Antimicrobial Resistance: Not a “New York State of Mind“

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Antimicrobial Resistance Issues Among

- *Klebsiella pneumoniae*
- *Pseudomonas aeruginosa*
- *Shigella* spp. (XDR)
- *Staphylococcus aureus* (vancomycin)
- *Trichophyton indotineae*

March 2005 Case Study

- A 48-year-old obese female was admitted for elective knee replacement surgery following an automobile accident
- Post-surgery she idiopathic heparin-induced thrombocytopenia
- Loss of perfusion to her intestines resulted in small bowel transplant
- Post-surgery # 2 she developed ARDS and was placed on a ventilator
- The patient's condition continued to deteriorate, and she developed a nosocomial pneumonia

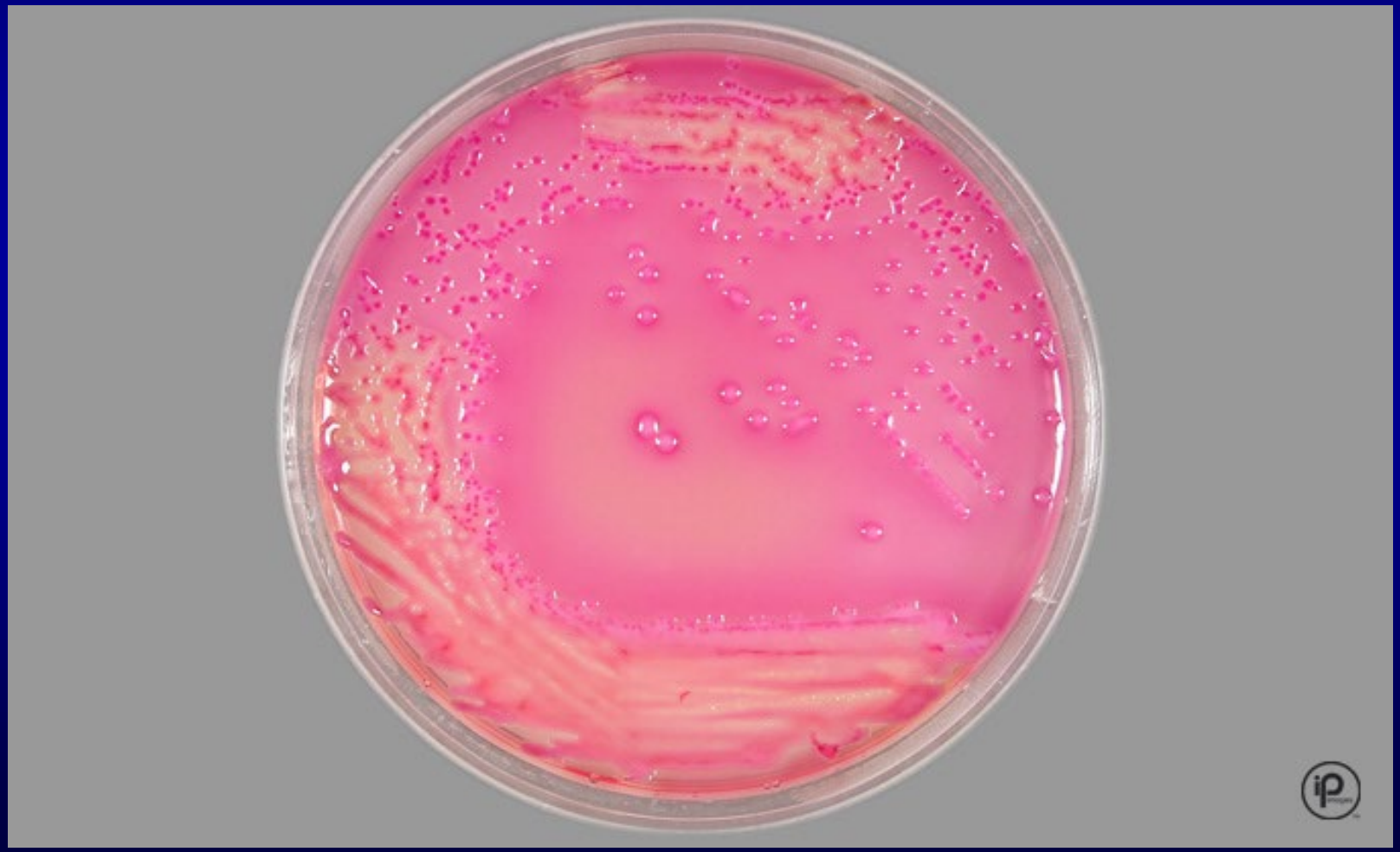
Case Study

- **The antimicrobial susceptibility pattern of the isolate was as follows:**
- **Resistant to ampicillin, piperacillin, amoxicillin-clavulanate, ampicillin-sulbactam, ticarcillin-clavulanate piperacillin-tazobactam, aztreonam, cefazolin, cefuroxime, cefotetan, ceftriaxone, cefotaxime, ceftazidime, cefepime, imipenem, meropenem, ertapenem, gentamicin, tobramycin, levofloxacin, ciprofloxacin, chloramphenicol, and trimethoprim-sulfamethoxazole**
- **Intermediate susceptibility to amikacin and tetracycline**
- **Susceptible to: tigecycline and polymyxin B**

Case Study

What gram-negative was recovered from BAL, an empyema collection, urine, and blood?

Klebsiella pneumoniae



Case Study

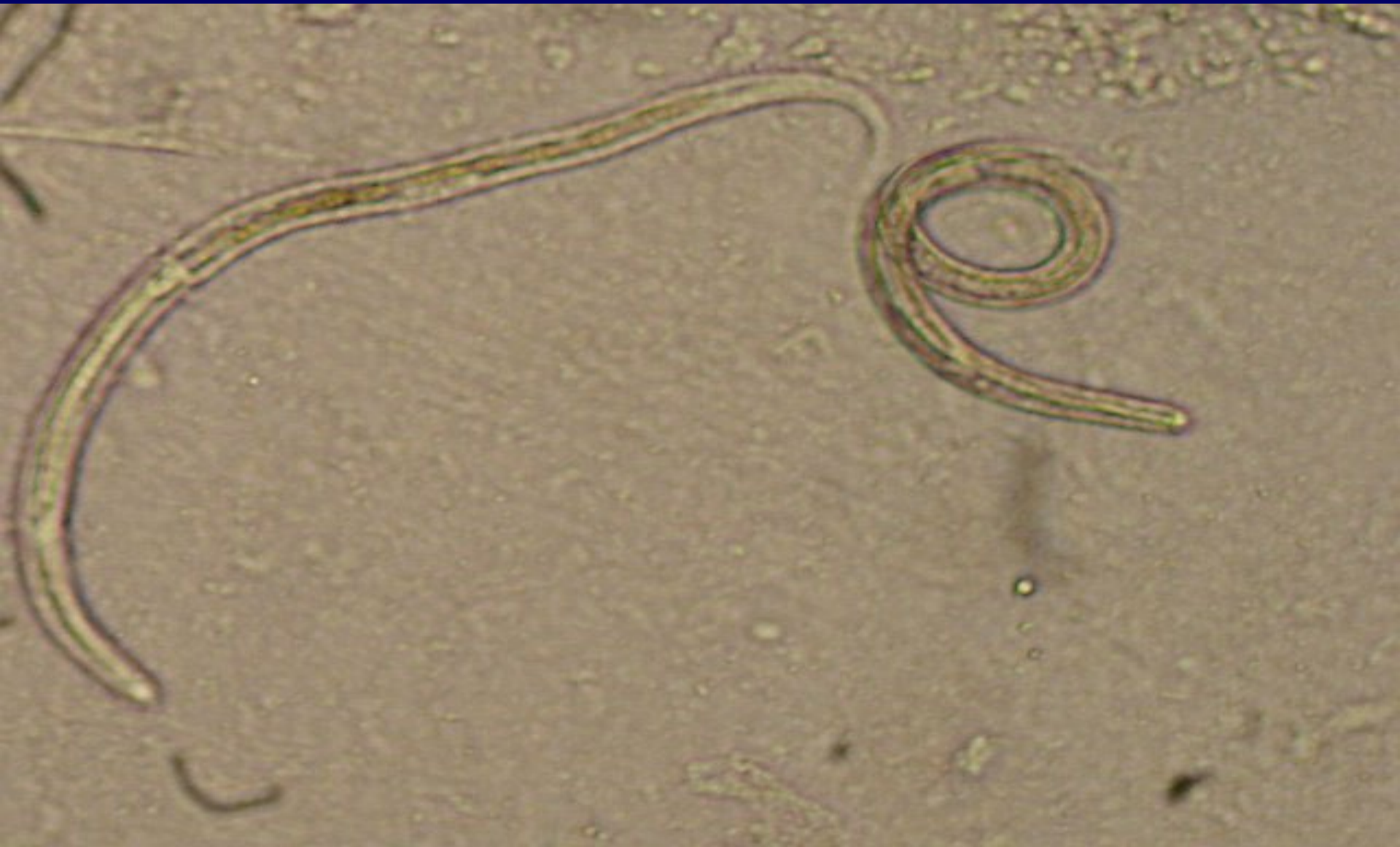
- **Patient treated with tigecycline and polymyxin B - responded**

Antibiotic Susceptibility Testing

Subsequent Stool Isolate

Isolate	***Klebsiella pneumoniae***	
ANTIBIOTICS (μg/mL)	MIC	
Ampicillin	>16 R	
Aztreonam	>16 R	
Ceftriaxone	>32 R	
Ceftazidime	>16 R	
Cefotaxime	>32 R	
Cefazolin	>16 R	S = Susceptible
Ciprofloxacin	>2 R	R = Resistant
Cefepime	>16 R	
Cefuroxime	>16 R	
Amikacin	32 R	
Imipenem	>8 R	
Meropenem	>8 R	
Ertapenem	>4 R	
Polymyxin B	**2 S (?)**	
Gentamicin	8 R	
Levofloxacin	>4 R	
Meropenem	>8 R	
Trimethoprim-Sulfamethox	>2/38 R	
Tetracycline	>8 R	
Tobramycin	>8 R	

The Patient Developed a Second Pneumonia Related to:



Follow-up

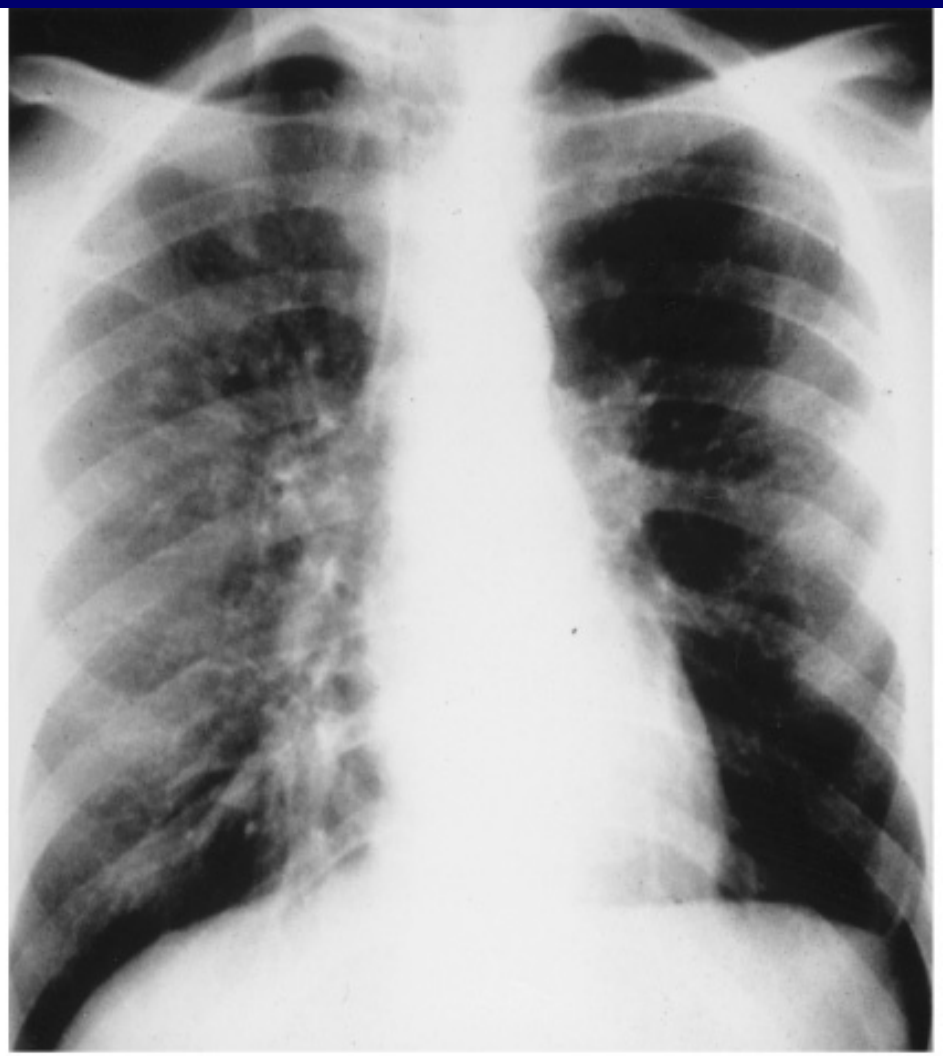
Hyperinfestation with *Strongyloides stercoralis*

Follow-up

Treated and recovered, only to develop a new pneumonia with:

Follow-up

- ***Aspergillus fumigatus***
- **Again responded to therapy (voriconazole), but developed bilateral CMV pneumonia**



Follow-up

Controlled with high-dose gancyclovir, but became septic with:

Multi-drug resistant strain of *Acinetobacter baumannii*

- β-lactam (including imipenem), aminoglycoside, and fluoroquinolone resistant
- Expired 13 months after initial surgery

KPC

- ***K****lebsiella* ***p****neumoniae* **c**arbapenemase
- Mostly found in *K. pneumoniae*, but also in other enteric bacteria.
- KPC_{bla} resides in plasmids.
- Hydrolyze all of the β-lactam antibiotics including cephalosporins and monobactams (as well as the carbapenems) → Very few therapeutic options until recently
- At the time, highly endemic in NYC

KPC

- First day back to Mt. Sinai in January 2005, reviewing reports
- Eight culture isolates of *K. pneumoniae* resistant to carbapenems (ertapenem, imipenem, and meropenem)
- Didn’t believe results and asked techs to repeat AST on isolates
- All confirmed

Class A, KPC Carbapenem-hydrolyzing Enzymes

- KPC-1; *Klebsiella pneumoniae* - North Carolina
- KPC-2; *Klebsiella pneumoniae* - Maryland, Brooklyn/Queens, New York, *Salmonella enterica* serotype Cubana - Maryland, *Klebsiella oxytoca* - New York, *Enterobacter cloacae* - Massachusetts, *Enterobacter aerogenes* - New York
- KPC-3, *Enterobacter cloacae* - New York, *Escherichia coli* - New Jersey
- Now KPC-1 $\rightarrow$ KPC-40 +
- 65 variants now described R to ceftazidime-avibactam
- KPC-positive isolates often possess additional beta-lactamases (average=3.5)

STATE OF NEW YORK
DEPARTMENT OF HEALTH

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Antonia C. Novello, M.D., M.P.H., Dr.P.H.
Commissioner

Dennis P. Whalen
Executive Deputy Commissioner

Reporting Cases of Klebsiella spp. Infection or Colonization

1. The New York State Sanitary Code mandates prompt reporting of hospital-associated clusters of infectious disease and single cases of emerging pathogens to the NYSDOH and the local health department. Please report using a DOH 4018 form, available on http://www.health.state.ny.us/nysdoh/infection/infecreport.pdf:
    a. Clusters of cases of *Klebsiella* spp. infection or colonization; and/or
    b. Single cases of carbapenem-resistant *Klebsiella* spp. infection or colonization.
2. The DOH 4018 form should be faxed to the Regional Epidemiology Program at 518-408-1745. Local health departments can be notified by telephone (a confidential case report does not need to be completed).

Advice from the Canadian Medical Association: Beware of US Hospitals

Elderly Canadians who spend their winters in Florida face and pose the most serious risk because they are more likely to find themselves in United States hospitals, in which carbapenem-resistant *Klebsiella pneumoniae* is rampant.

CMAJ • NOVEMBER 9, 2010 • 182(16)

Susceptibility Testing

Testing Method	Frequency of Very Major, Major, and Minor Errors Number (%) of Isolates with Indicated Result Very Major	Major	Minor
	2010 CLSI Meropenem Interpretive Criteria		
Etest	1 (2.2)	0 (0)	1 (2.2)
Vitek 2	11 (23.9)	0 (0)	18 (39.1)
Sensititre	3 (6.5)	0 (0)	12 (26.1)
Microscan	0 (0)	0 (0)	1 (2.2)
	FDA Meropenem Interpretive Criteria		
Etest	1 (2.2)	0 (0)	7 (15.2)
Vitek 2	27 (58.7)	0 (0)	8 (17.4)
Sensititre	27 (58.7)	0 (0)	12 (26.1)
Microscan	0 (0)	0 (0)	2 (4.3)

Bulik CC, Fauntleroy KA, Jenkins SG, Abuali M, LaBombardi VJ, Nicolau DP, Kuti JL. 2010. J Clin Microbiol. 48: 2402–2406.

Mount Sinai Experience

- **721 patients colonized/infected with carbapenem-resistant *K. pneumoniae* from 1/04 to 4/08**
- **97 patients colonized/infected with carbapenem-resistant Enterobacterales other than *Klebsiella pneumoniae* since 2006: (*Enterobacter* spp. – 73*; Providencia stuartii* – 1; *Morganella morganii* – 1; *Serratia marcescens* – 1; *Klebsiella oxytoca* – 6; *E. coli* – 11; *Citrobacter freundii* – 4)**
- **29 in patients concomitantly infected with KPC-producing *K. pneumoniae* (confirmed as KPCs by isoelectric focusing and PCR)**

Mount Sinai Hospital: Patients with Carbapenem-Resistant *K. pneumoniae* by Year

- **1998 – 2**
- **1999 – 1**
- **2000 – 1**
- **2001 – 7**
- **2002 – 2**
- **2003 – 13**
- **2004 – 40**
- **2005 – 167**
- **2006 – 219**
- **2007 – 225**

Cornell Experience
(Carbapenem-resistant *Enterobacterales*)

- *Klebsiella pneumoniae* –
  - 2007 – 61
  - 2008 – 77
  - 2009 – 64
  - 2010 – 79
  - 2011 – 64
  - 2012 – 75
  - 2013 – 120
- *Klebsiella oxytoca* – 8
- *E. coli* – 45
- *Citrobacter freundii* – 6
- *Serratia marcescens* – 2
- *Enterobacter cloacae* - 57; *Enterobacter aerogenes* – 6; *Enterobacter gergoviae* – 1; *Pantoea* spp. - 1

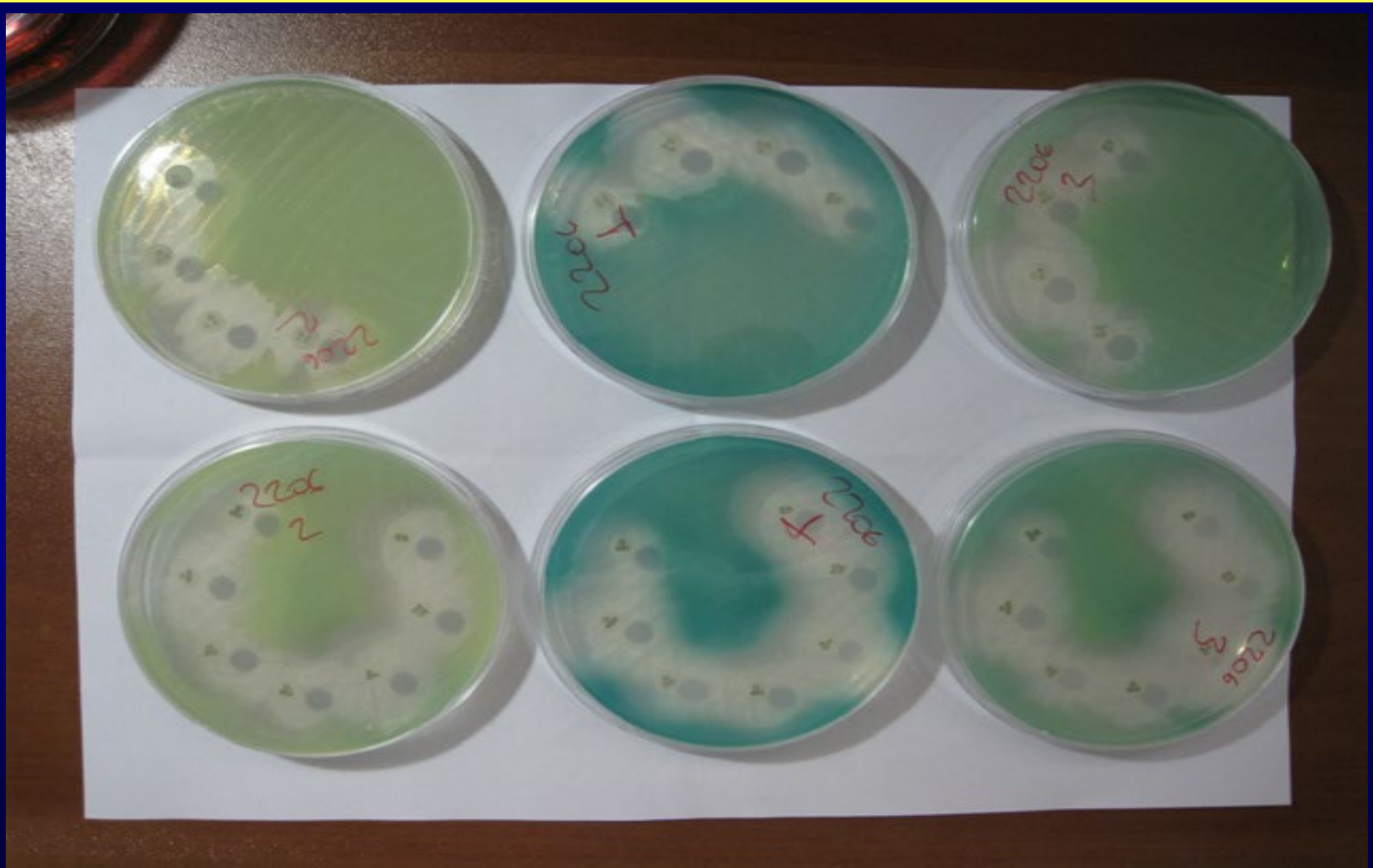
New Drugs Effective Against KPC

- Beta-lactamase inhibitors
  - Ceftazidime-avibactam (Avicaz)
  - Imipenem-relebactam (Recarbrio)
  - Meropenem-vaborbactam (Vabomere)
- Novel cephalosporin
  - Cefiderocol (Ceftroja)
    - Impact of iron in media

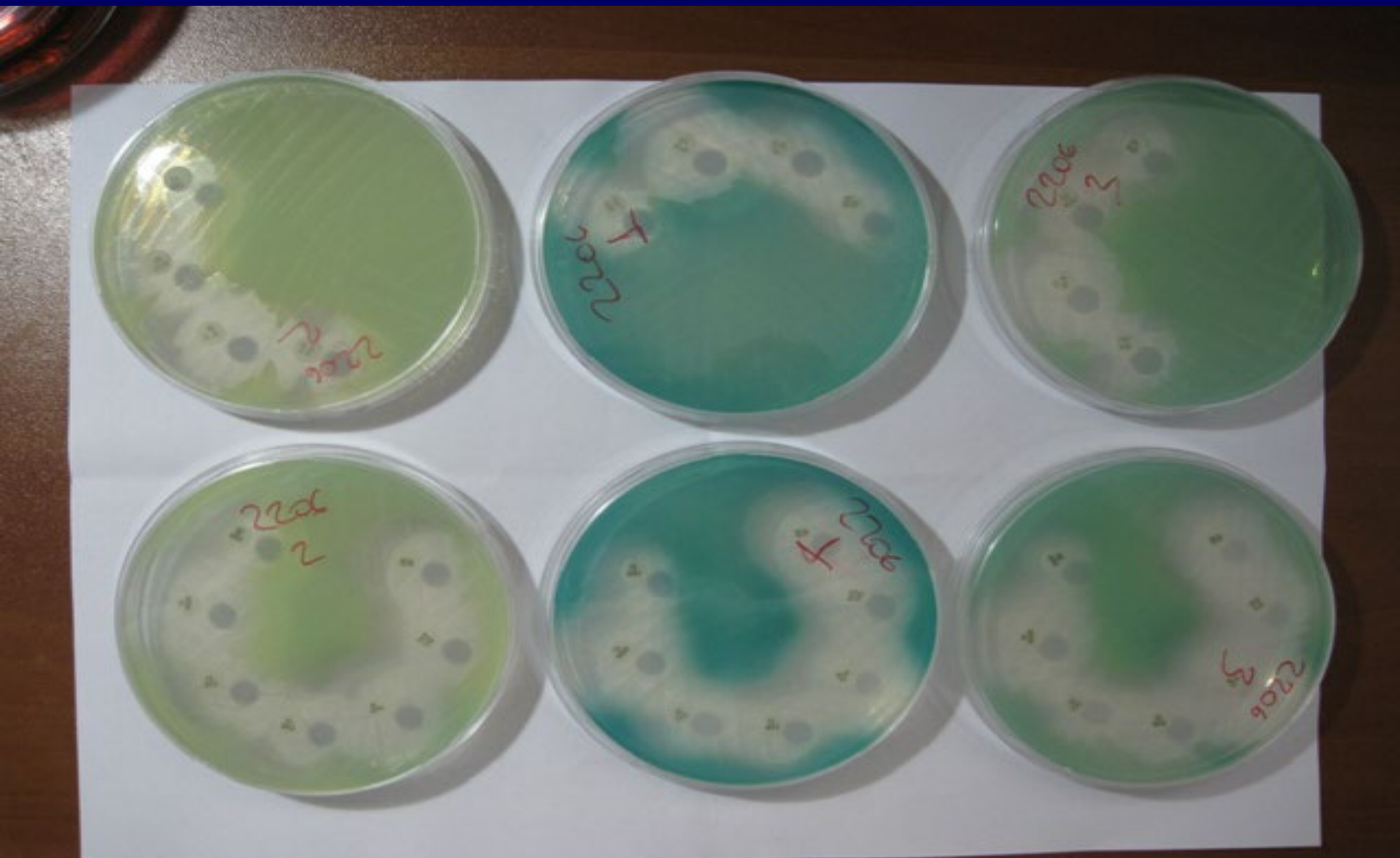
Artificial Tears

- How many of you or members of your family have used artificial tears?

Bug?



Pseudomonas aeruginosa



CDC Bulletin

- Multistate Outbreak:
  Extensively Drug-resistant *Pseudomonas aeruginosa* Associated with Artificial Tears
- The brand of artificial tears most commonly reported was EzriCare Artificial Tears. The manufacturer, Global Pharma, initiated a voluntary recall to the consumer level of all unexpired lots of EzriCare Artificial Tears and Delsam Pharma's Artificial Tears
- As of May 19, 81 cases and 4 deaths now reported across 18 states

Pseudomonas aeruginosa

- Before advent of modern medical microbiology, there was evidence that *P. aeruginosa* was a cause of serious wound and surgical infections
- 1850: Sédillot noted that blue-green discharges were sometimes seen on surgical dressings associated with infection
- 1862: Luke noted “rod-shaped microscopic entities” in the blue-green pus
- 1882: Gessard isolated the organisms and designated them *Bacillus pyocyaneus*

CDC Bulletin

- The isolates from the artificial tears are not susceptible to cefepime, ceftazidime, piperacillin-tazobactam, aztreonam, carbapenems, ceftazidime-avibactam, ceftolozane-tazobactam, fluoroquinolones, polymyxins, amikacin, gentamicin, and tobramycin
- The subset of isolates that underwent antimicrobial susceptibility testing for cefiderocol were susceptible to this agent.

Clinical Laboratory Information

- Clinical laboratories that identify *P. aeruginosa* resistant to imipenem or meropenem are encouraged to perform carbapenem resistance mechanism testing
- Isolates may also be submitted to CDC's Antimicrobial Resistance Laboratory Network for mechanism testing

Clinical Laboratory Information

- Laboratories wishing to apply a more specific definition when identifying isolates that might be related to this cluster for mechanism testing could limit testing to CRPA that are also resistant to cefepime, ceftazidime, and (if tested) ceftazidime-avibactam and ceftolozane-tazobactam

Clinical Laboratory Information

- Clinical laboratories that identify any CRPA from an ocular specimen or VIM-CRPA from any specimen source should submit the isolate to the Antimicrobial Resistance Laboratory Network for further characterization.
- Reach out to your health department's healthcare-associated infections contact or email haioutbreak@cdc.gov for assistance submitting isolates

Clinical Lab Information

- Clinical laboratories that perform whole genome sequencing (WGS) and identify *P. aeruginosa* ST1203 with $bla_{\text{VIM-80}}$ and $bla_{\text{GES-9}}$ should report cases to the health department's healthcare-associated infections program
- Contact (https://www.cdc.gov/hai/state-based/index.html) or CDC ASAP

Carbapenemase Detection

- CLSI states in M-100 that institutional treatment guidelines, infection prevention procedures, or epidemiologic investigations (Tables 3B and 3C) may necessitate ID of carbapenemase-producing Enterobacterales and *P. aeruginosa*
- The document describes 3 approaches: Carba-NP, mCIM, and molecular methods

Other Approaches

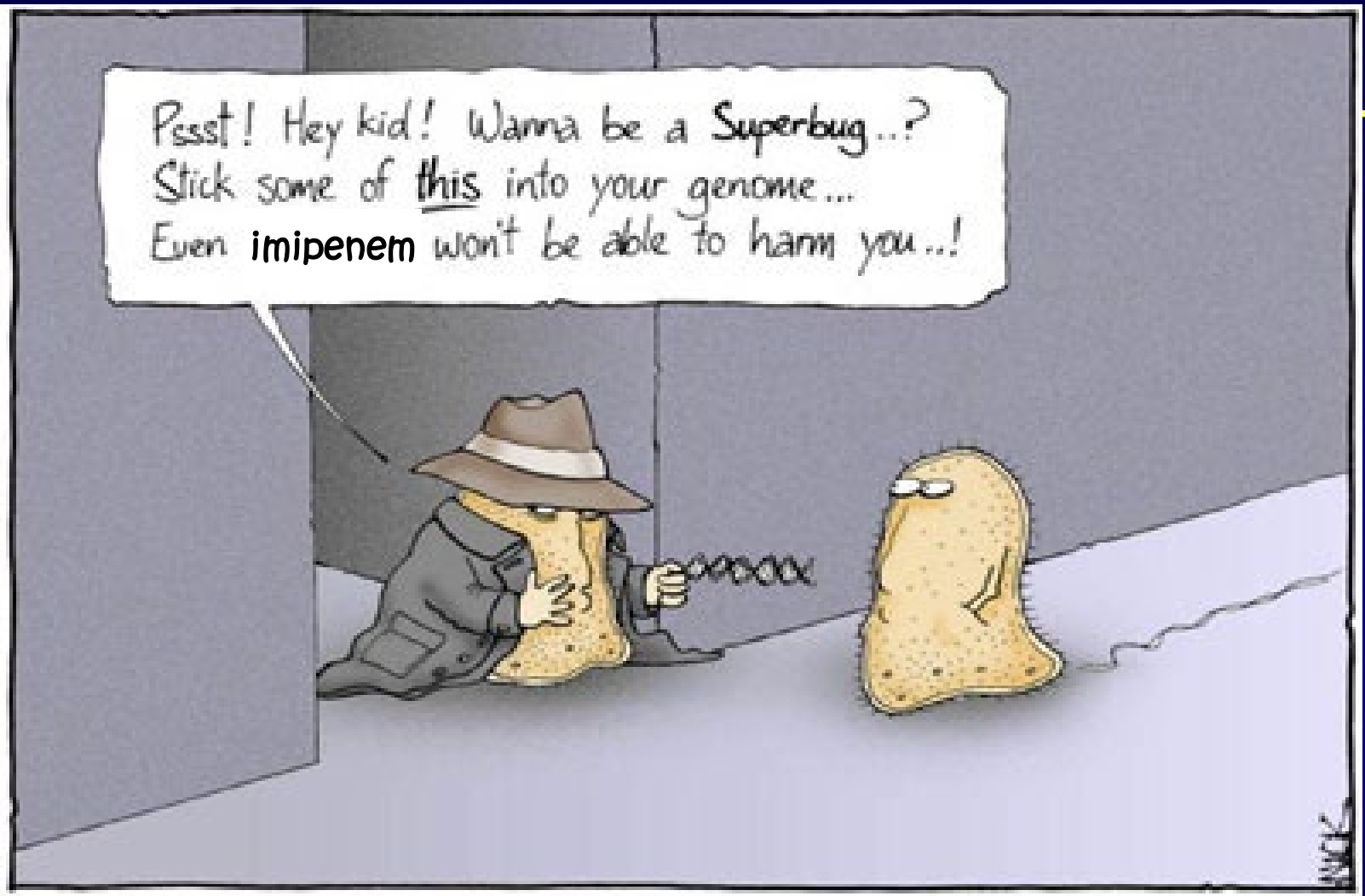
- NG-Test® CARBA 5 for Rapid Phenotypic Detection and Differentiation of Five Common Carbapenemase Families (Hardy)
- Xpert® Carba-R for detection and differentiation of KPC, NDM, VIM, IMP, and OXA-48 (Cepheid)

Test Utilization for Carbapenemase Detection

- How many of your labs are using:
  - mCIM?
  - Carba-NP?
  - NG-Test® CARBA 5?
  - Xpert® Carba-R?
  - WGS?
  - Another approach?
  - Not performing such testing?

Pseudomonas aeruginosa

- Carry multiple genetically based resistance determinants which may act independently or in concert with others:
  - AmpC cephalosporinase
  - OXA β-lactamases
  - TEM-, SHV, PER-1. VEB, GES, and IBC type class A β-lactamases
  - Metallo-carbapenemases
  - Outer membrane porin (OMP) changes
  - Aminoglycoside modifying enzymes
  - Efflux pumps
  - Quinolone resistance
  - Membrane changes causing polymyxin resistance

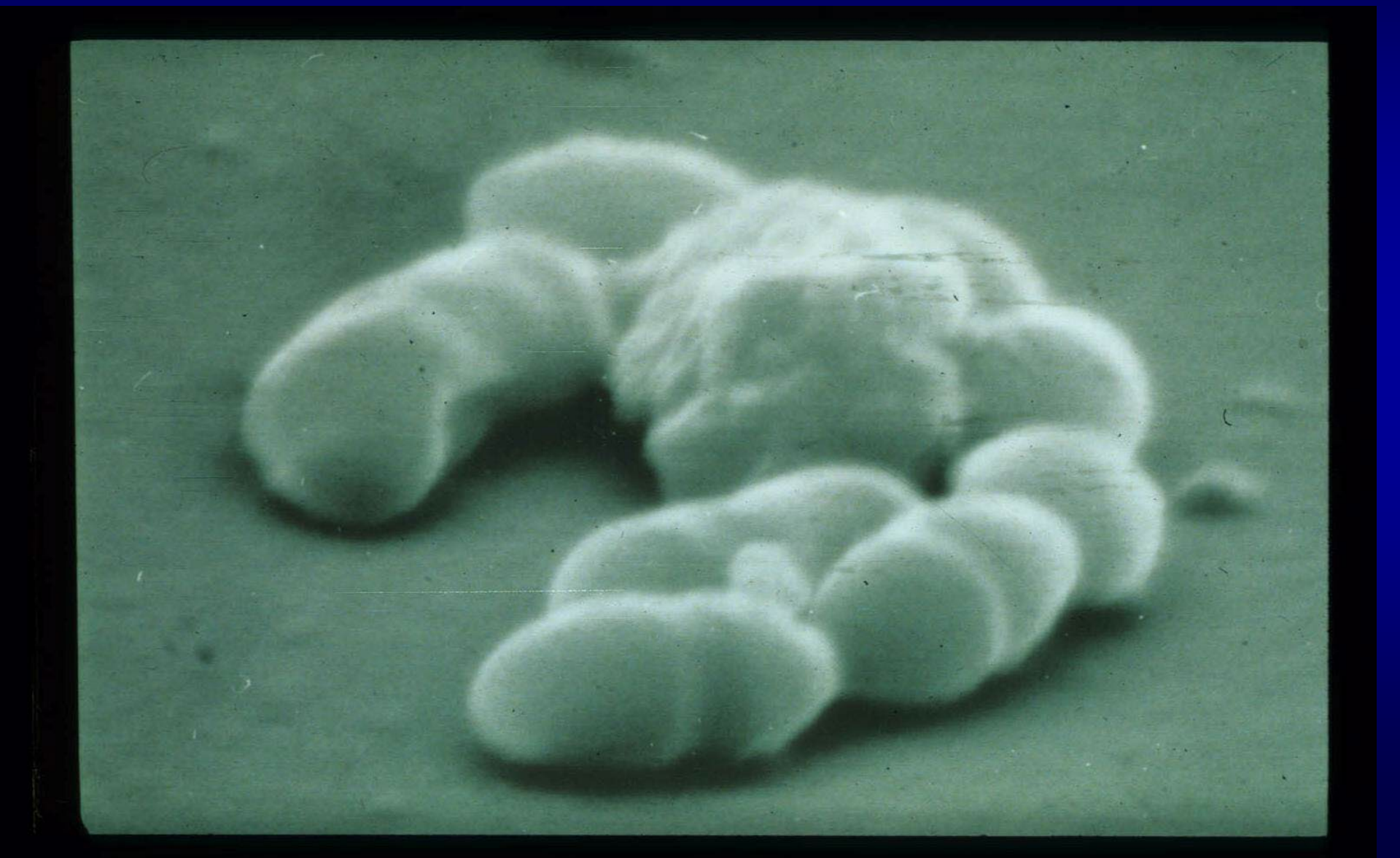


It was on a short-cut through the **Surgical ICU** that Albert was first approached by a member of the Antibiotic Resistance.

XDR- *Shigella*

- The Centers for Disease Control and Prevention (CDC) has been monitoring an increase in extensively drug-resistant (XDR) *Shigella* infections (shigellosis) reported through national surveillance systems
- In 2022, ≈ 5% of *Shigella* infections reported to CDC were caused by XDR strains, compared with 0% in 2015

Shigella sonnei; No flagella



XDR-*Shigella*

- Clinicians treating patients infected with XDR strains have limited antimicrobial treatment options
- *Shigella* bacteria are easily transmissible (Four F's)
- Low infectious dose (as few as 10–100 organisms)
- XDR *Shigella* strains can spread antimicrobial resistance genes to other enteric bacteria

XDR-*Shigella*

- CDC defines XDR *Shigella* bacteria as strains that are resistant to all commonly recommended empiric and alternative antibiotics — azithromycin, ciprofloxacin, ceftriaxone, trimethoprim-sulfamethoxazole (TMP-SMX), and ampicillin

XDR-*Shigella*

- Historically, shigellosis has predominantly affected young children (age 1–4 years) in the United States
- More recently, CDC has observed an increase in antimicrobial-resistant *Shigella* infections among adult populations

XDR-*Shigella*

- Gay, bisexual, and other men who have sex with men (MSM)
- People experiencing homelessness
- International travelers
- People living with HIV
- Between January 1, 2015, and January 22, 2023, CDC received reports of 239 XDR *Shigella* isolates, with *Shigella sonnei* accounting for the largest percentage (66%) followed by *Shigella flexneri* (34%)

XDR-*Shigella*

- 82% were men, 13% were women, and 5% were children
- Among 41 patients who answered questions about recent sexual activity, 88% reported male-to-male sexual contact

Recommendations for Laboratories

- Clinical laboratories should submit known or suspected XDR *Shigella* isolates to the local or state public health laboratory
- State laboratories should perform whole genome sequencing whenever possible

NYC Health Dept. Bulletin

- Since 2015, there have been three (3) NYC residents diagnosed with extensively drug-resistant shigellosis.
- In NYC, approximately 1,000 shigellosis cases are reported to the Health Department annually, of which approximately 40% are culture-confirmed, allowing for antimicrobial susceptibility testing to be performed

NYC Bulletin

- To continue to monitor antimicrobial R among Shigella strains, labs are required to forward all *Shigella* isolates to the PHL
- Log into:

eOrder (https://www2.pardot.health.nyc.gov/e/944933/PHLeOrder-/mnvv3/253683683?h=0utvPVAbknQt00xzL1RcbiKmwOnl_cUbuTykMMX9V7M

- Order "*Shigella* Isolate Serotyping & AST", and send isolates to :
- Public Health Laboratory

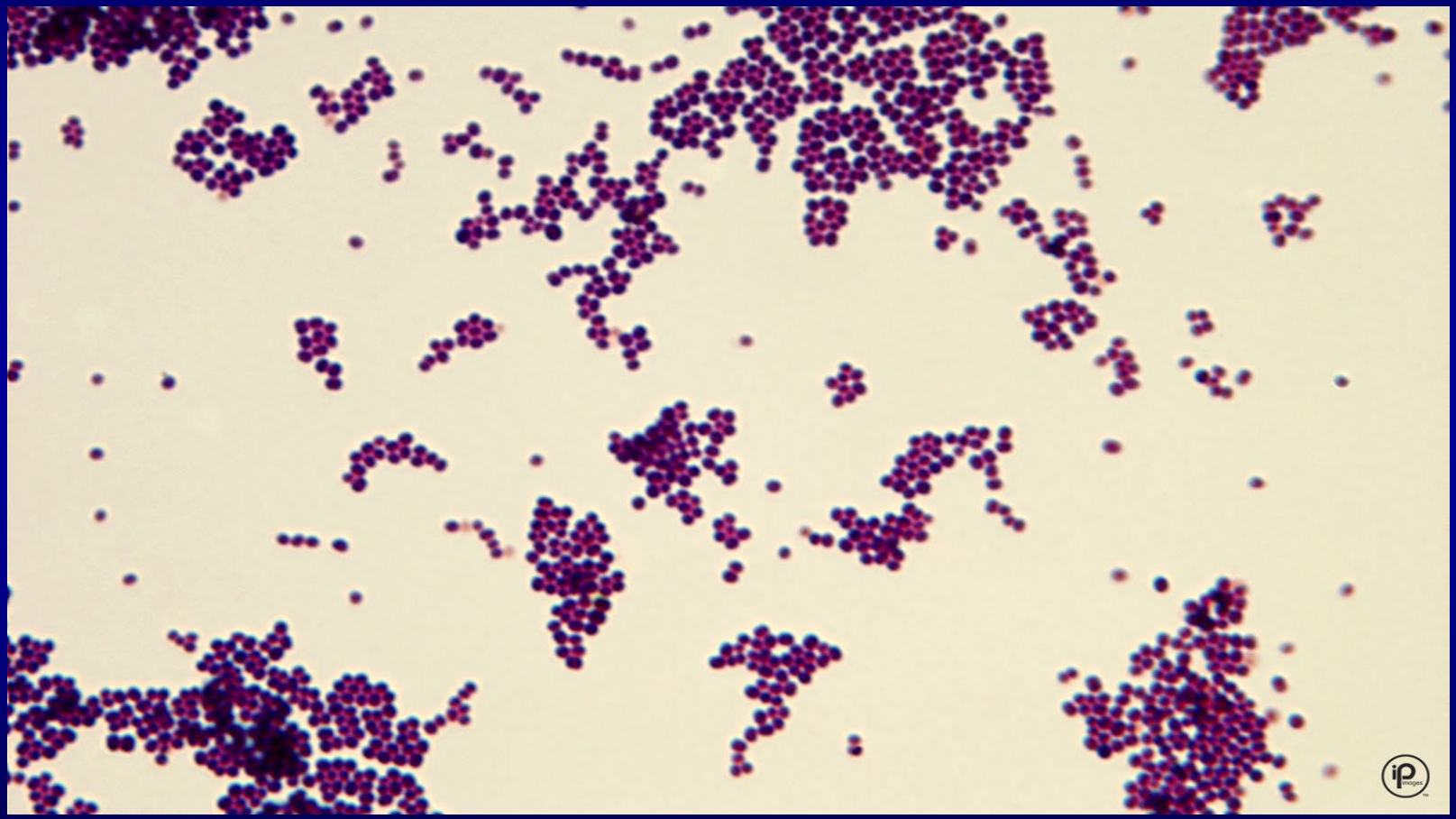
  455 First Ave.

  New York, NY 10016

CLSI AST Recommendations

- Azithromycin disk diffusion and MIC breakpoints now approved for *Shigella*:
  - KB: (R) ≤ 10; (I) 11 – 15; ≥ 16 (S)
  - MIC: (R) ≥ 32; (I) = 16; (S) ≤ 8
  - "Azithromycin disk diffusion zones can be hazy and difficult to measure, especially *S. sonnei*. If an isolate has a zone of inhibition that is difficult to measure, an MIC method is recommended. Media source may affect the clarity of the end points for disk diffusion tests."

Staphylococcus aureus
Gram Stain



Ogston 1883; Greek staphylé “Bunch of grapes”

MRSA with Reduced Susceptibility to Vancomycin

- Risk for vancomycin treatment failure in MRSA bacteremia begins to emerge with increasing vancomycin MICs well within the susceptible range (> 0.5 µg/mL)
- Many *in vitro* systems only test staphylococci down to a concentration of 2 µg/mL
- Measurement of cidal activity of vancomycin *in vitro* also predictive of success of vancomycin in treatment of MRSA bacteremia
- Very labor-intensive

Sakoulos G et al. JCM. 2004. 42: 2398-2402.

VISA and hVISA

- **CLSI definitions:**
  - **VISA: Vancomycin MICs from 4-8 µg/mL (E-test; > 2 µg/mL)**
  - **VRSA: MICs ≥16 µg/mL**
- **Japan and BSAC: vancomycin resistance ≥8 µg/mL**

MRSA with Reduced Susceptibility to Vancomycin

- Heterogeneous VISA (hVISA) appears to be the stage that precedes the development of intermediate level resistance in *S. aureus*
- Strains that contain subpopulations of vancomycin-intermediate daughter cells
- MICs of parent strains can fall within the susceptible range (1 - 2 μg/mL)
- Vancomycin imparts selective pressure favoring outgrowth of rare vancomycin-resistant clones leading to hVISA and, with continued exposure, to a uniform population of VISA

Original E-Test Method for Detection of VISA/GISA

- VISA/GISA defined as:
  - Teicoplanin MIC = 12 μg/mL or
  - Vancomycin MIC = 8 μg/mL and teicoplanin MIC = 8 μg/mL
- Sensitivity = 96%; specificity = 97%
- Consider confirmation by population analysis studies

Walsh et al. J Clin Microbiol. 39: 2439-2444. 2001

E-Test Method for Detection of VISA / GISA

- Double sided GRD strip (vancomycin/teicoplanin)
- Employ 0.5 McFarland on BBL MH agar plates with 5% sheep blood
- Read after 24 and again after 48 hours of incubation
- Cut-off value of ≥8 μg/mL for either teicoplanin or vancomycin

VISA Using Etest® GRD Strip

Mount Sinai Bacteremia Study

- Re-testing all MRSA isolates recovered from blood cultures from 2002 – May 2008 for susceptibility to vancomycin, daptomycin, linezolid, tigecycline, and teicoplanin
- Tested for hVISA using both E-test methods
- Clinical outcomes by MIC for all isolates (n=748)
  - 9 VISA (MIC ≥ 8 μg/mL)
  - 55 VISA (MIC ≥4 μg/mL)
  - 48 hVISA

Pastagia M, Kleinman LC, Lacerda de la Cruz EG, **Jenkins SG**. 2012. Calculating the Risk of Mortality Due to Methicillin-Resistant *Staphylococcus aureus* Bacteremia Using Vancomycin Minimum Inhibitory Concentration, Heteroresistance and Patient Correlates.
Emerging Infectious Diseases. Vol. 15:1072-1080.

St. Vincent's Study

- Dr. Vincent LaBombardi et al
- Almost identical results in subsequent study
- Clearly, VISA and hVISA strains were being missed in NYC
- How many of your labs test for VISA and/or hVISA?

Trichophyton indotineae

- First reported U.S. cases of tinea (commonly known as ringworm) caused by *Trichophyton indotineae* — New York City, December 2021–March 2023 (*MMWR* May 12, 2023 / 72(19);536–537)

Trichophyton indotineae

- Tinea is a common, highly contagious, superficial infection of the skin, hair, or nails caused by dermatophytic moulds.
- During the past decade, an epidemic of severe, antifungal-resistant tinea has emerged in South Asia because of the rapid spread of *Trichophyton indotineae*, a novel dermatophyte species

Trichophyton indotineae

- The epidemic has likely been driven by misuse and overuse of topical antifungals and corticosteroids
- *T. indotineae* infections are highly transmissible and characterized by widespread, inflamed, pruritic plaques on the body (tinea corporis), the crural fold, pubic region, and adjacent thigh (tinea cruris), or the face (tinea faciei)

Trichophyton indotineae

- *T. indotineae* isolates are frequently resistant to terbinafine, a mainstay of tinea treatment
- *T. indotineae* infections have been reported throughout Asia and in Europe and Canada but had not previously been described in the United States

Trichophyton indotineae

- On February 28, 2023, a New York City dermatologist notified public health officials of two patients who had severe tinea that did not improve with oral terbinafine treatment, raising concern for potential *T. indotineae* infection
- These patients shared no epidemiologic links.

Trichophyton indotineae

- Skin culture isolates from each patient were previously identified by a clinical laboratory as *Trichophyton mentagrophytes* and were subsequently forwarded to the Wadsworth Center, New York State Department of Health, for further review and analysis.

Trichophyton indotineae

- Sanger sequencing of the internal transcribed spacer region of the ribosomal gene, followed by phylogenetic analysis performed during March 2023, identified the isolates as *T. indotineae*
- Caution when reporting *T. mentagrophytes* from repeat cultures from a patient

Queries