

Antimicrobial Stewardship Considerations during the COVID-19 Pandemic

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September 24th, 2021



Disclosure

- I have no actual or potential conflicts of interest to disclose in relation to this presentation.



Objectives

1. Recognize antimicrobial stewardship strategies that can be applied during the COVID-19 pandemic response.
2. Describe the incidence and time course of bacterial co-infections in patients with COVID-19.
3. Explain antimicrobial stewardship interventions that should be performed for patients with COVID-19.

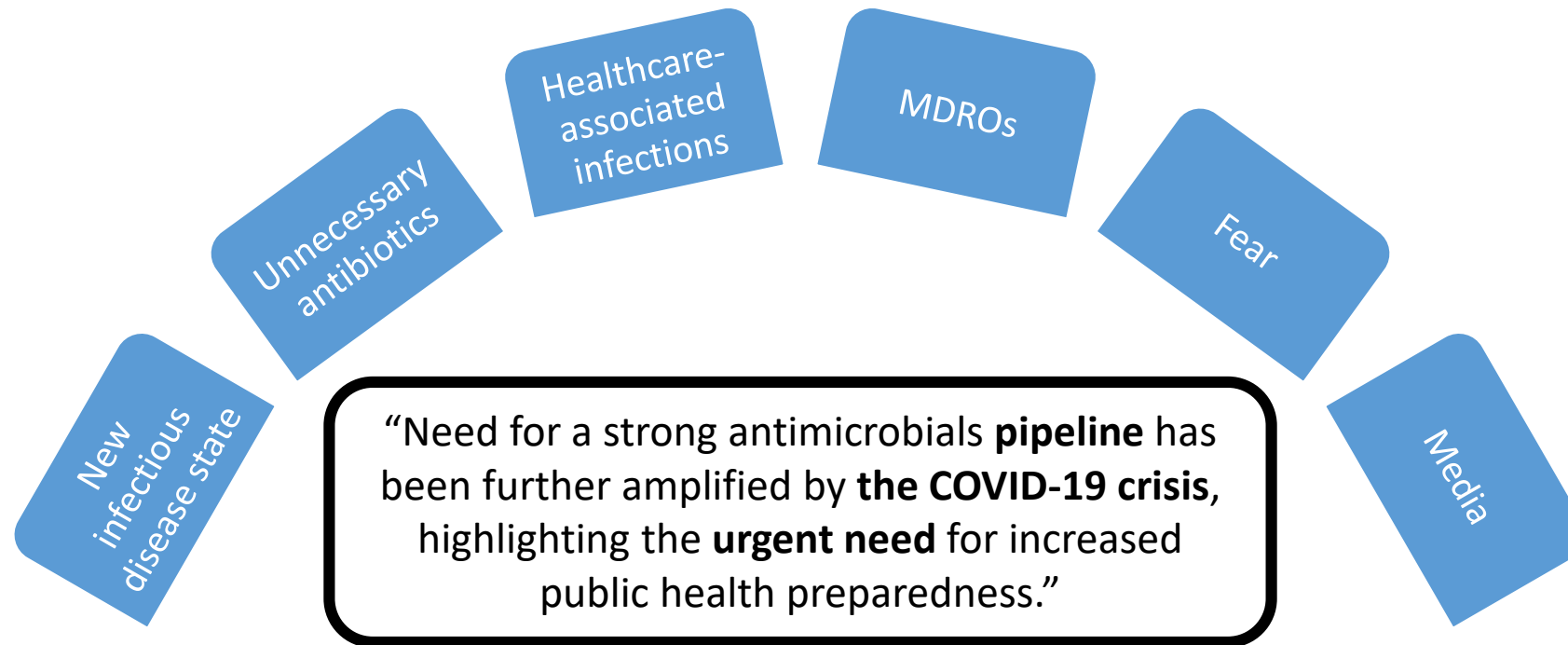


I. Antimicrobial Stewardship Strategies in COVID-19 Response



COVID-19 Adds to Antimicrobial Resistance

10 million deaths by 2050 = \$100 trillion



Pharmacy Challenges with COVID-19

Patient Surges

Medication
Delivery

Old & New Medications

- Emergency Use Authorization
- Compassionate Use
- Off-label use

Drug Shortages

Nursing
Coordination

Ethical
Considerations



Solution: Antimicrobial Stewardship

- interventions to **improve** & **measure** the appropriate use of antibiotics by promoting the **optimal** antibiotic regimen including **dosing, duration, & route**
- Goals:
 - outcomes
 - resistance
 - side effects
 - costs

***“precious
non-renewable
resource”***



World Health Organization (WHO)

“address gaps in research to ensure that **antimicrobial stewardship** activities become an integral part of the pandemic response and beyond.”

“**antimicrobial stewardship** activities should be integrated into the pandemic response across the broader health system.”



CDC: 7 Core Elements of Antimicrobial Stewardship

1. Leadership Commitment

IT* support, resources

2. Accountability

reporting structure

3. Drug Expertise

drug shortages, formulary

4. Action

guideline, pre-authorization

5. Tracking

CDI^, broad-spectrum antibiotics

6. Reporting

inventory, antibiotic trends

7. Education

guidelines, resources

*IT= Information Technology

^CDI= *C. difficile* Infection



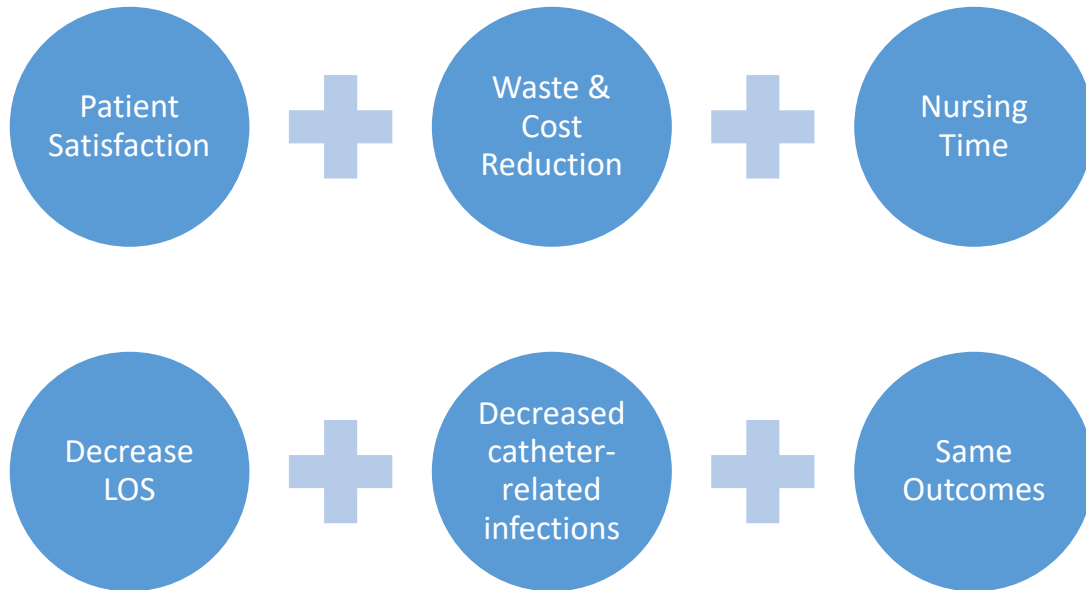
“Low Hanging Fruit” of Antimicrobial Stewardship

- IV to PO Conversion
- Medication Batching
- Therapeutic Substitutions
- Pre-authorization

**among
others.....**



IV to PO Conversion



Goff DA, et al. *Clin Infect Dis*. 2012;55: 87-592.

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<https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/216381>



Medication Batching

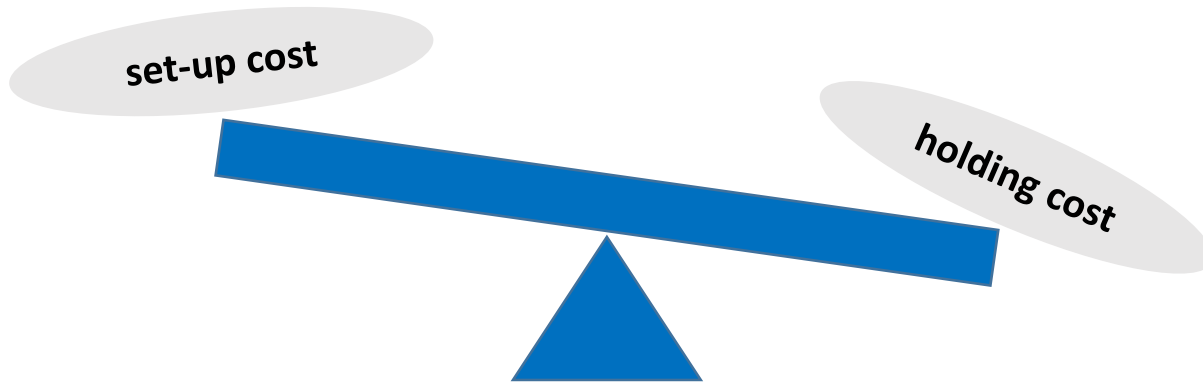


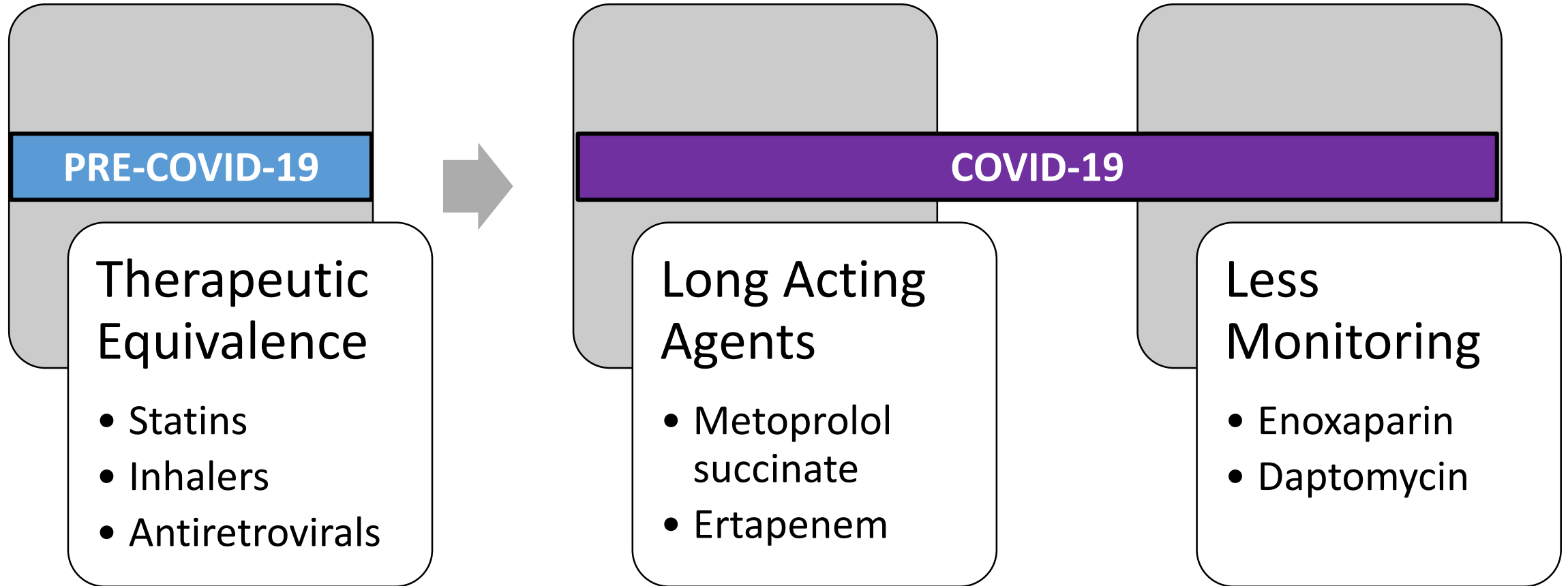
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<https://www.sciencedirect.com/science/article/abs/pii/S0167923615000330>

- Standard timing: preparation, administration
- ex. daptomycin batching --- 370 vials saved over 4 months (\$83,991)

Goff DA, et al. *Clin Infect Dis.* 2012;55: 87-592.



Therapeutic Substitutions



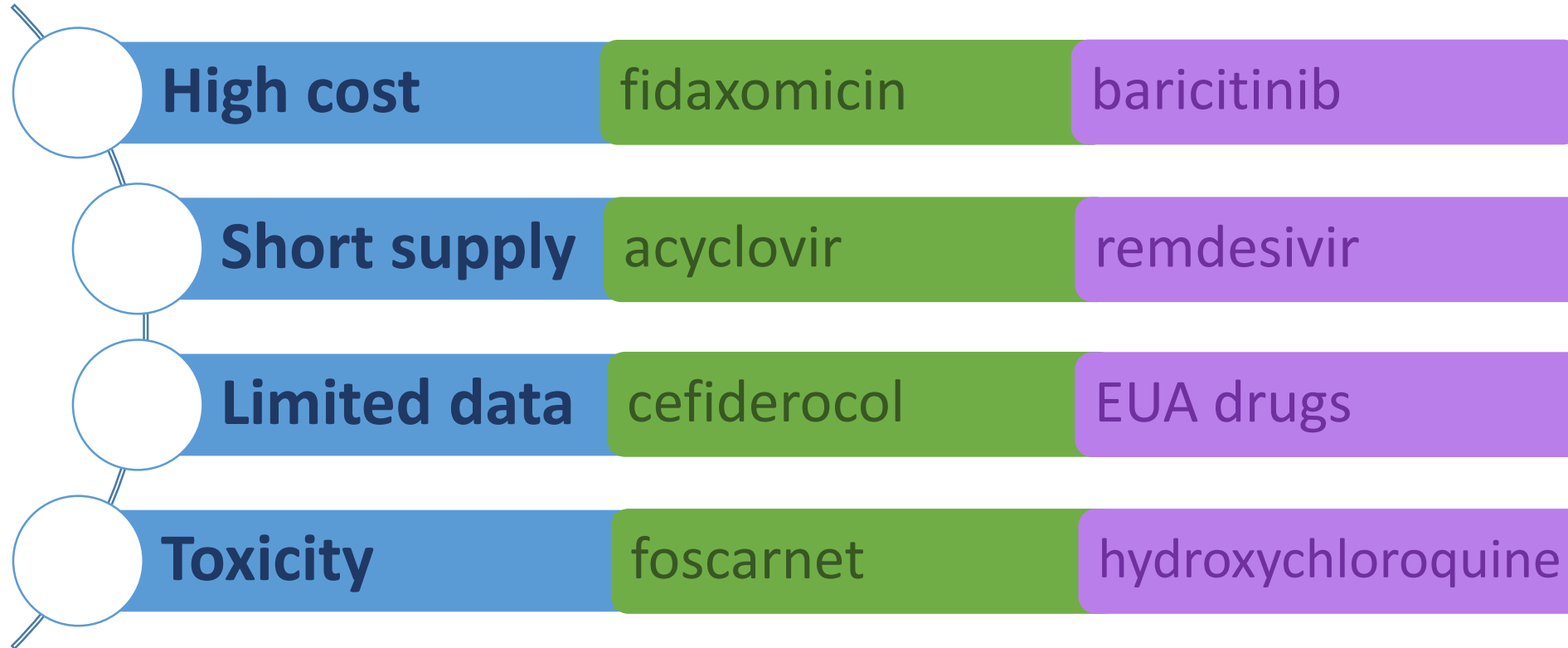
Consolidate dosing schedules!



Pre-authorization

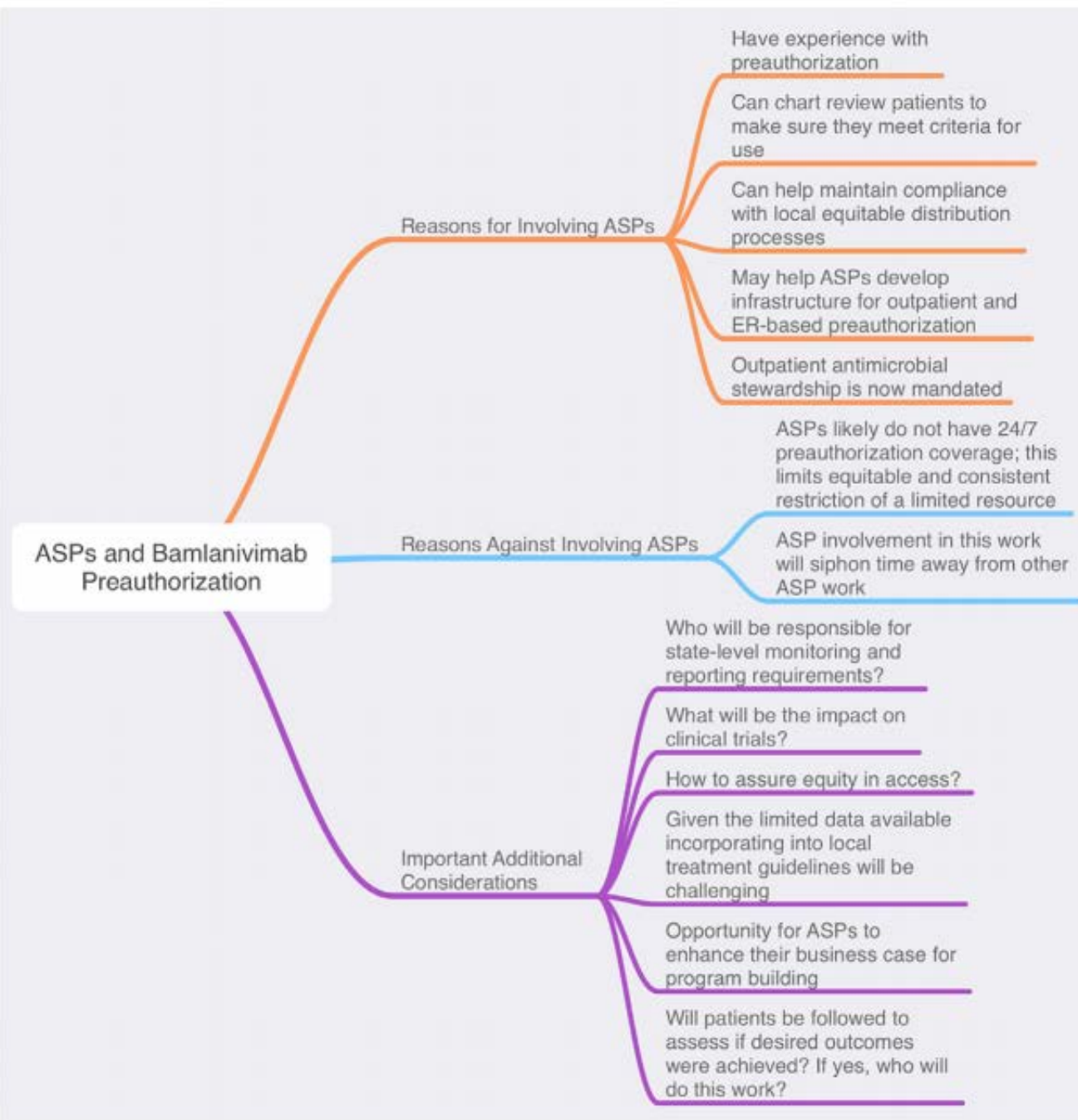
Pre-authorization

Medication
Order



Predominantly drug-driven





Prospective Audit & Feedback (PAF)



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Liew YX, et al. *Int J Antimicrob Agents*. 2015;45:168-173.

<https://www.sciencedirect.com/science/article/abs/pii/S0924857914003537?via%3Dihub>

More customizable targets

- Disease state
- Lab result
- Drug

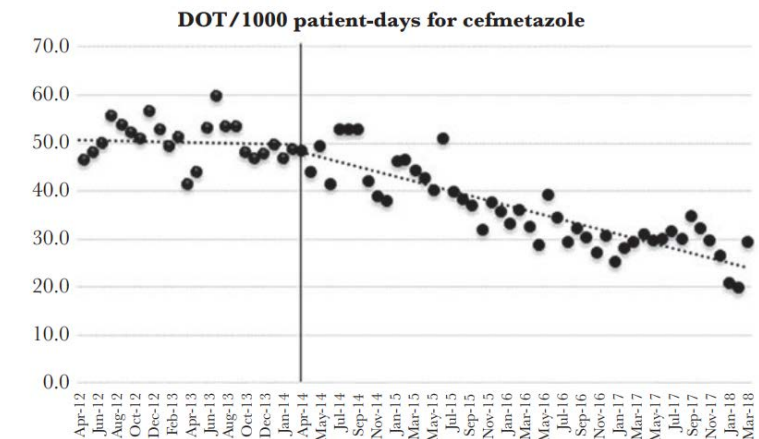


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Honda H, et al. *Open Forum Infect Dis*. 2018;5:ofy314.



PAF with IT Support

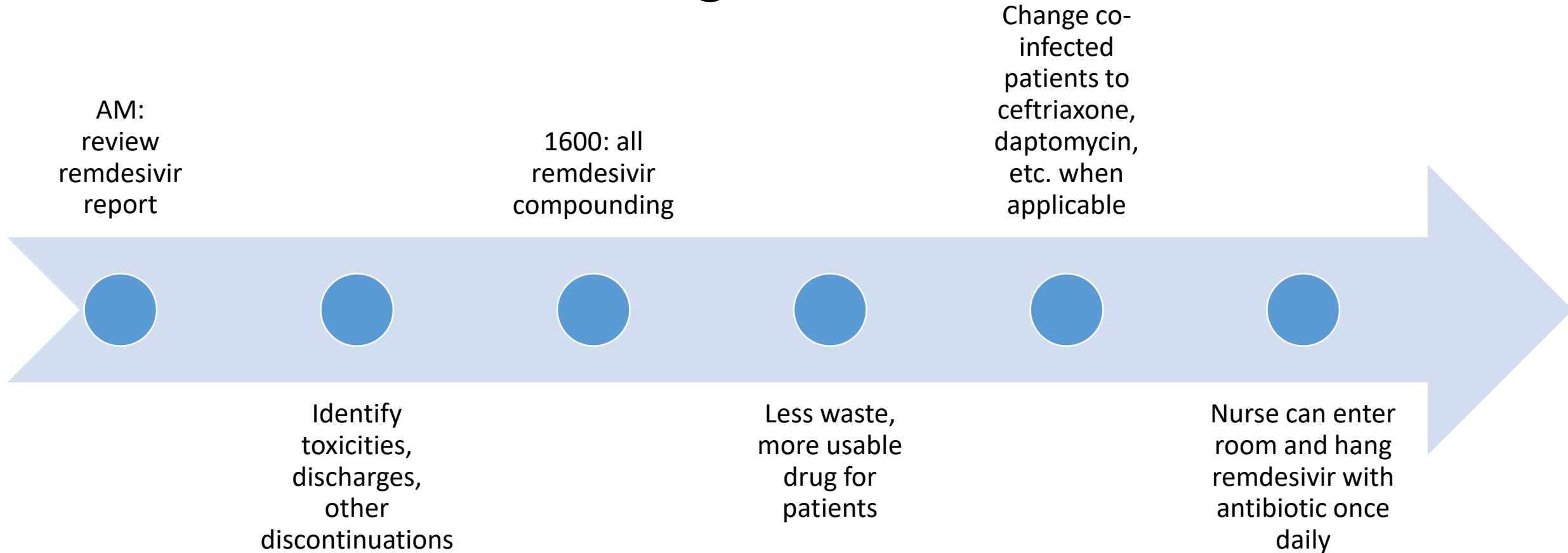
Table 1. Antimicrobial Stewardship COVID-19 Rule Logic

Name	Criteria	Display
ASP COVID-19 rule 1: negative SARS-COV-2 PCR w/ active drug order (inpatients only)	<ul style="list-style-type: none"> • IF <u>negative</u> COVID-19 PCR in last 7 days • AND • IF active order for 1 of the following: <ul style="list-style-type: none"> • Chloroquine • Darunavir/ritonavir • Hydroxychloroquine • Lopinavir/ritonavir • Nitazoxanide • Remdesivir • Ribavirin • Sarilumab • Tocilizumab • Lenzilumab • IVIg • THEN fire alert 	Rule Text <ul style="list-style-type: none"> • Rule name • COVID-19 medication that triggered flag • SARS-COV-2 test result, date, and time
ASP COVID-19 rule 2: positive SARS-COV-2 PCR or pending lab w/ active drug order (inpatients only)	<ul style="list-style-type: none"> • IF <u>positive</u> COVID-19 PCR in last 7 days • OR • IF <u>pending</u> COVID-19 PCR in last 7 days • AND • IF active order for 1 of the following: <ul style="list-style-type: none"> • Chloroquine • Darunavir/ritonavir • Hydroxychloroquine • Lopinavir/ritonavir • Nitazoxanide • Remdesivir • Ribavirin • Sarilumab • Tocilizumab • Lenzilumab • IVIg • THEN fire alert 	Rule Text <ul style="list-style-type: none"> • Rule name • COVID-19 medication that triggered flag • SARS-COV-2 test result, date, and time

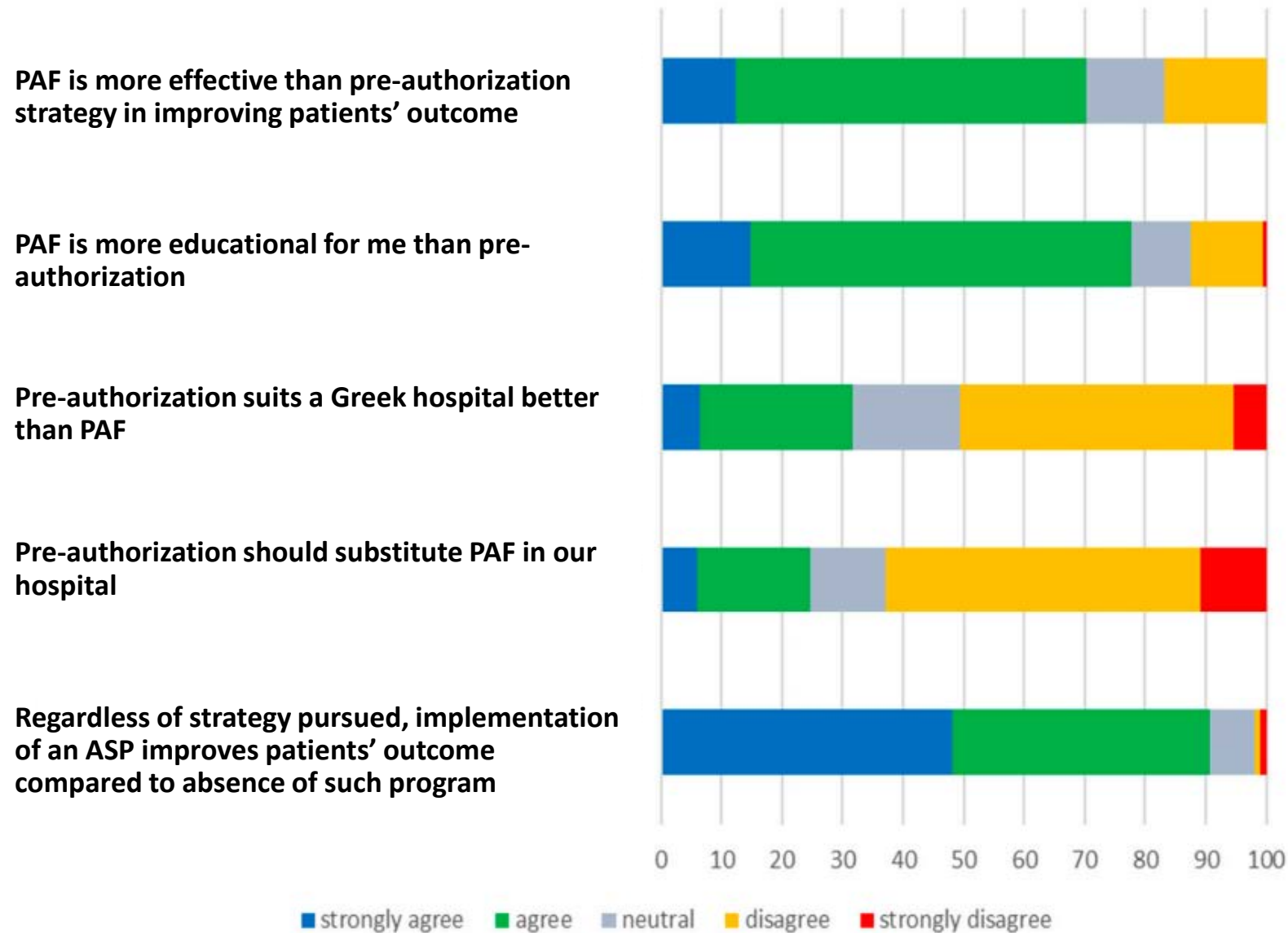
Image used with permission by: Stevens RW, et al. *Infect Control Hosp Epidemiol.* 2020;41:1108-1110.



Combination of Strategies



Physician Perspectives on Strategies by Stewardship Program Implemented During COVID-19





	Pre-authorization	PAF
Advantages	<ul style="list-style-type: none"> • Initiation/empiric therapy • Direct control • Quick mechanism 	<ul style="list-style-type: none"> • Definitive therapy • Prescriber autonomy → relationships • Hindsight/more data • Flexible
Disadvantages	<ul style="list-style-type: none"> • Resources: around the clock? • Limited lasting effects • Durations 	<ul style="list-style-type: none"> • Resources: IT vs. computer surveillance • Compliance voluntary • Starting from behind



Antibiotic “Time-Outs”

- Through prospective audit & feedback or electronic alerts

Image removed due to copyright. Refer to:

Wolfe JR, et al. *Infect Control Hosp Epidemiol*. 2019;40:1287-1289.

<https://www.cambridge.org/core/journals/infection-control-and-hospital-epidemiology/article/impact-of-an-automated-antibiotic-timeout-alert-on-the-deescalation-of-broad-spectrum-antibiotics-at-a-large-community-teaching-hospital/4CA0D7799D84CFF5D15C3EBE8F599392#>



Education

- Use in combination
- High frequency
- Multi-disciplinary
- Promote guidelines, workflows

**Weak recommendation,
low quality evidence**



Which of the following drugs would be most appropriate for management via pre-authorization?

- A. COVID-19 vaccine
- B. IV tocilizumab
- C. PO dexamethasone
- D. IV ondansetron



Summary

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Moehring RW, et al. *Current Infect Dis Rep*. 2012;14:592-600. <https://link.springer.com/content/pdf/10.1007/s11908-012-0289-x.pdf>



II. Bacterial Co-infection in COVID-19

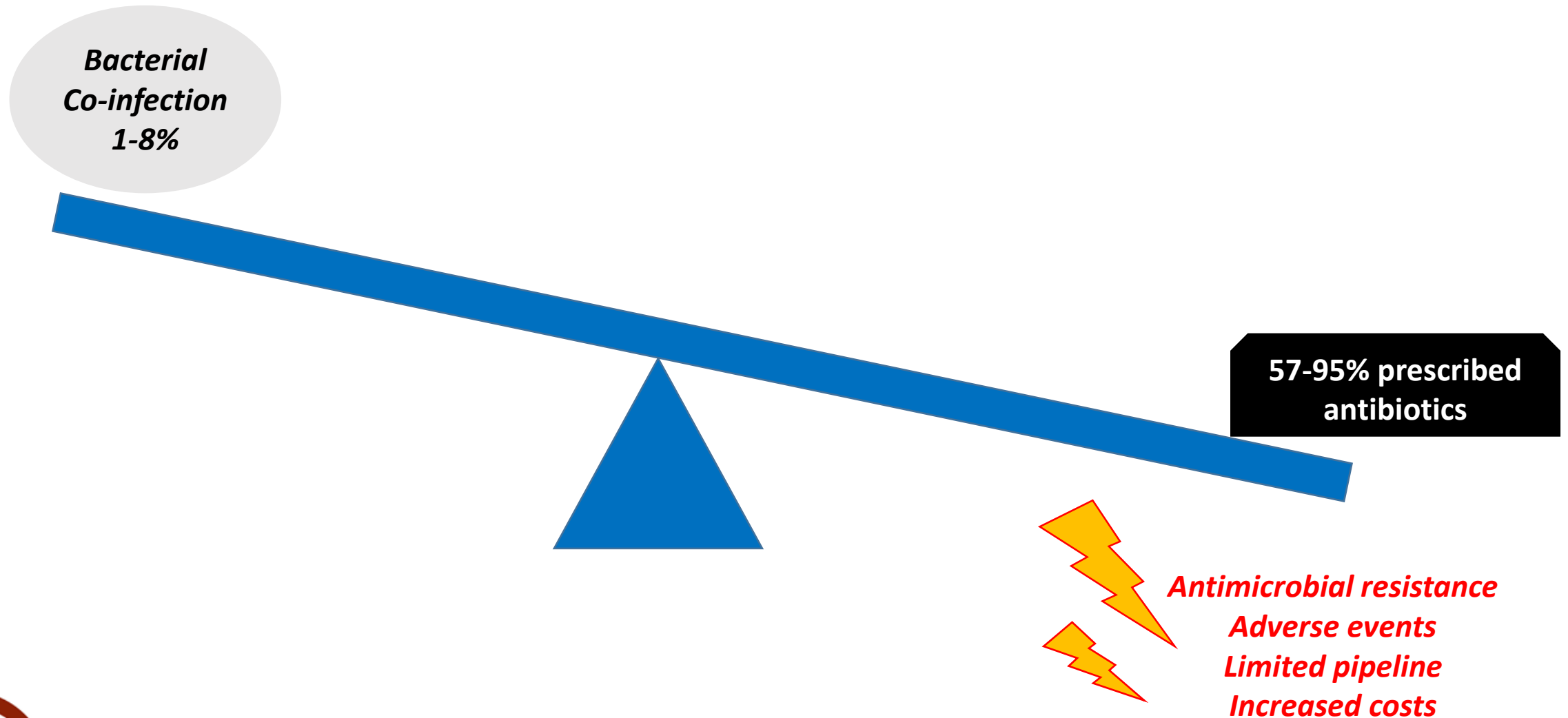


Co-infection Considerations

- Frequency of empiric antimicrobials
- Incidence
- Primary co-infection vs. secondary infection
 - Risk factors
 - Common pathogens
- Diagnostic criteria



Balance Needed



International “Snapshot” of Antibiotic Use 2020

166 prescribers (50% ID)
23 countries

29% do not routinely
prescribe antibiotics

Reason for antibiotics

- clinical presentation
- inflammatory markers
- radiology findings
- *piperacillin/tazobactam most common

Coverage

- atypical
- S. aureus*
- Pseudomonas*

Mean duration (days)

All countries: 7.12

Guidelines for antibiotics
in COVID-19: ~62%



Co-infection in Familiar Viruses

	Influenza	SARS/MERS-CoV
Most Common Bacterial Respiratory Pathogens	<ol style="list-style-type: none"> 1. <i>S. pneumoniae</i> 2. <i>S. aureus</i> 3. <i>H. influenzae</i> 4. <i>S. pyogenes</i> 	<p>Primary: atypical/community-acquired pneumonia (CAP) organisms</p> <p>Secondary: nosocomial pathogens</p>
Bacterial Co-infection	~20%	~10-30% co-infection
Outcomes	↑ morbidity & mortality	Higher levels of care
Co-infection Guideline Recommendations	Community-acquired Pneumonia (CAP): administer antibiotics to adults with clinical and radiographically diagnosed CAP who test positive for influenza (strong recommendation, low quality of evidence)	<p>n/a</p> <p>WHO refers to national guidelines for antibiotic management</p>



Limitations on Co-infection Reporting

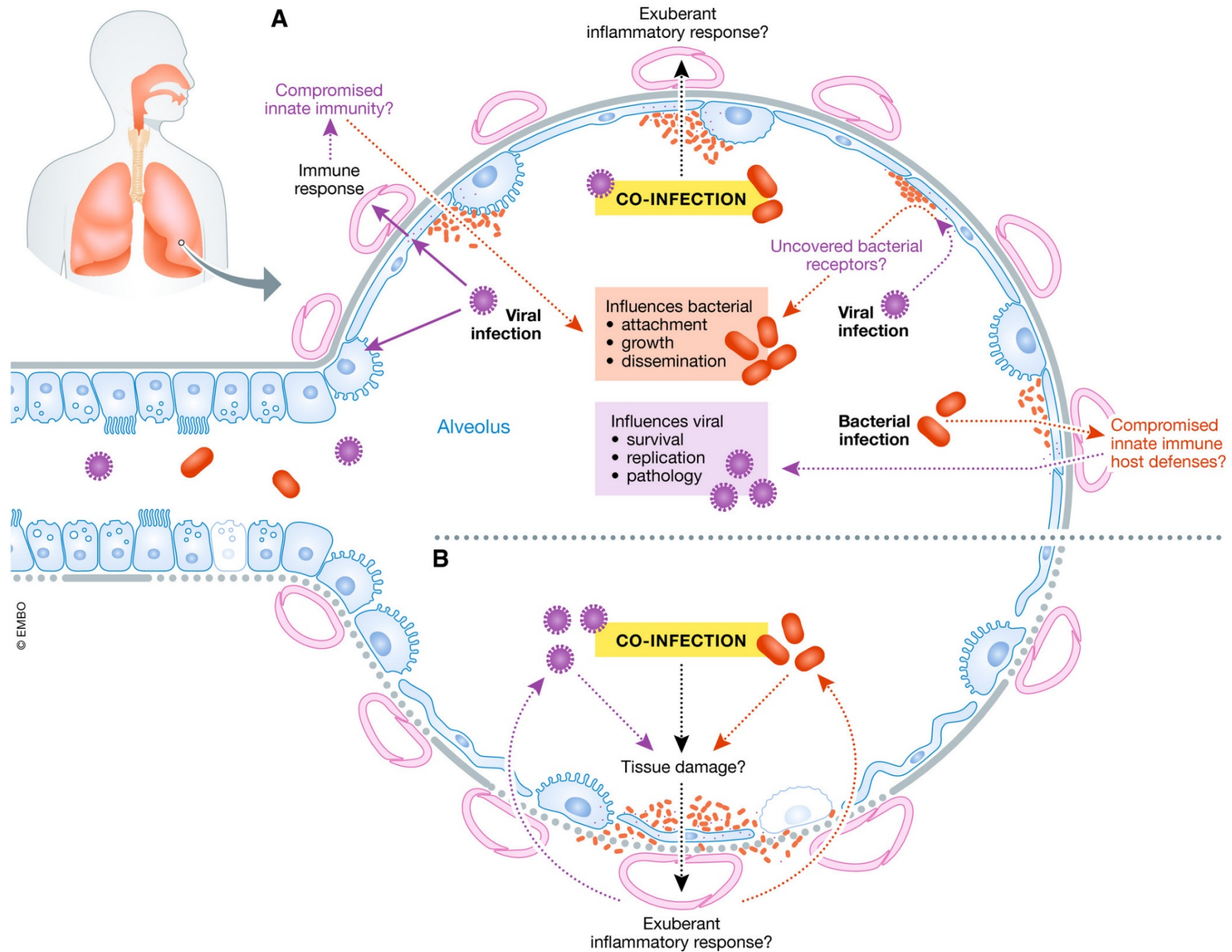
- COVID-19: largely early 2020 data
- Difficult to group or compare reports
- Differing definitions
 - ex. community-acquired, co-infection
 - timing
- Inconsistent diagnostics

Challenges Specific to Bacterial Pneumonia in COVID-19

- COVID-19 similarities to bacterial pneumonia
- Colonization
- Low pathogen yield, often empiric
- Abnormal inflammatory markers in COVID-19 (ex. CRP)
- Limited procedures/testing, staffing

Under- vs. over-reported?





Pooled Analyses of Co-infection

	Rawson (May 2020)	Langford (July 2020)
Methods	Review of 9 studies • 806 patients	Meta analysis of 24 studies • 3,338 patients
Co-infection	8%	6.9% • 3.5% co-infection • 14.3% secondary infection
Empiric Antibiotics	72%	71.8%
Pathogens Identified	<i>Limited: few atypical pathogens</i>	<i>Limited: pathogen data from 14% of patients Most common: Mycoplasma species, H. influenzae, & P. aeruginosa</i>
WARNING	<i>Co-infection may be misrepresented</i>	



Study **Patients** **% Infected** **95% C.I.**

Severity = All Patients

Cai Q, 2020	298	10.1	[6.9; 14.1]	
Chen N, 2020	99	1.0	[0.0; 5.5]	
Chen T, 2020	203	1.0	[0.1; 3.5]	
Feng Y, 2020	410	8.5	[6.0; 11.7]	
Lian J, 2020	788	0.0	[0.0; 0.5]	
Liu W, 2020	78	0.0	[0.0; 4.6]	
Liu Y, 2020	12	16.7	[2.1; 48.4]	
Mo P, 2020	155	1.3	[0.2; 4.6]	
Pongpirul W, 2020	11	45.5	[16.7; 76.6]	
Tan Y, 2020	10	0.0	[0.0; 30.8]	
Wang L, 2020	339	42.2	[36.9; 47.6]	
Wang Z, 2020	29	10.3	[2.2; 27.4]	
Wu C, 2020	148	0.0	[0.0; 2.5]	
Wu J, 2020	280	2.1	[0.8; 4.6]	
Wu J, 2020	80	0.0	[0.0; 4.5]	
Xia W, 2020	20	20.0	[5.7; 43.7]	
Young B, 2020	18	0.0	[0.0; 18.5]	
Zheng F, 2020	25	16.0	[4.5; 36.1]	
Zhou F, 2020	191	14.7	[10.0; 20.5]	

Percent with Bacterial Infection

Heterogeneity: $I^2 = 95\%$, $\tau^2 = 0.0014$, $\chi^2_{18} = 383.26$ ($p < 0.01$)

Severity = Critically Ill Only

Arentz M, 2020	21	4.8	[0.1; 23.8]	
Barrasa H, 2020	48	12.5	[4.7; 25.2]	
Bhatraju P, 2020	15	0.0	[0.0; 21.8]	
Ling L, 2020	8	25.0	[3.2; 65.1]	
Yang X, 2020	52	13.5	[5.6; 25.8]	

Percent with Bacterial Infection

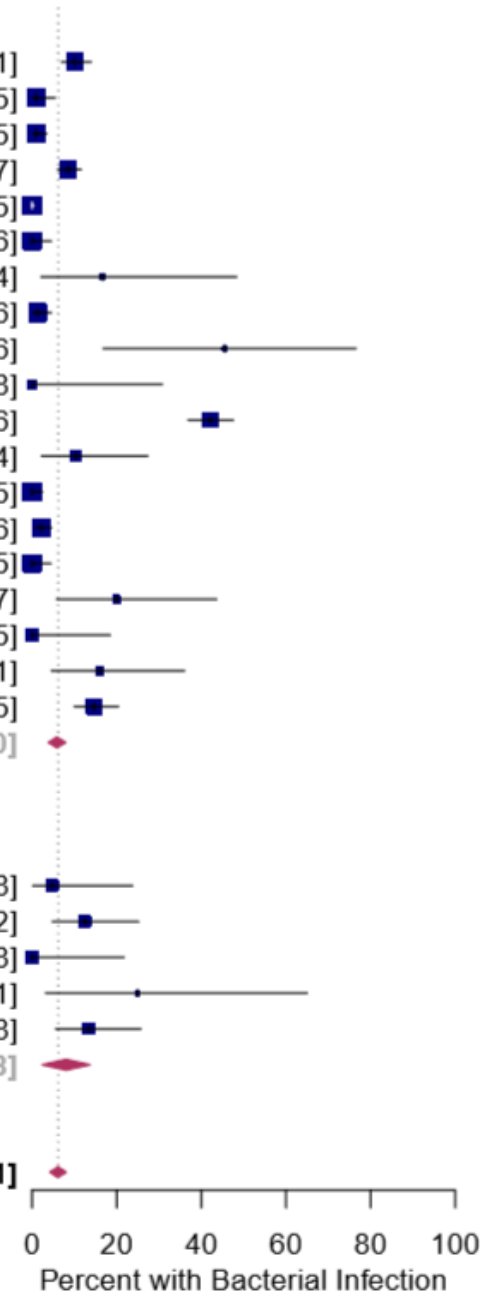
Heterogeneity: $I^2 = 45\%$, $\tau^2 = 0.0014$, $\chi^2_4 = 7.3$ ($p = 0.12$)

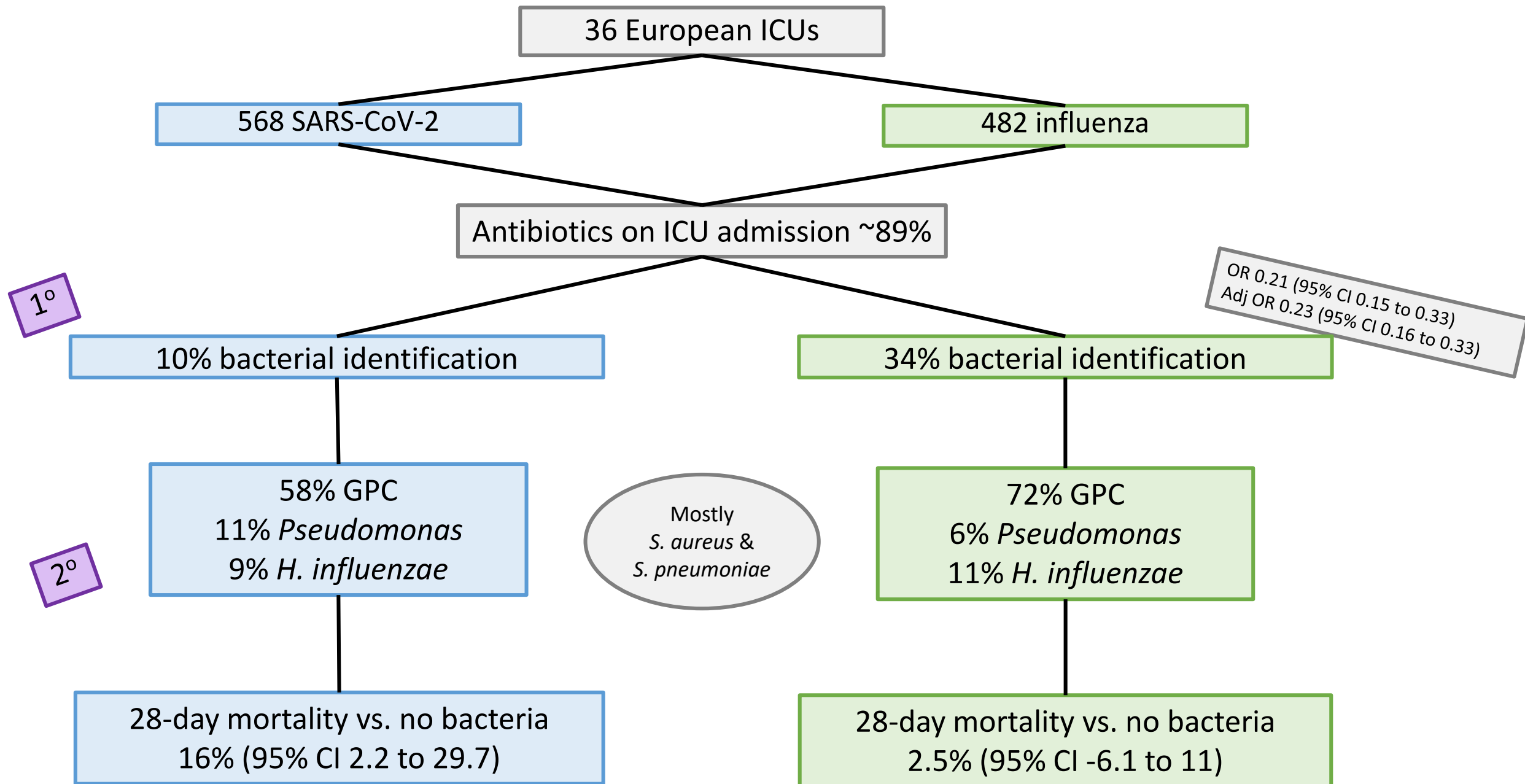
Percent with Bacterial Infection

Heterogeneity: $I^2 = 94\%$, $\tau^2 = 0.0014$, $\chi^2_{23} = 401.39$ ($p < 0.01$)

Residual heterogeneity: $I^2 = 94\%$, $\chi^2_{22} = 390.57$ ($p < 0.01$)

6.1 [4.2; 8.1]





Early Antibiotics in Critically Ill COVID-19 Patients

Outcome (n= 48)	Antibiotics (n= 19)	No Antibiotics (n= 29)	
mortality	5 (26%)	7 (24%)	p=0.86
VAP	14 (74%)	19 (66%)	p=0.55
CRBSI	5 (26%)	7 (24%)	p=0.86
UTI	2 (11%)	8 (28%)	p=0.28

50% steroids in ICU
10% tocilizumab



Risk Factors for Co-infection

	Incidence of Co-infection	Community-acquired Risk Factors	Hospital-associated Risk Factors
Petty LA, et al.	6.4% (141/2,205) <ul style="list-style-type: none"> 3% community-acquired 3.4% hospital-associated 	<ul style="list-style-type: none"> Day 1 admission to ICU Admission from LTCF 	<ul style="list-style-type: none"> Median 8 days Fever Higher respiratory support
Vaughn VM, et al.	3.5% (59/1,705)	<ul style="list-style-type: none"> Older age Lower BMI Mod-severe kidney disease SNF ICU admission Leukocytosis 	n/a
Conclusion	Consistent at <10%	Hold antibiotics at admission for non-ICU patients	Signs & symptoms of bacterial infection, timing



USA: Primary Co-infection at Admission

- 1,016 patients; 5 Johns Hopkins hospitals

Type of Co-infection	# of Patients (%)
Viral/atypical respiratory infection	2 (0.2)
Bacterial respiratory infection	
By any definition	497 (49)
Proven	1
Probable	11
Possible	483
Fungal Infection	
Fungal respiratory infection	0
Endemic mycoses	0
Bloodstream infection	20 (2)
Urinary tract infection	30 (3)
<i>Clostridioides difficile</i> colitis	2 (0.2)

71% received antibiotics

0.3% proven infection
1.1% probable infection

Proven/probable/possible
bCAP more likely admitted to
ICU vs. no co-infection
(33% vs. 16% vs. 7%; $P < .01$)



Bacterial Pneumonia Management Remains the Same

CAP
Duration:
5 days

HAP/VAP
Duration:
7 days

Obtain cultures!
De-escalate!
Discontinue!



Other Uncommon Co-infecting Pathogens

- Viral
 - Enterovirus/Rhinovirus
 - Influenza less common
 - Risk factor: older age
- Fungal
 - COVID-19-associated pulmonary aspergillosis (CAPA)
 - Candidiasis
 - Risk Factors: immunosuppression, corticosteroids



Other Pathogens: *Clostridioides difficile* Infections (CDI)

- Incidence lower than pre-COVID-19:
 - Infection control techniques
 - Less surgeries
- Unknowns:
 - Healthcare vs. community-acquired
 - Antibiotics vs. no antibiotics

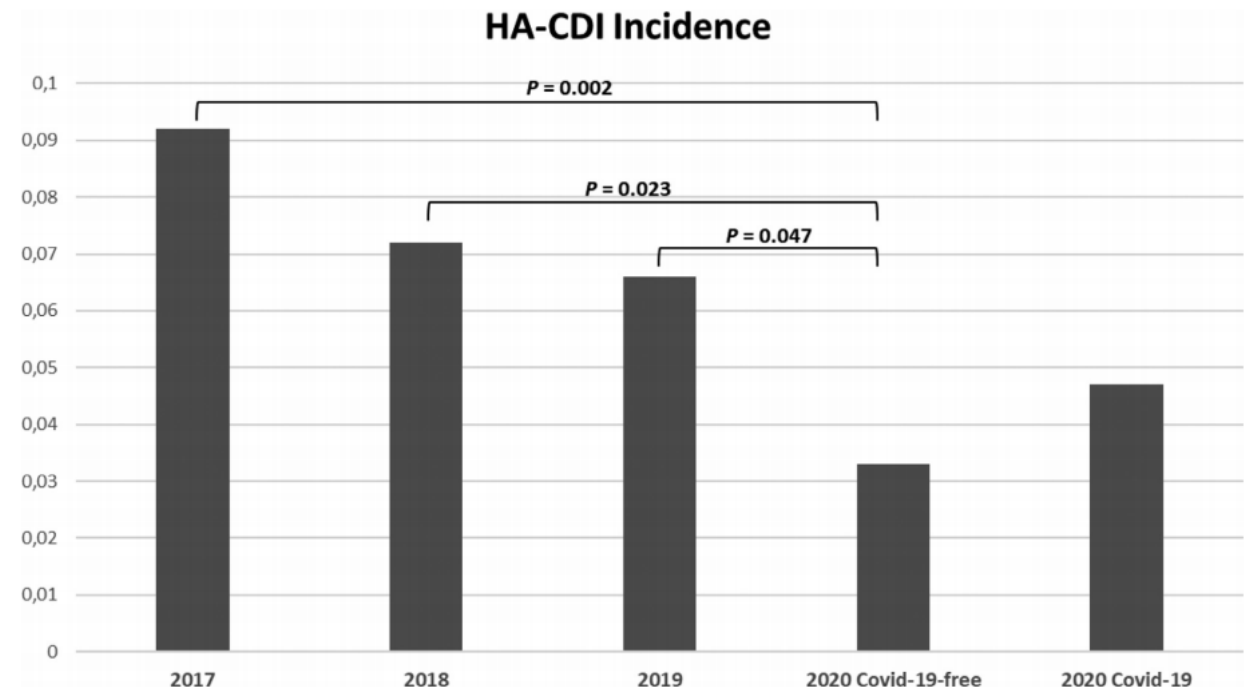
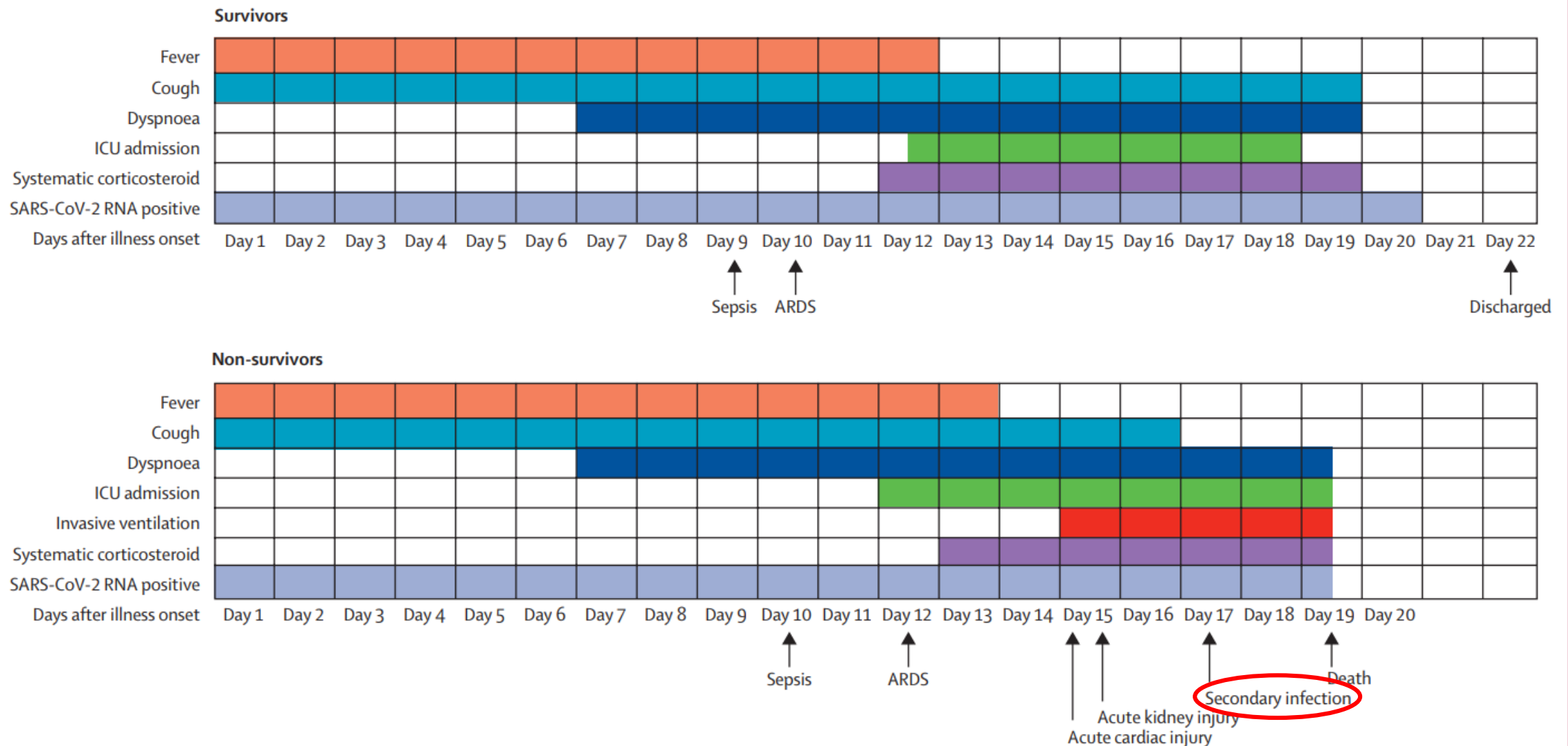


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Secondary Infection



Bacterial Co-infection Clues in Pneumonia

Respiratory
Setting Trends

- Nursing
- Respiratory therapy

Sputum
Gram stains

- ↑ sensitivity, specificity
- # bacteria/organisms
- Microbiology lab!

Primary vs.
Secondary
Infections

- ex. day of hospitalization
- central line, Foley catheter
- antibiogram



Procalcitonin (PCT) in COVID-19

- Critically ill COVID-19 patients?
- Vaughn, et al: community-onset bacterial co-infection

PCT >0.5ng/mL	PCT ≤0.1ng/mL
Positive predictive value 9.3%	Negative predictive value 98.3%

- Crotty, et al: bacterial respiratory co-infection

PCT >0.25ng/mL	PCT >0.5ng/mL
Sensitivity 73.9% Specificity 65.2%	Sensitivity 43.5% Specificity 81.3%,

- Possible role in antibiotic discontinuation and secondary infections



TA is a 48 yo F with a PMH of anxiety and hyperlipidemia who presented to the ED last night with SOB, cough, anosmia, and muscle aches. Her O2 saturations were 90% on room air and she was started on 2L nasal cannula. Upon admission to the general medicine floor, she was started on remdesivir and dexamethasone. Overnight she spiked a fever to 101°F and the covering physician ordered a one time dose of piperacillin/tazobactam.

- WBC 5.9 K/uL
- Procalcitonin 0.1 mcg/L
- Serum creatinine: 0.8 mg/dL
- Chest X-ray: mild patchy perihilar & peripheral airspace opacities
- Microbiology: blood cultures pending



Which of the following statements is most appropriate for the pharmacist to discuss with the ordering provider?

- A. Patient is at risk of a secondary nosocomial infection so meropenem should be started ASAP.
- B. The likelihood of bacterial co-infection is low so consider monitoring off antibiotics.
- C. Procalcitonin is < 0.5 mcg/L so order piperacillin/tazobactam for 6 more days to treat bacterial pneumonia co-infection.
- D. Add vancomycin to piperacillin/tazobactam to cover for resistant *S. pneumoniae*.



Guideline Recommendations

COVID-19 Guideline	Recommendation
Surviving Sepsis, March 2020	Empiric antimicrobials over no antimicrobials in mechanically ventilated patients with
WHO, Jan 2021	Severe: clinical judgement for antibiotics, attempt de-escalation daily
NIH, April 2021	“antimicrobial stewardship is critical”
NICE	Antibiotics for suspected bacterial infection but know risks and de-escalate rapidly
IDSA, June 2021	Review of controversy in literature
IDSA Real Time Learning Network	Pre-existing antimicrobial stewardship infrastructures for guidelines



COVID-19 vs. Influenza

	COVID-19	vs. Flu
Most Common Bacterial Respiratory Pathogens	? <i>CAP organisms</i> <i>S. aureus</i>	=
Bacterial Co-infection	1-10%	↓
Outcomes	↑ mortality	=
Co-infection Guideline Recommendations	n/a Weak, brief summaries across multiple guidelines	↓



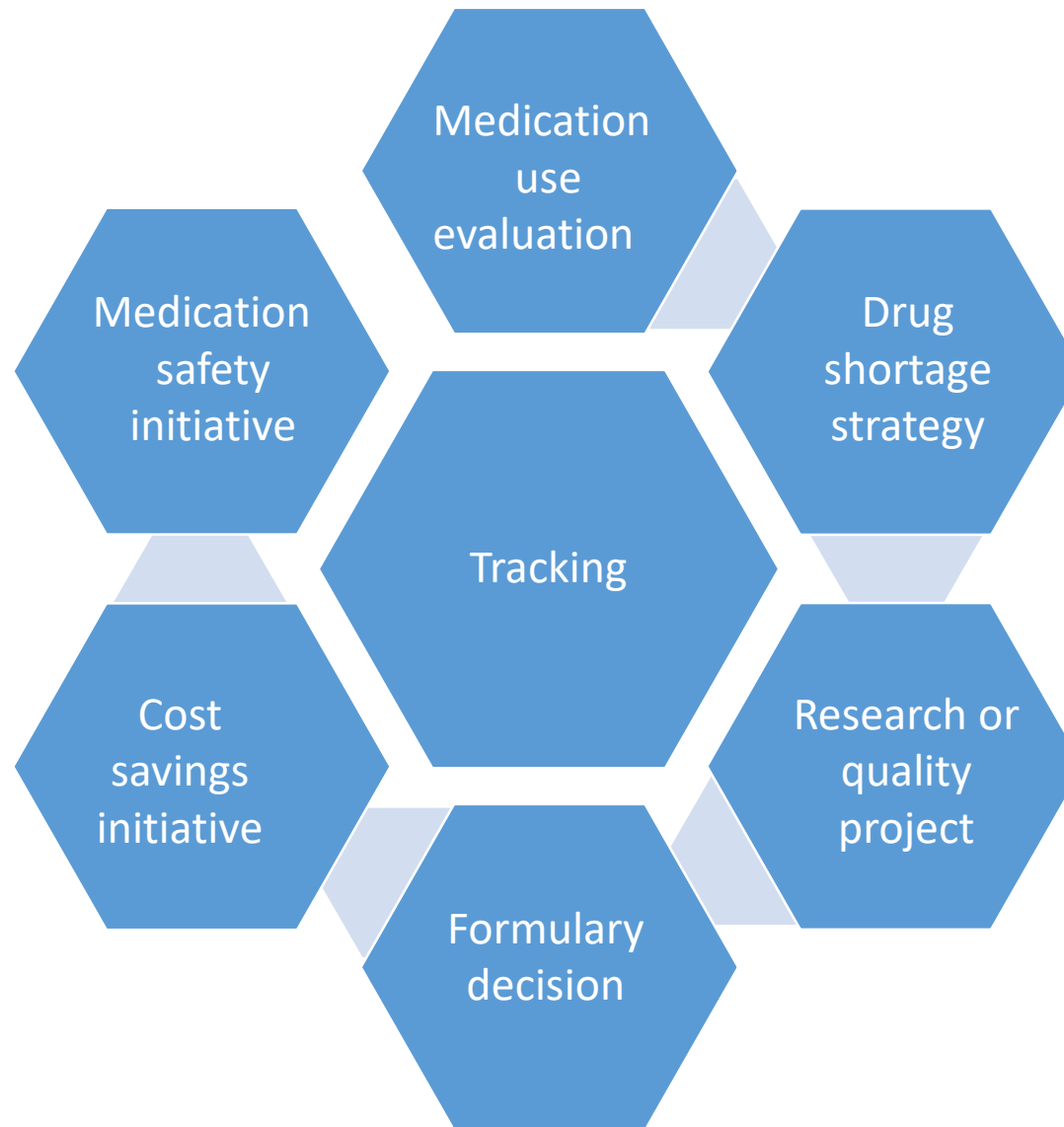
Co-infection Summary

- Low incidence of bacterial co-infection in COVID-19
- Distinction between co-infection and secondary infection
- Inconsistencies in reporting
- Pharmacists play an important role



III. Other Longitudinal Interventions to Enhance Care of Patients with COVID-19





Tracking & Reporting

- Antibigram
- Antimicrobial Utilization
 - Interventions
 - Opportunities for improvement
- Track by:
 - Institution vs. ward vs. prescriber/service
 - Drug, class, disease state

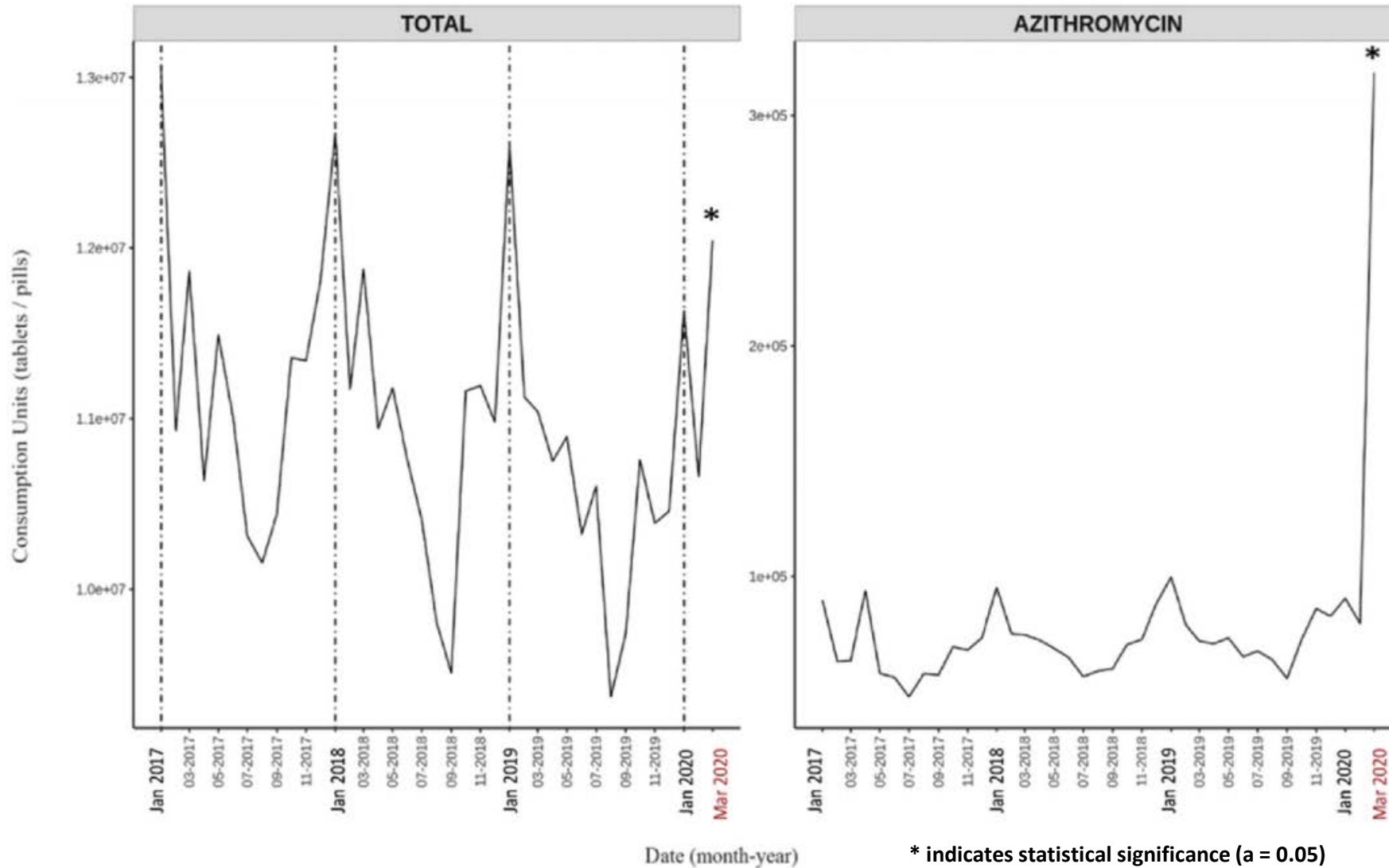
Example Metrics

- DOT/1,000 patient days
- DDD
- Costs
- Orders

DOT= days of therapy
DDD= defined daily dose



Spain, March 2020



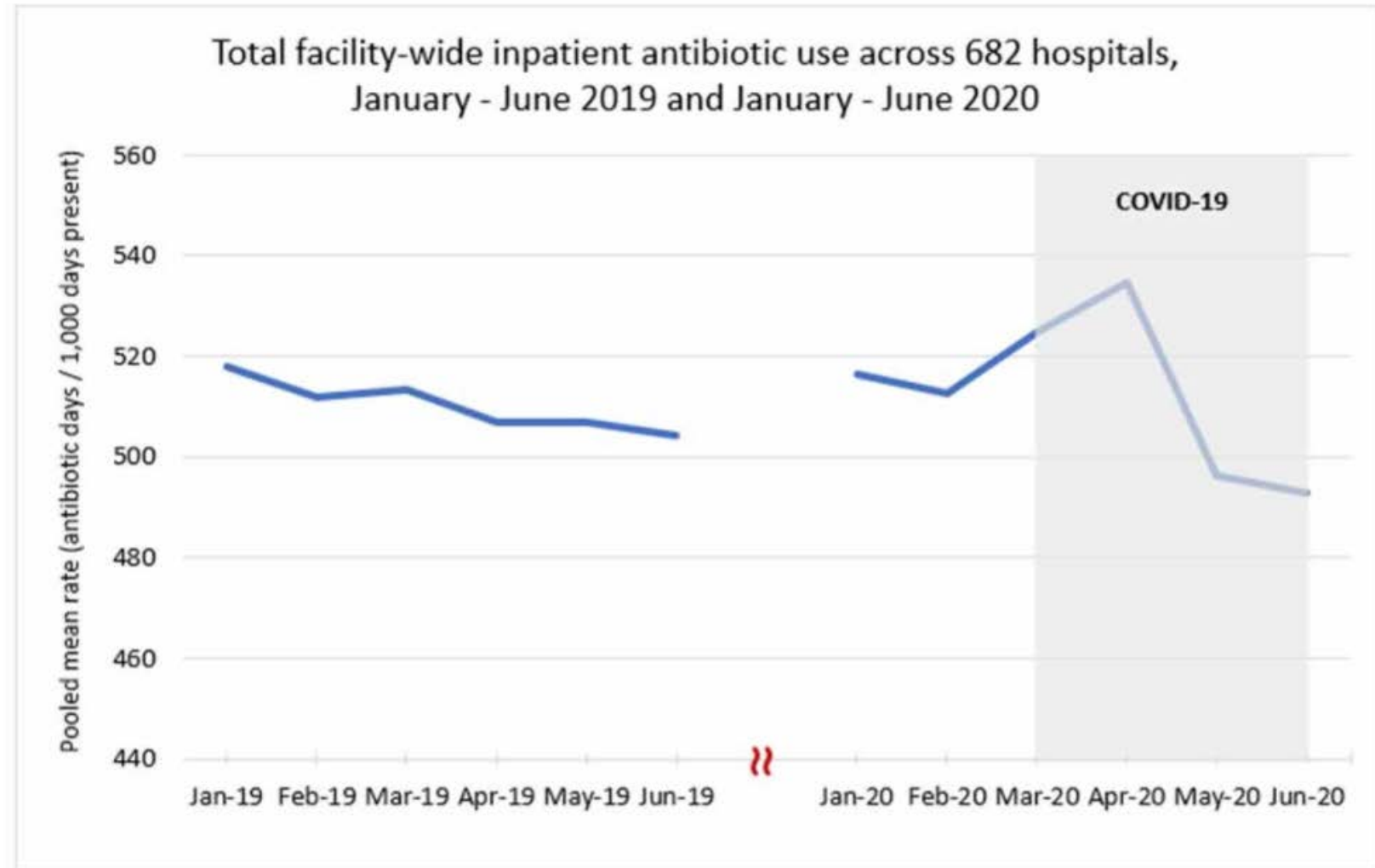
Other Antibiotics

1. ceftaroline (183%)
2. ceftolozane/tazobactam (103%)
3. ceftriaxone (204%)
4. colistin (145%)
5. doxycycline (517%)
6. linezolid (189%)



USA, CDC: Inpatient Antibiotic Prescribing

composite



Data Source: CDC National Healthcare Safety Network Antimicrobial Use Option



Standardized Antimicrobial Administration Ratio (SAAR)

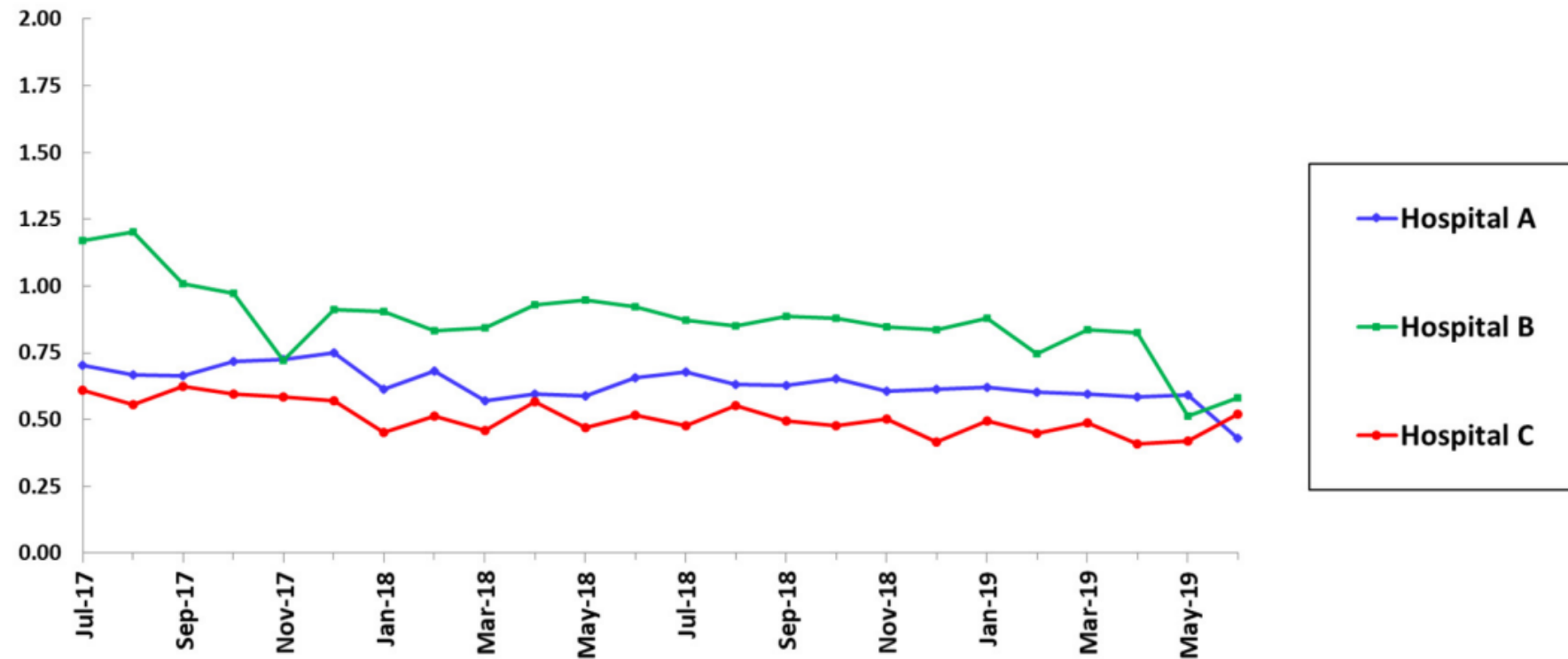
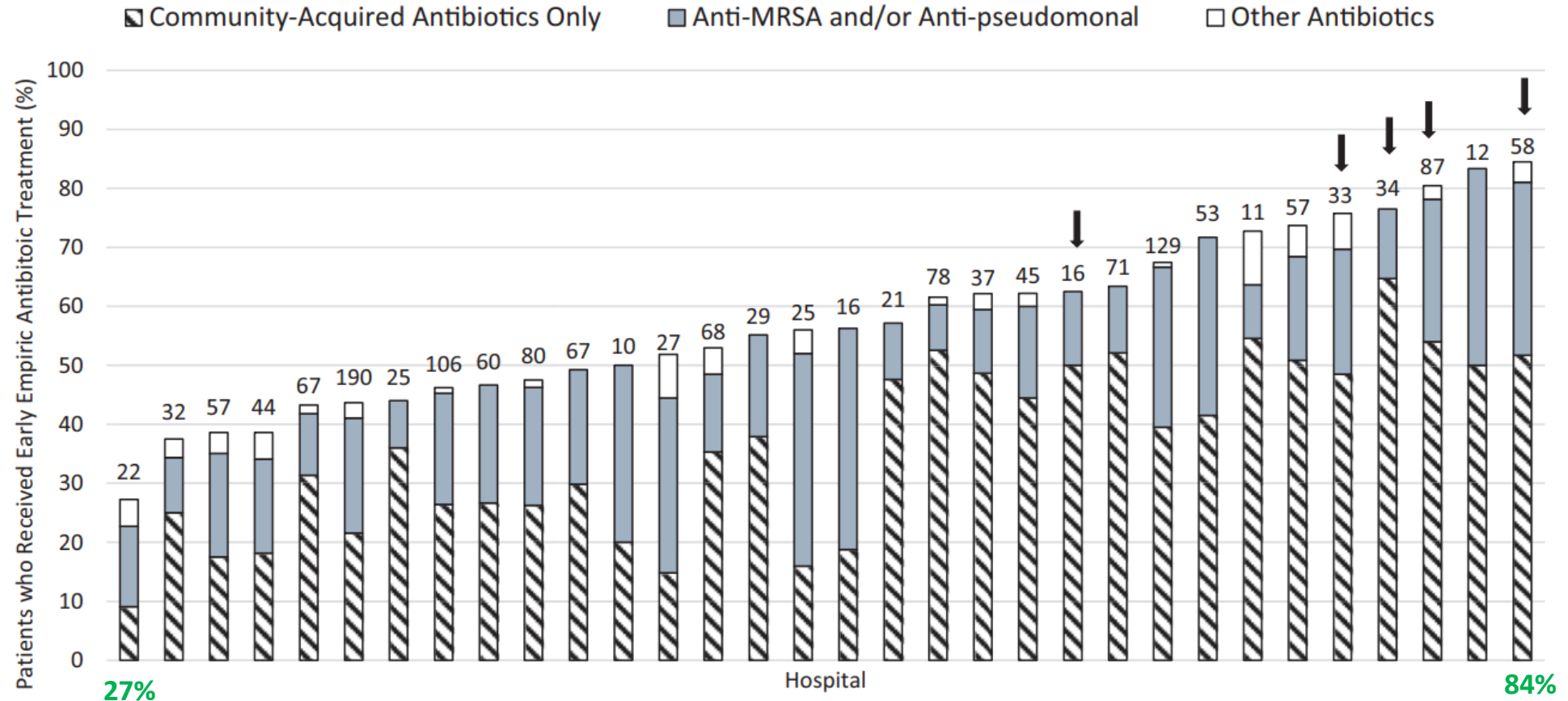


Figure 1. Standardized antimicrobial administration ratio (SAAR) trends for all antimicrobials used in adult intensive care units (ICUs), wards, step down units, and oncology units.



Antibiotics in Michigan Hospitals



4,628 antibacterial days/1,000 patients



Before & After Interventions

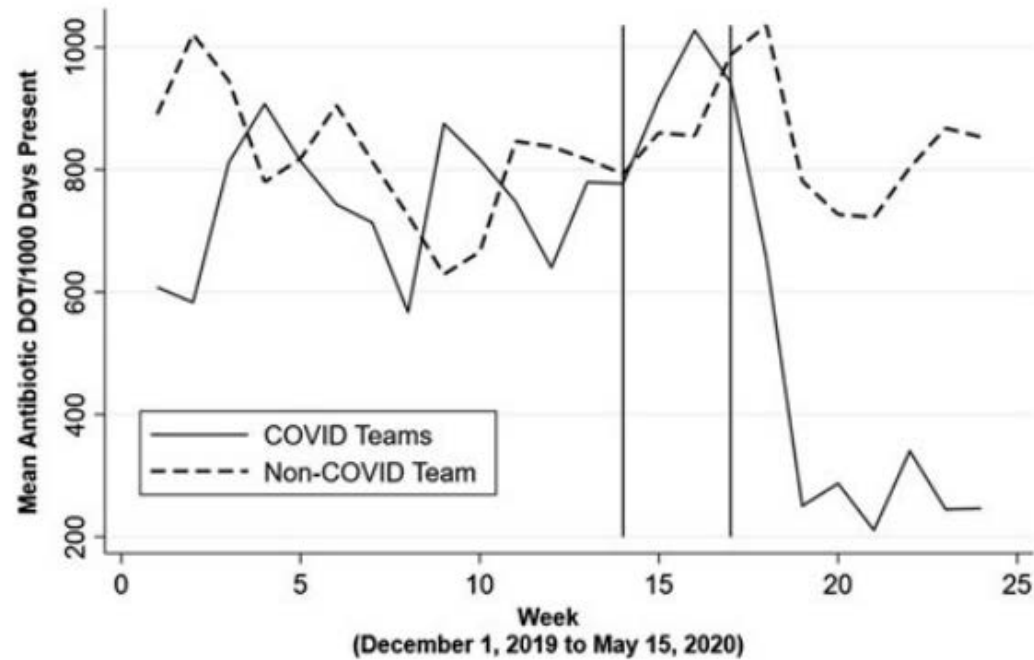


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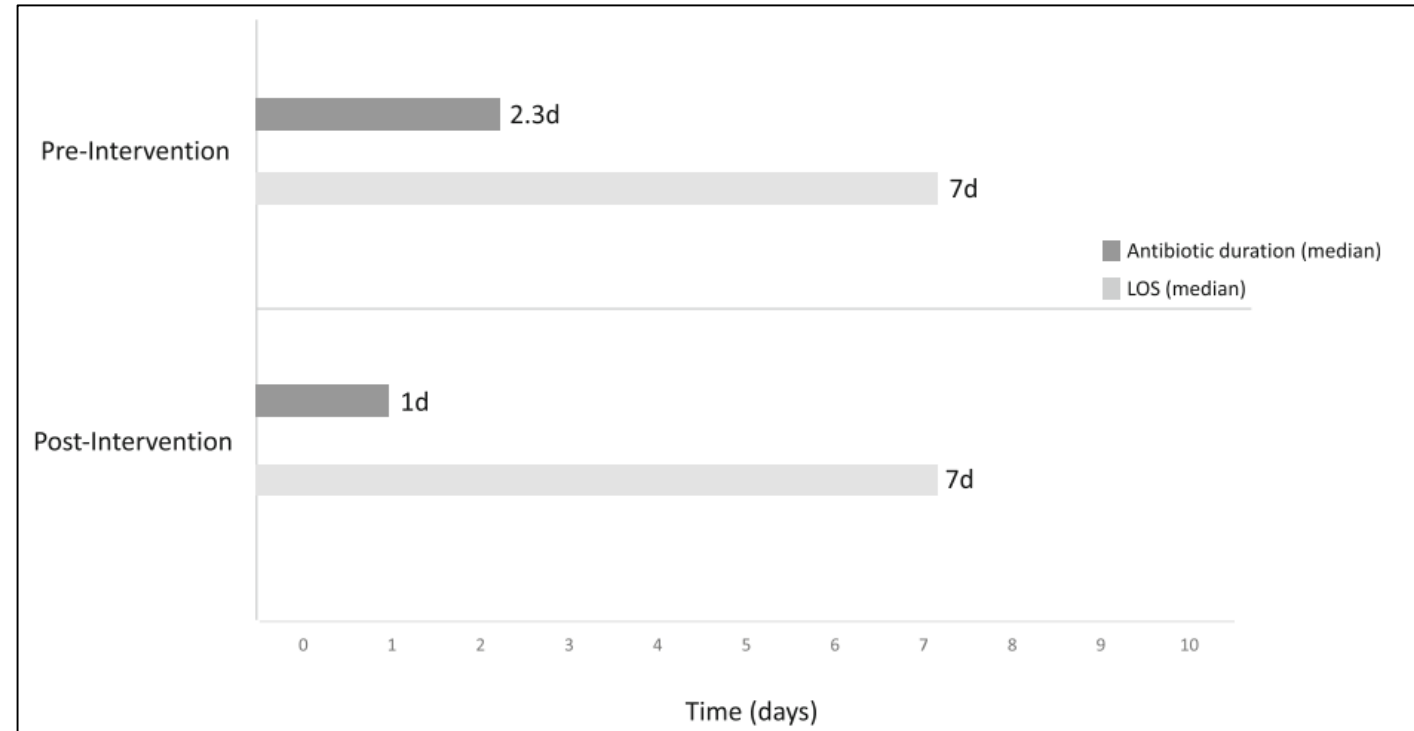


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Tracking Tocilizumab Administration

- Viral reactivation
- Live vaccines
- Contraindications
- Shortages

The FDA has issued Emergency Use Authorization for the emergency use of tocilizumab in the treatment of COVID-19.



The primary purpose of tracking antibiotic use during the COVID-19 era is to

- A. reduce the rate of healthcare-associated *Clostridioides difficile* (CDI).
- B. fulfill hospital accreditation requirements.
- C. report the highest antibiotic prescribers to leadership.
- D. identify and compare usage trends before COVID-19.



Summary

- Antimicrobial Stewardship strategies are useful for the COVID-19 response.
- Balance antibiotic use with low rates of co-infection.
- Pharmacists play an important role in multidisciplinary COVID-19 treatment teams.
- Use tracking and reporting to find and evaluate areas of opportunity.
- More antimicrobial stewardship research needed!



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Antimicrobial Stewardship Considerations during the COVID-19 Pandemic

Assessment Questions

1. Which antimicrobials stewardship strategy applicable to COVID-19 requires the most IT support?
 - a. Prospective audit & feedback
 - b. Therapeutic substitution
 - c. Pre-authorization
 - d. Guideline creation
2. Defaulting all remdesivir maintenance dose administration times to 1500 is a component of which antimicrobial stewardship strategy?
 - a. Batching
 - b. Prospective audit and feedback
 - c. Therapeutic substitution
 - d. IV to PO conversion
3. What is the estimated incidence of bacterial co-infection in COVID-19?
 - a. 0%
 - b. 1-10%
 - c. 15-20%
 - d. >25%
4. Antimicrobial utilization reports by hospital floor is an example of which Core Element of Antimicrobial Stewardship?
 - a. Pharmacy Expertise
 - b. Action
 - c. Tracking
 - d. Education

Answer key: 1. a, 2. a, 3. B, 4. c

1. Prospective audit & feedback (PAF) requires the most IT support. This is a disadvantage of PAF compared to pre-authorization. Therapeutic substitution and guideline creation do not require IT support for implementation.
2. Creating drug-specific, standard administration times for certain medications to avoid waste is a characteristic of the batching strategy. Prospective audit and feedback, therapeutic substitution, and IV to PO conversions do not affect administration times at the ordering phase of medications.
3. The estimated incidence of bacterial co-infection in COVID-19 is 1-10%. This finding is from meta analyses from limited reports in COVID-19 since the identification of the virus. This statistic varies according to country or region and the inclusion of primary vs. secondary bacterial infections.
4. Antimicrobial utilization reports by hospital floor is an example of the "Tracking" Core Element of Antimicrobial Stewardship. These reports are used to generate various "Action" or "Education" strategies. "Pharmacy Expertise" is used to interpret these reports in collaboration with other members of the antimicrobial stewardship multidisciplinary team.