RUTGERS
BIOMEDICAL AND HEALTH SCIENCES

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Keeping up with antibiotic resistance ……. The challenge may be to great!

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The Beginning of the Antibiotic Era

Antibiotic Resistance – Historical Perspective

- Oxford, England – 43 year old policeman
  Admitted to hospital October 1940
- *Staphylococcus aureus* facial infection; non-responsive to drainage and sulfapyridine
- Spread – face, lungs and osteomyelitis in his arm
- Penicillin tried on February 12, 1941
- 5 days of treatment: remarkable improvement

- NO MORE DRUG –

Died from overwhelming *S. aureus* infection- 3/15/41

PENICILLIN RESISTANCE

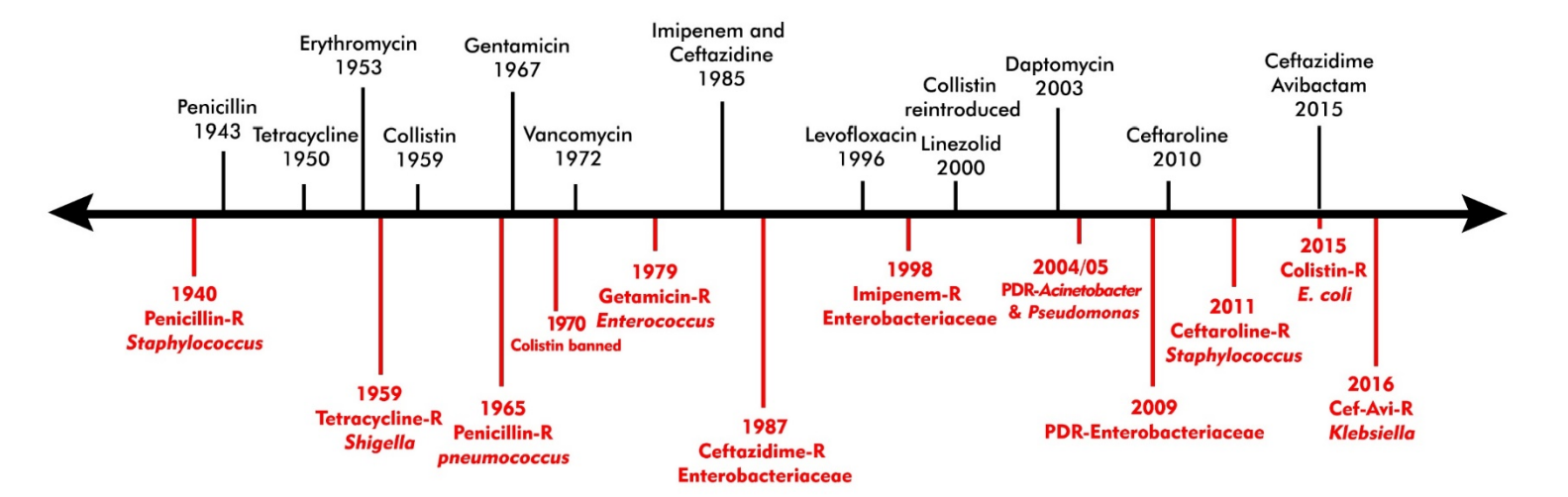
- Penicillin introduced in 1941
- Hammersmith hospital monitored the evolution of penicillin resistance in treating *S. aureus*

1941 - no resistance
1946 - 13% resistant
1947 - 38% resistant
1948 - 59% resistant

- By the mid-1950s penicillin was no longer an effective antibiotic to treat staphylococcal infections

Race against time: the introduction of new antibiotic and the emergence of resistance

ANTIBIOTIC INTRODUCED



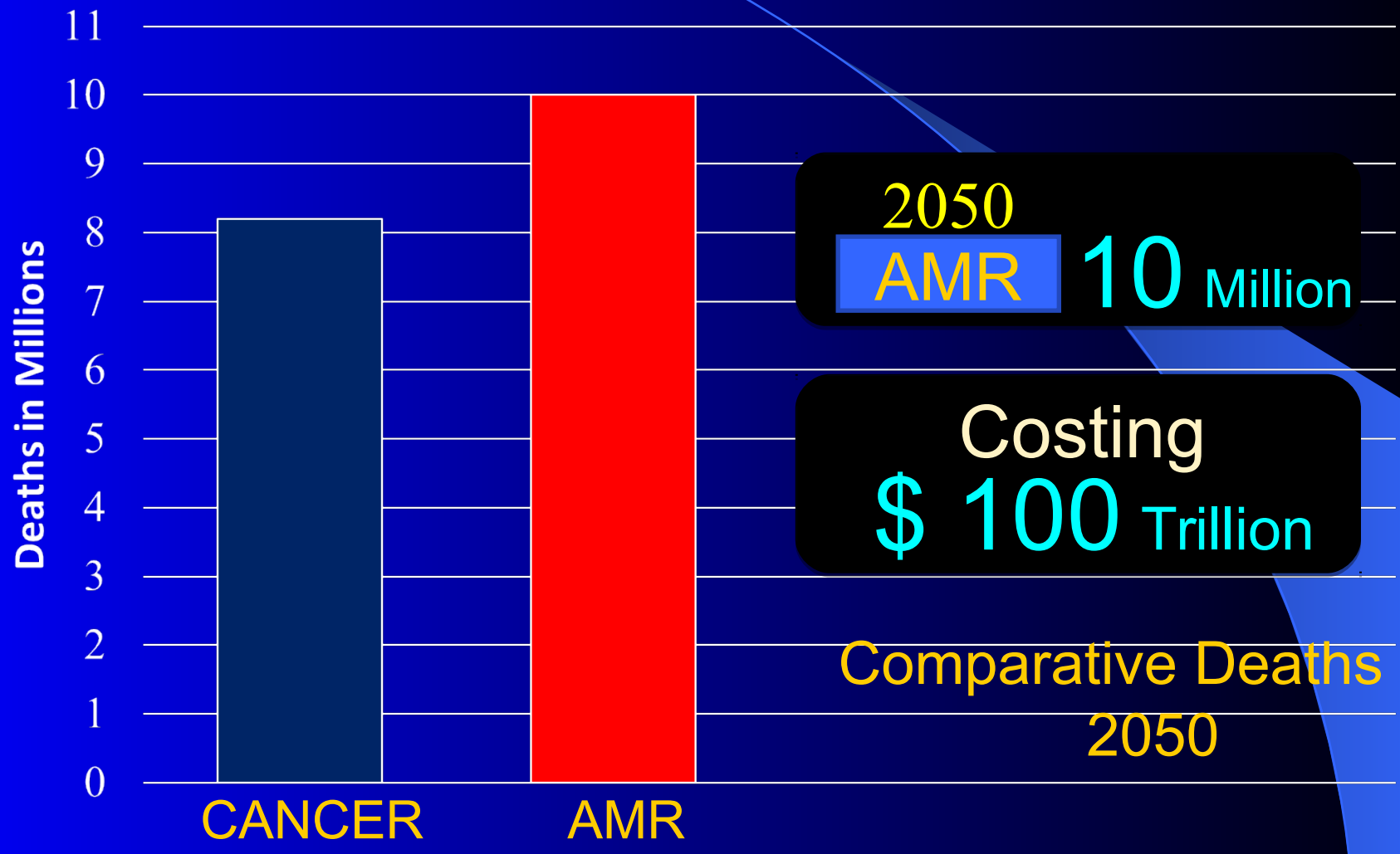
ANTIBIOTIC RESISTANCE IDENTIFIED

Antibiotic Resistance in the United States

* bacteria and fungus included in this report

https://www.cdc.gov/media/releases/2013/images/p0916-untreatable.jpg

Deaths from Drug-resistant infection Dramatically Rising



http://www.un.org/pga/71/event-latest/high-level-meeting-on-antimicrobial-resistance/

World Health Organization

WHO publishes list of bacteria for which new antibiotics are urgently needed

27 February 2017 | GENEVA

Priority 1: Critical

- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- **Enterobacteriaceae, carbapenem-resistant, ESBL-producing**

Priority 2: High

- *Enterococcus faecium*, vancomycin-resistant
- *Staphylococcus aureus*, methicillin-resistant, vancomycin-intermediate and resistant
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- *Salmonellae*, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: Medium

- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant

http://www.who.int/mediacentre/news/releases/2017/bacteria-antibiotics-needed/en/

The Problem

- The drug discovery pipeline is limited because big pharma has gotten out of the antibiotic business
- The population who are getting the infections are high risk transplant and CF patients who are immunosuppressed
- Resistance is spreading both by promiscuous conjugative plasmids and by clonal transmission

β-Lactam Antibiotics

- Narrow spectrum penicillins (4) – penicillin G
- Narrow spectrum penicillinase resistant penicillins (3) -methicillin
- Moderate spectrum penicillins (2)-amoxicillin
- Broad spectrum penicillins (1)-amoxicillin and clavulanic acid
- Extended spectrum penicillins (4)-piperacillin
- 1st generation cephalosporins (3)-cephalothin
- 2nd generation cephalosporins (2)-cefotetan
- 3rd generation cephalopsorins (3)-ceftriaxone
- 4th generation cephalosporins (2)-cefepime
- Carbapenems (3)-meropenem
- Monobactams (1)-aztreonam
- Beta-lactamase inhibitors (3)-clavulanic acid

β-Lactams vs β-Lactamases

There are more than 1,500 β-lactamases reported

Carbapenem Resistance Determinants

- Carbapenemases class A

  K. pneumoniae carbapenemase (KPC)

  GES, SME

- Carbapenemases class B

  Metallo-β-Lactamases: NDM-1, VIM, IMP

- Carbapenemases class D

  Oxa23, Oxa24, Oxa 48, Oxa58

CONFOUNDING PROBLEM:
MOST OF THESE GENES ARE ON MOBILE ELEMENTS

Extended Spectrum β-lactamases & Carbapenemases

β-lactam Drug	Gene
Ampicillin	CTXM1 CTXM2 CTXM8_25 CTXM9 TEM_WT TEME104K TEMR164S TEMR164C TEMR164H TEMG238S TEMG240 TEMG237 SHV_WT SHVG238S SHVG238A SHVE240K CMYI_MOX CMYIIFOX KPC NDM VIM IMP OXA48
Ampicillin/Sulbactam	SHV_WT CMYI_MOX CMYIIFOX KPC NDM VIM IMP OXA48
Amox/Clav	CMYI_MOX CMYIIFOX KPC NDM VIM IMP OXA48
Pip/Tazo	CMYI_MOX CMYIIFOX KPC NDM VIM IMP OXA48
Cefazolin (I)	CTXM1 CTXM2 CTXM8_25 CTXM9 TEMR164S TEMR164C TEMR164H TEMG238S TEMG240 TEMG237 SHV_WT SHVG238S SHVG238A SHVE240K CMYI_MOX CMYIIFOX KPC NDM VIM IMP OXA48
Cefoxitin (II)	CMYI_MOX CMYIIFOX KPC NDM VIM IMP OXA48
Cefotaxime (III)	CTXM1 CTXM2 CTXM8_25 CTXM9 TEMR164S TEMR164C TEMR164H TEMG238S TEMG240 TEMG237 SHVG238S SHVG238A SHVE240K CMYI_MOX CMYIIFOX KPC NDM VIM IMP
Ceftriaxone (III)	CTXM1 CTXM2 CTXM8_25 CTXM9 TEMR164S TEMR164C TEMR164H TEMG238S TEMG240 TEMG237 SHVG238S SHVG238A SHVE240K CMYI_MOX CMYIIFOX KPC NDM VIM IMP
Ceftazidime (III)	CTXM1 CTXM2 CTXM8_25 CTXM9 TEMR164S TEMR164C TEMR164H TEMG238S TEMG240 TEMG237 SHVG238S SHVG238A SHVE240K CMYI_MOX CMYIIFOX KPC NDM VIM IMP
Cefepime (IV)	CTXM1 CTXM2 CTXM8_25 CTXM9 TEMR164S TEMR164C TEMR164H TEMG238S TEMG240 TEMG237 SHVG238S SHVG238A SHVE240K CMYI_MOX CMYIIFOX KPC NDM VIM IMP
Aztreonam	CTXM1 CTXM2 CTXM8_25 CTXM9 TEMR164S TEMR164C TEMR164H TEMG238S TEMG240 TEMG237 SHVG238S SHVG238A SHVE240K CMYI_MOX CMYIIFOX KPC
Ertapenem	KPC NDM VIM IMP OXA48
Imipenem	KPC NDM VIM IMP OXA48
Meropenem	KPC NDM VIM IMP OXA48

Carbapenemases : A Global Epidemic

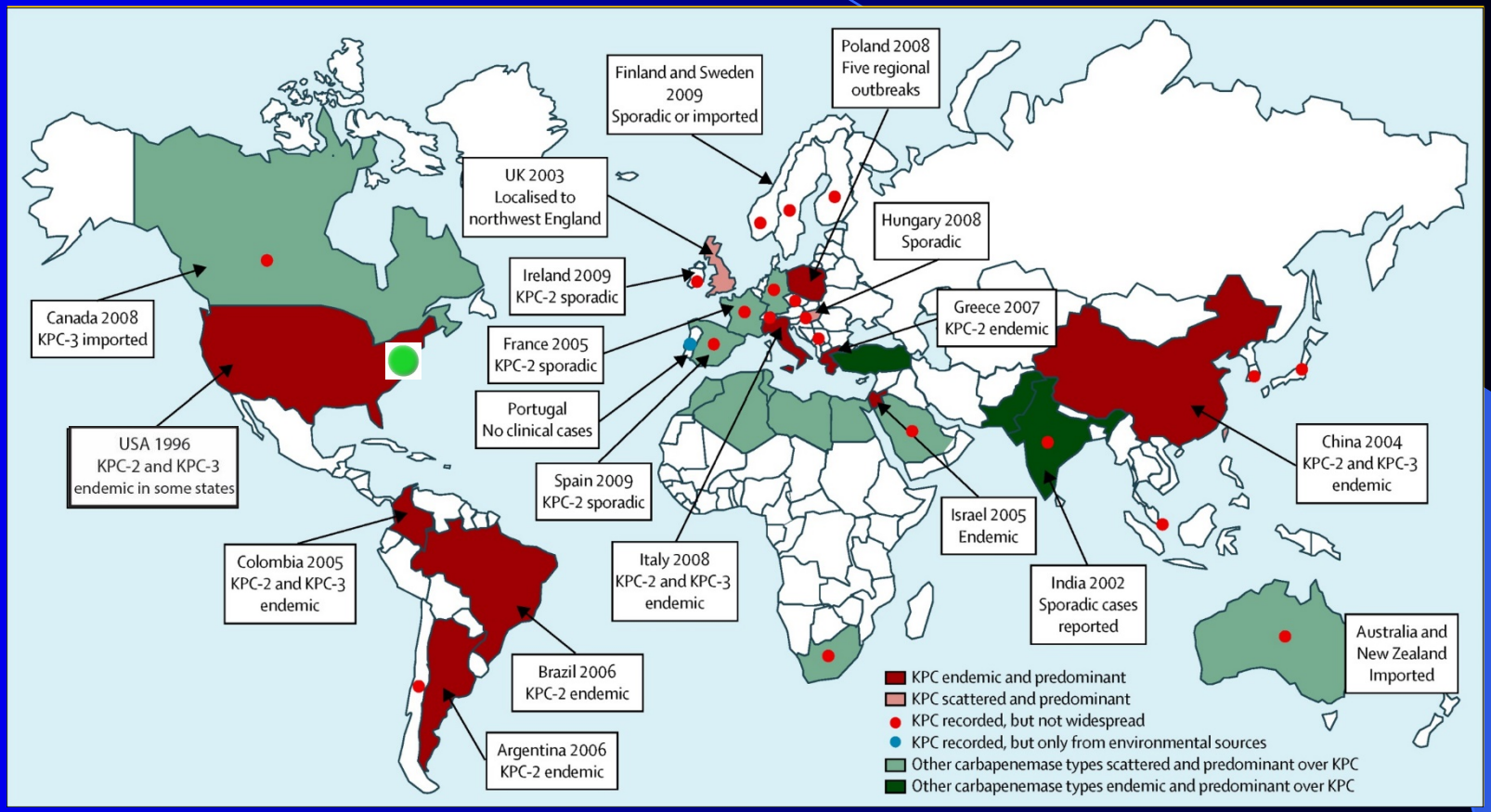


Figure: Epidemiological features of producers of Klebsiella pneumoniae carbapenemases by country of origin
Other carbapenemase types include VIM, OXA-48, or NDM. KPC=Klebsiella pneumoniae carbapenemase.

THE LANCET Infectious Diseases
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Airborne pathogen,
Mycobacterium tuberculosis
The cause of Tuberculosis

TB Statistics

- 2 billion infected (1/3 world population)
- 8-9 million new cases each year
- 1.6 million deaths per year (25% of all preventable deaths)
- This means **4, 000** deaths each day, a death every **20 seconds**
- **85% of the mortality in developing countries**

WHO report on TB

- Slow grower; doubles 24hrs; 3-4 weeks to culture
- Highly transmissible; requires BL3 facilities

HIV and Multidrug Resistance

HIV and Tuberculosis

- Co-infection of *M.tb* and HIV a deadly-duet
- 11% co-infected (range from 1% to over 60%)
- Reactivation of tuberculosis or rapid progression to disease are markers for HIV

Multidrug Resistance (INH & RIF)

- Multidrug resistance is emerging in virtually every country
- 425,000 new MDR cases annually
- Estimated 50 million infected with MDR

Drugs in the Clinical Pipeline for the World's Leading Causes of Mortality

Leading causes of global mortality:

1. Ischemic heart disease
2. Stroke
3. COPD
4. Lower respiratory infection
5. Lung cancer
6. HIV/AIDS
7. Diarrhea
8. Road traffic accidents
9. Diabetes
10. **Tuberculosis**
11. Malaria

Drugs in clinical development:

Heart Disease and stroke: 299

COPD: 54
Antibacterials and antivirals: 89

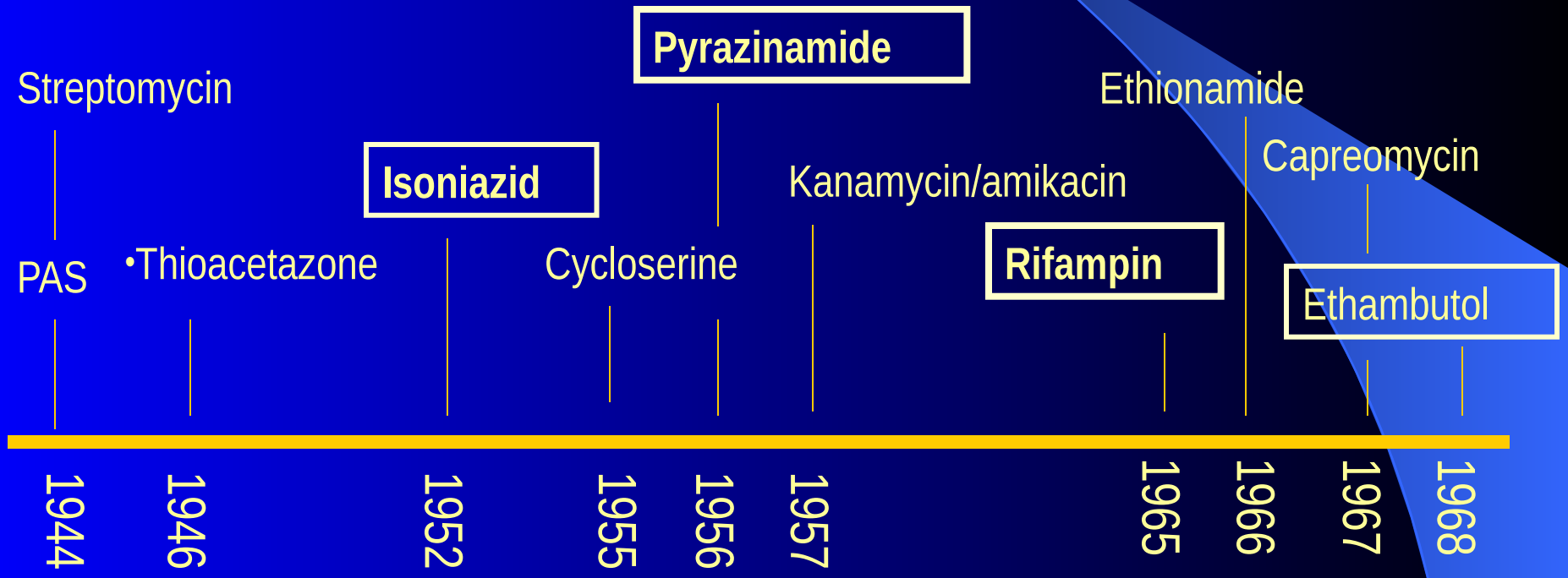
Cancer: > 900 (includes vaccines)
Lung Cancer: 121; Breast Cancer: 111
HIV/AIDS: 70

Diabetes: 221
Anti-tuberculosis: 5-8
Anti-malarials: 6

Sources: The Global Burden of Disease Report, 2012
The Pharmaceutical Research and Manufacturers of America (www.pharma.org)

The last TB-specific antibiotic, ethambutol, was discovered in 1968!

2013, > 40 years before FDA approved a new TB-drug: Bedaquiline



First line agents are in boxes

SO WHY?

- Slow growing, highly infectious airborne bacteria
- Requires very expensive BL3 facilities
- Drugs must work in combination with current drugs
- Drugs must be compatible with HIV therapy
- Treatment takes months to years and clinical trials are both long and costly
- Population is mostly in developing countries

FINAL COMMENT

- The antibiotic era, which began with the first use of penicillin in 1940, is rapidly coming to an abrupt end as a consequence of a sparse antibiotic pipeline and an evolved microbial population that harbor a diverse and mobile array of antibiotic resistance genes.

- Unless we collectively approach the problem with the urgency and commitment that drove the Manhattan project, the progress in medical advancements, such as transplants, will be compromised.