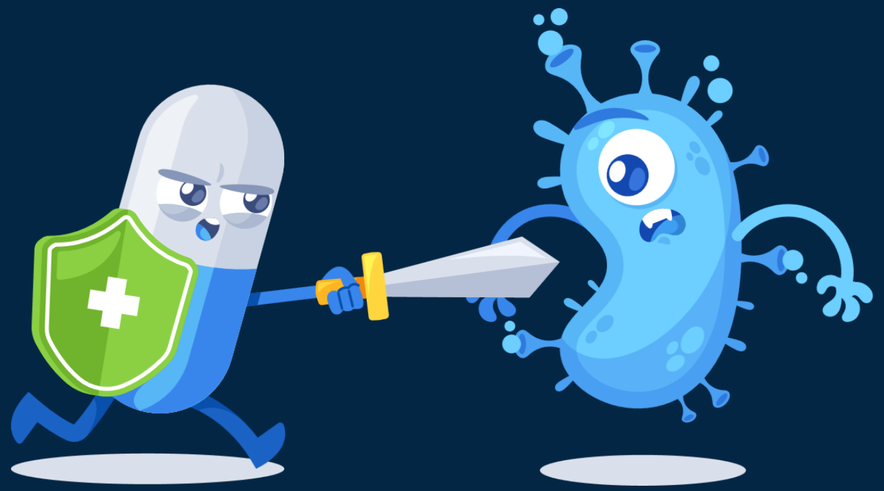


IS RESISTANCE FUTILE? ANTIMICROBIAL RESISTANCE IN PEDIATRICS

Amanda Goddard, MD
Pediatric Infectious Diseases

OBJECTIVES

1. Brief overview antibiotic development and resistance
2. Review gram negative cephalosporin resistant community acquired urinary tract infections
3. Discuss potentially avoidable and unavoidable selective pressures for bacterial antibiotic resistance

2 YEAR OLD FEMALE WITH 3 DAYS OF FEVER, DECREASED APPETITE AND ACTIVITY

Toilet training, has regressed with urination
On exam possible lower abdominal tenderness

URINE DIP STICK TESTING POSITIVE FOR LEUKOCYTE ESTERASE AND NITRITE

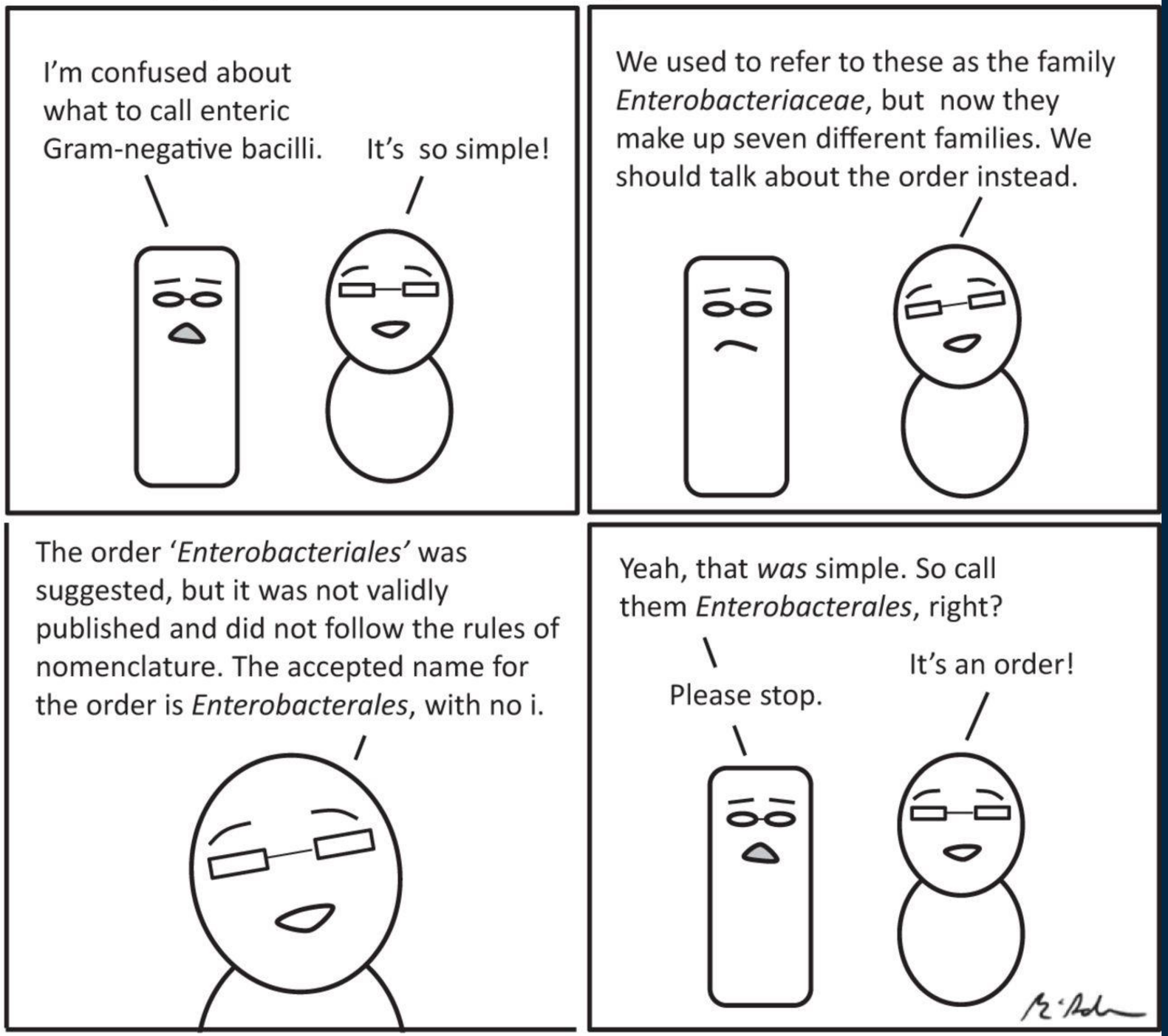
Cephalexin prescribed
Urine culture sent

LAB CALLS URINE CULTURE WITH ESBL ESCHERICHIA COLI

Plan to check lab report when break from clinic
Not your primary patient so wonder if risk factors

You have treated numerous MRSA skin infections but not extended spectrum beta-lactamase (ESBL) producing Enterobacterales (aka Enterobacteriaceae) UTIs, is this common in healthy outpatient children?

A Micro-Comic, Journal of Clinical Microbiology



https://journals.asm.org/doi/10.1128/jcm.01888-19

ANTIBIOTIC INTRODUCTIONS AND IDENTIFICATION OF RE

1928 Penicillin disco
(on S. aureus plate
1942 Cures S. aur
1943 Widespread use

1940 Penicillin R S. aureus
1950s PCN R acute cultures

1972 Vancomycin
1974 Amoxicillin
Daptomyci

2001 Linezolid
2002 Vancomyc
2004/5 Pan R P
2009 Ceftriaxon
Pan R Enteroba

1981 Comm
1987 Ceftaz
1988 Vancomycin R Enterococcus

Enterococcus

1984 C
1985
2010 Ceftarolin
2014 Ceftolozo
Dalbavancin (p
(>12 y
tazidir

6 of the **18** most alarming **antimicrobial resistance** threats cost the U.S. more than **$4.6 billion annually**[8]

Vancomycin-resistant
Enterococcus (VRE)

Carbapenem-resistant
Acinetobacter species

Methicillin-resistant
Staphylococcus aureus (MRSA)

Carbapenem-resistant
Enterobacterales (CRE)

Multidrug-resistant (MDR)
Pseudomonas aeruginosa

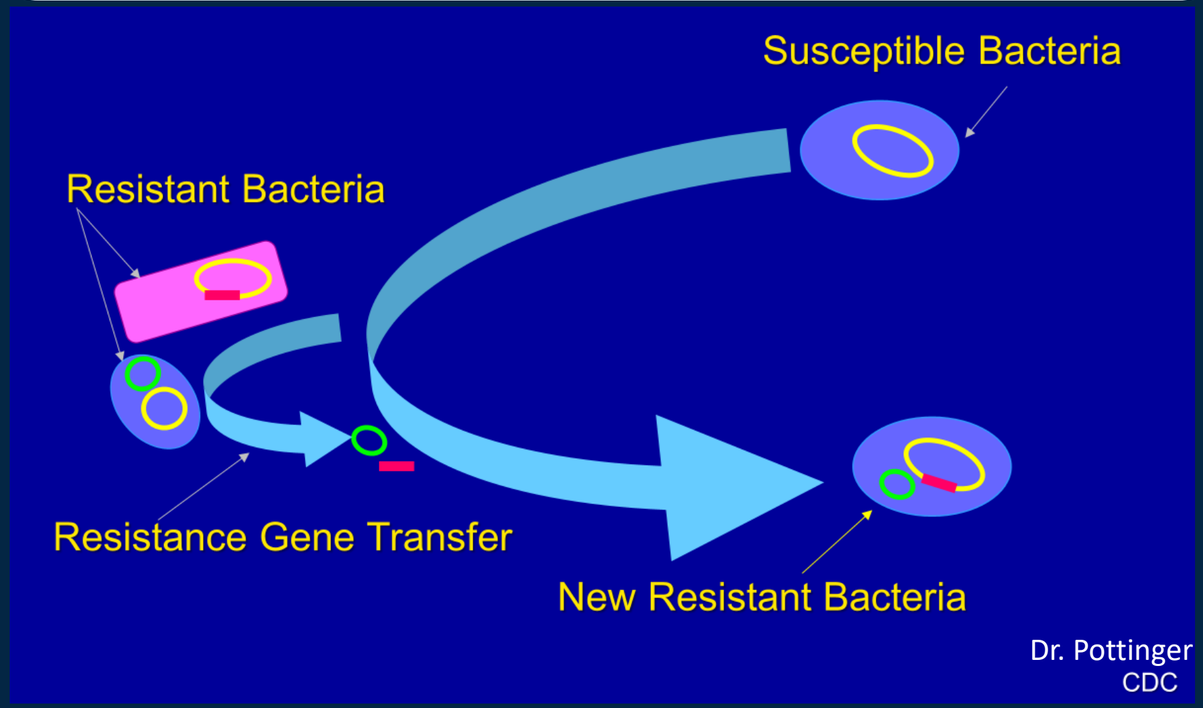
Extended-spectrum cephalosporin resistance in Enterobacterales suggestive of extended- spectrum β-lactamase **(ESBL)** production

ESBLs first described in 1980s

WHAT ARE BETA LACTAMASES?

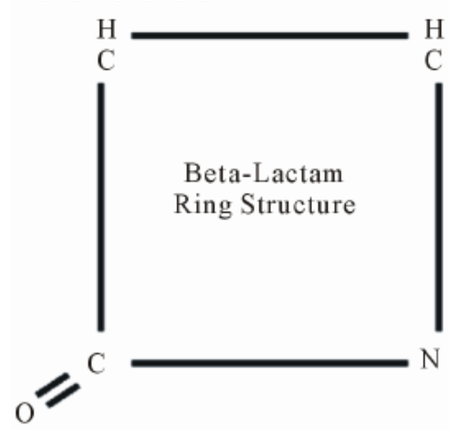
Beta-lactamases

– Bacterial enzymes that inactivate β-lactam antibiotics by hydrolysis
– First penicillinase identified E coli 1940
– Inhibitor-resistant β-lactamases
– Chromosome (AmpC), plasmid (ESBL), transposable elements



Beta-lactam antibiotics

– Penicillins
– Cephalosporins
– Monobactams
– Carbapenems



Beta-lactamase inhibitors

– Clavulanic acid (only oral option, 1980s)
– Sulbactam
– Tazobactam
– Avibactam, Vaborbactam, Relebactam

EXTENDED-SPECTRUM B-LACTAMASES (ESBLS)

Hydrolyze 3rd and 4th generation cephalosporins and monobactams

Gram-negative rods, most commonly E. coli, Klebsiella pneumoniae, K. oxytoca, P. mirabilis

CTX-M exploded in the 1990s and 2000s (first identified in a lab dog, then child in Munich (ceftriaxone, munich)

-hospital and community settings, the environment, the food supply and livestock

RISK FACTORS COMMUNITY ACQUIRED DRUG RESISTANT UTI ?

Hospitalization, antibiotic prophylaxis, recent antibiotic, +/- travel

Increasing incidence antibiotic resistant UTIs in pediatrics even without above risks over decade

3rd gen cephalosporin resistance used to infer ESBL

-British Columbia 12% of 294 UTIs resistant 3rd gen cephalosporin

-3 fold increase community acquired ESBL UTI 2015 to 2021 Alabama (tertiary referral hospital)

IMPACT OF CEFTRIAXONE RESISTANCE?

Limits treatment options

ESBL most common mechanism, often coupled with resistance other antibiotic classes (sulfonamides, aminoglycosides, fluoroquinolones)

Increased 90 day recurrence

WHAT IS KNOWN ABOUT PEDIATRIC ESBL COLONIZATION?

Preschools Uppsala, Sweden

– Diapers collected, 58 preschools 2016
- >6-fold increase ESBL compared to 2010
– 20% Cefotaxime resistant Enterobacteriaciae (67/334)
– 6 preschools ESBL carriage rate ≥40%
– 18 preschools no carriers

Daycare Centers Netherlands, Belgium

– 28 Dutch (499 children), 18 Belgian (448 children) DCCs
– ESBL-E prevalence higher Belgium (16%)
– Antimicrobial use, hospitalizations less Netherlands
-Travel Asia previous 6 months associated with ESBL-E carriage but antibiotic use was not

Vertical transmission, Israel

– Surveillance NICU over 1 year
– Mother rectal swab delivery room
– Infants NICU admit and twice weekly
– 478 infants, 409 mothers (313 screened)
– 21.4% mothers colonized, 14.8% infants
– 23 of 67 colonized mothers (34.3%) delivered 25 infants colonized with the same bacterial strain
– Colonized mother/infant more likely to be exposed to antibiotics during pregnancy and delivery than colonized mothers with non-colonized infants
– 4 of 71 colonized infants LOS with ESBL, 2 died

Susceptible Bacteria

Selective Pressure → Upregulation of resistance factors or novel mutations

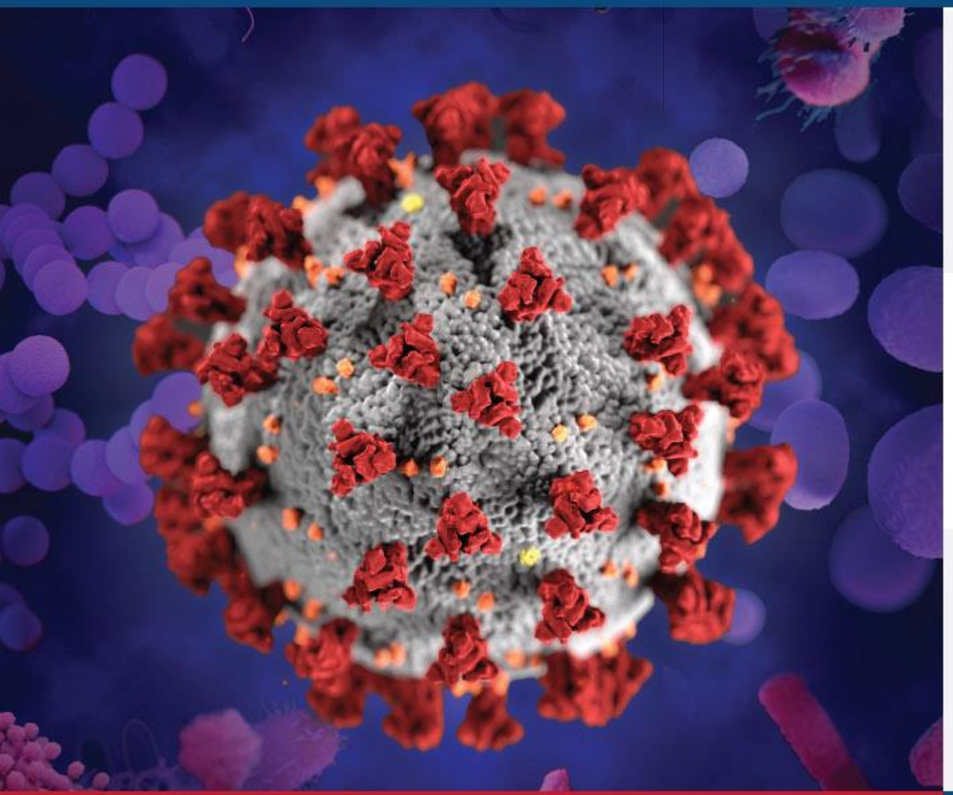
New Resistant Bacteria

Some selective pressures

Agriculture
-growth promotion
-80% US antibiotic use
Clinicians and patients
-Patient satisfaction models
Health system administration
Payment and reimbursement models
Supply chain
COVID

COVID-19 CREATED A PERFECT STORM

The U.S. lost progress combating antimicrobial resistance in 2020



↑15% Antimicrobal-resistant infections and deaths increased in hospitals in 2020.

~80% Patients hospitalized with COVID-19 who received an antibiotic March-October 2020.

⚠ Delayed or unavailable data, leading to resistant infections spreading undetected and untreated.

INVEST IN PREVENTION.

Setbacks to fighting antimicrobial resistance can and must be temporary.

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

FIGHT ANTIMICROBIAL RESISTANCE WITH INFECTION CONTROL

As a frontline healthcare worker, you play an important role in fighting antimicrobial resistance.

When you practice infection control, you stop resistant germs from:

Entering the body and causing infections through procedures and medical devices

Spreading to people from surfaces like bedrails or the hands of healthcare workers

Moving with patients when they are transferred between facilities

Spreading into the community, making them harder to control

Preventing new health care associated infections
Stopping the spread of resistant organisms
Reducing the need for antibiotics

https://www.cdc.gov/infectioncontrol/projectfirstline/

HEALTHCARE PROVIDERS: ACTIONS TO COMBAT RESISTANCE

Prevent infections and spread

Antimicrobial prescribing

Outpatient, inpatient antibiotic stewardship (health system support)
Treatment guidelines
Appropriate diagnostic tests

Be alert and take action

Maine Health Alert Network (HAN) System

PUBLIC HEALTH ADVISORY

Local antibiogram
Critical lab value calls
Maine CDC notifiable diseases and conditions list

Watchful Waiting for Ear Infections

BE ANTIBIOTICS AWARE
SMART USE, BEST CARE

What is an ear infection?

There are different types of ear infections. **Middle ear infection** (acute otitis media) is an infection in the middle ear, or behind the eardrum.

What does the term "watchful waiting" mean?

It means observing your child for 2–3 days to give your child's immune system time to fight off the infection rather than starting antibiotics immediately. Your healthcare professional will wait to see if your child gets better before giving your child a prescription for antibiotics.

Why would my healthcare professional recommend watchful waiting instead of giving antibiotics immediately?

Studies have shown that most children with mild ear infections get better without antibiotics. The child's immune system is often able to fight off the infection on its own. Antibiotics can sometimes improve symptoms more quickly, but antibiotics can also cause problems, such as side effects and antibiotic resistance. **Two out of 3 children with mild ear infections get better without receiving any antibiotics**.

Which children qualify for watchful waiting?

Children between ages 6 months and 23 months if only one ear is infected, and who have:

- Symptoms of ear infection that have lasted less than 2 days.
- Mild ear pain
- Temperature lower than 102.2°F (39°C)

OR

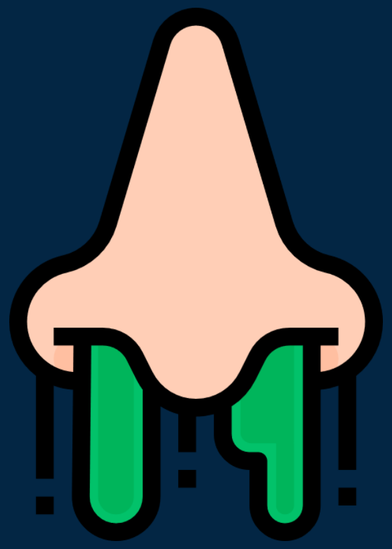
Children ages 2 years and older if one or both ears are infected, and who have:

How can I improve my child's symptoms if I don't give antibiotics?

The symptoms of an ear infection—like ear pain and fever—can be helped with ibuprofen or acetaminophen, rest, and extra fluids.

To learn more about antibiotic prescribing and use, visit **www.cdc.gov/antibiotic-use** or call **1-800-CDC-INFO**.

CDC



https://www.cdc.gov/antibiotic-use/training/materials.html

IMPROVE OUTPATIENT ANTIBIOTIC USE

CS336777-A

72%
of antibiotic prescriptions are likely necessary.

(But we still need to improve drug selection, dose and duration)

At least
28%
of antibiotic prescriptions are unnecessary.

In U.S Doctor's Offices and EDs

BE ANTIBIOTICS AWARE
SMART USE, BEST CARE

Learn more at cdc.gov/antibiotic-use.

DEPARTMENT OF HEALTH & HUMAN SERVICES · USA
CDC

Shorter antibiotic course for ventilator associated tracheitis was not associated with subsequent development of pneumonia. Longer course was associated with increased MDRO colonization (38% vs 8%) .

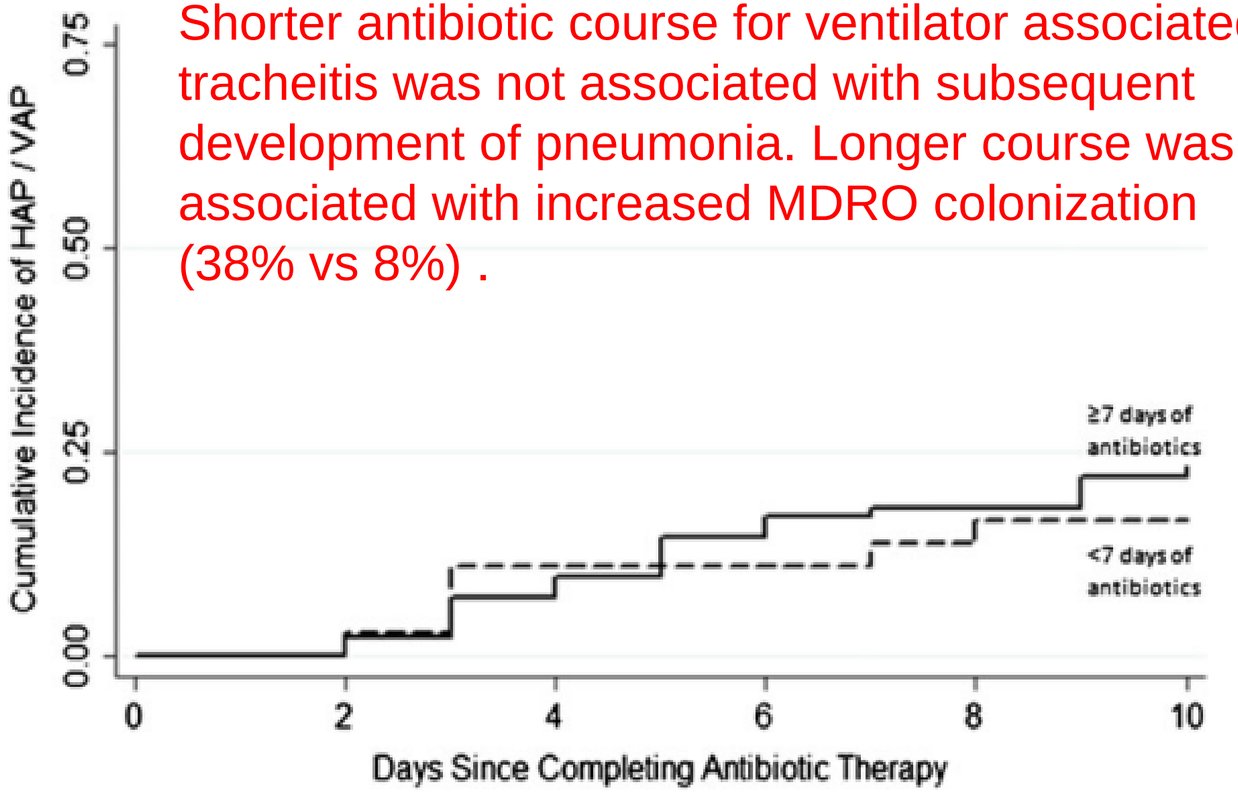


Figure 2. Cumulative distribution function of hospital-acquired pneumonia (HAP), shown for 118 children who met the definition of ventilator-associated tracheitis (VAT). $P = .46$, by log-rank test.

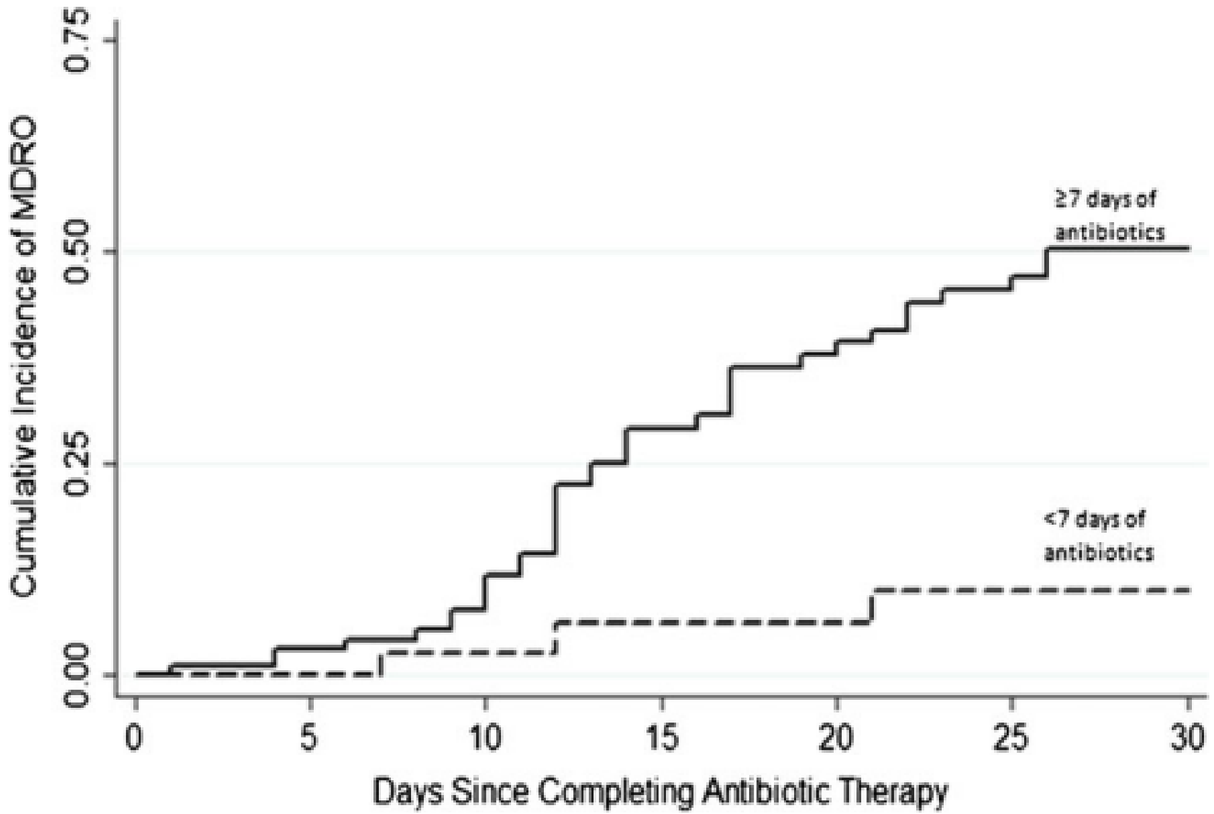
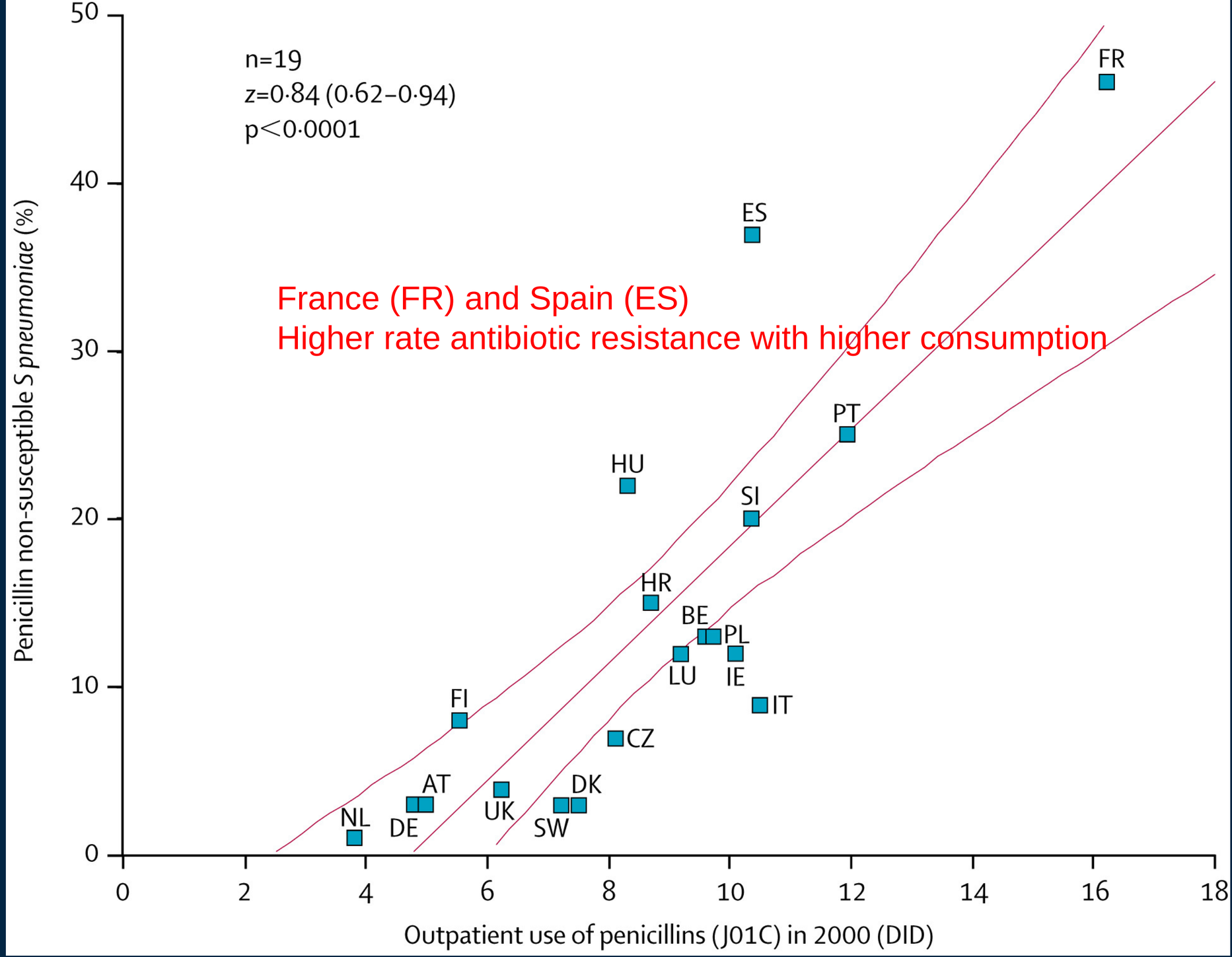


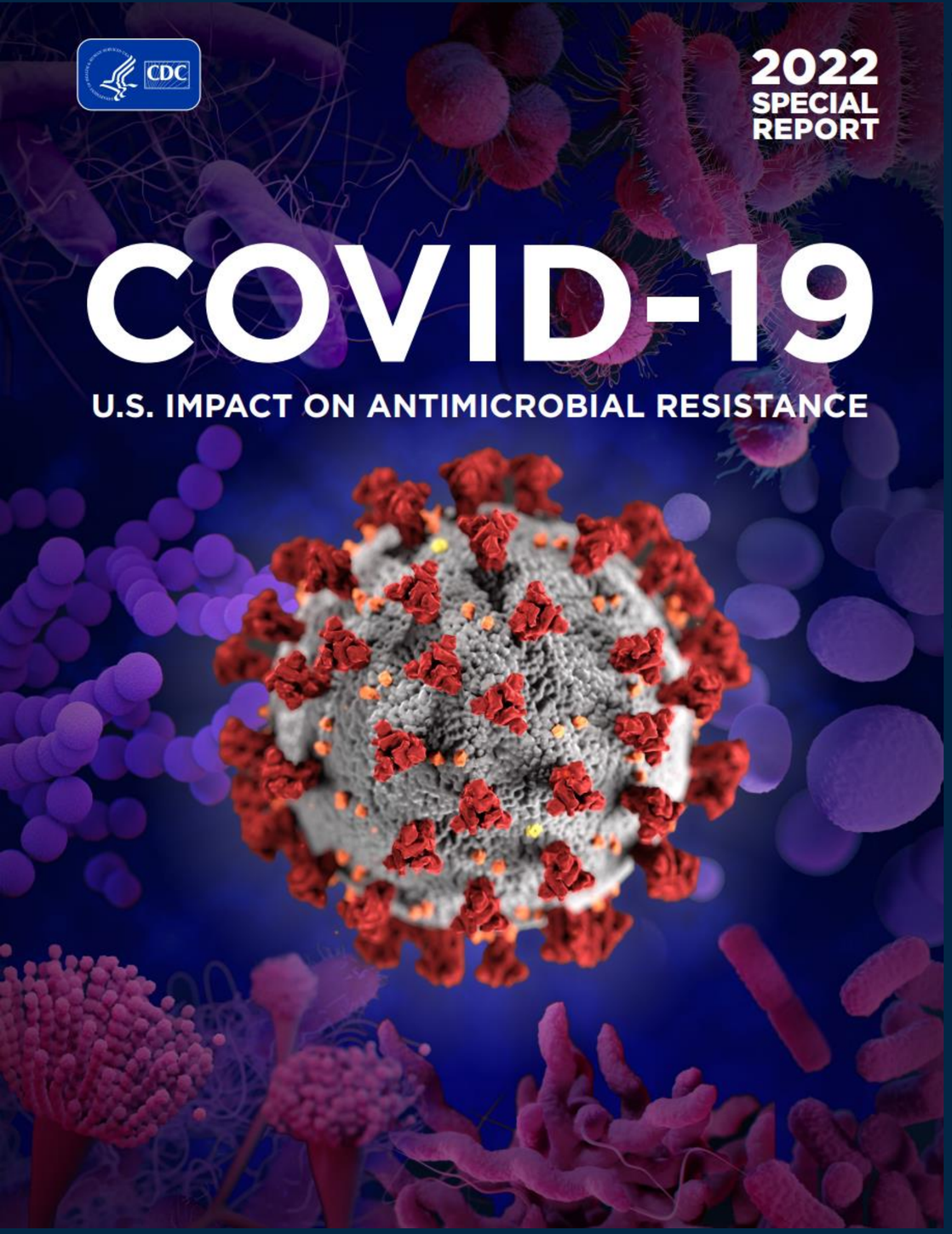
Figure 3. Cumulative distribution function of colonization or infection with a multidrug-resistant organism (MDRO), shown for 150 children receiving antibiotic therapy for ventilator-associated tracheitis (VAT). $P \leq .01$, by log-rank test.

Tamma 2011

2016 NEJM trail 5 days amoxicillin-clavulanate for otitis media in those 6-23 months of age associated with increased treatment failure (34% vs 16%). 10 days was not associated with nasopharyngeal colonization with penicillin resistant pathogens (Strep pneumo and H flu). N=520



Goossens 2005

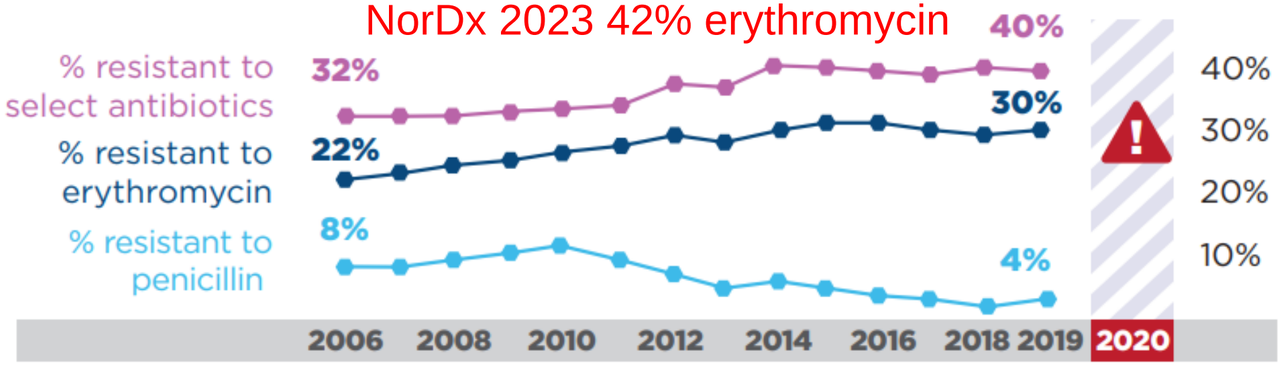


PEDIATRICS?

Streptococcus pneumoniae resistance data delay

New vaccines will be critical for *S. pneumoniae* as resistance to some important antibiotics continues to increase.*

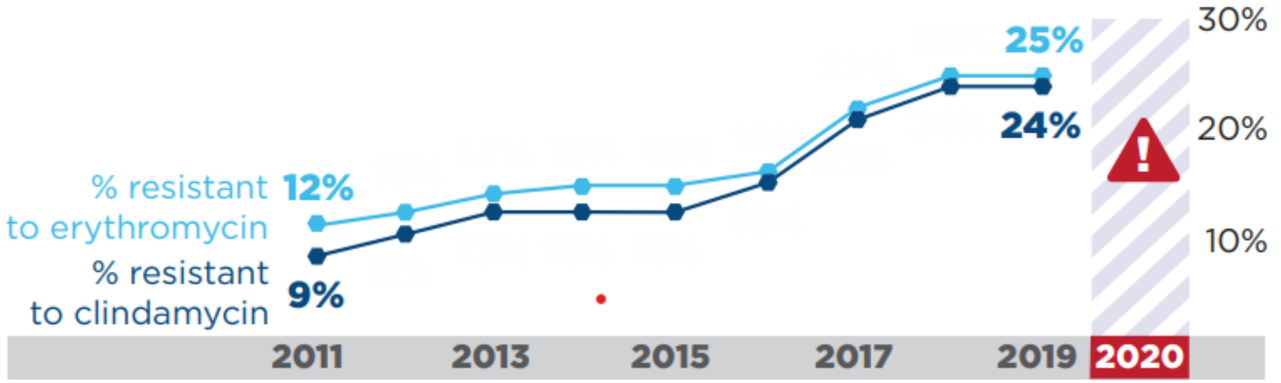
NorDx 2023 42% erythromycin



*Unable to compare data with 2019 report estimates, see Methods for details.

Streptococcus pyogenes

GAS resistance was already on the rise, emphasizing the need for antibiotic stewardship—especially for patients with viral infections like COVID-19 that are not treatable with antibiotics.



Primary Care, England

Patients were less satisfied in practices with frugal antibiotic prescribing

Patient surveys 2012

-2.7 million questionnaires, 982 999 responses; response rate 36%

-Practice antibiotic prescribing volumes

Primary Care, California

50% parents previsit expectation antibiotics for URI

Age 2-10 yo, 287 encounters, 10 physicians

Pre and post visit surveys, visit audiotaped (transcribed and coded)

Higher satisfaction if contingency plan given when no prescription

Viruses or Bacteria
What's got you sick?

BE ANTIBIOTICS AWARE

SMART USE, BEST CARE

Common Respiratory Infections	Common Cause			Are Antibiotics Needed?*
	Virus	Virus or Bacteria	Bacteria	
Common cold/runny nose	✓			No
Sore throat (except strep)	✓			No
COVID-19	✓			No
Flu	✓			No
Bronchitis/chest cold (in otherwise healthy children and adults)		✓		No**
Middle ear infection		✓		Maybe
Sinus infection		✓		Maybe
Strep throat			✓	Yes
Whooping cough			✓	Yes

*Antiviral drugs are available for some viral infections, such as COVID-19 or flu.
**Studies show that in otherwise healthy children and adults, antibiotics for bronchitis won't help patients feel better.

CS328461-A

To learn more about antibiotic prescribing and use, visit www.cdc.gov/antibiotic-use.

Report: Fragile supply chain causing antibiotic shortages, resistance threat

Chris Dall | News Reporter | CIDRAP News, May 31, 2018

Topics: Antimicrobial Stewardship

Antibiotic Shortages Are Fueling Antimicrobial Resistance

In countries worldwide, shortages of first-line antibiotics often lead to overuse of those that are specialized or kept in reserve for emergencies. Not only may these substitutes be less effective, but reliance on them increases the risk of drug resistance developing and infections becoming more difficult to treat in the long run.

24 November 2023 • 4 min read **by** Project Syndicate

https://www.cidrap.umn.edu/antimicrobial-stewardship/report-fragile-supply-chain-causing-antibiotic-shortages-resistance

https://www.gavi.org/vaccineswork/antibiotic-shortages-are-fueling-antimicrobial-resistance

ANTIBIOTIC RESEARCH AND DEVELOPMENT, HIGH COST AND LOW RETURNS FOR PHARMACEUTICAL INDUSTRY

GOV.UK

World-first scheme underway to tackle AMR and protect UK patients

A pioneering scheme to provide new antibiotics to NHS patients by offering to pay pharmaceutical companies upfront for their work will start...

Jun 17, 2020

NEWS RELEASE
June 5, 2019

DISARM Act Provides Framework Needed to Spur Antibiotic R&D, Protect Existing Drugs

PASTEUR (Pioneering Antimicrobial Subscriptions to End Upsurging Resistance) Act (introduced 4/2023)
-delink companies' profits from the volume of antibiotics sold

WE ARE CONNECTED

www.cdc.gov/DrugResistance

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

STOP ANTIBIOTIC RESISTANCE NOW

Antibiotic Resistance is driven by a wide variety of factors, ranging from contaminated bodies of water to misuse of antibiotics in food production and human medicine.

PROTECT YOUR COMMUNITY
KNOW THE FACTS

BECOME A STOP ANTIBIOTIC RESISTANCE NOW CAMPAIGN AMBASSADOR TODAY

CIDRAP
www.cidrap.umn.edu/asp

A Battle Over Antibiotics In Organic Apple And Pear Farming

APRIL 10, 2013 · 12:19 PM ET

Tyson chicken in 2017 “No antibiotics ever”, 2023 “No antibiotics important to human medicine”
-Restarting use ionophores for coccidia protozoal parasite but a study has shown presence of resistance genes for the ionophore salinomycin was correlated with the presence of resistance genes for erythromycin, tetracycline, and ampicillin, which are designated as medically important antibiotics

Herbicides promotes antibiotic resistance in soil microbiomes
Great Britian higher antibiotic resistant bacteria rural vs urban

WIRED

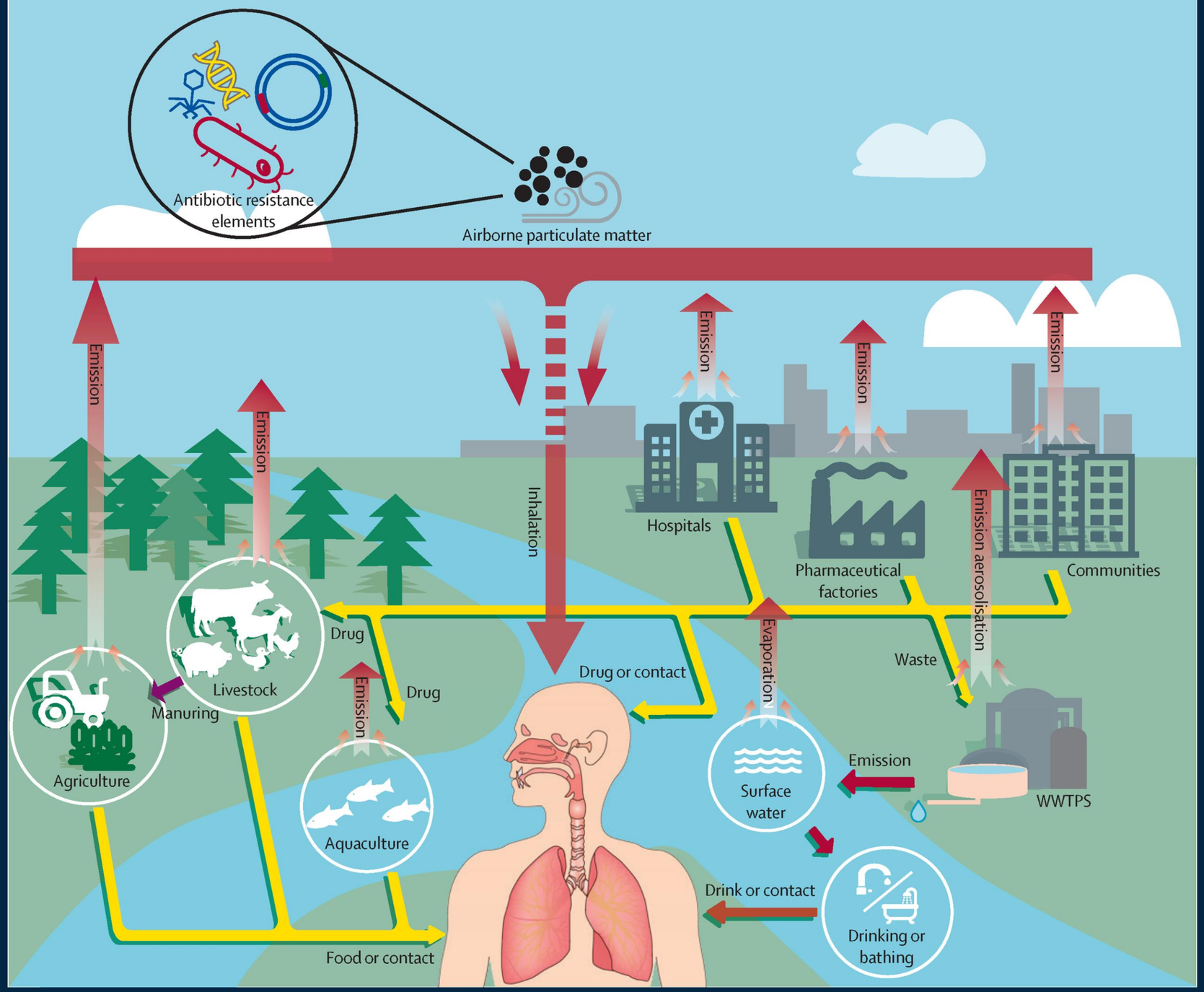
Seagulls: Pooping Resistant Bacteria on Your Beach

Resistance factors – the mutations that allow bacteria to defend themselves against the attack of antibiotics – spread around the world in...

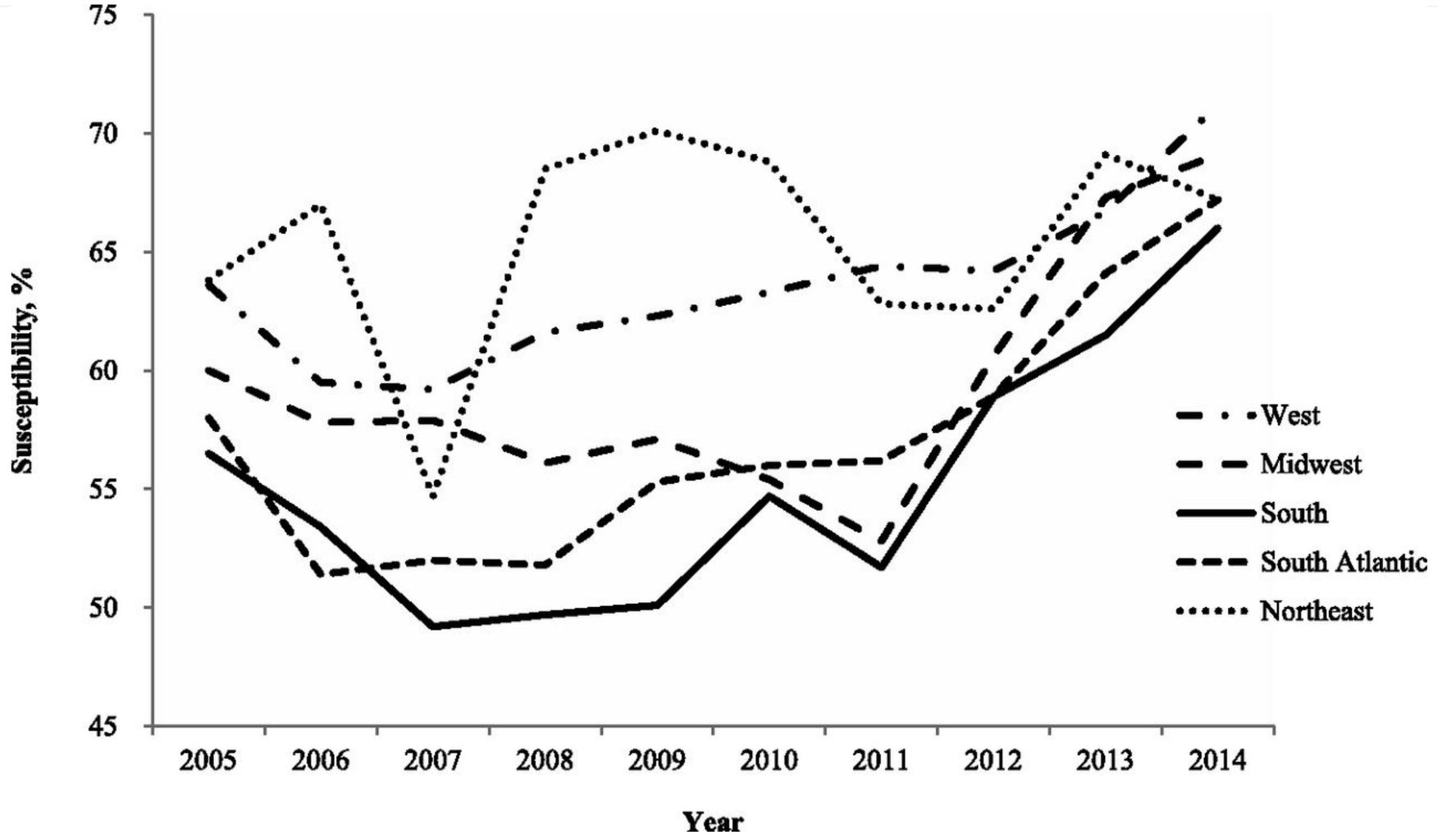
Air pollution may contribute to rising threat of antimicrobial resistance, study says

By Jen Christensen, CNN

5 minute read · Published 6:30 PM EDT, Mon August 7, 2023



Changing Susceptibility of Staphylococcus aureus in a US Pediatric Population



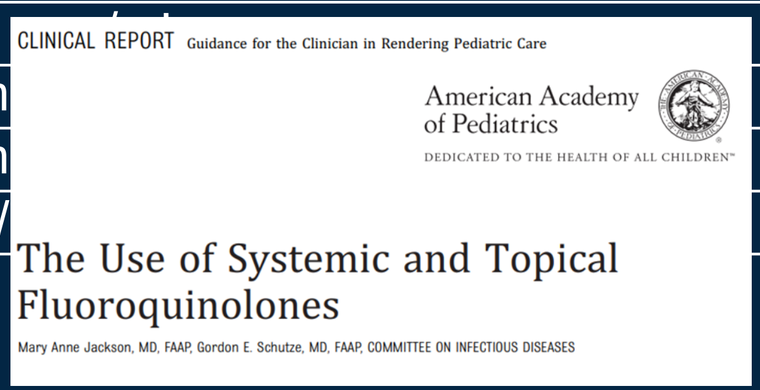
Percent of Staphylococcus aureus isolates susceptible to oxacillin by US region, 2005–2014

Pediatrics. 2016;137(4). doi:10.1542/peds.2015-3099

BACK TO CASE: 2 YO FEMALE WITH FEBRILE UTI ON CEPHALEXIN, LAB CALLED ESBL E COLI

>100,000 CFU/mL gram negative rod. Testing indicates that this isolate produces and extended spectrum beta lactamase. This organism is resistant to all penicillins, cephalosporins and aztreonam. Escherichia coli **ESBL Producer**		
Amikacin	Sensitive	<=8 mcg/mL
Ampicillin	Resistant	>16 mcg/mL
Ampicillin/sulbactam	Sensitive	8/4 mcg/mL
Aztreonam	Resistant	
Cefazolin	Resistant	>16 mcg/mL
Cefepime	Resistant	
Ceftazidime	Resistant	
Ceftriaxone	Resistant	>32 mcg/mL
Ertapenem	Sensitive	<=0.25 mcg/mL
Gentamicin	Sensitive	<=2 mcg/mL
Meropenem	Sensitive	<=0.5 mcg/mL
Nitrofurantoin	Sensitive	<=16 mcg/mL
Piperacill+Tazobactam	Sensitive	<=2/4
Tetracycline	Sensitive	<=2 m
Tobramycin	Sensitive	<=2 m
Trimethoprim + Sulfamethoxazole	Sensitive	<=0.5/

Change cephalexin to ……..?


CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

The Use of Systemic and Topical Fluoroquinolones

Mary Anne Jackson, MD, FAAP, Gordon E. Schutze, MD, FAAP, COMMITTEE ON INFECTIOUS DISEASES

WHAT ABOUT A 19 YO FEMALE WITH RELAPSED DYSURIA 5 DAYS AFTER COMPLETING NITROFURANTOIN?

>100,000 CFU/mL gram negative rod. Testing indicates that this isolate produces and extended spectrum beta lactamase. This organism is resistant to all penicillins, cephalosporins and aztreonam. Escherichia coli **ESBL Producer**		
Amikacin	Sensitive	<=8 mcg/mL
Ampicillin	Resistant	>16 mcg/mL
Ampicillin/sulbactam	Resistant	>16/8 mcg/mL
Aztreonam	Resistant	
Cefazolin	Resistant	>16 mcg/mL
Cefepime	Resistant	
Ceftazidime	Resistant	
Ceftriaxone	Resistant	32 mcg/mL
Ciprofloxacin	Resistant	>2 mcg/mL
Ertapenem	Sensitive	<=0.25 mcg/mL
Gentamicin	Sensitive	<=2 mcg/mL
Meropenem	Sensitive	<=0.5 mcg/mL
Nitrofurantoin	Sensitive	<=16 mcg/mL
Piperacill+Tazobactam	Sensitive	16/4 mcg/mL
Tetracycline	Resistant	>8 mcg/mL
Tobramycin	Resistant	>8 mcg/mL
Trimethoprim + Sulfamethoxazole	Resistant	>2/38 mcg/mL

What to start as does not want longer course nitrofurantoin?

WHAT ABOUT A 5 YO MALE WITH FEVER, VOMITING, DIARRHEA?

Urine culture outside hospital >100,000 CFU/mL ESBL E coli
Susceptible: ciprofloxacin, nitrofurantoin, amikacin, zosyn, ertapenem, levofloxacin, meropenem, tetracycline, cefoxitin, tobramycin

Prescribed nitrofurantoin but could not get liquid for 3 days so sent to outside ED. UA and urine culture requested but was after 2 doses meropenem (initial urine culture into hat, no UA)

Admission UA (3 days post initial presentation) negative nitrite/leuks +ketones. Fever, diarrhea improved, vomiting resolved prior to antibiotic. Entire household had less than 24 hours vomiting +/- diarrhea.

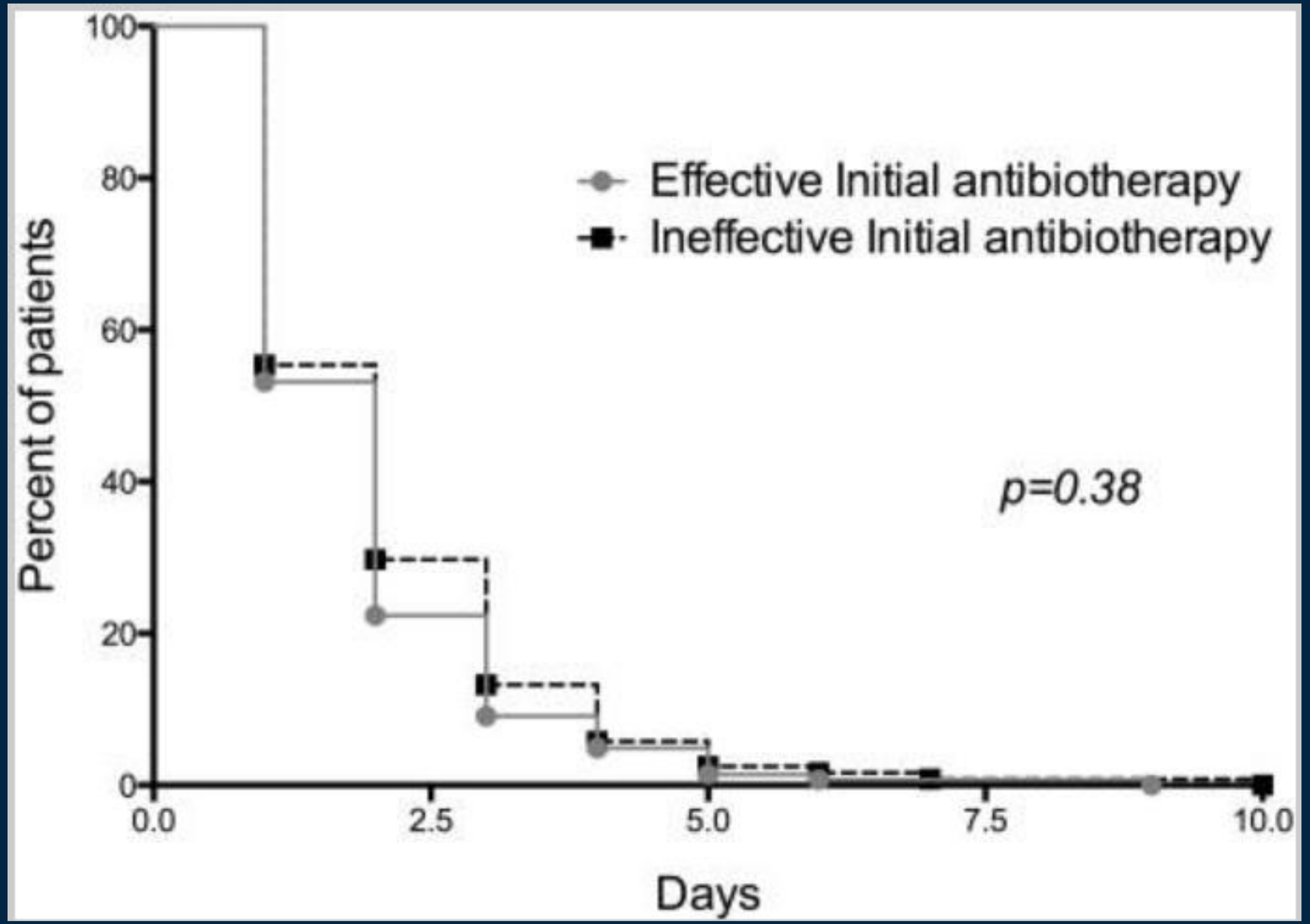
Treatment?

WHAT ABOUT A 17 YO FEMALE WITH HEADACHE, LOW BACK PAIN, ABDOMINAL PAIN, FEVER?

UA positive leuk, negative nitrite
Started Bactrim
UCX ESBL E coli resistant to Bactrim, levofloxacin (still symptomatic)
Started meropenem, discharged with ertapenem via midline to complete 10 days
CVA tenderness improving time of discharge (CRP 137.5 mg/L to 59.2)

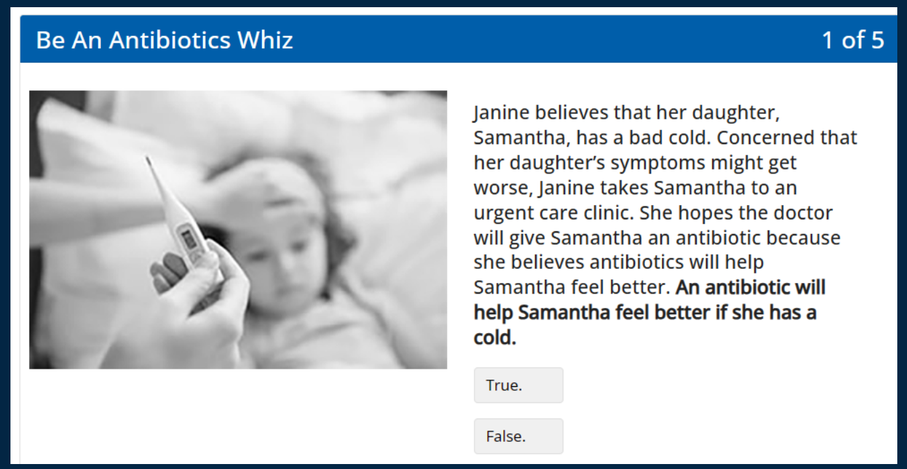
Seeing increased community acquired ESBL UTIs, do we need to alter empiric therapy?

NO: TIME TO APYREXIA WITH EXTENDED-SPECTRUM β-LACTAMASES (ESBLS) FEBRILE UTI

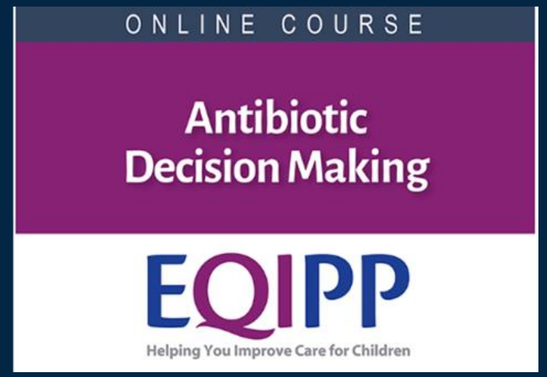


ONE HEALTH

Questions?



Be An Antibiotics Whiz | Antibiotic Use | CDC
https://www.cdc.gov/antibiotic-use/quiz.html



EQIPP: Antibiotic Decision Making | shopAAP
https://www.aap.org/EQIPP-Antibiotic-Decision-Making

Antibiotic Use | CDC
https://www.cdc.gov/antibiotic-use/index.html

Pediatric ASP Toolkit – Pediatric Infectious Diseases Society (pids.org)
https://pids.org/pediatric-asp-toolkit/

IDSA 2023 Guidance on the Treatment of Antimicrobial Resistant Gram-Negative Infections (idsociety.org)
https://www.idsociety.org/practice-guideline/amr-guidance/

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