Antimicrobial Resistance: Will it Win in the End?

A Case Study in How to Safely Analyze Resistance to a Last Line Antibiotic

Susan E. Vleck, PhD, RBP/CBSP(ABSA)

5December2022

CIHC

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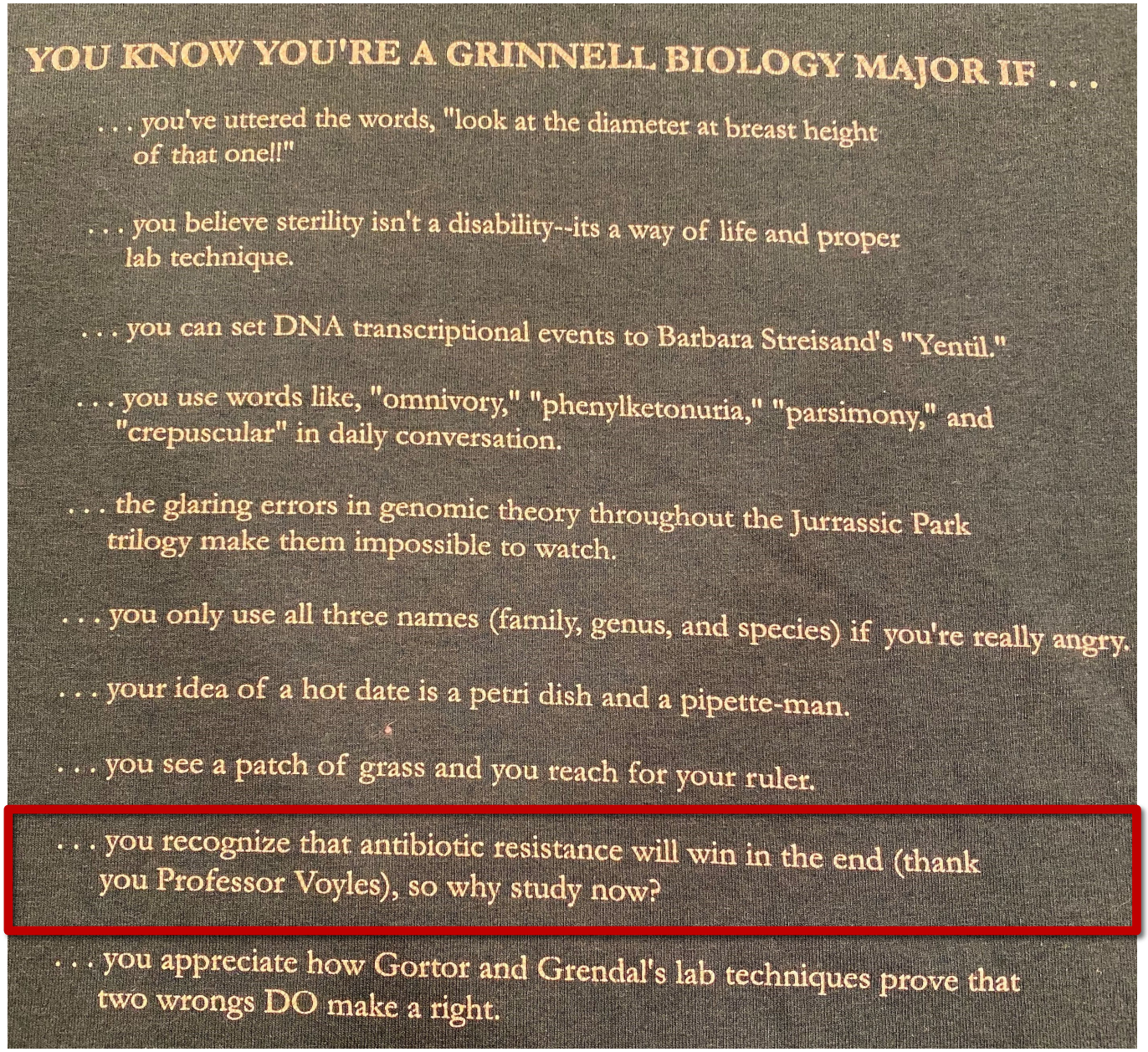
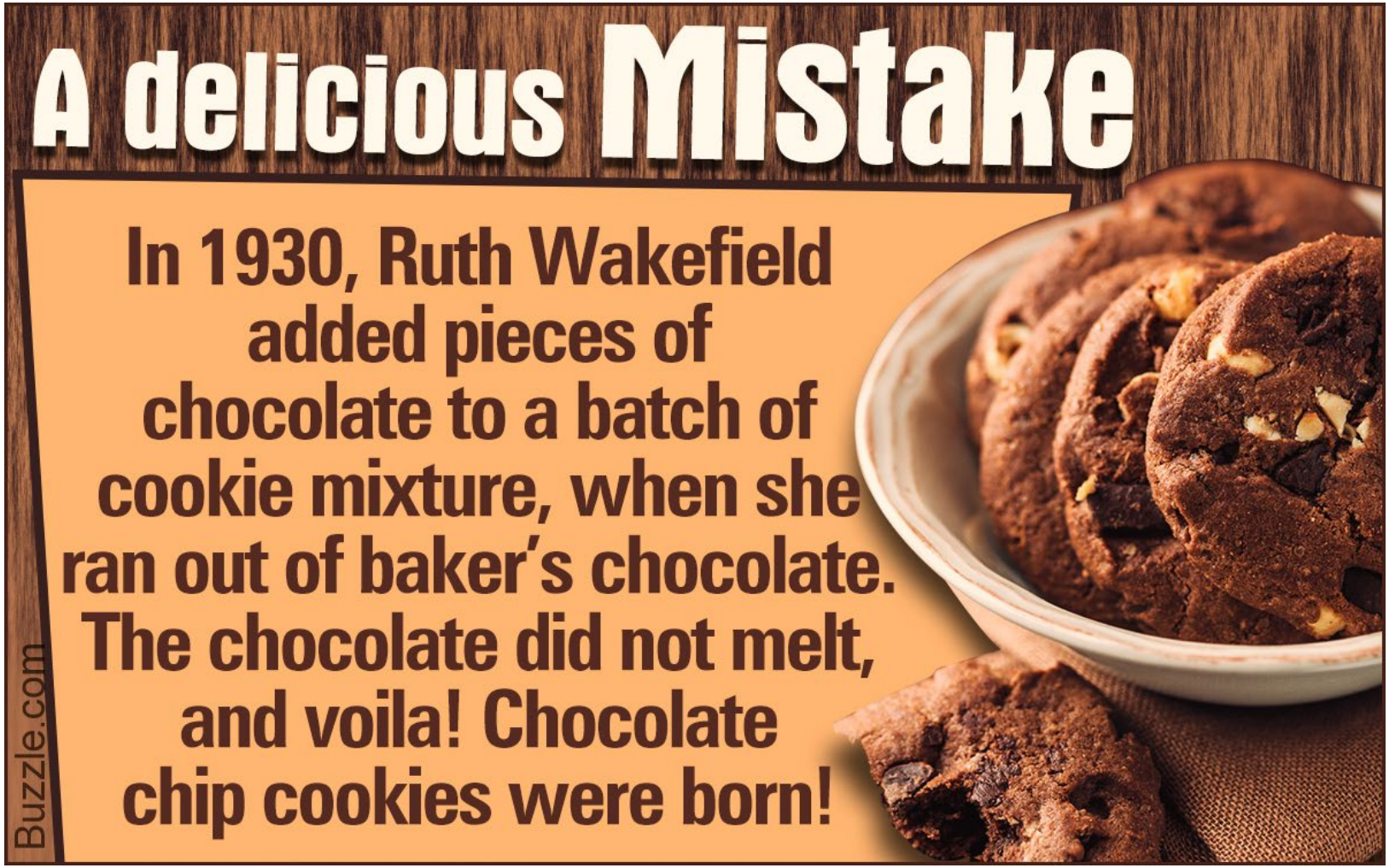
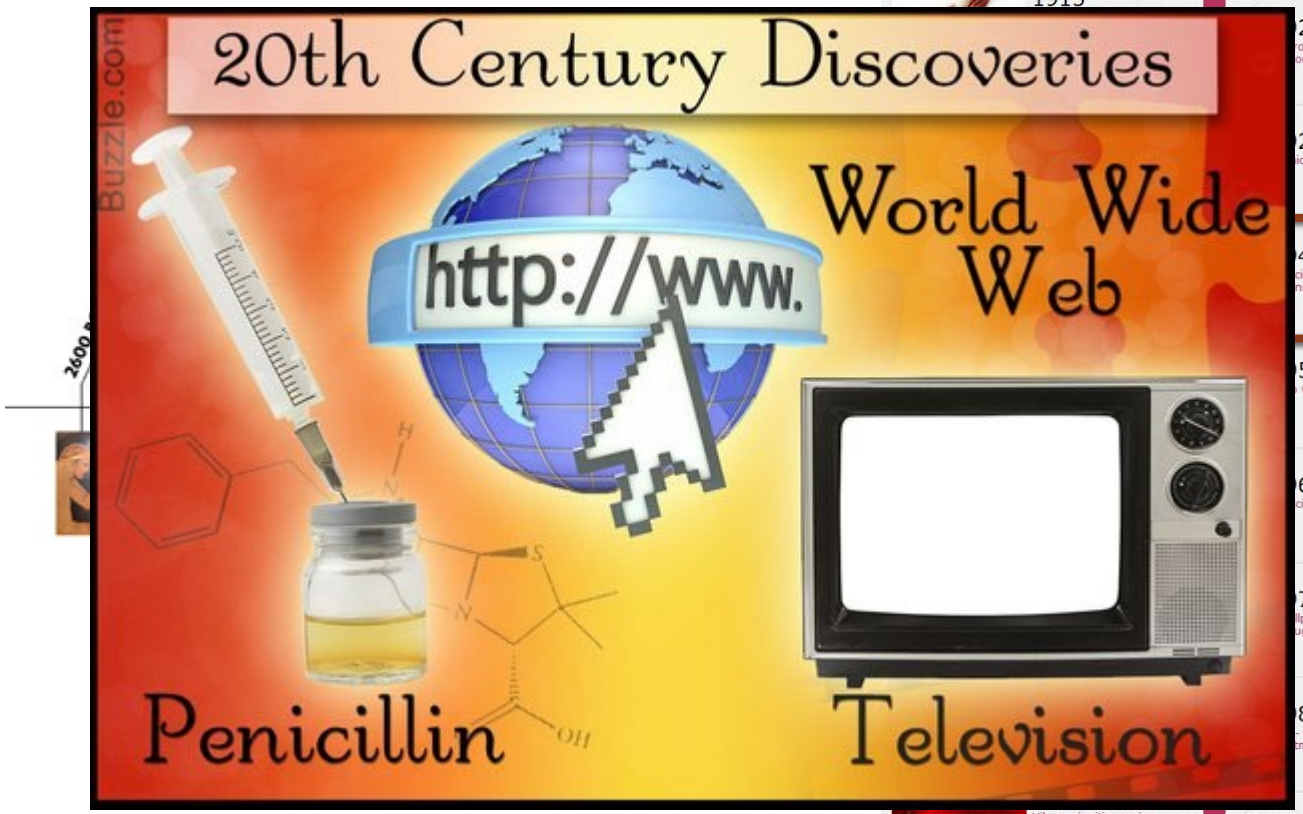

YOU KNOW YOU'RE A GRINNELL BIOLOGY MAJOR IF . . .
. . . you've uttered the words, "look at the diameter at breast height of that one!!"
. . . you believe sterility isn't a disability--its a way of life and proper lab technique.
. . . you can set DNA transcriptional events to Barbara Streisand's "Yentil."
. . . you use words like, "omnivory," "phenylketonuria," "parsimony," and "crepuscular" in daily conversation.
. . . the glaring errors in genomic theory throughout the Jurrassic Park trilogy make them impossible to watch.
. . . you only use all three names (family, genus, and species) if you're really angry.
. . . your idea of a hot date is a petri dish and a pipette-man.
. . . you see a patch of grass and you reach for your ruler.
. . . you recognize that antibiotic resistance will win in the end (thank you Professor Voyles), so why study now?
. . . you appreciate how Gortor and Grendal's lab techniques prove that two wrongs DO make a right.

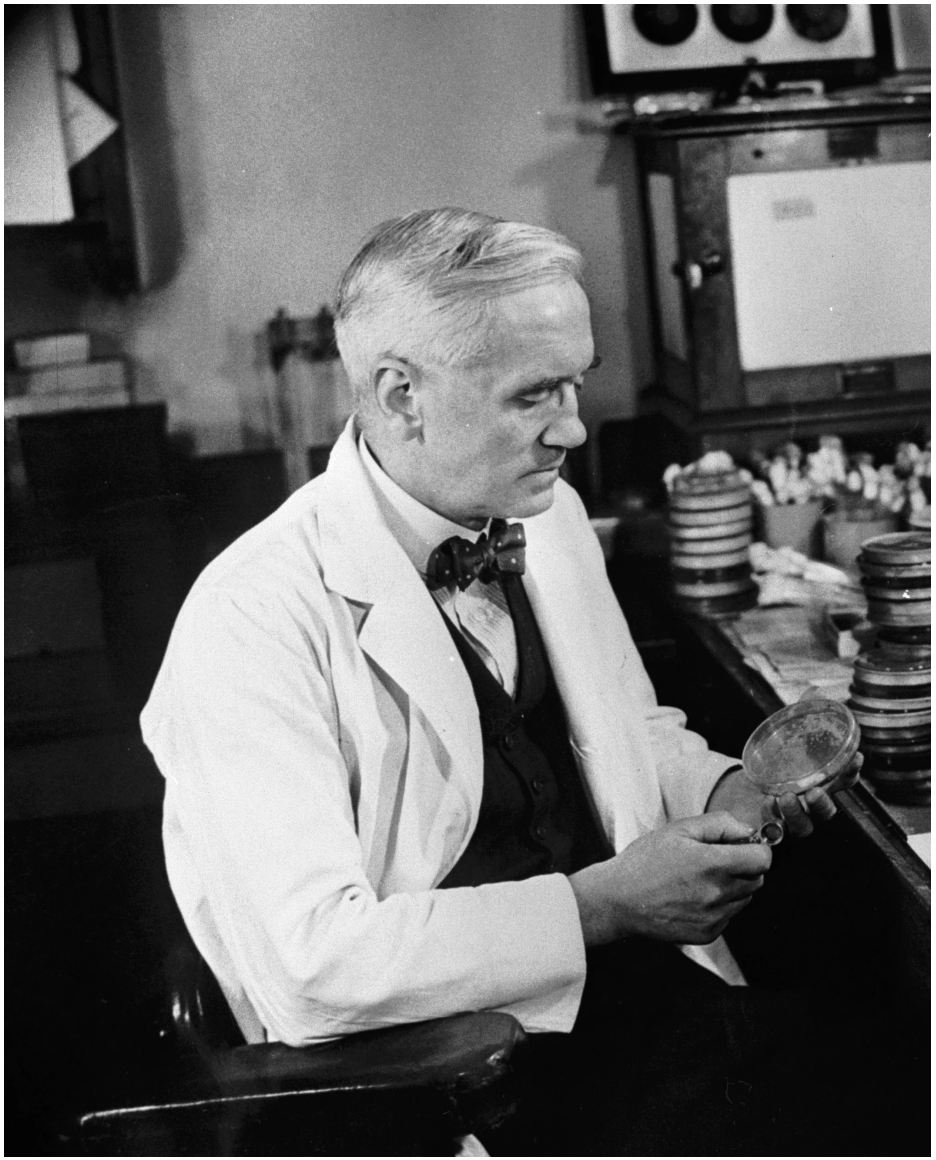
Scientific Breakthroughs from “Mistakes”



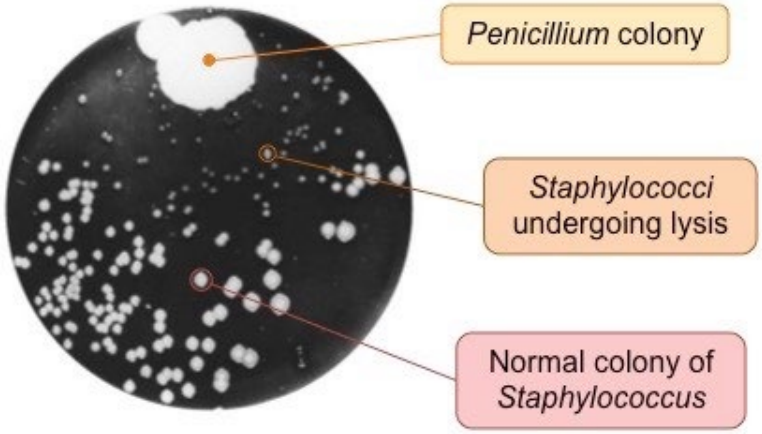
Medical Discoveries: Penicillin



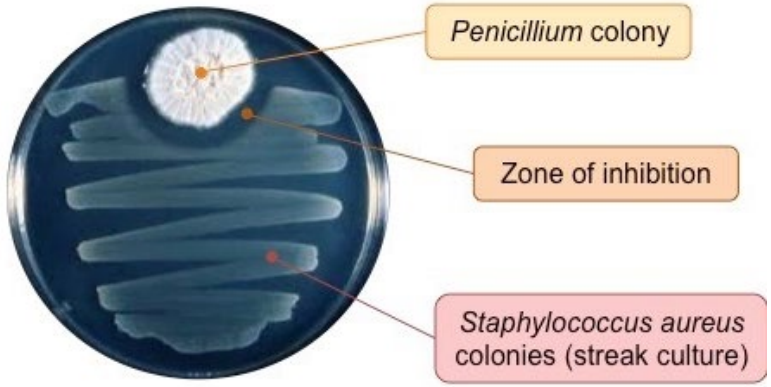
Alexander Fleming



Original Experiment (Fleming, 1928)



Modern Experiment (Streak Culture)



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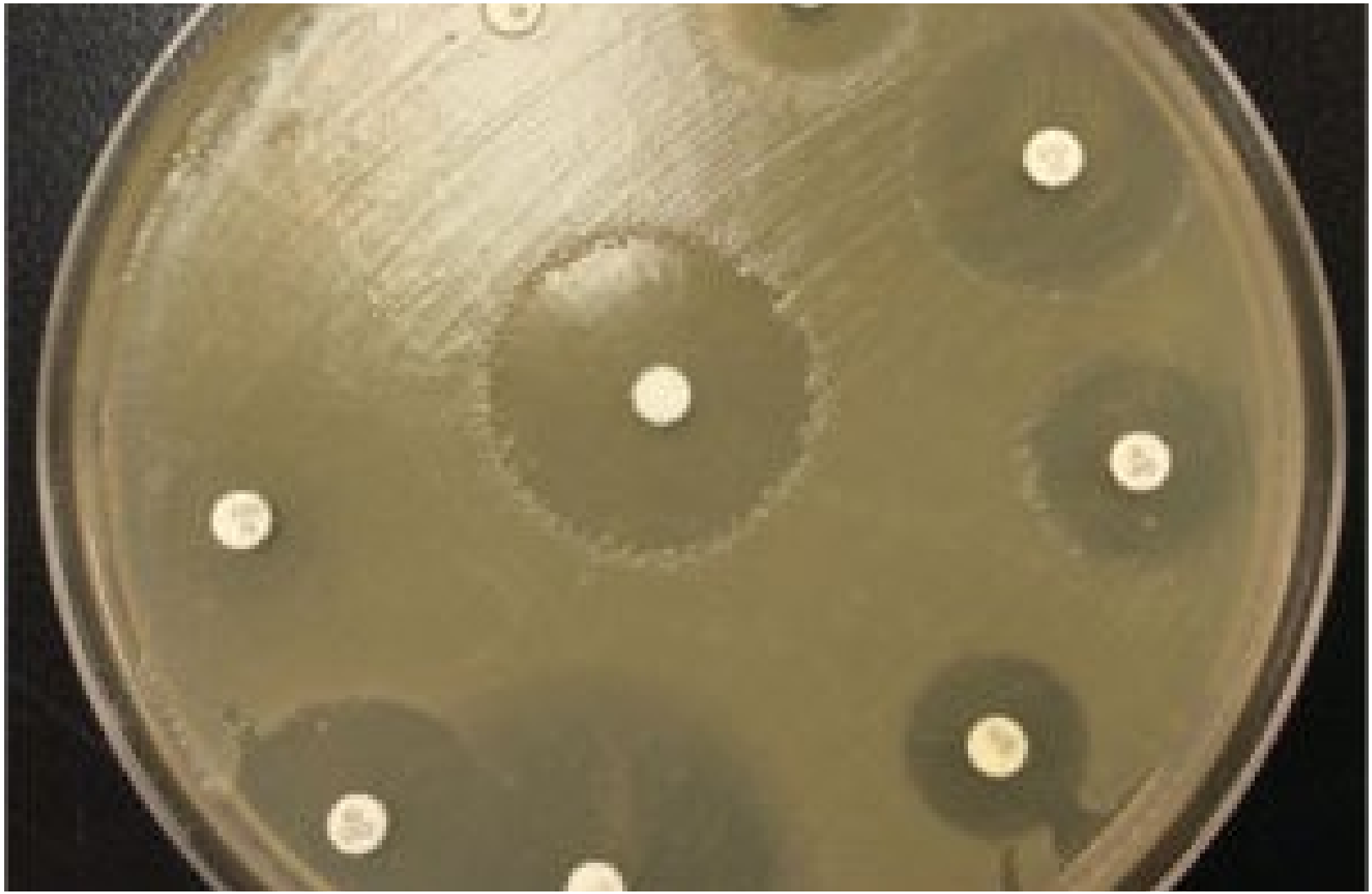
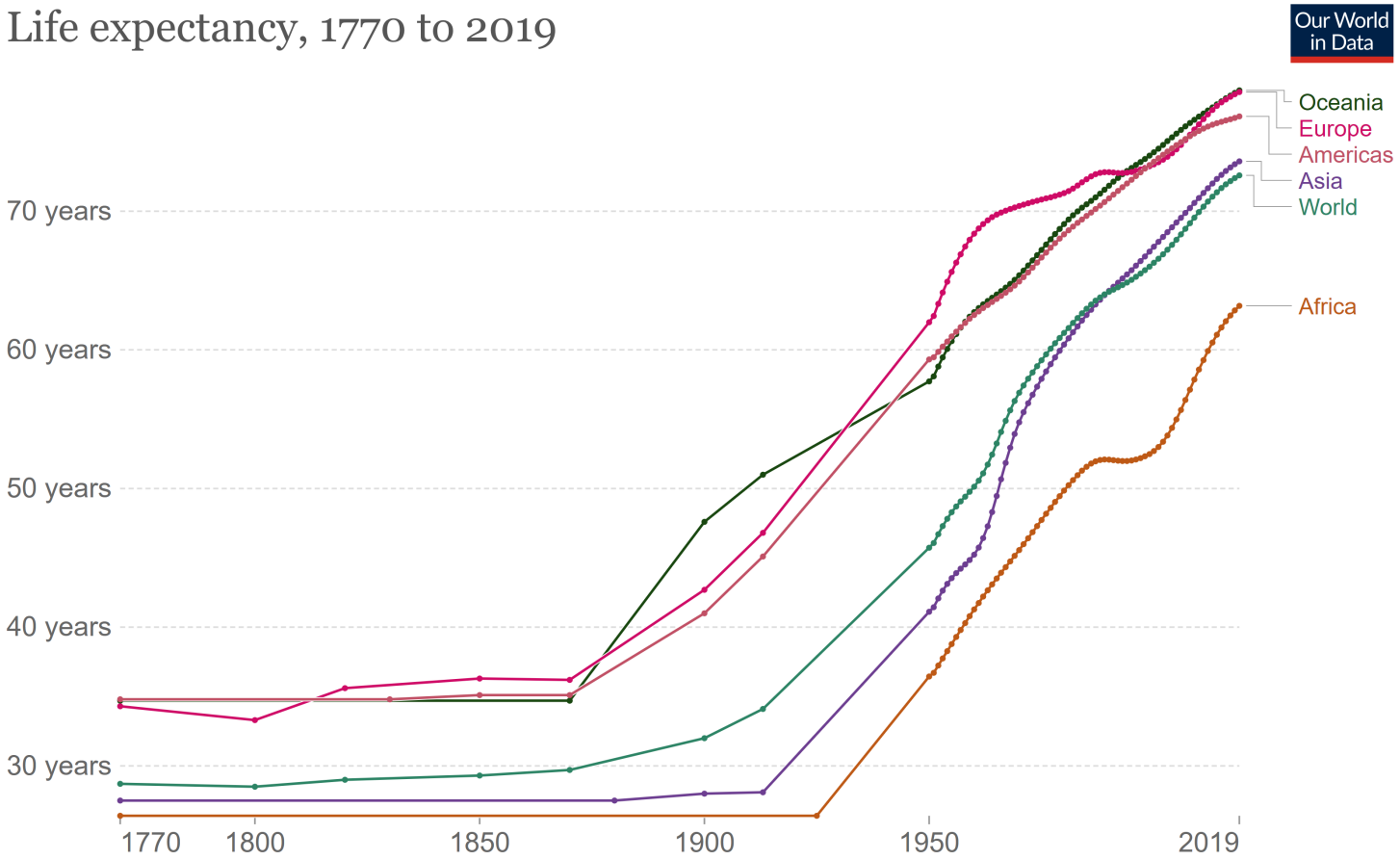
Modern Day Antibiotic Sensitivity Testing



The Golden Age of Antimicrobials (And Medical Hygiene)



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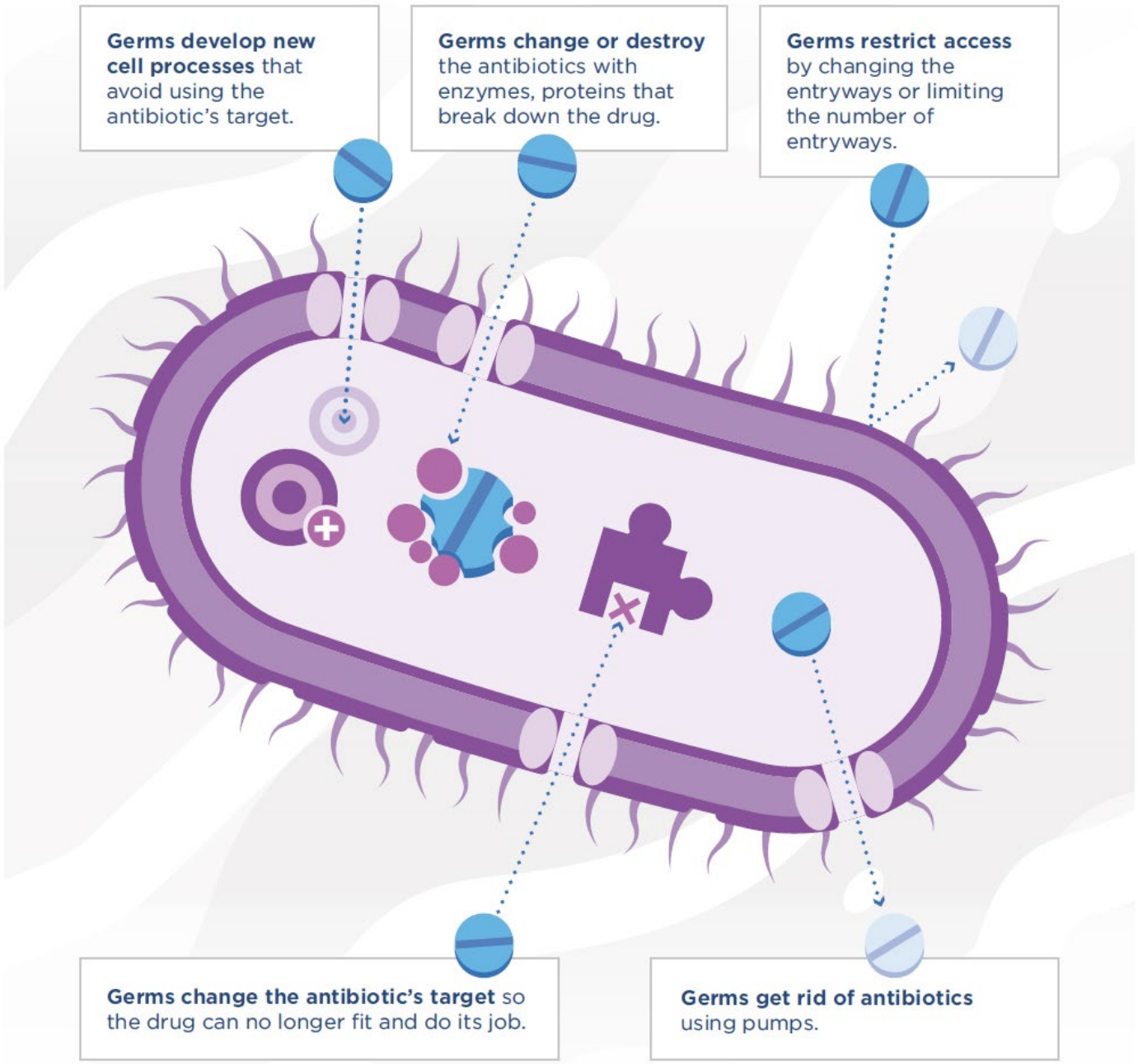
https://ourworldindata.org/life-expectancy



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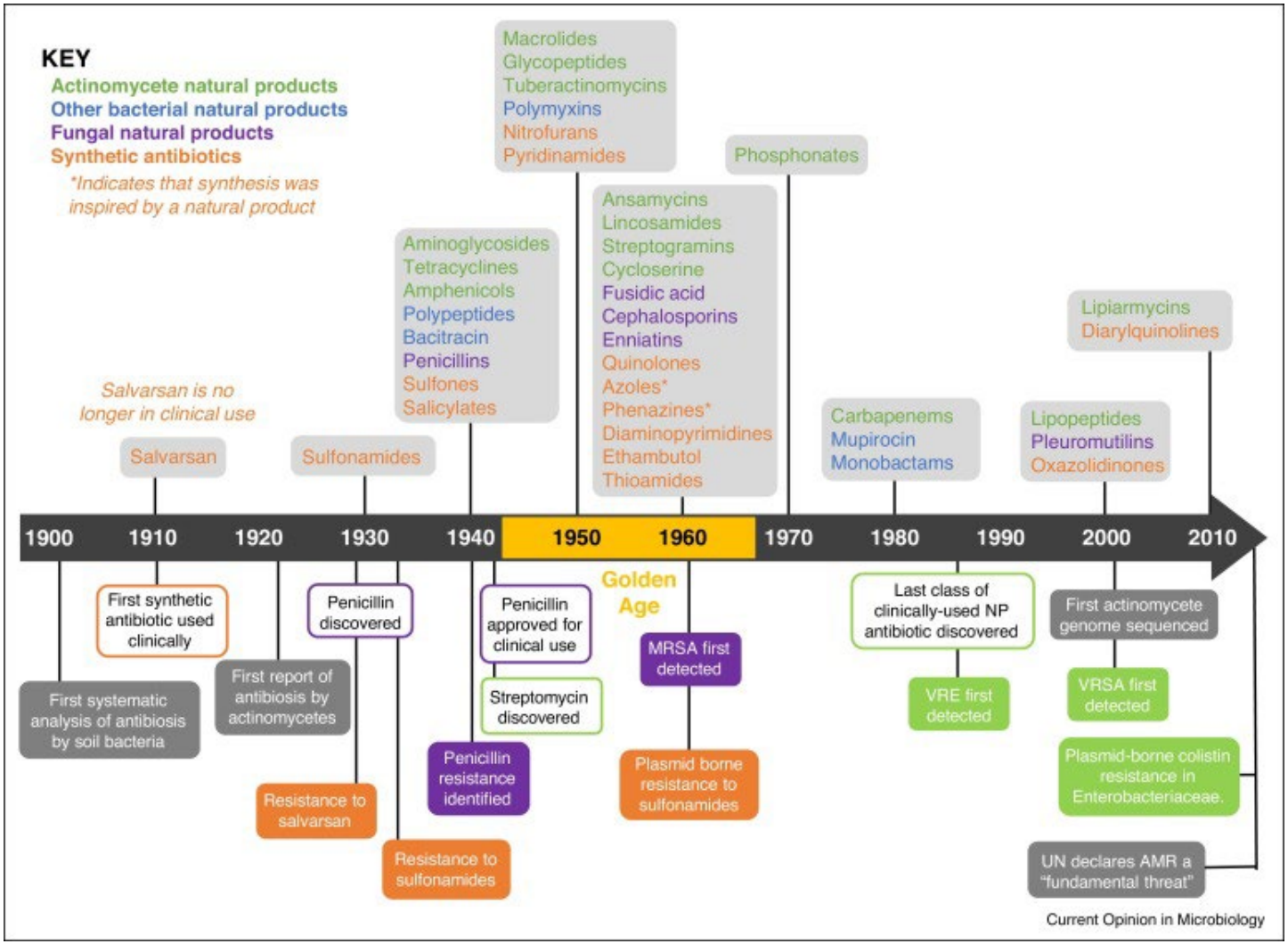
https://www.cdc.gov/drugresistance/about/how-resistance-happens.html

Antimicrobial Resistance: Resist, Tolerate, Mutate



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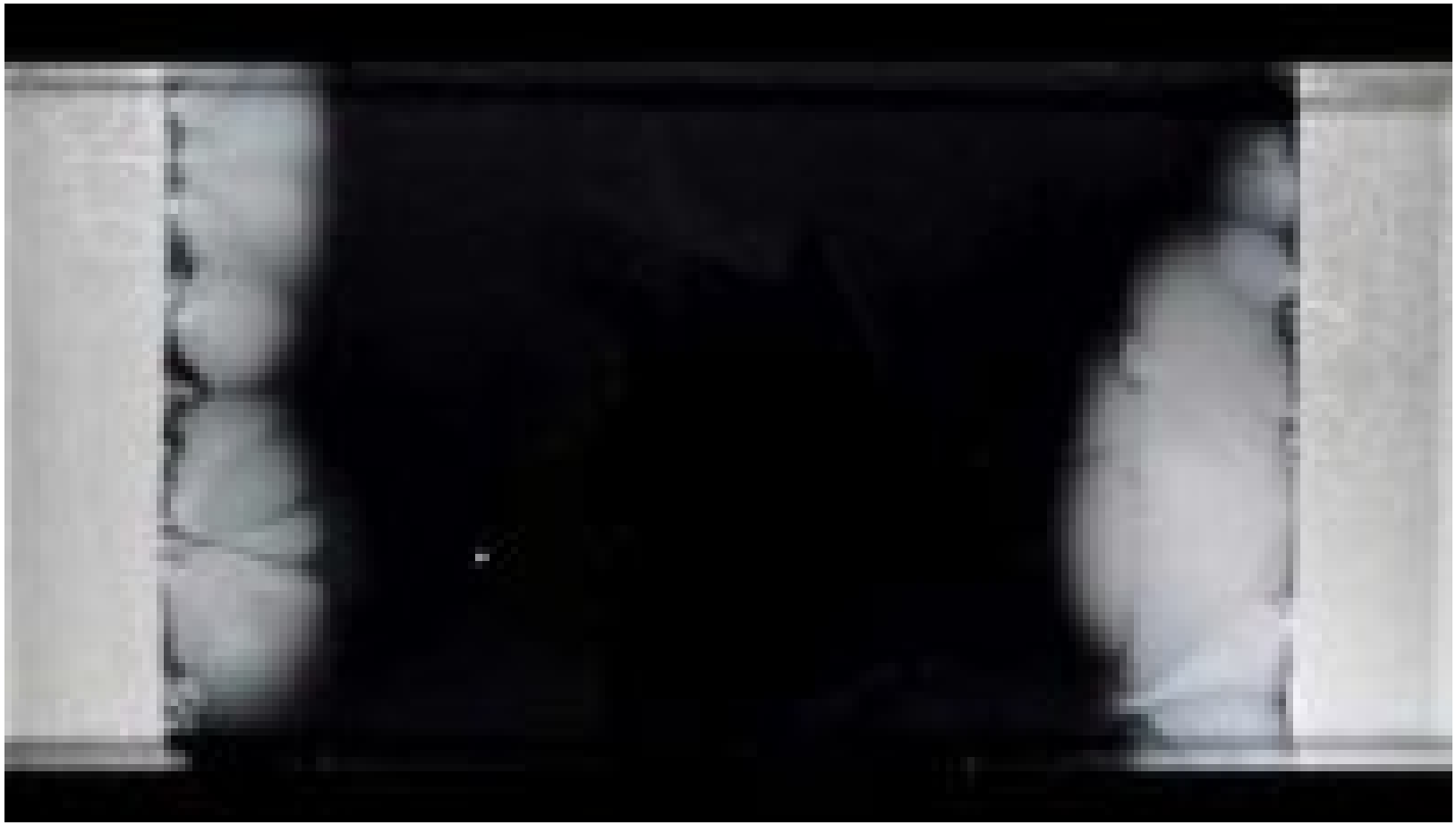
Antibiotics: past, present and future Hutchings, Truman and Wilkinson

Why 99% effective isn't good enough



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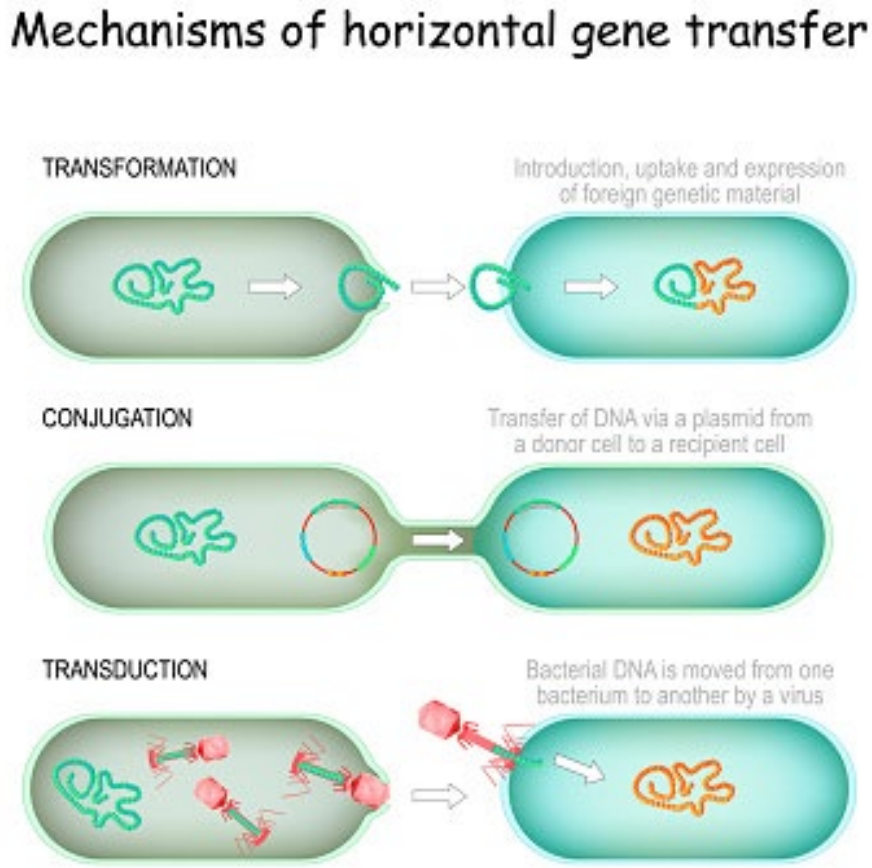
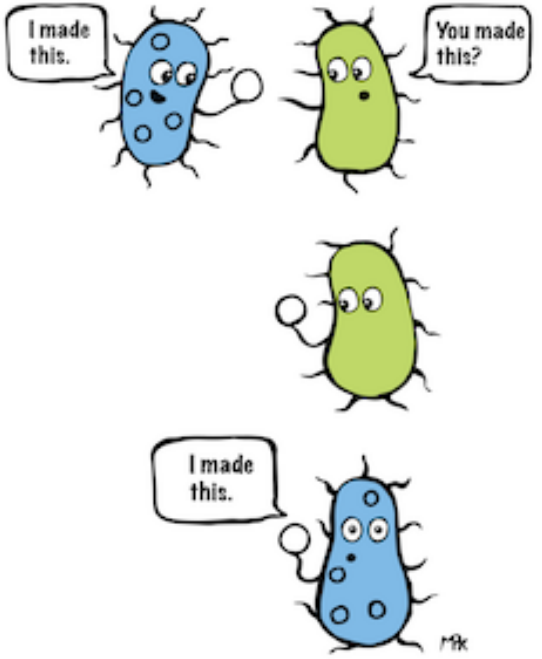
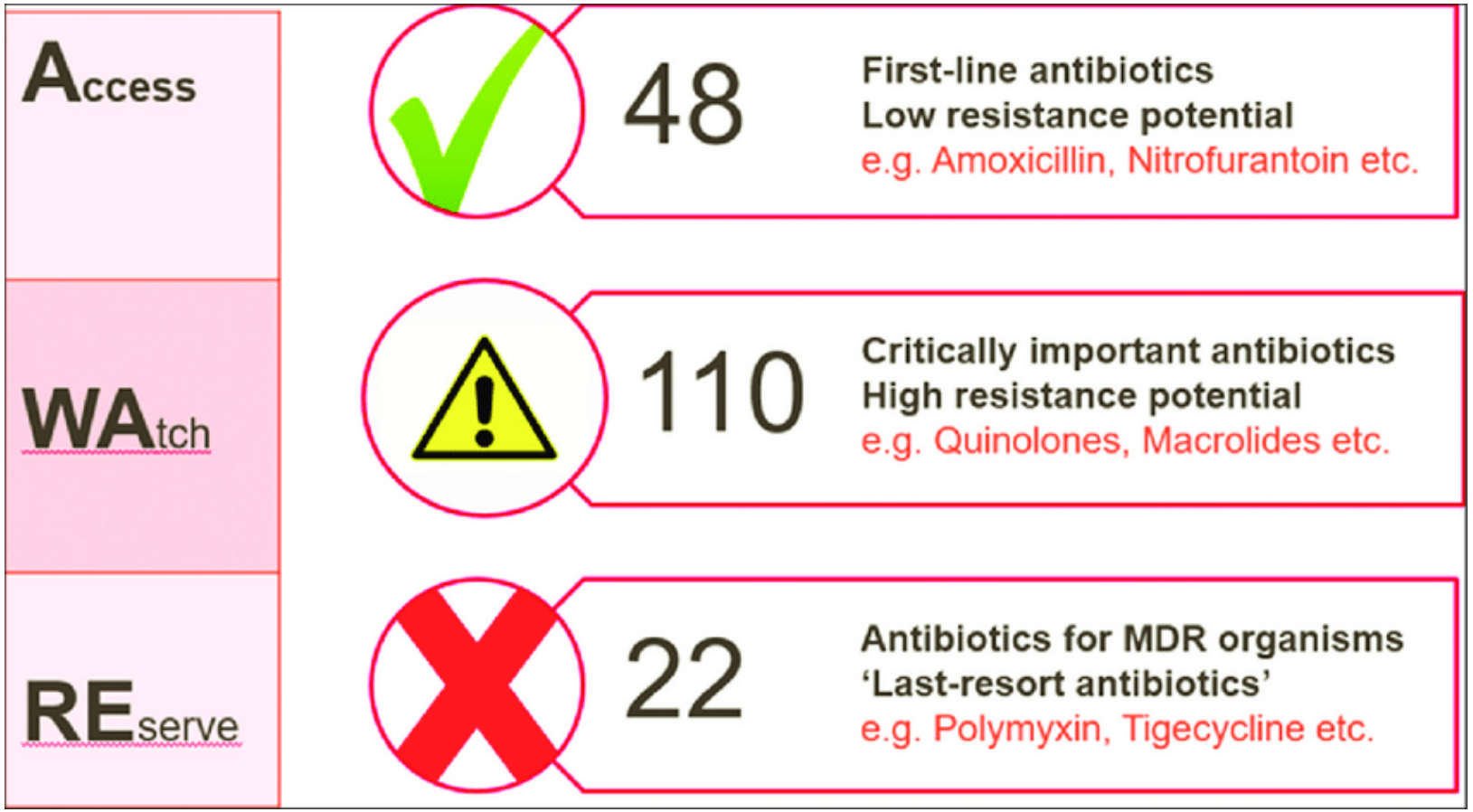
https://news.harvard.edu/gazette/story/2016/09/a-cinematic-approach-to-drug-resistance/

Bacteria don’t just grow, they share





WHO AWaRe 2019 Classification



Antibiotic Approved or Released	Year Released	Resistant Germ Identified	Year Identified
Penicillin	1941	Penicillin-resistant *Staphylococcus aureus*[20, 21]	1942
		Penicillin-resistant *Streptococcus pneumoniae*[9,10]	1967
		Penicillinase-producing *Neisseria gonorrhoeae*[11]	1976
Vancomycin	1958	Plasmid-mediated vancomycin-resistant *Enterococcus faecium*[12,13]	1988
		Vancomycin-resistant *Staphylococcus aureus*[14]	2002
Amphotericin B	1959	Amphotericin B-resistant *Candida auris*[15]	2016
Methicillin	1960	Methicillin-resistant *Staphylococcus aureus*[16]	1960
Extended-spectrum cephalosporins	1980 (Cefotaxime)	Extended-spectrum beta-lactamase- producing *Escherichia coli*[17]	1983
Azithromycin	1980	Azithromycin-resistant *Neisseria gonorrhoeae*[18]	2011
Imipenem	1985	*Klebsiella pneumoniae* carbapenemase (KPC)-producing *Klebsiella pneumoniae*[19]	1996
Ciprofloxacin	1987	Ciprofloxacin-resistant *Neisseria gonorrhoeae*[20]	2007
Fluconazole	1990 (FDA approved)	Fluconazole-resistant *Candida*[21]	1988
Caspofungin	2001	Caspofungin-resistant *Candida*[22]	2004
Daptomycin	2003	Daptomycin-resistant methicillin-resistant *Staphylococcus aureus*[23]	2004
Ceftazidime-avibactam	2015	Ceftazidime-avibactam-resistant KPC-producing *Klebsiella pneumoniae*[24]	2015

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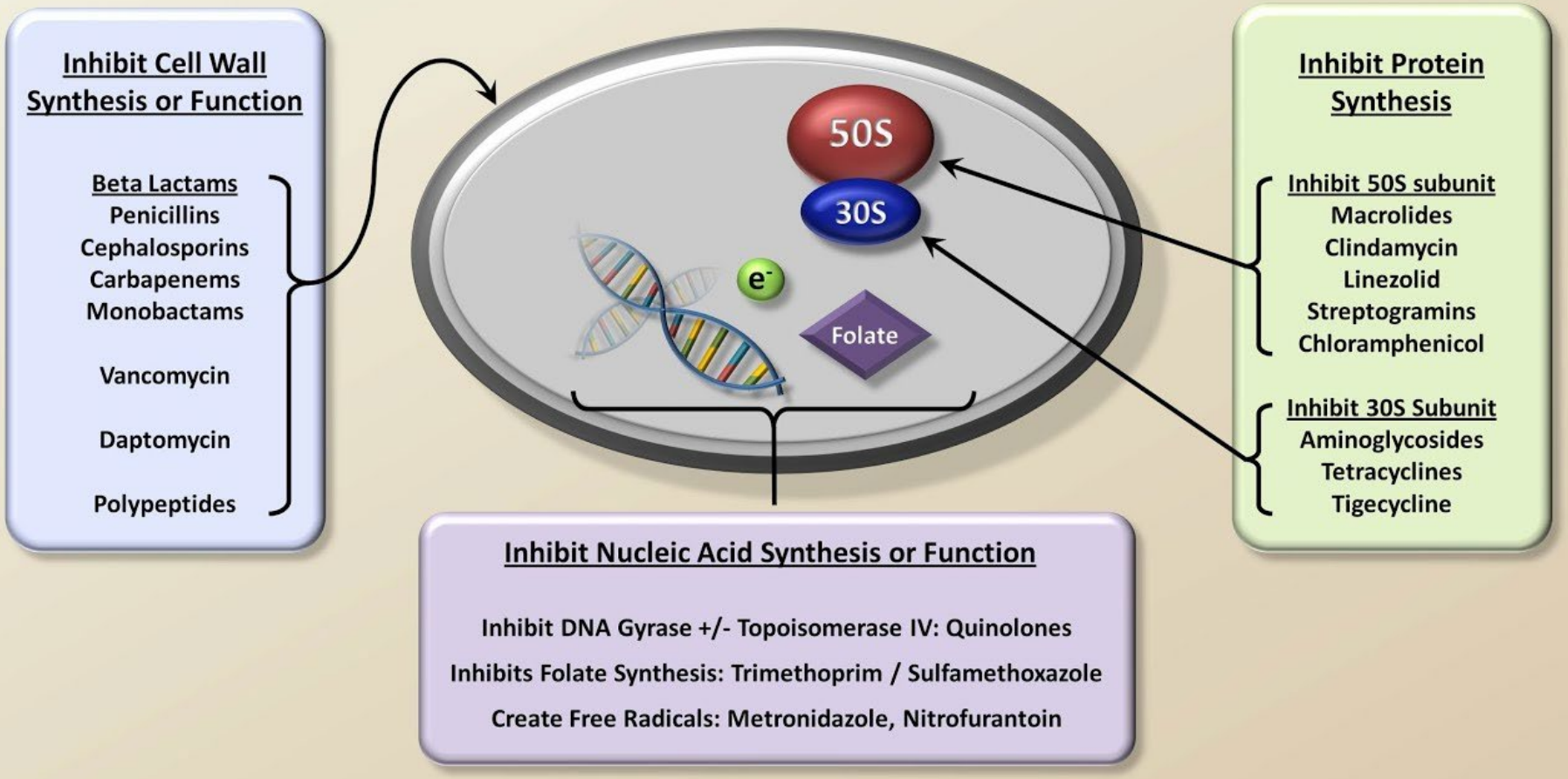
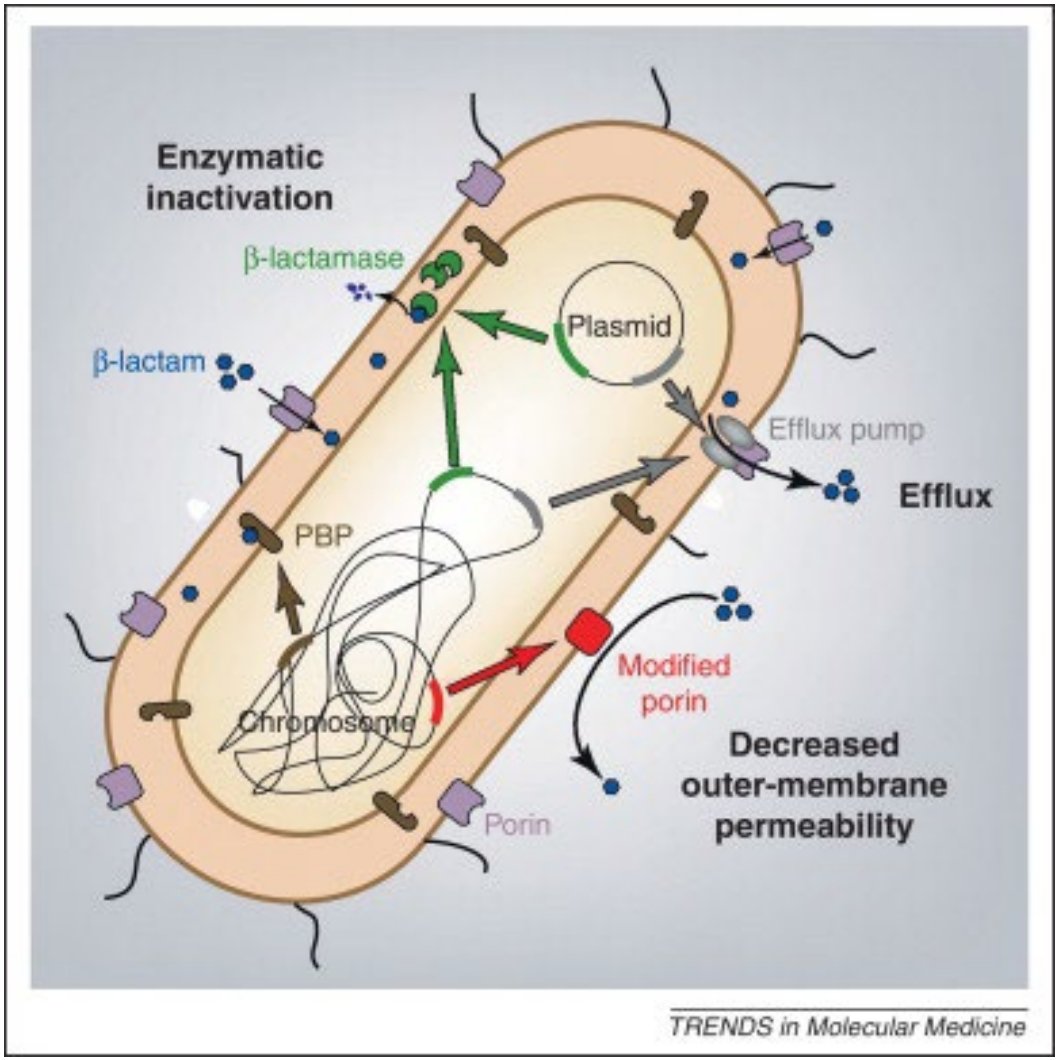
https://www.cdc.gov/drugresistance/about/how-resistance-happens.html

Mechanisms of Antibiotics



B-lactams and B-lactamases



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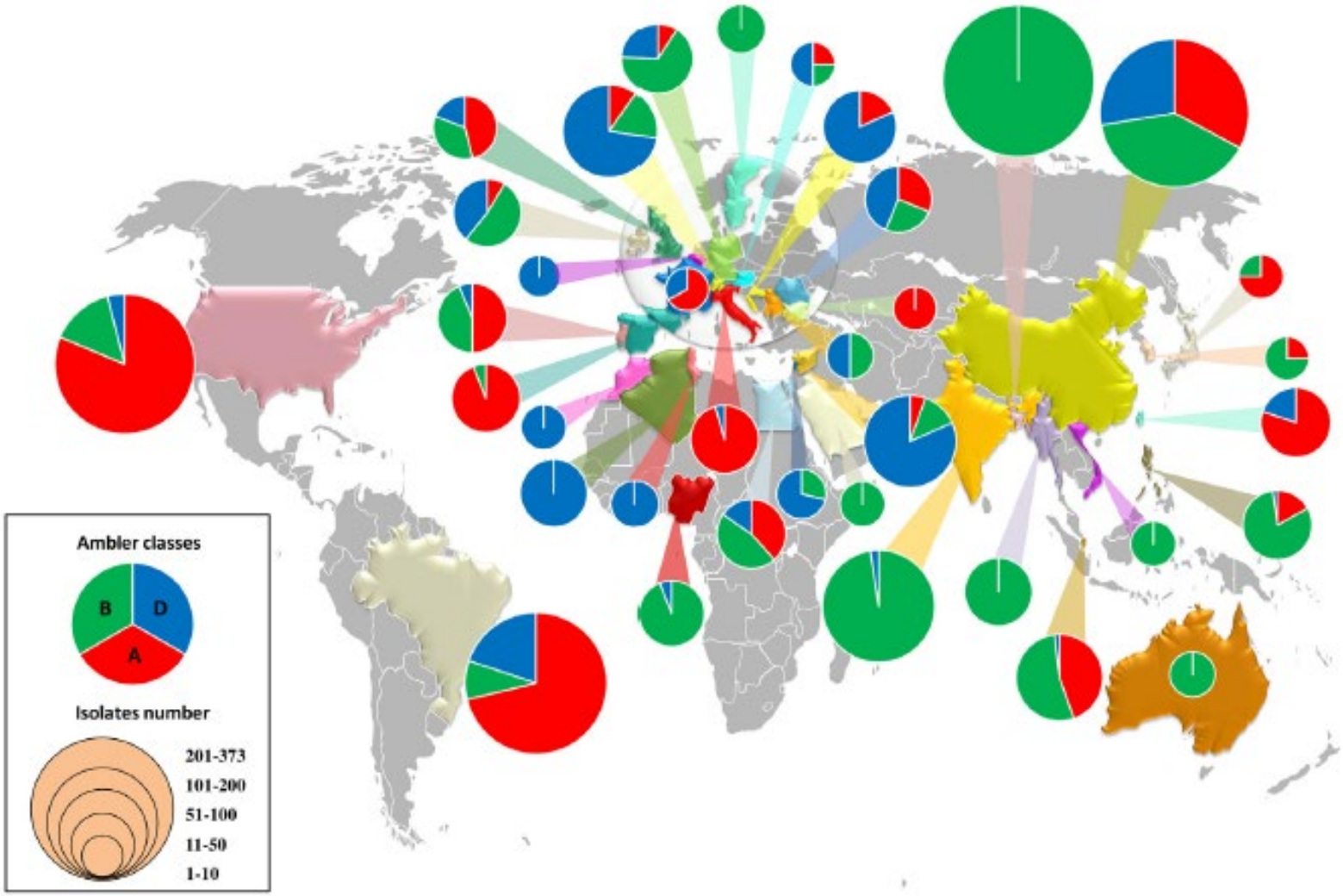
https://www.cell.com/action/showPdf?pii=S1471-4914%2812%2900037-8

Carbapenem-resistant Bacteria (2021)



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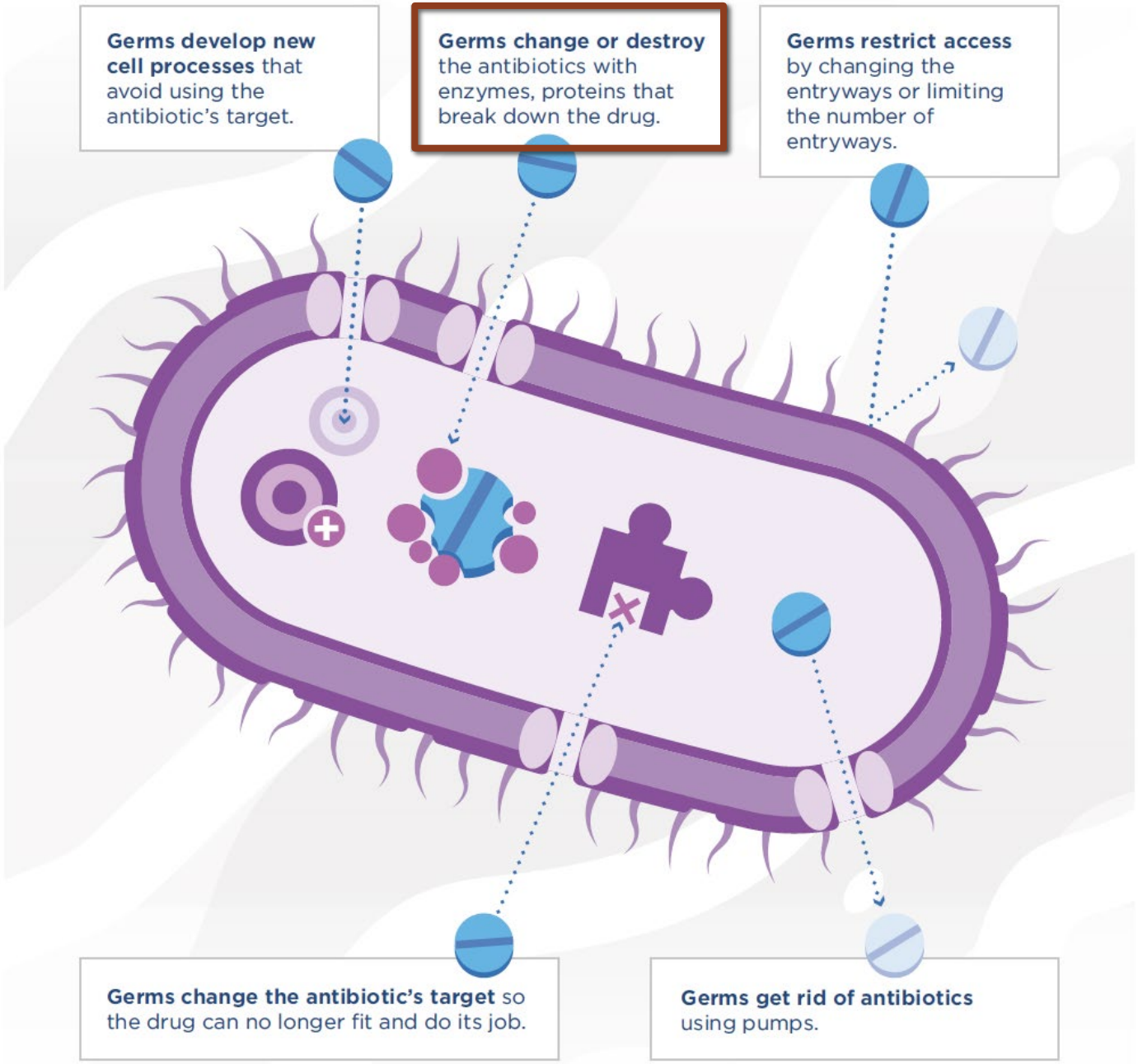
Z. Cherak, L. Loucif, A. Moussi et al. Journal of Global Antimicrobial Resistance 25 (2021) 287–309



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https://www.cdc.gov/drugresistance/about/how-resistance-happens.html

Our Case Study Begins…

- Stanford Administrative Panel on Biosafety (APB)
  - Non-exempt recombinant DNA (NIH Guidelines)
  - Infectious agents

Biosafety Protocol Application Form

Protocol ID :

Title : Detection of BlaC beta-lactamase in BCG & carbapenamase in carbapenamase-expressing bacteria strains

Goal(s) of the project

Development of fluorogenic probes specific for carbapenem-resistant bacteria strains

Methods, assays and experimental procedures to be used

Fluorescent measurement assay will be done. Specifically, the indicated bacteria will be cultured until it reached the log phase (optical density at 600 of 1), designed fluorogenic probes will be added to a series of dilutions of bacteria for fluorescence measurement using a spectrafluorometer.

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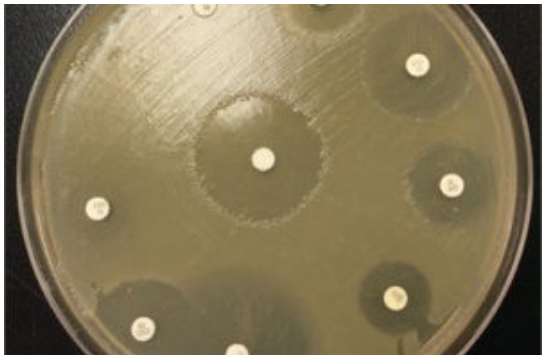
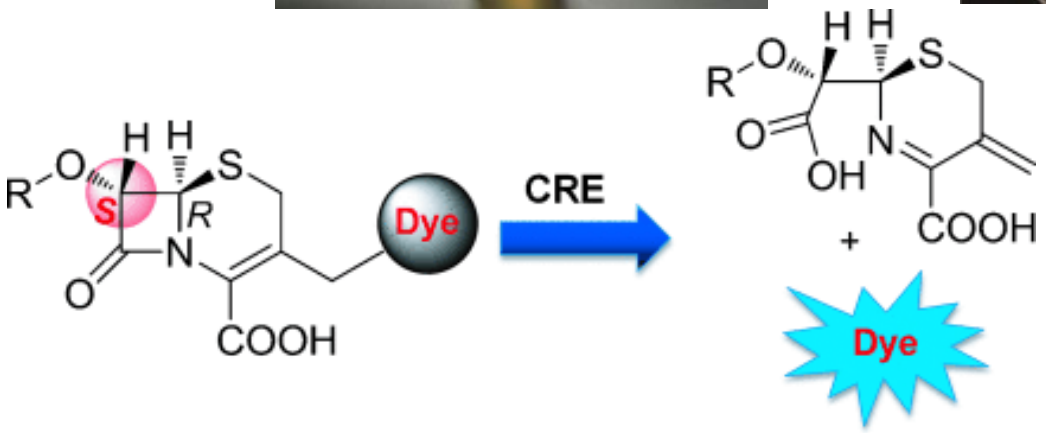
Title : Detection of BlaC beta-lactamase in BCG & carbapenamase in carbapenamase-expressing bacteria strains





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Biosafety Protocol Application Form

Protocol ID :

Title : Detection of BlaC beta-lactamase in BCG & carbapenamase in carbapenamase-expressing bacteria strains

Request 1: Escherichia coli NDM1

Microbiology Results

View in table format Sort by sensitivity results

View in interim format

	patients <18 years of age. RESISTANCE TO AMIKACIN, ERTAPENEM, IMIPENEM, MEROPENEM AND CEFEPIME CONFIRMED. The antimicrobial agent(s) or diagnostic testing device used here is not yet FDA approved and the Clinical and Laboratory Standards Institute (CLSI) interpretive criteria are not available to validate it. MIC results provided are reported as No Interpretation (NI) since neither CLSI nor the FDA has interpretive criteria for this organism and antimicrobial agent(s): E. COLI AND POLYMIXIN B ETEST.
METHOD	KIRBY BAUER
ERTAPENEM	RESISTANT
MEROPENEM	RESISTANT
FOSFOMYCIN	SENSITIVE
IMIPENEM	RESISTANT
AMIKACIN	RESISTANT
SUSCEPTIBILITY	
ORGANISM	>100,000 cfu/ml [Escherichia coli] ID CONSULT RECOMMENDED. This organism harbors resistance to third-generation cephalosporins and/or carbapenems. ***Therapy Note*** In isolates with resistance to 3rd and 4th generation cephalosporins, treatment with beta-lactam/beta-lactamase inhibitor combo drugs may be associated with treatment failure. NOTE: Ciprofloxacin and other fluoroquinolones are not generally recommended for patients <18 years of age. RESISTANCE TO AMIKACIN, ERTAPENEM, IMIPENEM, MEROPENEM AND CEFEPIME CONFIRMED. The antimicrobial agent(s) or diagnostic testing device used here is not yet FDA approved and the Clinical and Laboratory Standards Institute (CLSI) interpretive criteria are not available to validate it. MIC results provided are reported as No Interpretation (NI) since neither CLSI nor the FDA has interpretive criteria for this organism and antimicrobial agent(s): E. COLI AND POLYMIXIN B ETEST.
METHOD	MIC (mcg/ml)
AMPICILLIN	>16 RESISTANT
PIP/TAZOBACTAM	>64 RESISTANT
GENTAMICIN	>8 RESISTANT
TOBRAMYCIN	>8 RESISTANT
AMIKACIN	>32 RESISTANT
CEFEPIME	>16 RESISTANT
CEFOXITIN	>16 RESISTANT
CIPROFLOXACIN	>2 RESISTANT
NITROFURANTOIN	>64 RESISTANT
LEVOFLOXACIN	>4 RESISTANT
MEROPENEM	>8 RESISTANT
AZTREONAM	>16 RESISTANT
CEFTAZIDIME	>16 RESISTANT
CEFTRIAXONE	>32 RESISTANT
IMIPENEM	>8 RESISTANT
POLYMYXIN B	1 NO INTERP
AMPICILLIN/SULBACTAM	>16/8 RESISTANT
TRIMETH-SULFAMETHOX.	>2/38 RESISTANT
TIGECYCLINE	<=2 SENSITIVE

Biosafety Protocol Application Form

Protocol ID :

Title : Detection of BlaC beta-lactamase in BCG & carbapenamase in carbapenamase-expressing bacteria strains

Request 2: Klebsiella pneumonia KPC-3

Microbiology Results

View in table format | Sort by sensitivity results

View in interim format

	in sterile container
CULT/OTHER RSLT:	4+ [Klebsiella pneumoniae] ID consult recommended. This isolate produces an EXTENDED SPECTRUM BETA-LACTAMASE (ESBL). The final susceptibility results reflect clinical efficacy AMIKACIN, POLYMYXIN B, TIGECYCLINE, IMIPENEM, MEROPENEM, and ERTAPENEM MIC'S CONFIRMED BY ETEST. ID CONSULT RECOMMENDED. This organism harbors resistance to carbapenems. 4+ [Klebsiella pneumoniae] - SECOND STRAIN ID consult recommended. This isolate produces an EXTENDED SPECTRUM BETA-LACTAMASE (ESBL). The final susceptibility results reflect clinical efficacy ERTAPENEM MIC DETERMINED BY ETEST Called to: DR.SPAIN 53234, RE: POSSIBLE CARBAPENEM RESISTANCE 2/18/11 1400 Faxed results to Infection Control: 2/18/11 1425 The following antimicrobial agent or diagnostic testing device is not yet FDA approved, and results should be considered investigational only: POLYMYXIN B The Clinical and Laboratory Standards Institute (CLSI) has no standardized susceptibility test for this organism, and MIC results provided will therefore be reported as No Interpretation (NI). POLYMYXIN B Called to: DIANE TSENG, MED STUDENT AT 53234 RE:CARBAPENEMS, 2/20/11 1330 Called to: DR. MICHAEL MA (53234) @1115 2/21/11. RE: CARBAPENEM RESISTANCE. Also faxed Infection Control
REPORT STATUS	FINAL 02/21/2011
SUSCEPTIBILITY	
ORGANISM	4+ [Klebsiella pneumoniae] ID consult recommended. This isolate produces an EXTENDED SPECTRUM BETA-LACTAMASE (ESBL). The final susceptibility results reflect clinical efficacy AMIKACIN, POLYMYXIN B, TIGECYCLINE, IMIPENEM, MEROPENEM, and ERTAPENEM MIC'S CONFIRMED BY ETEST. ID CONSULT RECOMMENDED. This organism harbors resistance to carbapenems.
METHOD	MIC (mcg/ml)
AMPICILLIN	>16 RESISTANT
GENTAMICIN	>8 RESISTANT
TOBRAMYCIN	>8 RESISTANT
AMIKACIN	64 RESISTANT
CEFEPIME	>16 RESISTANT
CEFUROXIME (IV)	>16 RESISTANT
CIPROFLOXACIN	>2 RESISTANT
TRIMETH-SULFAMETHOX.	>2/38 RESISTANT
AZTREONAM	>16 RESISTANT
IMIPENEM	>32 RESISTANT
CEFTRIAXONE	>32 RESISTANT
CEFOXITIN	>16 RESISTANT
LEVOFLOXACIN	>4 RESISTANT
MEROPENEM	>32 RESISTANT
CEFTAZIDIME	>16 RESISTANT
ERTAPENEM	>32 RESISTANT
TIGECYCLINE	4 INTERMED.
CEFTAZIDIME/CLAV.ACID	>2 NO INTERP <<not reported>>
CEFOTAXIME	>32 RESISTANT
CEFOTAXIME/CLAV.ACID	4 NO INTERP <<not reported>>
CEFAZOLIN	>16 RESISTANT
POLYMYXIN B	2 NO INTERP

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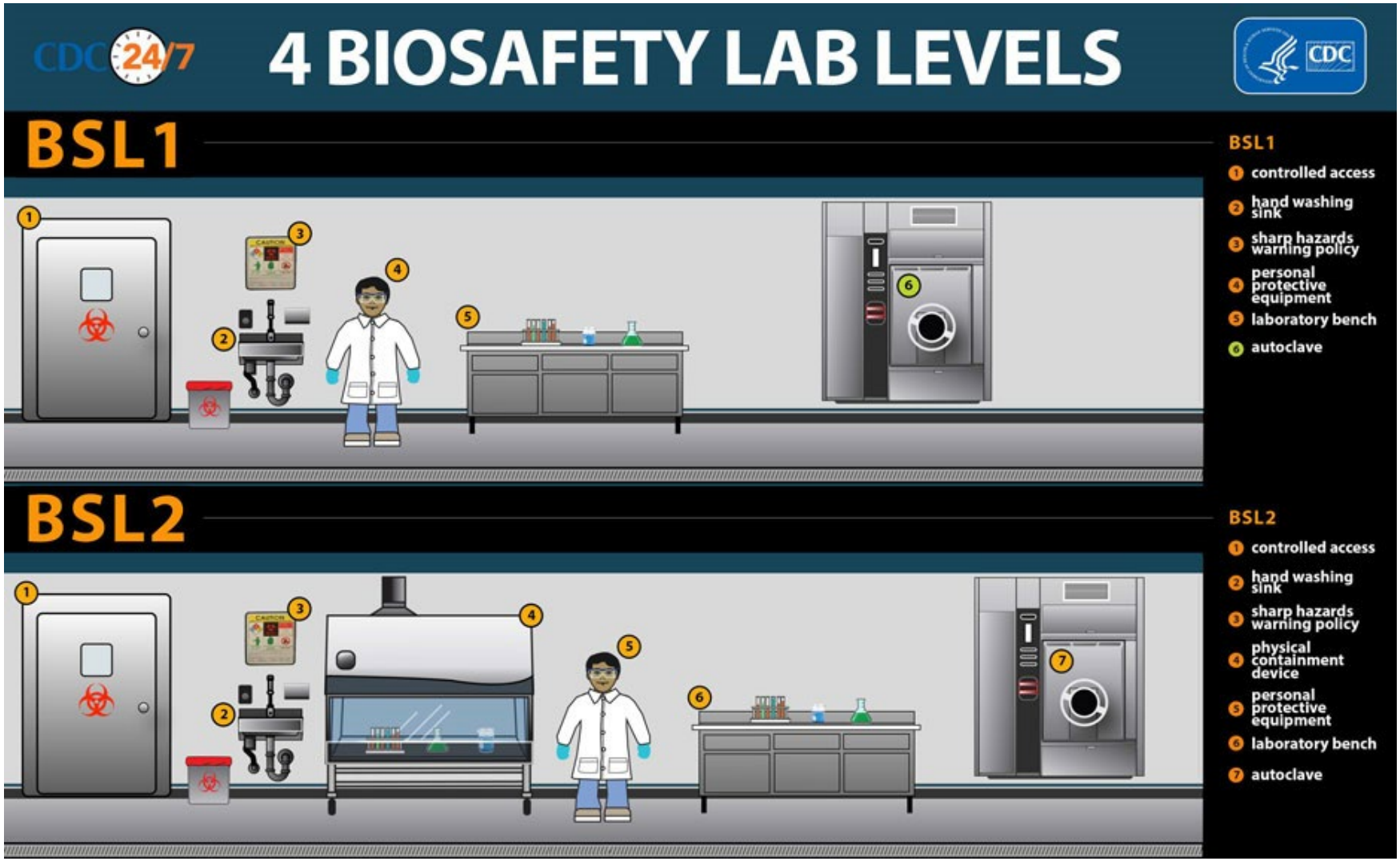
Biosafety Protocol Application Form	Protocol ID :	
	Title :	Detection of BlaC beta-lactamase in BCG & carbapenamase in carbapenamase-expressing bacteria strains

- Agents:
  - E. coli with minimal treatment options
  - K. pneumonia with NO treatment options
- Processes:
  - High level with few details
  - Lack of BSL2 safeguards incorporated
- Personnel:
  - Little or no experience in working with pathogenic organisms
  - Previous work with bacterial culture for protein expression (BSL1)
  - Not trained at Biosafety Level 2 (BSL2)

Biosafety Level 1 and 2 Facilities



https://www.cdc.gov/cpr/infographics/biosafety.htm

Good Microbial Technique (and some not so good)

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Biosafety Protocol Application Form

Protocol ID :

Title : Detection of BlaC beta-lactamase in BCG & carbapenamase in carbapenamase-expressing bacteria strains

Biosafety Protocol Application Form	Protocol ID :	
	Title :	Detection of BlaC beta-lactamase in BCG & carbapenamase in carbapenamase-expressing bacteria strains

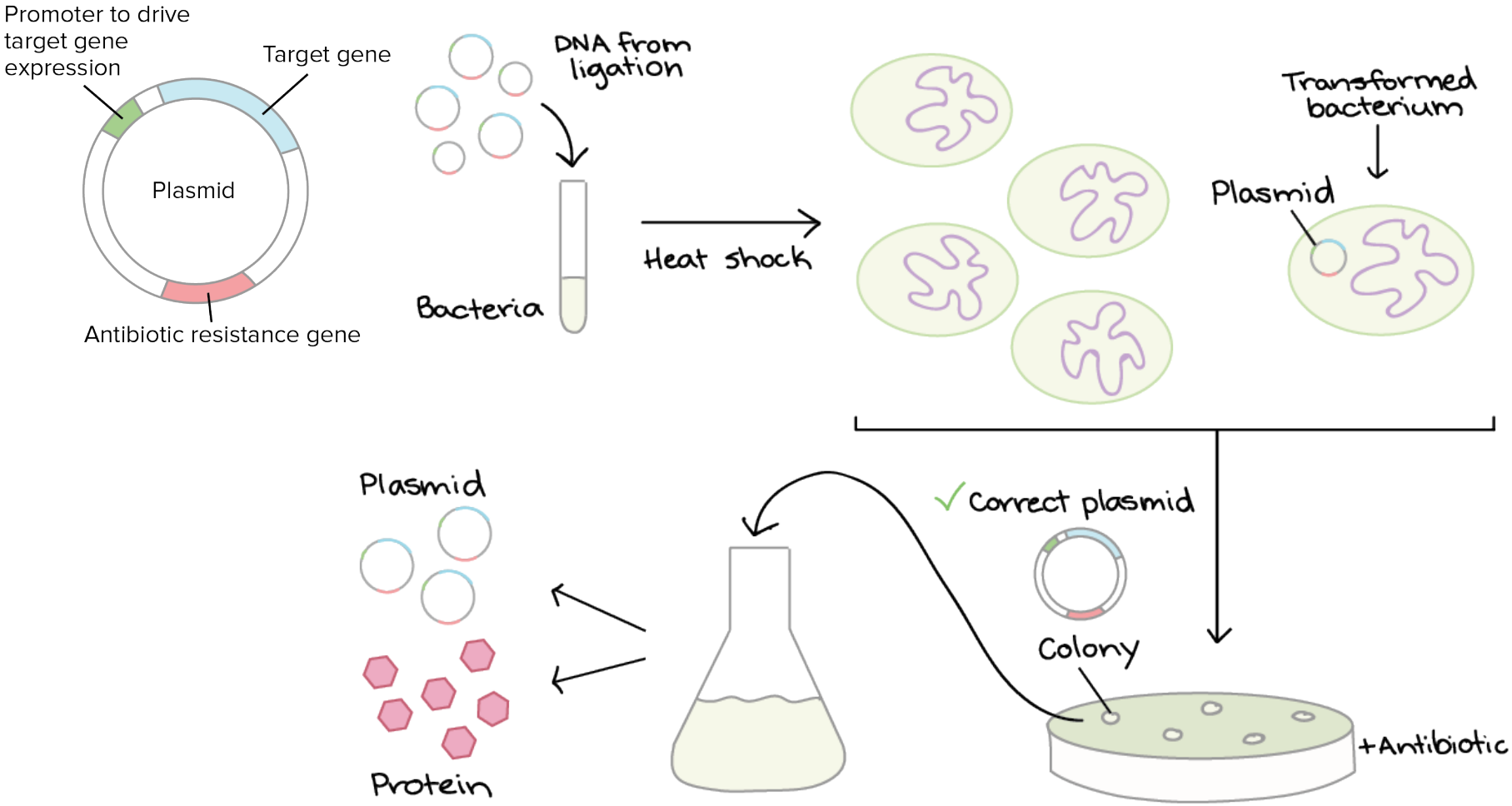
- Does this have to be done with these bacteria?
  - Yes, we want to test clinically relevant samples
- How can you gain experience with microbial technique?
  - The Clinical Micro lab folks will teach us
    - Will they? Trust but verify…
- What safe-guards can you put in place?
  - Appropriate BSL2 procedures and practices

Biosafety Best Practice

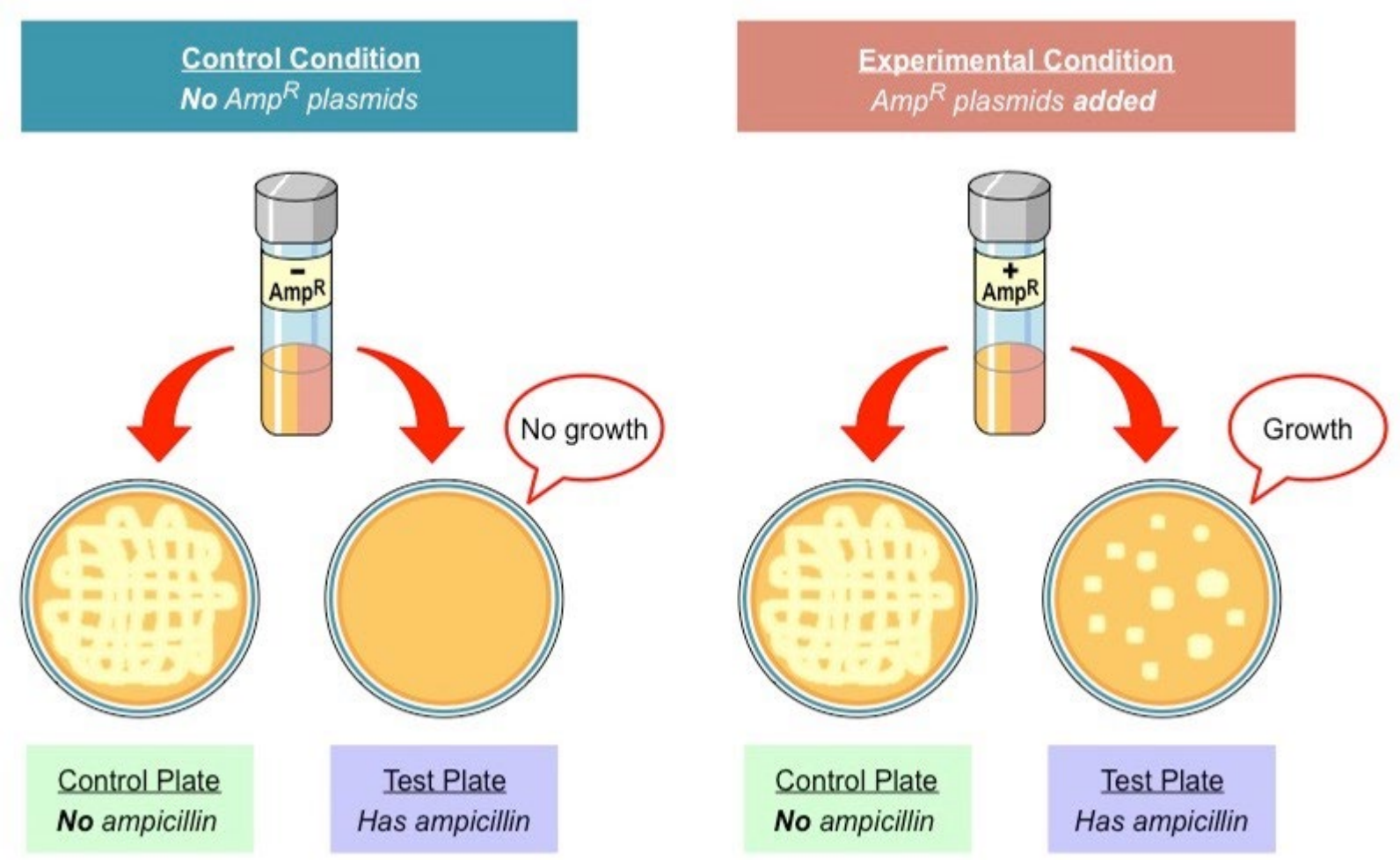
Don’t learn new techniques or processes with biohazardous agents if you can try it first with non-biohazardous agents!

Work with non-pathogenic E. coli before you work with Enteropathogenic E. coli!

Cloning E. coli?



Antibiotic Resistance on Purpose!?!?

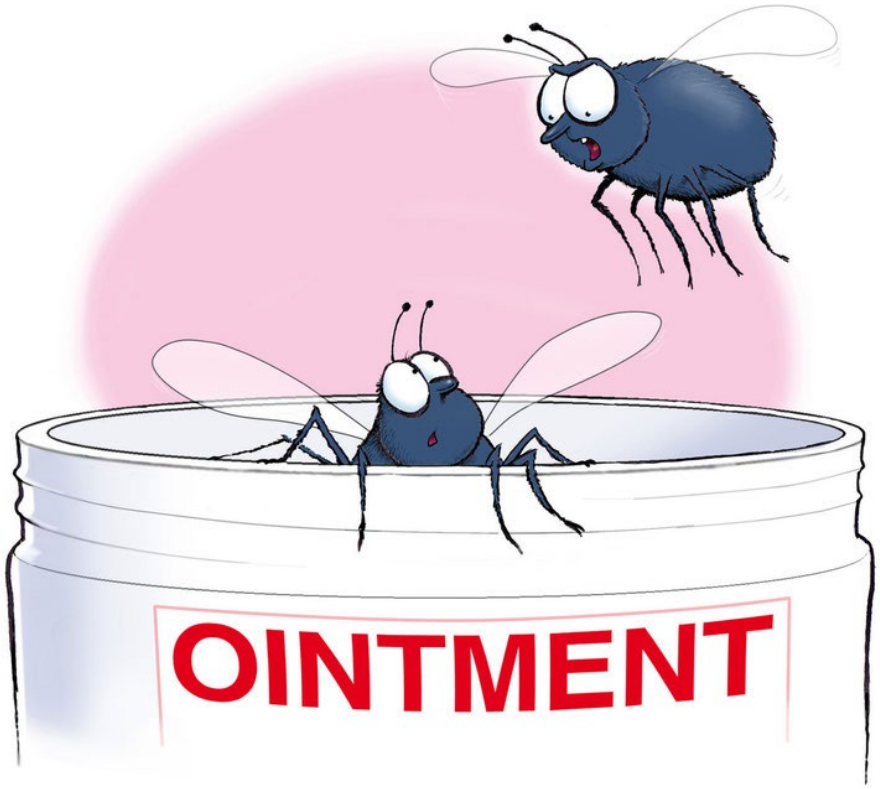


Biosafety Protocol Application Form	Protocol ID :	
	Title :	Detection of BlaC beta-lactamase in BCG & carbapenamase in carbapenamase-expressing bacteria strains

Can they clone the carbapenamase resistance gene into standard cloning E. coli?

YES!

Except the NIH Guidelines may not allow this!



"How many times have I got to tell you?..
Stay out of that stuff!"

CartoonStock.com

NIH Guidelines for Research involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

Section III-A. Experiments that Require NIH Director Approval and Institutional Biosafety Committee Approval Before Initiation (See Section IV-C-1-b-(1), Major Actions).

Section III-A-1. Major Actions under the *NIH Guidelines*

Experiments considered as *Major Actions* as defined in Section III-A-1-a under the *NIH Guidelines* cannot be initiated without submission of relevant information on the proposed experiment to the Office of Science Policy, National Institutes of Health, preferably by e-mail to: NIHGuidelines@od.nih.gov, the publication of the proposal in the *Federal Register* for a minimum of 15 days of comment, and specific approval by NIH. The containment conditions or stipulation requirements for such experiments will be set by NIH at the time of approval. Such experiments require Institutional Biosafety Committee approval before initiation. Specific experiments already approved are included in Appendix D, *Major Actions Taken under the NIH Guidelines*.

Section III-A-1-a. The deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally (see Section V-B, *Footnotes and References of Sections I-IV*), if such acquisition could compromise the ability to control disease agents in humans, veterinary medicine, or agriculture, will require NIH Director approval.

Consideration should be given as to whether the drug resistance trait to be used in the experiment would render that microorganism resistant to the primary drug available to and/or indicated for certain populations, for example children or pregnant women.

At the request of an Institutional Biosafety Committee, NIH OSP will make a determination regarding whether a specific experiment involving the deliberate transfer of a drug resistance trait falls under Section III-A-1-a and therefore requires NIH Director approval. An Institutional Biosafety Committee may also consult with NIH OSP regarding experiments that do not meet the requirements of Section III-A-1-a but nonetheless raise important public health issues.

NIH Guidelines for Research involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

Deliberate transfer?

Section III-A-1-a. The deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally (see Section V-B, *Footnotes and References of Sections I-IV*), if such acquisition could compromise the ability to control disease agents in humans, veterinary medicine, or agriculture, will require NIH Director approval.

Compromise the ability to control disease?

NIH Guidelines for Research involving Recombinant or Synthetic Nucleic Acid Molecules (NIH Guidelines)

Section III-A-1-a. The deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally (see Section V-B, *Footnotes and References of Sections I-IV*), if such acquisition could compromise the ability to control disease agents in humans, veterinary medicine, or agriculture, will require NIH Director approval.

Section V-B. Section III, *Experiments Covered by the NIH Guidelines*, describes a number of places where judgments are to be made. In all these cases, the Principal Investigator shall make the judgment on these matters as part of his/her responsibility to "make the initial determination of the required levels of physical and biological containment in accordance with the *NIH Guidelines*" (see Section IV-B-7-c-(1)). For cases falling under Sections III-A through III-E, *Experiments Covered by the NIH Guidelines*, this judgment is to be reviewed and approved by the Institutional Biosafety Committee as part of its responsibility to make an "independent assessment of the containment levels required by the *NIH Guidelines* for the proposed research" (see Section IV-B-2-b-(1), *Institutional Biosafety Committee*). The Institutional Biosafety Committee may refer specific cases to NIH OSP as part of NIH OSP's functions to "provide advice to all within and outside NIH" (see Section IV-C-2).

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Request 1: Escherichia coli NDM1

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METHOD	KIRBY BAUER
ERTAPENEM	RESISTANT
MEROPENEM	RESISTANT
FOSFOMYCIN	SENSITIVE
IMIPENEM	RESISTANT
AMIKACIN	RESISTANT
SUSCEPTIBILITY	
ORGANISM	>100,000 cfu/ml [Escherichia coli] ID CONSULT RECOMMENDED. This organism harbors resistance to third-generation cephalosporins and/or carbapenems. ***Therapy Note*** In isolates with resistance to 3rd and 4th generation cephalosporins, treatment with beta-lactam/beta-lactamase inhibitor combo drugs may be associated with treatment failure. NOTE: Ciprofloxacin and other fluoroquinolones are not generally recommended for patients <18 years of age. RESISTANCE TO AMIKACIN, ERTAPENEM, IMIPENEM, MEROPENEM AND CEFEPIME CONFIRMED. The antimicrobial agent(s) or diagnostic testing device used here is not yet FDA approved and the Clinical and Laboratory Standards Institute (CLSI) interpretive criteria are not available to validate it. MIC results provided are reported as No Interpretation (NI) since neither CLSI nor the FDA has interpretive criteria for this organism and antimicrobial agent(s): E. COLI AND POLYMIXIN B ETEST.
METHOD	MIC (mcg/ml)
AMPICILLIN	>16 RESISTANT
PIP/TAZOBACTAM	>64 RESISTANT
GENTAMICIN	>8 RESISTANT
TOBRAMYCIN	>8 RESISTANT
AMIKACIN	>32 RESISTANT
CEFEPIME	>16 RESISTANT
CEFOXITIN	>16 RESISTANT
CIPROFLOXACIN	>2 RESISTANT
NITROFURANTOIN	>64 RESISTANT
LEVOFLOXACIN	>4 RESISTANT
MEROPENEM	>8 RESISTANT
AZTREONAM	>16 RESISTANT
CEFTAZIDIME	>16 RESISTANT
CEFTRIAXONE	>32 RESISTANT
IMIPENEM	>8 RESISTANT
POLYMYXIN B	1 NO INTERP
AMPICILLIN/SULBACTAM	>16/8 RESISTANT
TRIMETH-SULFAMETHOX.	>2/38 RESISTANT
TIGECYCLINE	<=2 SENSITIVE

E. coli NDM1

Section III-A-1-a. The deliberate transfer of a drug resistance trait to microorganisms that are not known to acquire the trait naturally (see Section V-B, *Footnotes and References of Sections I-IV*), if such acquisition could compromise the ability to control disease agents in humans, veterinary medicine, or agriculture, will require NIH Director approval.

- Trait acquired naturally
- Already evident in clinical isolates
- Yes, could compromise the ability to control disease
  - But it's already compromised!
  - This is why we want a quick identification method!

- Cloning E. coli will remain susceptible to multiple other antibiotics

Biosafety Protocol Application Form	Protocol ID :	
	Title :	Detection of BlaC beta-lactamase in BCG & carbapenamase in carbapenamase-expressing bacteria strains

- Research group must partner with the Clinical Microbiology group to learn technique

- Biosafety also worked with the research group to ensure the lab space was appropriate
  - Aware of safety precautions
  - Shared space
    - Educate others in the area
    - Appropriate signage

- Three-month initial approval
  - Only cloning E. coli transformed with resistance plasmid
  - Report back to APB before requesting additional strains

Research Success!

Science Translational Medicine

Current Issue First release papers

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Rapid and specific labeling of single live *Mycobacterium tuberculosis* with a dual-targeting fluorogenic probe

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Fluorogenic Probes with Substitutions at the 2 and 7 Positions of Cephalosporin are Highly BlaC-Specific for Rapid *Mycobacterium tuberculosis* Detection†

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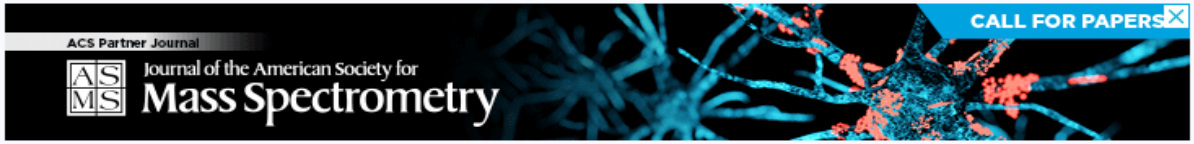
Engineering the Stereochemistry of Cephalosporin for Specific Detection of Pathogenic Carbapenemase-Expressing Bacteria†

Biomicrofluidics. 2015 Aug 20;9(4):044120. doi: 10.1063/1.4928879. eCollection 2015 Jul.

Quantitative detection of cells expressing BlaC using droplet–based microfluidics for use in the diagnosis of tuberculosis

JOURNAL ARTICLE

Real–Time Imaging of *Mycobacterium tuberculosis* Using a Novel Near–Infrared Fluorescent Substrate



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A Fluorogenic Trehalose Probe for Tracking Phagocytosed *Mycobacterium tuberculosis*

Visualizing the dynamics of tuberculosis pathology using molecular imaging

Stanford | Environmental Health & Safety

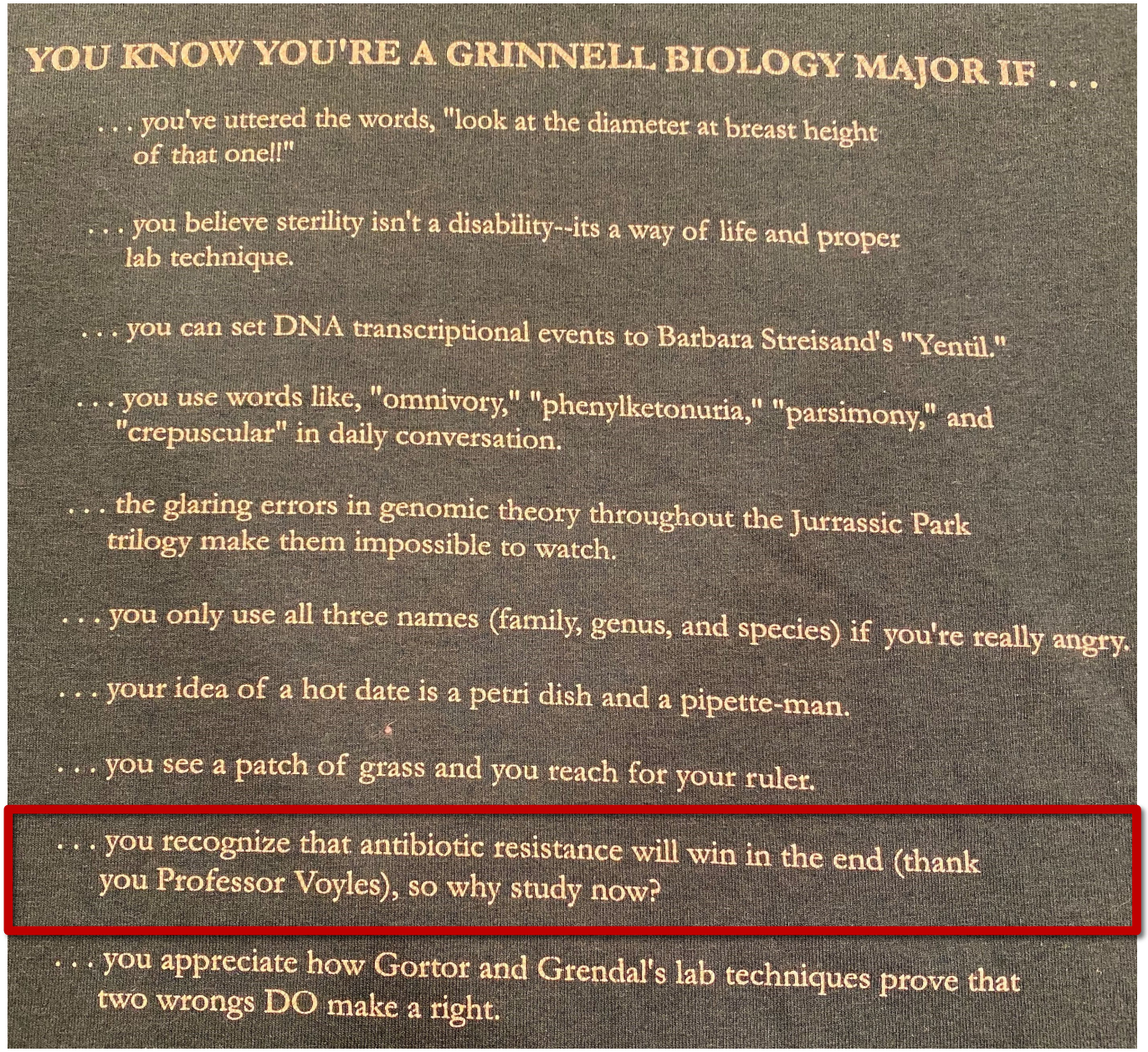
The War on Microbes: The Future

- Nosocomial (hospital) infections remain a problem
  - Handwashing, good hygiene
- Use antibiotics appropriately
- Use in combination where necessary

- Explore alternatives:
  - Novel molecules
  - Analogs of current molecules
  - Phage therapy
  - Anti-sense RNA
  - Microbiome replacement / probiotic strategies
  - Small molecules
  - Antimicrobial peptides
  - Monoclonal antibodies
  - Drug delivery methods
  - Vaccines

Antimicrobial Resistance: Will it Win in the End?

- Work within the bounds of regulations/guidelines and common sense
- Safety is paramount, but can be learned
- Work WITH your researchers to find ways to do work safely
- Be ready to support cross-field research


YOU KNOW YOU'RE A GRINNELL BIOLOGY MAJOR IF . . .
. . . you've uttered the words, "look at the diameter at breast height of that one!!"
. . . you believe sterility isn't a disability--its a way of life and proper lab technique.
. . . you can set DNA transcriptional events to Barbara Streisand's "Yentil."
. . . you use words like, "omnivory," "phenylketonuria," "parsimony," and "crepuscular" in daily conversation.
. . . the glaring errors in genomic theory throughout the Jurrassic Park trilogy make them impossible to watch.
. . . you only use all three names (family, genus, and species) if you're really angry.
. . . your idea of a hot date is a petri dish and a pipette-man.
. . . you see a patch of grass and you reach for your ruler.
. . . you recognize that antibiotic resistance will win in the end (thank you Professor Voyles), so why study now?
. . . you appreciate how Gortor and Grendal's lab techniques prove that two wrongs DO make a right.

Questions?

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