



Multi-Drug Resistant Organisms (MDROs) Reported to the DPHSS from Morbidity Reports 2009-2020 and from the Guam Memorial Hospital Authority (GMHA) 2016-2020

Office of Epidemiology and Research

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All clinics and hospitals on Guam report to the Department of Public Health and Social Services (DPHSS) any infectious diseases of significance, which are included in the Guam Official Reportable Disease List. This on-going collaboration also includes summary morbidity data on reportable infectious diseases, including multi-drug resistant organisms (MDRO's).

Multi-drug resistant organisms (MDRO's) are an important public health problem because, by definition, these bacteria and other microorganisms have developed resistance to one or more classes of anti-microbial drugs.^{2,3} An example is Methicillin resistant Staphylococcus aureus or MRSA. MRSA is the most common MDRO reported on Guam (Figures 1 and 2). Notice that there is a definitive decrease in reported MDRO's as a result of the SARS-CoV-2/COVID-19 pandemic.

Figure 1 illustrates how MRSA comprises Guam's main MDRO, which has been increasing each year since 2009. Figure 2, which omits MRSA, shows that Guam has increasing problems with MDRO's, including Escherichia (E. coli), Acinetobacter, Klebsiella and Pseudomonas. The data for 2009-2020 are provide in Table 1. All MDRO's are showing increases since 2009, except as noted above, for the decrease in MDRO's due to SARS-CoV-2/COVID-19 pandemic. Guam does have a problem with the ESBL producing bacteria. This stands for "Extended Spectrum Beta-Lactamase" which is produced by some bacteria of the Enterobacter family, such as Escherichia coli and Klebsiella pneumonia. The reason this is significant is ESBL enzymes break down and destroy some commonly used antibiotics and make these drugs ineffective for treating infections. Most infections associated with ESBLs have been associated with poor outcomes based on literature.

The Guam Memorial Hospital Authority (GMHA) is the public hospital utilized by the people of Guam. The GMHA provides real-time notification to the Department of Public Health and Social Services (DPHSS) of any infectious diseases of significance and weekly data on syndromic

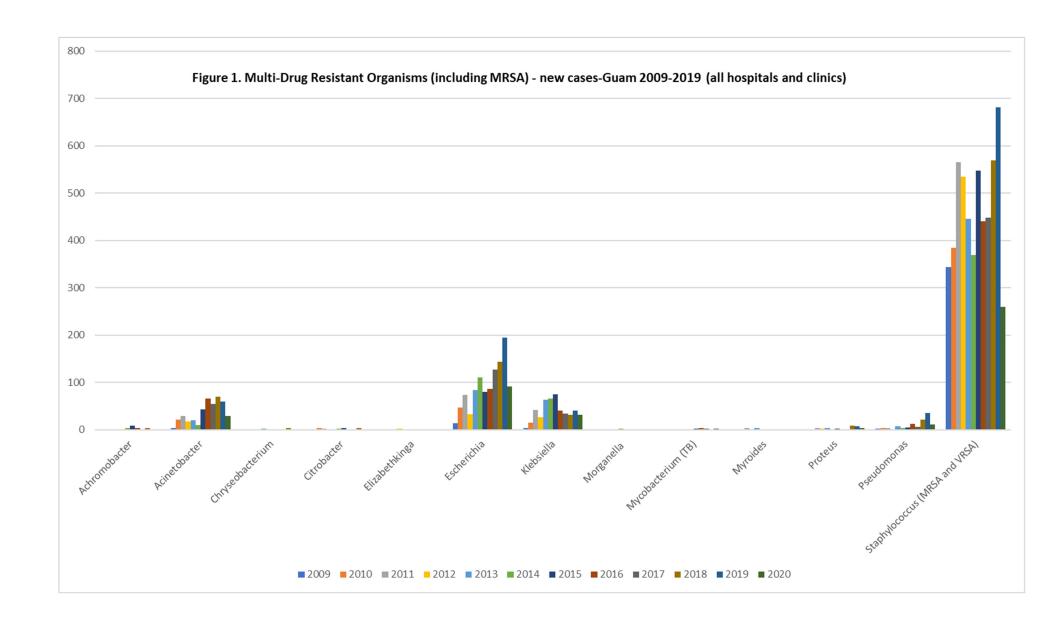
surveillance of diseases related to potential outbreaks. This on-going DPHSS and GMHA collaboration also includes summary morbidity data on reportable infectious diseases on a monthly basis, including multi-drug resistant organisms (MDRO's).

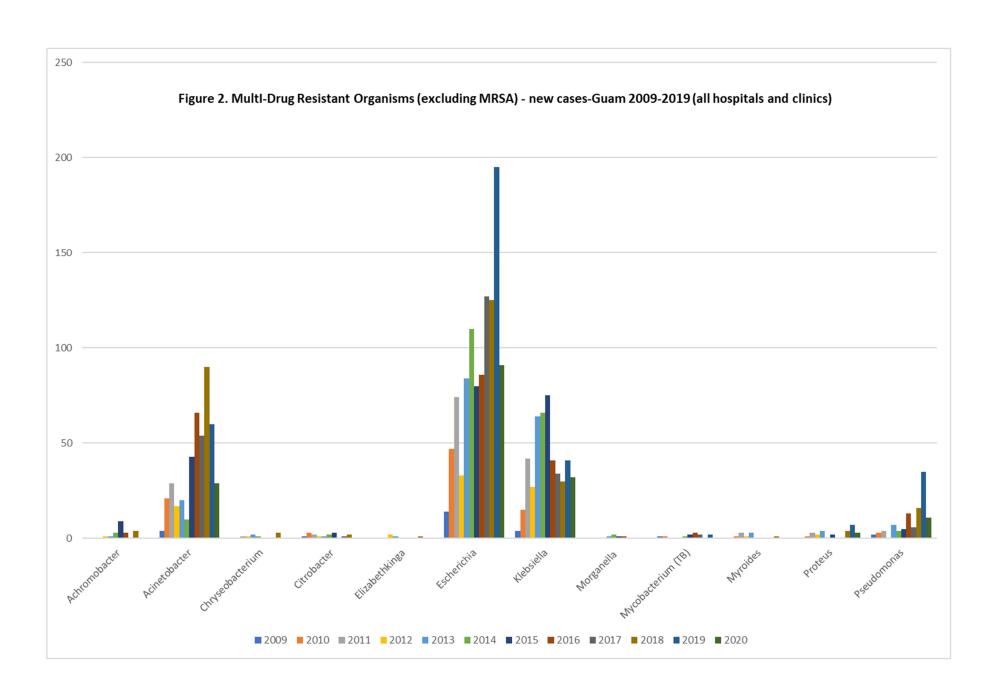
Five years of data (2016-2020) on multi-drug resistant organisms (MDRO's) at GMHA, were compiled and analyzed, utilizing the definition of HAI from the Centers for Disease Control and Prevention (CDC) National Healthcare Safety Network's Report <u>Identifying Healthcare-associated infections (HAI) for NHSN Surveillance</u>, whereby "an infection is considered a Healthcare-associated infection (HAI) if the date of event of the NHSN site-specific infection criterion occurs on or after the 3rd calendar day of admission to an inpatient location where day of admission is calendar day 1."² Utilizing the date of admission to the hospital and the date that the MDRO specimen was taken were the criteria used to define and HAI (i.e. the specimen date subtracted from the admission date). Therefore an infection occurring less than 3 days before hospitalization is defined as a community acquired infection, and a MDRO infection occurring 3 or more days after hospitalization, is considered a hospital acquired infection (HAI). Note that this is a basic measure that doesn't account for all variables associated with the treatment and/or reporting of MDROs.

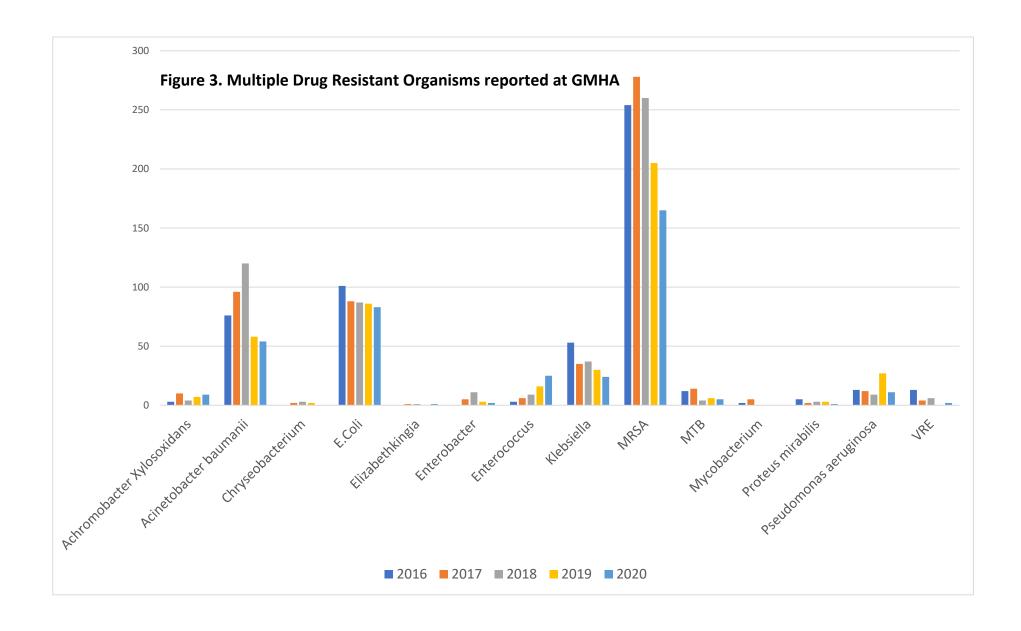
Data analysis (Table 2, Figure 3) shows that hospital acquired infections (HAI) from 2016-2020 at GMHA, utilizing the NHSN definition, include 60.1% of Acinetobacter baumanii, 74.1% of Chryseobacterium and 66.7% of Elizabethkingia organisms. E.coli was more likely to be community acquired (83.1%) than hospital acquired (16.9%), as was Achromobacter Xylosoxidans (66.7% community acquired and 33.3% hospital acquired), MRSA (81.1% community acquired and 19.9% hospital acquired), Klebsiella (78.2% community acquired and 21.8% hospital acquired), VRE (68% community acquired and 32% hospital acquired) along with 95.1% of mycobacterium and 100% of MTB (community acquired). Slightly more than one-half of Enterobacter (57.1%), Entercoccus (52.5%), Proteus (64.3%) and Pseudomonas (54.2%) were community acquired, with almost

one-half hospital acquired: Enterobacter (42.9%), Enterococcus (47.5%), Pseudomonas (45.8%), along with just over one-third 35.7% Proteus. Notice that the GMHA reported MDRO's also decreased in 2020, however MDRO's at GMHA have shown decreases for several years prior to 2020, showing that infection control practices implemented by the GMHA Antimicrobial Stewardship Program (ASP) are working. The GMHA ASP charter states that the purpose is to serve as a panel of experts for reviewing and investigating multi-drug resistant cases and antibiotic reviews. This team seeks to improve and promote optimal clinical outcomes related to the use of antimicrobials by guiding appropriate selection of antimicrobial drug regimens, dose, duration of therapy, and route of administration and thus, reducing adverse events, and minimizing toxicity. The team consists of the GMHA Clinical Pharmacist (PharmD), Infectious Disease physician, Infection Preventionist, and Microbiology Supervisor.

The Guam Epidemiology and Laboratory Capacity (ELC) program participates in two key CDC funded grant activities related to the prevention and abatement of MDRO's: an Infection Prevention Control (IPC) project and an overall set of activities related to MDROs/HAI prevention. The Infection Prevention and Control (IPC) project completed an initial baseline assessment of clinics on the island is to determine existing infection prevention and control practices at the beginning of the COVID-19 pandemic. A second assessment is being conducted in 2021 to ensure widespread participation in infection prevention practices, including site visits to clinics and a more extensive survey of current IPC practices, as well as training on infection control practices, if needed. ELC program staff also attend meetings of the GMHA Infection Control Committee. Other activities are planned for MDRO/HAI prevention and anti-microbial stewardship as well as community health education about MDROs.







In 2019 the Centers for Disease Control and Prevention released the latest report on <u>Antibiotic Resistant Threats in the United States</u> (2019 AR Threats Report).⁵ The bacteria and fungi listed in the 2019 AR Threats Report include the following:

Urgent Threats:

- Carbapenem-resistant Acinetobacter
- Candida auris
- Clostridioides difficile
- Carbapenem-resistant Enterobacterales
- Drug-resistant Neisseria gonorrhoeae

Serious Threats:

- Drug-resistant Campylobacter
- Drug-resistant Candida
- ESBL-producing Enterobacterales
- Vancomycin-resistant Enterococci (VRE)
- Multidrug-resistant Pseudomonas aeruginosa
- Drug-resistant nontyphoidal Salmonella
- <u>Drug-resistant Salmonella serotype Typhi</u>
- Drug-resistant *Shigella*
- Methicillin-resistant Staphylococcus aureus (MRSA)
- Drug-resistant Streptococcus pneumoniae
- Drug-resistant Tuberculosis

Concerning Threats:

- Erythromycin-Resistant Group A Streptococcus
- Clindamycin-resistant Group B Streptococcus

Watch List:

- Azole-resistant *Aspergillus fumigatus*
- Drug-resistant Mycoplasma genitalium
- Drug-resistant Bordetella pertussis

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¹ Official-Guam-Reportable-Disease-List-updated-12.29.2020.pdf

² Centers for Disease Control and Prevention, National Healthcare Safety Network: https://www.cdc.gov/nhsn/index.html

³ Centers for Disease Control and Prevention in Healthcare Settings-Background: https://www.cdc.gov/infectioncontrol/guidelines/mdro/background.html

⁴ National Healthcare Safety Network January 2021. Identifying Healthcare-associated infections (HAI) for NHSN Surveillance, page 2-7: https://www.cdc.gov/nhsn/pdfs/pscmanual/2psc identifyinghais nhsncurrent.pdf

⁵ Centers for Disease Control and Prevention, Infection Control in Healthcare Settings-Epidemiology: https://www.cdc.gov/infectioncontrol/guidelines/mdro/epidemiology.html

⁶ Centers for Disease Control and Prevention Antibiotic Resistant Threats in the United States (2019 AR Threats Report). https://www.cdc.gov/drugresistance/biggest-threats.html

	Table 1: N											
	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Achromobacter	0	0	0	1	1	3	9	3	0	3	0	0
Acinetobacter	4	21	29	17	20	10	43	66	54	70	60	29
Chryseobacterium	0	0	1	1	2	1	0	0	0	3	0	0
Citrobacter	1	3	2	1	1	2	3	0	1	4	0	0
Elizabethkinga	0	0	0	2	1	0	0	0	0	1	0	0
Escherichia	14	47	74	33	84	110	80	86	127	144	195	91
Klebsiella	4	15	42	27	64	66	75	41	34	32	41	32
Morganella	0	0	0	0	1	2	1	1	0	1	0	0
Mycobacterium (TB)	1	1	0	0	0	1	2	3	2	0	2	0
Myroides	0	1	3	1	3	0	0	0	0	1	0	0
Proteus	0	1	3	2	4	0	2	0	0	9	7	3
Pseudomonas	2	3	4	0	7	4	5	13	6	21	35	11
Staphylococcus (MRSA and VRSA)	344	385	565	535	445	369	548	440	448	569	681	259
TOTAL	370	477	723	620	633	568	768	653	672	858	1021	425

				Table 2: Multi-drug resistance organisms reported at GMHA														
		2016			2017			2018			2019			2020			5 year	
	date		ROW	date		ROW	date		ROW	date		ROW	date		ROW	date	total	ROW
l .	difference		Total	difference		Total	difference		Total	difference		Total	difference		Total	difference		Total
	less than		Total	less than		Total	less than		Total	less than		Total	less than		Total	less than		Total
	3 days	3 + days		3 days	3 + days		3 days	3 + days		3 days	3 + days		3 days	3 + days		3 days	3 + days	
Achromobacter Xylosoxidans	3	0	3	6	4	10	3	1	4	5	2	7	5	4	9	22	11	33
Acinetobacter baumanii	58	18	76	31	65	96	48	72	120	18	40	58	6	48	54	161	243	404
Chryseobacterium	0	0	0	0	2	2	1	2	3	1	1	2	0	0	0	2	5	7
E.Coli	88	13	101	70	18	88	74	13	87	68	18	86	70	13	83	370	75	445
Elizabethkingia	0	0	0	1	0	1	0	1	1	0	0	0	0	1	1	1	2	3
Enterobacter	0	0	0	5	0	5	5	6	11	1	2	3	1	1	2	12	9	21
Enterococcus	3	0	3	1	5	6	2	7	9	9	7	16	16	9	25	31	28	59
Klebsiella	43	10	53	27	8	35	30	7	37	21	9	30	19	5	24	140	39	179
MRSA	239	15	254	225	53	278	194	66	260	156	49	205	128	37	165	942	220	1162
MTB	12	0	12	13	1	14	4	0	4	6	0	6	4	1	5	39	2	41
Mycobacterium	2	0	2	5	0	5										7	0	7
Proteus mirabilis	5	0	5	2	0	2	0	3	3	2	1	3	0	1	1	9	5	14
Pseudomonas aeruginosa	11	2	13	8	4	12	8	1	9	10	17	27	2	9	11	39	33	72
VRE	10	3	13	2	2	4	4	2	6	0	0	0	1	1	2	17	8	25
total	474	61	535	396	162	558	373	181	554	297	146	443	252	130	382	1792	680	2472
d	date difference		ROW Total	date difference		ROW Total	date difference		ROW Total	date difference		ROW Total	date difference		ROW Total	date difference		ROW Total
	less than 3 days	3 + days		less than 3 days	3 + days		less than 3 days	3 + days		less than			less than	0		less than		
Achromobacter Xylosoxidans	100.0						J uays			3 days	3 + days			3 + days		3 days	3 + days	
Acinetobacter baumanii		0.0	100.0	60.0	40.0	100.0	75.0	25.0	100.0		3 + days 28.6	100.0	3 days 55.6	3 + days	100.0	3 days 66.7	3 + days 33.3	100.0
Characab ti	76.3	23.7	100.0	60.0	40.0 67.7	100.0		25.0 60.0	100.0	3 days	·	100.0	3 days	,	100.0	,	,	100.0
Chryseobacterium	76.3 0.0						75.0			3 days 71.4	28.6		3 days 55.6	44.4		66.7	33.3	
E.Coli		23.7	100.0	32.3	67.7	100.0	75.0 40.0	60.0	100.0	3 days 71.4 31.0	28.6	100.0	3 days 55.6 11.1	44.4	100.0	66.7	33.3 60.1	100.0
	0.0	23.7	100.0	32.3	67.7	100.0	75.0 40.0 33.3	60.0	100.0	3 days 71.4 31.0 50.0	28.6 69.0 50.0	100.0	3 days 55.6 11.1	44.4 88.9 0.0	100.0	66.7 39.9 28.6	33.3 60.1 71.4	100.0
E.Coli	0.0 87.1	23.7 0.0 12.9	100.0 0.0 100.0	32.3 0.0 79.5	67.7 100.0 20.5	100.0 100.0 100.0	75.0 40.0 33.3 85.1	60.0 66.7 14.9	100.0 100.0 100.0	3 days 71.4 31.0 50.0 79.1	28.6 69.0 50.0 20.9	100.0 100.0 100.0	3 days 55.6 11.1 0.0 84.3	44.4 88.9 0.0 15.7	100.0 0.0 100.0	66.7 39.9 28.6 83.1	33.3 60.1 71.4 16.9	100.0 100.0 100.0
E.Coli Elizabethkingia	0.0 87.1 0.0	23.7 0.0 12.9 0.0	100.0 0.0 100.0 0.0	32.3 0.0 79.5 100.0	67.7 100.0 20.5 0.0	100.0 100.0 100.0 100.0	75.0 40.0 33.3 85.1 0.0	60.0 66.7 14.9 100.0	100.0 100.0 100.0 100.0	3 days 71.4 31.0 50.0 79.1 0.0	28.6 69.0 50.0 20.9 0.0	100.0 100.0 100.0 0.0	3 days 55.6 11.1 0.0 84.3 0.0	44.4 88.9 0.0 15.7 100.0	100.0 0.0 100.0 100.0	66.7 39.9 28.6 83.1 33.3	33.3 60.1 71.4 16.9 66.7	100.0 100.0 100.0 100.0
E.Coli Elizabethkingia Enterobacter	0.0 87.1 0.0 0.0	23.7 0.0 12.9 0.0 0.0	100.0 0.0 100.0 0.0 0.0	32.3 0.0 79.5 100.0	67.7 100.0 20.5 0.0	100.0 100.0 100.0 100.0 100.0	75.0 40.0 33.3 85.1 0.0 45.5	60.0 66.7 14.9 100.0 54.5	100.0 100.0 100.0 100.0 100.0	3 days 71.4 31.0 50.0 79.1 0.0 33.3	28.6 69.0 50.0 20.9 0.0 66.7	100.0 100.0 100.0 0.0 100.0	3 days 55.6 11.1 0.0 84.3 0.0 50.0	44.4 88.9 0.0 15.7 100.0 50.0	100.0 0.0 100.0 100.0 100.0	66.7 39.9 28.6 83.1 33.3 57.1	33.3 60.1 71.4 16.9 66.7 42.9	100.0 100.0 100.0 100.0 100.0
E.Coli Elizabethkingia Enterobacter Enterococcus	0.0 87.1 0.0 0.0 100.0	23.7 0.0 12.9 0.0 0.0 0.0	100.0 0.0 100.0 0.0 0.0 100.0	32.3 0.0 79.5 100.0 100.0 16.7	67.7 100.0 20.5 0.0 0.0 83.3	100.0 100.0 100.0 100.0 100.0 100.0	75.0 40.0 33.3 85.1 0.0 45.5 22.2	60.0 66.7 14.9 100.0 54.5 77.8	100.0 100.0 100.0 100.0 100.0 100.0	3 days 71.4 31.0 50.0 79.1 0.0 33.3 56.3	28.6 69.0 50.0 20.9 0.0 66.7 43.8	100.0 100.0 100.0 0.0 100.0 100.0	3 days 55.6 11.1 0.0 84.3 0.0 50.0 64.0	44.4 88.9 0.0 15.7 100.0 50.0 36.0	100.0 0.0 100.0 100.0 100.0 100.0	66.7 39.9 28.6 83.1 33.3 57.1 52.5	33.3 60.1 71.4 16.9 66.7 42.9 47.5	100.0 100.0 100.0 100.0 100.0 100.0
E.Coli Elizabethkingia Enterobacter Enterococcus Klebsiella	0.0 87.1 0.0 0.0 100.0 81.1	23.7 0.0 12.9 0.0 0.0 0.0 18.9	100.0 0.0 100.0 0.0 0.0 100.0 100.0	32.3 0.0 79.5 100.0 100.0 16.7 77.1	67.7 100.0 20.5 0.0 0.0 83.3 22.9	100.0 100.0 100.0 100.0 100.0 100.0 100.0	75.0 40.0 33.3 85.1 0.0 45.5 22.2 81.1	60.0 66.7 14.9 100.0 54.5 77.8 18.9	100.0 100.0 100.0 100.0 100.0 100.0 100.0	3 days 71.4 31.0 50.0 79.1 0.0 33.3 56.3 70.0	28.6 69.0 50.0 20.9 0.0 66.7 43.8 30.0	100.0 100.0 100.0 0.0 100.0 100.0	3 days 55.6 11.1 0.0 84.3 0.0 50.0 64.0 79.2	44.4 88.9 0.0 15.7 100.0 50.0 36.0 20.8	100.0 0.0 100.0 100.0 100.0 100.0 100.0	66.7 39.9 28.6 83.1 33.3 57.1 52.5 78.2	33.3 60.1 71.4 16.9 66.7 42.9 47.5 21.8	100.0 100.0 100.0 100.0 100.0 100.0 100.0
E.Coli Elizabethkingia Enterobacter Enterococcus Klebsiella MRSA	0.0 87.1 0.0 0.0 100.0 81.1 94.1	23.7 0.0 12.9 0.0 0.0 0.0 18.9 5.9	100.0 0.0 100.0 0.0 0.0 100.0 100.0 100.0	32.3 0.0 79.5 100.0 100.0 16.7 77.1 80.9	67.7 100.0 20.5 0.0 0.0 83.3 22.9	100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0	75.0 40.0 33.3 85.1 0.0 45.5 22.2 81.1 74.6	60.0 66.7 14.9 100.0 54.5 77.8 18.9 25.4	100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0	3 days 71.4 31.0 50.0 79.1 0.0 33.3 56.3 70.0 76.1	28.6 69.0 50.0 20.9 0.0 66.7 43.8 30.0 23.9	100.0 100.0 100.0 0.0 100.0 100.0 100.0	3 days 55.6 11.1 0.0 84.3 0.0 50.0 64.0 79.2 77.6	44.4 88.9 0.0 15.7 100.0 50.0 36.0 20.8 22.4	100.0 0.0 100.0 100.0 100.0 100.0 100.0 100.0	66.7 39.9 28.6 83.1 33.3 57.1 52.5 78.2 81.1	33.3 60.1 71.4 16.9 66.7 42.9 47.5 21.8 18.9	100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0
E.Coli Elizabethkingia Enterobacter Enterococcus Klebsiella MRSA MTB	0.0 87.1 0.0 0.0 100.0 81.1 94.1	23.7 0.0 12.9 0.0 0.0 0.0 18.9 5.9 0.0	100.0 0.0 100.0 0.0 0.0 100.0 100.0 100.0 100.0	32.3 0.0 79.5 100.0 100.0 16.7 77.1 80.9 92.9	67.7 100.0 20.5 0.0 0.0 83.3 22.9 19.1 7.1	100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0	75.0 40.0 33.3 85.1 0.0 45.5 22.2 81.1 74.6 100.0	60.0 66.7 14.9 100.0 54.5 77.8 18.9 25.4	100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0	3 days 71.4 31.0 50.0 79.1 0.0 33.3 56.3 70.0 76.1 100.0	28.6 69.0 50.0 20.9 0.0 66.7 43.8 30.0 23.9 0.0	100.0 100.0 100.0 0.0 100.0 100.0 100.0 100.0	3 days 55.6 11.1 0.0 84.3 0.0 50.0 64.0 79.2 77.6 80.0	44.4 88.9 0.0 15.7 100.0 50.0 36.0 20.8 22.4 20.0	100.0 0.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0	66.7 39.9 28.6 83.1 33.3 57.1 52.5 78.2 81.1 95.1	33.3 60.1 71.4 16.9 66.7 42.9 47.5 21.8 18.9	100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0
E.Coli Elizabethkingia Enterobacter Enterococcus Klebsiella MRSA MTB Mycobacterium	0.0 87.1 0.0 0.0 100.0 81.1 94.1 100.0	23.7 0.0 12.9 0.0 0.0 0.0 18.9 5.9 0.0 0.0	100.0 0.0 100.0 0.0 0.0 100.0 100.0 100.0 100.0	32.3 0.0 79.5 100.0 100.0 16.7 77.1 80.9 92.9 100.0	67.7 100.0 20.5 0.0 0.0 83.3 22.9 19.1 7.1 0.0	100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0	75.0 40.0 33.3 85.1 0.0 45.5 22.2 81.1 74.6 100.0 0.0	60.0 66.7 14.9 100.0 54.5 77.8 18.9 25.4 0.0	100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 0.0	3 days 71.4 31.0 50.0 79.1 0.0 33.3 56.3 70.0 76.1 100.0 0.0	28.6 69.0 50.0 20.9 0.0 66.7 43.8 30.0 23.9 0.0	100.0 100.0 100.0 0.0 100.0 100.0 100.0 100.0 100.0	3 days 55.6 11.1 0.0 84.3 0.0 50.0 64.0 79.2 77.6 80.0 0.0	44.4 88.9 0.0 15.7 100.0 50.0 36.0 20.8 22.4 20.0	100.0 0.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 0.0	66.7 39.9 28.6 83.1 33.3 57.1 52.5 78.2 81.1 95.1 100.0	33.3 60.1 71.4 16.9 66.7 42.9 47.5 21.8 18.9 4.9	100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0
E.Coli Elizabethkingia Enterobacter Enterococcus Klebsiella MRSA MTB Mycobacterium Proteus mirabilis Pseudomonas	0.0 87.1 0.0 0.0 100.0 81.1 94.1 100.0 100.0	23.7 0.0 12.9 0.0 0.0 0.0 18.9 5.9 0.0 0.0	100.0 0.0 100.0 0.0 0.0 100.0 100.0 100.0 100.0 100.0	32.3 0.0 79.5 100.0 100.0 16.7 77.1 80.9 92.9 100.0 100.0	67.7 100.0 20.5 0.0 0.0 83.3 22.9 19.1 7.1 0.0	100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0	75.0 40.0 33.3 85.1 0.0 45.5 22.2 81.1 74.6 100.0 0.0	60.0 66.7 14.9 100.0 54.5 77.8 18.9 25.4 0.0 0.0	100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0	3 days 71.4 31.0 50.0 79.1 0.0 33.3 56.3 70.0 76.1 100.0 0.0 66.7	28.6 69.0 50.0 20.9 0.0 66.7 43.8 30.0 23.9 0.0 0.0	100.0 100.0 100.0 0.0 100.0 100.0 100.0 100.0 100.0 100.0	3 days 55.6 11.1 0.0 84.3 0.0 50.0 64.0 79.2 77.6 80.0 0.0	44.4 88.9 0.0 15.7 100.0 50.0 36.0 20.8 22.4 20.0 0.0 100.0	100.0 0.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0	66.7 39.9 28.6 83.1 33.3 57.1 52.5 78.2 81.1 95.1 100.0 64.3	33.3 60.1 71.4 16.9 66.7 42.9 47.5 21.8 18.9 4.9 0.0 35.7	100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0 100.0