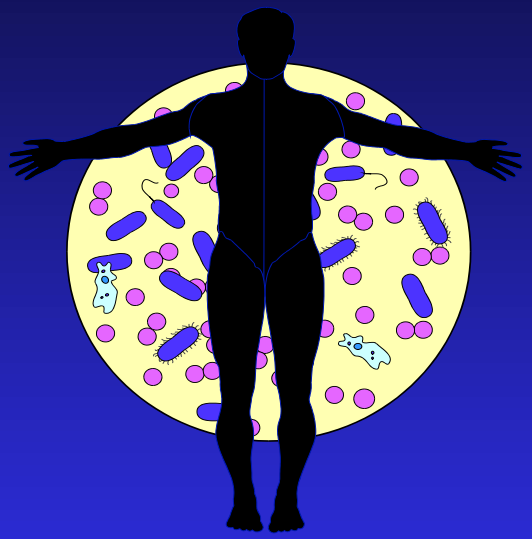
Antimicrobial Use and Resistance in Humans



John Conly CM MD CCFP FRCPC FCAHS FAMMI FACP FIDSA FSHEA
Professor of Medicine, Microbiology, Immunology & Infectious Diseases
Medical Director IPC and Antimicrobial Stewardship, Calgary and Area
University of Calgary and Alberta Health Services, Calgary, Canada

Sept 29 2020

AMR: A One Health Approach Graduate Online Course

SARS-CoV-2 Modes of Transmission and Related IPC Measures

July 7, 2020

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Territorial Acknowledgement

I acknowledge the traditional territories of the Blackfoot and Treaty 7 peoples including the Siksika, Piikuni, Kainai, Tsuut'ina, and Stoney Nakoda First Nations. Calgary is also h to the Metis Nation of Alberta, Region III.

Faculty/Presenter Disclosure/Acknowledgements

- **Honoraria**: None
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- **Grants/Clinical Trials**: Local PI for the STRIVE *S. aureus* vaccine trial spinal surgery (Pfizer) and holds grants from CIHR, AI-HS, PHAC, AH, AHS, EDT
- **Patents, royalties:** None
- **Investments in health organizations:** None
- **Other influential affiliations:** Member of committees with PHAC, WHO and CIHR

Objectives

- Impact and implications
- Antibiotics in ecosystems
- Epidemiology
- Origins of resistance
- Mechanisms of resistance
- Use and abuse
- Emerging threats

What is the impact of antimicrobial resistance ?

- Increase in morbidity and mortality initially confounded by other factors associated with a poor outcome
- More recent studies have elucidated the health and economic impacts

Risk of Death is Higher in Patients Infected with Resistant Strains

		Deaths (%)		
	Outcome (number of studies included)	**Resistant**	**Not resistant**	**RR (95% CI)**
***Escherichia coli* resistant to:**				
3rd gen. cephalosporins	Bacterium attributable mortality (n=4)	23.6	12.6	2.02 (1.41 to 2.90)
Fluoroquinolones	Bacterium attributable mortality (n=1)	0	0	
***Klebsiella pneumoniae* resistant to:**				
3rd gen. cephalosporins	Bacterium attributable mortality (n=4)	20	10.1	1.93 (1.13 to 3.31)
Carbapenems	Bacterium attributable mortality (n=1)	27	13.6	1.98 (0.61 to 6.43)
***Staphylococcus aureus* resistant to:**				
Methicillin (MRSA)	Bacterium attributable mortality (n=46)	26.3	16.9	1.64 (1.43 to 1.87)

Estimates of Burden of Antibacterial Resistance

European Union
population 500m

25,000 deaths per year

2.5m extra hospital days

Overall societal costs
(€ 900 million, hosp. days)
Approx. €1.5 billion per year

Source: ECDC 2007

Thailand
population 70m

>38,000 deaths

>3.2m hospital days

Overall societal costs
US$ 84.6–202.8 mill. direct
>US$1.3 billion indirect

Source: Pumart et al 2012

United States
population 300m

>23,000 deaths

>2.0m illnesses

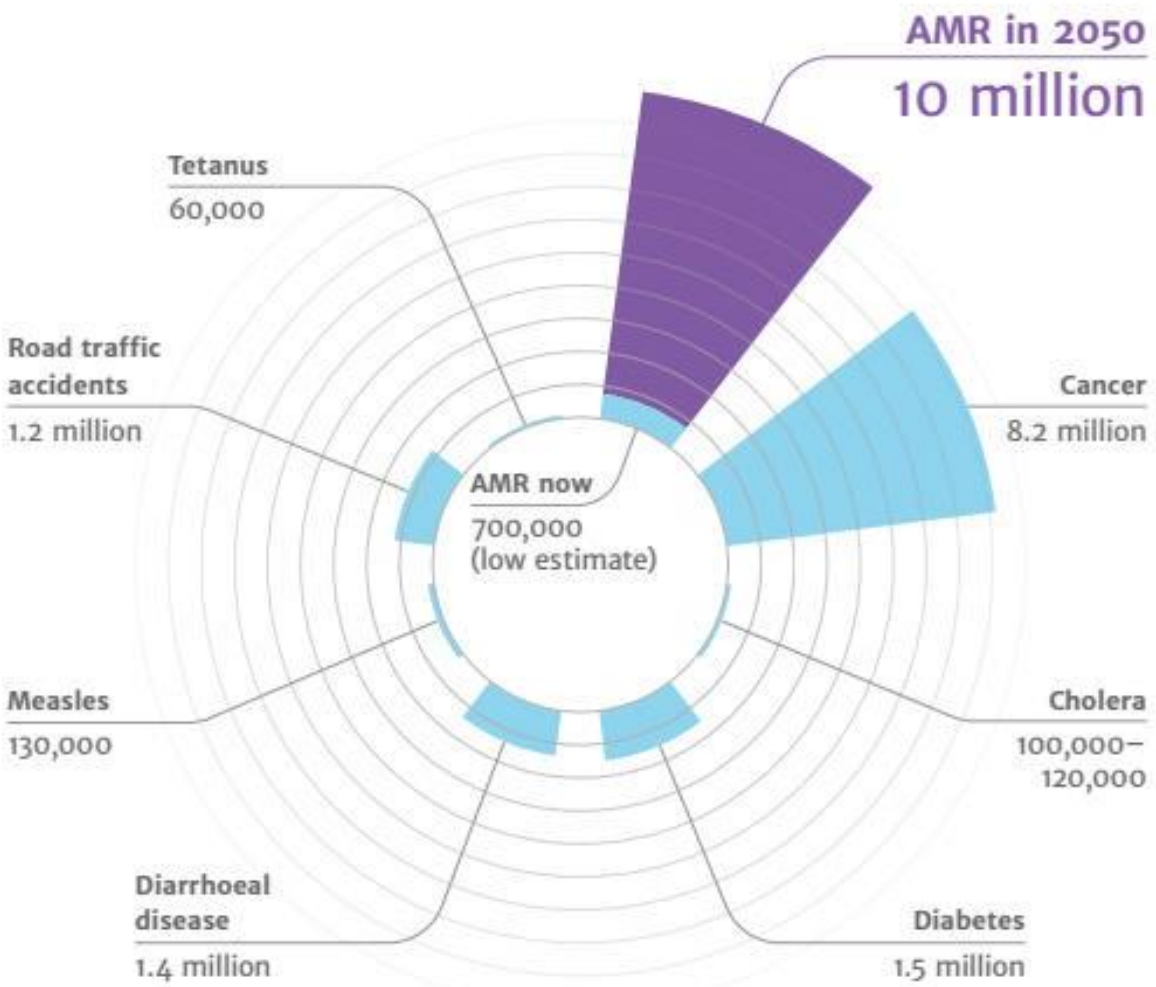
Overall societal costs
Up to $20 billion direct
Up to $35 billion indirect

Source: US CDC 2013

Global information is insufficient to show complete disease burden impact and costs


Review on
Antimicrobial
Resistance
TACKLING DRUG-RESISTANT
INFECTIONS GLOBALLY:
FINAL REPORT AND
RECOMMENDATIONS
THE REVIEW ON
ANTIMICROBIAL RESISTANCE
CHAIRED BY JIM O'NEILL
MAY 2016

DEATHS ATTRIBUTABLE TO AMR EVERY YEAR



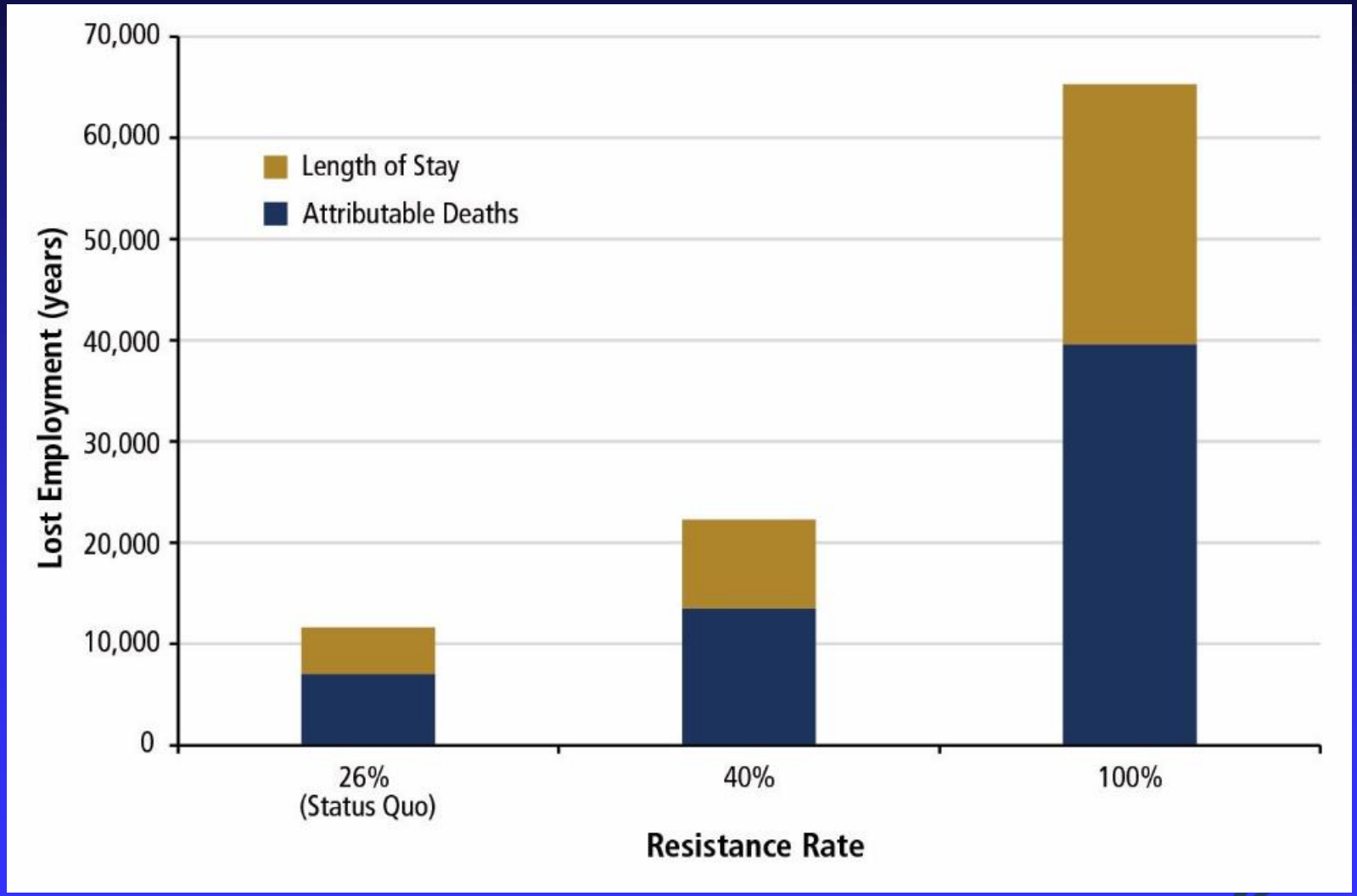
When Antibiotics Fail

The Expert Panel on the Potential Socio-Economic Impacts of Antimicrobial Resistance in Canada

CCA | CAC

ASSESSING **EVIDENCE**
INFORMING **DECISIONS**

AMR IS REDUCING THE SIZE OF THE CANADIAN WORKFORCE



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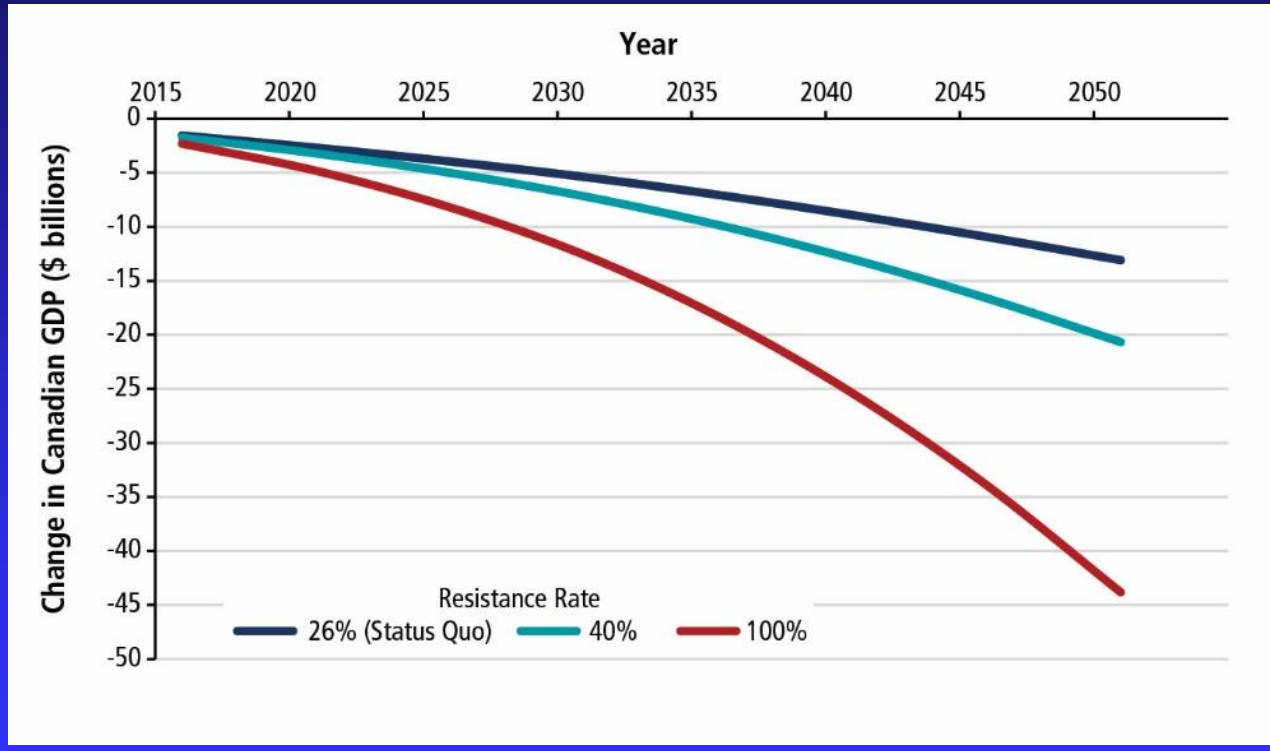
AMR IS REDUCING CANADA'S GDP

- AMR reduced Canada's GDP by an estimated $2B in 2018
- Canada's economy may lose an estimated $268-$386B in GDP by 2050 if resistance rates remain constant or continue to rise to 40%



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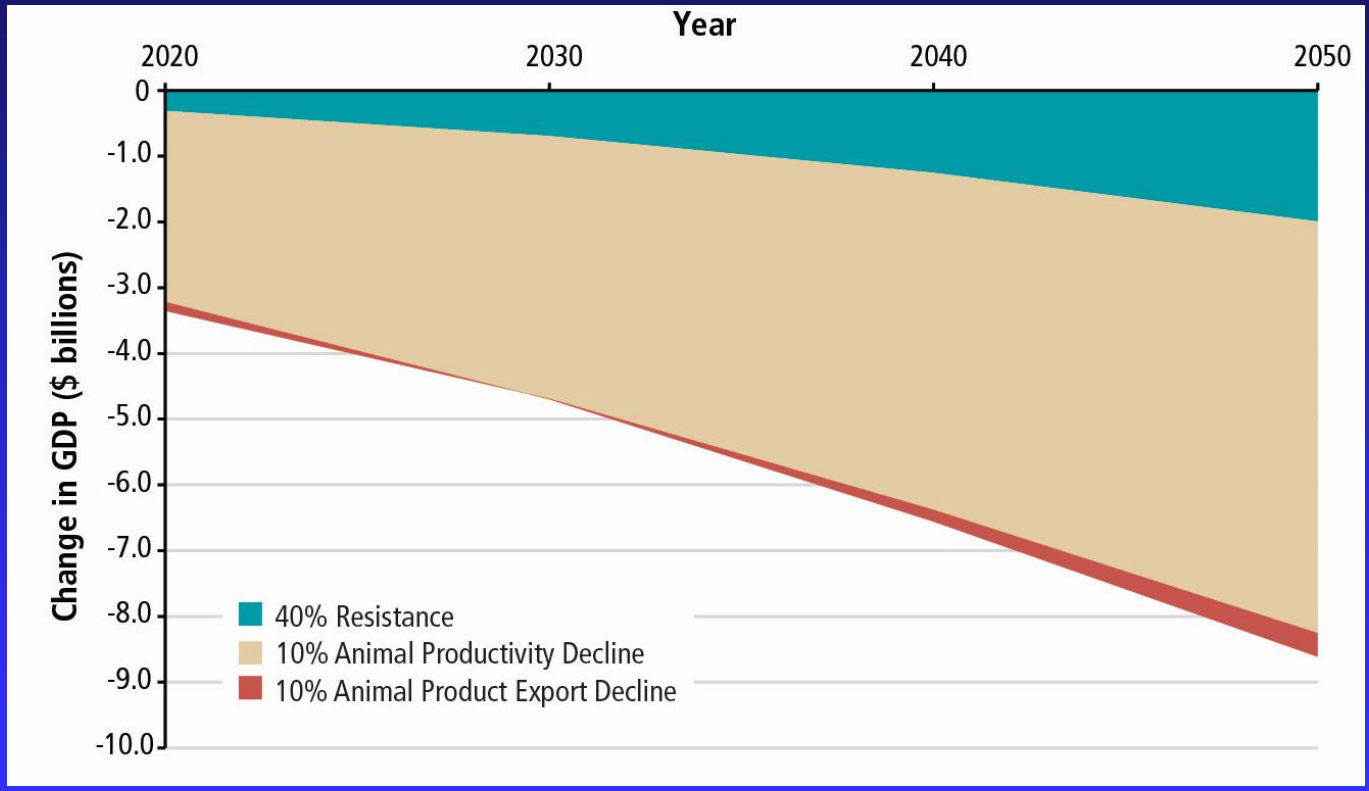
AMR MAY IMPACT ANIMAL FARMING INDUSTRY

- The Canadian animal farming industry may lose $37B by 2050 due to a reduction in the labour force if resistance increases to 40%
- Additional losses due to decreases in animal productivity and exports could amount to $190B



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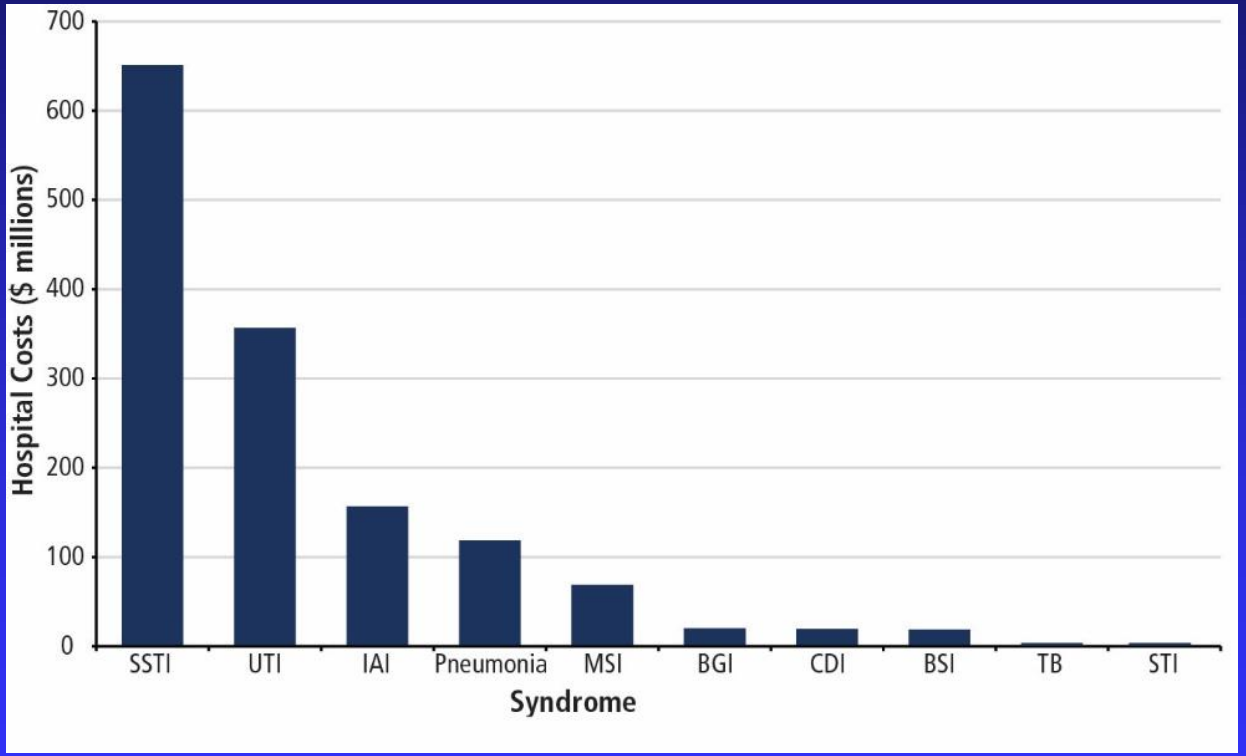
AMR Already Costs The Canadian Healthcare System an Estimated $1.4 B In 2018

Costs related to:

- lengthier hospital stays
- longer courses of treatment
- other expenses attributable to hospital-acquired resistant infections

0.6% of national healthcare spending



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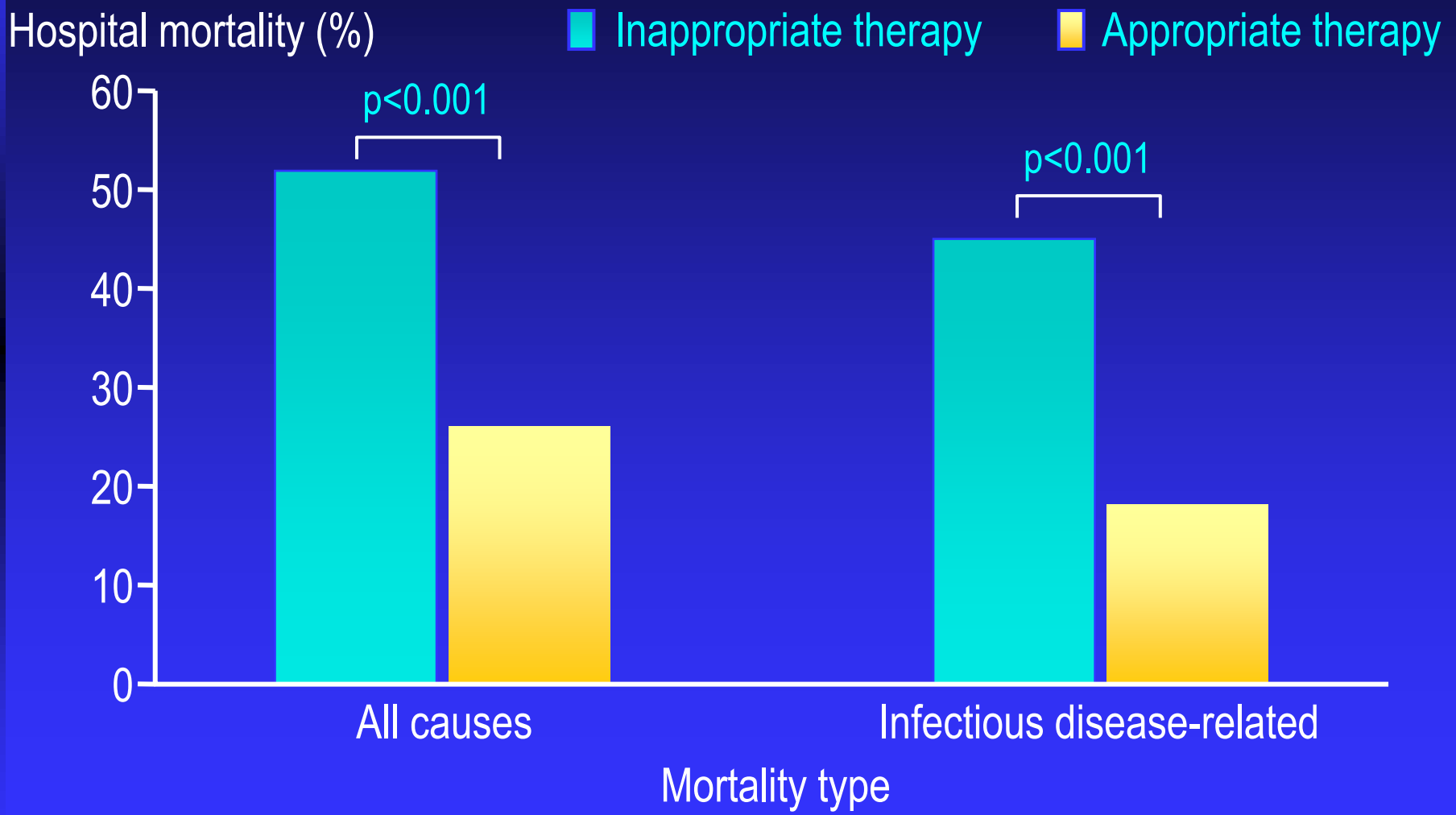
What are the implications of resistance at the individual level?

- Treatment failure due to wrong choice
- Use of more toxic alternatives
- Possibility of few or no alternate agents (egs. vancomycin-gentamicin-ampicillin resistant enterococci, vancomycin-resistant *S. aureus* and TDR-Mtb)
- Rise of vancomycin and methicillin -resistant *S aureus* an illustration – now multiple cases globally

Inappropriate antibiotic therapy is a risk factor for mortality among patients in the ICU

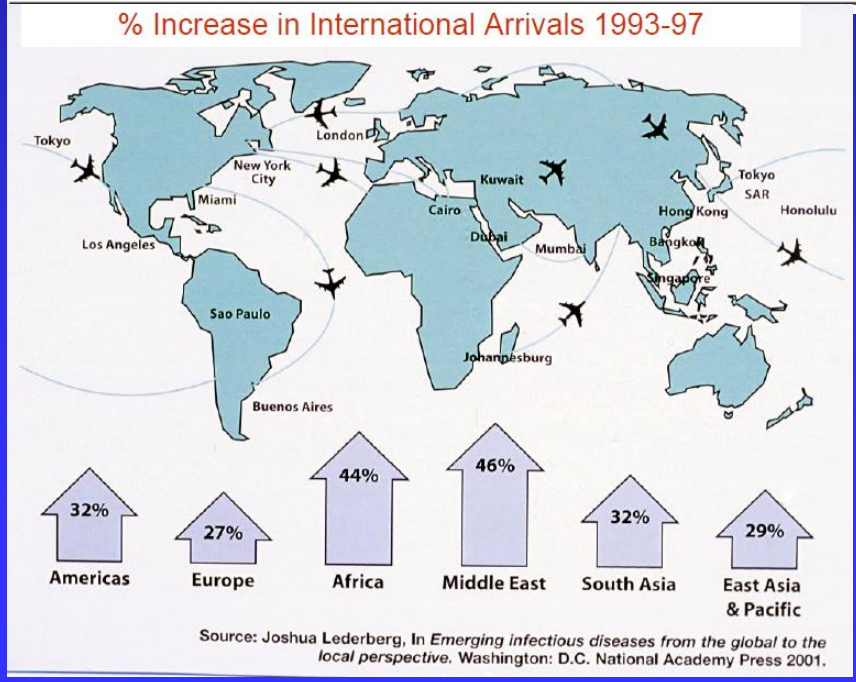


Kollef et al. Chest 1999;115:462–474

Propensity for Spread in a Shrinking World

Table. Global estimates of annual migrant populations

Administrative category	Population estimates and year	Reference
Refugees	16 million in 2007	(*18*)
Asylum seekers or refugee claimants	650,000 in 2007	(*18*)
Internally displaced persons	51 million in 2007, includes those displaced by natural disasters and conflict	(*18*)
Temporary (recreational or business travel) movement	924 million in 2008	(*19*)
Regular immigrants	Annual flow of 2.4 million, reported in 2005 (from a stock of 200 million immigrants worldwide)	(*20*)
International students	2.1 million in 2003	(*21*)
Migrant workers	81–86 million in 2005	(*22*)
Trafficked (across international borders) persons	Estimated 800,000 in 2006	(*23*)
Domestic arrivals, by air	Estimated 900 million in 2007	(*24*)

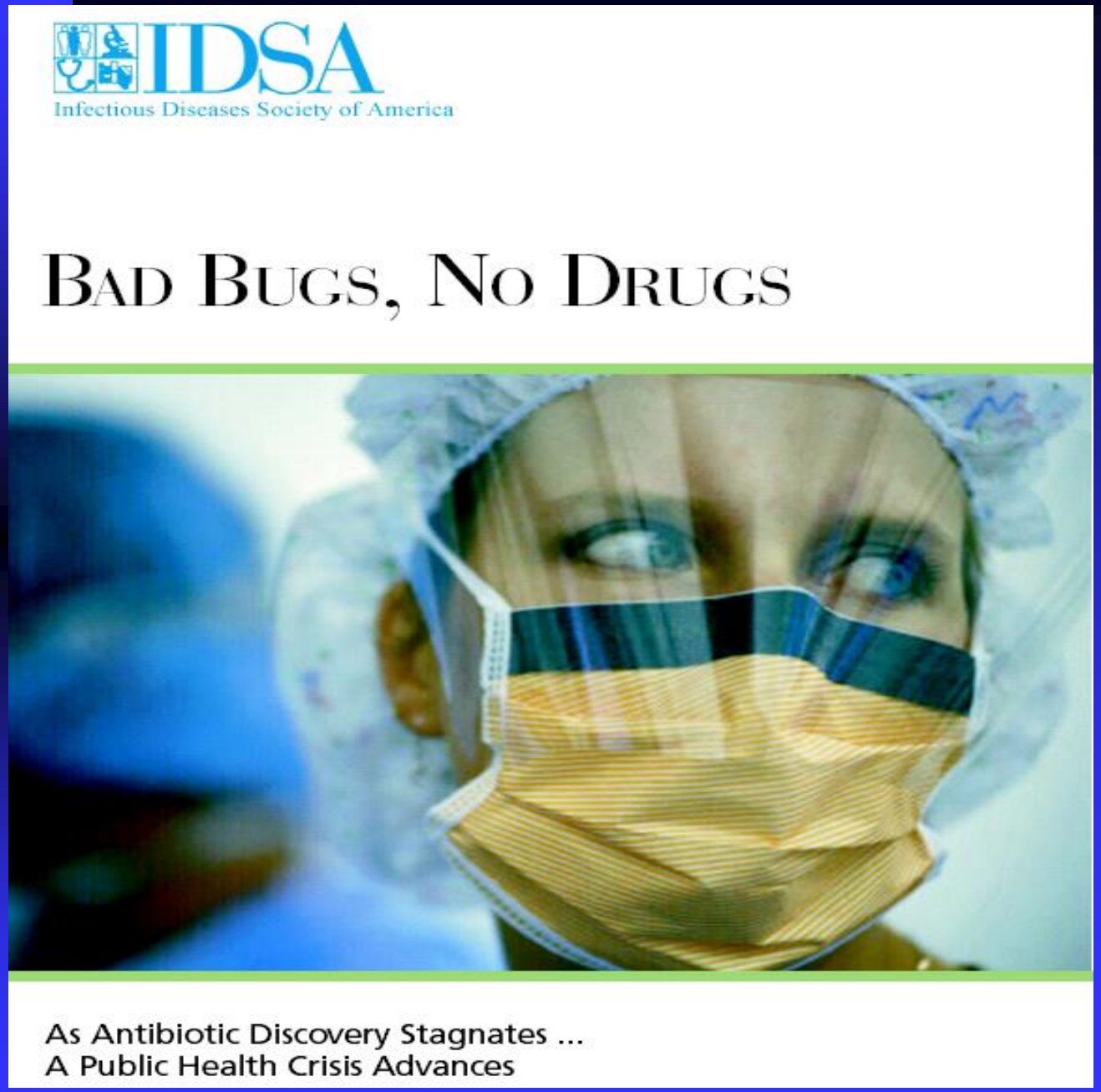


Source: Joshua Lederberg, In *Emerging infectious diseases from the global to the local perspective*. Washington: D.C. National Academy Press 2001.

MacPherson D, Gushulak B et al .Population Mobility, Globalization and Antimicrobial Resiatnce . Emerg Inf Dis 2009; 15: 1727-31

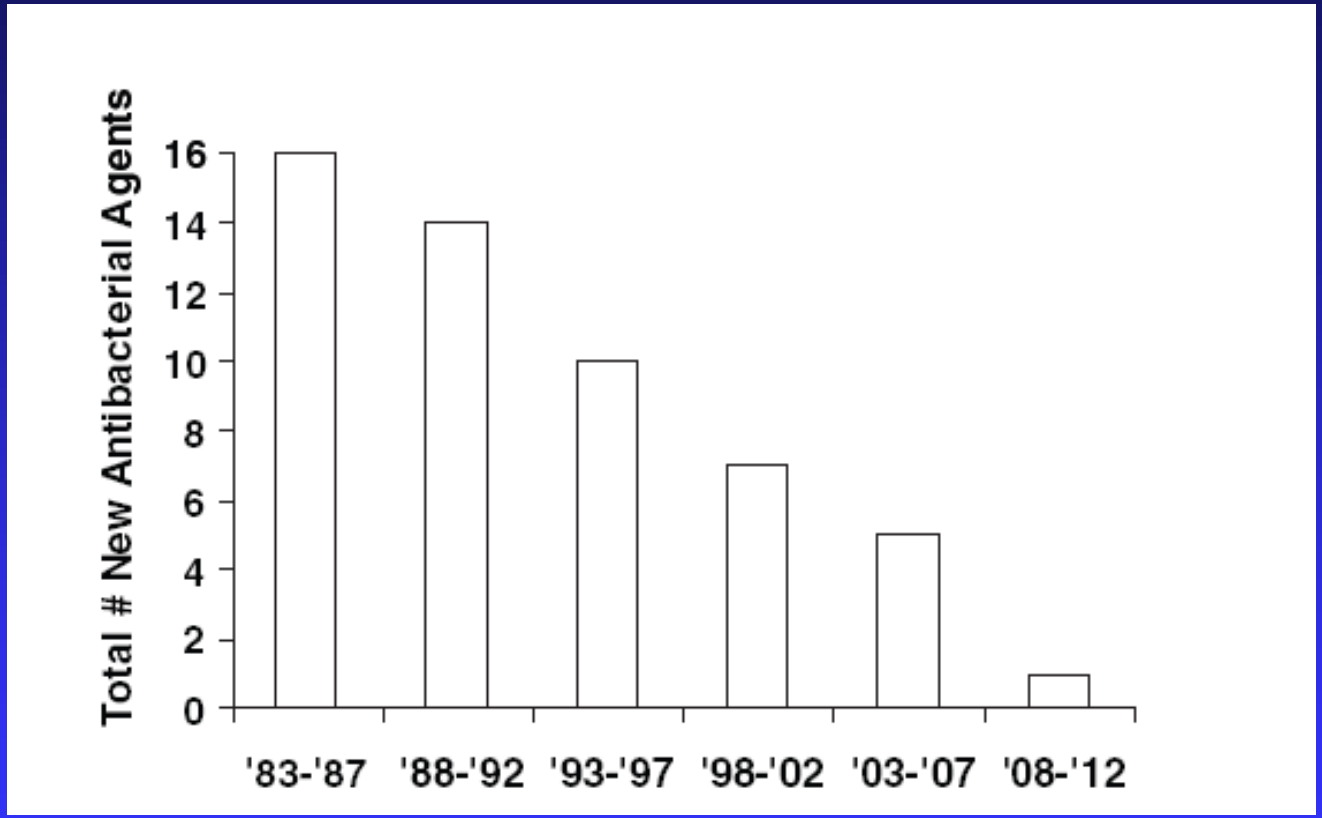
World.wmv

World.wmv



IDSA's 2004 Report: "Bad Bugs, No Drugs : As Antibiotic Discovery Stagnates, A Public Health Crisis Brews"

No Drugs: Pipeline is Dry and Shortages Abound



Source: Spellberg et al. Clinical Infectious Diseases, May 1, 2004

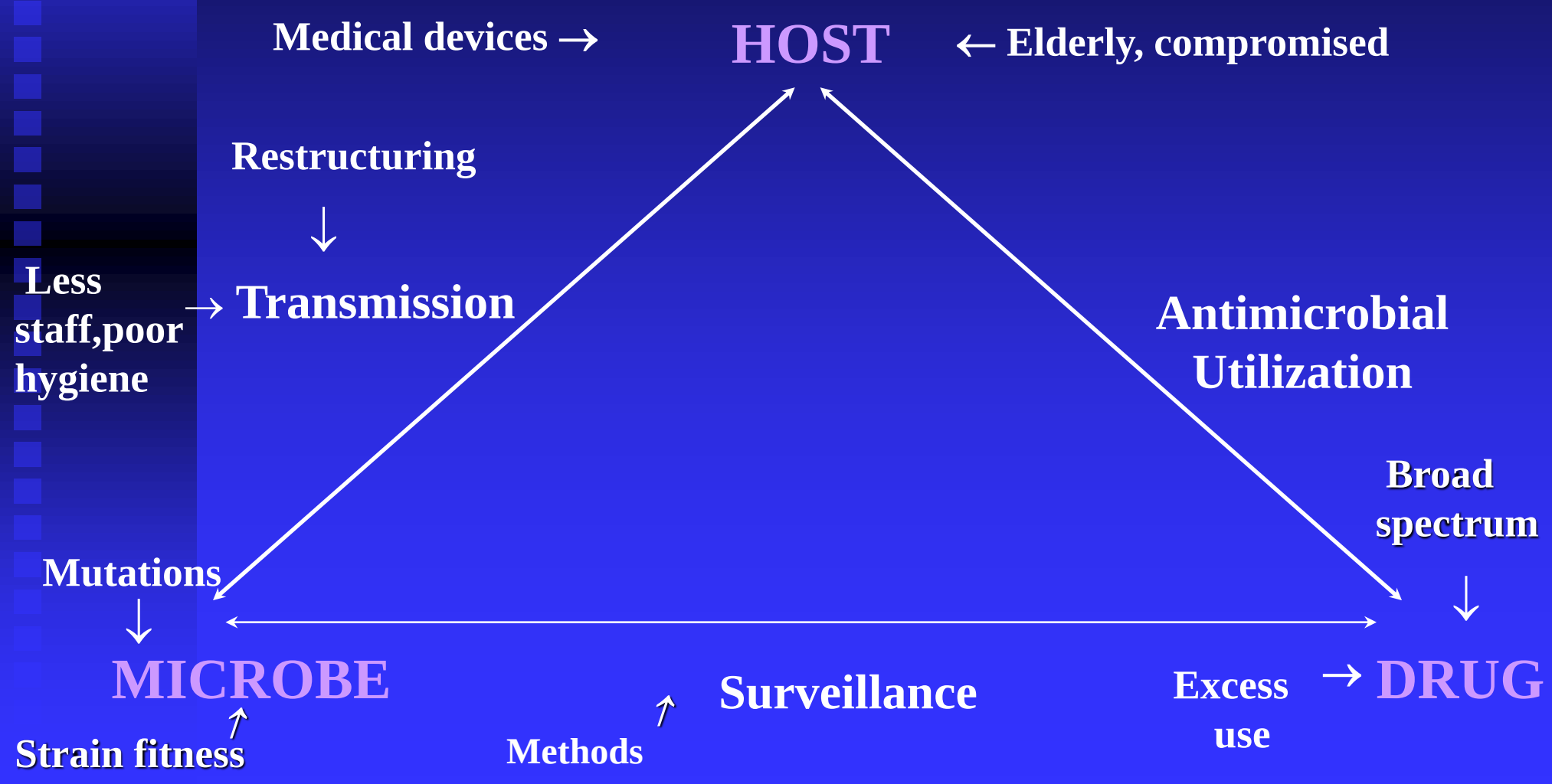
www.canadadrugshortage.com

No Drugs : New Antibacterial Agents Approved Since 1998

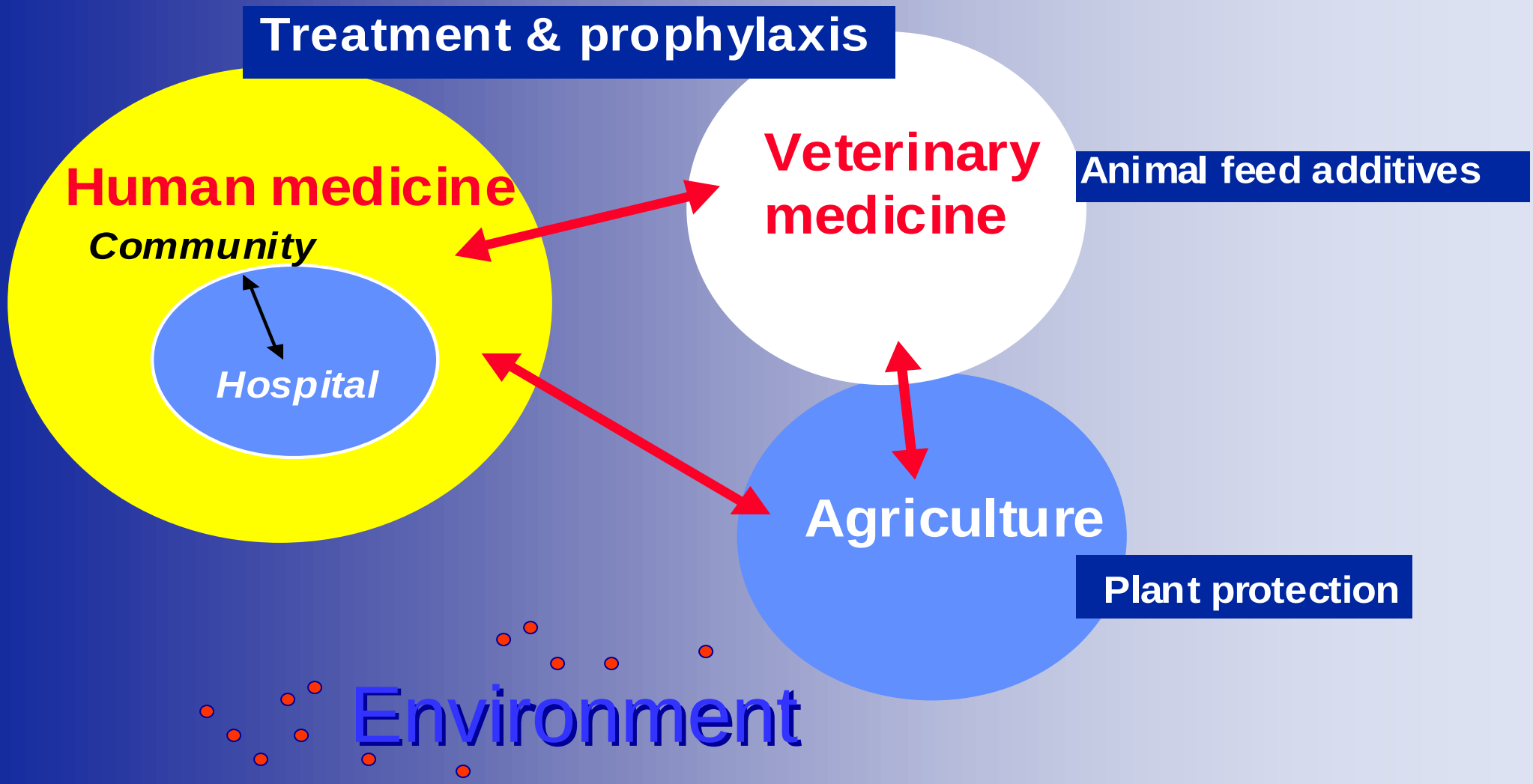
ANTIBACTERIAL	YEAR	Novel
Rifapentine	1998	No
Quinupristin/dalfopristin	1999	No
Moxifloxacin	1999	No
Gatifloxacin	1999	No
Linezolid	2000	Yes
Cefditoren pivoxil	2001	No
Ertapenem	2001	No
Gemifloxacin	2003	No
Daptomycin	2003	Yes
Telithromycin	2004	No
Tigecycline	2005	No
Doripenem	2007	No

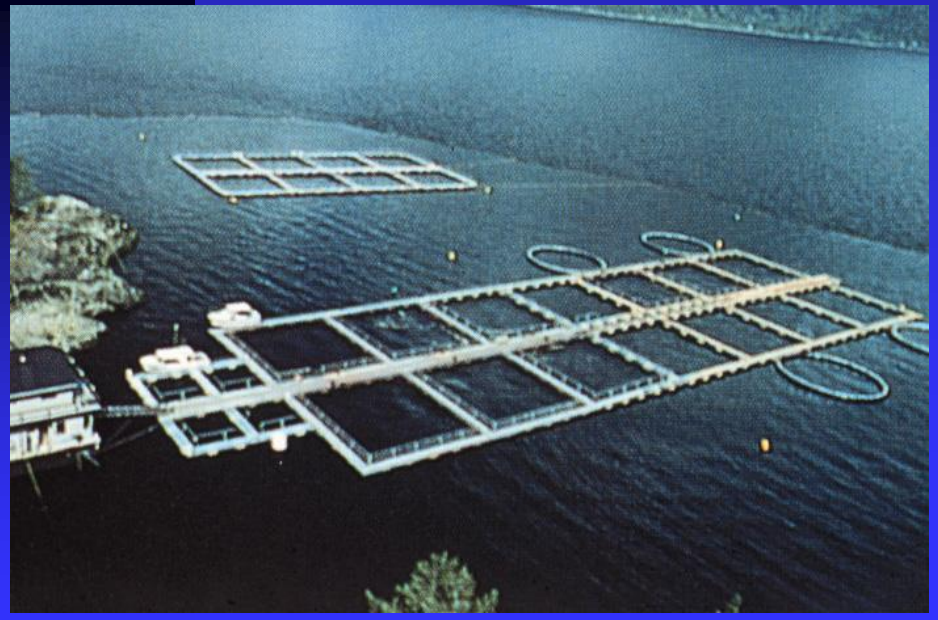
Spellberg *CID* 2004, modified

Antimicrobial resistance and the classic host-microbe-drug paradigm



ANTIBIOTIC ECOSYSTEMS



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Food Animal Sources and Animimicrobial Resistance

- 80% infections with Salmonella and Campylobacter in humans acquired from food animals
- Estimates of 4.5 million infections/yr NA due to Salmonella and Campylobacter and 50% resistant
- Implicated are the 24 million tons subtherapeutic use A/Bs used each year as growth promoters
- US FDA found 20% pork , turkey, beef and chicken samples Washington area + for Salmonella of which 84 % resistant to at least 1 antibiotic, including ceftriaxone

Aquaculture Sources and Animicrobial Resistance

- Recent studies farmed shrimp (raw or frozen) Switzerland revealed 41% of 17 different samples mostly from SE Asia + for MDR organisms mainly ESBL *E. coli* and *K. pneumoniae*
- Testing of 121 seafood products originating in Asia purchased from retail groceries in Canada
- *bla* $_{\text{OXA-48}}$ were isolated from 4 (3.3%) of the samples tested from China (n=2) and Korea (n=2) and included squid, sea squirt, clams and seafood medley

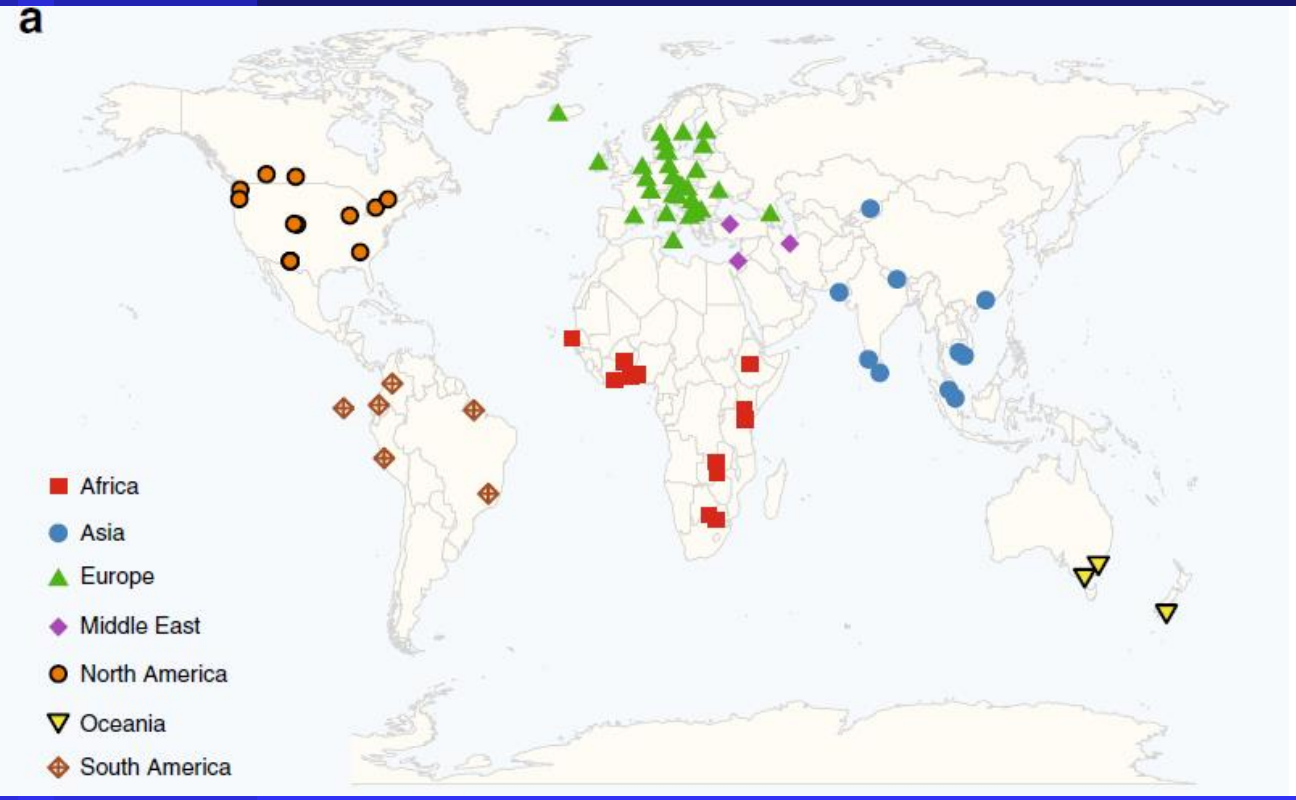
Morrison B, Rubin J. Carbapenemase producing bacteria in the food supply escaping detection. PLoS One 2015; 10(5): e0126717

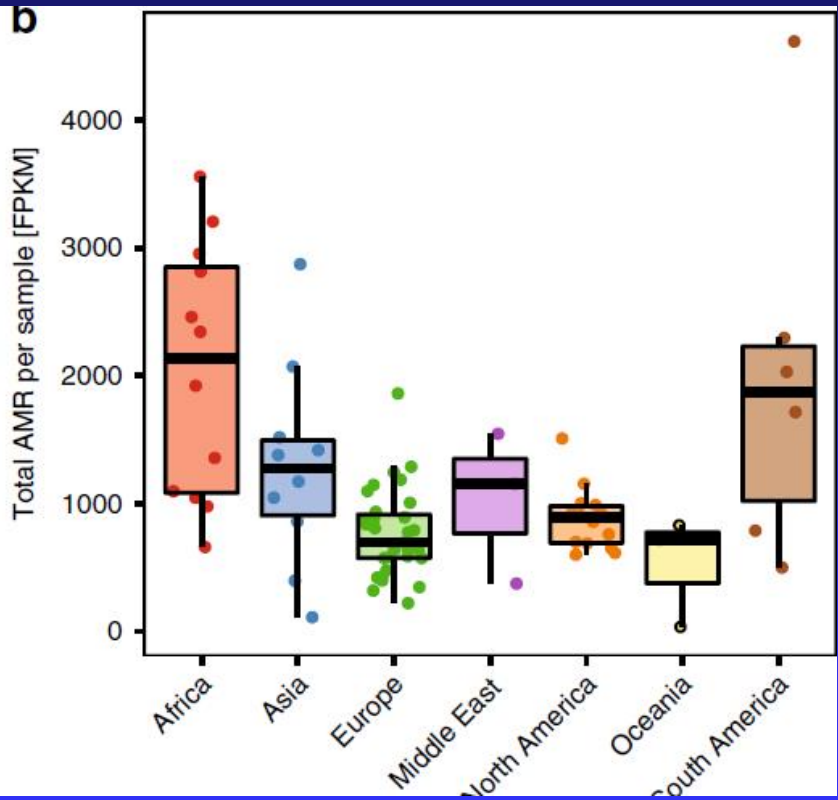
Source, identification and antimicrobial susceptibility of organisms producing carbapenemases

Seafood Product	Seafood Medley*	Clams	Sea Squirt	Squid
Market Location	Saskatoon	Saskatoon	Vancouver	Toronto
Country of Origin	China	China	Korea	Korea
Bacterial Species	*Stenotrophomonas maltophila*	*Myroides odoratimimus*	*Stenotrophomonas* spp.	*Pseudomonas putida*
***bla* Gene**	OXA-48	OXA-48	OXA-48	OXA-48
E-test MIC (µg/ml)				
Ertapenem	>32	0.75	>32	3
Meropenem	>32	3	>32	1.5
Tigecycline	1	1.5	0.38	3
Colistin	>256	16	0.5	1

Morrison B, Rubin J. Carbapenemase producing bacteria in the food supply escaping detection. PLoS One 2015; 10(5): e0126717

Sampling Sites Sewage and Boxplots of AMR Fragments/KB/10^6 Fragments in each Sample

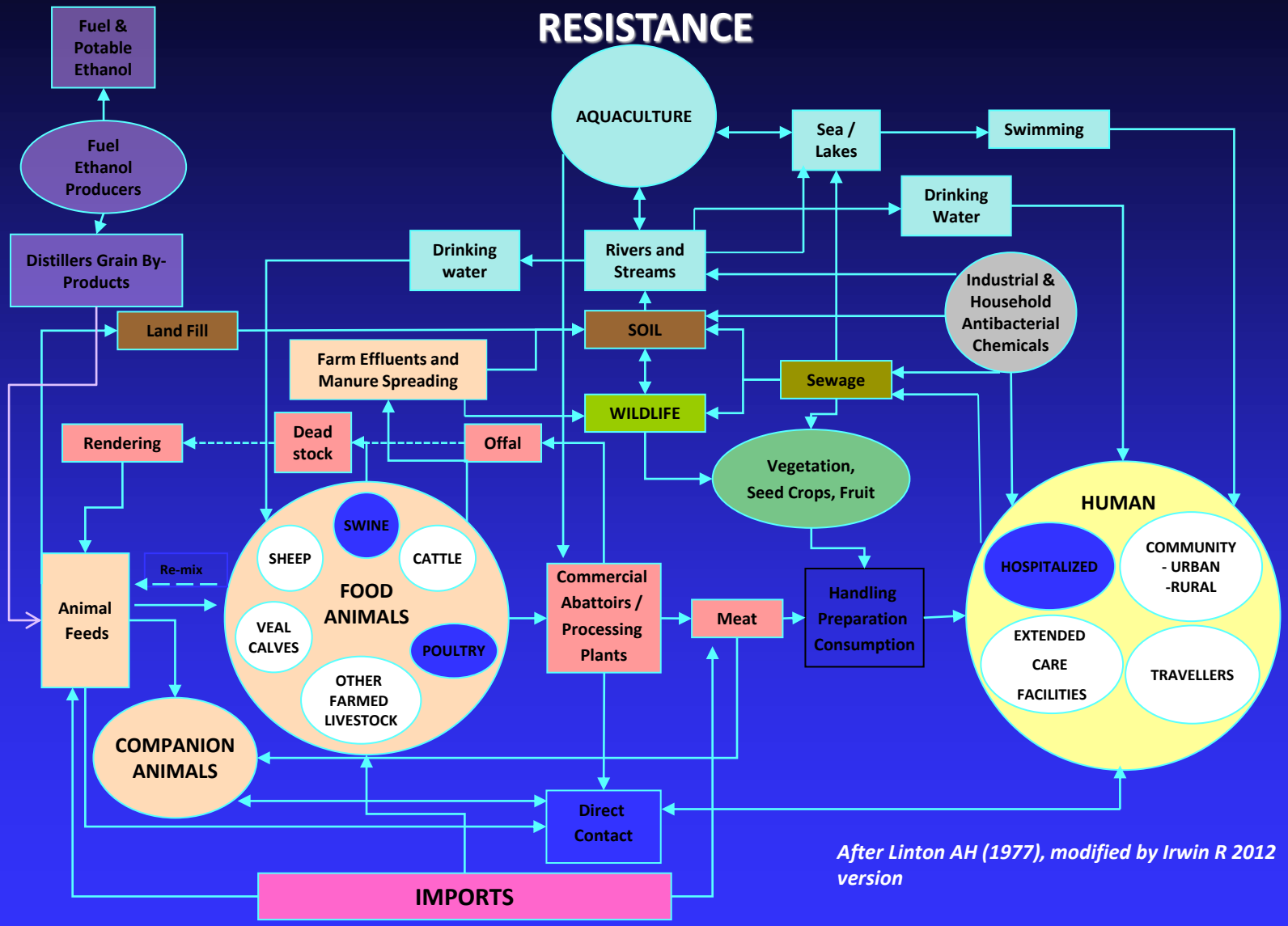




Hendriksen R et al. Global monitoring of antimicrobial resistance based on metagenomics analyses of urban sewage. Nature Comm. March 2019

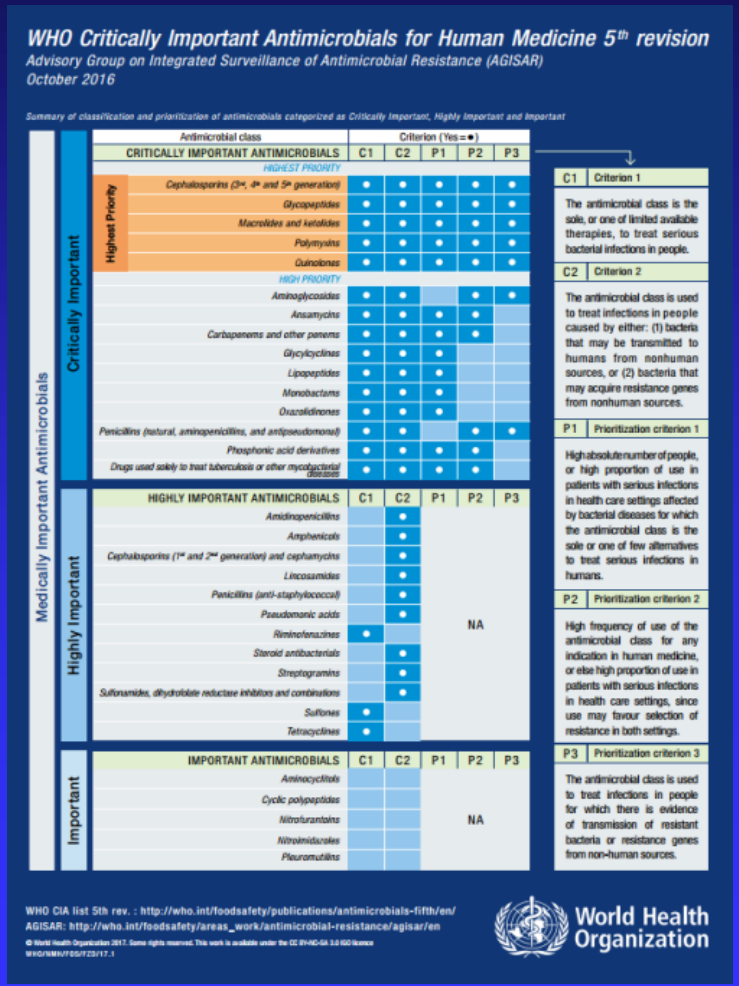
AMR Ecosystem

EPIDEMIOLOGY OF ANTIMICROBIAL RESISTANCE



After Linton AH (1977), modified by Irwin R 2012 version

WHO optimal use of antimicrobials in food producing animals to protect global health



Reference :

Antimicrobial Resistance and Susceptible Populations

- Elderly
- Organ transplantation /immunosuppression
- Cancer/chemotherapy
- HIV/AIDS
- Chronic renal/hepatic disease
- Chronic organ dysfunction
- Alcohol/substance abuse
- Multiplicity/complexity of medical devices

Factors that may Increase Antimicrobial Resistance in Hospitals

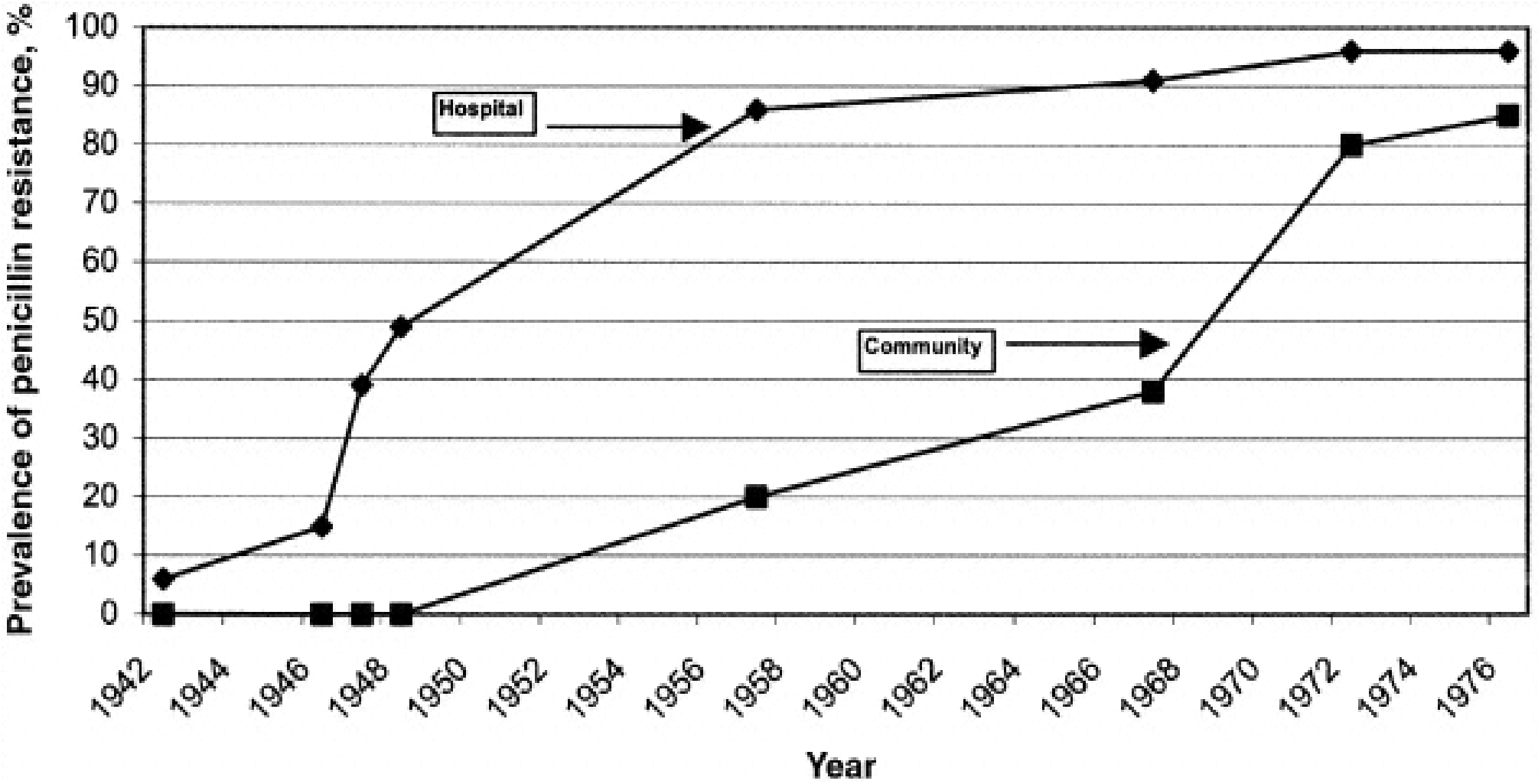
- Ineffective infection control and isolation practices and compliance
- Increased use of antimicrobial prophylaxis
- Increased empiric polymicrobial antimicrobial therapy
- High antimicrobial usage per geographic area per unit time

Modified from McGowan JE Jr. Is antimicrobial resistance in hospital microorganisms related to antibiotic use? Bull NY Acad Med 1987;63:253-268.
DM Shlaes, et al. Society for Healthcare Epidemiology of America and Infectious Disease Society of America Joint Committee… Infect Contr & Hosp Epidemiol 1997;18(4)275-91.

Emergence of Antibiotic Resistant Bacteria 1950-2020

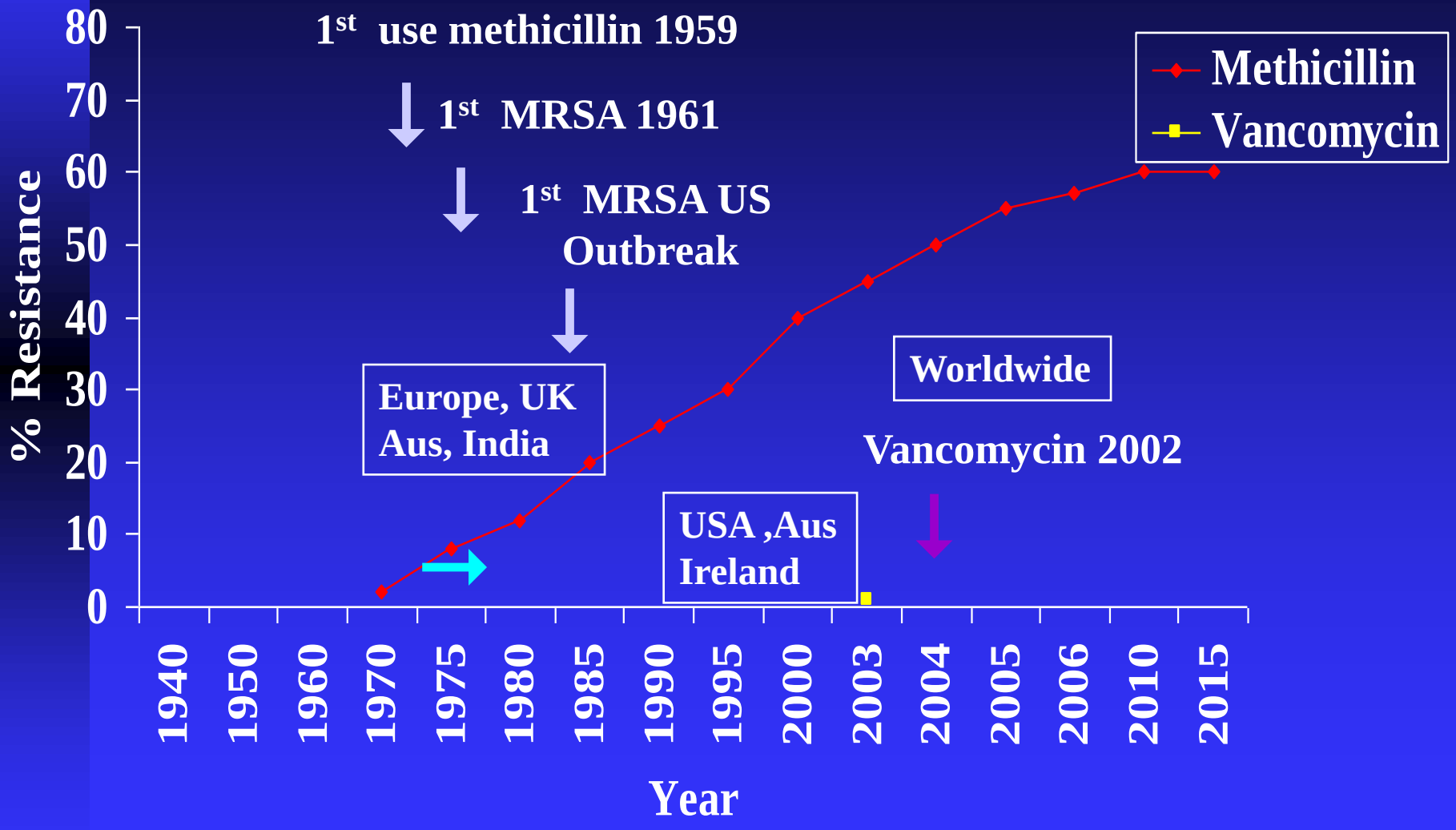
Source: Cohen;Science 1992;257:1050

Emergence of Penicillin Resistant *S aureus* ***1946-76***



Chambers et al EID 2001

S. aureus Resistance Timelines



The Changing Epidemiology of MRSA in the 21st Century

- Until the 1990s, community acquired-MRSA cases HCF-related or 2° IVDU
- Increasing reports of CA-MRSA without usual identifiable risk factors US and France
  - MMWR 1999 Minnesota/ND cases with a Type IV SCC*mec* – 4 deaths children and national attention
  - High infection rate among <16 year old subjects
  - Now widespread US and Western Canada

Conly J, Johnston L Can J Inf Dis 2003
Gilbert et al CMAJ 2006

Now We Have 'Flesh-Eating Pneumonia'

Norton

Drug-Resistant Germ Spreading Outside US Hospitals

By Maggie Fox

Killer Staph Is Hitting The Streets

by Catherine Arnst in New Y

The normally rob
basketh

Doctors Worry About Drug-Resistant Staph Infections

POSTED: 11:57 am EDT September 30, 2004

TRENTON, N.J. -- Flesh-eating bacteria cases, fatal pneumonia and life-threatening heart infections suddenly are popping up around the country, striking healthy people and stunning their doctors.

The cause? Staph, a bacteria better known for causing skin boils easily treated with standard antibiotic pills.

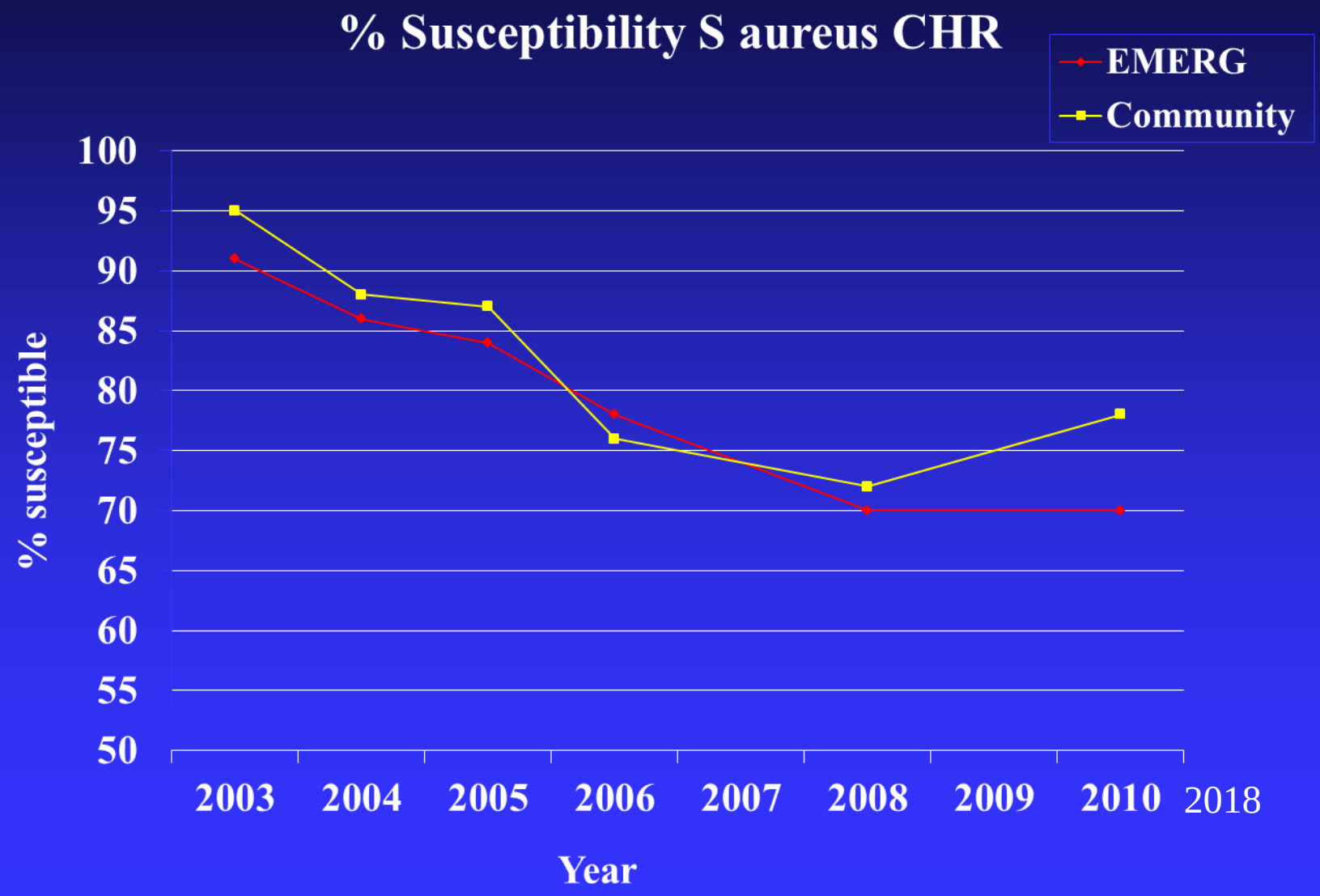
No more, say infectious disease experts, who increasingly are seeing these "super bugs" -- strains of Staphylococcus aureus unfazed by the entire penicillin family and other first-line drugs.

Increase in staph infections bewilders local physicians

By LEIGH HOPPER
Copyright 2003 Houston Chronicle Medical Writer

A 14-year-old baseball player from Alief, unconscious and on a breathing machine in the Texas Children's Hospital intensive care unit since Oct. 22, is the latest in an alarming series of hospitalizations triggered by antibiotic-resistant bacteria known as MRSA.

Emerging Trends in Resistance



Selection of AROs

- Multiple factors
- Predicted as early as 1942 by Rene Dubos
- Importance of maintaining ecological balance paramount
- Overuse of antibiotics provides selective pressure for emergence of resistant organisms

Evolution, Microbes and Humans

- Bacteria 3.5-3.8 billion years
- Mammals 60 million years
- Homo erectus 2.5 million years
- Homo sapiens 125,000 years
- Antimicrobials 70 years

Evolutionary Changes in Microbes

- Arrival of first bacteria 3.5 billion years ago
- Constant evolution
- Selection pressure “survival of the fittest”
- Comparison of rRNA divergence between *E. coli* and Salmonella suggests a common ancestor 120-160 million years ago at same time as the evolving of mammals

Genetics of Antimicrobial Resistance

- Microevolutionary change-minor change in DNA; point mutation e.g. alters target site
- Macroevolutionary change-major change in DNA; large segment rearrangement; inversion duplication e.g. new protein production
- Acquisition of new DNA-plasmids; phages; transposable elements (unlimited capacity to adapt and change)

Biochemical mechanisms of resistance and their genetic basis

Biochemical mechanism	*Antibiotic Examples*	*Genetics*			*Example Organisms*
		Mutation		*Gene acquisition*	
Inactivation of drug	Aminoglycosides			+	Enterococci , *E. coli*
	β-Lactams	+		+	Enterococci ,*S. aureus* , *E. coli*
	Chloramphenicol			+	Staphylococci

Biochemical mechanisms of resistance and their genetic basis

Biochemical mechanism	*Antibiotic Examples*	*Genetics*		*Example Organisms*
		Mutation	*Gene acquisition*	
Alteration of target	**Erythromycin**		+	***S. pneumoniae***
	Fluoroquinolones	+		***S. aureus , E. coli***
	Rifampin	+		**Staphylococci, Enterococci**
	Tetracyclines		+	***N. gonorrhoeae***
	β-Lactams		+	***S.aureus,S. pneumoniae***
	Vancomycin		+	**Enterococci**

Biochemical mechanism	*Antibiotic Examples*	*Genetics* *Mutation acquisition*	*Gene*	*Example Organisms*
Active efflux	**Erythromycin**		+	**Staphylococci,** *S. pneumoniae*
	Fluoroquinolones	+		***P. areuginosa***
	Tetracyclines		+	**Enterococci ,** ***S. aureus , E. coli***
Reduced permeability	**Aminoglycosides** **β-Lactams**	+ +	+ +	***P. aeruginosa, E coli*** ***P.aeruginosa, Enterobacter sp.***
Bypass step	**Sulphonamides**		+	***S. pneumoniae, E. coli***

Selected current problems with antimicrobial drugs, according to organism

Organism	Problem
Gram-positive cocci	Methicillin-resistant *Staph aureus* and coagulase-negative staphylococci; penicillin-resistant pneumococci; macrolide-resistant streptococci; vancomycin-resistant enterococci
Gram-negative cocci	Penicillin-resistant meningococci; quinolone-resistant gonococci ceftriaxone resistant gonococci

Selected current problems with antimicrobial drugs, according to organism

Organism	Problem
Acid-fast bacilli	Multidrug-resistant *Mycobacterium tuberculosis*; multidrug-resistant *M. avium* complex

Selected current problems with antimicrobial drugs, according to organism

Organism	Problem
Gram-negative bacilli	*Enterobacter* and other Enterobacteriaceae with chromosomal B-lactamases; multidrug- resistant *Pseudomonas* and *S maltophilia;*Enterobacteriaceae with ES B-lactamases; multidrug-resistant diarrheal pathogens (shigella species, salmonella species, *Escherichia coli*, campylobacter species); carbapenemase producing organisms

Headlines Aug 11 2010 NDM-1 New Superbug

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NDM1 - New Super Bug - The Death Of Us All? 78

By MrHACCP

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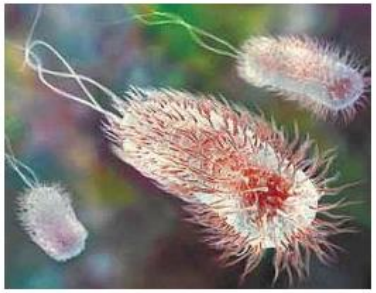
New Super Bug NDM1 - The Name of Death?

Its official, we have a new super bug in the UK, USA and Canada and It's called NDM 1. NDM1 deaths are rising and it will be the death of us all sooner or later, or will it? First off, let's get this straight; it's not a super bug as such but rather a super weapon used by bugs or bacteria that are already dangerous and infectious.



E.Coli Bacterium - A Killer

The Reaper Is On The March

11 August 2010 Last updated at 09:14 ET

New 'superbug' found in UK hospitals

By Michelle Roberts
Health reporter, BBC News

A new superbug that is resistant to even the most powerful antibiotics has entered UK hospitals, experts warn.

They say bacteria that make an enzyme called NDM-1 have travelled back with NHS patients who went abroad to countries like India and Pakistan for treatments such as cosmetic surgery.

NDM-1 Bacteria

Tracking the rise of a new superbug

NDM-1 NEWS

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www.Google.com/AdWords

Earls vs. Albino

Carbapenem-Non-Susceptible Acinetobacter baumannii in the United States

SEPTEMBER 26, 2011

Acinetobacter baumannii is emerging as an important nosocomial pathogen worldwide. We report molecular epidemiology of 65 carbapenem-non-susceptible A. baumannii isolates identified from hospitals in New York, Pennsylvania, Florida, Missouri, Nevada and California between 2008 and 2009. All isolates were

KPC – hard to shed, more likely to cause illness

SEPTEMBER 26, 2011

"But in the hospitals, we're always concerned about antimicrobial resistance, especially in the very ill patients that are immunocompromised. And the fact that these are multi-drug resistant and the odd one is now pan-resistant, it certainly is a concern in the hospitals." At the Jewish General, the first KPC case was discovered in August of [...]

Read the full article →

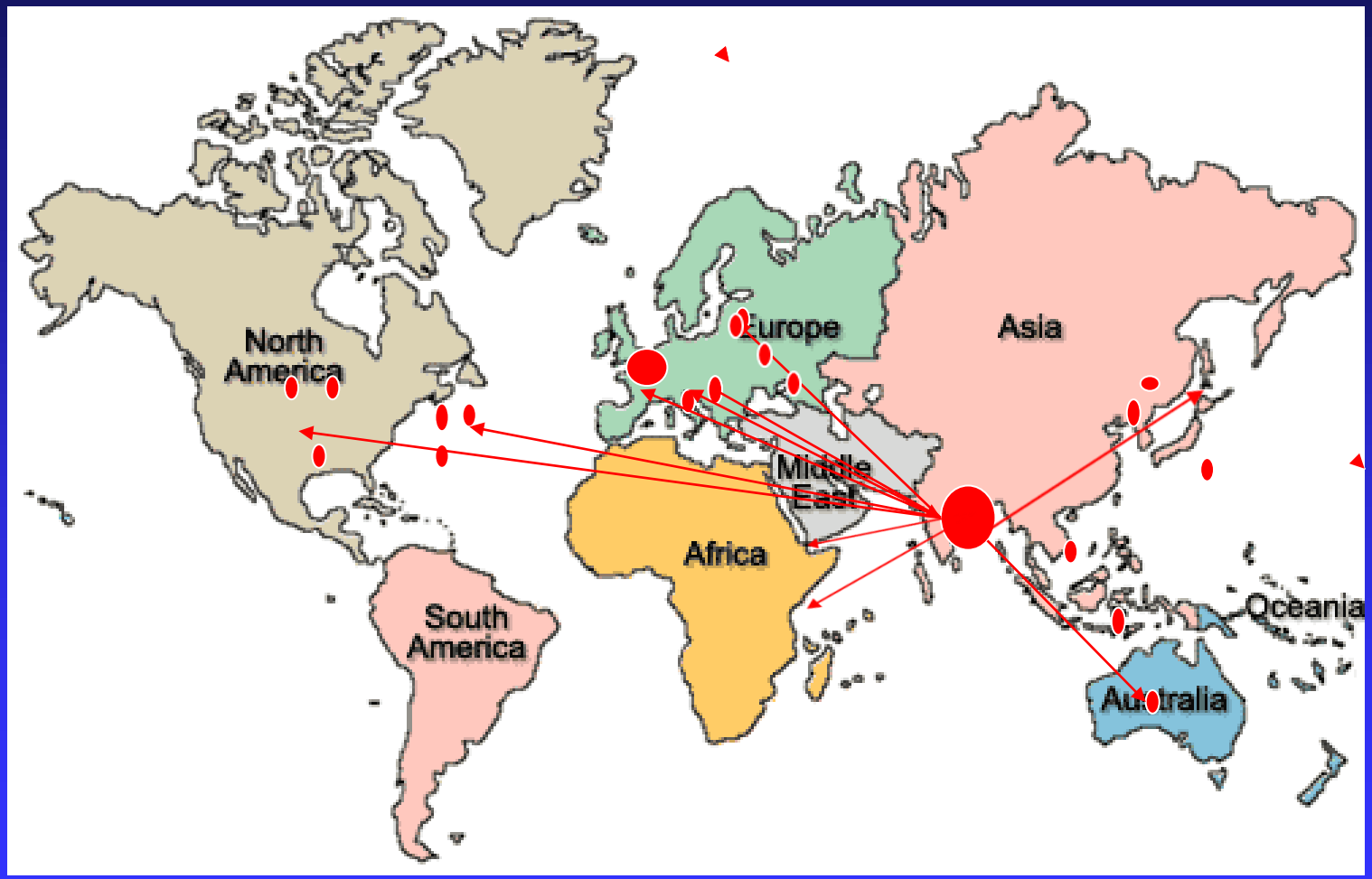
NDM1 and Pan-Resistance

	UK (n=37)		Chennai (n=44)		Haryana (n=26)	
	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*	MIC_{50}; MIC_{90} (mg/L)	Proportion susceptible*
Imipenem	32; 128	0%	64; 128	0%	32; 128	0%
Meropenem	32; 32	3%	32; >32	3%	>32; >32	3%
Piperacillin-tazobactam	>64; >64	0%	>64; >64	0%	>64; >64	0%
Cefotaxime	>256; >256	0%	>256; >256	0%	>256; >256	0%
Ceftazidime	>256; >256	0%	>256; >256	0%	>256; >256	0%
Cefpirome	>64; >64	0%	>64; >64	0%	>64; >64	0%
Aztreonam	>64; >64	11%	>64; >64	0%	>64; >64	8%
Ciprofloxacin	>8; >8	8%	>8; >8	8%	>8; >8	8%
Gentamicin	>32; >32	3%	>32; >32	3%	>32; >32	3%
Tobramycin	>32; >32	0%	>32; >32	0%	>32; >32	0%
Amikacin	>64; >64	0%	>64; >64	0%	>64; >64	0%
Minocycline	16; >32	0%	32; >32	0%	8; 16	0%
Tigecycline	1; 4	64%	4; 8	56%	1; 2	67%
Colistin	0·5; 8	89%†	1; 32	94%†	1; 2	100%†

MIC=minimum inhibitory concentration. *Susceptibility defined by British Society for Antimicrobial Chemotherapy and European Committee on Antimicrobial Susceptibility Testing breakpoints; doxycycline breakpoints were used for minocycline. †Colistin-resistant UK isolates were one isolate of *Morganella morganii* and one *Providencia* sp (both intrinsically-resistant species), also one *Klebsiella pneumoniae* and one *Enterobacter* sp.

Table: **Antibiotic susceptibilities for NDM-1-positive Enterobacteriaceae isolated in the UK and north (Chennai) and south India (Haryana)**

Global Spread NDM1



Note : Visitors, medical tourism, and intracountry secondary transmissions

Global Spread CROs [KPCs NDMs, Oxa-48]

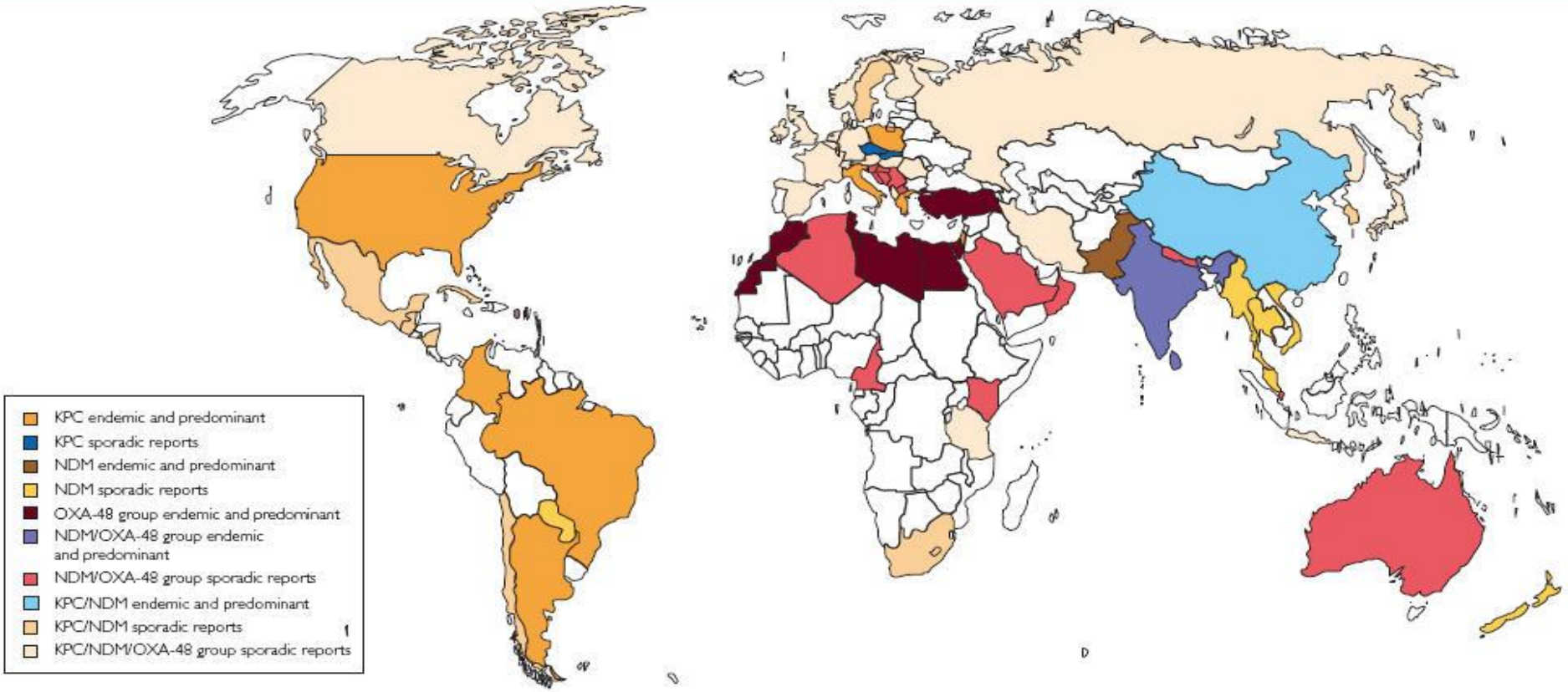


FIGURE. Distribution of *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo-β-lactamase (NDM), and OXA-48 group carbapenemases worldwide.

Vasoo S et al. Mayo Clin Proc. March 2015;90(3):395-403
http://dx.doi.org/10.1016/j.mayocp.2014.12.002

CARBAPENEM-RESISTANT ENTEROBACTERIACEAE

9,000 DRUG-RESISTANT INFECTIONS PER YEAR

600 DEATHS

CARBAPENEM-RESISTANT *KLEBSIELLA* SPP. **7,900**

1,400 CARBAPENEM-RESISTANT *E. COLI*

CRE HAVE BECOME RESISTANT TO ALL OR NEARLY ALL AVAILABLE ANTIBIOTICS

THREAT LEVEL
URGENT

This bacteria is an immediate public health threat that requires urgent and aggressive action.

Untreatable and hard-to-treat infections from carbapenem-resistant Enterobacteriaceae (CRE) bacteria are on the rise among patients in medical facilities. CRE have become resistant to all or nearly all the antibiotics we have today. Almost half of hospital patients who get bloodstream infections from CRE bacteria die from the infection.

RESISTANCE OF CONCERN

- Some Enterobacteriaceae are resistant to nearly all antibiotics, including carbapenems, which are often considered the antibiotics of last resort.
- More than 9,000 healthcare-associated infections are caused by CRE each year.
- CDC laboratories have confirmed at least one type of CRE in healthcare facilities in 44 states.
- About 4% of U.S. short-stay hospitals had at least one patient with a serious CRE infection during the first half of 2012. About 18% of long-term acute care hospitals had one.

PUBLIC HEALTH THREAT

An estimated 140,000 healthcare-associated Enterobacteriaceae infections occur in the United States each year; about 9,300 of these are caused by CRE. Up to half of all bloodstream infections caused by CRE result in death. Fortunately, bloodstream infections account for a minority of all healthcare-associated infections caused by Enterobacteriaceae. Each year, approximately 600 deaths result from infections caused by the two most common types of CRE, carbapenem-resistant *Klebsiella* spp. and carbapenem-resistant *E. coli*.

	Percentage of Enterobacteriaceae healthcare-associated infections resistant to carbapenems	Estimated number of infections	Estimated number of deaths attributed
Carbapenem-Resistant *Klebsiella* spp.	11%	7,900	520
Carbapenem-resistant *E. coli*	2%	1,400	90

For more information about data, methods and references, please see technical appendix.

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

What is NDM-1?

- New Delhi metallo-β-lactamase-1(MBL)
- Enzyme which confers resistance to one of the most potent classes of antibiotics, known as carbapenems
- Part of broad family of β-lactamase enzymes, carried by many microorganisms
- 4 major classes acting by a serine or zinc based mechanism
  - Major serine -β-lactamase carbapenemase is the KPC (Klebsiella pneumoniae carbapenemase)
  - Major metallo-β-lactamase carbapenemase : IMP- type, VIM-type and now NDM-1 type

Why is NDM-1 Different?

- Multi co-resistance carriage
  - Co-carriage of up to 14 other resistance traits (ß-lactamase genes, quinolone resistance genes, and 16S RNA methylase genes)
  - Pan resistance in some strains
- Present in common bacteria
  - *E. coli* most common cause UTI worldwide
  - Multiple other species of high public health importance – *Shigella*, *Vibrio* , *Salmonella*
- Highly mobile and promiscuous plasmids

Why is NDM-1 Different?

- Presence in environment and potable water
- Carriage in large segment of population
- Propensity for rapid spread
- No geographic/political boundaries for microorganisms
- Unabetted and massive use of antibiotics in all sectors of society
- Paucity of drugs available

Sanitation Nightmare

More than half of India's 203 million households lack a toilet—a situation that spreads disease; causes malnutrition and death; cuts growth; and undermines the nation's quest to become a global economic power.

Story and photograph by JASON GALE

World Health Organization

WHO PRIORITY PATHOGENS LIST FOR R&D OF NEW ANTIBIOTICS

Priority 1: CRITICAL[#]

Acinetobacter baumannii, carbapenem-resistant

Pseudomonas aeruginosa, carbapenem-resistant

Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant

Priority 2: HIGH

Enterococcus faecium, vancomycin-resistant

Staphylococcus aureus, methicillin-resistant, vancomycin intermediate and resistant

Helicobacter pylori, clarithromycin-resistant

Campylobacter, fluoroquinolone-resistant

Salmonella *spp.*, fluoroquinolone-resistant

Neisseria gonorrhoeae, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant

Reference: WHO Feb 2017

But ..... Can We Wait ?

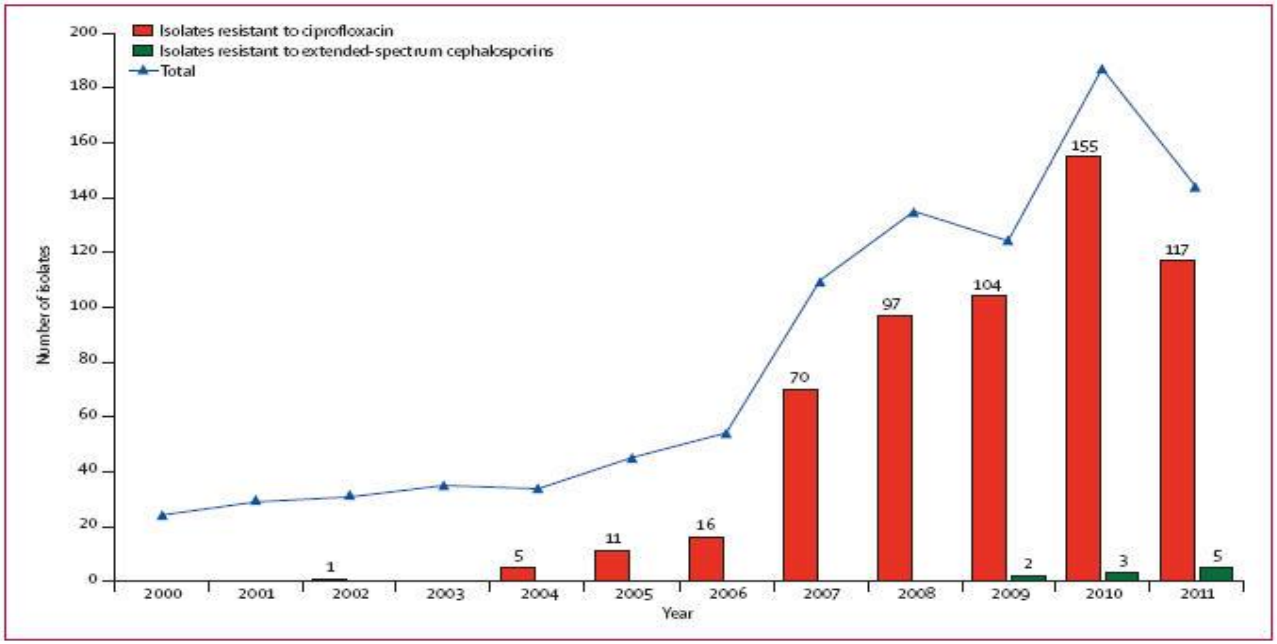


Figure: Human *Salmonella enterica* serotype Kentucky isolates identified at the French National Reference Centre for *Salmonella* in 2000–11
Overall yearly number of *Salmonella enterica* serotype Kentucky isolates is shown with blue triangles. During this period, 128 836 isolates of *Salmonella* spp were registered at the French National Reference Centre (12 883 in 2000, 12 601 in 2001, 11 775 in 2002, 10 472 in 2003, 10 589 in 2004, 11 439 in 2005, 10 154 in 2006, 8124 in 2007, 10 378 in 2008, 9947 in 2009, 9405 in 2010, and 11 069 in 2011).

Superbugs in food: a severe public health concern

In *The Lancet Infectious Diseases*, Simon Le Hello and colleagues outline a worrying progression towards potentially untreatable salmonella infections.[1] In the past decade resistance in *Salmonella enterica* serotype Kentucky (*S* Kentucky) has progressed relentlessly. Strains are increasingly multidrug resistant, not only to fluoroquinolones and third-generation cephalosporins but also to carbapenems.[1]

Previously, such resistance was mainly a problem in north Africa, but resistant strains can now be acquired in parts of Asia and Europe.[1,2] Although mainly associated with poultry, such bacteria are noted in other food production animals (eg, pigs), as are other multiresistant serotypes.[1–5]

unnecessary deaths—in the USA, estimates suggest more than a thousand extra deaths every year.[1,6] These resistant strains also seem to be more virulent and associated with increased rates of hospital admission.[2,7]

People acquire these resistant bacteria not only by direct ingestion of meat. Multidrug-resistant salmonella can spread in many ways, within countries and internationally. These bacteria can be transmitted via runoff from farms into waterways, in animal feed, and between breeding stocks.

Aquaculture (farming of aquatic organisms) probably helped lead to genetic transfer of multidrug-resistant *S* Kentucky.[2] Large amounts of antibiotics are added to waterways in fish feed. In many developing countries,

Dr Jeremy Burgess/Science Photo Library

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- Finding of highly drug-resistant *Salmonella* Enterica serotype Kentucky ST198-X1 France and Morocco
- CTX-M-1, CTX-M-15. CMY-2, OXA-48, VIM-2 In cipro-resistant isolates of S Kentucky from the Mediterranean basin since 2009
- Origins East and North Africa, Middle East, India

Le Hello et al Lancet Infect Dis 2013;13: 672–79
http://dx.doi.org/10.1016/S1473-3099(13)70124-5

Emergence of plasmid-mediated colistin resistance mechanism MCR-1 in animals and human beings in China: a microbiological and molecular biological study

Yi-Yun Liu, Yang Wang*, Timothy R Walsh, Ling-Xian Yi, Rong Zhang, James Spencer, Yohei Doi, Guobao Tian, Baolei Dong, Xianhui Huang, Lin-Feng Yu, Danxia Gu, Hongwei Ren, Xiaojie Chen, Luchao Lv, Dandan He, Hongwei Zhou, Zisen Liang, Jian-Hua Liu, Jianzhong Shen*

Summary

Background Until now, polymyxin resistance has involved chromosomal mutations but has never been reported via horizontal gene transfer. During a routine surveillance project on antimicrobial resistance in commensal *Escherichia coli* from food animals in China, a major increase of colistin resistance was observed. When an *E coli* strain, SHP45, possessing colistin resistance that could be transferred to another strain, was isolated from a pig, we conducted further analysis of possible plasmid-mediated polymyxin resistance. Herein, we report the emergence of the first plasmid-mediated polymyxin resistance mechanism, MCR-1, in Enterobacteriaceae.

Methods The *mcr-1* gene in *E coli* strain SHP45 was identified by whole plasmid sequencing and subcloning. MCR-1 mechanistic studies were done with sequence comparisons, homology modelling, and electrospray ionisation mass spectrometry. The prevalence of *mcr-1* was investigated in *E coli* and *Klebsiella pneumoniae* strains collected from five provinces between April, 2011, and November, 2014. The ability of MCR-1 to confer polymyxin resistance in vivo was examined in a murine thigh model.

Findings Polymyxin resistance was shown to be singularly due to the plasmid-mediated *mcr-1* gene. The plasmid carrying *mcr-1* was mobilised to an *E coli* recipient at a frequency of 10^{-1} to 10^{-3} cells per recipient cell by conjugation, and maintained in *K pneumoniae* and *Pseudomonas aeruginosa*. In an in-vivo model, production of MCR-1 negated the efficacy of colistin. MCR-1 is a member of the phosphoethanolamine transferase enzyme family, with expression in *E coli* resulting in the addition of phosphoethanolamine to lipid A. We observed *mcr-1* carriage in *E coli* isolates collected from 78 (15%) of 523 samples of raw meat and 166 (21%) of 804 animals during 2011–14, and 16 (1%) of 1322 samples from inpatients with infection.

Interpretation The emergence of MCR-1 heralds the breach of the last group of antibiotics, polymyxins, by plasmid-mediated resistance. Although currently confined to China, MCR-1 is likely to emulate other global resistance mechanisms such as NDM-1. Our findings emphasise the urgent need for coordinated global action in the fight against pan-drug-resistant Gram-negative bacteria.

Lancet Infect Dis 2016; 16: 161–68

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See Comment page 132

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Summary Key Points

- Antimicrobial resistance is a predictable outcome associated with antimicrobial use
- Appropriate antimicrobial use is the most important strategy to limit resistance
- Basic infection-control strategies - hand hygiene and appropriate cleaning of the environment and shared equipment, reduce the transmission of AROs

Discussion Questions

- Is human use or animal use the major source of antimicrobial resistance ?
- What should be done to curtail inappropriate antibiotic use across the spectrum of One Health ?