Impact of the COVID-19 Pandemic on Antibiotic Overuse & Resistance

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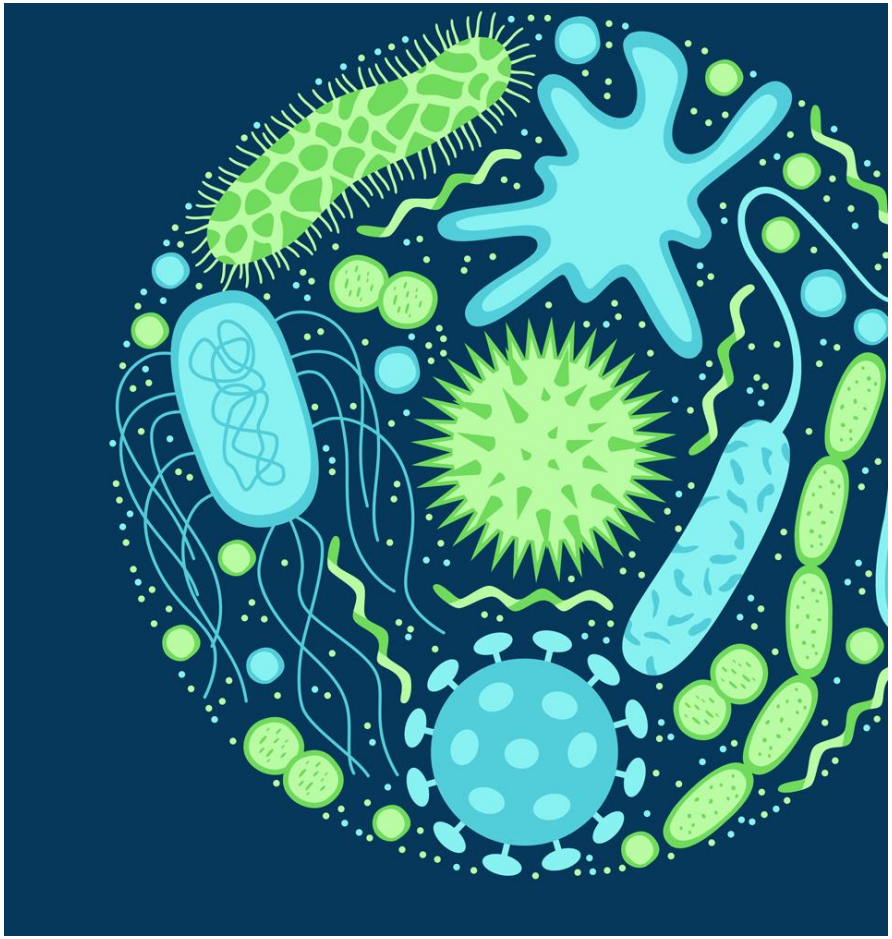

Disclosures

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- Speaker's bureau: Regeneron

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Learning Objectives

At the conclusion of this presentation, attendees will:

1. Evaluate patterns of antibiotic use during COVID-19 surge conditions
2. Describe the impact of the pandemic on multidrug resistant pathogens and healthcare associated infections (HAIs)
3. Apply antimicrobial stewardship lessons learned to the Omicron surge

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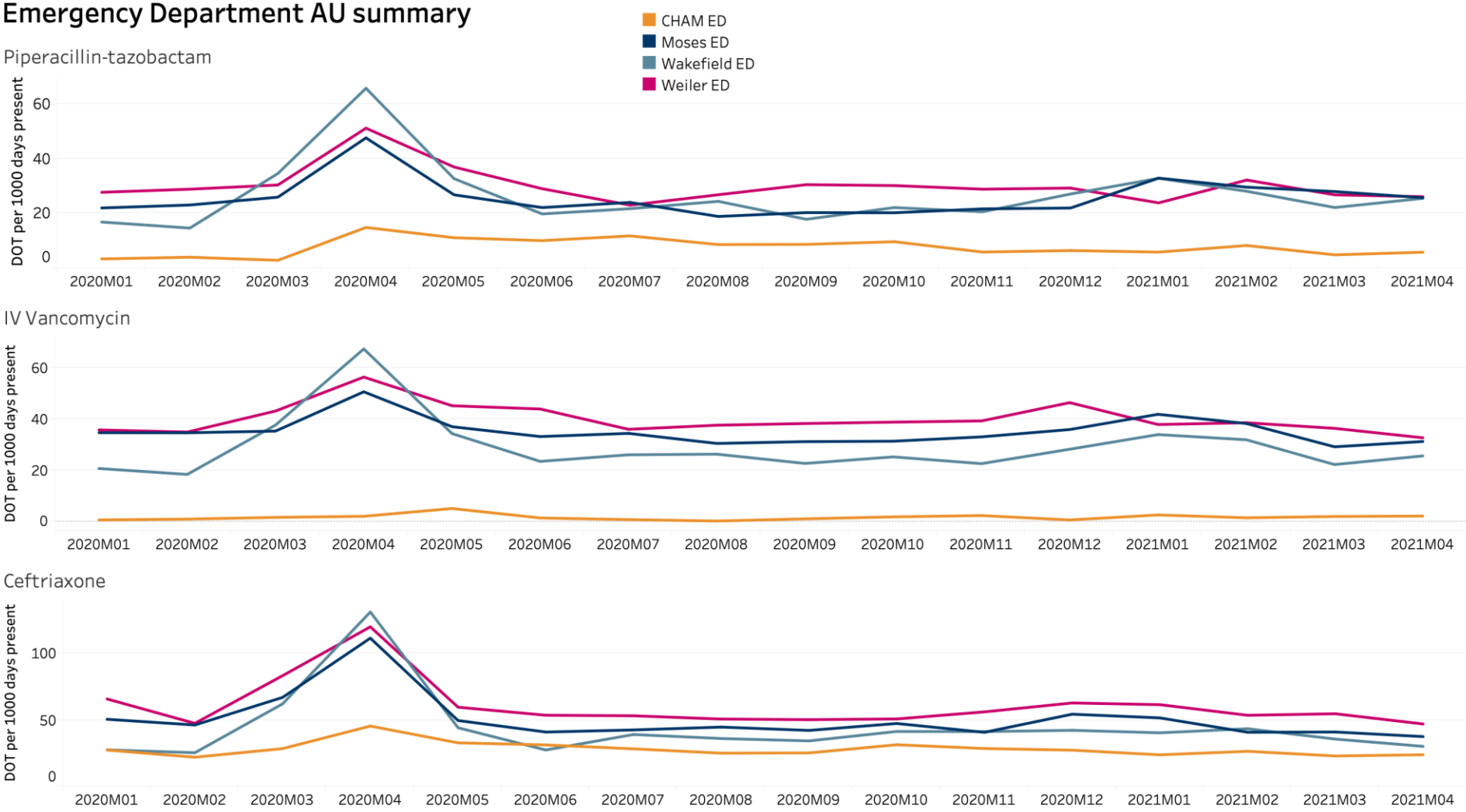
What happened to inpatient antibiotic use at your institution during COVID-19 surges

- Increased at first then stabilized
- Decreased from baseline
- Unchanged from 2019
- I’m not sure

What happened to antibiotic prescriptions in your ambulatory network during the pandemic?

- Increased
- Decreased from baseline
- Unchanged from 2019
- I'm not sure

Emergency Department AU summary



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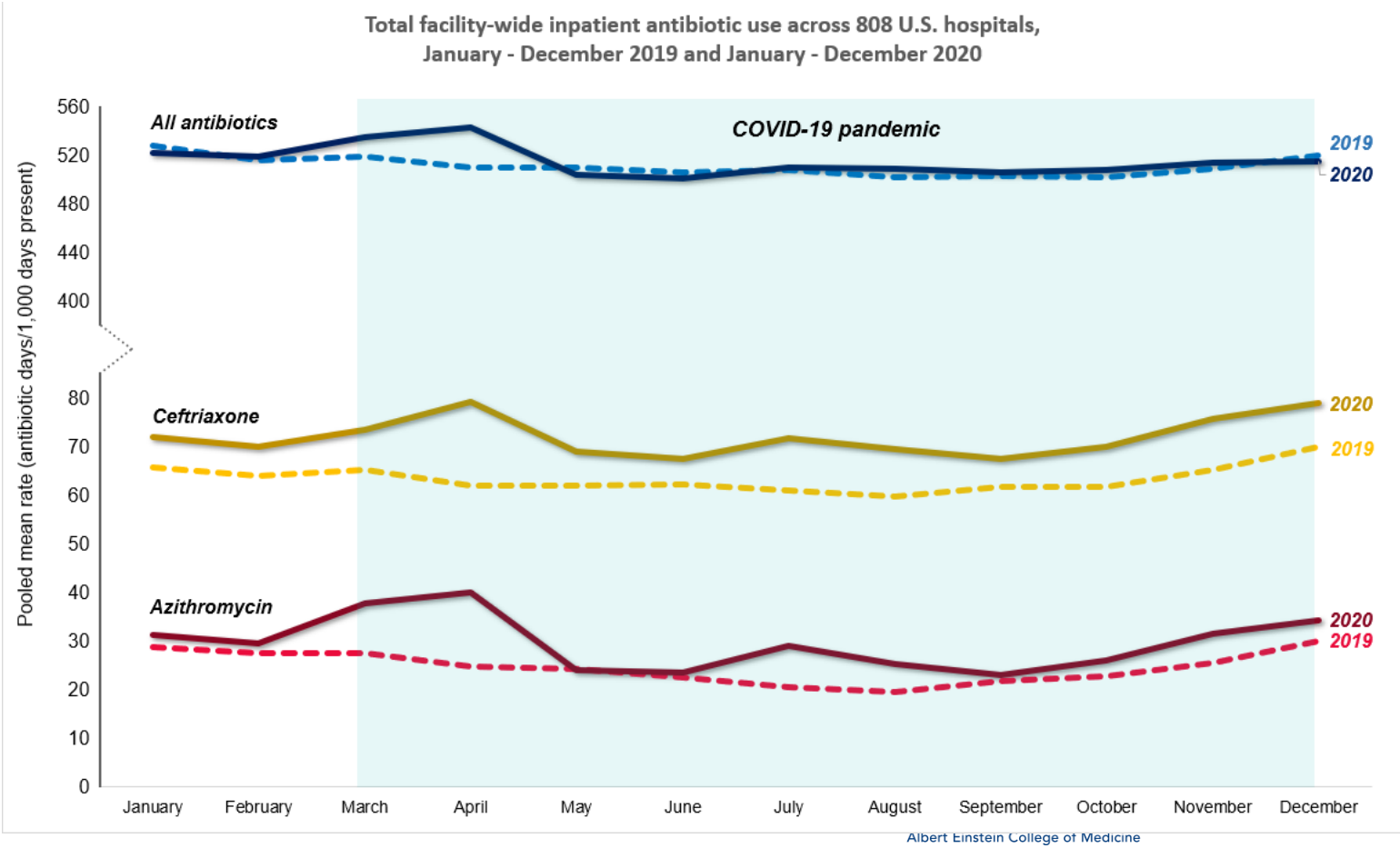
CDC NHSN Antibiotic Use Data



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Doctors Heavily Overprescribed Antibiotics Early in the Pandemic

Now they are using lessons from the experience to urge action on the growing problem of drug-resistant infections before it's too late.

Nori et al. ICHE 2020: retrospective study of 5,853 COVID-19 patients in first surge, 4130 (71%) received at least one antibiotic dose. **Less than 5% had a confirmed bacterial or fungal coinfection.**

Langford et al Clin Micro Infect. 2020 : meta-analysis showed that 72% of COVID-19 patients receive broad spectrum antibiotics and only 8% had a confirmed coinfection

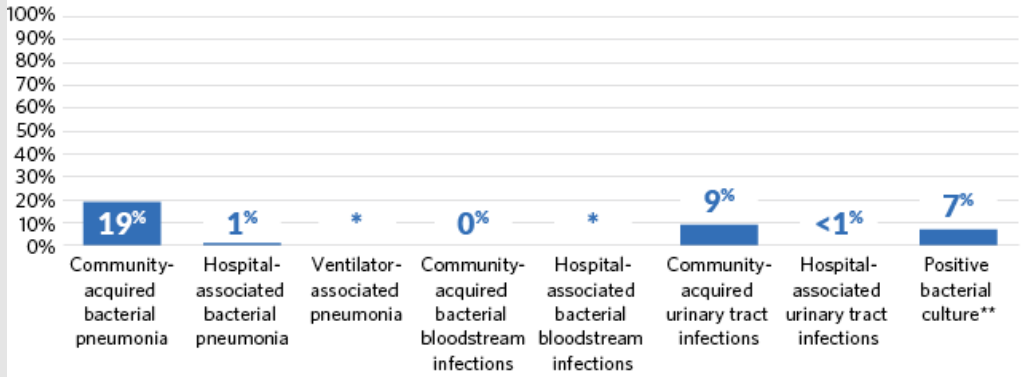
Rose et al, OFID 2021: **80% of inpatients** hospitalized with COVID-19 received antibiotics

Previous progress in AMR reductions could be lost

Pew study showed excess antibiotic use but infrequent bacterial infections in the first 6 months of the pandemic

Figure 1

Occurrence of Bacterial Infections in Hospitalized COVID-19 Patients, as a Percentage of Unique Hospital Admissions



* The occurrence of these infections was too infrequent to report.

** Positive bacterial culture based on presence of susceptibility test results. Includes only respiratory, blood, and urine cultures. All other diagnoses listed are based on ICD-10 diagnosis codes.

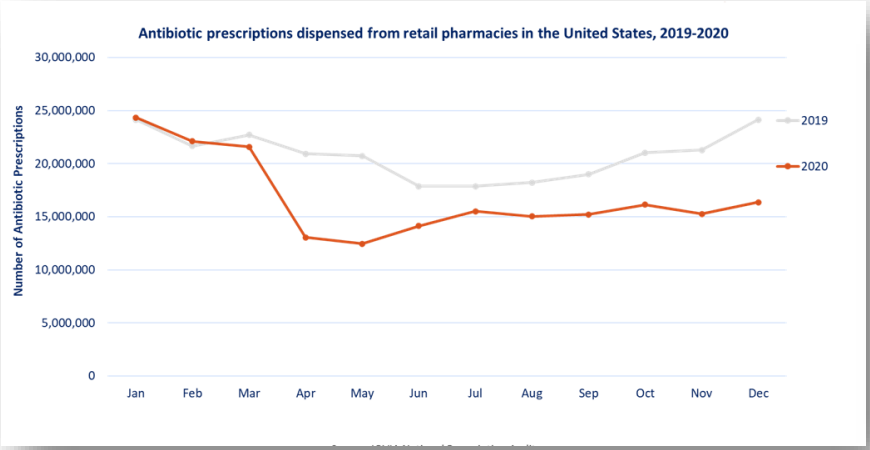
https://www.pewtrusts.org/en/research-and-analysis/issue-briefs/2021/03/could-efforts-to-fight-the-coronavirus-lead-to-overuse-of-antibiotics

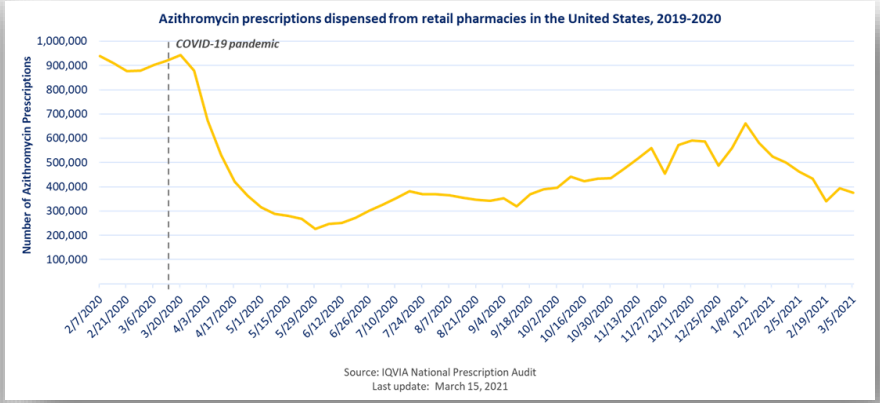
- IBM Watson Health's EHR database of approximately 6,000 hospital admissions from February through July 2020:

1. A majority (52%) of COVID-19 hospital admissions led to **one or more antibiotics** being given to patients; (36% received multiple)
2. Only **20%** of those admitted with COVID-19 were diagnosed with suspected or confirmed bacterial pneumonia, and **9%** were diagnosed with a community acquired urinary tract infection.
3. In most cases, antibiotics were administered **prior to confirmation** of a bacterial infection (within the first 48h of admission).

During initial surge, outpatient antibiotic prescriptions decreased substantially (?access) except azithromycin

- Trends in U.S. Outpatient Antibiotic Prescriptions During the Coronavirus Disease 2019 Pandemicexternal icon
  King LM, Lovegrove MC, Shehab N et al, Clin Infect Dis. 2020 Dec 29





HAIs rates vs. COVID-19 Surges

- MA Baker et al, CID 2021:
- Aim: explore association between COVID-19 surges and HAIs, hospital-onset pathogens, and cluster rates; accounting for local variation in surge timing
- Central line-associated blood stream infections (CLABSI), catheter-associated urinary tract infections (CAUTI), and methicillin-resistant Staphylococcus aureus (MRSA) bacteremia increased above expected rates as COVID-19 burden increased
  - 60% more CLABSIs
  - 43% more CAUTIs,
  - 44% more MRSA bacteremias
- *Clostridioides difficile* infection was not significantly associated
- Hospital-onset bloodstream infections, multidrug resistant organisms, (MRSA, VRE, GNs), and clusters of HO infections each significantly associated with surges

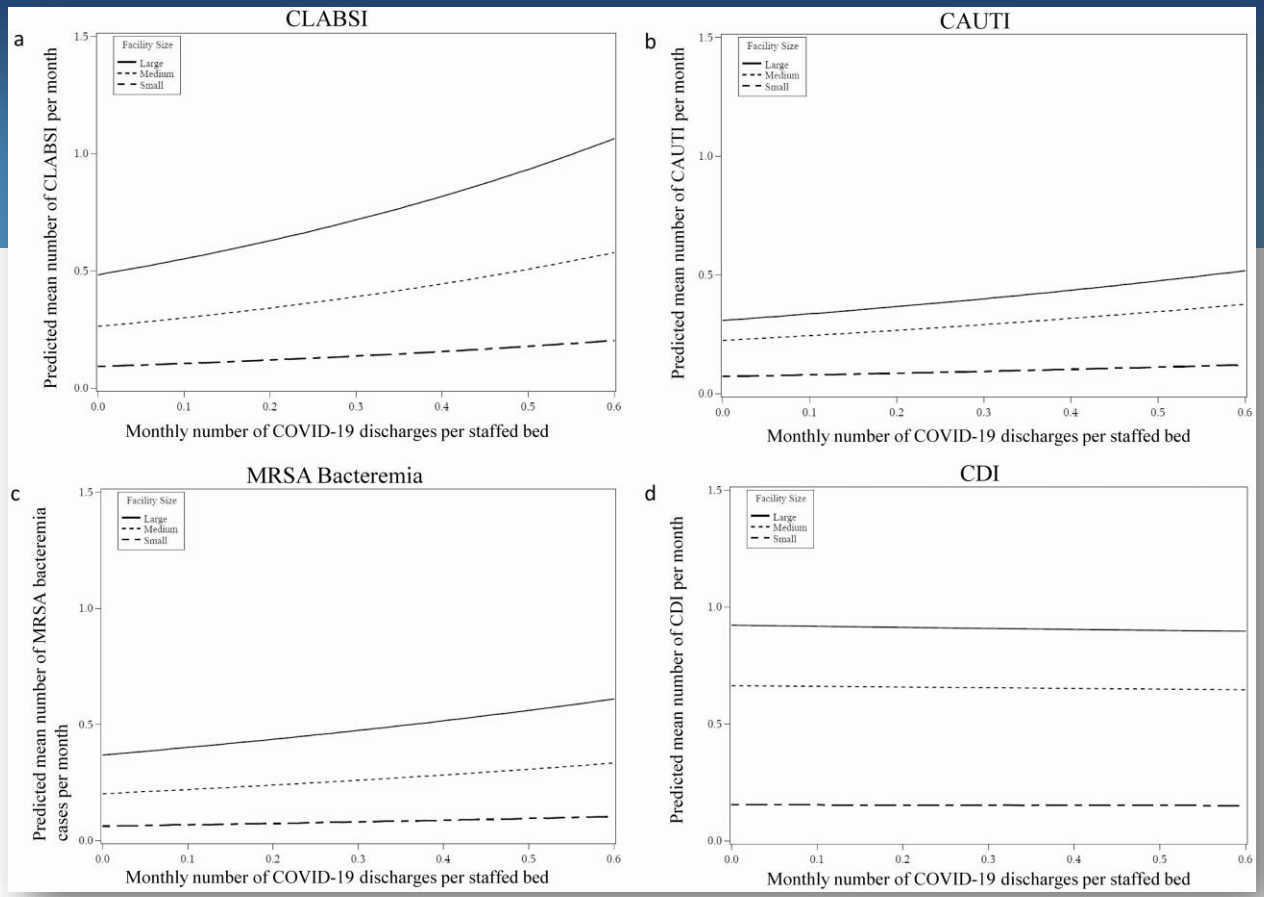


Figure 2. Predicted mean HAI rates as COVID-19 discharges increase. Predicted mean HAI rate by increasing monthly ...

Clin Infect Dis, ciab688, https://doi.org/10.1093/cid/ciab688

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Nationally, significant increases in 2020 were observed for CLABSI, CAUTI, VAE, and MRSA bacteremia compared to 2019. The largest increases occurred during quarter 4 (October, November, December) of 2020

- Weiner-Lastinger et al. *Infect Cont Hosp Epidemiol.* 2021 https://doi.org/10.1017/ice.2021.362

	2020 Q1	2020 Q2	2020 Q3	2020 Q4
CLABSI	-11.8%	27.9%	46.4%	47.0%
CAUTI	-21.3%	No Change[1]	12.7%	18.8%
VAE	11.3%	33.7%	29.0%	44.8%
SSI: Colon surgery	-9.1%	No Change[1]	-6.9%	-8.3%
SSI: Abdominal hysterectomy	-16.0%	No Change[1]	No Change[1]	-13.1%
Laboratory-identified MRSA bacteremia	-7.2%	12.2%	22.5%	33.8%
Laboratory-identified CDI	-17.5%	-10.3%	-8.8%	-5.5%

*Significant decreases were observed in *C. difficile* throughout 2020, compared to 2019

Which COVID-19 patients are at highest risk of antibiotic exposure?

Table 1. Characteristics of Inpatients With COVID-19[a] Stratified by Antibiotic Receipt

Inpatient Characteristics	Inpatients With COVID-19		
	Total N = 213 338 (%)	Received Antibiotics N = 164 943 (77.3%)	Did Not Receive Antibiotics N = 48 395 (22.7%)
Antibiotic started on admission[b]	134 071 (62.8)	134 071 (81.3)	-
Length of therapy (LOT)[c], mean (IQR), days	4.7 (5.0)	6.0 (5.0)	-
Critical care admission[d]	96 218 (45.1)	81 139 (49.2)	15 079 (31.2)
Invasive mechanical ventilation[d]	30 944 (14.5)	29 662 (18.0)	1282 (2.6)
Length of hospital stay, mean (IQR), days	8.4 (7.0)	9.4 (8.0)	5.0 (4.0)
In-hospital mortality	29 082 (13.6)	26 677 (16.2)	2405 (5.0)

"antibiotic use increased with higher COVID-19 burden"

AN Rose et al. Trends in Antibiotic Use in United States Hospitals During the Coronavirus Disease 2019 Pandemic, *Open Forum Infectious Diseases*, Volume 8, Issue 6, June 2021, ofab236, https://doi.org/10.1093/ofid/ofab236

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Why does antibiotic overuse occur?

- Severe COVID-19 indistinguishable from bacterial/fungal sepsis and septic shock
  - Unstable hemodynamics, **elevated inflammatory markers**, persistent fevers, impressive CXRs
- HCW strain, fatigue, fear
- Deployment of non-typical staff, stretched staffing ratios
- Rationing/sharing of PPE during initial surge
- **Increases in device utilization (central line, urinary catheter, and ventilators)**
  - Ventilator utilization increased by 25 – 31% in 2020 Q2 – 2020 Q4

➢Antimicrobials not considered a "precious resource" unlike ICU beds, ventilators, EUA antivirals or immunomodulators

Rawson et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing, *Clinical Infectious Diseases*
https://www.cdc.gov/hai/data/portal/covid-impact-hai.html

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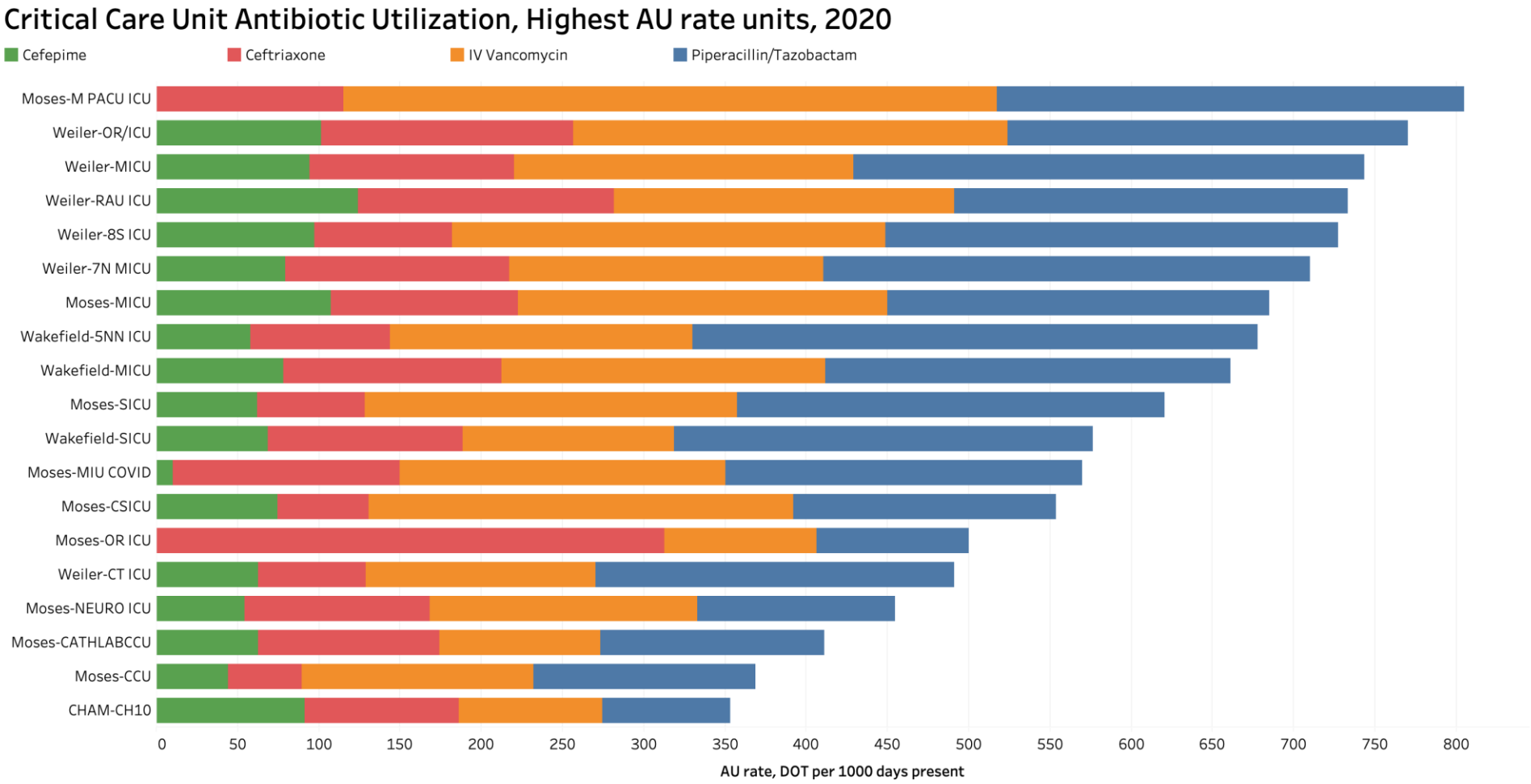
Highest use in newly established surge ICUs



What is known about bacterial & fungal co-infections and COVID-19?

- Risk factors[1]: severe COVID-19, prolonged hospital exposure, critical illness, intubation, indwelling catheters, combination antibiotic therapy, corticosteroids, IL-6 inhibition[2], DM
- <10% of total hospitalized population[3]
- Potentially terminal events[4]
- Pathogenic organisms reported are often hospital-acquired/multi-drug resistant like SARS-1, MERS[3]
- IDSA EIN Survey, May 11-June 3, 2020:
  - 214 physicians responded that superinfections are rarely (42%) or occasionally (44%) observed; predominantly while on mechanical/assisted ventilation (76%)

1. Zhou P, et al Bacterial and fungal infections in COVID-19 patients: A matter of concern [published online ahead of print, 2020 Apr 22]. *Infect Control Hosp Epidemiol*. 2020;1-2. doi:10.1017/ice.2020.156
2. Lucas M Kimmig et al. IL6 inhibition in critically ill COVID-19 patients is associated with increased secondary infections. doi: https://doi.org/10.1101/2020.05.15.20103531
3. Timothy M Rawson et al. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing, *Clinical Infectious Diseases*, , ciaa530,
4. Cornelius J Clancy, M Hong Nguyen, Coronavirus Disease 2019, Superinfections, and Antimicrobial Development: What Can We Expect?, *Clinical Infectious Diseases*, , ciaa524,

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bla_{NDM} as part of Polymicrobial Milieu

Micro	**C. albicans (peritoneal fluid and urine -catheter)** **C. albicans, E. faecalis, S. epi (blood)** **C. albicans (blood)** **CR E. cloacae (respiratory)** **CR E. cloacae (blood)** **CR K. pneumoniae** (blood)**	**CR E. cloacae (urine - catheter)** **E. aerogenes x 2* (blood)** **CR E. cloacae (Resp)**	**S. capitis (blood)** **CR E. cloacae (blood)** **C. albicans (blood)** **CR E. cloacae (resp)**	**MSSA (resp)** **C. koseri (resp)** **CR E. cloacae, P. aeruginosa (resp)** **CR E. cloacae (urine – catheter)** **CR E. cloacae & VRE (urine – catheter)**	**MRSA (resp)** **CR E. cloacae & MRSA (resp)** **CR E. cloacae & MRSA, S. marcescens (resp)** **CR E. cloacae & CR K. pneumoniae (blood)** **E. cloacae (blood)**
Intubation & CVC	**Y**	**Y**	**Y**	**Y**	**Y**
Preceding Abx	Ceftriaxone Doxycycline Ampicillin Micafungin Fluconazole Piperacillin-tazobactam	Azithromycin Ceftriaxone Vancomycin Piperacillin-tazobactam Gentamicin Fluconazole	Ceftriaxone Azithromycin Vancomycin Cefepime Piperacillin-tazobactam	Vancomycin Piperacillin-tazobactam Cefepime Micafungin	Ceftriaxone Doxycycline Piperacillin-tazobactam Vancomycin Cefoxitin Linezolid
Targeted Abx	Tigecycline*** Ceftazidime-Avibactam Aztreonam	Tigecycline***	Tigecycline*** + Gentamicin	Ceftazidime-Avibactam Aztreonam	Tigecycline*** Gentamicin Aztreonam Ceftazidime-Avibactam

Nori et al. Emerging Co-Pathogens: New Delhi Metallo-beta-lactamase producing Enterobacterales Infections in New York City COVID-19 Patients. J Antimicrob Agents. 2020 Sep 25:106179. doi: 10.1016/j.ijantimicag.2020.106179. Online ahead of print.PMID: 32987104

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$_{bla}$NDM, class B Carbapenemase-Producing *E. cloacae*: Bad Bugs… Still No Drugs

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	Female	Male	Male	Female	Male
Age (years)	68	57	63	63	54
Race/Ethnicity	Black/African American	Hispanic/Latino	Black/African American	Hispanic/Latino	Hispanic/Latino
NDM risk factors	No	No	No	No	No
Blood culture d0	Negative	Negative	Negative	Negative	Negative
$_{bla}$NDM, class B carbapenemase gene confirmation	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**
Outcome	Deceased day 34	Deceased day 24	Deceased day 6	Deceased day 39	Discharged to chronic vent facility day 44, then readmitted

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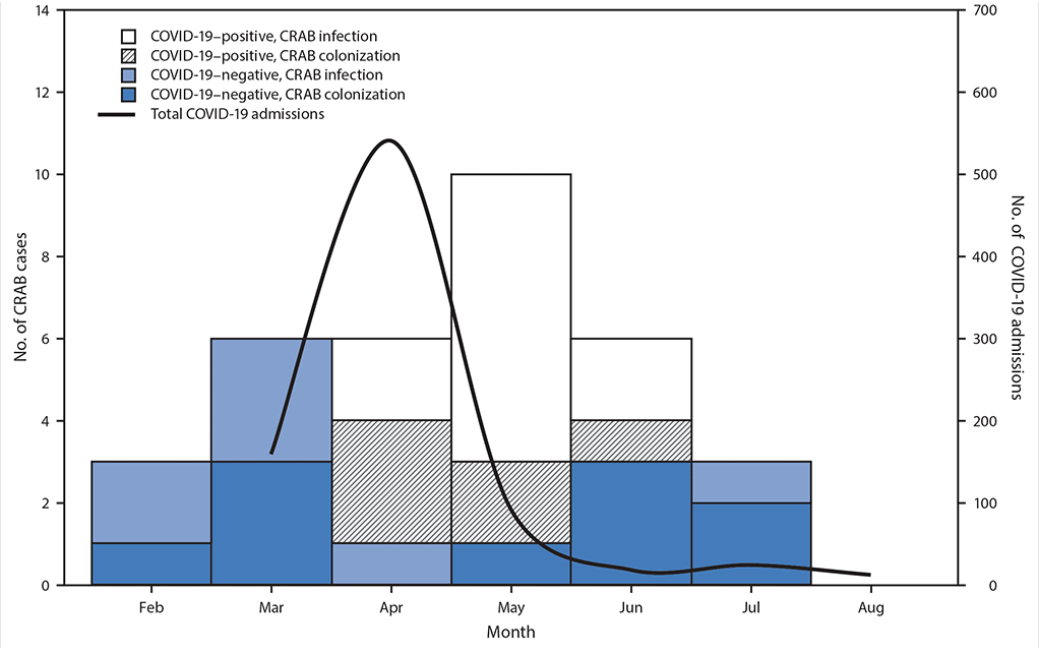
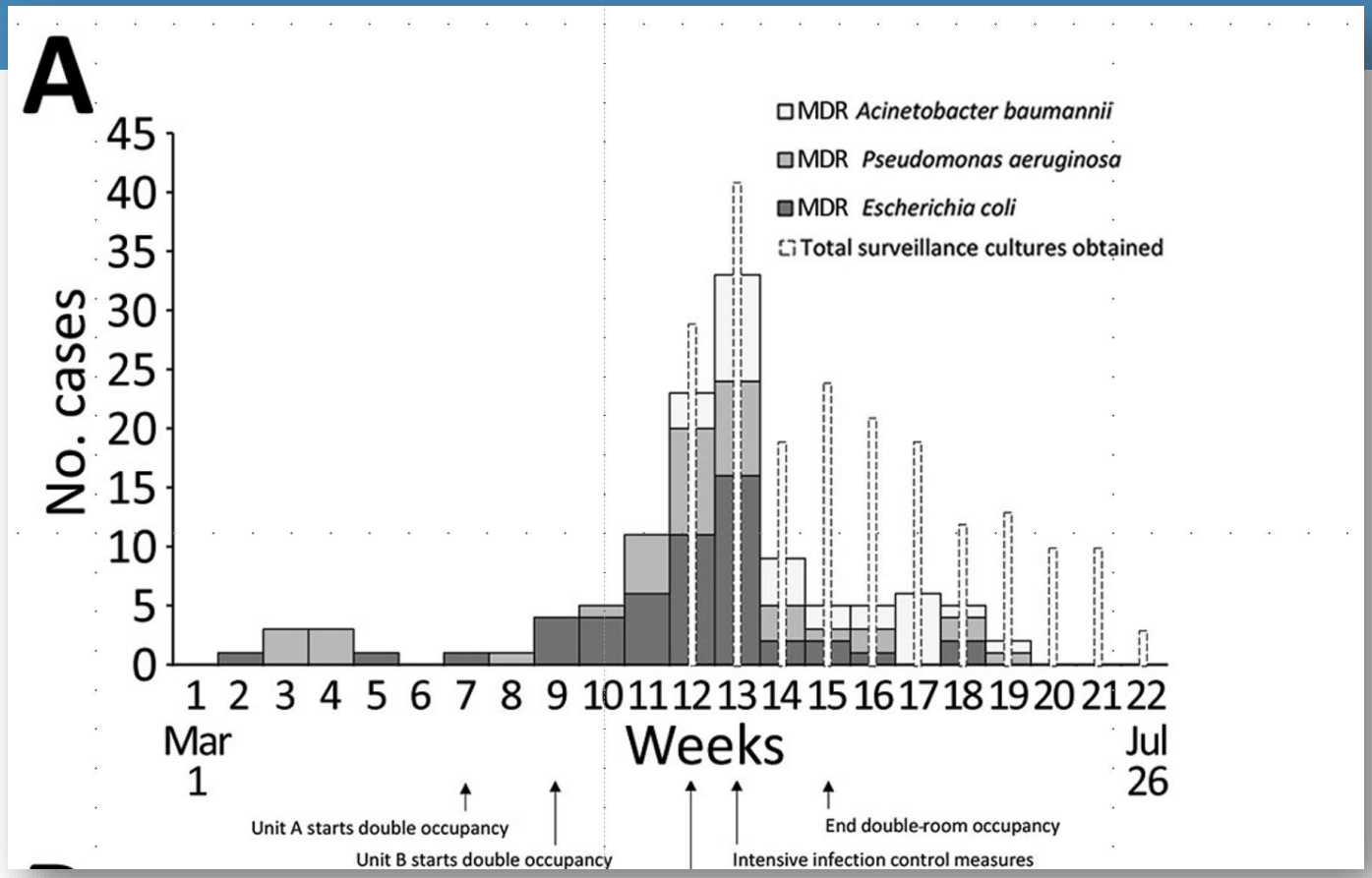
CRAB and COVID-19



Perez S. et al. Increase in Hospital-Acquired Carbapenem-Resistant *Acinetobacter baumannii* Infection and Colonization in an Acute Care Hospital During a Surge in COVID-19 Admissions — New Jersey, February–July 2020. MMWR Morb Mortal Wkly Rep 2020;69:1827–1831. DOI: http://dx.doi.org/10.15585/mmwr.mm6948e1external icon

- Clusters of Carbapenem-resistant *Acinetobacter baumanii* reported in several states during surge conditions
- Impacted COVID and non-COVID patients
- Attributed to deviations in infection prevention practices
- 82% from home
- 73% in ICU
- Source of CRAB = respiratory in 50%
- CRAB cases decreased once normal operations resumed

In Maryland…



Patel A et al. Emerg Infect Dis. 2021

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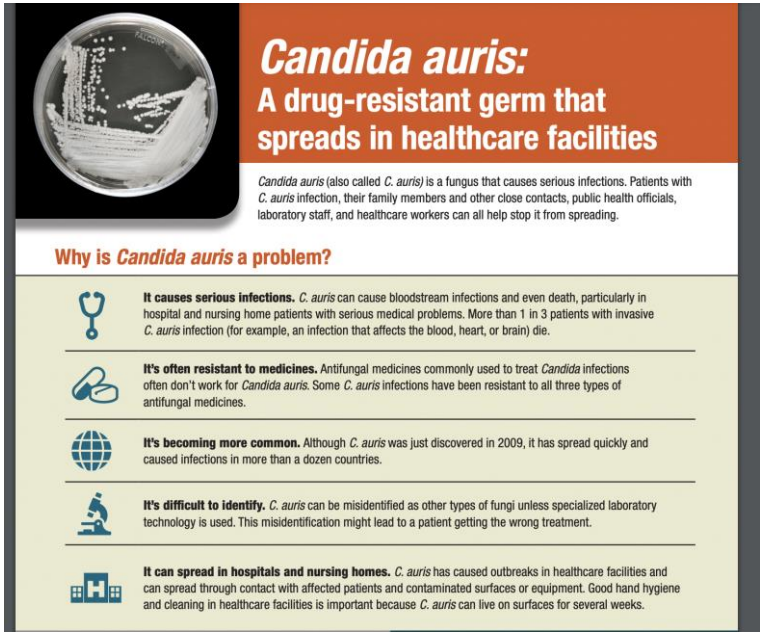
C. Auris and COVID-19

- C. auris outbreak among 35 patients in FLA COVID-19 unit, July-August 2020
- 17% with positive clinical culture
- 40% mortality within 30-days of screening
- 10% admit from LTCF
- 25% had known other MDRO prior to screening for C.auris (VRE, ESBL, MRSA)
- Attributed to deviations from usual infection control practices during surge conditions



Candida auris:
A drug-resistant germ that spreads in healthcare facilities

Candida auris (also called *C. auris*) is a fungus that causes serious infections. Patients with *C. auris* infection, their family members and other close contacts, public health officials, laboratory staff, and healthcare workers can all help stop it from spreading.

Why is *Candida auris* a problem?

It causes serious infections. *C. auris* can cause bloodstream infections and even death, particularly in hospital and nursing home patients with serious medical problems. More than 1 in 3 patients with invasive *C. auris* infection (for example, an infection that affects the blood, heart, or brain) die.

It's often resistant to medicines. Antifungal medicines commonly used to treat *Candida* infections often don't work for *Candida auris*. Some *C. auris* infections have been resistant to all three types of antifungal medicines.

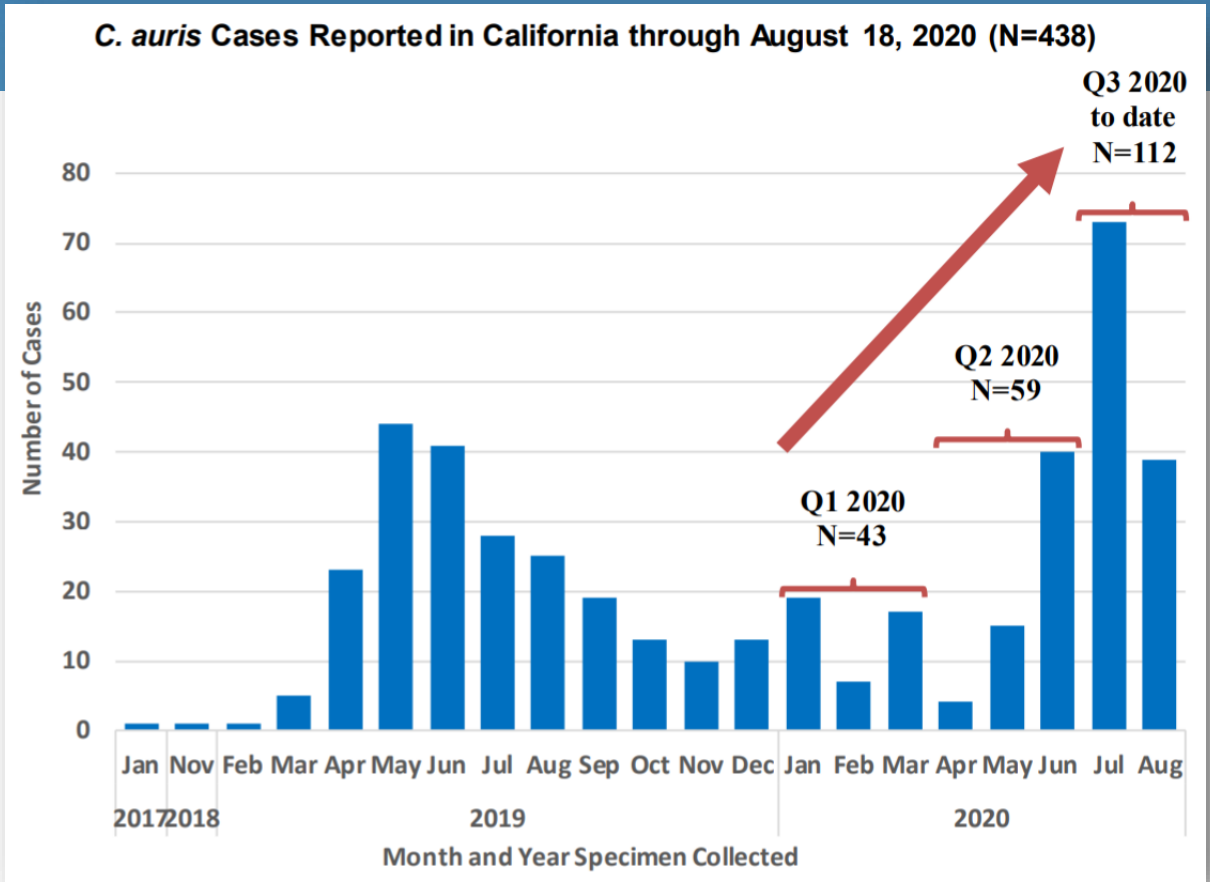
It's becoming more common. Although *C. auris* was just discovered in 2009, it has spread quickly and caused infections in more than a dozen countries.

It's difficult to identify. *C. auris* can be misidentified as other types of fungi unless specialized laboratory technology is used. This misidentification might lead to a patient getting the wrong treatment.

It can spread in hospitals and nursing homes. *C. auris* has caused outbreaks in healthcare facilities and can spread through contact with affected patients and contaminated surfaces or equipment. Good hand hygiene and cleaning in healthcare facilities is important because *C. auris* can live on surfaces for several weeks.

Prestel C, Anderson E, Forsberg K, et al. MMWR Morb Mortal Wkly Rep 2021;70:56–57.
DOI: http://dx.doi.org/10.15585/mmwr.mm7002e3external icon

In California…



California Dept of Health Bulletin

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Drug-resistant Gonorrhea

- Diversion of public health resources from STI surveillance to the pandemic
- Reduced access to care and testing
- Decrease in regular screenings leading to underdiagnosis and increased spread

https://www.cdc.gov/drugresistance/covid19.html

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Stewardship strategies to prevent antibiotic overuse and AMR during surges

#1 Local Guidelines

- Rationale: provide parameters for empiric antibiotic use
  - Recommendations for ventilator-associated pneumonia, line-sepsis, CAUTI, etc.
  - Use shortest accepted antibiotic duration
  - Encourage antibiotic "time-out" at 48-72 hours; de-escalate or stop antibiotics if negative cultures
  - Escalate for "bad bugs;" Candida spp., multidrug resistant Gram negatives, MRSA, VRE, etc.
- Pettit et al, 2021: bacterial pneumonia guideline significantly reduced antibiotic initiations and days of therapy within impacting clinical outcomes

Pettit NN, et al. BMC Infect Dis. 2021 Jun 2;21(1):516. doi: 10.1186/s12879-021-06219-z. PMID: 34078301; PMCID: PMC8170434.

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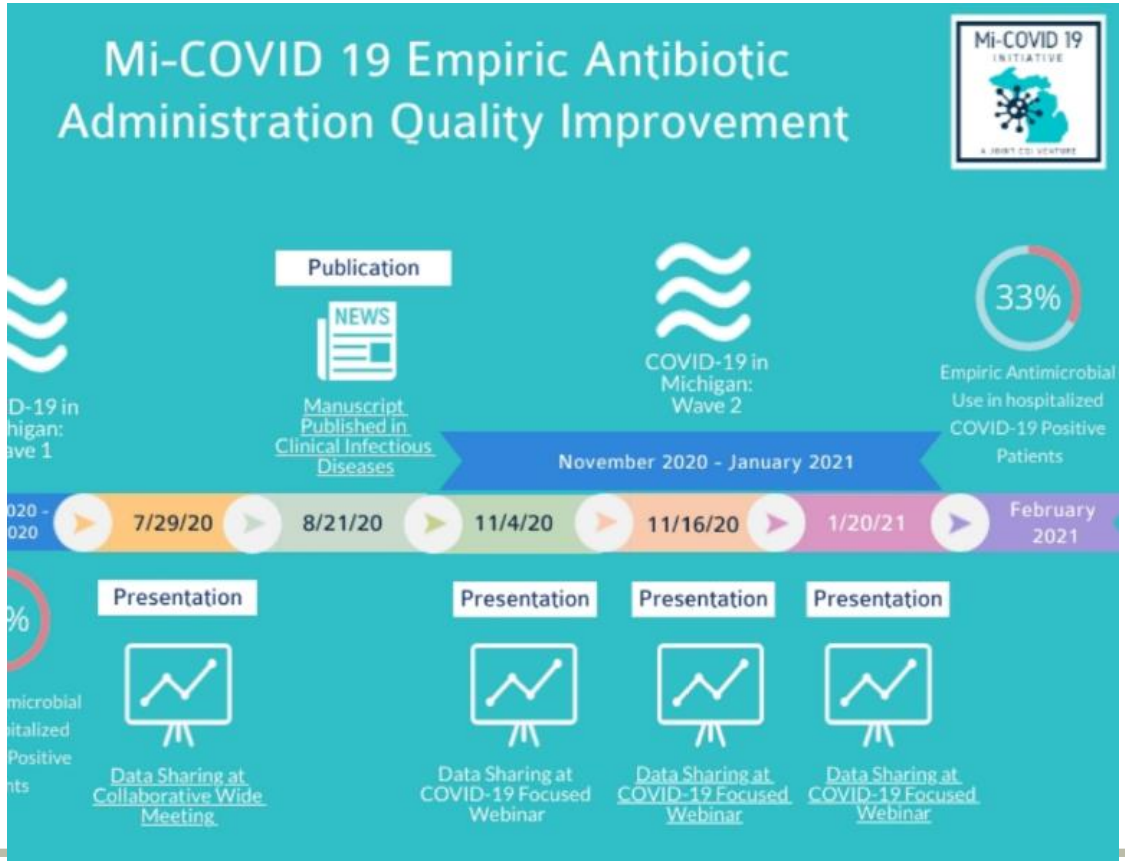
#2 Sharing of AU data and best practices



- Mi-COVID Quality Collaborative of 40 hospitals, April 2020 to January 2021: sharing of AU data, focused education, and risk factors for bacteria co-infections
- Decrease from 53% to 33% ($p < .0001$) in early empiric antibiotic use among non-critically ill patients

#3 Rapid diagnostics (e.g., MRSA nares PCR)

- High volume of empiric IV vancomycin use in critically-ill COVID-19 patients (>20%); high-risk of renal failure at baseline
- Low prevalence of +MRSA PNA upfront which increased to 5.7% at day 28
- Excellent diagnostic performance of the MRSA nares PCR test
  - 100% negative predictive value

Table 1. Prevalence of Methicillin-Resistant *Staphylococcus aureus* (MRSA) in Respiratory Cultures at Different Time Points of Hospital Stay

Days from Admission	Day 3	Day 7	Day 14	Day 28
Total patients with respiratory cultures obtained, no.	158	285	405	472
Patients with MRSA in respiratory cultures, no	1	7	18	27
Prevalence, %	0.6	2.4	4.4	5.7

Punjabi et al. ICHE, 2020

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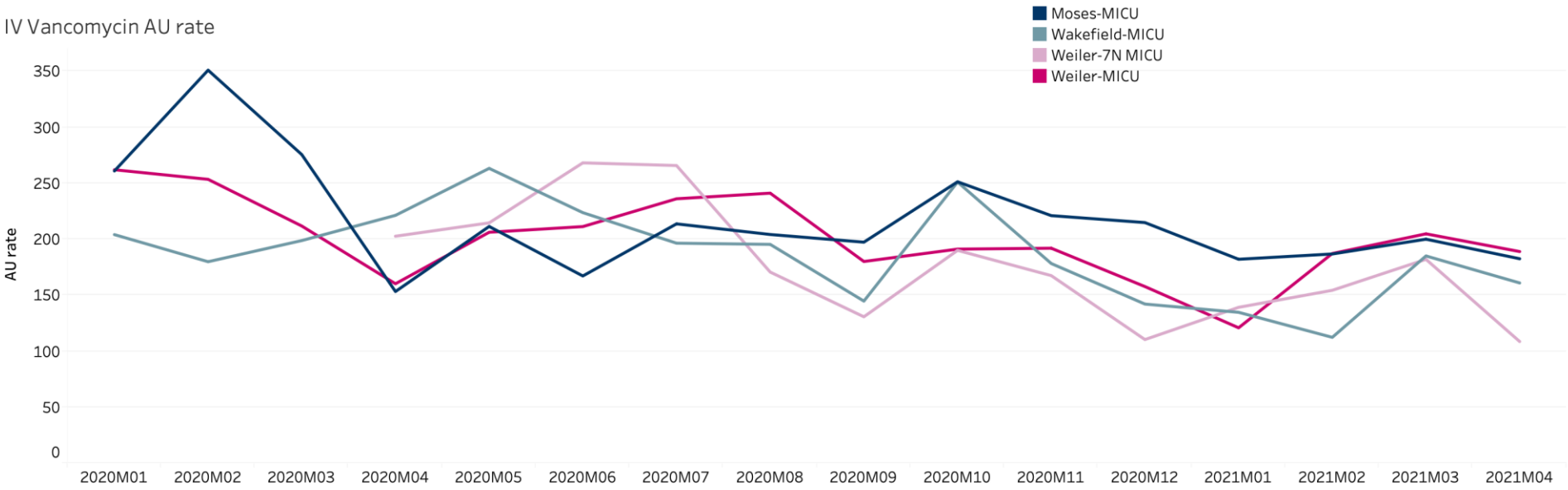
MICU IV Vancomycin AU



IV Vancomycin Details

		Jan 2020	Feb 2020	Mar 2020	Apr 2020	May 2020	Jun 2020	Jul 2020	Aug 2020	Sep 2020	Oct 2020	Nov 2020	Dec 2020	Jan 2021	Feb 2021	Mar 2021	Apr 2021
MOSES MICU	# Patients Initiated	49	38	36	25	28	29	30	33	27	35	26	21	22	24	33	32
	Average Duration	2.00	2.50	2.86	2.28	2.75	1.69	2.47	2.06	2.67	2.29	2.77	3.71	3.05	2.63	2.73	2.03
WAKEFIELD	# Patients Initiated	32	33	49	28	38	14	30	33	21	37	37	30	30	25	41	34
MICU	Average Duration	2.31	2.27	1.98	3.39	2.37	2.36	2.23	1.85	2.10	2.41	2.08	2.27	2.27	2.08	2.12	2.12
WEILER MICU	# Patients Initiated	41	42	35	21	31	31	42	35	29	34	35	33	30	24	28	34
	Average Duration	2.39	2.02	2.37	2.29	1.94	2.74	2.12	2.54	2.24	2.32	2.09	1.94	1.77	2.58	2.93	2.41
WEILER MICU	# Patients Initiated			15	36	31	28	23	14	16	17	16	22	25	27	27	16
7NORTH	Average Duration			1.93	2.81	2.84	2.57	2.65	2.43	1.44	2.24	1.88	2.05	2.96	2.78	2.78	2.38
WEILER SICU	# Patients Initiated	28	24	27	28	12	4	20	16	14	18	17	31	32	31	30	32
	Average Duration	2.29	2.63	2.52	3.82	2.00	2.75	1.90	2.63	1.86	2.44	2.00	1.71	2.16	2.65	3.00	2.28

#4 Utilize procalcitonin with caution

	Low PCT </=0.5ng/mL (n=484)		High PCT >0.5ng/mL (n=335)		p-value
	n/median	%/IQR	n/median	%/IQR	
Maximum CRP (mg/dL)	12.8	4.4-23.3	24.7	11.7-37.5	<0.001
Co-infection	**31**	**6**	**42**	**13**	**0.01**
No co-infection	**453**	**94**	**293**	**87**	
Received any antibiotics	**397**	**82**	**323**	**96**	**<0.001**
Received >=3 classes of antibiotics	75	15	140	42	
Median duration of antibiotic therapy (days)	4	2-7	6	3-10	

K. Cowman et al. unpublished data

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LRTI vs. sepsis PCT thresholds & detection of co-infection

	>0.25 ng/mL	>0.5 ng/mL	>1 ng/mL
Sensitivity	82%	58%	44%
Specificity	47%	61%	71%
PPV	13%	13%	13%
NPV	**96%**	**94%**	**93%**

K. Cowman et al. unpublished data

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PCT: Institutional Experience

- Co-infection cohort found to have a higher median initial PCT (0.9 ng/mL vs 0.3 ng/mL)
- **However, many patients without a co-infection had an elevated PCT (39%) due to critical illness and immune activation**
- *6% of patients in the low initial PCT cohort had confirmed co-infections*
- Initial low PCT has a **high NPV (94%)**
  - Highly unlikely to have a bacterial co-infection
- **Low PPV (13%)** for co-infection demonstrated in multiple studies

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What will happen to antibiotic use and AMR during the Omicron surge?

- Increase again
- Decrease compared with non-surge months
- Remain unchanged due to lessons learned
- I’m not sure

My observations: what's happening during NY's Omicron surge? Regression

Lots of broad-spectrum antibiotic use in admitted COVID-19 patients if positive CXR findings

Lots of prescriptions for azithromycin in ambulatory patients with COVID-19

Staff and resource shortages leading to diagnostic delays in microbiologic testing

Hospitalists clamoring for unrestricted access to PCT

Stewardship team diverted to SARS-CoV-2 antivirals

Why? Fear, lack of other therapeutic options (scarcity of monoclonal antibodies and oral antivirals)

We should continue to apply what works (infection prevention and stewardship best practices)

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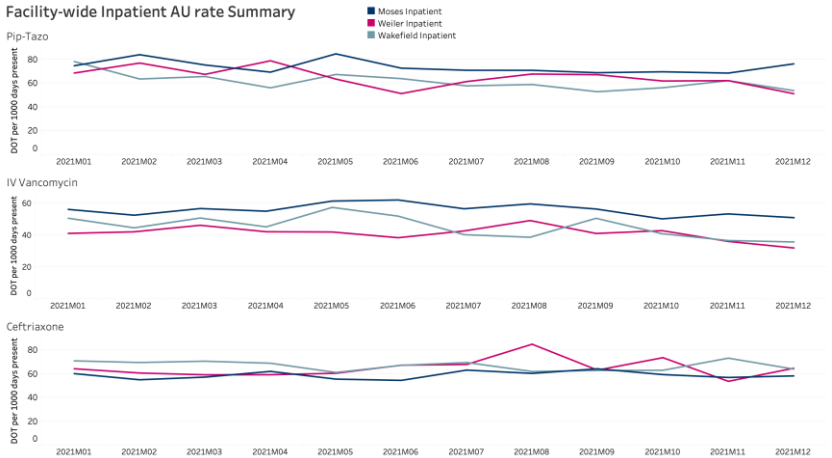
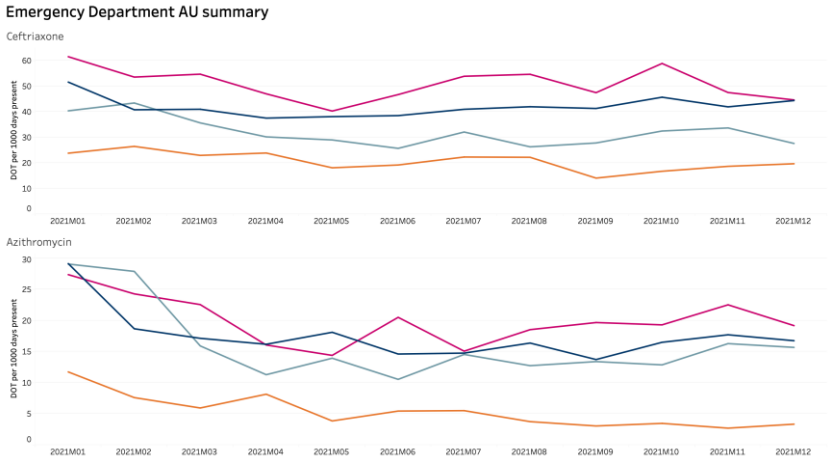
Maintain Vigilance!





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