)		2.11 (1.35-3.31)		2.96 (1.98-4.43)		1.80 (1.13-2.85)		2.78 (1.85-4.18)		1.53 (0.96-2.43)	
Geographic region																
Java	5.90 (1.62-21.38)		-	-	3.05 (0.81-11.46)		-	-	3.43 (0.87-13.59)		-	-	10.33 (1.93-55.16)		-	-
Sumatra	4.42 (1.18-16.62)		-	-	2.71 (0.70-10.60)		-	-	2.14 (0.52-8.79)		-	-	7.76 (1.43-42.26)		-	-
Bali	4.25 (0.98-18.34)		-	-	2.56 (0.58-11.23)		-	-	1.69 (0.37-7.85)		-	-	4.38 (0.69-27.71)		-	-
Nusa Tenggara	6.23 (1.28-30.33)		-	-	3.90 (0.74-20.50)		-	-	2.79 (0.51-15.44)		-	-	15.48 (2.18-109.94)		-	-
Kalimantan	3.81 (0.94-15.40)		-	-	2.15 (0.52-9.00)		-	-	1.69 (0.38-7.47)		-	-	6.98 (1.19-40.76)		-	-
Sulawesi	3.41 (0.80-14.56)		-	-	3.30 (0.74-14.65)		-	-	2.85 (0.63-1292)		-	-	7.65 (1.26-46.54)		-	-
Maluku	2.32 (0.30-17.97)		-	-	1.73 (0.21-14.31)		-	-	0.54 (0.04-7.10)		-	-	3.49 (0.28-43.84)		-	-
Papua	ref	0.476	-	-	ref	0.687	-	-	ref	0.567	-	-	ref	0.661	-	-
District-level human development index																
Lowest (0.00-71.8)	ref	0.001	ref	0.435	ref	0.758	-	-	ref	0.001	ref	0.196	ref	<0.001	ref	0.229
Lower-middle (71.9-77.6)	1.52 (0.98-1.36)		0.89 (0.46-1.71)		1.07 (0.67-1.70)		-	-	1.00 (0.63-1.58)		0.53 (0.26-1.05)		1.93 (1.21-3.06)		0.89 (0.46-1.72)	
Higher-middle (77.5-81.4)	2.27 (1.39-3.72)		0.58 (0.21-1.60)		1.08 (0.69-1.70)		-	-	1.78 (1.15-2.76)		0.43 (0.14-1.30)		3.22 (1.98-5.23)		0.64 (0.22-1.88)	
Highest (81.5-86.6)	2.63 (1.64-4.22)		0.38 (0.12-1.23)		1.28 (0.81-2.02)		-	-	2.15 (1.37-3.37)		0.34 (0.10-1.21)		4.12 (2.54-6.69)		0.44 (0.13-1.52)	
District-level public health																

Characteristic	Overall ASP implementation				Hospital leadership support				ASP team and infectious disease training				Hospital infrastructure			
	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P
development index																
Lowest (0.00-0.63)	ref	<0.001	ref	0.004	ref	0.150	ref	0.654	ref	0.002	ref	0.247	ref	<0.001	ref	0.750
Lower-middle (0.64-0.65)	2.20 (1.55-3.81)		2.04 (1.17-3.58)		1.06 (0.67-1.68)		0.67 (0.39-1.16)		2.01 (1.26-3.19)		1.27 (0.70-2.30)		2.84 (1.77-4.57)		1.54 (0.85-2.79)	
Higher-middle (0.66-0.67)	2.49 (1.60-3.88)		2.13 (1.17-3.87)		1.62 (1.02-2.57)		1.06 (0.60-1.87)		2.06 (1.29-3.28)		1.37 (0.73-2.59)		2.80 (1.73-4.53)		1.37 (0.72-2.63)	
Highest (0.68-0.75)	3.10 (1.93-4.95)		2.43 (1.26-4.68)		1.03 (0.64-1.67)		0.61 (0.33-1.12)		2.29 (1.41-3.71)		1.31 (0.64-2.69)		3.00 (1.81-4.95)		1.31 (0.65-2.67)	
District-level doctors per 100 000 population																
Lowest (0.00-4.7)	ref	0.124	ref	0.460	ref	0.530	-	-	ref	0.180	ref	0.640	ref	0.009	ref	0.701
Lower-middle (4.8-18.4)	1.05 (0.63-1.76)		0.74 (0.42-1.31)		1.02 (0.62-1.68)		-	-	1.14 (0.68-1.90)		0.95 (0.51-1.78)		1.13 (0.69-1.88)		0.66 (0.37-1.19)	
Higher-middle (18.5-33.2)	1.71 (0.86-3.41)		0.74 (0.32-1.70)		0.72 (0.37-1.39)		-	-	1.68 (0.86-3.29)		0.89 (0.37-2.16)		1.74 (0.90-3.36)		0.46 (0.20-1.08)	
Highest (33.3-100.00)	1.39 (44.90-3.91)		0.56 (0.22-1.43)		1.17 (0.59-2.33)		-	-	2.15 (0.89-5.24)		1.21 (0.43-3.46)		4.04 (1.63-10.04)		1.09 (0.41-2.95)	
District-level hospitals per 100 000 population																
Lowest (0.00-0.60)	ref	0.896	-	-	ref	0.798	-	-	ref	0.708	-	-	ref	0.598	-	-
Lower-middle (0.61-0.91)	0.94 (0.58-1.55)		-	-	0.95 (0.61-1.50)		-	-	1.04 (0.64-1.69)		-	-	1.26 (0.77-2.06)		-	-
Higher-middle (1.00-0.92)	1.06 (0.64-1.76)		-	-	1.18 (0.75-1.85)		-	-	1.03 (0.62-1.71)		-	-	1.01 (0.59-1.72)		-	-
Highest (1.10-1.30)	0.90 (0.54-1.50)		-	-	1.10 (0.70-1.75)		-	-	1.30 (0.78-2.16)		-	-	0.91 (0.53-1.56)		-	-
District-level midwives per 100 000 population																
Lowest (0.00-17.0)	ref	0.395	-	-	ref	0.622	-	-	ref	0.294	-	-	ref	0.081	ref	0.425
Lower-middle (22.7-17.1)	1.10 (0.67-1.82)		-	-	1.13 (0.71-1.81)		-	-	0.78 (0.47-1.30)		-	-	0.74 (0.44-1.27)		0.57 (0.32-1.00)	

Characteristic	Overall ASP implementation				Hospital leadership support				ASP team and infectious disease training				Hospital infrastructure			
	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P
Higher-middle (22.8-28.7)	0.82 (0.52-1.29)		-	-	0.91 (0.60-1.39)		-	-	0.74 (0.46-1.19)		-	-	0.64 (0.40-1.05)		0.57 (0.30-1.06)	
Highest (28.8-118.8)	1.28 (0.79-2.09)		-	-	1.22 (0.77-1.94)		-	-	1.18 (0.72-1.92)		-	-	1.26 (0.77-2.07)		1.14 (0.64-2.01)	
District-level primary health centres per 100 000 population																
Lowest (0.00-0.20)	ref	0.444	-	-	ref	0.347	-	-	ref	0.519	-	-	ref	0.167	ref	0.588
	0.81 (0.50-1.33)		-	-	1.08 (0.71-1.66)		-	-	1.25 (0.76-2.07)		-	-	1.35 (0.80-2.27)		0.91 (0.51-1.61)	
Higher-middle (0.39-0.35)	1.22 (0.72-2.08)		-	-	1.26 (0.75-2.10)		-	-	1.17 (0.66-2.06)		-	-	1.49 (0.85-2.64)		1.58 (0.82-3.05)	
Highest (0.40-0.46)	0.58 (0.35-0.97)		-	-	0.80 (0.51-1.26)		-	Lower-middle (0.34-0.21)	0.86 (0.49-1.52)		-	-	0.91 (0.50-1.66)		1.19 (0.57-2.50)	
District-level life expectancy at birth (years)																
Lowest (0.00-71.4)	ref	0.001	ref	0.160	ref	0.080	ref	0.878	ref	0.001	ref	0.271	ref	<0.001	ref	0.005
Lower-middle (71.4-73.2)	2.40 (1.49-3.86)		1.66 (0.95-2.87)		1.64 (1.03-2.60)		1.65 (0.97-2.80)		2.21 (1.39-3.53)		2.13 (1.20-3.78)		2.40 (1.47-3.91)		1.42 (0.79-2.53)	
Higher-middle (73.3-74.3)	2.28 (1.42-3.65)		1.23 (0.66-2.28)		1.68 (1.09-2.60)		1.46 (0.83-2.57)		2.44 (1.54-3.85)		2.39 (1.24-4.60)		2.77 (1.63-4.70)		1.29 (0.66-2.53)	
Highest (74.4-77.7)	2.50 (1.43-4.37)		1.05 (0.54-2.03)		1.28 (0.79-2.08)		0.97 (0.52-1.78)		2.24 (1.34-3.75)		1.89 (0.93-3.84)		5.75 (3.08-10.72)		2.52 (1.22-5.20)	
District-level average duration of formal education																
Lowest (0.00-8.1)	ref	0.002	ref	0.821	ref	0.809	-	-	ref	0.007	ref	0.444	ref	<0.001	ref	0.051
Lower-middle (8.2-10.0)	1.36 (0.87-2.12)		1.12 (0.59-2.12)		1.10 (0.69-1.74)		-	-	1.17 (0.73 -1.89)		1.33 (0.68-2.62)		1.77 (1.09-2.88)		1.33 (0.70-2.55)	
Higher-middle (10.01-10.9)	2.23 (1.40-3.56)		1.27 (0.49-3.31)		1.19 (0.76-1.87)		-	-	1.70 (1.06-2.71)		1.19 (0.42-3.36)		3.85 (2.38-6.23)		2.69 (0.98-7.43)	

Characteristic	Overall ASP implementation				Hospital leadership support				ASP team and infectious disease training				Hospital infrastructure			
	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P
Highest (11.0-12.7)	2.28 (1.39-3.74)		1.49 (0.52-4.23)		1.24 (0.78-1.97)		-	-	2.22 (1.34-3.65)		1.53 (0.47-4.93)		4.45 (2.54-7.78)		2.82 (0.92-8.66)	
District-level national health insurance coverage (%)																
Lowest (0.00-62.1)	ref	0.002	ref	0.100	ref	0.385	-	-	ref	0.022	ref	0.241	ref	0.001	ref	0.585
Lower-middle (62.2-75.2)	1.36 (0.87-2.14)		0.80 (0.47-1.35)		1.23 (0.78-1.96)		-	-	1.56 (0.99-2.48)		1.17 (0.67-2.03)		2.52 (1.57-4.05)		1.24 (0.71-2.17)	
Higher-middle (75.3-85.5)	2.60 (1.58-4.28)		1.76 (1.00-3.10)		1.33 (0.84-2.10)		-	-	2.05 (1.24-3.37)		1.74 (0.94-3.21)		2.60 (1.54-4.36)		1.35 (0.67-2.32)	
Highest (85.6-100.00)	1.46 (0.91-2.35)		0.93 (0.54-1.59)		*0.83 (0.52-1.33)*		-	-	1.91 (1.17-3.10)		1.59 (0.89-2.83)		2.16 (1.21-3.55)		1.09 (0.61-1.95)	
District-level per-capita domestic health expenditure																
Lowest (0.00-2.5)	ref	<0.001	ref	0.002	ref	0.173	ref	0.047	ref	0.013	ref	0.365	ref	<0.001	ref	0.080
Lower-middle (2.6-4.7)	1.64 (1.04-2.59)		1.49 (0.85-2.60)		1.13 (0.72-1.78)		1.28 (0.76-2.13)		1.28 (0.79-2.07)		1.61 (0.90-2.90)		1.82 (1.12-2.98)		1.58 (0.88-2.82)	
Higher-middle (4.8-7.4)	2.66 (1.68-4.21)		2.05 (1.12-3.75)		1.13 (0.71-1.78)		1.12 (0.67-1.85)		2.09 (1.30-3.35)		1.75 (0.94-3.29)		2.96 (1.83-4.79)		1.77 (0.95-3.32)	
Highest (7.5-47.5)	2.95 (1.74-5.00)		2.33 (1.25-4.35)		1.64 (1.03-2.61)		1.70 (1.02-2.85)		1.75 (1.03-2.96)		1.23 (0.63-2.38)		3.46 (1.98-6.03)		1.50 (0.79-2.85)	

Table shows results of multilevel ordinal regression to estimate associations between total ASP scores (overall and per domain) and independent variables at the hospital and district level. Province was included as the random-effect variable to adjust for clustering of observations within provinces. District-level data were categorized into quartiles (i.e., lowest, low-middle, middle-high, and highest). Each independent variable with a $p<0.20$ in the univariable model was forwarded to the multivariable model. Final model selection was based on forward selection informed by likelihood ratio test. Independent variables geographic region and district-level midwives per 100 000 population were examined in univariable models and were not associated. See Figure 4 for a summary of the regression results.

Abbreviations: aOR, adjusted odds ratio; ASP, antimicrobial stewardship program; CI, confidence interval; cOR, crude odds ratio.

Appendix 4. Analysis of hospital and district-level factors associated with ASP self-assessment scores for ASP interventions, monitoring, reporting and feedback, and education.

Characteristic	ASP interventions				Monitoring, reporting and feedback				Education			
	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P
Hospital level												
A	6.01 (2.87-12.59)		5.58 (2.37-13.17)		5.29 (2.54-11.03)		3.29 (1.41-7.69)		1.15 (0.57-2.33)		-	-
B	3.69 (2.27-6.02)		3.51 (1.93-6.37)		3.86 (2.32-6.43)		2.55 (1.40-4.66)		1.01 (0.62-1.66)		-	-
C	1.90 (1.25-2.90)		2.11 (1.30-3.42)		1.41 (0.91-2.18)		1.33 (0.82-2.16)		0.97 (0.63-1.49)		-	-
D	Ref	<0.001	ref	<0.001	ref	<0.001	Ref	<0.001	ref	0.965	-	-
Hospital size												
<101	ref	0.002	ref	0.656	ref	0.001	Ref	0.789	ref	0.921	-	-
101-250	1.33 (0.95-1.88)		0.91 (0.61-1.36)		1.38 (0.98-1.96)		1.07 (0.71-1.59)		1.07 (0.76-1.51)		-	-
>250	2.32 (1.45-3.72)		1.17 (0.65-2.11)		2.75 (1.69-4.49)		1.09 (0.59-2.01)		1.08 (0.67-1.74)		-	-
Hospital ownership												
Private	0.89 (0.65-1.22)	0.454	-	-	0.83 (0.60-1.15)	0.269	-	-	0.91 (0.66-1.25)	0.553	-	-
Public	ref		-	-	ref		-	-	ref		-	-
Hospital accreditation												
Not accredited	ref		ref		ref		ref		ref		-	-
Accredited	1.47 (1.08-2.02)	0.015	1.14 (0.82-1.60)	0.436	1.78 (1.29-2.46)	<0.001	1.35 (0.95-1.91)	0.093	1.00 (0.73-1.37)	0.991	-	-
National health insurance service provider												
No	ref		-	-	ref		-	-	ref		ref	
Yes	1.17 (0.67-2.03)	0.577	-	-	1.16 (0.64-2.08)	0.628	-	-	0.62 (0.36-1.08)	0.090	0.62 (0.35-1.11)	0.108
ASP duration (years)												
<2	ref	0.008	ref	0.431	ref	<0.001	ref	0.002	ref	0.528	-	-
2-5	1.04 (0.72-1.50)		0.95 (0.64-1.42)		1.54 (1.06-2.24)		1.28 (0.85-1.92)		1.18 (0.81-1.72)		-	-
>5	1.76 (1.20-2.58)		1.30 (0.83-2.04)		2.79 (1.87-4.18)		1.95 (1.24-3.07)		1.22 (0.83-1.81)		-	-
Geographic region												

Characteristic	ASP interventions				Monitoring, reporting and feedback				Education			
	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P
Java	2.66 (0.80-8.89)		-	-	21.08 (2.49-178.39)		-	-	2.14 (0.64-7.20)		-	-
Sumatra	2.57 (0.74-9.96)		-	-	15.22 (1.76-131.77)		-	-	2.05 (0.59-7.15)		-	-
Bali	2.49 (0.64-9.78)		-	-	24.87 (2.57-240.65)		-	-	4.42 (1.12-17.48)		-	-
Nusa Tenggara	0.96 ((0.20-4.70)		-	-	26.80 (2.58-278.09)		-	-	1.93 (0.39-.9.56)		-	-
Kalimantan	1.59 (0.43-5.95)		-	-	13.32 (1.47-121.05)		-	-	2.30 (0.61-8.64)		-	-
Sulawesi	1.93 (0.50-7.48)		-	-	12.65 (1.36-117.34)		-	-	1.34 (0.34-5.30)		-	-
Maluku	2.20 (0.29-16.85)		-	-	4.00 (0.26-62.27)		-	-	2.68 (0.37-19.49)		-	-
Papua	ref	0.314	-	-	ref	0.429	-	-	ref	0.346	-	-
District-level human development index												
Lowest (0.00-71.8)	ref	0.194	ref	0.583	ref	0.001	ref	0.944	ref	0.171	ref	0.404
Lower-middle (71.9-77.6)	1.32 (0.85-2.03)		0.86 (0.46-1.63)		1.75 (1.11-2.75)		1.24 (0.63-2.42)		1.35 (0.86-2.11)		0.95 (0.58-1.57)	
Higher-middle (77.5-81.4)	1.45 (0.93-2.25)		0.37 (0.13-1.01)		2.02 (1.24-3.28)		0.77 (0.27-2.20)		1.27 (0.82-1.97)		0.71 (0.39-1.28)	
Highest (81.5-86.6)	1.50 (0.97-2.32)		0.31 (0.10-1.01)		2.56 (1.59-4.12)		0.75 (0.23-2.48)		1.38 (0.88-2.17)		0.70 (0.37-1.36)	
District-level public health development index												
Lowest (0.00-0.63)	ref	0.009	ref	0.108	ref	<0.001	ref	0.002	ref	0.015	ref	0.003
Lower-middle (0.64-0.65)	2.06 (1.33-3.17)		2.05 (1.18-3.58)		2.35 (1.49-3.71)		1.88 (1.07-3.33)		1.49 (0.97-2.31)		1.59 (0.97-2.62)	
Higher-middle (0.66-0.67)	1.60 (1.03-2.46)		1.82 (0.99-3.32)		2.49 (1.57-3.95)		1.95 (1.04-3.65)		1.59 (1.03-2.47)		1.74 (1.03-2.94)	
Highest (0.68-0.75)	1.73 (1.10-2.71)		2.26 (1.14-4.48)		3.34 (2.06-5.42)		2.74 (1.38-5.44)		2.10 (1.32-3.34)		2.27 (1.27-4.07)	
District-level doctors per 100 000 population												
Lowest (0.00-4.7)	ref	0.938	-	-	ref	0.195	ref	0.995	ref	0.157	ref	0.951
Lower-middle (4.8-18.4)	0.90		-	-	1.27		0.93		1.30		1.36	

Characteristic	ASP interventions				Monitoring, reporting and feedback				Education			
	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P
	(0.56-1.47)				(0.76-2.10)		(0.54-1.63)		(0.80-2.13)		(0.64-2.87)	
Higher-middle (18.5-33.2)	1.04 (0.55-1.98)		-	-	1.84 (0.93-3.63)		0.92 (0.40-2.10)		1.59 (0.84-3.01)		1.16 (0.69-1.97)	
Highest (33.3-100.00)	0.93 (0.45-1.92)		-	-	1.66 (0.60-4.60)		1.21 (0.45-3.23)		1.23 (0.61-2.50)		1.01 (0.44-2.30)	
District-level hospitals per 100 000 population												
Lowest (0.00-0.60)	ref	0.335	-	-	ref	0.998	-	-	ref	0.524	-	-
Lower-middle (0.61-0.91)	1.03 (0.67-1.60)		-	-	0.98 (0.60-1.58)		-	-	0.91 (0.58-1.43)		-	-
Higher-middle (1.00-0.92)	1.11 (0.71-1.74)		-	-	0.97 (0.59-1.62)		-	-	1.22 (0.77-1.93)		-	-
Highest (1.10-1.30)	0.75 (0.48-1.18)		-	-	1.01 (0.60-1.70)		-	-	1.21 (0.76-1.93)		-	-
District-level midwives per 100 000 population												
Lowest (0.00-17.0)	ref	0.188	ref	0.330	ref	0.434	-	-	ref	0.774	-	-
Lower-middle (22.7-17.1)	1.22 (0.78-1.90)		1.01 (0.59-1.73)		1.14 (0.68-1.92)		-	-	1.30 (0.76-2.23)		-	-
Higher-middle (22.8-28.7)	0.92 (0.62-1.38)		1.38 (0.75-2.54)		0.82 (0.50-1.32)		-	-	1.18 (0.78-1.78)		-	-
Highest (28.8-118.8)	1.34 (0.87-2.08)		1.63 (0.94-2.85)		1.25 (0.76-2.04)		-	-	1.09 (0.69-1.72)		-	-
District-level primary health centres per 100 000 population												
Lowest (0.00-0.20)	ref	0.088	ref	0.390	ref	0.017	ref	0.116	ref	0.251	-	-
Lower-middle (0.34-0.21)	0.78 (0.52-1.17)		0.66 (0.38-1.14)-		0.68 (0.41-1.13)		0.55 (0.34-0.91)		0.94 (0.61-1.46)		-	-
Higher-middle (0.39-0.35)	1.10 (0.68-1.79)		0.85 (0.45-1.59)		0.98 (0.57-1.68)		0.88 (0.51-1.51)		1.29 (0.77-2.14)		-	-
Highest (0.40-0.46)	0.64 (0.42-0.98)		0.51 (0.25-1.05)		0.47 (0.28-0.79)		0.65 (0.39-1.07)		0.76 (0.48-1.20)		-	-
District-level life expectancy at birth (years)												
Lowest (0.00-71.4)	ref	0.029	ref	0.241	ref	0.002	ref	0.255	ref	0.936	-	-
Lower-middle (71.4-73.2)	1.97 (1.25-3.09)		1.30 (0.75-2.27)		2.17 (1.34-3.50)		0.81 (0.43-1.55)		1.09 (0.69-1.72)		-	-

Characteristic	ASP interventions				Monitoring, reporting and feedback				Education			
	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P	cOR (95%CI)	P	aOR (95%CI)	P
Higher-middle (73.3-74.3)	1.46 (0.96-2.21)		0.87 (0.47-1.63)		1.93 (1.18-3.17)		1.11 (0.42-2.93)		0.95 (0.61-1.47)		-	-
Highest (74.4-77.7)	1.27 (0.79-2.03)		0.71 (0.36-1.41)		2.71 (1.51-4.87)		1.00 (0.51-1.98)		1.01 (0.61-1.67)		-	-
District-level average duration of formal education												
Lowest (0.00-8.1)	ref	0.195	ref	0.674	Ref	0.006	ref	0.951	ref	0.729	-	-
Lower-middle (8.2-10.0)	1.10 (0.72-1.70)		1.06 (0.57-1.97)		1.22 (0.77-2.00)		0.81 (0.43-1.55)		0.92 (0.58-1.44)		-	-
Higher-middle (10.01-10.9)	1.46 (0.95-2.26)		1.38 (0.52-3.62)		2.09 (1.32-3.33)		1.11 (0.42-2.93)		1.17 (0.75-1.83)		-	-
Highest (11.0-12.7)	1.38 (0.88-2.14)		1.50 (0.53-4.26)		1.97 (1.18-3.28)		1.19 (0.41-3.48)		1.09 (0.68-1.75)		-	-
District-level national health insurance coverage (%)												
Lowest (0.00-62.1)	ref	0.012	ref	0.744	Ref	0.073	ref	0.618	ref	0.598	-	-
Lower-middle (62.2-75.2)	1.42 (0.91-2.20)		1.27 (0.76-2.13)		1.54 (0.97-2.44)		0.87 (0.51-1.48)		0.77 (0.50-1.20)		-	-
Higher-middle (75.3-85.5)	2.04 (1.29-3.34)		2.11 (1.16-3.82)		1.91 (1.15-3.17)		1.04 (0.58-1.85)		0.75 (0.48-1.19)		-	-
Highest (85.6-100.00)	1.12 (0.71-1.75)		0.91 (0.54-1.55)		1.53 (0.94-2.50)		0.82 (0.47-1.42)		0.85 (0.54-1.35)		-	-
District-level per-capita domestic health expenditure												
Lowest (0.00-2.5)	ref	0.036	ref	0.299	Ref	0.002	ref	0.020	ref	0.184	ref	0.732
Lower-middle (2.6-4.7)	1.07 (0.70-1.65)		0.85 (0.49-1.47)		1.74 (1.09-2.77)		1.39 (0.80-2.43)		1.56 (0.99-2.45)		1.30 (0.79-2.14)	
Higher-middle (4.8-7.4)	1.74 (1.12-2.69)		1.23 (0.69-2.19)		2.24 (1.40-3.60)		1.52 (0.82-2.80)		1.38 (0.88-2.15)		1.26 (0.74-2.17)	
Highest (7.5-47.5)	1.51 (0.97-2.34)		1.03 (0.57-1.86)		2.55 (1.50-4.33)		1.89 (1.01-3.56)		1.29 (0.81-2.03)		1.19 (0.66-2.13)	

Table shows results of multilevel ordinal regression to estimate associations between total ASP scores (overall and per domain) and independent variables at the hospital and district level. Province was included as the random-effect variable to adjust for clustering of observations within provinces. District-level data were categorized into quartiles (i.e., lowest, low-middle, middle-high, and highest). Each independent variable with a $p<0.20$ in the univariable model was forwarded to the multivariable model. Final model selection was based on forward selection informed by likelihood ratio test. Independent variables geographic region and district-level midwives per 100 000 population were examined in univariable models and were not associated. See Figure 4 for a summary of the regression results.

Abbreviations: aOR, adjusted odds ratio; ASP, antimicrobial stewardship program; CI, confidence interval; cOR, crude odds ratio.

Appendix 5. Data table of COVID-19 impacts on ASP implementation

Item#	COVID-19 impacts	N hospitals who were asked the pertinent item*	Likert scale responses						Yes/No responses	
	To what extent has the COVID-19 pandemic influenced:		**Largely decreased**	**Moderately decreased**	**No impact**	**Moderately increased**	**Largely increased**	**Don't know**	**Yes**	**No**
	Hospital leadership support									
B1.1	The provision of budgeted financial support for ASP activities in your hospital	429	31 (7.2%)	84 (19.6%)	164 (38.2%)	60 (14.0%)	11 (2.6%)	79 (18.4%)		
	ASP team and infectious disease training									
B2.1	Infectious disease physician to perform ASP activities	300	50 (16.7%)	71 (23.7%)	67 (22.3%)	58 (19.3%)	15 (5.0%)	39 (13%)		
B2.2	Pharmacist/clinical pharmacist to perform ASP activities	505	81 (16.0%)	120 (23.8%)	112 (22.2%)	84 (16.6%)	22 (4.4%)	86 (17%)		
B2.3	IPC staff to perform ASP activities	462	60 (13.0%)	115 (24.9%)	92 (19.9%)	93 (20.1%)	24 (5.2%)	78 (16.9%)		
B2.4	Microbiologist/ doctors who deliver microbiology services to perform ASP activities	186	21 (11.3%)	37 (19.9%)	56 (30.1%)	35 (18.8%)	8 (4.3%)	29 (15.6%)		
B2.5	Nurse to perform ASP activities	446	81 (18.2%)	105 (23.5%)	91 (20.4%)	74 (16.6%)	34 (7.6%)	61 (13.7%)		
B2.6	IT to perform ASP activities	277	25 (9%)	56 (20.2%)	89 (32.1%)	50 (18.1%)	12 (4.3%)	45 (16.2%)		
	Hospital infrastructure									
B3.1	The provision of budgeted funding for AMR surveillance	170	11 (6.5%)	15 (8.8%)	68 (40.0%)	45 (26.5%)	3 (1.8%)	28 (16.5%)		
B3.2	Availability of quality laboratory reagents/consumables for bacteriology and antimicrobial susceptibility testing	166	5 (3.0%)	10 (6.0%)	68 (41.0%)	54 (32.5%)	9 (5.4%)	20 (12.0%)		
B3.3	Ability of laboratories to service their machines and equipment	171	9 (5.3%)	9 (5.3%)	75 (43.9%)	52 (30.4%)	4 (2.3%)	22 (12.9%)		
B3.4	Access to advanced technologies	283	10 (3.5%)	34 (12.0%)	103 (36.4%)	91 (32.3%)	26 (9.2%)	19 (6.7%)		
B3.5	Number of clinical cultures	240	8 (3.3%)	16 (6.7%)	52 (21.7%)	60 (25.0%)	11 (4.6%)	93 (38.8%)		

Item#	COVID-19 impacts	N hospitals who were asked the pertinent item*	Likert scale responses						Yes/No responses	
	To what extent has the COVID-19 pandemic influenced:		**Largely decreased**	**Moderately decreased**	**No impact**	**Moderately increased**	**Largely increased**	**Don't know**	**Yes**	**No**
B3.6	Number of screening cultures to detect MDR	157	10 (6.4%)	12 (7.6%)	66 (42%)	41 (26.1%)	6 (3.8%)	22 (14.0%)		
B3.7	Turnaround time for antimicrobial susceptibility results	240	8 (3.3%)	14 (5.8%)	73 (30.4%)	38 (15.8%)	7 (2.9%)	100 (41.7%)		
B3.8	Ability to carry out routine laboratory quality management activities	171	3 (1.8%)	18 (10.5%)	60 (35.1%)	61 (35.7%)	8 (4.7%)	21 (12.3%)		
B3.9	Ability to carry out molecular testing, including whole genome sequencing for MDR	129	3 (2.3%)	14 (10.9%)	49 (38%)	20 (15.5%)	6 (4.7%)	37 (28.7%)		
B3.10	Availability of procedures and infrastructure of laboratory information systems for AMR reporting	161	5 (3.1%)	9 (5.6%)	80 (49.7%)	44 (27.3%)	5 (3.1%)	18 (11.2%)		
B3.11	Availability of procedures and infrastructure of hospital clinical information systems for AMR response	159	8 (5.0%)	13 (8.2%)	63 (39.6%)	50 (31.4%)	6 (3.8%)	19 (11.9%)		
B3.12	The provision of antibiotics supply in your hospital	516	16 (3.1%)	45 (8.7%)	101 (19.6%)	102 (19.8%)	60 (11.6%)	192 (37.2%)		
	ASP interventions									
B4.1	Preauthorization in your hospital	221	13 (5.9%)	37 (16.7%)	63 (28.5%)	61 (27.6%)	12 (5.4%)	35 (15.8%)		
B4.2	Prospective audit and feedback in your hospital	189	12 (6.3%)	26 (13.8%)	46 (24.3%)	41 (21.7%)	6 (3.2%)	58 (20.7%)		
B4.3	Community-acquired pneumonia (CAP)	233							232 (99.6 %)	1 (0.4%)
B4.4	Hospital-acquired pneumonia (HAP) or ventilator-associated pneumonia (VAP)	185							177 (95.7 %)	8 (4.3%)
B4.5	Intra-abdominal infections	185							172 (93.0 %)	13 (7.0%)

Item#	COVID-19 impacts	N hospitals who were asked the pertinent item*	Likert scale responses						Yes/No responses	
	To what extent has the COVID-19 pandemic influenced:		**Largely decreased**	**Moderately decreased**	**No impact**	**Moderately increased**	**Largely increased**	**Don't know**	**Yes**	**No**
B4.6	Urinary tract infections	229							224 (97.8 %)	5 (2.2%)
B4.7	Skin and soft tissue infections	234							224 (95.7 %)	10 (4.3%)
B4.8	Sepsis	249							208 (83.5 %)	41 (16.5 %)
	Monitoring, reporting and feedback									
B5.1	DDD (defined daily dose) audit of the targeted antimicrobial consumption	246	24 (9.8%)	42 (17.1%)	60 (24.4%)	75 (30.5%)	6 (2.4%)	39 (15.9%)		
B5.2	DOT (duration of treatment) audit of the targeted antimicrobial consumption	185	17 (9.2%)	41 (22.2%)	37 (20.0%)	57 (30.8%)	6 (3.2%)	27 (14.6%)		
B5.3	PPS (point prevalence survey) audit of the targeted antimicrobial consumption	190	11 (5.8%)	29 (15.3%)	34 (17.9%)	47 (24.7%)	4 (2.1%)	65 (34.2%)		
B5.4	Gyssens audit of the targeted antimicrobial consumption	190	27 (14.2%)	43 (22.6%)	55 (28.9%)	57 (30.0%)	5 (2.6%)	3 (1.6%)		
B5.5	Total antibiotic prescription	516	22 (4.3%)	39 (7.6%)	74 (14.3%)	180 (34.9%)	73 (14.1%)	128 (24.8%)		
B5.6	Antibiotic availability	516	7 (1.4%)	49 (9.5%)	98 (19%)	234 (45.3%)	76 (14.7%)	52 (10.1%)		
B5.7	Prescription of WHO Access antibiotics or the first- or second-line treatment for common infections	516	12 (2.3%)	46 (8.9%)	183 (35.5%)	190 (36.8%)	34 (6.6%)	51 (9.9%)		
B5.8	Prescription of WHO Watch antibiotics or treatment for limited group of syndromes should be monitored	516	5 (1.0%)	36 (7.0%)	120 (23.3%)	215 (41.7%)	92 (17.8%)	48 (9.3%)		
B5.9	Prescription of WHO Reserve antibiotics or "last resort" to treat multi- or extensively-drug resistant bacteria	471	15 (3.2%)	22 (4.7%)	156 (33.1%)	191 (40.6%)	63 (13.4%)	24 (5.1%)		
B5.10	Antibiotic use monitoring activities	461	41 (8.9%)	71 (15.4%)	144 (31.2%)	150 (32.5%)	26 (5.6%)	29 (6.3%)		

Item#	COVID-19 impacts	N hospitals who were asked the pertinent item*	Likert scale responses						Yes/No responses	
	To what extent has the COVID-19 pandemic influenced:		**Largely decreased**	**Moderately decreased**	**No impact**	**Moderately increased**	**Largely increased**	**Don't know**	**Yes**	**No**
	Education									
B6.1	The provision of educational activities related to optimizing antibiotic prescribing	318	40 (12.6%)	81 (25.5%)	77 (24.2%)	75 (23.6%)	8 (2.5%)	37 (11.6%)		
	Infection and prevention control									
B7.1	The provision of budgeted funding for IPC	485	10 (2.1%)	45 (9.3%)	106 (21.9%)	191 (39.4%)	107 (22.1%)	26 (5.4%)		
B7.2	Compliance with hand hygiene	516	1 (0.2%)	5 (1%)	23 (4.5%)	168 (32.6%)	298 (7.8%)	21 (4.1%)		
B7.3	Availability of alcohol-based hand rub	516	2 (0.4%)	8 (1.6%)	16 (3.1%)	147 (28.5%)	324 (62.8%)	19 (3.7%)		
B7.4	Availability of personal protective equipment (PPE)	516	4 (0.8%)	8 (1.6%)	15 (2.9%)	138 (26.7%)	333 (64.5%)	18 (3.5%)		
B7.5	Inappropriate IPC practices	516	28 (5.4%)	40 (7.8%)	75 (14.5%)	176 (34.1%)	157 (30.4%)	40 (7.8%)		
B7.6	Ability to cohort patient by multi drug resistant organism (MDRO) status	463	24 (5.2%)	54 (11.7%)	154 (33.3%)	128 (27.6%)	29 (6.3%)	74 (16.0%)		
B7.7	Ability to provide IPC training for healthcare workers	487	20 (4.1%)	54 (11.1%)	65 (13.3%)	242 (49.7%)	80 (16.4%)	26 (5.3%)		

Table showing hospital responses to the 41 COVID-19 items included in the ASP self-assessment.

*The questionnaire was programmed in such a manner that some of the COVID-19-related items were asked as a follow-up to a related core item that was responded "Yes", which explains the varying denominators; for example: "Does your hospital allocate any budgeted financial support for ASP activities?" (item# A1.2), if answered "Yes" was followed by "To what extent has the COVID-19 pandemic influenced the provision of budgeted financial support for ASP activities in your hospital? (item# B1.1).