



# The Other Side of Stewardship: Antibiotic Roots in the Midwest

Kellie Wark, MD, MPH | November 15, 2023



# Presenters

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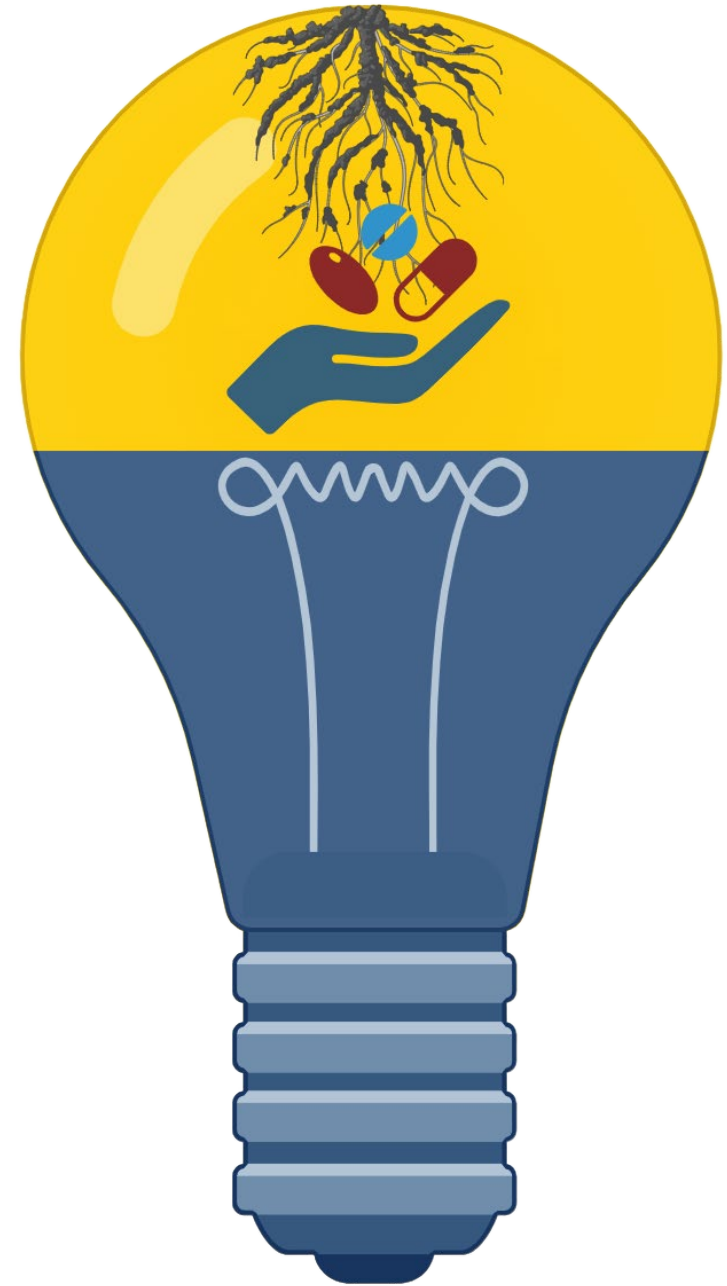
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# Objectives

1. Describe the historical importance of antibiotics.
2. Identify how Midwest played a key role in antibiotic discoveries.
3. Encourage antibiotic research and development.





# The Power of Antibiotics

Disease	Pre-Antibiotic Death Rate	Death with Antibiotics	Change in Death
Community Associated Pneumonia	35%	10%	-25%
Hospital Associated Pneumonia	60%	30%	-30%
Endocarditis	100%	25%	-75%
Gram negative bacteremia	80%	10%	-70%
Meningitis	>80%	<20%	-60%
Skin infection	11%	<0.5%	-10%
Compare to....			
Heart attack with fibrinolytics or aspirin			-3%



# Potpourri of Pneumonia Treatment Pre-Antibiotics

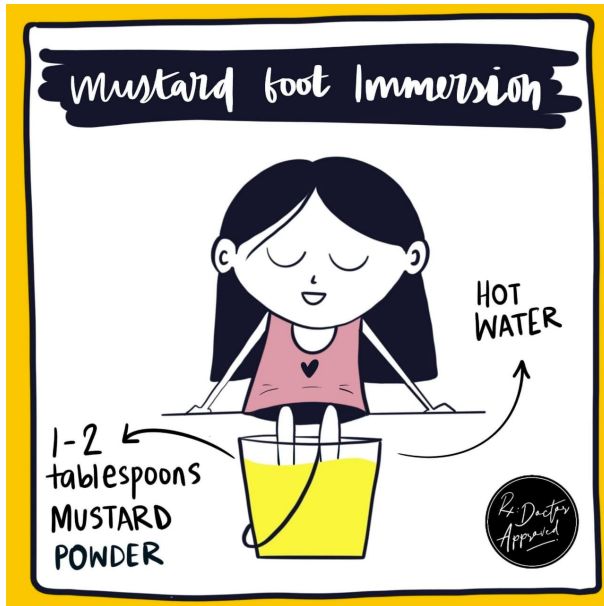


Image Source: [Doctor Approved](#) (a Naturopathic Doctor website)

- Cold compresses and hot mustard foot baths
- Inhalations of chloroform
- Subcutaneous injections gold, silver, platinum
- Oral mercury, quinine or digitalis
- Mercury chloride to “clean out the intestinal tract”
- “Two or three ounces of good whiskey” recommended by William Osler in 1901 Edition of Principles & Practice of Medicine
- Bloodletting and Leeching remained in Osler’s 1942 Edition



# Bloodletting

- Four humors (blood, phlegm, black bile, yellow bile) must remain in balance to preserve health
- Infection thought to be caused by an excess of blood
- Recommended by physicians, but the “cutter’s art” was below their station and performed by barbers or barber-surgeons
- Barbers used to place congealed putrid blood in their storefront until London law passed stating “no barbers shall be so bold or so hardy as to put blood in their windows”
- Red and white striped pole advertised bleeding services





# Modern Era: Pneumococcal serum

1881 George Sternberg and Louis Pasteur independently discovered *S. pneumoniae*

- Dr. Sternberg was also a paleontologist, stationed as captain at Ft. Riley, Ft. Hays and Ft. Harker (Ellsworth) where there was a cholera outbreak, he responded to, his wife joined him and died
- Known as the American Father of Bacteriology



## ASIATIC CHOLERA!

Cholera is an intestinal disease spread when infected human waste comes into contact with water or food consumed by others. It first appeared at Fort Harker in the early summer of 1867. A civilian living about a mile from the fort and employed by the fort's beef contractor was stricken and died on June 28. Private George Groom, a Black soldier with the 38th U.S. Infantry enroute to New Mexico died the next day.

Little was known about the cause or treatment of cholera in the mid-1800s. As a result, the disease spread quickly and the mortality rate was high. Cholera soon spread to other troops stationed at the fort, civilian employees at the post, civilians traveling through, and settlers in the vicinity.

Post surgeons did not know how the disease was brought to Fort Harker. Surgeon J. W. Brewer argued that conditions at the fort were conducive to the disease. Trash, food refuse, and dead animals had been allowed to collect

at once taken to remedy these evils; a strict system of policing was inaugurated; the camps were all moved to new grounds, and disinfectants were procured and freely used. The men were in wedge tents, from two to four in a tent. On my recommendation a hospital tent was pitched for the use of the sick in the quarters of each company, (for slight cases of diarrhea, etc.). The hospital patients were all treated in hospital tents, which were pitched about fifty yards in rear of the hospital. Convalescent and uncertain cases were kept in separate tents from the cholera patients. The discharges from patients were all disinfected as soon as passed.

In addition to the surgeons, the sick were cared for by a number of nurses, attendants, and enlisted hospital stewards, the majority of whom were Black. Two priests and several Sisters of Mercy arrived from Fort Leavenworth to nurse the disease victims.

According to reports of the post surgeons, 892 cases of cholera occurred at Fort Harker between late June and August 1867. The deaths of 46 soldiers were attributed to the disease. Many of these soldiers were encamped at or near the fort but were not part of the command assigned to Fort Harker. In addition, at least 83 cases and 29 deaths were reported during June and July among local citizens and civilian employees. Soldiers carrying supplies, escorting stages, and patrolling the trails spread the disease across the region. The disease finally was brought under control in the fall, as much by the change in weather as by anything that the military doctors could do.

The police [sanitation] of the camps was not good when cholera first made its appearance. Some of the company sinks [privies] were in wretched condition, and there were several offensive holes about the post where slops and garbage from the kitchen had been thrown. Measures were

Surgeon George M. Sternberg

Hospital Tent

FOR POST & FIELD HOSPITAL

KANSAS FRONTIER FORTS



# Modern Era: Pneumococcal serum

- 1895 pneumococcal serum appeared in H.K Mulford catalog
- 1913 serum used to treat 19 patients with pneumonia



Every dose furnished in Aseptic Glass Syringe with sterile needle, ready for instant use.

Pneumonia mortality with serum and without		
<i>S. pneumoniae</i> serotype	Serum	No serum
Serotype 1	13%	22%
Serotype 2	28%	40%
Serotype 3	40%	40%



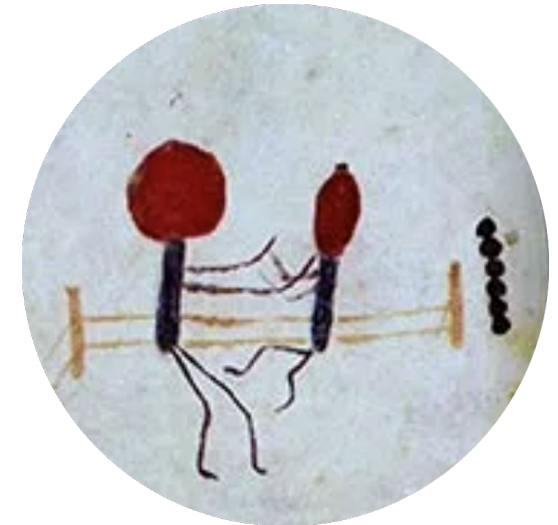
# Penicillin's Path to Production



Fleming's Laboratory Museum, St Mary's Hospital, London UK  
Floor below: fungal lab of Dr. CJ La Touche



Fleming's Petri Dish Artwork





# Penicillin's Path to Production

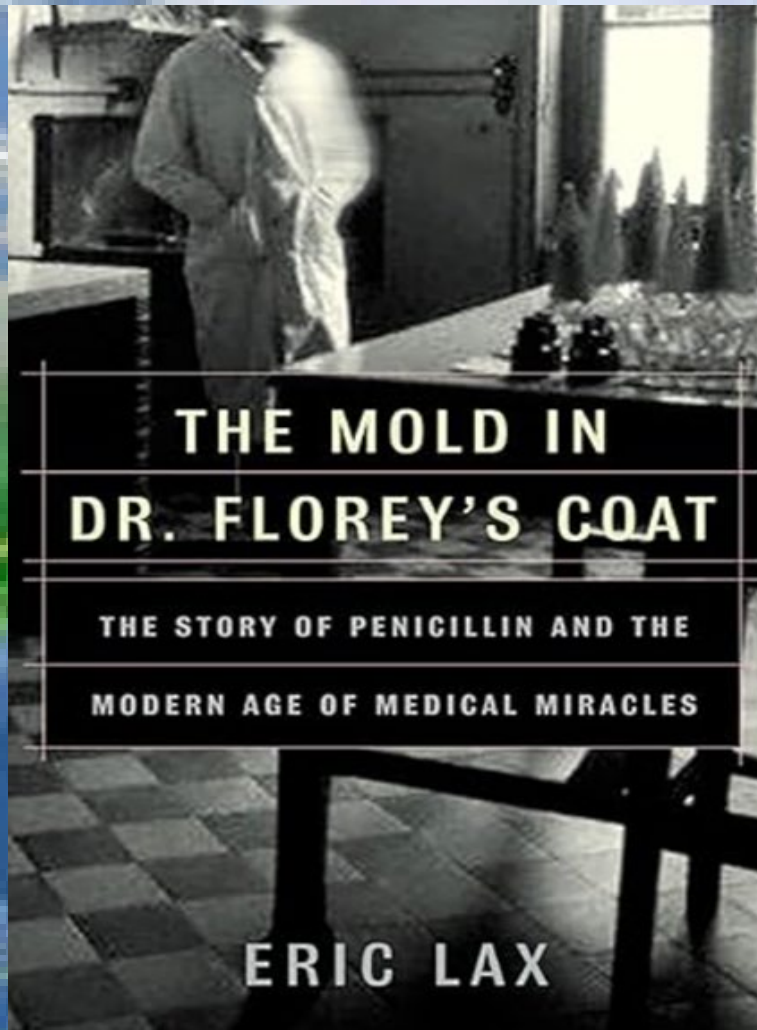
Howard Florey and Earnst Chain's  
Oxford Group

**“The mold is as temperamental  
as an opera singer, the yields  
are low, isolation is difficult,  
extraction is murder, the  
purification invites disaster, and  
the assay is unsatisfactory.”**

- John Smith







Peoria,  
Illinois

Oxford,  
England

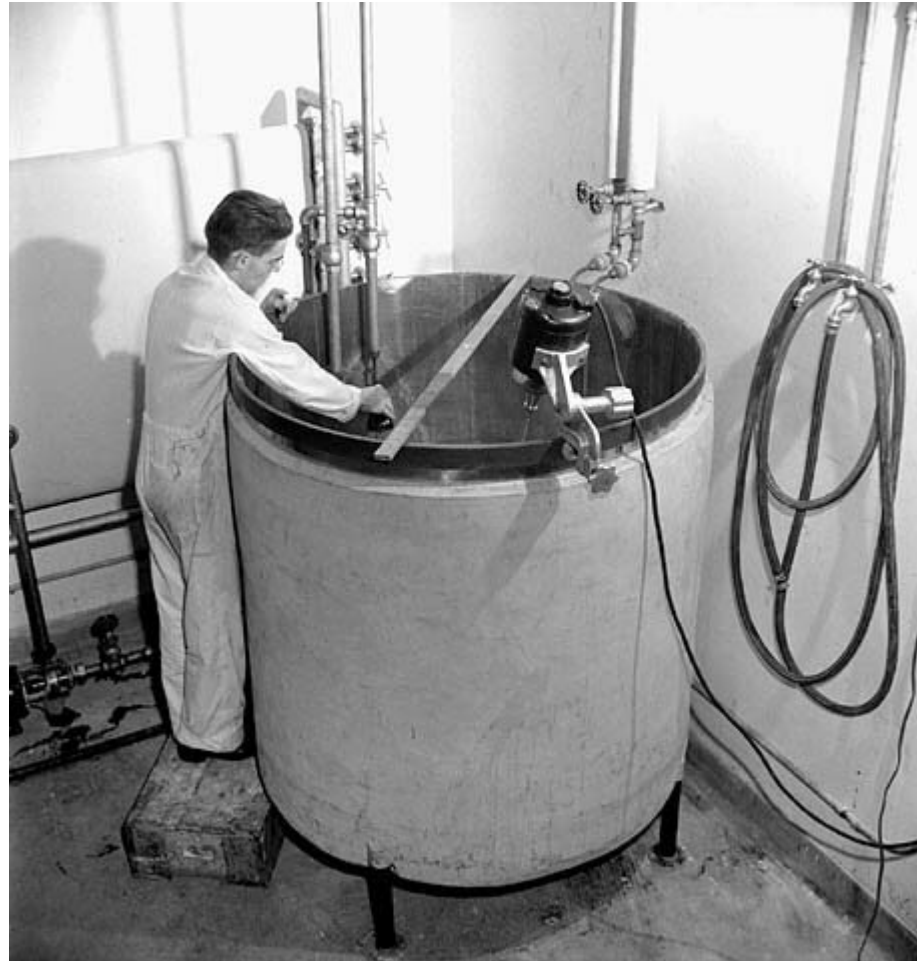


# Penicillin's Path to Production



Dr. Andrew Moyer's lab

Penicillin fermentation  
deep vat process



From a Spoiled Cantaloupe in Peoria...  
*the best of 100,000 strains of Penicillium*

"Moldy Mary"

[hhistory.com/2016/08/andrew-j-moyer-penicillin-pioneer.html](http://hhistory.com/2016/08/andrew-j-moyer-penicillin-pioneer.html)  
Gaynes R., Emerg Infect Dis; 2017 May; 23(5): 849–853.  
[peoriamagazine.com/article/moldy-mary-or-simple-messenger-girl](http://peoriamagazine.com/article/moldy-mary-or-simple-messenger-girl)

*To protect and improve the health and environment of all Kansans*



# Penicillin's Path to Production

- 1942: 10 patients treated with American-made penicillin; distribution determined by penicillin “czar” National Research Council’s Dr. Chester Keefer
- 1943: a total of 300 patients had been treated
- 1944: production in US increased from 21 billion units (1943) → 1.6 trillion units
- 1945: penicillin estimated to have saved 12-15% Allied soldiers
- March 15, 1945: distributors allowed to sell through normal trade channels



# Streptomycin - the first Aminoglycoside



Grad student Albert Schatz working in his Rutgers basement lab



Home / News & Opinion

## New Jersey Makes *Streptomyces griseus* Its Official State Microbe

Governor Phil Murphy signs a bill honoring the bacterium discovered in his state's soil, now known for its antibiotic compounds used to treat tuberculosis.

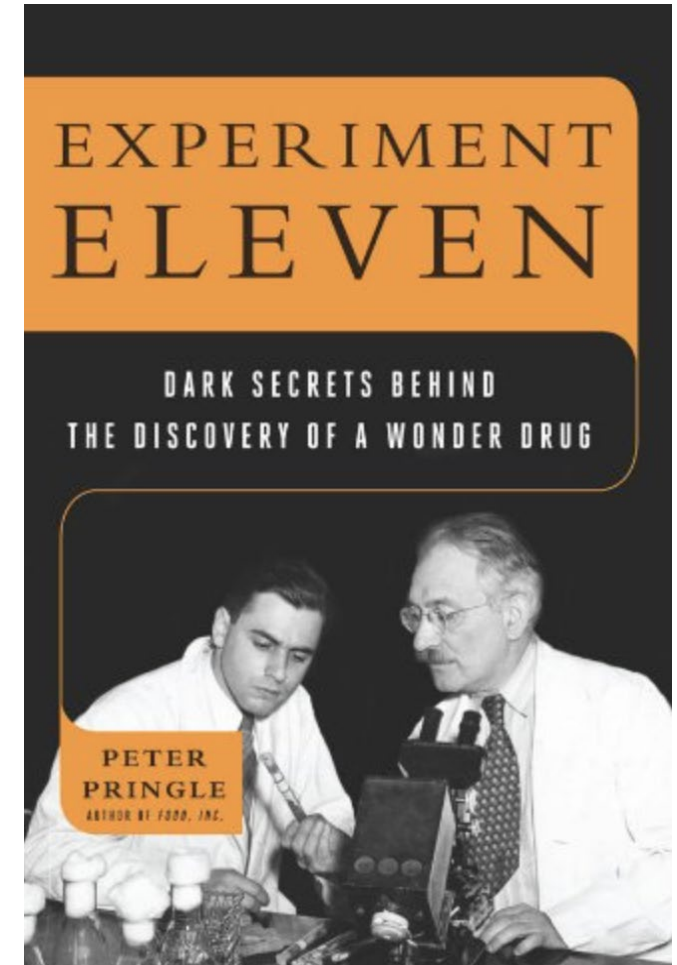
Chia-Yi Hou

May 13, 2019 | 2 min read



# Streptomycin - the first Aminoglycoside

- William Feldman and Corwin Hinshaw from Mayo visited in 1943 presenting an opportunity for TB clinical trial
- Waksman assigned this task to grad student Albert Schatz (and rarely visited him where he was delegated to the basement to avoid researchers from becoming ill from TB exposure)
- Oct. 19, 1943 - 23-year-old Schatz
  - Isolated streptomycin in the basement,
  - Where he frequently slept overnight
  - Fermenting 1L flasks with *S. griseus*





# Streptomycin - The First Aminoglycoside



- April 1945 Northern mountains of Italy, Bob Dole was hit by mortar (after volunteering following his first year at KU where he was pre-med) evacuated stateside to Winter General Army Hospital in Topeka.
- Transferred to Percy Jones Battle Creek Hospital, febrile to 109, his parents were called to his bedside three times in anticipation of death.
- March 1946 streptomycin started clinical trials - Bob Dole was third patient to receive (and first person to survive).



# East vs. Midwest Pharmaceutical Competition

## Eastern Group

- Pfizer (Brooklyn, NY)
- Lederle (Pearl River, NY)
- Bristol-Myers (Syracuse, NY)
- Hoffmann-La Roche (Nutley, NJ)
- Scuibb (New Brunswick, NJ)
- Merck (Rahway, NJ)

## Midwest Group

- Eli Lilly (Indianapolis, IN)
- Abbott (Chicago, IL)
- Upjohn (Kalamazoo, MI)
- Parke Davis (Houston, TX)



# East vs. Midwest Pharmaceutical Competition

## Midwest Group

- Eli Lilly (Indianapolis, IN)
  - Abbott (Chicago, IL)
  - Upjohn (Kalamazoo, MI)
  - Parke Davis (Houston, TX)
- Initially these companies pooled synthesis of penicillin
  - Collaborated on streptomycin synthesis
  - 1947 Parke Davis left the partnership when it discovered chloramphenicol
  - By 1952 the three remaining Midwest groups collaborated on erythromycin until Upjohn abandoned it as nothing more than “a weak penicillin”
    - Erythromycin went on to become Abbott’s flagship antibiotic and one of the most successful of all the golden era’s discoveries



# East vs. Midwest Pharmaceutical Competition

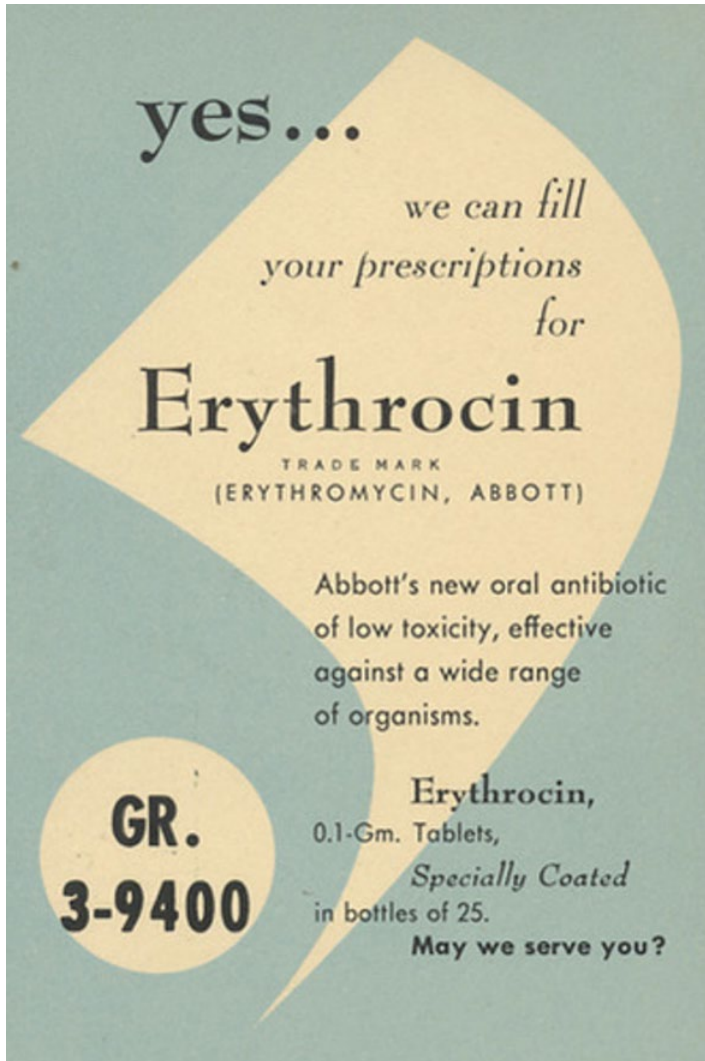
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- Scuibb (New Brunswick, NJ)
- Merck (Rahway, NJ)

This group split up immediately after working together on penicillin. Their next antibiotic successes came from soil originating from the Midwest.



# Erythromycin: Soil from Philippines, Isolated in Indianapolis



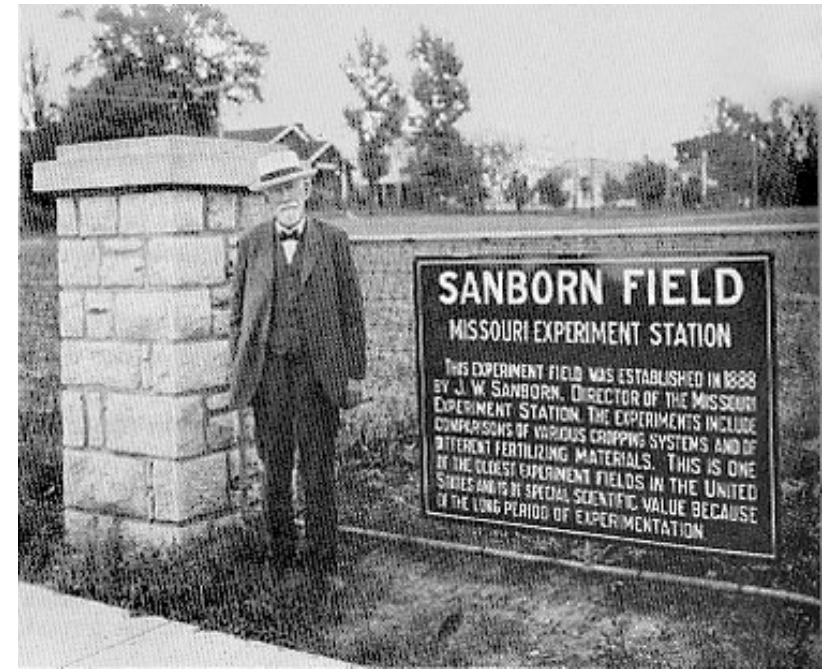
## *Streptomyces erythraeus*

- 1949 Filipino physician Dr. Abelardo Aguilar was studying soil samples from a Molo cemetery (some accounts it was from his own backyard) shipped it to Eli Lilly
- 1952 at Eli-Lilly produced an active substance called Ilotycin after Llonggo (now called erythromycin) active against the increasingly problematic penicillin-resistant *Staphylococcus aureus*



# A Mizzou Field - the First Tetracycline

- Benjamin Duggar (MU mycologist) & William Albrecht (MU botanist)
- Dr. Duggar retired at age 71 in 1943, when he read in his retirement notice commemoration “Dr. Duggar will be remembered for his noteworthy inquiry into the physiology of mushrooms”
- He unretired when he decided he did not want to be remembered as a “mushroom man”



75 years later: Discovery of 'wonder drug' aureomycin at MU changed the world

Amelia Hurley, Columbia Missourian Jul 7, 2023



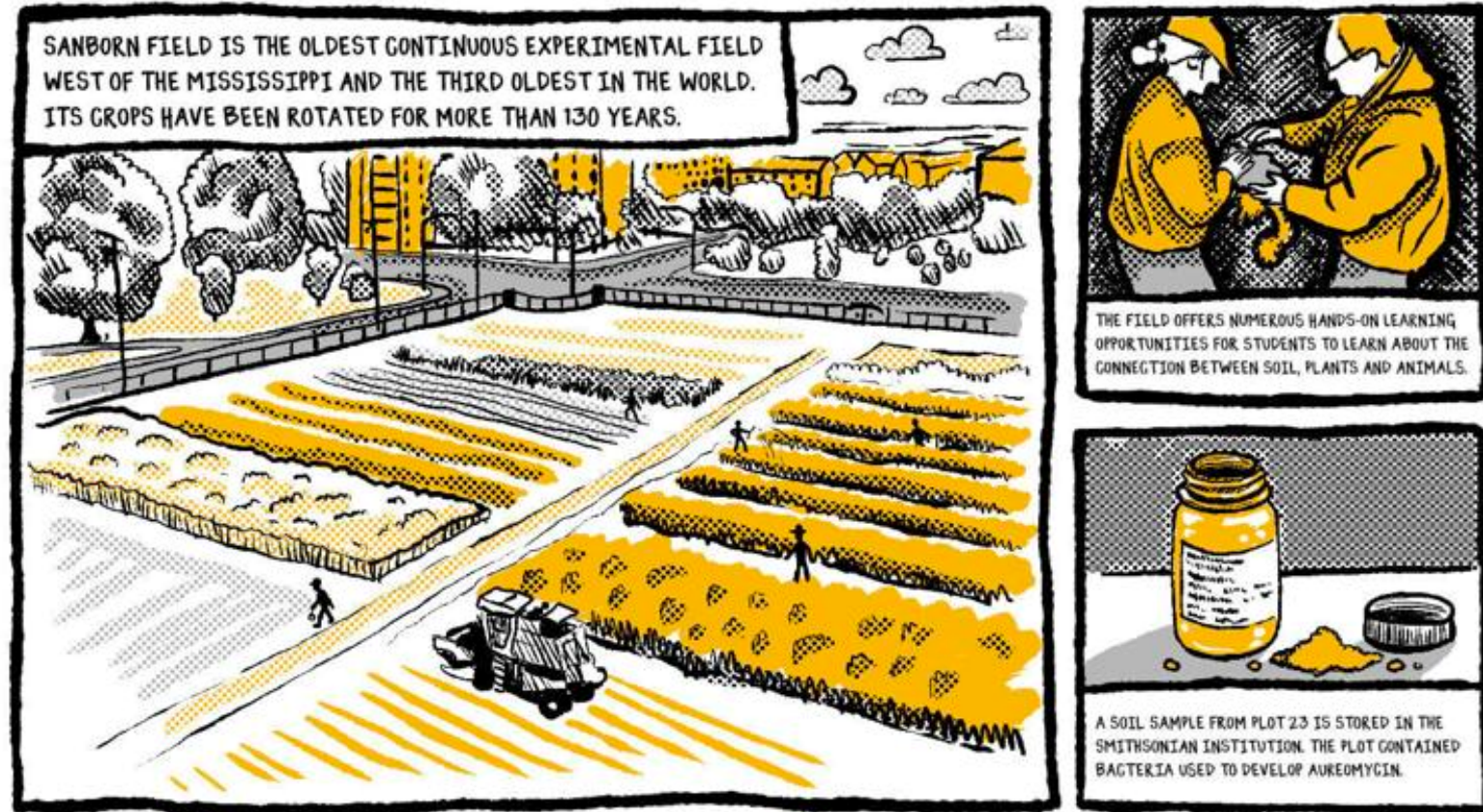
Tim Reinbott stands between plots at Sanborn Field on the MU campus. This year marks the 75th anniversary of the discovery of the drug aureomycin, found by conducting experiments on the land. “This is the grandmother of soil health,” Reinbott said.  
Tess Jagger-Wells/Missourian

Source: MU Archives [muarchives.missouri.edu/historic/buildings/sanborn/files/aureomycin.pdf](https://muarchives.missouri.edu/historic/buildings/sanborn/files/aureomycin.pdf)  
[komu.com/news/midmissourinews/75-years-later-discovery-of-wonder-drug-aureomycin-at-mu-changed-the-world/article\\_bcdb0b51-62ab-59c6-8aa5-415fa6445e8d.html](https://komu.com/news/midmissourinews/75-years-later-discovery-of-wonder-drug-aureomycin-at-mu-changed-the-world/article_bcdb0b51-62ab-59c6-8aa5-415fa6445e8d.html)



# A Mizzou Field - the First Tetracycline

- 1945 Duggar contacted Albrecht for soil samples
- Plot 23, a Timothy plot (grass for horse feed) had been used since 1888 without fertilizer or treatment
- 11 samples sent to Duggar at Lederle
- In 1948 at age 76 Duggar published his findings

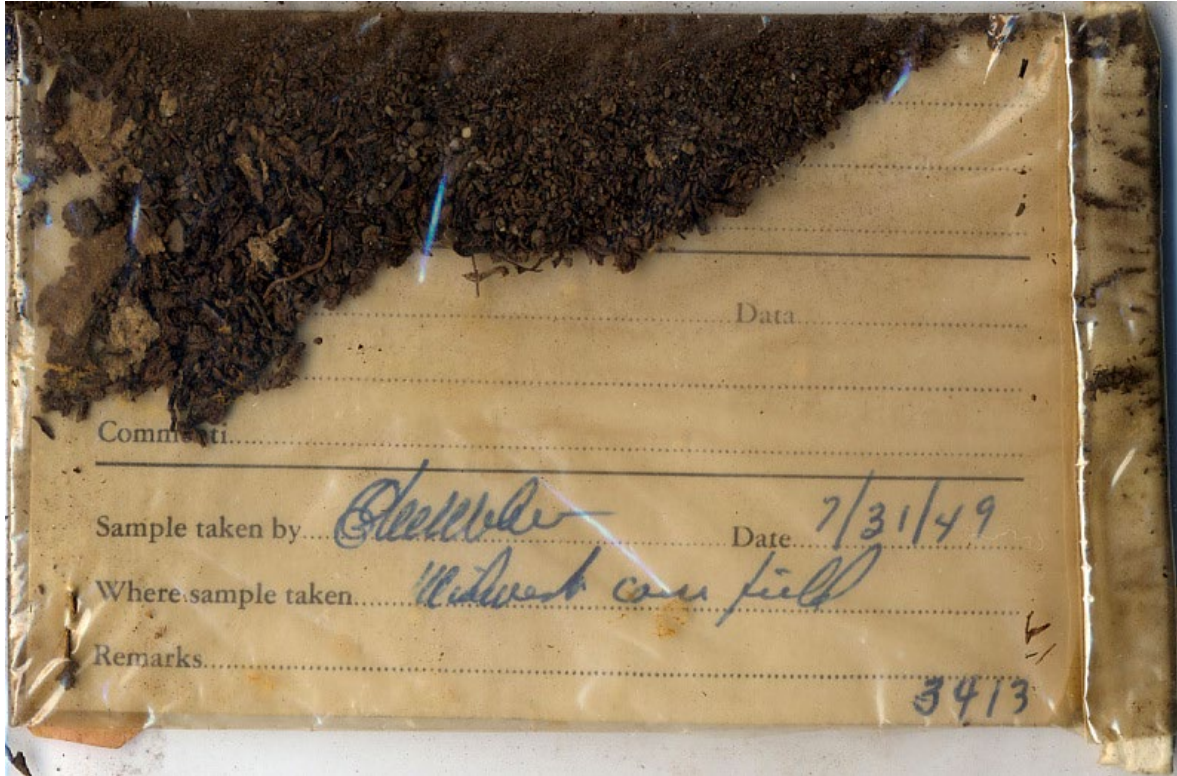


Source: MU Archives [muarchives.missouri.edu/historic/buildings/sanborn/files/aureomycin.pdf](https://muarchives.missouri.edu/historic/buildings/sanborn/files/aureomycin.pdf)

The Missourian [komu.com/news/midmissourinews/75-years-later-discovery-of-wonder-drug-aureomycin-at-mu-changed-the-world/article\\_bcd0b51-62ab-59c6-8aa5-415fa6445e8d.html](https://komu.com/news/midmissourinews/75-years-later-discovery-of-wonder-drug-aureomycin-at-mu-changed-the-world/article_bcd0b51-62ab-59c6-8aa5-415fa6445e8d.html)



# Chlorotetracycline Aureomycin®



- Named aureomycin because it had a golden aura surrounding bacterial growth
- Soil sample is stored at the Smithsonian

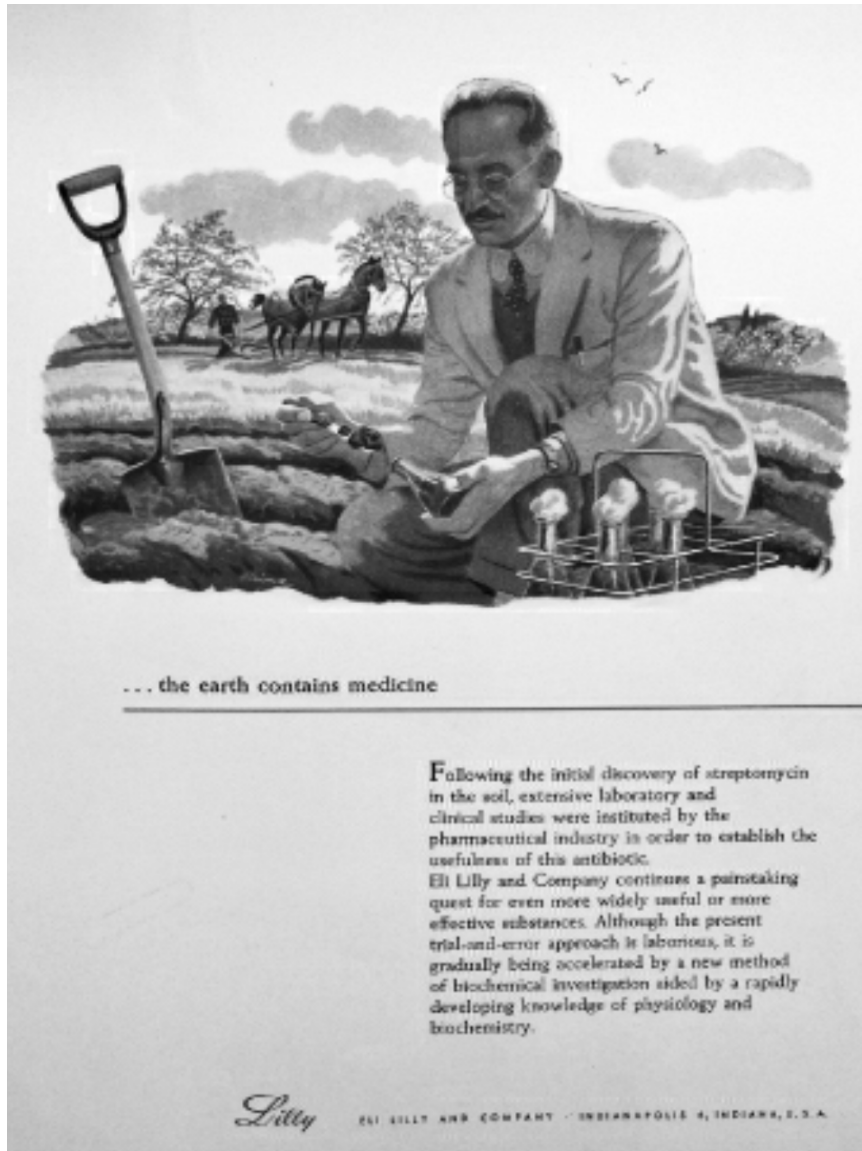




## Chlorotetracycline Aureomycin ®

- FDA approved in 1948
- Five-year-old Tobey Hockett, one of the first patients treated with Aureomycin





## Pharmaceutical Advertising

- The wholesomeness of these medicines originating from soil came to be part of their ad campaigns, Pfizer (Terramycin) encapsulated the entire soil-sifting model of antibiotic discovery linking globally dispersed soil-gatherers **“from Alaska to Australia, from the banks of the Amazon to the shores of the Ganges, from the Swamps of Florida and from the Swiss Alps”**
- Antiseptically enshrouded mycologists, bacteriologists, engineers involved in the scanning, screening, testing and production were featured as soil-searchers



# Pharmaceutical Advertising

## Doctor, why is Aureomycin best?

“There are many reasons, which may be summed up by describing this versatile drug as at present the nearest approach to a ‘perfect’ antibiotic...Experience has shown that Aureomycin achieves better results with lower dosages...without serious side reactions...and with less likelihood that disease germs will build up immunity to its health-restoring powers”



*Photograph by Ethel*

### "Doctor, why is aureomycin best?"

Have you ever wondered why doctors prescribe AUREOMYCIN for so many different illnesses? There are many reasons, which may be summed up by describing this versatile drug as at present the nearest approach to a "perfect" antibiotic.

The medical literature, which already contains over 7,000 references to AUREOMYCIN, continues to give proof of its effectiveness against an increasing number of infections. In many cases, it has proved successful where other antibiotics have failed. Experience has shown that AUREOMYCIN achieves better results with lower dosages...without serious side reactions...and with less likelihood that disease germs will build up immunity to its health-restoring powers.

AUREOMYCIN, developed by Lederle Laboratories Division of American Cyanamid Company, is today hailed by the medical profession as the greatest of the new weapons against infectious disease.

**AMERICAN Cyanamid COMPANY**  
30 ROCKEFELLER PLAZA, NEW YORK 20, N. Y.

*Materials for the Medical Profession—one of Cyanamid's Many Services*



# Terramycin

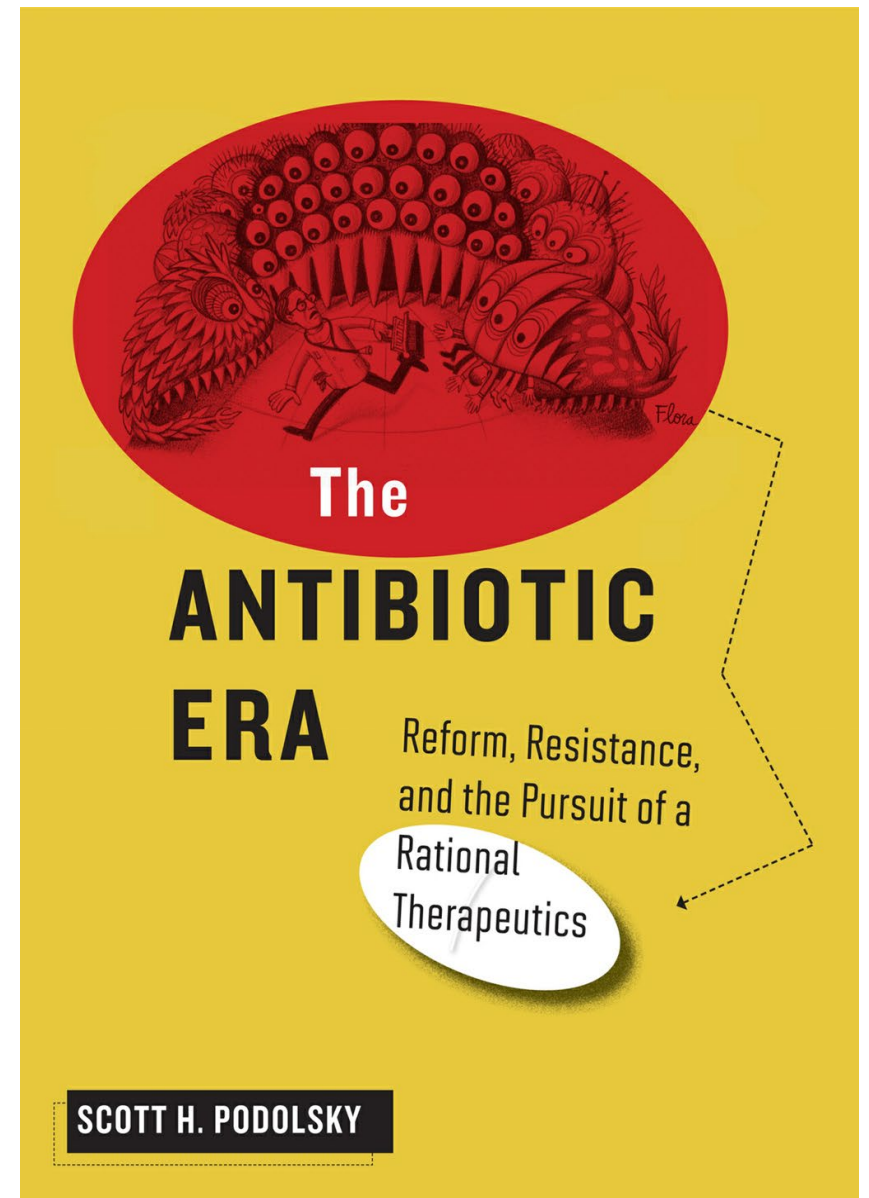
- Terre Haute Indiana soil sample
- FDA approved 1950
- First “broad-spectrum” antibiotic
- Pfizer’s Terramycin campaign changed the pharmaceutical marketing landscape
- Psychiatrist Arthur Sackler’s (father to Oxycontin’s Richard Sackler) ad agency William Douglas McAdams developed campaign materials based on illustrated and scientifically written materials, disseminated en masse to physicians and the public termed the “advertising blitz”





# Antibiotic Advertising and FDA Pharmaceutical Reform

- Pharma reformers Dr. Max Finland (Harvard) and Harry Dowling (Univ of IL)
- AMA sent monthly “marketing” reports of physician prescribing habits to pharmaceutical companies
- By 1953 Pfizer abx ads accounted for 50% JAMA’s ad revenue
- 1959-1962 Sen. Kefauver’s (D-TN) congressional reform hearings uncovered FDA Div. of Antibiotics Director Henry Welch profited from selected publishing of two journals he served as chief editor (*Antibiotics and Chemotherapy* and *Antibiotic Therapy*)
- FDA at the time only adjudicated safety but not efficacy





# Promoting Growth

## Terramycin

- Chickens fed by-products of terracycline fermentation noted higher rates of growth than those not fed the by products
- 2001 – 70% of global antibiotics (25 million pounds) non-therapeutic animal use
  - 10.5 million pounds in poultry
  - 10.3 million pounds in hogs
  - 3.7 million pounds in cattle

Source: Castanon J. Production Modeling, Education;2007;86(11):2466-2471.

Ronquillo M, Food Control 2017; 72:255-67.

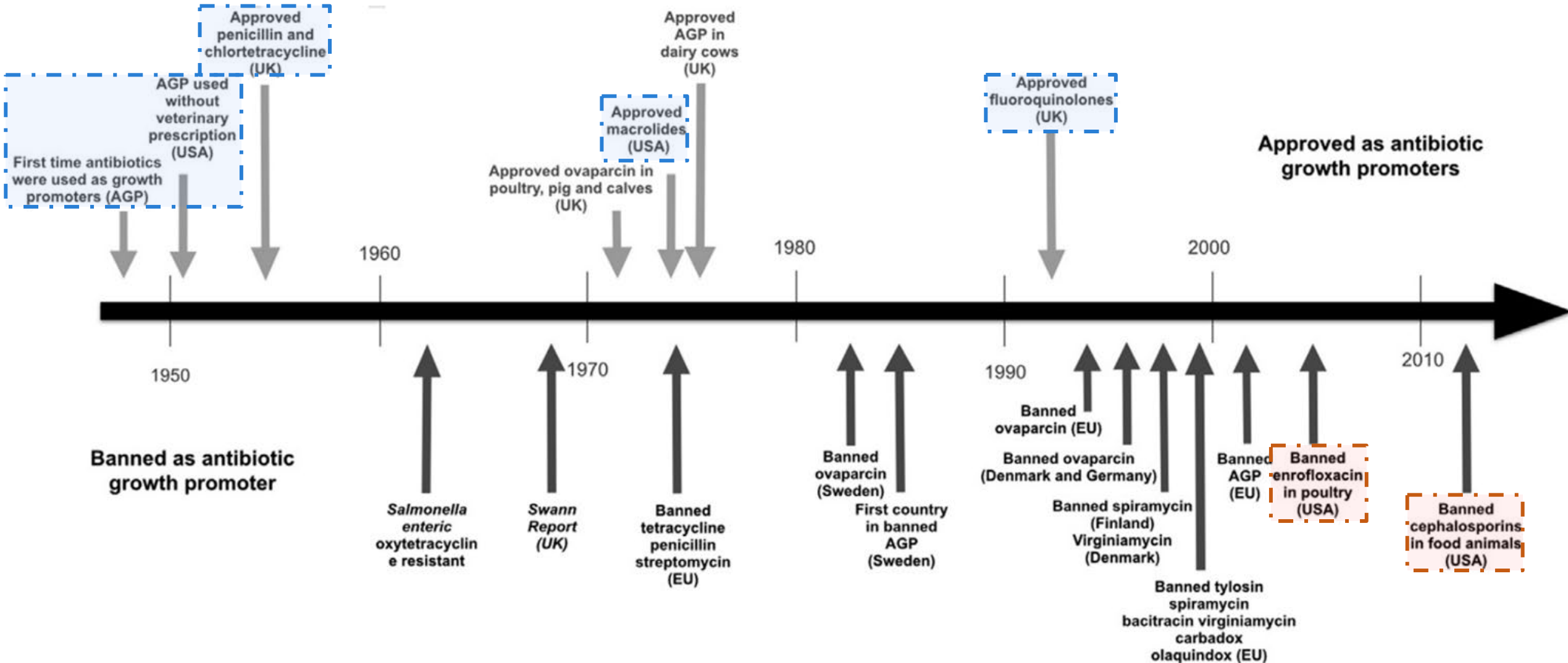
Union Concerned Scientists [ucsusa.org/resources/hogging-it-estimates-antimicrobial-abuse-livestock](https://ucsusa.org/resources/hogging-it-estimates-antimicrobial-abuse-livestock)

Photo Source: National Museum American History [americanhistory.si.edu/collections/search/object/nmah\\_714840](https://americanhistory.si.edu/collections/search/object/nmah_714840)





# Antibiotic Growth Promoters





# Mississippi Mud

## Vancomycin

- Soil from exotic locations was solicited when American soil was thought to have been exhausted
- Dr. Edmund Kornfeld sought out his friend, Rev. William Conley, who was a Borneo missionary to send dirt samples back to Indianapolis
- The first batch was unrevealing, Kornfeld send a second request to “...collect samples off the beaten track, away from towns and villages”
- A certain reddish dirt sample caught the missionary's attention and was returned
- In 1953 *Streptomyces orientalis* discovered (renamed *Amycolatopsis orientalis*) producing an antibacterial substance “compound 05865”
- Compound 05865 killed all staphylococci, stable in serial passages suggesting it might be clinically useful for long periods of time (a property lacking in penicillin, chloramphenicol, and tetracycline discovered up to that point)

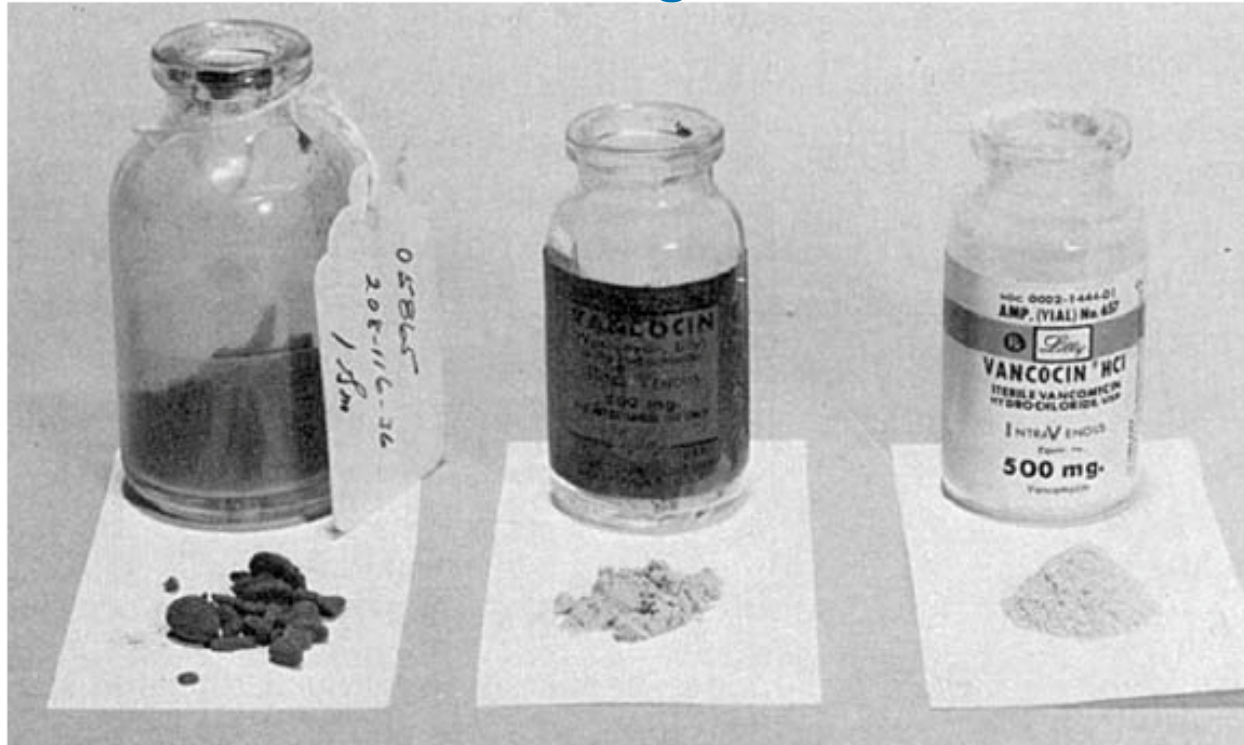


# Mississippi Mud

## Vancomycin

- Because it was thought this potent agent would vanquish *Staphylococcus*, it was named vancomycin
- Kornfeld had difficulty purifying vancomycin, the original purification method resulted in an explosive chemical picric acid, and early impurities resulted in it being labeled “Mississippi Mud”

## Stages of Vancomycin Development 1956 through 1981



1956 sample of  
compound 05865

Purified with picric acid

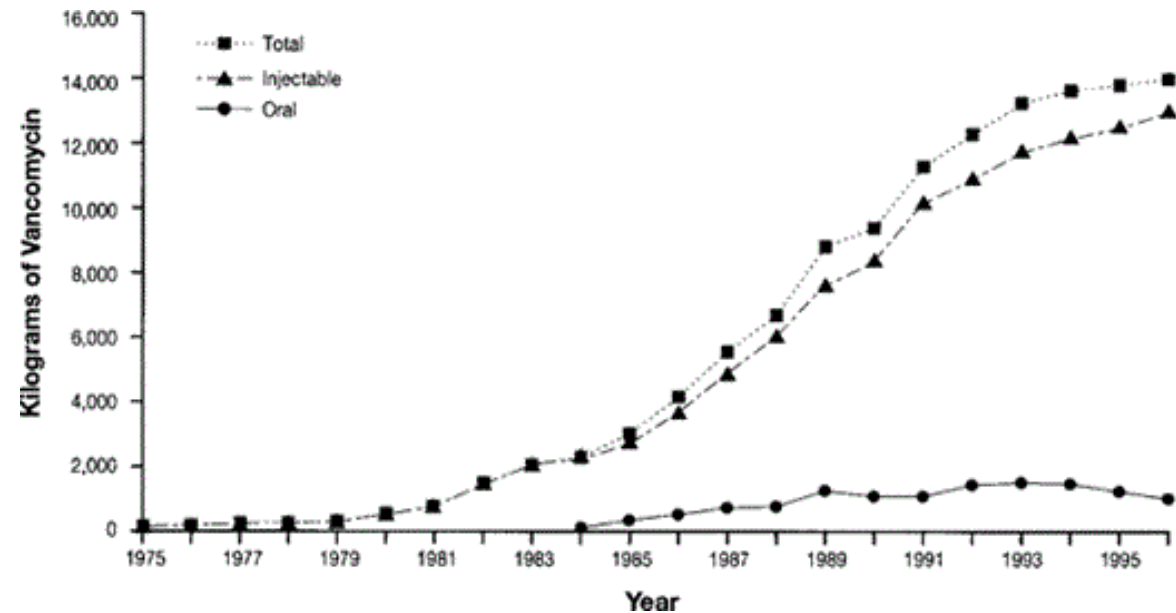
1981 vancomycin  
hydrochloride



# Mississippi Mud

- Eventually it yielded a material with 82% purity (still brown) but felt safe enough for human use
- Richard Griffen a physician and co-Primary Investigator of vancomycin wrote “The relatively low toxicity in animals warranted clinical trial as soon as possible. We need a patient...”
- An Indianapolis surgical resident called Eli Lilly “We have a patient for your new antibiotic” of a post-op surgical infection with MDR *S. aureus*
- 1958 FDA approved

## Use of Vancomycin 1975-1995







# Soil in Lincoln: Lincosamides

## *Streptomyces lincolnensis*

- Soil from a field in Lincoln NE produced a culture of *S. lincolnensis* which prevented gram positive and anaerobic growth
- 1962 discovered at Upjohn and named Lincomycin in honor of its source
- Lincomycin was rapidly replaced by the more efficacious semi-synthetic derivative containing chlorine, clindamycin (1966)

**A handful  
of earth  
that may save  
your life**

This scene might have happened anywhere in the world — a wilderness in Brazil, a plantation in Brazil, a sheep ranch in New Zealand, a back yard in the U.S.A.

From this field comes one of thousands of soil samples sent year after year to our Parke-Davis research laboratories.

By using new microorganisms from these samples, we are trying to create antibiotics to combat the uncontrolled infectious diseases still rampant. For example, in one year, Parke-Davis scientists isolated and worked with 34,000 cultures of microorganisms. With these, they produced a few antibiotics which came amazingly

close to meeting our existing standards of acceptability, but none made the grade. Perhaps 34,000 to 35,000 like your odds, but twice in recent years research work at Parke-Davis has been thousands to provide antibiotics now used around the world.

Parke-Davis frequently takes calculated risks. It may seem to discourage us. Your health and your family's health demand our continuing efforts.

Copyright 1965 Parke, Davis & Co., Inc., Detroit, Mich.

**PARKE-DAVIS**

... FOUNDED IN 1896



# Linezolid, a New Generation of Synthetic Antibiotics

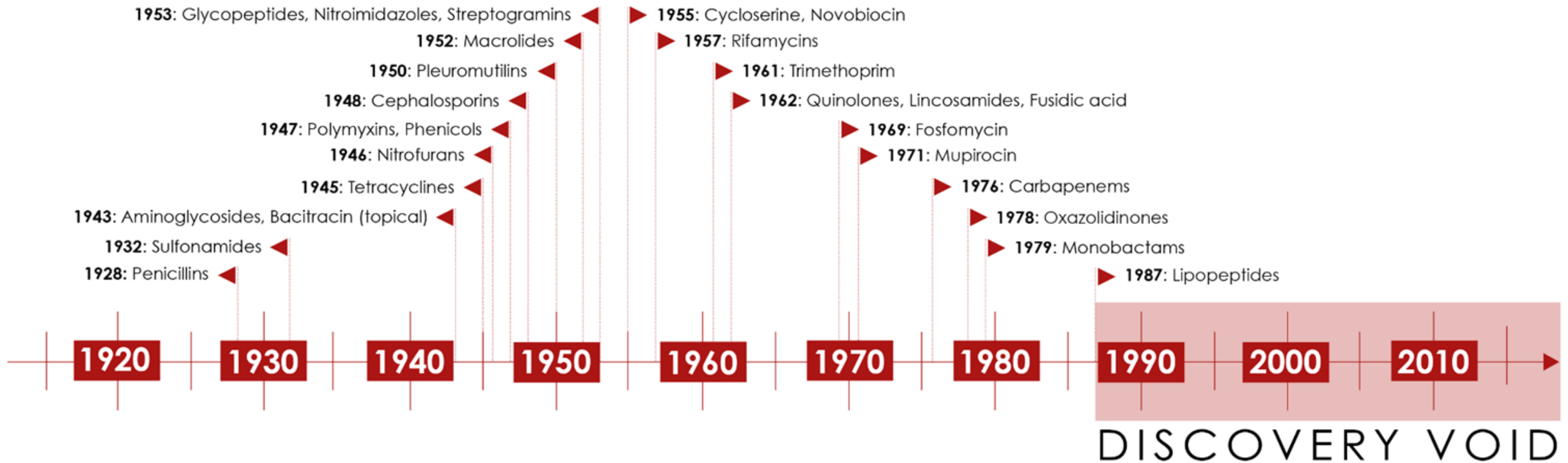
- Late 1970s first synthetic oxazolidinone discovered at Dupont, abandoned because of poor in vitro activity and high toxicity
- Upjohn (Michigan) scientist Steve Brickner initiated his own personal project on this novel class in 1987
- At the time, Upjohn encouraged scientists to invest up to 10% of their time on their own 'self-initiated' projects
- By 1995 two analogs - linezolid and eperezolid - proceeded to phase 1 trials
- Linezolid was FDA approved in 2002, the first new class in 35 years



# Moving From Natural Products to Lab Synthesis

## Synthetic Antibiotics

The last 2 classes discovered in past 40 years were discovered from Midwest companies (Linezolid at Upjohn in Kalamazoo, Daptomycin at Eli Lilly in Indianapolis)





# PASTEUR ACT: Pioneering Antimicrobial Subscriptions to End Upsurging Resistance

**Introduced 2020**

**Re-introduced 2021 - bipartisan**

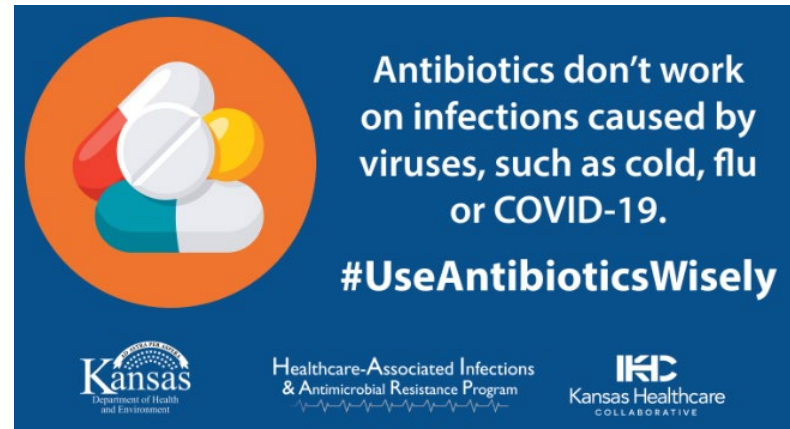
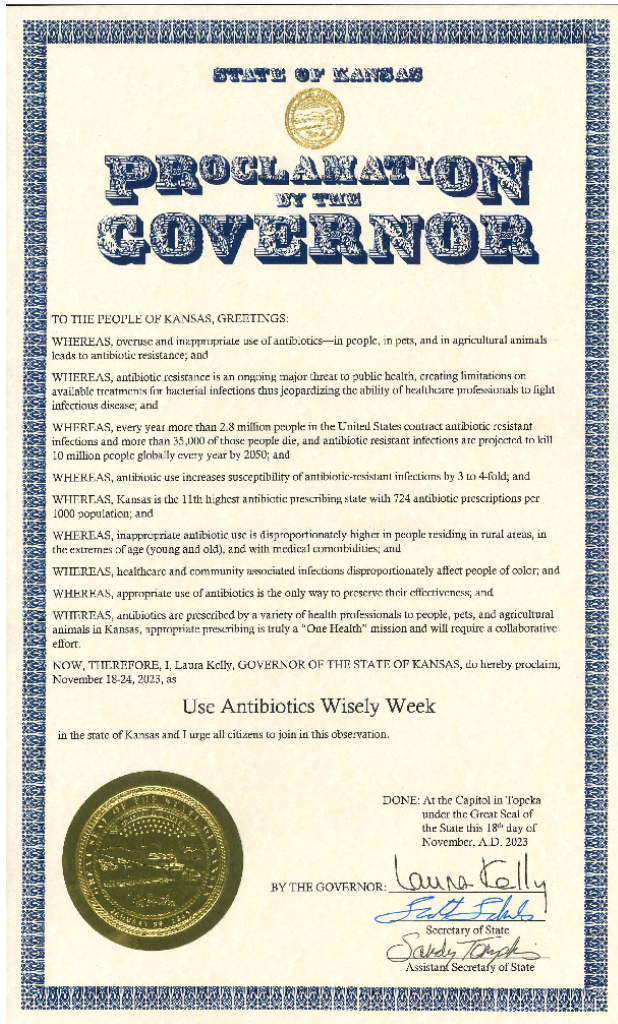
- CO senator Michael Bennet (D)
- IN senator Todd Young (R)
- CA representative Scott Peters (D)
- GA representative Drew Ferguson (R)
- Co-drafted with IDSA assistance

**Bill aiming to spur abx development and Strengthen antimicrobial stewardship**

- Establish subscription program to provide federal contracts for critically needed novel antibiotics and antifungals
- Payments delinked from sales volume to provide a predictable ROI for abx developers
- Strengthen stewardship programs in hospitals + LTCFs



# Happy Use Antibiotics Wisely Week!



## DO YOUR PART TO REDUCE ANTIBIOTIC RESISTANCE

Antibiotic resistance is a major threat to public health—and it is only getting worse. It is caused by overuse and misuse of antibiotics. We are all part of the problem. We must all be part of the solution.

**Know the facts.**

## HAGA SU PARTE PARA REDUCIR LA RESISTENCIA A LOS ANTIBIÓTICOS

La resistencia a los antibióticos es una grave amenaza a la salud pública y solo está empeorando. Es causada por el exceso de uso o uso indebido de los antibióticos. Todos somos parte del problema. Todos debemos ser parte de la solución.

**Conozca los hechos.**

**Before antibiotics, simple bacterial infections could kill.**

**Overuse and misuse of antibiotics** — in people, pets, and livestock — leads to antibiotic resistance.

**Developing new antibiotics is not enough.** The time it takes for resistance to develop is getting shorter.

**WHAT YOU CAN DO**

Kansas Department of Health and Environment

**Antes de los antibióticos, las infecciones bacterianas más simples podían matar.**

**La penicilina se descubrió hace apenas 90 años pero la efectividad de los antibióticos ya se ve amenazada por el uso indebido.**

**Exceso de uso o uso indebido de los antibióticos** — en personas, mascotas, y ganado — lleva a la resistencia a los antibióticos.

**Desarrollar nuevos antibióticos no es suficiente.** El tiempo que toma el desarrollo de la resistencia se está acortando cada vez más.

**La resistencia a los antibióticos ya está afectando a personas, y provocando epidemias en el hospital más prolongadas y una mayor tasa de mortalidad.**

**Si no luchamos contra la resistencia a los antibióticos, para 2050 hasta 10 millones de personas pueden morir cada año de infecciones no tratables.**

**Reducir la resistencia a los antibióticos es la responsabilidad de todos — doctores y pacientes.**

**Los antibióticos no funcionan para todas las infecciones. Solo funcionan en bacterias. NO en enfermedades causadas por virus, como los resfriados y gripe. "Haga como la droga con el germen"**

**El moco verde no significa que necesite antibióticos.**

**Solo use antibióticos en mascotas según las indicaciones del veterinario. Las bacterias resistentes a los antibióticos pueden ser transmitidas a otros, incluyendo de mascotas a humanos.**

**LO QUE PUEDE HACER**

- No pedirá antibióticos para infecciones virales y gripe, dado que no afectan los virus.
- Comprenderá que los antibióticos no me quitan la infección, me hacen más rápido de una infección viral.
- Solo tomaré antibióticos si la receta me ha sido recetada.
- Comprenderé que es posible transmitir la resistencia a los antibióticos a otros.
- Haré mi parte para prevenir la propagación de bacterias lavándome las manos meticulosamente.
- Compartiré la información con otros y les haré saber cómo **Usar Antibióticos Sabiamente**

Más información y recursos en:  
[UseAntibioticsWisely.org](https://UseAntibioticsWisely.org)

Kansas Department of Health and Environment  
 Healthcare-Associated Infections & Antimicrobial Resistance Program  
 IKC Kansas Healthcare Collaborative



# November 18-24, 2023

## World Antimicrobial Awareness Week



All Healthcare Professionals  
can *Be Antibiotics Aware*



For more information, visit [www.cdc.gov/antibiotic-use](http://www.cdc.gov/antibiotic-use).



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## U.S. Antibiotic Awareness Week



*To protect and improve the health and environment of all Kansans*



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# Thank You!

The Creation of Antibiotics  
and the Birth of Modern Medicine

**MIRACLE CURE**  
**WILLIAM ROSEN**