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Dr. Jerry Bell, Chair, ACS Presidential Climate Science Working Group
Dr. Bassam Z. Shakhashiri, 2012 President, ACS



Thursday, March 14, 2013

Getting A Head Through Chemistry: Great Beer and A Frothy Foam

Dr. Charlie Bamforth, Professor of Malting & Brewing Sciences at UC Davis
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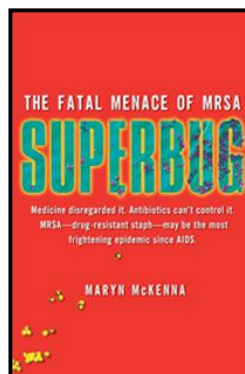
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ACS WEBINARS™
February 28, 2013



SUPERBUG: The Quest for Drug Developers



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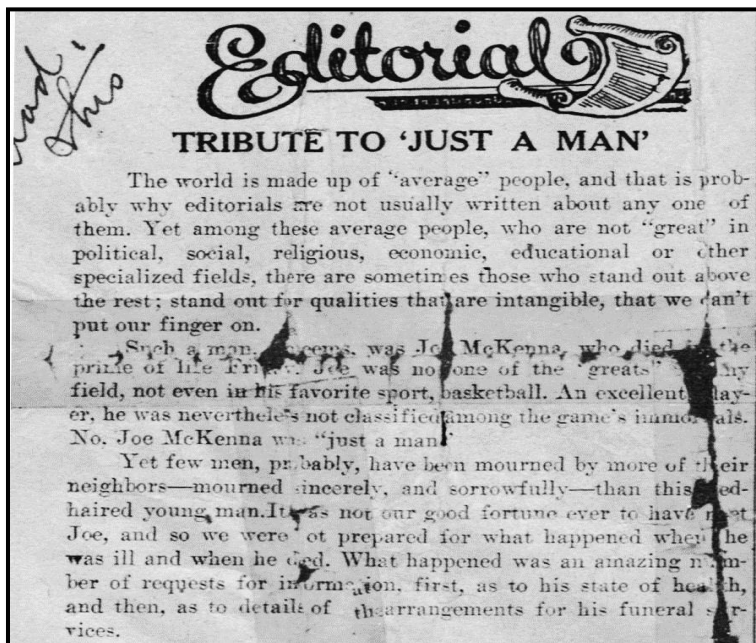
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Superbugs: The Quest for Drug Developers

Maryn McKenna, journalist and author
For the American Chemical Society
28 February 2013



+

"It is a rarity for a physician in the developed world to have a patient die of an overwhelming infection for which there are no therapeutic options. These cases were the first instance in our clinical experience in which we had no effective treatment to offer."

- Azza Elemam, Joseph Rahimian, William Mandell, St. Vincent's Hospital, NYC, 2009

+ Resistant organisms have become ubiquitous...

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- In hospitals and health-care institutions
- In everyday life (“the community”)
- In sexually transmitted diseases
- In agriculture and food animals
- In insect-borne diseases
- In sewage and surface water

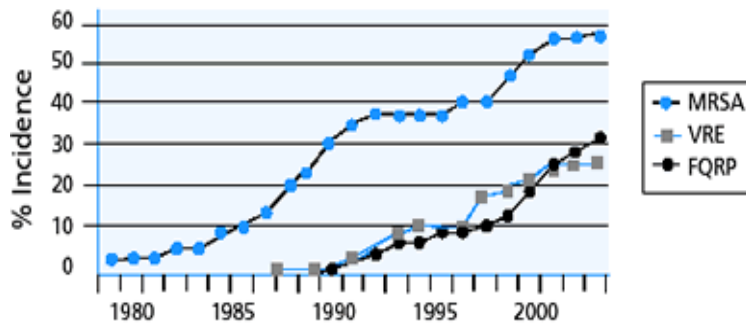
+ ... and are costly + destructive

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- Cause illness and unnecessary death
- Roll back control of infectious diseases
- Prevent societies from reaching public-health goals
- Increase the cost of health care
- Divert spending from other social goals
- Complicate agricultural development
- Decrease food security and creates vast waste
- Undermine international relationships and trade

+ *EX: Rise in MDR organisms, US*

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Source: Centers for Disease Control and Prevention

MRSA = Methicillin-resistant *Staphylococcus Aureus*

VRE = Vancomycin-resistant Enterococci

FQRP = Floroquinolone-resistant *Pseudomonas aeruginosa*

+ About how many more people does MRSA kill each year compared to the Swine Flu?

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- 1,200
- 5,000
- 7,000
- 13,000
- 20,000

+ EX: Spread + cost of MRSA, US

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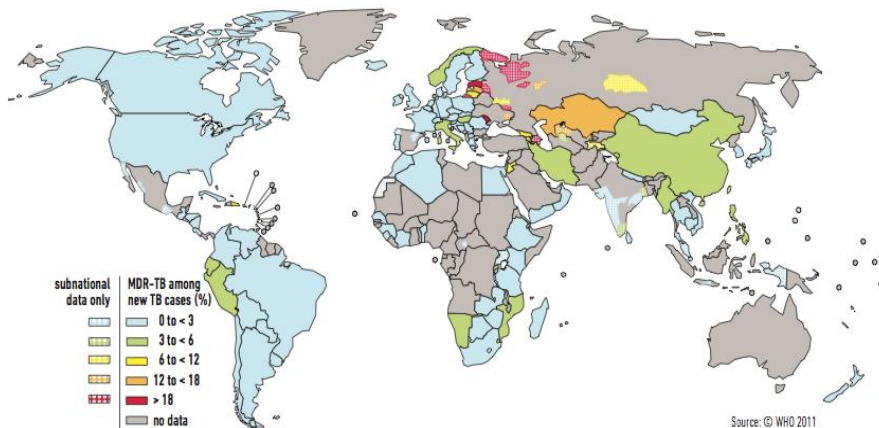
- 19,000 deaths/year
 - "swine flu" H1N1 ~12,000
- 369,000 hospitalizations/year
 - 2x average length of stay, 4x average cost of stay
- ~7 million office or ER visits/year
- \$4 billion to \$38 billion in additional healthcare costs/year

+ EX: Spread MDR-TB worldwide

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WHO: 440,000 new cases, 150,000 deaths/year

Percentage of MDR-TB among new TB cases, 1994–2010



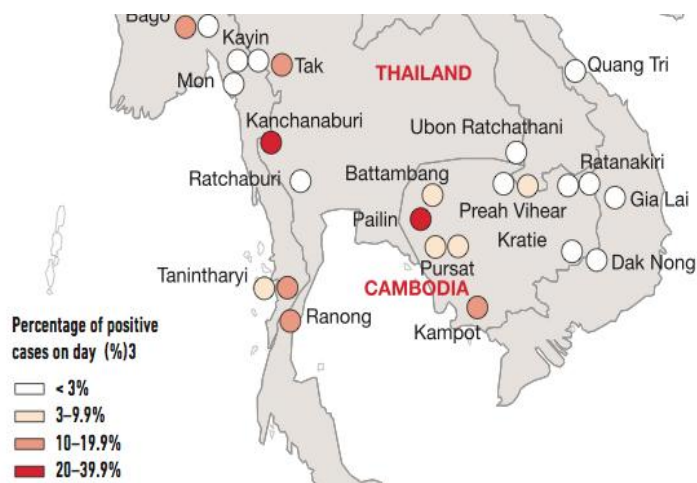
+ Many factors foster emergence

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- Mis-use in the industrialized world:
 - Primary care prescriptions for viral illnesses
 - Agricultural growth promotion, prophylactic dosing
- Over-use and under-dosing in the developing world:
 - Sold for profit by physicians, veterinarians
 - Sold without prescription for self-administration
 - Counterfeit and sub-standard drugs
- Little (human or veterinary) surveillance in either

+ *EX: Losing new malaria regimen, artemisinin resistance, SE Asia*

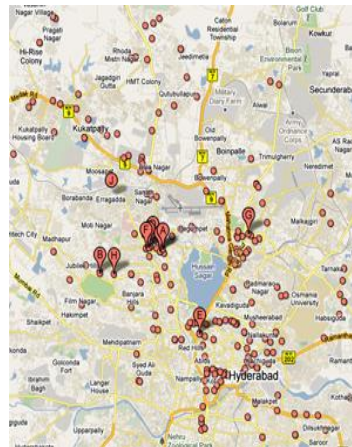
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Percentage of artemisinin resistance along Thailand-Cambodia border, WHO 2010

EX: Resistant organisms from environmental contamination

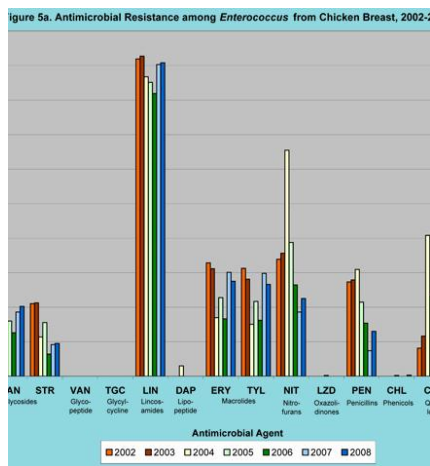
- India: Two new resistance genes found in pharma plant effluent
- China: High tetracycline resistance in river below pharma plant
- US: Prescription-drug residue in 80% of streams sampled



Pharma plant locations, Hyderabad, India 2010

EX: Drug-resistant organisms widespread in meat, produce

- EU *E. coli* O104 in sprouts: resistance to 14 antibiotics
- US: resistant staph in 25% supermarket meat samples
- Hong Kong: MRSA ST9 in pigs imported from Guangdong



MDR *Salmonella* in chicken meat, US FDA 2008

+ The history of drug development is also the history of losing drugs to resistance

- 1944: penicillin released to market
- 1945: Alexander Fleming, Nobel Prize speech:
"There is the danger that the ignorant man may easily underdose himself, and by exposing his microbes to nonlethal qualities of the drug, make them resistant."
- 1947: penicillin-resistant staph spreads worldwide
- 1960: introduction of methicillin
- 1961: identification of MRSA
- ~1980: increased used of vancomycin against MRSA
- 1986: first identification VRE
- 2002: first identification VRSA

+ And there are no new drugs to replace them

- Current last-resort drugs date to the 1950s
- Most antibiotic-focused companies have withdrawn from the market
- Old drugs more toxic, incur more drug-drug interactions
- New-drug pipeline running dry
 - The easy drugs have all been identified
 - "Me-too" formulations only gain months
 - Truly new compounds, possibly a year
 - Several new-new compounds withdrawn from trials

+ 2 new resistance factors, NDM-1 and CRE, illustrate the emergency

- **NDM-1**
 - Originated in developing world, moved to industrialized world
 - 2008: Indian patient in Sweden
 - 2009: 22 cases in UK with S. Asian ties
 - 2010: 3 cases US
 - By 2013: Canada, Europe, Asia, S. Asia, Africa...
- **CRE (also KPC or CRKP)**
 - Originated in United States, spread through Europe, S. America, Middle East
 - 1996: First identification in North Carolina
 - 2000: NYC outbreaks
 - 2002: Arizona, Florida
 - 2005: Israel, France
 - By 2013: Canada, UK, Europe, South America...

+ What links them: Responding to only a few existing drugs — or none

Antimicrobial	MIC ^a	Interpretation ^b
Amikacin	≥64	R
Amoxicillin / Clavulanic Acid	≥32	R
Ampicillin	≥32	R
Ampicillin / Sulbactam	≥32	R
Aztreonam	≥64	R
Cefalotin	≥64	R
Cefazolin	≥64	R
Cefepime	≥64	R
Cefotaxime	≥64	R
Cefotetan	≥64	R
Cefoxitin	≥64	R
Cefpodoxime	≥8	R
Ceftazidime	≥64	R
Ceftizoxime	≥64	R
Ceftriaxone	≥64	R
Cefuroxime	≥64	R
Cefuroxime Axetil	≥64	R
Ciprofloxacin	≥4	R
Gentamicin	≥16	R
Imipenem	≥16	R
Levofloxacin	≥8	R
Meropenem	≥16	R
Moxifloxacin	≥8	R
Nalidixic Acid	≥32	R
Nitrofurantoin	≥512	R
Norfloxacin	≥16	R
Piperacillin	≥128	R
Piperacillin / Tazobactam	≥128	R
Tetracycline	≥16	R
Ticarcillin	≥128	R
Ticarcillin / Clavulanic Acid	≥128	R
Tigecycline	≥8	R
Tobramycin	≥16	R
Trimethoprim / Sulfamethoxazole	≥320	R

a. Antibiotic susceptibility was obtained using Vitek® 2 AST-GN24 and AST-EXN7 cards
b. Parameter Set: MIC Interpretation Guideline: CLSI M100-S16 (2006)
Therapeutic Interoretation Guideline: Natural Resistance

■ World Health Organization:

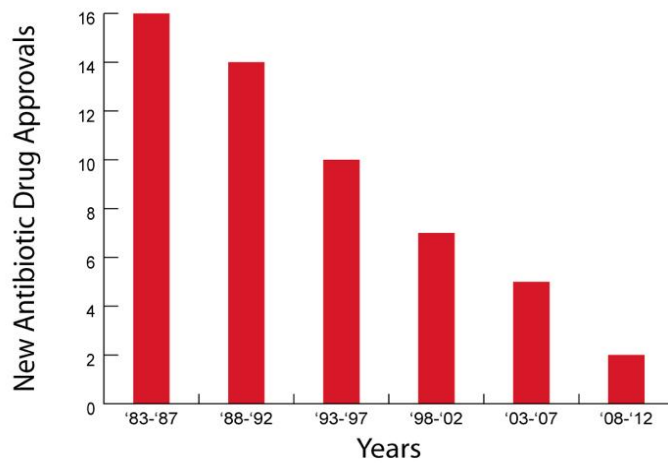
“The potential ...to be a worldwide public health problem is great, and coordinated international surveillance is needed.”

+ How many new antibiotics were approved by the FDA from 2008 – 2012



- 14
- 7
- 5
- 3
- 0

+ New-drug approvals are falling



*Declining approvals for new-drug applications, US FDA
Spellberg 2004 + Infectious Diseases Society of America 2010*

+ The math of drug development makes no sense to markets

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- To develop an antibiotic: 10 years, \$1 billion
- Even without resistance, antibiotics would self-limit profit because they effect a cure
 - As opposed to chronic-disease drugs which manage but do not cure
 - And “lifestyle” drugs which can be taken indefinitely at will
- Resistance imposes further financial obstacles
 - If hold on shelf to protect against development of resistance, no profit
 - If deployed against infections and resistance develops, limited market life

+ Incentives for pharmacos: necessary but disputed

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- Supported by:
 - Infectious Diseases Society of America
 - World Health Organization, European Commission, US Congress
 - Vast array of private research
- Proposed:
 - Priority review and approval
 - Rewards for simultaneous development of diagnostics
 - Patent extension (and wild-card patents)
 - Rewards for effectiveness targets/public health goals
 - Cash prizes
- Enacted: Not yet.

+ For more:

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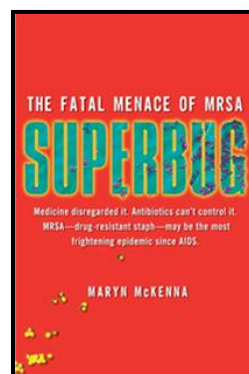
- MarynMcKenna.com
- <http://www.wired.com/wiredscience/superbug>
- www.Superbugthebook.com
- www.BeatingBacktheDevil.com
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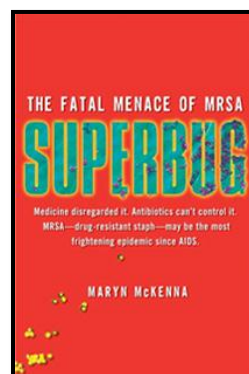
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