# Antibiotic Stewardship Webinar Series: Why It's Important for Your Practice and Patients

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GEORGIA PEDIATRIC
ANTIBIOTIC STEWARDSHIP

# Antibiotic Stewardship Webinar Series:

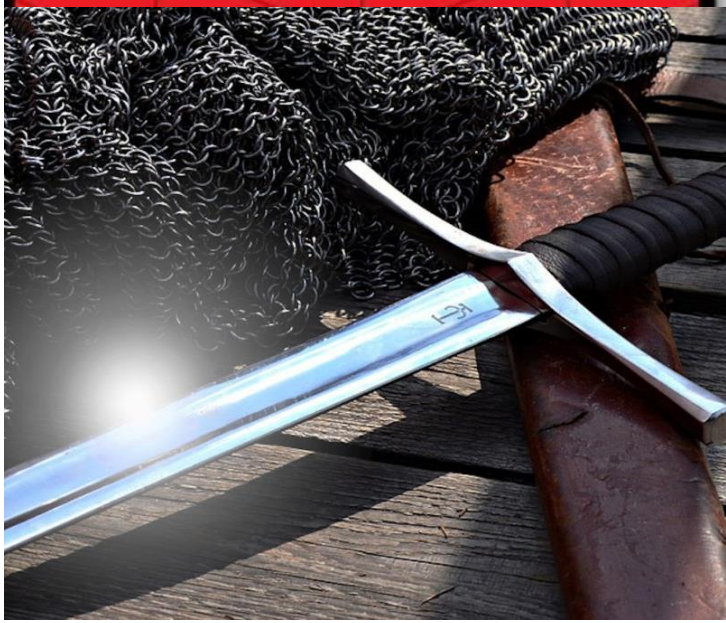
## #1: How to Access and Use the Website

**Preeti Jaggi, MD**

**Matt Linam, MD, MS**

# Why is This Important?

- Antibiotics are a double-edged sword
- Resistance is a problem!
- Adverse effects are a problem!
- Aminoglycosides, beta-lactams, trimethoprim, and metronidazole
- Preservation of the pediatric microbiome
- We only want to kill the bacteria causing the problem

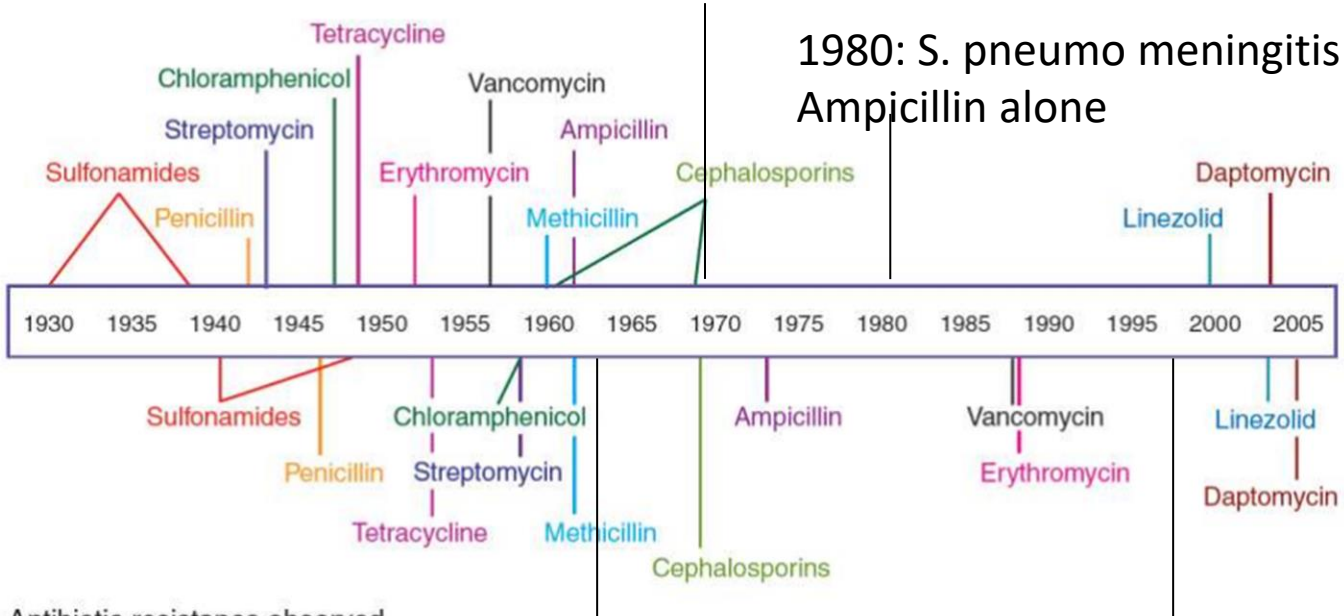
Courtesy of Stan Shulman

# The Harms of Antibiotic Treatment

- **Antimicrobial resistance**
- *C. difficile* infections
- Idiosyncratic reactions
- Changes to the pediatric microbiome
- Adverse clinical outcomes

1970: AOM, pneumonia, sulfa/EES

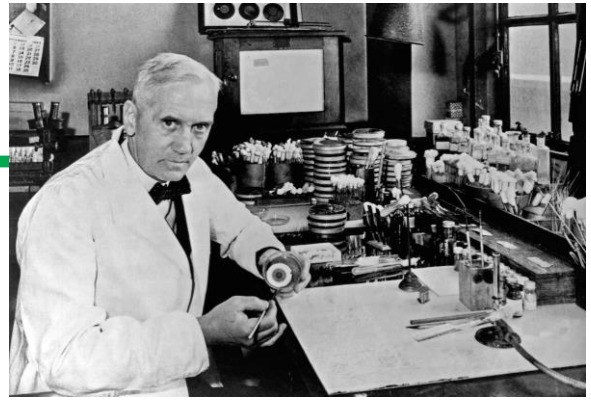
1980: S. pneumo meningitis Ampicillin alone




1964: urinary infection sulfa

1990: SSTI
1st generation ceph

# A Brief History of Penicillin



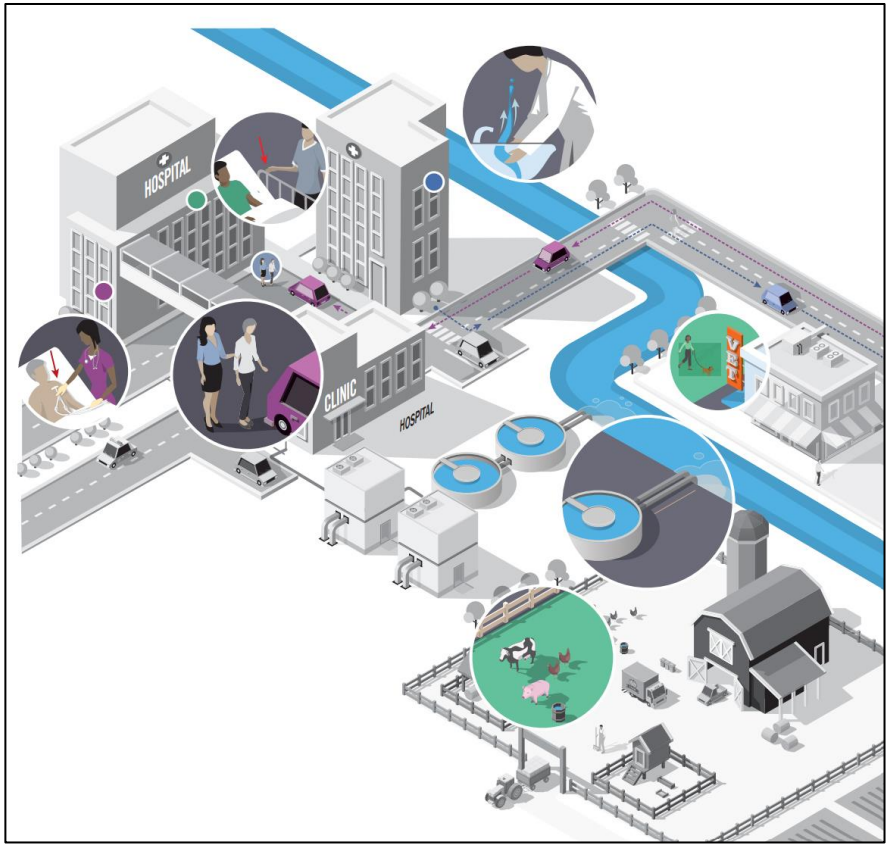
- In 1928, Alexander Fleming discovered penicillin
- In 1939, Howard Florey, Ernst Chain and Norman Heatley were able to successfully extract penicillin for the *Penicillium* mold
- In March 1942, Anne Miller was the first US civilian patient to be successfully treated with penicillin, at New Haven Hospital in Connecticut
- As the US entered World War II, the US government took over all production of penicillin. Reduced mortality by 12-15%
- In March 1945, penicillin was made available to the public in the US

Gaynes R, Emerging Infectious Diseases. Volume 23, Number 5—May 2017
Goyotte D, The Surgical Technologist. 2017. I09: 257-64

"**It is not difficult to make microbes resistant to penicillin in the laboratory** by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body. The time may come when penicillin can be bought by anyone in the shops. Then **there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant**."

Dr. Alexander Fleming

# The Interconnectedness of Antibiotic Resistance





Antibiotic Resistance Threats in the United States, 2019 (cdc.gov)

# There is a Direct Correlation Between Antibiotic Use and Antibiotic Resistance

**Table 1.** Cumulative Days of Antipseudomonal β-Lactam Antibiotic Exposure and New Resistance Development

| Cumulative Days of Antipseudomonal Exposure | No. of Patients | New Resistance Events, No. (%) | Hazard Ratio (95% Confidence Interval) |
|---|---|---|---|
| 1–3 | 1,816 | 38 (2.09) | 1.00 (reference) |
| 4–6 | 1,632 | 85 (5.21) | 1.01 (0.93–1.10) |
| 7–9 | 1,249 | 98 (7.85) | 1.85 (1.69–2.02) |
| 10–12 | 709 | 66 (9.31) | 2.93 (2.66–3.24) |
| 13–15 | 474 | 44 (9.28) | 3.94 (3.54–4.39) |
| 16–18 | 326 | 30 (9.20) | 6.29 (5.62–7.04) |
| 19–21 | 234 | 27 (11.5) | 7.05 (6.19–8.02) |
| ≥22 | 678 | 56 (8.3) | 8.52 (7.62–9.53) |

Teshome B., et al. (2020). *Infection Control & Hospital Epidemiology, 41*(4), 484-485.

# Antibiotic Resistance Threats

**Urgent threats:**

- Carbapenem-resistant *Acinetobacter*
- *Candida auris*
- *Clostridioides difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant *Neisseria gonorrhoeae*

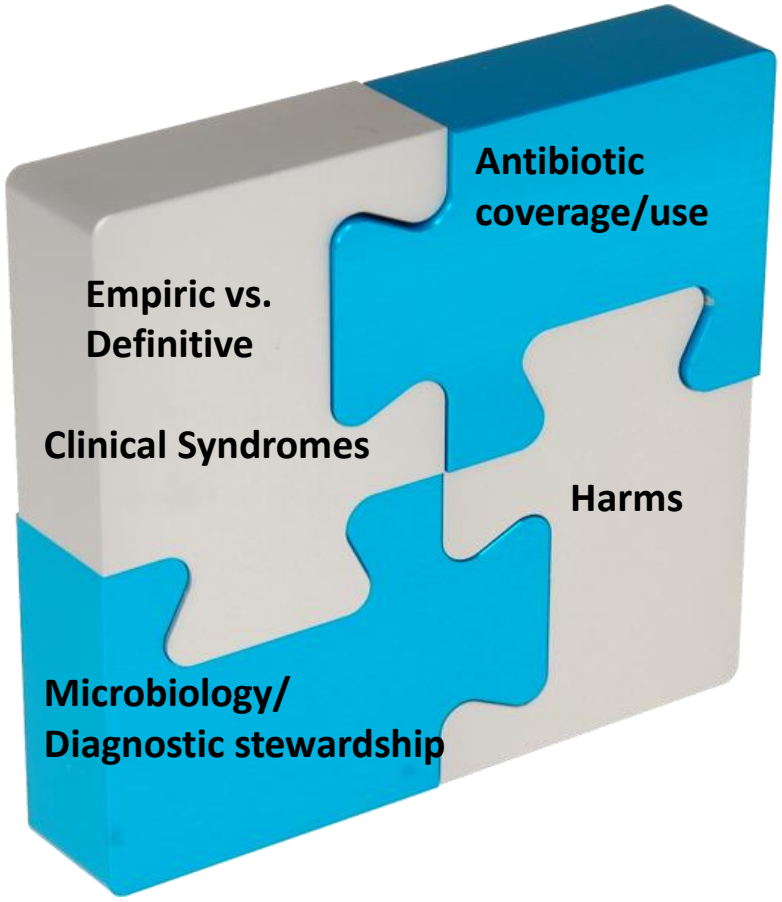
**Serious threats:**

- Drug-resistant *Campylobacter*
- Drug-resistant *Candida*
- ESBL-producing Enterobacteriaceae
- Vancomycin-resistant Enterococci
- Multidrug-resistant *Pseudomonas aeruginosa*
- Drug-resistant nontyphoidal *Salmonella*
- Drug-resistant *Salmonella* serotype Typhi
- Drug-resistant *Shigella*
- MRSA
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant Tuberculosis

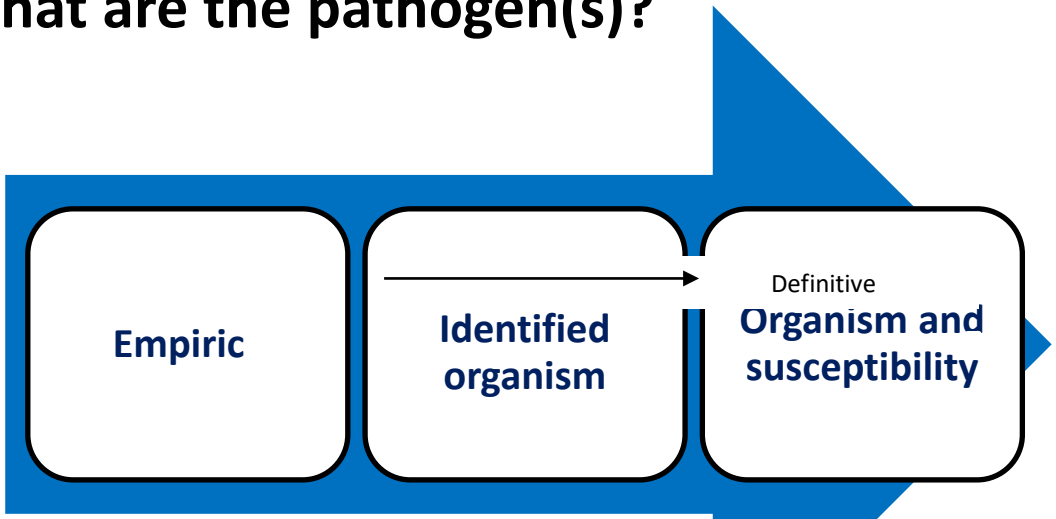
Antibiotic Resistance Threats in the United States, 2019 (cdc.gov)


AN ANTIBIOTIC IS THE WRONG TOOL TO TREAT A VIRUS.
Make sure you use the right tool for the job.
Antibiotics save lives by treating certain infections caused by bacteria, not viruses like colds or flu. When they're not needed, antibiotics won't help you, and the side effects could still hurt you. Ask your doctor when an antibiotic is the right tool for your illness and when it's not.
To learn more about antibiotic prescribing and use, visit www.cdc.gov/antibiotic-use.

# The pieces of the puzzle of prescribing..



**Is there/where is the bacterial infection?**
**What is the diagnosis/differential?**
**What are the pathogen(s)?**




Are there national or local guidelines to guide choice of antibiotic?

Is the bacteria/test relevant? Narrow?

Now that I have susceptibilities, can I narrow?

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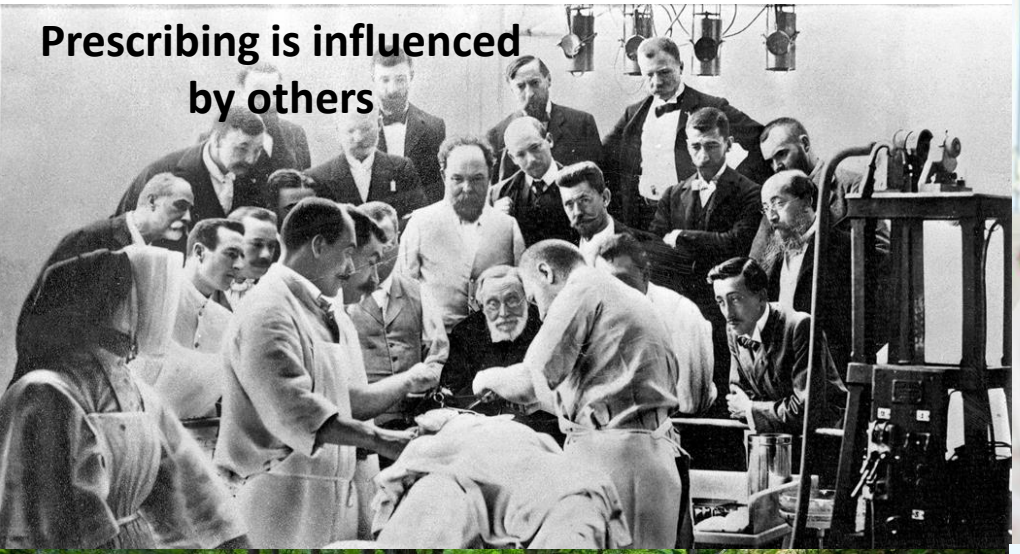
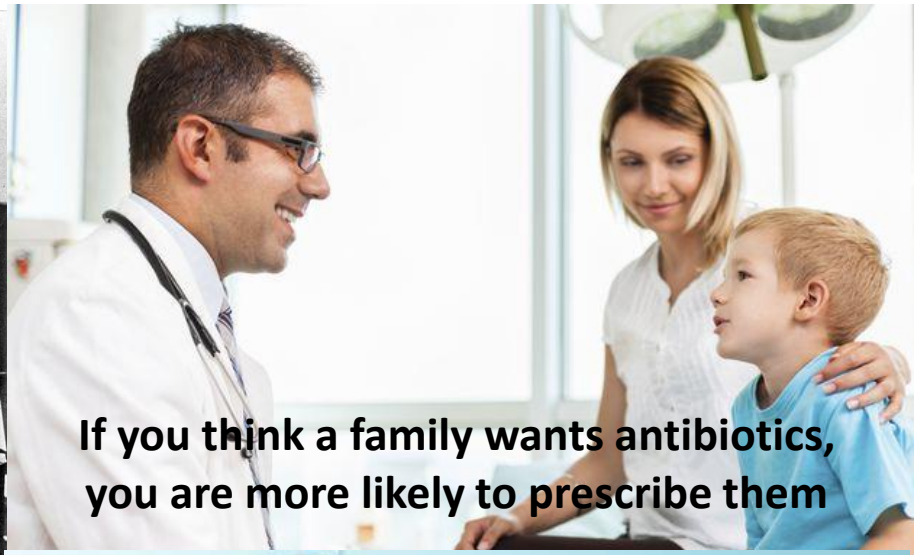

Prescribing is influenced by others


If you think a family wants antibiotics, you are more likely to prescribe them


Prescribing antibiotics is often the path of least resistance


Fatigue can lead to inappropriate prescribing

# The Harms of Antibiotic Treatment

- Antimicrobial resistance
- ***C. difficile* infections**
- Idiosyncratic reactions
- Changes to the pediatric microbiome
- Adverse clinical outcomes

# CDI in children

- Approximately 76% of 151 episodes of CDI showed a history of antibiotic use in the preceding 4 weeks, and OR of quinolone exposure were more associated with CDI
- 7-12 admissions per 10,000 (KIDS database)
- Pediatric CDI is associated with increased mortality, longer LOS, and higher costs among hospitalized children
- Incidence of *C. difficile* infection in children <18 years was 24.2 cases per 100,000 population; approximately two-thirds of cases were community–associated

Sandora T, et al. PIDJ. July 2011. 30(7):p 580-584.
Zilberg et al. Emerg Infect Dis. 2010;16:604–9
Sammons JS, et al. Clin Infect Dis. 2013, vol. 57 (pg. 1-8)

# CDI Risk from Community Exposure

| | Adjusted OR | 95%CI |
|---|---|---|
| Any antibiotic exposure | 6.91 | (4.17-11.44) |
| Clindamycin | 20.43 | (8.50-49.09) |
| Fluoroquinolones | 5.65 | (4.38-7.28) |
| Cephalosporins | 4.47 | (1.60-12.50) |
| Penicillins | 3.25 | (1.89-5.57) |
| Macrolides | 2.55 | (1.91-3.39) |

# The Harms of Antibiotic Treatment

- Antimicrobial resistance
- *C. difficile* infections
- **Idiosyncratic reactions**
- Changes to the pediatric microbiome
- Adverse clinical outcomes

# Idiosyncratic Reactions

- Nicolau syndrome
- Stevens Johnson syndrome
  - 1 per million
  - 18 million doses of amoxicillin were prescribed to children in 2010
  - 9 million doses of azithromycin, 4 million doses of tmp/sulfa to children
- DRESS syndrome
- Interstitial nephritis
- Drug fever
- Serum sickness
- Liver injury

Patel A, et al. PIDJ. 34(8):p 849-850, August 2015.

# Harm Even From Penicillin

- 5-year-old boy with a 2-day history of fever, sore throat, abdominal pain and vomiting
- Given an IM injection of benzathine penicillin
- After he developed pain, itching, and erythema of the arm and pale, reticulated skin of the right hand, he developed compartment syndrome and required fasciotomy


Quincer E and Jaggi P. J Pediatr 2019;212:238.

# The Harms of Antibiotic Treatment

- Antimicrobial resistance
- *C. difficile* infections
- Idiosyncratic reactions
- **Changes to the pediatric microbiome**
- Adverse clinical outcomes

# Systemic Consequences of Decreasing Microbial Diversity of Normal Flora?

- Changes in microbiome
  - Linked to obesity?[1]
  - Linked to auto-immune illness?[2]
    - Inflammatory bowel disease
    - Celiac
    - Juvenile arthritis
  - Linked to asthma and/or allergies[3]
    - Asthma
    - Food or other allergies

1. Lassiter C. J Dairy Sci. 1955; Cho, Nature 2012; Trehan, NEJM 2013, 2016, Gough EK BMJ, Saari et al, Pediatrics, 2015, Bailey JAMA peds 2014, Gerber 2016
2. Horton, Pediatrics, 2015, *Pediatrics 2012;130:e794-e803*
3. Hirsch, AG Clin Exp Allergy, 2016, Metsala, Clinical and Experimental Immunology, 2014

# The Harms of Antibiotic Treatment

- Antimicrobial resistance
- *C. difficile* infections
- Idiosyncratic reactions
- Changes to the pediatric microbiome
- **Adverse clinical outcomes**

# What's the harm in a bit broader therapy?

- Children diagnosed with an acute respiratory tract infection + received an antibiotic
- Matched retrospective cohort
- Compared those with broad (amox/clav, cephalosporins, macrolides) vs. narrow spectrum antibiotics; 14% received broad therapy
- Retrospective cohort: outcomes were treatment failure and adverse events 14 days after diagnosis.
- Broad-spectrum treatment-not associated with a lower rate of treatment failure
- Broad-spectrum treatment was associated with a higher risk of adverse events (3.7% for broad vs 2.7% for narrow)

Gerber JS, et al. JAMA.2017 Dec 19;318(23):2325-2336.

# Over-Prescribing of Antibiotics by the Numbers

- Antibiotics are the most common class of medications prescribed to children
- 30% of all antibiotics prescribed in US acute care hospitals are unnecessary
- 60% of US antibiotic expenditures for humans are related to outpatient care
- 20% of pediatric visits and 10% of adult visits in outpatient settings result in an antibiotic prescription
- 50% of outpatient antibiotic prescribing might be inappropriate (choice, dose, or duration)

Chai G. Pediatrics. 2012
Core Elements of Hospital Antibiotic Stewardship Programs | Antibiotic Use | CDC

## Summary of Core Elements of Outpatient Antibiotic Stewardship

**Commitment**
Demonstrate dedication to and accountability for optimizing antibiotic prescribing and patient safety.

**Action for policy and practice**
Implement at least one policy or practice to improve antibiotic prescribing, assess whether it is working, and modify as needed.

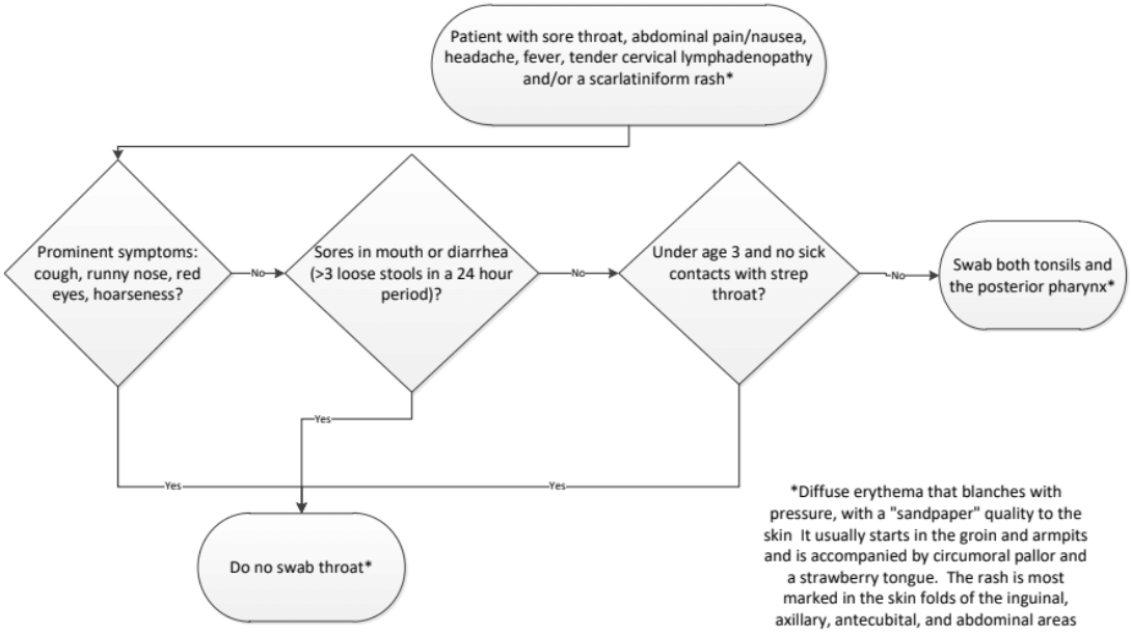
**Tracking and reporting**
Monitor antibiotic prescribing practices and offer regular feedback to clinicians, or have clinicians assess their own antibiotic prescribing practices themselves.

**Education and expertise**
Provide educational resources to clinicians and patients on antibiotic prescribing, and ensure access to needed expertise on optimizing antibiotic prescribing.

Core Elements of Outpatient Antibiotic Stewardship | Antibiotic Use | CDC

- 15-20% of children may be carriers for *S. pyogenes*
- Do not treat for strep throat without a positive test
- Do not test for strep throat if the patient likely has a viral illness

## Licensed Professional Initiated Protocol: Obtaining Throat Swab for Group A Streptococcal Pharyngitis




*Diffuse erythema that blanches with pressure, with a "sandpaper" quality to the skin It usually starts in the groin and armpits and is accompanied by circumoral pallor and a strawberry tongue. The rash is most marked in the skin folds of the inguinal, axillary, antecubital, and abdominal areas and about pressure points.

References

Shulman ST, Bisno AL, Clegg HW, et al. Clinical practice guidelines for the diagnosis and management of group A streptococcal pharyngitis: 2012 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2012;55(10):e86-e102. doi:10.1093/cid/cis629.

Hersh AL, Jackson MA, Hicks LA & Committee on Infectious Diseases. Principles of judicious antibiotic prescribing for upper respiratory tract infections in pediatrics. *J Pediatr*. 2013;132(6): 1146-1154. doi: 10.1542/peds.2013-3260.

# Developing the First Pediatric-Specific Antibiogram for the State of Georgia

# Georgia Pediatric Antibiogram

- Antibiograms from the five children's hospitals in Georgia were combined into a single antibiogram
- Hospitals provided annual antibiograms from 2014 – 2021
- Local antibiograms were developed based on Clinical and Laboratory Standards Institute (CLSI) guidelines for antibiogram development
- Isolates are primarily from ED and inpatient isolates

The PEDIATRIC HEALTHCARE IMPROVEMENT COALITION

Dwaine & Cynthia Willett Children's Hospital of Savannah | Piedmont Columbus Regional The Children's Hospital | Your Children's Miracle Network Hospital | Children's Healthcare of Atlanta | Children's Hospital of Georgia Augusta University | Atrium Health Navicent Beverly Knight Olson Children's Hospital

# Bacteria Included in the Georgia Pediatric Antibiogram

- *Staphylococcus aureus* (methicillin resistant and susceptible isolates are reported separately)
- *Enterococcus faecalis*
- *Streptococcus pneumoniae*
- *Escherichia coli*
- *Enterobacter cloacae* complex
- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*

# Methods

- Antibiogram data were reported as percent susceptible and total number of isolates
- The combined antibiogram data from 2014 - 2021 were used to show antibiotic susceptibility trends over time

# Interhospital Differences in Antibiotic Susceptibility

| | 2021 | | | | | |
|---|---|---|---|---|---|---|
| | Atlanta | Augusta | Columbus | Macon | Savannah | p-value |
| MSSA | | | | | | |
| Clindamycin | 778 (80%) | 78 (83%) | NA | 36 (84%) | NA | 0.665 |
| TMP/SMX | 963 (99%) | 90 (96%) | NA | 41 (95%) | NA | **0.009** |
| MRSA | | | | | | |
| Clindamycin | 381 (84%) | 60 (92%) | NA | 30 (85%) | NA | 0.207 |
| TMP/SMX | 449 (99%) | 58 (89%) | NA | 33 (94%) | NA | **<0.0001** |
| *Eschericia coli* | | | | | | |
| Cefazolin (urine breakpoints) | 1693 (88%) | NA | NA | 88 (96%) | 195 (99%) | **<0.0001** |
| Ceftriaxone | 1789 (93%) | 223 (95%) | 141 (95%) | 22 (95%) | 211 (98%) | **0.018** |
| Gentamicin | 1751 (91%) | 223 (95%) | 135 (91%) | 22 (96%) | 202 (94%) | 0.123 |
| Ciprofloxacin | NA | 219 (93%) | 138 (93%) | NA | NA | 0.984 |
| TMP/SMX | 1366 (71%) | 181 (77%) | 102 (69%) | 18 (77%) | 161 (78%) | **0.037** |
| *Klebsiella pneumoniae* | | | | | | |
| Ceftriaxone | 290 (94%) | 46 (85%) | NA | NA | NA | **0.025** |
| Gentamicin | 300 (97%) | NA | NA | NA | NA | NA |
| Ciprofloxacin | NA | 47 (87%) | NA | NA | NA | NA |
| TMP/SMX | 266 (86%) | 40 (74%) | NA | NA | NA | **0.025** |

MSSA is methicillin-susceptible *Staphylococcus aureus* . MRSA is methicillin-resistant *S. aureus* . Total number of isolates (percent susceptibility)
TMP/SMX is trimethoprim/sulfamethoxazole. NA - data points were removed due to isolate number <30

**Table. Combined Pediatric Antibiotic Susceptibility Data for the Cumulative Year 2021 for the State of Georgia**

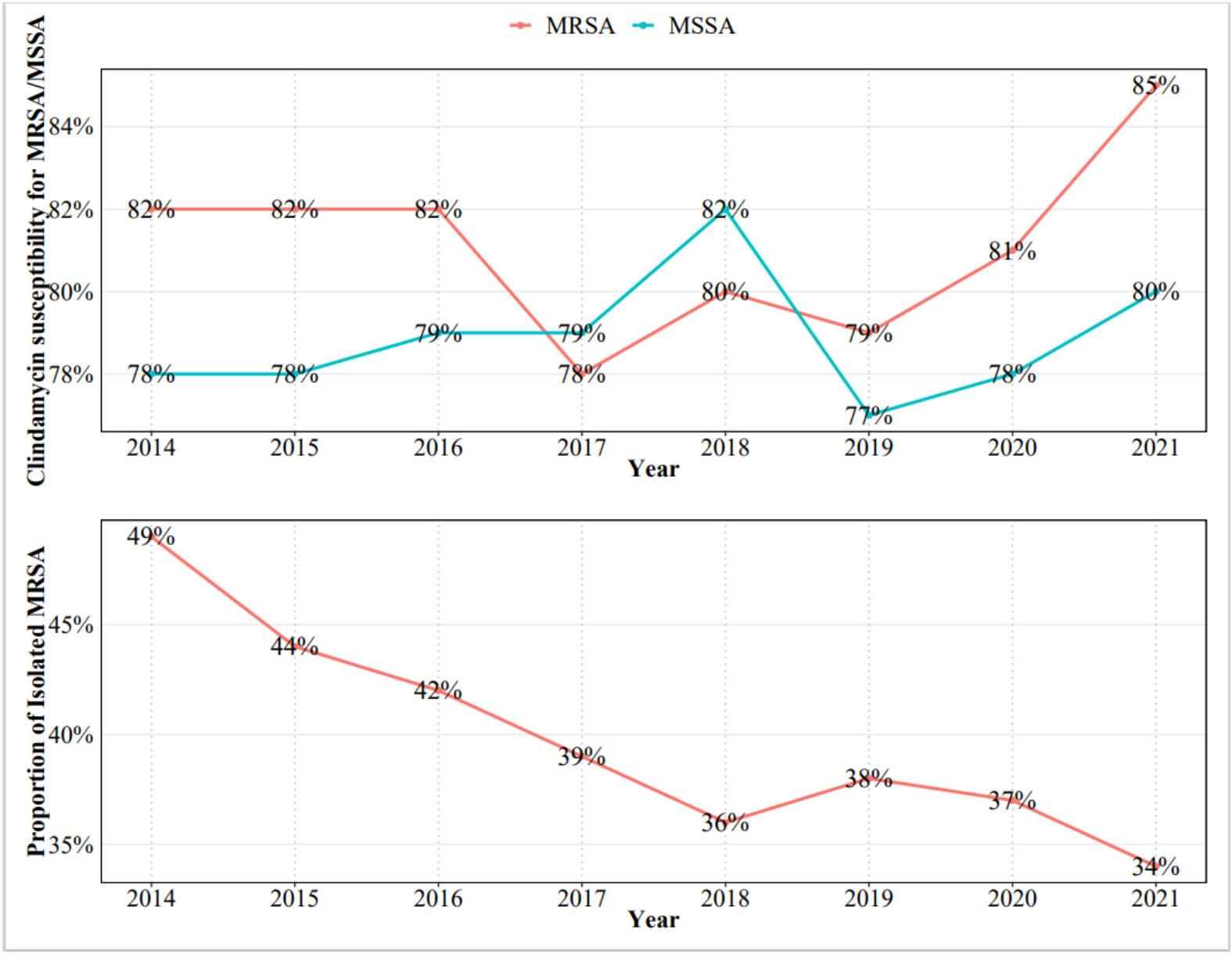
| % susceptible (total number of isolates) | ampicillin | amox/clav | oxacillin | ceftriaxone (non-meningitic) | ceftriaxone (meningitic) | clindamycin | TMP/SMX | vancomycin | linezolid | levofloxacin | nitrofurantoin (urine) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Gram positive organisms** | | | | | | | | | | | |
| Methicillin-susceptible *S. aureus* | - | - | 100 (1159) | - | - | 80 (1152) | 99 (1154) | 100 (1156) | - | - | - |
| Methicillin-resistant *S. aureus* | - | - | 0 (592) | - | - | 85 (588) | 97 (592) | 99 (592) | - | - | - |
| *Enterococcus faecalis* | 100 (209) | - | - | - | - | - | - | 99 (206) | 100 (206) | - | 100 (209) |
| *Streptococcus pneumoniae* | - | 91 (116) | - | 98 (129) | 85 (122) | 9 (128) | - | 100 (122) | - | 99 (123) | - |

| | ampicillin | cefazolin | ceftriaxone | ceftazidime | cefepime | pip/tazo | meropenem | gentamicin | tobramycin | amikacin | TMP/SMX | ciprofloxacin | levofloxacin | cefazolin (urine) | nitrofurantoin (urine) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Gram negative organisms** | | | | | | | | | | | | | | | |
| *Escherichia coli* | 49 (2545) | 74 (2338) | 94 (2545) | - | 95 (2335) | 98 (2545) | 99 (2105) | 92 (2545) | - | 99 (2108) | 72 (2536) | 93 (408) | - | 89 (2213) | 99 (2604) |
| *Klebsiella pneumoniae* | - | 87 (410) | 92 (410) | - | 96 (382) | 95 (410) | 100 (333) | 96 (356) | 95 (410) | 100 (329) | 83 (405) | 89 (74) | - | - | 34 (405) |
| *Enterobacter cloacae* complex | - | - | - | - | 88 (125) | - | 100 (109) | 98 (138) | 97 (138) | 100 (101) | 88 (130) | 92 (25) | - | - | - |
| *Pseudomonas aeruginosa* | - | - | - | 93 (433) | 91 (433) | 96 (433) | 95 (371) | 83 (433) | 96 (433) | 96 (355) | - | 98 (84) | 93 (110) | - | - |

*S. aureus* is *Staphylococcus aureus*. Amox/clav is amoxicillin/clavulanate. Pip/tazo is piperacillin/tazobactam. TMP/SMX is trimethoprim/sulfamethoxazole.
For a given bacterium, the differences in the total number of isolates is the result of differences in antibiotics included in susceptibility testing for the different hospitals

# Key Findings from the Combined 2021 Pediatric Antibiogram

- **MSSA**
  - Clindamycin: 80%
  - TMP/SMX: 99%
- **MRSA**
  - Clindamycin: 85%
  - TMP/SMX: 97%
- ***S. pneumoniae***
  - Amoxicillin-clavulanate: 91%
  - Ceftriaxone (non-meningitic): 98%
  - Clindamycin: 91%
- ***E. coli***
  - TMP/SMX: 72%
  - Nitrofurantoin: 99%
  - Cefazolin (urine breakpoints): 89%
  - Ceftriaxone: 94%
- ***K. pneumoniae***
  - TMP/SMX: 83%
  - Nitrofurantoin: 34%
  - Cefazolin: 87%
  - Ceftriaxone: 92%


MRSA
MSSA
Clindamycin susceptibility for MRSA/MSSA
84%
82%
80%
78%
82%
82%
82%
78%
78%
79%
79%
82%
78%
80%
79%
81%
85%
77%
78%
80%
2014
2015
2016
2017
2018
2019
2020
2021
Year
Proportion of Isolated MRSA
45%
40%
35%
49%
44%
42%
39%
36%
38%
37%
34%
2014
2015
2016
2017
2018
2019
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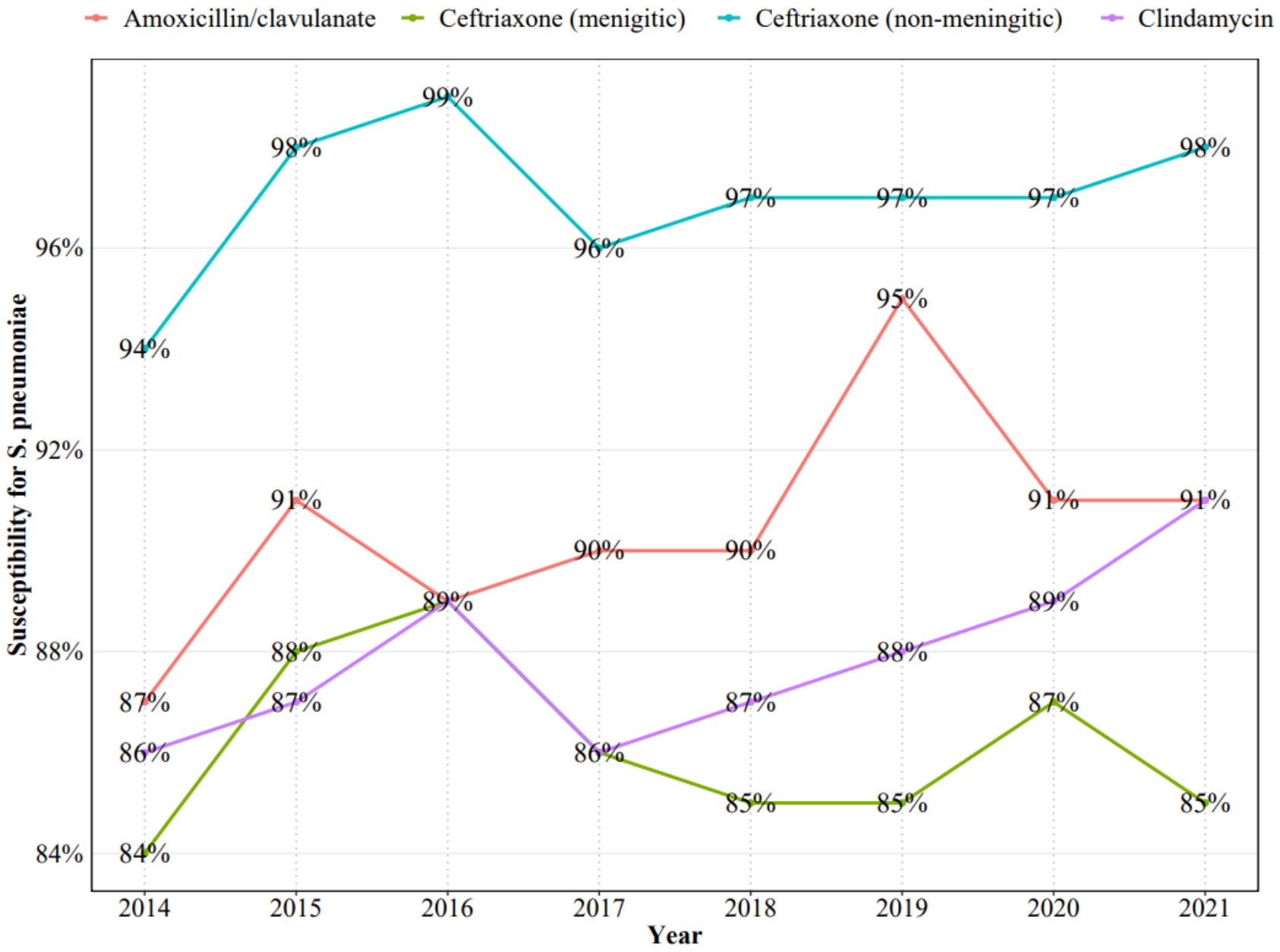
2021
Year


Amoxicillin/clavulanate
Ceftriaxone (menigitic)
Ceftriaxone (non-meningitic)
Clindamycin
Susceptibility for S. pneumoniae
96%
92%
88%
84%
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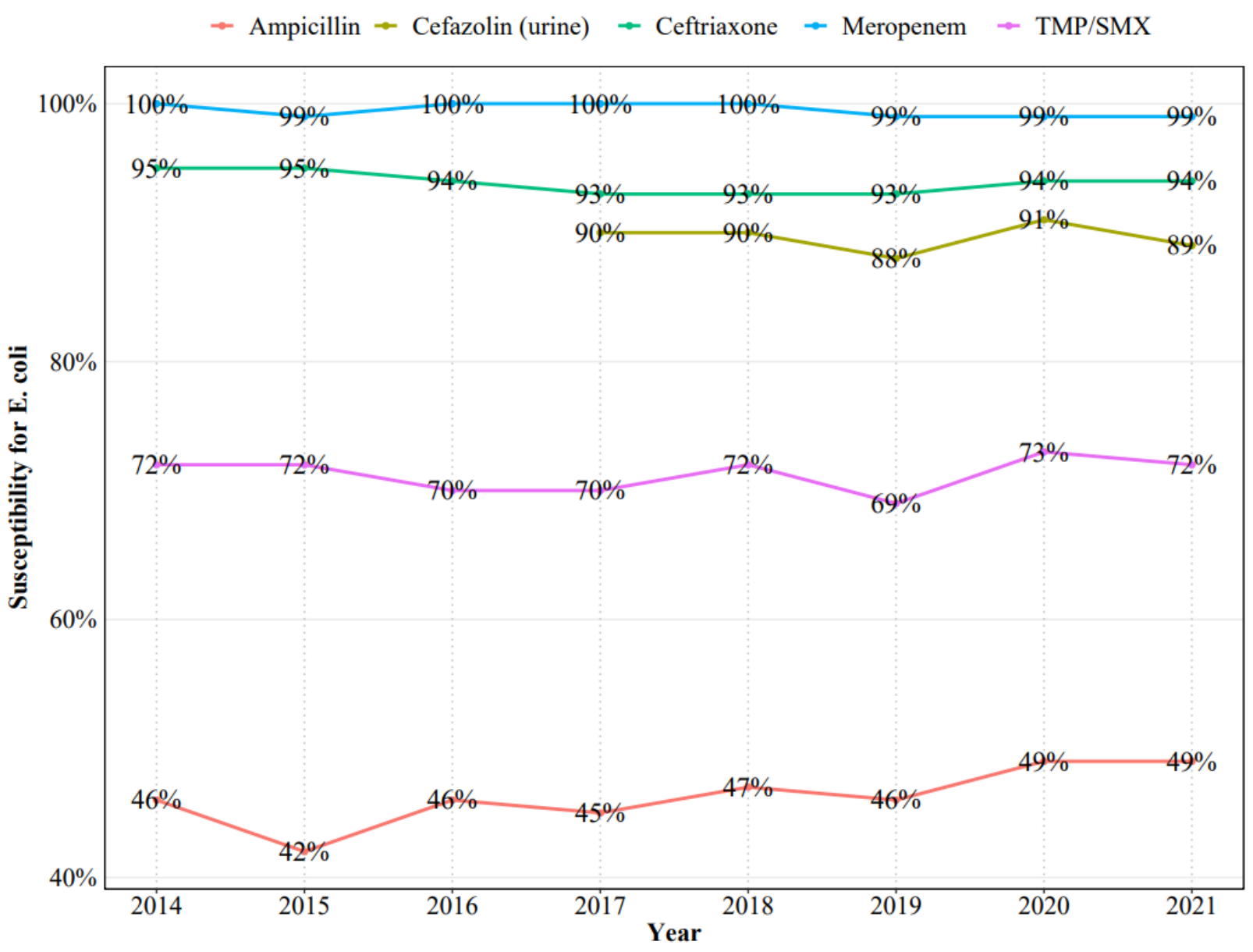
Ampicillin
Cefazolin (urine)
Ceftriaxone
Meropenem
TMP/SMX
100%
80%
60%
40%
Susceptibility for E. coli
100%
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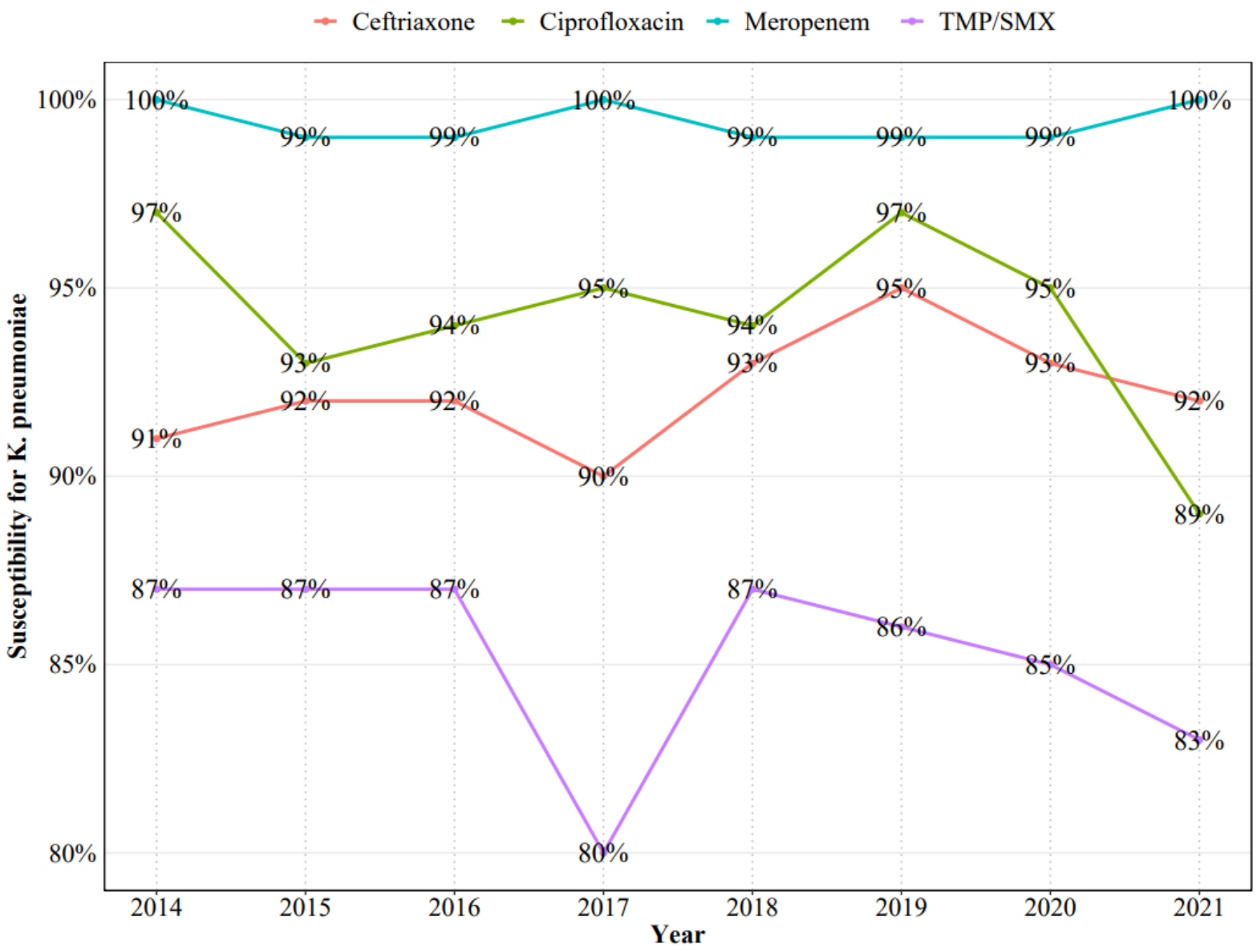
Ceftriaxone
Ciprofloxacin
Meropenem
TMP/SMX
Susceptibility for K. pneumoniae
100%
95%
90%
85%
80%
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87%
87%
87%
80%
87%
86%
85%
83%

# Trends in Multi-Drug Resistant Gram-Negative Bacilli

## *E. coli*

| Antibiotic | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|---|---|---|---|
| Ceftriaxone | 95% (2058) | 95% (2329) | 94% (2277) | 93% (2346) | 93% (2413) | 93% (2165) | 94% (2309) | 94% (2545) |
| Meropenem | 100% (2058) | 99% (2329) | 100% (2277) | 100% (2187) | 100% (2173) | 99% (1993) | 99% (2003) | 99% (2105) |

## *K. pneumoniae*

| Antibiotic | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 |
|---|---|---|---|---|---|---|---|---|
| Ceftriaxone | 91% (452) | 92% (563) | 92% (477) | 90% (547) | 93% (570) | 95% (436) | 93% (432) | 92% (410) |
| Meropenem | 100% (452) | 99% (563) | 99% (477) | 100% (517) | 99% (489) | 99% (388) | 99% (375) | 100% (333) |

# Conclusion

- Antibiotic susceptibility for pediatric bacterial isolates in Georgia remained stable over time
- The antibiogram data support the narrow spectrum empiric antibiotic treatment recommended in national evidence-based guidelines for SSTIs, CAP and uncomplicated UTIs
- MRSA rates decreased over time
- Gram-negative bacilli with resistance to broader beta-lactam antibiotics were uncommon and remained stable

# Antibiotic Susceptibility Data at Your Fingertips

https://pediatric-biostatistics-core-emory.shinyapps.io/Hospital_Infection_Disease/

Children's Healthcare of Atlanta

EMORY UNIVERSITY

# GEORGIA PEDIATRIC ANTIBIOTIC STEWARDSHIP

www.gpas-online.org

# Summary

- Antibiotics are essential for modern medicine
- Antibiotic resistance is a global threat to health
  - 2.8 million infections and 35,000 deaths
- Antibiotics, while life-saving, are also associated with significant harms
  - C. difficile
  - Alterations of the microbiome
  - Adverse drug events
- We must prescribe antibiotics wisely
  - Avoid using antibiotics for viral infections
  - Diagnostic stewardship
  - Evidence-based guidelines
- Pediatric antibiotic susceptibility in Georgia
  - Remains stable
  - Supports clinical practice guidelines

# Thank you for joining us!

## Give feedback and help us enhance our program!

- Complete the survey and submit questions using the QR code

**Save the dates for the next lunchtime webinars in this series:**
Webinar #2: August 16 – Prescribing Guide
Webinar #3: November 1 – Antibiotic Dosing