

Antimicrobial Case Studies: No One Can Resist!

Don't Be Negative! Case Studies of Gram-Negative Bacterial Antimicrobial Resistance

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Case 1

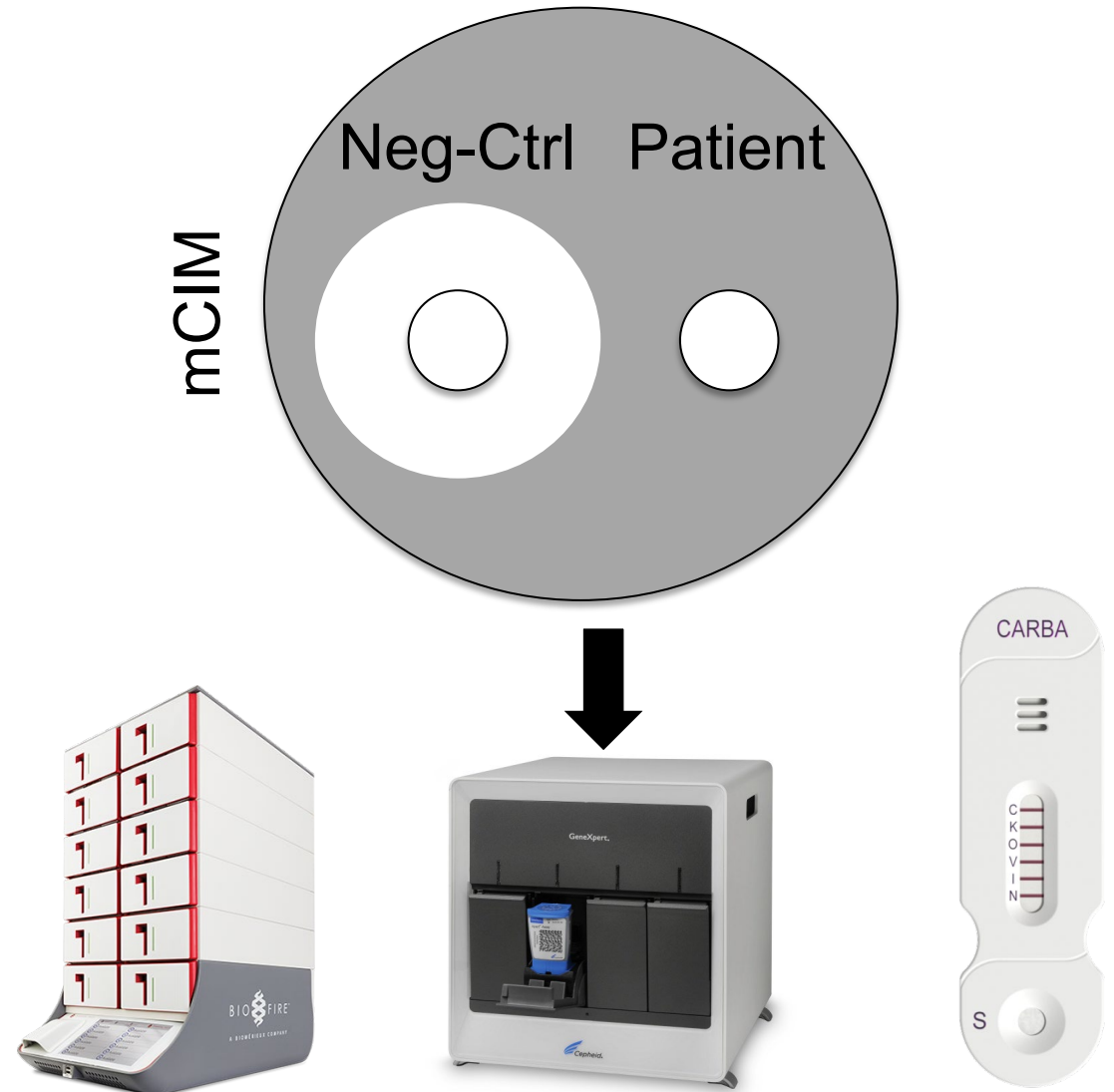
- 37 year old male with T-cell lymphoma
 - Presents 56 days post transplant with pneumonia.
- Respiratory culture grew...



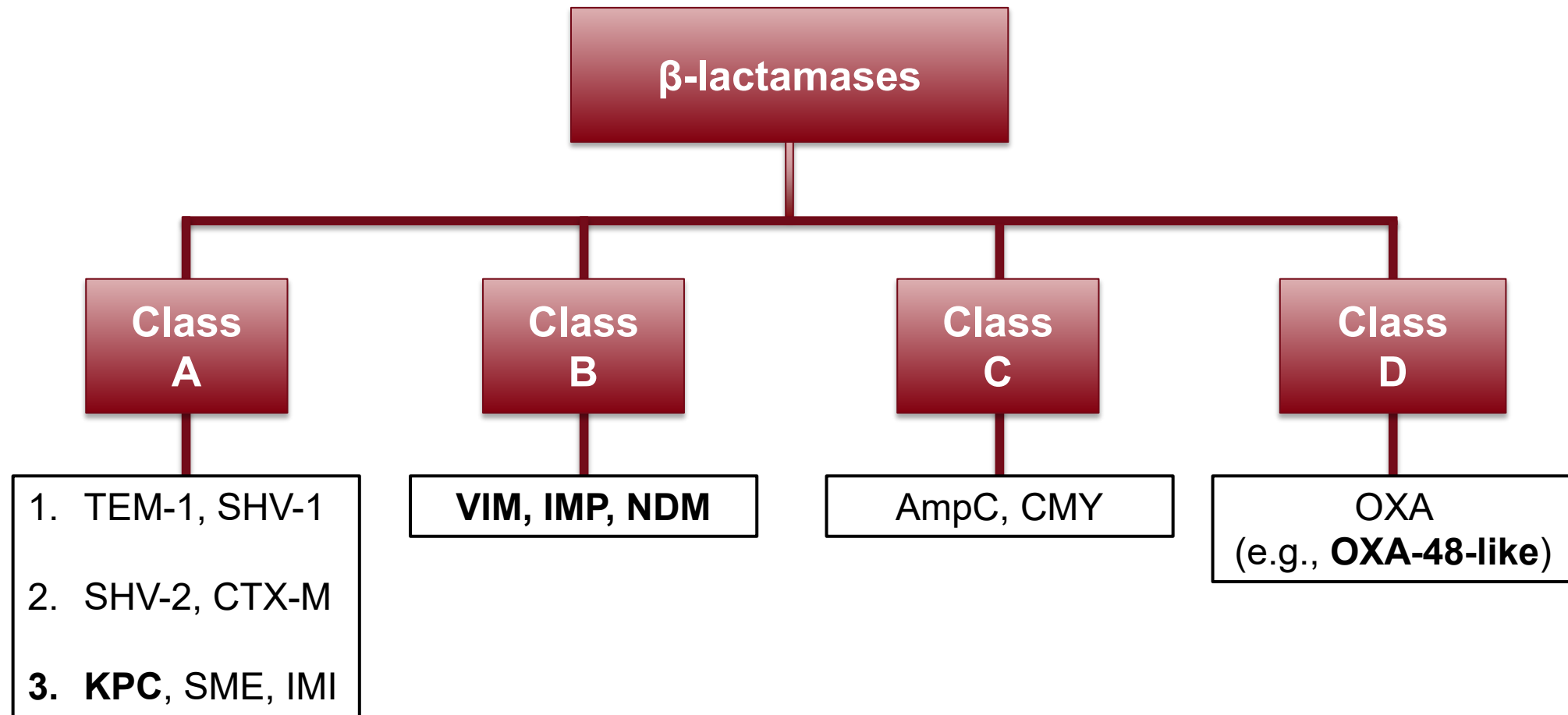
Klebsiella pneumoniae

Susceptibility Testing & Workflow

Drug	Interpretation (MIC)
Ampicillin	R
Amoxicillin-Clavulanate	R
Cefazolin	R
Ceftriaxone	R (8)
Ceftazidime	S (2)
Cefepime	R
Meropenem	R
Imipenem	R
Amikacin	R
Levofloxacin	R
Trimethoprim-Sulfamethoxazole	R
Tigecycline	I



Ambler Classification of β -lactamases



β-lactamase Mechanism Predicts Drug Activity

- Piperacillin-Tazobactam
- Ceftolozane-Tazobactam
- Ceftazidime-Avibactam
- Meropenem-Vaborbactam
- Imipenem-Relebactam



Enzyme	Inhibited by:			
	Avibactam	Tazobactam	Vaborbactam	Relebactam
Class A				
KPC	Yes	No	Yes	Yes
SHV	Yes	Yes	Yes	Yes
TEM	Yes	Yes	Yes	Yes
CTX-M	Yes	Yes	Yes	Yes
Class B				
MBL	No	No	No	No
Class C				
AmpC	Yes	No	Yes	Yes
Class D				
OXA	VD ^a	No	No	VD

^a | VD, variable data.

Yahav D et al. New β-Lactam-β-Lactamase Inhibitor Combinations. *Clin Microbiol Rev.* 2020 PMID: 33177185.

OXA β -lactamases

- Class D beta-lactamases
- Activity varies by enzyme (>100 enzymes)
 - Named after preferred OXAicillin vs penicillin hydrolysis
 - Some ES β L (OXA-10, OXA-15)
 - Some carbapenemases (OXA-48, OXA-23)
- Found in *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Burkholderia*, and *Enterobacterales*, especially *Klebsiella pneumoniae*, *Escherichia coli*, and *Enterobacter cloacae*
- In 2017, 1.6 percent of carbapenem-resistant *Enterobacterales* in the United States were found to possess OXA-48.
 - Woodworth KR et al. Vital Signs: Containment of Novel Multidrug-Resistant Organisms and Resistance Mechanisms - United States, 2006-2017. *MMWR Morb Mortal Wkly Rep*. 2018. PMID: 29621209.

Drug	Interpretation
Ampicillin	R
Amoxicillin-Clavulanate	R
Cefazolin	R
Ceftriaxone	S
Ceftazidime	S
Cefepime	S
Meropenem	I
Imipenem	R

OXA Subgroups

Cluster	Enzyme subfamily	Additional OXA member(s)
1	OXA-23 (ARI-1)	OXA-27 OXA-49
2	OXA-24/OXA-40	OXA-25 OXA-26 OXA-72
3	OXA-51	OXA-64 through OXA-71 OXA-75 through OXA-78

Cluster	Enzyme subfamily	Additional OXA member(s)
4	OXA-58	OXA-96 OXA-97
5	OXA-48	OXA-162 OXA-163 OXA-181 OXA-204 OXA-232

Table 9. Summary of Variants Detected by NG-Test CARBA 5

		Variants Detected Analytically	Variants Detected in US clinical trial (Table 1)	Variants Detected in publications ^{8,9,11}	Variants Not Detected ¹
<i>Enterobacteriaceae</i>	KPC	2, 3, 4, 6, 12	2, 3, 4, 12	2, 3, 4, 9, 23	
	OXA-48-like	48, 181, 163, 232	48, 181, 232	48, 162, 163, 181, 204, 232, 244, 245, 370, 405, 436, 484, 517, 519, 535	
	VIM	1, 4, 5, 6, 23, 27, 31	1, 4, 5, 6, 23, 27, 31	1, 2, 4, 5, 19, 26, 27, 31, 39, 46, 51, 52, 54, 56, 58, 59	
	IMP	4, 8, 26	1, 4, 8	1, 4, 6, 7, 8, 10, 11, 22, 29	14
	NDM	1, 5, 6, 7	1, 5, 6, 7	1, 2, 3, 4, 5, 6, 7, 8, 9	

Modified from Queenan AM, Bush K. Carbapenemases: the versatile beta-lactamases. *Clin Microbiol Rev.* 2007.
NG-Test CARBA 5 Package Insert.

Case 1: Take-home Points

- Carbapenemase testing is useful for clinical laboratories.
 - Guide treatment decision-making
 - Infection Prevention and Control
- OXA enzymes are diverse and most commonly found in *Acinetobacter* species.
- Alternative clinical workflow for *Enterobacterales*

1. Ertapenem I/R
2. Meropenem I/R
3. Imipenem I/R
4. Doripenem I/R

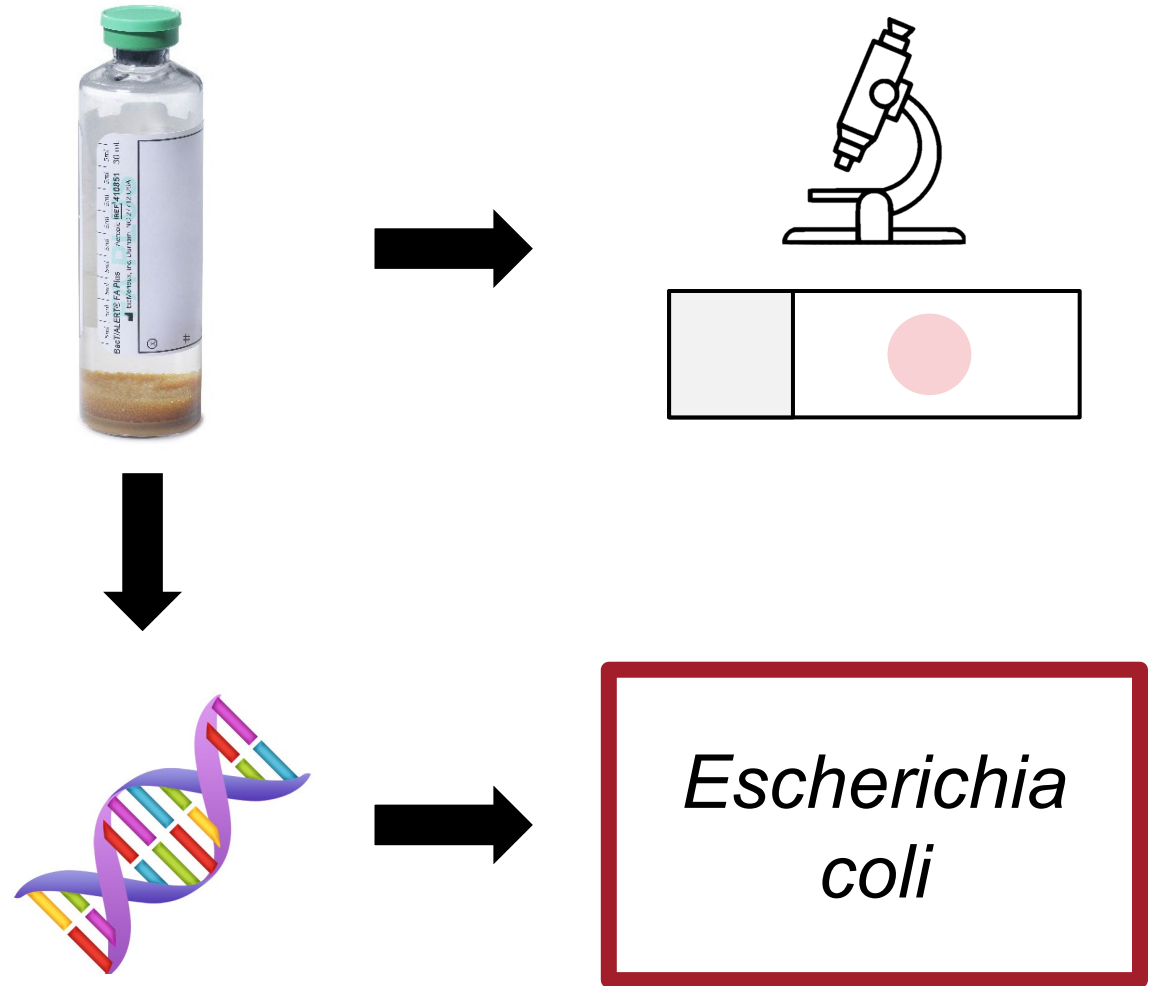


Case 1: Additional Resources

- Quale J et al. Overview of carbapenemase-producing gram-negative bacilli. *UpToDate*. 2022. <https://www.uptodate.com/contents/overview-of-carbapenemase-producing-gram-negative-bacilli>
- Walther-Rasmussen J, Høiby N. OXA-type carbapenemases. *J Antimicrob Chemother*. 2006. PMID: 16446375.
- Sawa, T. et al. Molecular diversity of extended-spectrum β -lactamases and carbapenemases, and antimicrobial resistance. *J Intensive Care*. 2020. <https://doi.org/10.1186/s40560-020-0429-6>

Case 2

- 21 day old female presents to PCP with 2 days of fever and increasing spit ups.
- Transferred to ED
 - Later admitted
- Concern for sepsis and meningitis/encephalitis
- Cefepime + Vancomycin



Disk Diffusion Direct from Positive Blood Culture

Drug	Zone Size	Interpretation
Ampicillin	≤ 6	R
Ceftriaxone	≤ 6	R
Ceftazidime	21	S
Aztreonam	10	R
Tobramycin	14	I
Trimethoprim-sulfamethoxazole	≤ 6	R

What resistance mechanism is likely responsible for this resistance pattern?

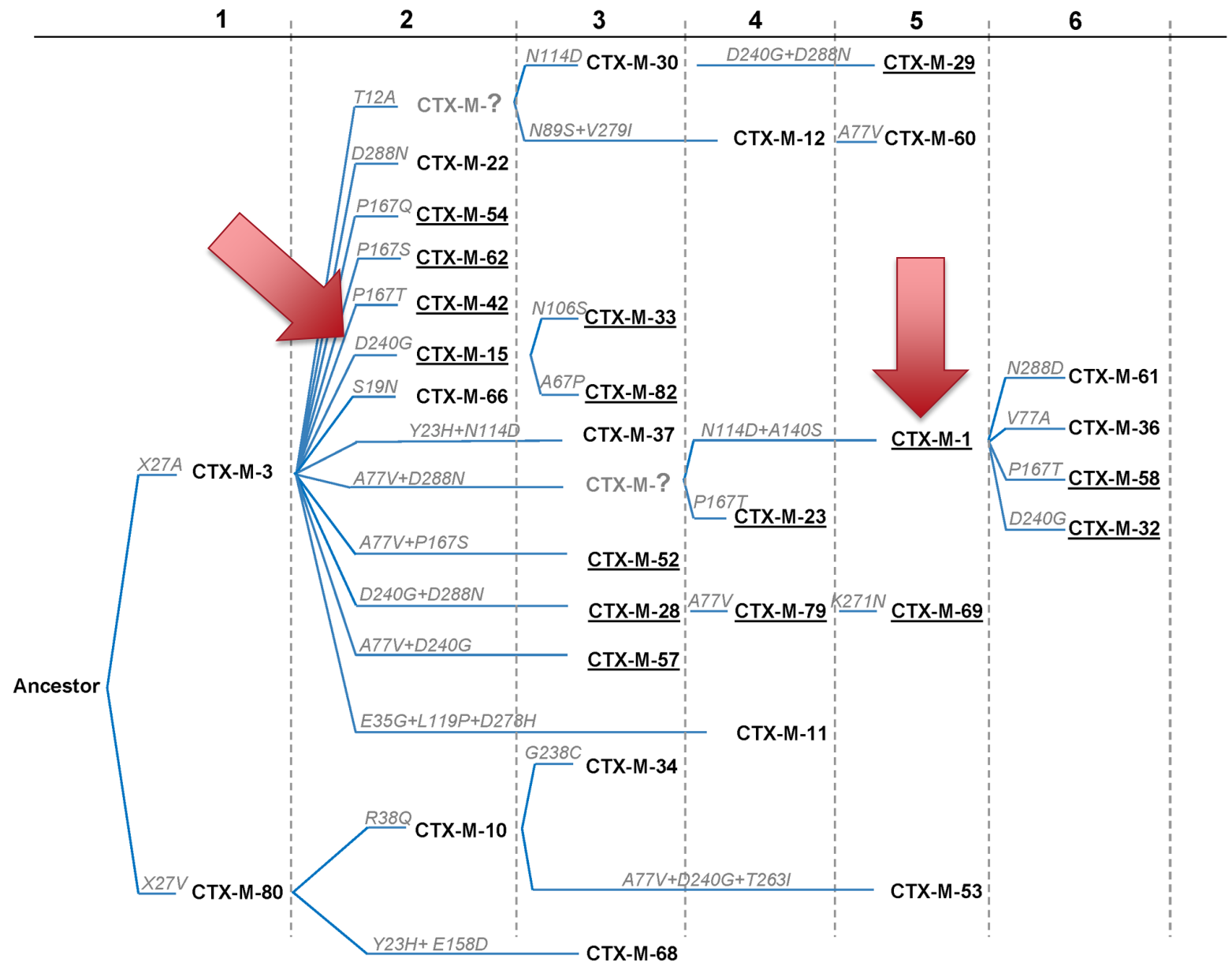
- A. Carbapenemase
- B. AmpC
- C. ES β L
- D. Need more information



CTX-M

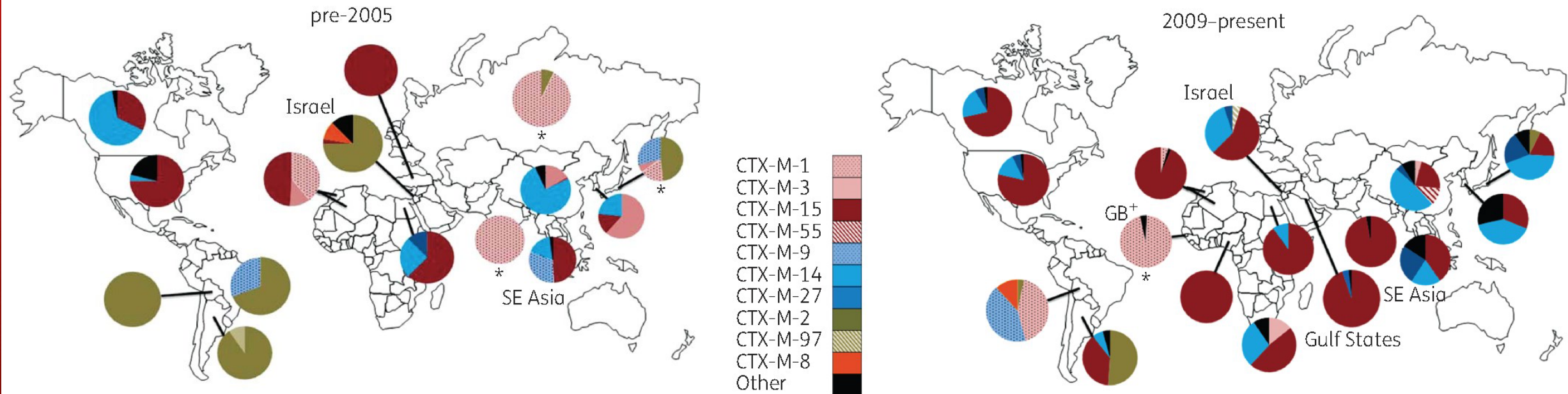
- Molecular class A β -lactamases
 - Extended Spectrum Beta-Lactamase (ES β L)
- Normally resistant to Cefotaxime, ceftriaxone, and cefpodoxime but susceptible to ceftazidime.
 - CTX-M mutants with increased ceftazidimase activity have been described.

CTX-M-Type



Novais Â et al. Evolutionary Trajectories of Beta-Lactamase CTX-M-1 Cluster Enzymes: Predicting Antibiotic Resistance. PLoS Pathog. 2010. <https://doi.org/10.1371/journal.ppat.1000735>

CTX-M “Epidemic”



J Antimicrob Chemother, Volume 72, Issue 8, August 2017, Pages 2145–2155, <https://doi.org/10.1093/jac/dkx146>

CTX-M Testing in Clinical Laboratories

- CLSI
 - “When using the current breakpoints, routine ES β L testing is no longer necessary before reporting results. However, ES β L testing may still be useful for epidemiological or infection prevention purposes.”
- ES β L testing options
 - Automated testing (VITEK, MicroScan, Phoenix)
 - Disk diffusion
 - Gradient diffusion
 - Molecular from positive blood cultures
 - Sequencing

CTX-M Treatment Options

- Some CTX-M-types (and OXA-types) test resistant to cefepime.
- Carbapenems are stable to CTX-M-type enzymes.
 - Carbapenem resistant *K. pneumoniae* strain with CTX-M-15, following the loss of an outer-membrane porin.
- High-rates of co-resistance to fluoroquinolones and aminoglycosides.

Case 2: Take-home Points

- CTX-M is a common ES β L and often escalates antimicrobial coverage to a carbapenem.
- While routine ES β L testing is no longer necessary before reporting AST results, ES β L testing may still be useful for epidemiological or infection prevention purposes.

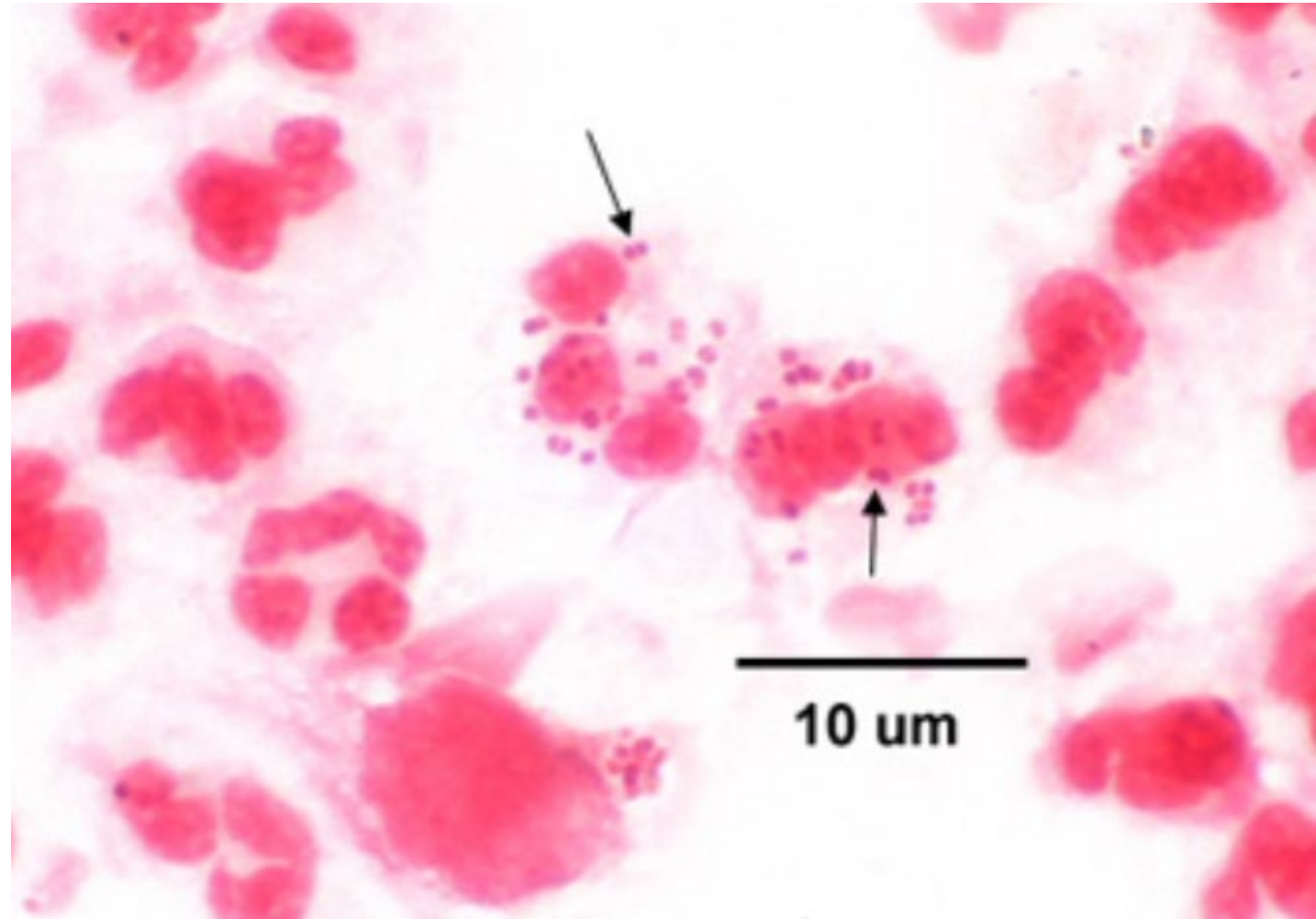
Case 2: Additional Resources

- Rossolini GM et al. The spread of CTX-M-type extended-spectrum beta-lactamases. *Clin Microbiol Infect.* 2008. PMID: 18154526.
- Edward R. Bevan et al. Global epidemiology of CTX-M β -lactamases: temporal and geographical shifts in genotype, *Journal of Antimicrobial Chemotherap.* 2017.
<https://doi.org/10.1093/jac/dkx146>
- <https://www.uptodate.com/contents/extended-spectrum-beta-lactamases>
- Cantón R et al. CTX-M Enzymes: Origin and Diffusion. *Front Microbiol.* 2012. PMID: 22485109.

Case 3

- 26 year old male presents to STI clinic for painful urination and purulent discharge.
- Direct Gram stain
 - Not routinely performed

Intracellular Gram-negative diplococci with slightly flattened adjacent edges

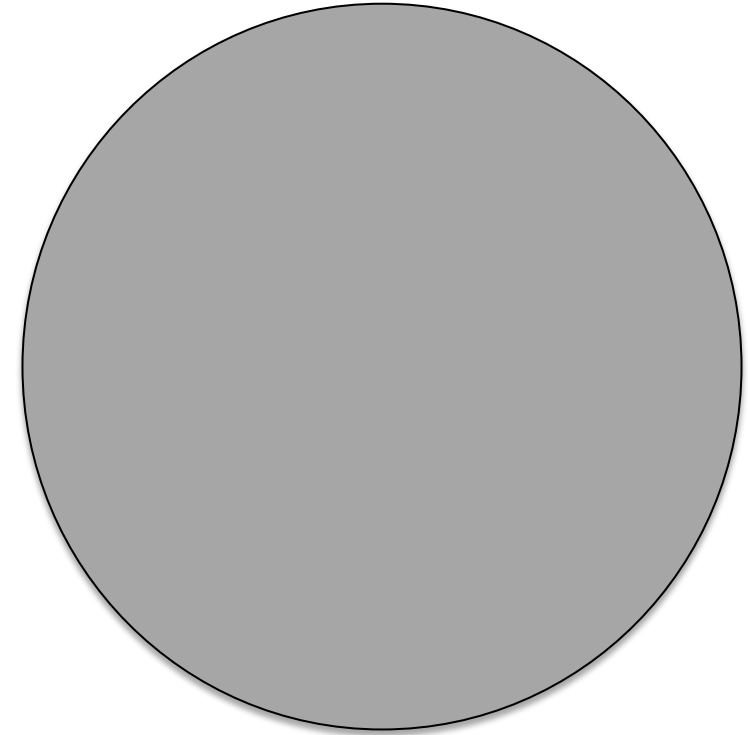


Photomicrograph of a Gram Stain of Urethral Discharge from a Male by Gary E. Kaiser, Ph.D. The Community College of Baltimore County.

Neisseria gonorrhoeae Detection

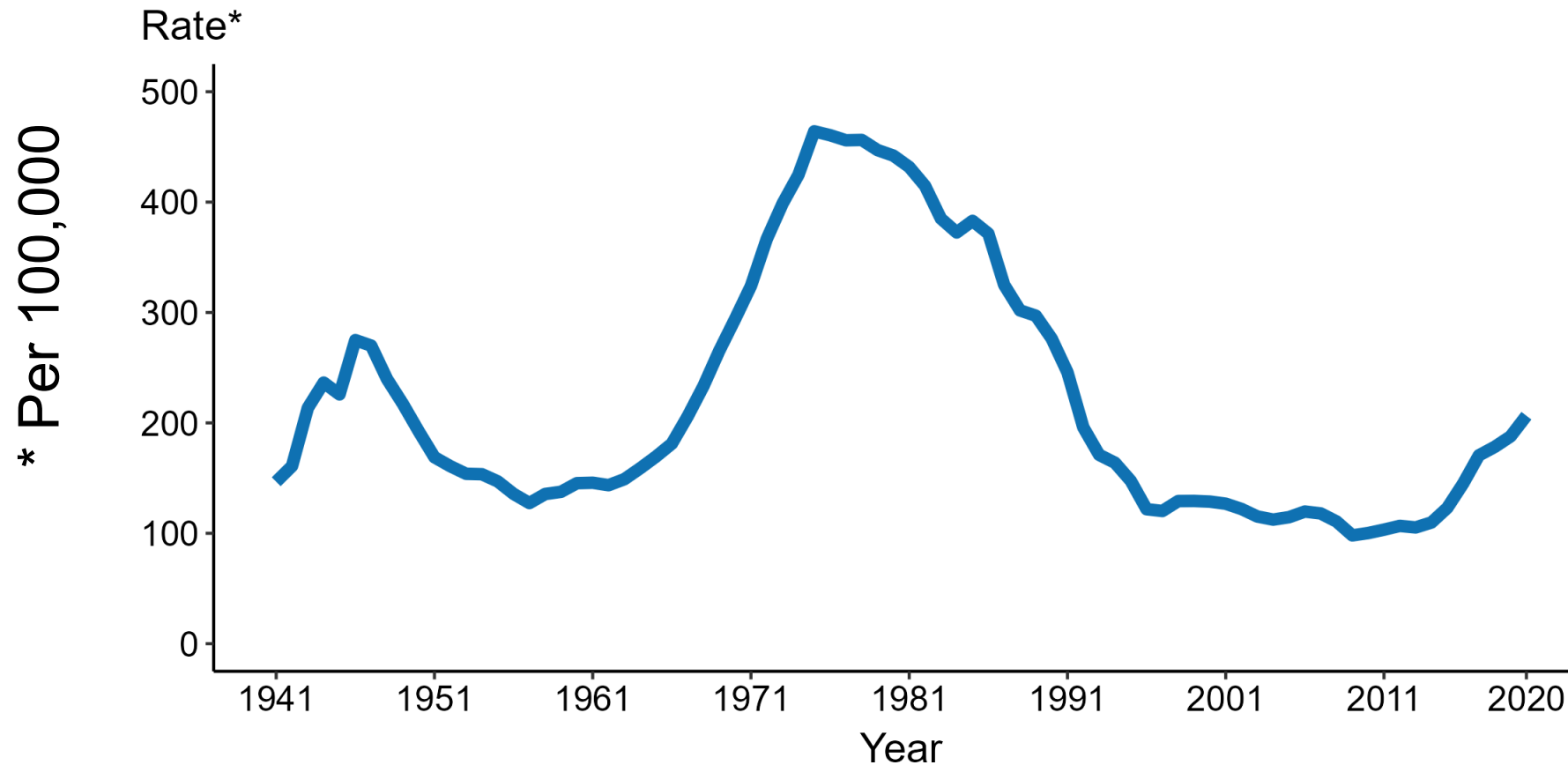


VS



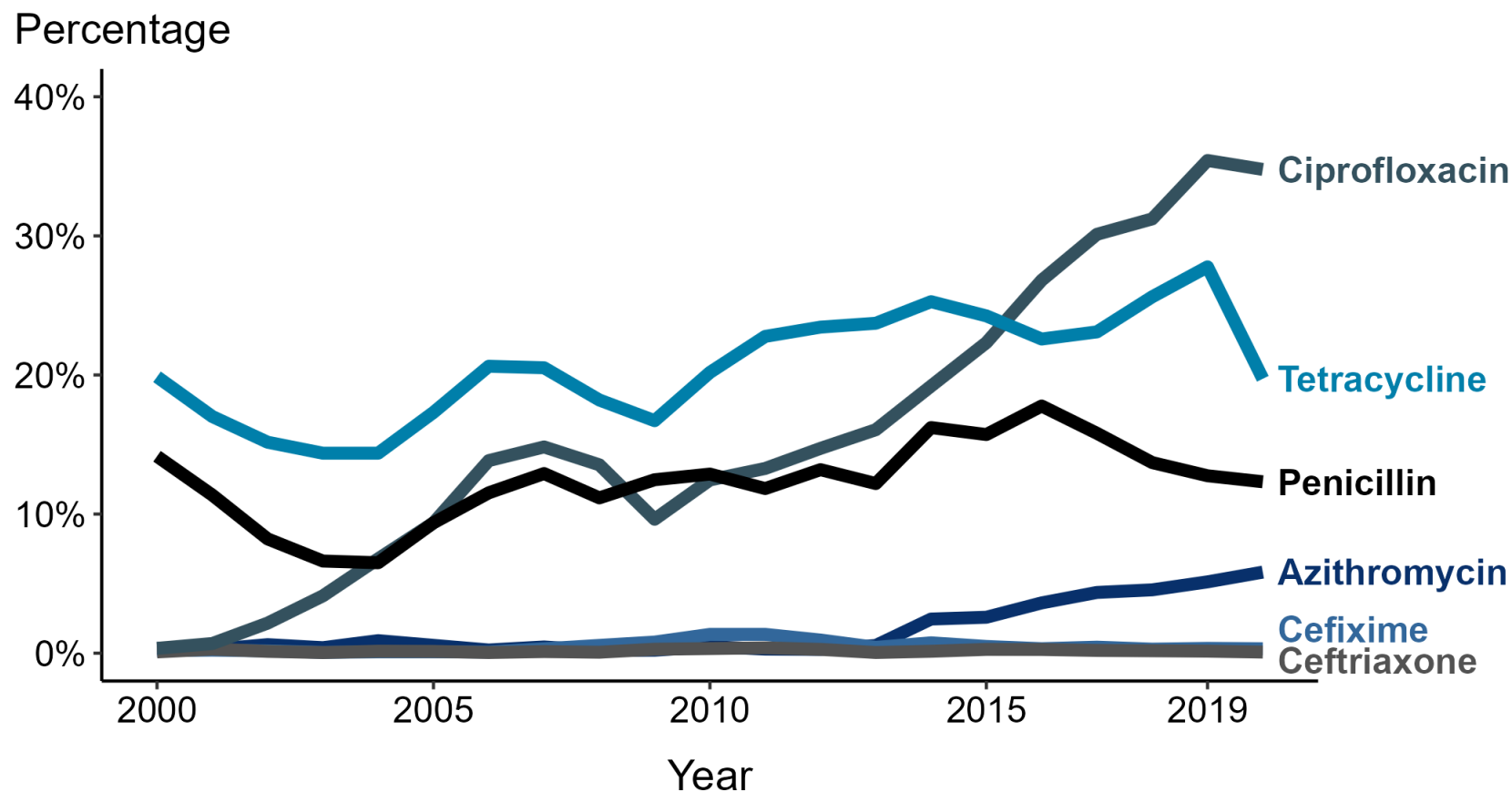
US Gonorrhea Rates on the Rise

Data from Gonococcal Isolate Surveillance Project (GISP)



Increasing Rates of Resistance or Elevated MICs

Data from Gonococcal Isolate Surveillance Project (GISP)





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CLINICAL ALERT

January 19, 2023

MULTI-DRUG NON-SUSCEPTIBLE GONORRHEA IN MASSACHUSETTS

- A novel strain of multidrug-non-susceptible *Neisseria gonorrhoeae* with reduced susceptibility to ceftriaxone, cefixime, and azithromycin, and resistance to ciprofloxacin, penicillin, and tetracycline, has been identified in a Massachusetts resident. Although ceftriaxone 500 mg IM was effective at clearing infection for this case, this is the first isolate identified in the United States to demonstrate resistance or reduced susceptibility to all drugs that are recommended for treatment.
- Enhanced surveillance has identified a second isolate that, based on its genome, likely has similarly reduced susceptibility to ceftriaxone and cefixime.
- Identification of this strain, the same as what was recently reported in the United Kingdom¹ and previously reported as circulating in Asia-Pacific countries, is a warning that *N. gonorrhoeae* is becoming less responsive to a limited arsenal of antibiotics.



Centers for Disease
Control and Prevention

AAA



Suspected Gonorrhea Treatment Failure Consultation Form

Suspected gonorrhea cephalosporin treatment failure or any *N. gonorrhoeae* specimen with decreased cephalosporin susceptibility should be reported directly to CDC by either clinicians or health departments by completing the Suspected Gonorrhea Treatment Failure Consultation Form. **Clinicians should contact their state or local health department to coordinate completion of the report form prior to submitting it to CDC.**

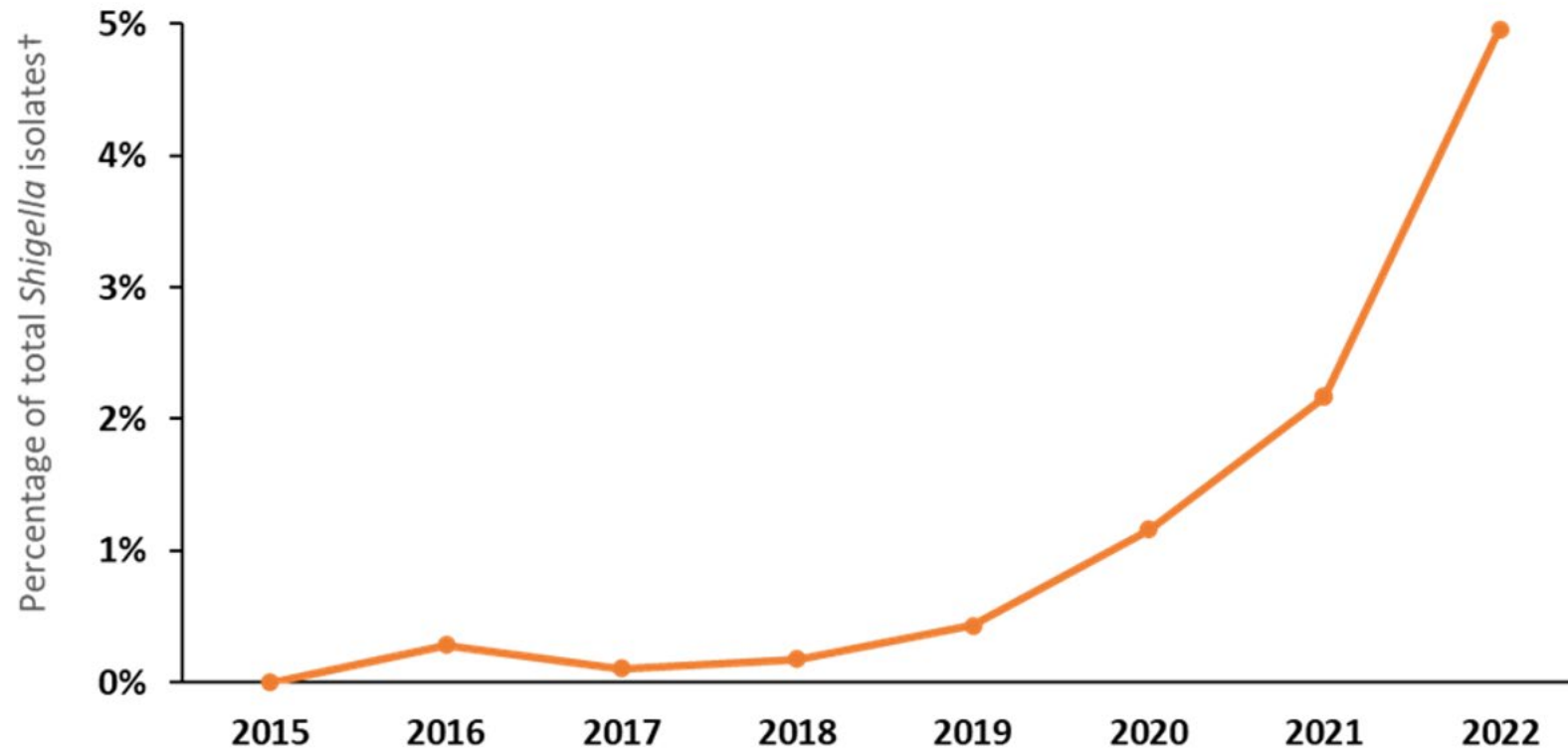
To report a suspected gonorrhea treatment failure to CDC, please complete and submit this REDCap Survey form. It may be necessary to perform a **medical record review** or to **ask the patient** additional questions to complete some parts of the form. Specific sections of the form **require** completion to submit the form. However, if you do not have all information, please complete the form with as much information as you can. Please do not include any Identifying patient information (e.g., patient name, date of birth, medical record number, social security number).

Clinicians in CDC's Division of STD Prevention will review the form and follow up with submitting providers. **If you need immediate clinical assistance, please contact your local or state public health department.**

If you have **questions about reporting a case to CDC or need assistance with treatment, please contact the Gonorrhea Treatment Failure team** (gcfailure@cdc.gov; 404-718-5447; Centers for Disease Control and Prevention, Division of STD Prevention).

Extensively Drug-Resistant Shigellosis in US

Distributed via the CDC Health Alert Network



XDR *Shigella* (n=239)

- Defined as resistant to azithromycin, ciprofloxacin, ceftriaxone, trimethoprim-sulfamethoxazole, and ampicillin.

Case 3: Take-home Points

- *N. gonorrhoeae* prevalence and resistance rates are increasing.
- NAATs are more common than cultures for gonorrhoeae detection in most clinical microbiology laboratories. Discuss culture ordering and collection processes with key stakeholders.

Case 3: Additional Resources

- <https://www.cdc.gov/std/statistics/2020/default.htm>
- <https://www.cdc.gov/std/labguidelines/rr5115.pdf>
- <https://www.mass.gov/news/departments-of-public-health-announces-first-cases-of-concerning-gonorrhea-strain>

Thank you!