CAPTURA

Capturing data on Antimicrobial resistance Patterns and Trends in Use in Regions of Asia

CAPTURA Epidemiology report

World Health Organization

WHO Test Laboratory

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1. Data volume

Documenting the volume of testing performed by a laboratory is useful for monitoring changes in sampling practices over time and for comparing the workloads between laboratories. One may also identify time periods where data entry is incomplete, and many laboratories experienced a significant decrease in bacteriological testing in April 2020 with the arrival of COVID-19.

Some laboratories enter all bacteriological results into WHONET, whereas other only enter the results for positive samples. Some laboratories enter the results from other laboratory sections, including mycology, parasitology, and virology.

The below table and figure present the number of isolate records and the number of patients over time.

Laboratory	Number of isolates	Number of patients	Isolates per patient	2000
TST	622	277	2.2	277

Table 1: The number of isolates and patients by laboratory over time. For each time period, the numbers indicate the number of patient records, including negative results.

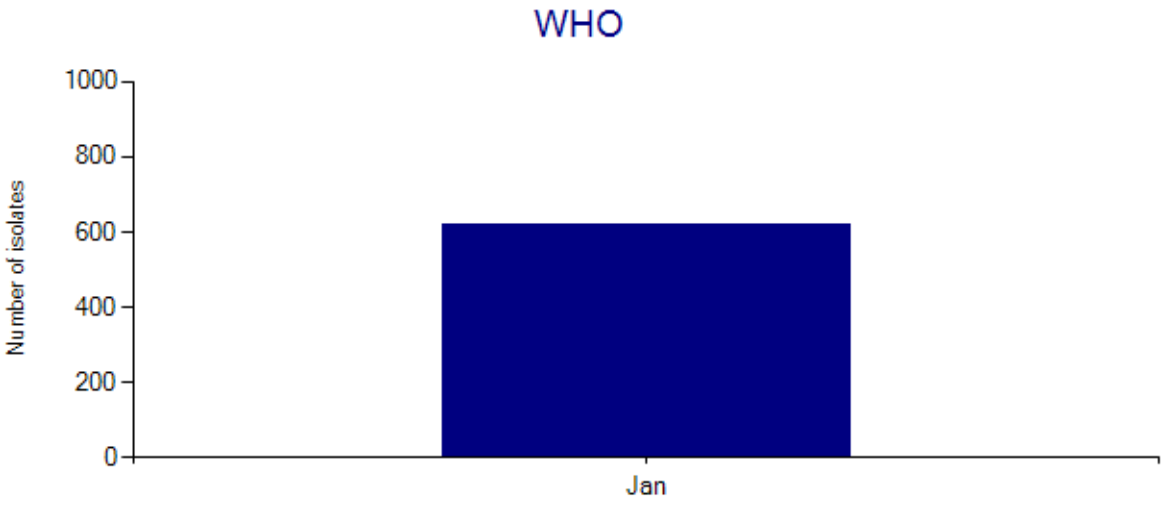

Figure 1: The distribution of isolates over time, including negative results.

The table includes the average number of isolate records per patient. This metric quantifies how often patients have multiple samples taken over time. In low-resource settings, this number is typically between 1.1 and 1.5 isolates per patient. A lower number may indicate that there are few patients with multiple samples, but it may also suggest that there are no meaningful identification numbers that can be used to track patients over time. A higher number may suggest one of two problems: 1) identification numbers are reused for different patients over time; or 2) there may be a problem in the data export from a laboratory information system or in the BacLink configuration.

2. Patient and sample details

2.1 Patient demographics

The distribution of patients by sex and age group is displayed in the below figures.

- Sex: Male - 47.1%, Female - 52.9%
    - In many countries, the number of isolates from female patients exceeds the number of isolates from male patients for a number of reasons: 1) a large proportion of laboratory samples are often from urinary tract infections in women; 2) women may seek medical assistance more frequently than men; and 3) in many countries, women have a longer lifespan than men.
- Median age group: Male = 25-34, Female = 25-34
    - The age distribution will reflect the patient population served by the laboratory.

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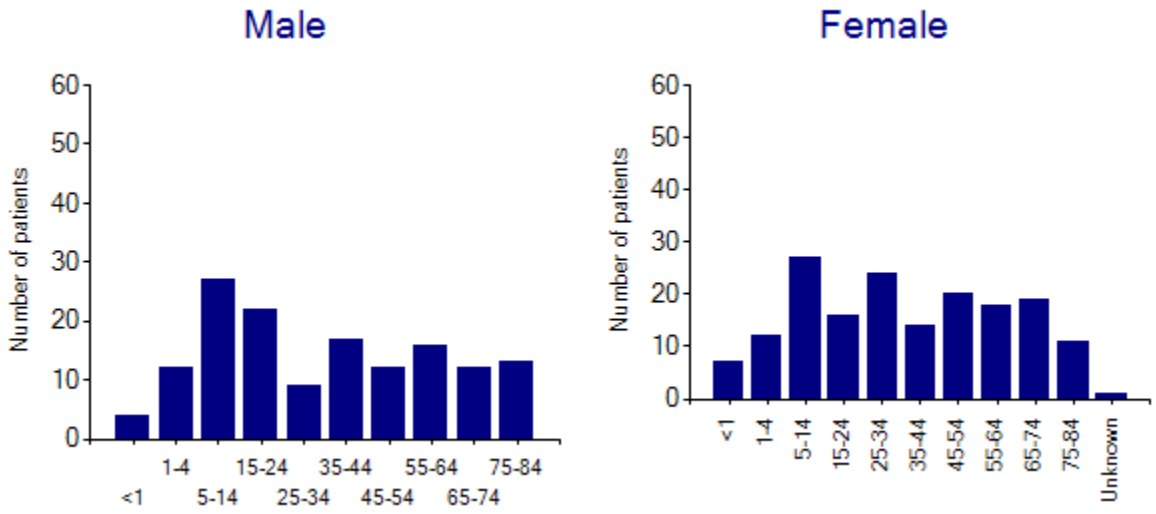

Figure 2: Distribution of the number of patients by sex and age group

2.2 Location details

The distributions of patients by top ten "location" and "location type" are displayed below. The location generally refers to the specific location where samples are collected, such as "Neurology", "Diabetes clinic", or the name of a town, farm, restaurant, or environmental site.

Location type is a category of location such as "inpatient", "outpatient", "farm", "restaurant", or "river". The use of standard WHONET codes is recommended to facilitate comparison of results between laboratories, but this is not required.

Location	Number of isolates	(%)	Number of patients	Isolates per patient
Outpatient	124	19.9	99	1.3
Emergency Unit	85	13.7	69	1.2
oncol	68	10.9	49	1.4
med1	59	9.5	48	1.2
icu1	52	8.4	44	1.2
card	50	8	45	1.1
csurg	44	7.1	40	1.1
neuro	42	6.8	36	1.2
id	37	5.9	31	1.2
med2	26	4.2	24	1.1

Table 2: The distribution of isolates and patients by location. The location codes are those used by the laboratory to identify the specimen collection site.

Location type	Number of isolates	(%)	Number of patients	Isolates per patient
inx	328	52.7	196	1.7
out	123	19.8	98	1.3
eme	85	13.7	69	1.2
icu	81	13	66	1.2
oth	5	0.8	5	1

Table 3: The distribution of isolates and patients by location type. The user of standard WHONET location types is recommended to facilitate comparisons with other laboratories, but is not required.

2.3 Sample details

As displayed in the below figure, WHONET specimen types can be grouped into eight broad categories: Blood, Genital, Respiratory, Soft tissue and body fluids, Stool, Urine, Other, and Unknown.

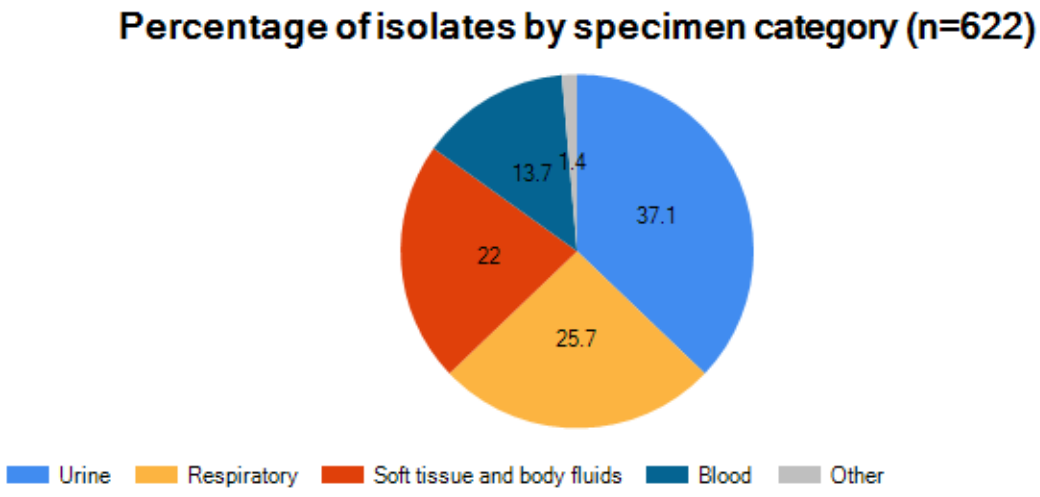

Figure 3: The figure shows the number of isolates stratified by specimen category.

3. Organism statistics

3.1 Organism frequencies

The most common use of WHONET is for bacterial results. However, WHONET can be used to manage results from other pathogens. The below table summarizes results according to organism type.

Organism type	Number of isolates	(%)	Number of patients	Isolates per patient
Aerobic Gram-positive bacteria	334	53.7	197	1.7
Aerobic Gram-negative bacteria	287	46.1	180	1.6
Other results	1	0.2	1	1

Table 4: Distribution of results by organism type.

** Negative results: This category includes findings such as "No growth", "No enteric pathogens found", "Normal flora", and "Mixed bacterial species present".*

The below table displays the most frequent results and the average number of isolates per patient. For community pathogens, this average number of isolates per patient is usually low, for example less than 1.2. For hospital pathogens, the average number of isolates per patient is often much higher, especially in intensive care units.

Organism	Code	Number of isolates	(%)	Number of patients	Isolates per patient
Staphylococcus, coagulase negative	scn	105	16.9	82	1.3
Escherichia coli	eco	86	13.8	71	1.2
Staphylococcus aureus	sau	86	13.8	76	1.1
Enterococcus sp.	ent	81	13	67	1.2
Pseudomonas aeruginosa	pae	32	5.1	31	1
Haemophilus influenzae	hin	24	3.9	24	1
Klebsiella pneumoniae	kpn	23	3.7	23	1
Proteus mirabilis	pmi	22	3.5	18	1.2
Corynebacterium sp. (diphtheroids)	cdp	21	3.4	19	1.1
Streptococcus viridans, alpha-hem.	svi	18	2.9	16	1.1

Table 5: The distribution of the most common organism results.

The below table summarizes WHONET's alerts for "important species". Such pathogens are typically of public health importance because of their potential for outbreaks. They are often included in national disease control programs.

Organisms	Number of isolates	Priority
Neisseria meningitidis	2	High priority
Bordetella bronchiseptica	4	Medium priority
Pseudomonas aeruginosa	32	Medium priority
Pseudomonas fluorescens	4	Medium priority
Stenotrophomonas maltophilia	10	Medium priority

Table 6: Public health alerts - important species

3.2 Organism frequencies by specimen categories

The below figures display the most frequent results by specimen category. The most common pathogens are listed below by category.

Specimen category	Most common organism (%)
Blood	Staphylococcus, coagulase negative - (48%)
Other	Staphylococcus aureus ss. aureus - (44%)
Respiratory	Staphylococcus aureus ss. aureus - (19%)
Soft tissue and body fluids	Staphylococcus, coagulase negative - (25%)
Urine	Escherichia coli - (25%)

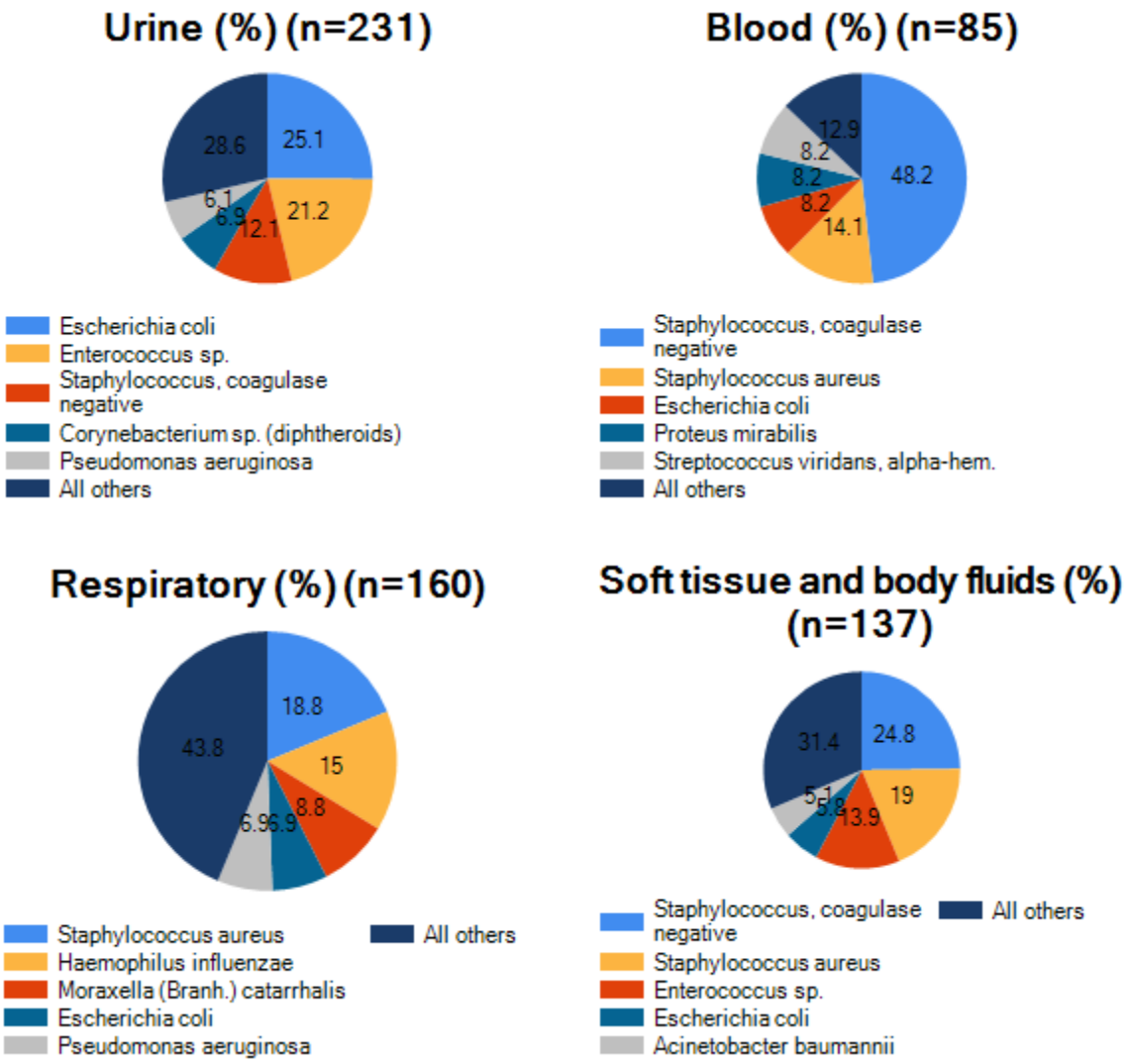

Figure 4: Most common organisms by specimen category. Numbers represent the percentage of isolates.

3.3 Organism trends

It is valuable to study changes in organism isolation over time. Organism frequencies depend on several factors.

The frequency of organisms seen in a microbiology laboratory may change over time for different reasons.

- Microbial factors

    - Long-term changes in organism epidemiology related to organism dissemination, virulence factors, and disease prevention measures such as vaccination and improved sanitation
    - Short-term changes suggestive of disease outbreaks. Statistical algorithms for automated outbreak detection are described in a separate section.
- Non-microbial factors
    - Healthcare services provided and patient populations
    - Sampling practices
    - Laboratory capacity and practices for organism identification

A simple way to look for long-term changes is with simple linear regression of organism counts over time, as shown in the below table.

No results found

Table 7: Organisms with statistically significant increases in organism frequency over time using simple linear regression. p<0.05 - The slope indicates that estimated change in the number of patients by quarter.

No results found

Table 8: Organisms with statistically significant decreases in organism frequency over time using simple linear regression. p<0.05 - The slope indicates that estimated change in the number of patients by quarter.

4. Antimicrobial statistics

4.1 Gram-positive and Gram-negative antibiograms

Appendix A contains the cumulative antimicrobial susceptibility test statistics for Gram-positive and Gram-negative bacteria, typically known as an "antibiogram". The number of isolates tested is greater than or equal to 20. The official recommendation from the CLSI M39 document and others is at least 30 isolates, but a limit of 20 is still useful, especially in a low-resource setting with smaller data volumes and for organisms of clinical importance.

Policymakers must be very aware of problems in laboratory test quality and different types of bias due to patient presentation, sampling practices, and laboratory test practices. Routine microbiology laboratory data typically underestimates the incidence of microbial disease but overestimates the proportion of resistance.

4.2 Isolate alerts - Important resistance

The below table summarizes WHONET's high- and medium-priority "important resistance" alerts. The findings should be confirmed to ensure that there is no error in the organism identification or in the antimicrobial susceptibility test.

WHO has defined a "Global Priority List of Antimicrobial Resistant Bacteria". These are summarized in a separate section.

Organisms	Alert	Number of isolates	Priority
Enterobacteriaceae	Carbapenems = Non-susceptible	31	High priority
Streptococcus sp.	Vancomycin or Teicoplanin = Non-susceptible	1	High priority
Streptococcus, beta-hemolytic	Penicillins = Non-susceptible	3	High priority
Enterobacteriaceae	Possible ESBL-producing Enterobacteriaceae	9	Medium priority
Enterococcus sp.	Vancomycin-resistant Enterococcus	11	Medium priority
Staphylococcus aureus	Methicillin-resistant Staphylococcus aureus	23	Medium priority

Table 9: Public health alerts - important resistance

4.3 Multidrug resistance: ECDC definitions of MDR/XDR/PDR

In a 2012 publication, the European Centre for Disease Prevention and Control (ECDC) proposed definitions for common bacterial pathogens resistant to multiple antimicrobials. MDR/XDR/PDR results are summarized in the below table.

- MDR Multidrug resistance
- XDR Extensive drug resistance
- PDR Pan-drug resistance

Organism	Number of isolates	MDR	Possible XDR	Possible PDR
Staphylococcus aureus	86	25 (29%)	10 (12%)	4 (5%)
Enterococcus faecalis	1			
Escherichia coli	86	4 (5%)		
Klebsiella pneumoniae	23			
Pseudomonas aeruginosa	32	2 (6%)	2 (6%)	
Acinetobacter sp.	8	1 (13%)		

Table 10: MDR, XDR, PDR summary

4.4 Multidrug resistance: Resistance profiles

One of the most valuable, but least utilized, analyses in WHONET is "resistance profiles" for studying multidrug resistance. The study of multidrug resistance has several applications:

- Phenotypic strain tracking facilitates the monitoring of distinct microbial subpopulations, greatly improving the recognition of 1) new strains; and 2) hospital and community outbreaks. Clusters identified by phenotypic tracking could be investigated by molecular typing to confirm clonality.
- The study of cross-resistance is useful in the development of treatment guidelines, including: 1) the determination of recommended "first-line" and "second-line" treatment options; and 2) estimating the value of combination therapy on local pathogens.
- Predicting resistance mechanisms based on the results from antimicrobials within a specific antimicrobial class or subclass or related classes.
- Exploring potential errors in laboratory test practices, for example the finding of isolates of Escherichia coli susceptible to ampicillin but resistant to imipenem is unlikely, and may be due to a testing error, for example with imipenem disks that have lost their disk potency.

In a section on "Antimicrobial susceptibility test practices", a set of "core antimicrobials" for Staphylococcus aureus and Escherichia coli has been proposed based on the data analyzed in this report. The below tables use these core antimicrobials to create resistance profiles. The tables only include isolates that were tested against all core antimicrobials.

Organism	Number of antibiotics	Core antibiotics	Number of isolates tested against all antimicrobials (%)
Staphylococcus aureus	7	Penicillin G, Erythromycin, Clindamycin, Oxacillin, Gentamicin, Trimethoprim/Sulfamethoxazole, Ciprofloxacin	86/86 (100%)
Escherichia coli	9	Cephalothin, Ampicillin, Gentamicin, Trimethoprim/Sulfamethoxazole, Cefotaxime, Imipenem, Cefuroxime, Mezlocillin, Aztreonam	84/86 (98%)

Resistance profile	Number of isolates	%Isolates	Number of patients
PEN	23	26.7	22
PEN ERY	17	19.8	17
(Susceptible)	9	10.5	9
PEN OXA	5	5.8	5
ERY	4	4.7	4
ERY CIP	4	4.7	4
PEN ERY CLI OXA CIP	4	4.7	4
PEN ERY CLI OXA GEN SXT CIP	4	4.7	4
PEN ERY CIP	3	3.5	3
PEN ERY OXA CIP	3	3.5	3

Table 11: Multi-drug resistance profiles for Staphylococcus aureus

Resistance profile	Number of isolates	%Isolates	Number of patients
(Susceptible)	45	53.6	41
CEP AMP MEZ	10	11.9	9
CEP	6	7.1	6
CEP AMP	4	4.8	4
AMP MEZ	3	3.6	3
AMP SXT MEZ	3	3.6	3
CTX	2	2.4	2
CEP AMP CXM	2	2.4	2
CEP AMP CTX CXM	2	2.4	2
SXT	1	1.2	1

Table 12: Multi-drug resistance profiles for Escherichia coli

5. Reporting to the World Health Organization and the United Nations

5.1 WHO Global Priority List of Antibiotic-Resistant Bacteria

Priority	Organism	Antibiotic results	Number (%)
Critical	Acinetobacter spp.	Carbapenem-resistant	-
	Pseudomonas aeruginosa	Carbapenem-resistant	-
	Escherichia coli	Cefotaxime-resistant	0/70 (0%)
	Escherichia coli	Ceftriaxone-resistant	-
	Escherichia coli	Meropenem-resistant	-
High	Enterococcus faecium	Vancomycin-resistant	-
	Staphylococcus aureus	Methicillin-resistant (MRSA)	-
	Staphylococcus aureus	Vancomycin-resistant	0/76 (0%)
	Staphylococcus aureus	Vancomycin-intermediate	0/76 (0%)
	Helicobacter pylori	Clarithromycin-resistant	-
	Campylobacter spp.	Fluoroquinolone-resistant	-
	Salmonella spp.	Fluoroquinolone-resistant (Ciprofloxacin)	-
	Neisseria gonorrhoeae	Third generation cephalosporin-resistant	-
	Neisseria gonorrhoeae	Fluoroquinolone-resistant	-
Medium	Streptococcus pneumoniae	Penicillin non-susceptible	-
	Haemophilus influenzae	Ampicillin-resistant	8/24 (33%)
	Shigella spp.	Fluoroquinolone-resistant	-

Table 13: WHO Global priority list of antibiotic-resistant bacteria

5.2 WHO GLASS results

The WHO Global Antimicrobial Resistance Surveillance System (GLASS) collects annual data on specific antimicrobials from eight pathogens from four specimen types. Two of the GLASS statistics have been selected as indicators for the United Nations Sustainable Development Goals.

Specimen type	Organisms
Blood	Staphylococcus aureus, Streptococcus pneumoniae, Escherichia coli, Klebsiella pneumoniae, Acinetobacter spp., Salmonella spp.
Urine	Escherichia coli, Klebsiella pneumoniae
Stool	Salmonella spp., Shigella spp.
Genital	Neisseria gonorrhoeae

The below tables present the statistics for the number of patients with the samples, organisms, and antibiotics requested by the WHO GLASS protocol.

Specimen	Number of patients
BLOOD	66
URINE	171

Table 14: The number of patients with the specimen types requested by WHO GLASS.

Specimen	Pathogen	Number of patients
BLOOD	ESCCOL	6
BLOOD	KLEPNE	2
BLOOD	STAAUR	11
BLOOD	STRPNE	5
URINE	ESCCOL	51
URINE	KLEPNE	12

Table 15: The number of patients with the specimen types and organisms requested by WHO GLASS.

Specimen	Pathogen	Antibiotic	Number of patients	Number tested	%Resistant	%Intermediate	%Susceptible
URINE	ESCCOL	AMP	51	50	22	2	76
URINE	ESCCOL	CTX	51	50		4	96
URINE	ESCCOL	IPM	51	50			100
URINE	ESCCOL	J01C	51	50	22	2	76
URINE	ESCCOL	J01DD	51	51		3.9	96.1
URINE	ESCCOL	J01DH	51	50			100
URINE	ESCCOL	J01EE	51	50	8		92
URINE	ESCCOL	SXT	51	50	8		92

Table 16: The number of patients and antimicrobial statistics for the specimen types, organisms, and antimicrobials requested by WHO GLASS.

5.3 United Nations Sustainable Development Goals

The United Nations has selected two of the above metrics as indicators for the United Nations Sustainable Developments Goals.

SDG 3.d.2: Percentage of bloodstream infection due to methicillin-resistant Staphylococcus aureus (MRSA) and Escherichia coli resistant to 3rd-generation cephalosporin (e.g., ESBL- E. coli) among patients seeking care and whose blood sample is taken and tested.

1. % Methicillin-resistant Staphylococcus aureus in blood (Oxacillin): Insufficient data
2. % Methicillin-resistant Staphylococcus aureus in blood (Cefoxitin): No results found
3. % Third-generation cephalosporin-resistance Escherichia coli in blood: Insufficient data

6. Cluster detection

It is possible to find statistically significant "case clusters" from routine microbiology laboratory data using mathematical algorithms, such as those offered by the free SaTScan software, SaTScan.org. The most valuable use of these approaches is to find possible community and hospital infectious disease outbreaks. However, the data analyst must keep in mind that there are both "outbreak" and "pseudo-outbreak" explanations for statistically significant case clusters.

- True infectious disease outbreak
- Changes in patient identification and sampling practices
- Changes in laboratory testing practices
- Contamination rates of clinical samples
- Deficiencies in laboratory reagents leading to incorrect results
- Variable availability of laboratory reagents leading to variability capabilities
- Variable completeness and practices for data entry

Ultimately, these algorithms cannot make the definitive ascertainment that certain findings represent a true disease outbreak. Rather, the goal is to use laboratory data to identify statistical findings that merit further investigation and possible response by infection control staff for possible hospital breakpoints and public health authorities for possible community outbreaks.

One must also keep in mind that statistical algorithms applied to microbiology laboratory data may not be able to find all outbreaks.

- Many patients involved in an outbreak do not have diagnostic samples taken because they are asymptomatic or have mild symptoms or because there is limited capacity and resources to support sample collection and laboratory testing.
- Small patient numbers and slowly developing clusters may be indistinguishable for baseline random variation.
- The cluster detection algorithm model and algorithm parameters may be poorly optimized for detecting certain types of cluster curves.

6.1 Cluster detection by species

Using "Organism" as the cluster detection variable, the below figures display a number of statistically significant case clusters.

Cluster description	Cluster start date	Cluster end date	p-value - Lowest	Number observed - Total	Total days in cluster
TST - Corynebacterium sp. (diphtheroids)	25/1/2000	25/1/2000	0.00689	7	1
TST - Klebsiella pneumoniae	28/1/2000	30/1/2000	0.021	10	3

Table 17: Cluster detection by species

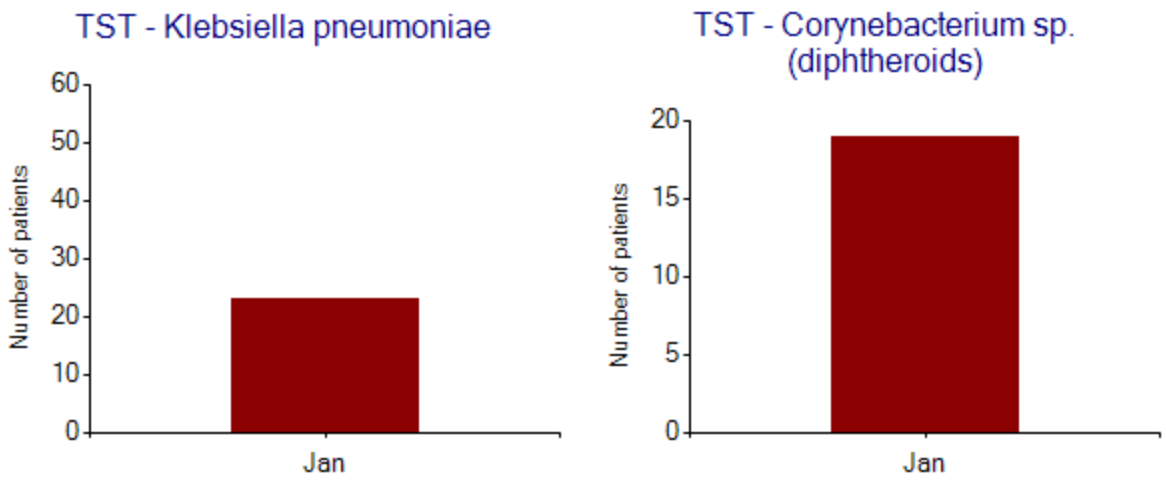

Figure 5: Statistically significant case clusters detected by organism identification (p <= 0.05). The monthly count of patients is presented, and the statistically significant time period detected by SaTScan is indicated in red.

6.2 Cluster detection by resistance profile

The above examples illustrate an approach to cluster detection using the "organism" name. This can be further extended to include cluster detection by geographic location, by hospital ward, by resistance profile, and also be combinations of variables, such as "location + resistance profile". For example, Figure 7 displays statistically significant clusters of phenotypic subpopulations of Escherichia coli defined by the multidrug resistance profile. Each letter represents a particular antimicrobial.

Cluster description	Cluster start date	Cluster end date	p-value - Lowest	Number observed - Total	Total days in cluster
TST: E	22/1/2000	22/1/2000	0.000822	4	1

Table 18: Cluster detection for Staphylococcus aureus detected by resistance profile.

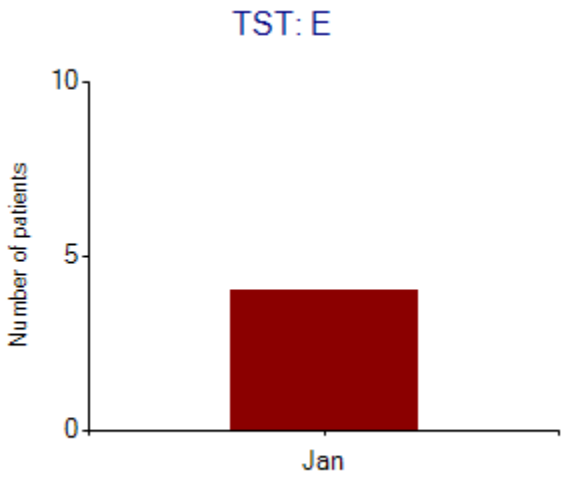

Figure 6: Statistically significant case clusters of Staphylococcus aureus detected by resistance profile (p <= 0.05). The weekly count of patients is presented, and the statistically significant time period detected by SaTScan is indicated in red.

No results found

Table 19: Cluster detection for Escherichia coli detected by resistance profile.

No results found

Figure 7: Statistically significant case clusters of Escherichia coli detected by resistance profile (p <= Not applicable). The weekly count of patients is presented, and the statistically significant time period detected by SaTScan is indicated in red.

Appendix A. Antibiograms

Organism	Number of patients	AMC	AMP	CEP	CIP	CLI	ERY	GEN	NIT	OXA	PEN	SXT	VAN
Staphylococcus, coagulase negative	82	39			66	77	46	79	91	39	17	60	
Staphylococcus aureus	76				75	86	45	95		76	18	95	
Enterococcus sp.	67		88	8			14	60	90		85		85

Table 20: Gram-positive antibiogram. %Susceptible, first isolate per patient

Code	Antibiotic	Code	Antibiotic	Code	Antibiotic
AMC	Amoxicillin/Clavulanic acid	CLI	Clindamycin	OXA	Oxacillin
AMP	Ampicillin	ERY	Erythromycin	PEN	Penicillin G
CEP	Cephalothin	GEN	Gentamicin	SXT	Trimethoprim/Sulfamethoxazole
CIP	Ciprofloxacin	NIT	Nitrofurantoin	VAN	Vancomycin

Table 21: Gram-positive antibiotics.

Organism	Number of patients	AMK	AMC	AMP	ATM	CRB	CTX	FOX	CAZ	CXM	CEP	CHL	CIP	GEN	IPM	MEZ	NIT	NOR	PIP	TOB	SXT
Escherichia coli	71		84	70	99		93	76		93	64		76	97	99	80	96	100	88		93
Pseudomonas aeruginosa	31	97			81	77			100			6	77	87	94	29			94	97	6
Haemophilus influenzae	24		100	62			100			100			100		100						96
Klebsiella pneumoniae	23			9	100		96			100	100			100	96	70					96

Table 22: Gram-negative antibiogram. %Susceptible, first isolate per patient

Code	Antibiotic	Code	Antibiotic	Code	Antibiotic
AMK	Amikacin	CAZ	Ceftazidime	MEZ	Mezlocillin
AMC	Amoxicillin/Clavulanic acid	CXM	Cefuroxime	NIT	Nitrofurantoin
AMP	Ampicillin	CEP	Cephalothin	NOR	Norfloxacin
ATM	Aztreonam	CHL	Chloramphenicol	PIP	Piperacillin
CRB	Carbenicillin	CIP	Ciprofloxacin	TOB	Tobramycin
CTX	Cefotaxime	GEN	Gentamicin	SXT	Trimethoprim/Sulfamethoxazole
FOX	Cefoxitin	IPM	Imipenem		

Table 23: Gram-negative antibiotics.