The Coming Crisis in Antibiotics

Ramanan Laxminarayan
SDRI Conference, Brisbane
April 2017
I. Drug resistance is rising worldwide and threatens gains made in reducing the burden of infectious diseases
First reported cases of bacterial resistance against key antibiotics

Carbapenem and 3rd. gen. cephalosporin resistance among *K. pneumoniae* highest along the East Coast, but present in all regions of the country.

**Carbapenem**

1999–2001

2002–2005

2006–2010

**Proportion of resistant isolates:**

- 0 - .001
- .001 - .01
- .01 - .02
- .02 - .03
- .03 - .04
- .04 - .05
- .05 - 1

**3rd Gen. Cephalosporins**

1999–2001

2002–2006

2006–2010

**Proportion of resistant isolates:**

- 0 - .025
- .025 - .05
- .05 - .075
- .075 - .1
- .1 - .125
- .125 - .15
- .15 - 1

Note: Data for 2010 available through July.

It is not difficult to make microbes resistant to penicillin in the laboratory by exposing them to concentrations not sufficient to kill them, and the same thing has occasionally happened in the body...

*Alexander Fleming, 1945*
Antibiotic resistance is ancient

Vanessa M. D’Costa1,2*, Christine E. King3,4*, Lindsay Kalan1,2, Mariya Morar1,2, Wilson W. L. Sung4, Carsten Schwarz3, Duane Froese5, Grant Zazula6, Fabrice Calmels5, Regis Debruyne7, G. Brian Golding4, Hendrik N. Poinar1,3,4 & Gerard D. Wright1,2

The discovery of antibiotics more than 70 years ago initiated a period of drug innovation and implementation in human and animal health and agriculture. These discoveries were tempered in all cases by the emergence of resistant microbes.1,2 This history has been interpreted to mean that antibiotic resistance in pathogenic bacteria is a modern phenomenon; this view is reinforced by the fact that collections of microbes that predate the antibiotic era are highly susceptible to antibiotics. Here we report targeted metagenomic analyses of rigorously authenticated ancient DNA from 30,000-year-old Beringian permafrost sediments and the identification of a highly diverse collection of genes encoding resistance to β-lactam, tetracycline and glycopeptide antibiotics. Structure and function studies on the complete vancomycin resistance element VanA confirmed its similarity to modern variants. These results show conclusively that antibiotic resistance is a natural phenomenon that predates the modern selective pressure of clinical antibiotic use.

Recent studies of modern environmental and human commensal microbial genomes have a much larger concentration of antibiotic resistance genes than has been previously recognized.3,6 In addition, with high concentrations of Escherichia coli harbouring the gfp (green fluorescent protein) gene from Aequorea victoria (Supplementary Information).

After fracturing of the samples (Supplementary Fig. 3), total DNA was extracted from a series of five subsamples taken along the radius of each core (Supplementary Information). Quantitative polymerase
At Last! Something Pleasurable That's Good for You.
The Health Benefits of Sex
Cosmo's Update on Antibiotics. What's Okay and What's Dangerous

Why Marry Instead of Just Fooling Around?

The Heart-Pounding Bawdiness of Brad Pitt, Who Couldn't Care Less

Makeup Tricks

November 1995

COSMOPOLITAN

$2.95
CRE rates in children grew between 2000 and 2012

Logan et al, EID, 2015
Increasing *Klebsiella pneumoniae* resistance to carbapenems (CRKP) and third-generation cephalosporins (G3CRKP) over time.

Braykov et al ICHE, 2012
Percentage of Staphylococcus aureus that are methicillin resistant (MRSA), by country (most recent year, 2011-14)

Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

Where available, data from hospital-associated MRSA and invasive isolates have been used. In their absence, data from community-associated MRSA or all specimen sources are included. Only countries that reported data for at least 30 isolates are shown. Depending on the country, resistance to one or more of the following drugs were used to test for MRSA: Oxacillin, cefoxitin, flucloxacillin, cloxacinil, dicloxacillin, and methicillin. Intermediate-resistant isolates are included as resistant in some calculations, as in the original data source.
Percentage of extended-spectrum beta-lactamase producing *Escherichia coli*, by country (most recent year, 2011-2014)

Where available, data from invasive isolates have been used. In their absence, data from all specimen sources are included. Only countries that reported data for at least 30 isolates are shown. Depending on the country, resistance to one or more of the following drugs were used: Ceftazidime, ceftriaxone and cefotaxime. Intermediate-resistant isolates are included as resistant in some calculations, as in the original data source.

*Indicated by third-generation cephalosporin resistance

Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming
Percentage of carbapenem-resistant *Klebsiella pneumoniae*, by country (most recent year, 2011-2014)

Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming

Where available, data from invasive isolates have been used. In their absence, data from all specimen sources are included. Only countries that reported data for at least 30 isolates are shown. Depending on the country, resistance to one or more of the following drugs were used: imipenem, meropenem, ertapenem and doripenem. Intermediate-resistant isolates are included as resistant in some calculations, as in the original data source.
The drugs work less
Effectiveness of antibiotics* in selected countries
0=best, 100=worst

Source: Centre for Disease Dynamics, Economics & Policy
*By index of six bacteria’s resistance to six classes of drug
†Except US (2012), Poland (2013) and Thailand (2013)
Spread of New Delhi metallo beta-lactamase: first detection, by country

Source: Johnson and Woodford 2013 (adapted)
Clonal spread of *S. pneumoniae* 23F

Slide courtesy: Keith Klugman
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.
Countries reporting plasmid-mediated colistin resistance encoded by mcr-1

Isolate source(s):
- Animals
- Humans
- Animals and humans
- Animals and environment
- Animals, humans and environment

Numbers of unique β-lactamase enzymes identified since introduction of first β-lactam antibiotics

Mortality outcomes are worse in neonates with resistant infections

<table>
<thead>
<tr>
<th>Gram negative</th>
<th>Number of resistant isolates</th>
<th>CFR in culture-positive sepsis due to resistant pathogens</th>
<th>CFR in culture-positive sepsis due to sensitive pathogens</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acinetobacter spp (n=222)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ES cephalosporins</td>
<td>85/222 (38%)</td>
<td>59/85 (69%)</td>
<td>71/137 (52%)</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>174/222 (78%)</td>
<td>106/174 (61%)</td>
<td>24/48 (50%)</td>
</tr>
<tr>
<td>MDR</td>
<td>181/222 (82%)</td>
<td>112/181 (62%)</td>
<td>18/41 (44%)</td>
</tr>
<tr>
<td><strong>Klebsiella spp (n=169)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ES cephalosporins</td>
<td>105/169 (62%)</td>
<td>57/104 (55%)</td>
<td>38/65 (58%)</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>59/169 (35%)</td>
<td>36/59 (61%)</td>
<td>59/110 (54%)</td>
</tr>
<tr>
<td>MDR</td>
<td>91/169 (54%)</td>
<td>52/91 (57%)</td>
<td>43/78 (55%)</td>
</tr>
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<td><strong>Escherichia coli (n=137)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ES cephalosporins</td>
<td>65/137 (47%)</td>
<td>40/64 (63%)</td>
<td>43/73 (59%)</td>
</tr>
<tr>
<td>Carbapenems</td>
<td>21/137 (15%)</td>
<td>12/21 (57%)</td>
<td>71/116 (61%)</td>
</tr>
<tr>
<td>MDR</td>
<td>52/137 (38%)</td>
<td>30/52 (58%)</td>
<td>53/85 (62%)</td>
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<td><strong>Pseudomonas spp (n=68)</strong></td>
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<td>ES cephalosporins</td>
<td>32/68 (47%)</td>
<td>29/32 (91%)</td>
<td>24/36 (67%)</td>
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<tr>
<td>Carbapenems</td>
<td>21/68 (31%)</td>
<td>19/21 (90%)</td>
<td>34/47 (72%)</td>
</tr>
<tr>
<td>MDR</td>
<td>13/68 (19%)</td>
<td>11/13 (85%)</td>
<td>42/55 (76%)</td>
</tr>
</tbody>
</table>
Figure: Case fatality rates from the DeNIS study (unshaded) compared with earlier studies (in solid colours)
Figure 2: Estimated neonatal sepsis deaths caused by bacteria resistant to first-line antibiotics in five high-burden countries

Laxminarayan et al Lancet, 2015
U.S. and Iran Both Attack ISIS, But Try Not to Look Like Allies

By TIM ARANGO and THOMAS ERDBRINK

BAGHDAD — Iran is again striking at what it deems to be an enemy of Iran, the Islamic State. Iran has launched air strikes against the Islamic State in Syria and Iraq. The United States has also launched air strikes against the Islamic State. The United States and Iran have been working together to combat the Islamic State.

Superbugs Kill India’s Babies And Pose an Overseas Threat

By GARDINER HARRIS

AMRAVATI, India — A deadly drug-resistant strain of the superbug known as MRSA has been found in India. The superbug has been killing children in the Amravati district of Maharashtra. The superbug has been spreading rapidly in hospitals and nursing homes. The superbug has been detected in children as young as one month old. The superbug has also been found in newborns in hospitals in other parts of India.

NEW YORK OFFICER FACING NO CHARGES IN CHOKEHOLD CASE

Grand Jury’s Decision in Fatal Encounter Draws Protests — U.S. to Investigate

By J. DAVID GOODMAN and AL BAKER

A Staten Island grand jury on Wednesday found no cause to indict a white New York police officer who killed an unarmed black man last July. The grand jury’s findings are expected to pave the way for the officer, Daniel Pantaleo, to be dismissed from the force. The officer was charged with second-degree manslaughter, a crime that does not carry a prison term.

Protesters at Grand Central Terminal on Wednesday after a grand jury decided not to indict a police officer in Eric Garner’s death.

The officer, Pantaleo, who has been on the force for eight years, appeared before the grand jury on Nov. 21, testifying that he did not intend to choke Mr. Garner, who was being arrested for allegedly selling loose cigarettes. He described the encounter as a “meltdown,” adding that he never thought Mr. Garner was in mortal danger.

The decision came barely a week after another grand jury found no cause to indict an officer in the death of Eric Garner, an unarmed black man in Ferguson, Mo. After the moves from Staten Island and Ferguson, there were renewed calls for Justice Department intervention.
Absolute risk reduction (ARR) of infection with antibiotic prophylaxis in common surgical procedures and blood cancer chemotherapy in the USA

Teillant et al, Lancet Infect Dis, 2015
Number of additional infections per year in the USA under a 30% decreased efficacy of antibiotic prophylaxis

Teillant et al, Lancet Infect Dis, 2015
Post-biopsy infections attributable to fluoroquinolone resistance in the US

Teillant et al, Lancet Infect Dis, 2015
II. Rising incomes and increasing access to antibiotics are saving lives (although lack of access still kills more people than antibiotic resistance) but are not a good substitute for public health
Bacterial diseases are still major killers in developing countries because of lack of access to antibiotics

O’Brien et al, Lancet 2009
Pneumococcal pneumonia deaths avertable with improved antibiotic access

Laxminarayan et al, Lancet, 2015
What are we asking of antibiotics?

**Figure 1.1**

Crude infectious disease mortality rate in the United States, 1900–1996

- Influenza pandemic
- 40 states have health departments
- Last human-to-human transmission of the plague
- First continuous municipal use of chlorine in water in United States
- First use of penicillin
- Salk vaccine introduced
- Passage of Vaccination Assistance Act

Source: Adapted from Armstrong, Conn et al. (1999).
Substitute for immunization, infection control and water/sanitation

Source: Adapted from Armstrong, Conn et al. (1999).
Substitute for immunization, infection control and water/sanitation

**FIGURE 1.1**

**Crude infectious disease mortality rate in the United States, 1900–1996**

- 1900: 1,000 deaths per 100,000 per year
- 1910: 700 deaths per 100,000 per year
- 1920: 500 deaths per 100,000 per year
- 1930: 300 deaths per 100,000 per year
- 1940: 200 deaths per 100,000 per year
- 1950: 100 deaths per 100,000 per year
- 1960: 70 deaths per 100,000 per year
- 1970: 40 deaths per 100,000 per year
- 1980: 20 deaths per 100,000 per year
- 1990: 10 deaths per 100,000 per year
- 2000: 5 deaths per 100,000 per year

- **1918**: Influenza pandemic
- **1920**: Last human-to-human transmission of the plague
- **1950**: First continuous municipal use of chlorine in water in United States
- **1940**: First use of penicillin
- **1954**: Salk vaccine introduced
- **1955**: Passage of Vaccination Assistance Act
- **1960**: 40 states have health departments

**Sub-Saharan Africa**
Population without access to improved sanitation, by MDG region 2012

Source: WHO/UNICEF 2014
Vaccines can be effective

Invasive disease caused by Pneumococci in children under two declined in the US post pneumo vaccination.

Effect of PCV7 introduction in 2000 on antibiotic prescriptions and ambulatory care visits

Zhou et al, Pediatrics 2008
Effect of PCV7 introduction in 2000 on antibiotic prescriptions and ambulatory care visits

Antibiotic prescriptions attributable to acute otitis media decreased from 1244 to 722 prescriptions per 1000 person-years – a 41.9% reduction.

Zhou et al, Pediatrics 2008
Figure 3: Days on antibiotics for suspected pneumonia, averted by provision of pneumococcal conjugate vaccine (PCV)
Bar represents antibiotic days avoided with PCV coverage.
Antibiotic consumption is increasing in developing countries...

Per capita total antibiotic use, retail sector, 2005-2010

Source: Based on data obtained under license from IMS Health MIDAS™ (January 2005-December 2010); IMS Health Incorporated. All Rights Reserved.
Per capita antibiotic consumption 2010*, by country

*Data for Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama were available only as a group classified as Central America. Similarly, data for Benin, Burkina Faso, Cameroon, Côte d’Ivoire, Gabon, Guinea, Mali, Republic of the Congo, Senegal, and Togo were grouped and classified as French West Africa. The data for these countries represent the estimates for the corresponding regional groupings they belong to. For countries that did not have data available for 2000, the values for the earliest years for which data were available after 2000 were used to calculate the percentage changes. These countries and initial years are Algeria (2002), Bangladesh (2007), Croatia (2005), Netherlands (2015), and Vietnam (2005).
Percentage change in antibiotic consumption per capita 2000–2010*, by country

*Data for Costa Rica, El Salvador, Guatemala, Honduras, Nicaragua and Panama were available only as a group classified as Central America. Similarly, data for Benin, Burkina Faso, Cameroon, Côte d’Ivoire, Gabon, Guinea, Mali, Republic of the Congo, Senegal, and Togo were grouped and classified as French West Africa. The data for these countries represent the estimates for the corresponding regional groupings they belong to. For countries that did not have data available for 2000, the values for the earliest years for which data were available after 2000 were used to calculate the percentage changes. These countries and initial years are Algeria (2002), Bangladesh (2007), Croatia (2005), Netherlands (2005), and Vietnam (2005).
Consumption increased substantially in Australia (from 25 in 2000 to 87 units per person in 2010) and New Zealand (from 26 in 2000 to 70 units per person in 2010).

*Data for Costa Rica, El Salvador, Guatemala, Honduras and Panama were available only as a group classified as Central America. Similarly, data for Benin, Burkina Faso, Cameroon, Côte d’Ivoire, Gabon, Guinea, Mali, Republic of the Congo, Senegal, and Togo were grouped and classified as French West Africa. The data for these countries represent the estimates for the corresponding regional groupings they belong to. For countries that did not have data available for 2000, the values for the earliest years for which data were available after 2000 were used to calculate the percentage changes. These countries and initial years are Algeria (2002), Bangladesh (2007), Croatia (2005), Netherlands (2005), and Vietnam (2005).
Total antibiotic consumption in selected countries, 2000 and 2010

Van Boeckel et al. 2014 (based on IMS MIDAS)
Top 10 antibiotic consumers in 2014, ordered by total consumption, and global median consumption per capita.
A). Top 12 consumers of antibiotic use per capita and global median consumption per capita

B). Total global use and global use if countries with use above global median per capita are reduced to global median

C). Percentage reduction in total global use when countries above global median per capita are reduced to global median

20.5%
Antibiotic use per capita by income in selected countries, 2010

Source: Van Boeckel et al. 2014 (based on IMS MIDAS) and World Bank 2015
Carbapenem retail sales in selected countries, 2005–2010 (per 1,000 population)

Source: Laxminarayan et al. 2013 (based on IMS MIDAS)

*An IMS grouping of Benin, Burkina Faso, Cameroon, Côte d’Ivoire, Gabon, Guinea, Mali, Republic of the Congo, Senegal, and Togo
Use of cephalosporins and broad spectrum penicillins is rising in India:

[Graph showing the increase in use of various antibiotics from 2000 to 2005, with cephalosporins seeing the most significant rise.]
Faropenem consumption has increased by 154% since it was approved for use in India in 2010

Gandra et al, Clin Inf Dis, 2016
Carbapenem consumption in the hospital sector in selected European countries, 1997–2013
Non-prescription use of antimicrobials is common

Figure 2: Frequency of non-prescription use of antimicrobials in the general population based on published works
In small areas, countries with similar frequency of non-prescription antimicrobial use have been grouped.

Morgan et al, Lancet ID, 2011
<table>
<thead>
<tr>
<th>Country or Region</th>
<th>Population in millions</th>
<th>Doctors in thousands</th>
<th>Nurses</th>
<th>Doctors and Nurses/1000 Population</th>
<th>Nurse-to-Doctor Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Country</td>
<td></td>
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<tr>
<td>China</td>
<td>1338</td>
<td>1915</td>
<td>1,864</td>
<td>2.8</td>
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<tr>
<td>India</td>
<td>1225</td>
<td>768</td>
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<td>United States</td>
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<td>Brazil</td>
<td>195</td>
<td>338</td>
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<td>United Kingdom</td>
<td>62</td>
<td>166</td>
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<tr>
<td>South Africa</td>
<td>50</td>
<td>37</td>
<td>198</td>
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<td>Region</td>
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<tr>
<td>Americas</td>
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<td>1974</td>
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<td>Europe</td>
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<tr>
<td>Middle East and North Africa</td>
<td>590</td>
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<tr>
<td>Southeast Asia</td>
<td>1795</td>
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<tr>
<td>Sub-Saharan Africa</td>
<td>847</td>
<td>150</td>
<td>778</td>
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<td>5.2</td>
</tr>
<tr>
<td>Western Pacific</td>
<td>1,821</td>
<td>2,696</td>
<td>3,814</td>
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<td>1.4</td>
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<td>World</td>
<td>6,888</td>
<td>9,216</td>
<td>18,114</td>
<td>4.0</td>
<td>2.0</td>
</tr>
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*A doctor or nurse is defined as a person with the appropriate qualifications recognized in his or her own country. In this table, the nurse workforce includes nurses and midwives. Data are from the World Health Organization.*
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The flu season is a key driver of antibiotic consumption

Van Boeckel et al, Lancet Inf Dis, 2014
Influenza in the United States is nearly perfectly predicted by antibiotic sales data

**Figure 1.** Observed and fitted antibiotics series from 2000 to 2007. The solid line represents the actually observed antibiotics series; the dashed line represents the fitted antibiotics series from the time series regression model that uses influenza-like illness as an explanatory series.

Polgreen et al Inf Cont Hosp Epi, 2011
Hospital use of carbapenems is rapidly growing
Extended-spectrum macrolide use is highly prevalent in the United States, and increasing in developing countries.
Global availability of colistin

Wertheim et al, JGAR 2013
III. Drivers of antibiotic use relate to incentives and behavior of patients, physicians, pharma, payers and healthcare institutions.
Antibiotic prescribing: a complex interaction

- Beliefs, attitudes, knowledge
- Public campaigns
- Diagnostic uncertainty
- POC and other tests
- Decision support
- Antibiotic prescription
- Perceived patient demand / communication skills
- Communication training
- Delayed prescribing
- Audit & feedback
- Education
- Restriction policies

Slide courtesy – Benedikt Huttner, HUG
Incentives for Physicians

- Satisfying patient expectations
## TABLE 5

**Frequency of Antibiotic Prescribing by Factors Related to Patients’ Expectations of Antibiotics (N = 482)**

<table>
<thead>
<tr>
<th>Factor</th>
<th>No. (%)</th>
<th>Antibiotic Prescribed No. (%)</th>
<th>OR (95% CI)</th>
</tr>
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<tbody>
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<td><strong>Patient expects antibiotic</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>290 (60)</td>
<td>213 (73)</td>
<td>2.6 (1.7-3.9)</td>
</tr>
<tr>
<td>No</td>
<td>150 (31)</td>
<td>78 (52)</td>
<td></td>
</tr>
<tr>
<td>No answer</td>
<td>42 (9)</td>
<td>28 (67)</td>
<td></td>
</tr>
<tr>
<td><strong>Clinician believes patient expects an antibiotic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>298 (62)</td>
<td>236 (79)</td>
<td>4.7 (3.2-7.1)</td>
</tr>
<tr>
<td>No</td>
<td>182 (38)</td>
<td>81 (45)</td>
<td></td>
</tr>
<tr>
<td>No answer</td>
<td>2 (&lt;1)</td>
<td>2 (100)</td>
<td></td>
</tr>
<tr>
<td><strong>Antibiotic helped similar illness in the past</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>284 (59)</td>
<td>212 (75)</td>
<td>4.5 (2.9-6.9)</td>
</tr>
<tr>
<td>No</td>
<td>170 (35)</td>
<td>88 (52)</td>
<td></td>
</tr>
<tr>
<td>Don't know</td>
<td>19 (4)</td>
<td>12 (63)</td>
<td></td>
</tr>
<tr>
<td>No answer</td>
<td>9 (2)</td>
<td>5 (56)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Because some questions were unanswered, the numbers may not add up to 482.

*In outpatients with nonspecific upper respiratory infections, acute bronchitis, or acute sinusitis. OR denotes odds ratio; CI, confidence interval.
Decision fatigue increases inappropriate prescribing

Relative to the first hour of a session, the adjusted odds ratios of antibiotic prescribing in the fourth hour was 1.26 (95% CI, 1.13–1.41)

Linder et al, JAMA IM, 2014
Hospital Incentives

- Antibiotics are a substitute for infection control
- Infection control is often not compensated
Compared with absence of complications, complications were associated with a $39,017 higher contribution margin per patient with private insurance ($55,953 vs $16,936) and a $1,749 higher contribution margin per patient with Medicare ($3,629 vs $1,880).
Assessment of empirical antibiotic therapy optimisation in six hospitals: an observational cohort study


Summary

Background  Modification of empirical antimicrobials when warranted by culture results or clinical signs is recommended to control antimicrobial overuse and resistance. We aimed to assess the frequency with which patients were started on empirical antimicrobials, characteristics of the empirical regimen and the clinical characteristics of patients at the time of starting antimicrobials, patterns of changes to empirical therapy and differences...
At the start of therapy, 220 (30%) patients were afebrile and had normal white blood cell counts. Appropriate cultures were collected from 432 (59%) patients, and 250 (58%) were negative. By the 5th day of therapy, 12.5% of empirical antimicrobials were escalated, 21.5% were narrowed or discontinued, and 66.4% were unchanged. Narrowing or discontinuation was more likely when cultures were collected at the start of therapy and no infection was noted on an initial radiological study.
Presence of Fever and High WBC among Patients with Empiric Antibiotic Therapy

Number of Patients (N=730)

- No: 30.1%
- Yes: 69.9%

Breakdown of Infection Site for "No" Patients

- Respiratory: 43%
- Urinary tract: 18%
- Soft tissue: 18%
- Gastro-Intestinal: 8%
- Bloodstream: 6%

Braykov et al, Lancet Inf Dis, 2015
IV. Antibiotic use in animal sector is increasing globally in response to the tremendous growth in demand for animal protein
Antibiotic use for growth promotion and disease prevention
2/3\textsuperscript{rd}s of the tonnage of antibiotics sold worldwide are used in agriculture
Demand for poultry in India and China is set to increase two to seven fold between 2000 and 2030

FAO, 2011
Pig Run
Swine output has surged to feed pork-hungry China

Per-capita Pork Consumption

Number of Pigs Produced

Source: Bloomberg data
Drug Binge

China consumes half the world’s antibiotics, with the majority administered to animals

- **Humans**
  - China: 77,760

- **Animals**
  - China: 84,240

162,000 of antibiotics used in total

Antibiotics consumed (metric tons) in 2013

Total consumption in China - 92,700 tons in 2013,
54,000 tons of antibiotics excreted by human and animals - much of this entered into the receiving environment following various wastewater treatments into 58 river basins of China

Zhang et al, Env Sci Tech, 2015
High-capacity quantitative PCR arrays detected 149 unique resistance genes among all of the farm samples, the top 63 ARGs being enriched 192-fold (median) up to 28,000-fold (maximum) compared with their respective antibiotic-free manure or soil controls.
High amounts of four antibiotics were measured in the lakes that do not take in wastewater from the sewage plant. The levels of ciprofloxacin (2.5 mg/L) and cetirizine (20 µg/L) in one of the lakes was higher than previously measured levels in the blood of people taking the medications, report the authors. This suggests there are other unknown sources – perhaps illegal dumping – of wastewater responsible for polluting the lakes.

In addition, effluents from a wastewater treatment had concentrations of ciprofloxin of 14 milligrams per liter (mg/L) and cetirizine as high as 1.2 mg/L. These concentrations are approaching therapeutic doses (concentrations that would kill some microorganisms outright). Concentration reported in the US range in the nanograms per liter (ng/L), which are one million fold less.

contaminated by the treatment plant. Water samples were also taken from wells in six nearby villages. The samples were analyzed for the presence of 12 pharmaceuticals with liquid chromatography–mass spectrometry. All wells were determined to be contaminated with drugs. Ciprofloxacin, enoxacin, cetirizine, terbinafine, and citalopram were detected at more than 1 µg/L in several wells. Very high concentrations of ciprofloxacin (14 mg/L) and cetirizine (2.1 mg/L) were found in the effluent of the treatment plant, together with high concentrations of seven additional pharmaceuticals. Very high concentrations of ciprofloxacin (up to 6.5 mg/L), cetirizine (up to 1.2 mg/L), norfloxacin (up to 0.52 mg/L), and enoxacin (up to 0.16 mg/L) were also detected in the two lakes, which clearly shows that the investigated area has additional environmental sources of insufficiently treated industrial waste. Thus, insufficient wastewater management in one of the world’s largest centers for bulk drug production leads to unprecedented drug contamination of surface, ground, and drinking water. This raises serious concerns regarding the development of antibiotic resistance, and it creates a major challenge for producers and regulatory agencies to improve the situation.
Increase of antibiotic resistance genes among soils collected at five sites in The Netherlands from 1940 to 2008.

Knapp et al Env Sci Tech, 2010
Figure 3
Trends in the prevalence of fluoroquinolone resistance in clinical isolates of *Campylobacter jejuni*, in Spain, examined for resistance from 1987 to 1996. Before approval of fluoroquinolones in poultry and livestock production, resistance was relatively rare (<10%); after approval, the prevalence of resistance rose quickly. Data used with permission from Reference 47.
Temporal association between contamination of retail chicken with ceftiofur-resistant *Salmonella* Heidelberg strains and incidence of ceftiofur resistant *Salmonella* Heidelberg infection in humans

Dutil et al, EID, 2010
Amounts, in mg, of veterinary antibacterial agents sold in 2007 per kg biomass of pig meat, poultry meat and cattle meat produced plus estimated live weight of dairy cattle. *2005 data. **The substances included vary from country to country.
Antimicrobial use per unit of meat has increased every year from 2009 to 2014 in the US.

Data sources:
*2014 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals*. FDA. 2015.
Global antibiotic consumption in livestock (mg per 10 km² pixels) 2010

Van Boeckel et al., PNAS, 2015
Global antibiotic consumption in livestock (mg per 10 km² pixels) 2010

Global consumption of antimicrobials in food animal production
• estimated at 63,151 (±1,560) tonnes in 2010
• projected to rise by 67%, to 105,596 (±3,605) tonnes by 2030
• hotspots like India where areas of high consumption (30 kg per km²) for industrial poultry production are expected to grow 312% by 2030

Log10 [(mg/pixel) + 1]

Van Boeckel et al., PNAS, 2015
Antibiotic consumption in livestock, top ten countries 2010–2030 (projected for 2030)

Van Boeckel et al., PNAS, 2015
Sales of active ingredients of antibiotics for food-producing animals in Denmark

DANMAP 2013 (adapted)
Improvement in the Average Daily Growth (ADG) of pigs fed antibiotics over time

- Zimmerman, 1986
- Hays, 1978
- Hays, 1978
- Hays, 1978
- Hays, 1978
- Zimmerman, 1986
- Dritz, 2002
- Miller, 2005
- Miller, 2003
- Van Lunen, 2003
- Dritz, 2002
- % improvement ADG, Nursery pigs
- % improvement ADG, Growing-finishing pigs

Laxminarayan et al, OECD Report, 2015
Productivity reductions and costs per produced pig incurred by removing AGPs

**Increased workload**
(30 sec./pig at $25/hour)

$0.21

**Increased medication**
(25500 kg valued at $9.09 million for 23.5 million pigs)

$0.39

**Excess feeding days**
(1.6 days * $0.19/day)

$0.30

**Excess mortality**
(0.6% * $73/pig (20kg))

$0.44

**Total cost** = $1.34

Laxminarayan et al, OECD Report, 2015
V. Is finding new antibiotics the answer?
History of antibiotic discovery and concomitant development of antibiotic resistance

Events in the Age of Antibiotics

- **Penicillinase discovery**
  - 1940
  - Primordial
  - The Dark Ages (Semmelweis)

- **Antibiotic resistance plasmids**
  - 1950
  - Golden

- **FDA Office of New Drugs**
  - 1960
  - Pharmacologic
  - Genomic HTS

- **Increasing Antibiotic Resistance**
  - 1970
  - Biochemical
  - Target

- **Transmissible fluoroquinolone resistance**
  - 1980
  - Target
  - Genomic HTS

- **Disenchantment (Semmelweis) (again!)**
  - 1990

- **?**

First reported cases of bacterial resistance against key antibiotics

Loss of first line drugs increases drug costs

The rich pay with their wallets, the poor with their lives.

Developed world cost per course of therapy

- **Linezolid**: $1,480
- **Vancomycin**: $666.80
- **Gemifloxacin**: $145
- **Ammox./Clav.**: $144.8
- **Ceftriaxone**: $121
- **Levofoxacin**: $103
- **Ciprofloxacin**: $39
- **Azithromycin**: $39

Developing world

- **Cotrimoxazole**: $16
- **Amoxacillin**: $14
- **Chloramphenicol**: $5
- **Tetracycline**: $3.60
- **Ceftriaxone**: $1,500 (IDC)

**Suppliers**:
- Pfizer
- Eli Lilly
- Oscent
- GSK
- Roche
- Ortho-McNeill
- Bayer
- Pfizer
- Roche
- GSK
- IDA
- Various

Notes: *Chloramphenicol is not available in developed world—price is therefore estimated. †Ceftriaxone and ciprofloxacin may be available in some tertiary settings in developing world.

Discovery of new classes of antibiotics

- Sulfonamides
- Oxazolidinones
- Tetracyclines
- Macrolides
- Glycopeptides
- Aminoglycosides
- Penicillins
- Lincosamides
- Streptogramins
- Quinolones
- Trimethoprim

Timeline:
- 1930s
- 1940s
- 1950s
- 1960s
- 1970s
- 1980s
- 1990s
- 2000s
Pipeline of new anti-microbial drugs growing after a long lag

But prices are likely to be high

Significant gap in first introduction of new antimicrobial classes...

<table>
<thead>
<tr>
<th>Year</th>
<th>Class of drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>1935</td>
<td>Sulfonamides</td>
</tr>
<tr>
<td>1941</td>
<td>Penicillins</td>
</tr>
<tr>
<td>1944</td>
<td>Aminoglycosides</td>
</tr>
<tr>
<td>1945</td>
<td>Cephalosporins</td>
</tr>
<tr>
<td>1949</td>
<td>Chloramphenicol</td>
</tr>
<tr>
<td>1950</td>
<td>Tetracyclines</td>
</tr>
<tr>
<td>1952</td>
<td>Macrolides / Lincosamides / Streptogramins</td>
</tr>
<tr>
<td>1956</td>
<td>Glycopeptides</td>
</tr>
<tr>
<td>1957</td>
<td>Rifamycins</td>
</tr>
<tr>
<td>1959</td>
<td>Nitroimidazoles</td>
</tr>
<tr>
<td>1962</td>
<td>Quinolones</td>
</tr>
<tr>
<td>1968</td>
<td>Trimethoprim</td>
</tr>
</tbody>
</table>

2000: Oxazolidinones
2003: Lipopeptides
2005: Glycylcyclines
2007: Pleuromutilins

30 year development gap

# of molecules in non-standard antimicrobial classes in all phases of development

Source: “Bad Bugs, No Drugs” white paper, Pharmaprojects, Rodman and Renshaw, Nature Reviews Drug Discovery, BCG Analysis
Trends in development of new antibiotics
Of the 61 new antibiotics approved between 1980 and 2009, 26 (43%) were withdrawn either because of toxicity or lack of market, compared with a 13% withdrawal rate for other therapeutic categories (Outterson et al 2013)
New antibiotic launches since 1994

<table>
<thead>
<tr>
<th>Launch Year</th>
<th>Product name</th>
<th>Antimicrobial class (old)</th>
<th>Antimicrobial class (new)</th>
<th>Pharmaceutical Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>1994</td>
<td>Meropenem</td>
<td>Carbapenem</td>
<td>AstraZeneca</td>
<td>Toyama Chemical Co.</td>
</tr>
<tr>
<td>1999</td>
<td>Moxifloxacin</td>
<td>Fluoroquinolone</td>
<td>Bayer</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>2000</td>
<td>Linezolid</td>
<td>Oxazolidinone</td>
<td>Pfizer</td>
<td>Pfizer</td>
</tr>
<tr>
<td>2001</td>
<td>Telithromycin</td>
<td>Macrolide</td>
<td>Sanofi-Aventis</td>
<td>Targanta Therapeutics</td>
</tr>
<tr>
<td>2002</td>
<td>Balofloxacin</td>
<td>Fluoroquinolone</td>
<td>Choongwae Pharma</td>
<td>Daiichi Pharmaceutical Co.</td>
</tr>
<tr>
<td></td>
<td>Biapenem</td>
<td>Carbapenem</td>
<td>Wyeth</td>
<td>Theravance</td>
</tr>
<tr>
<td></td>
<td>Ertapenem</td>
<td>Carbapenem</td>
<td>Merck</td>
<td></td>
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<tr>
<td></td>
<td>Prulifloxacin</td>
<td>Fluoroquinolone</td>
<td>Nippon Shinyaku Co.</td>
<td>Anhui Global</td>
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<tr>
<td></td>
<td>Pazufloxacin</td>
<td>Fluoroquinolone</td>
<td>Toyama Chemical Co.</td>
<td>SSP Co.</td>
</tr>
<tr>
<td>2004</td>
<td>Gemifloxacin</td>
<td>Fluoroquinolone</td>
<td>LG Life Sciences</td>
<td>Johnson &amp; Johnson</td>
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<tr>
<td>2005</td>
<td>Tigecycline</td>
<td>Glycylcycline</td>
<td>Wyeth</td>
<td>Arpida</td>
</tr>
<tr>
<td></td>
<td>Doripenem</td>
<td>Carbapenem</td>
<td>Janssen Pharmaceuticals</td>
<td>Meiji Seika Pharma Co.</td>
</tr>
<tr>
<td>2006</td>
<td>Daptomycin</td>
<td>Lipopeptide</td>
<td>Cubist Pharmaceuticals</td>
<td>Corixa</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Optimer Pharmaceuticals</td>
</tr>
</tbody>
</table>

Fig. 3. Antibiotic pipeline for the past 20 years.

Laxminarayan, Science, 2014
Incentives for new antibiotics, as proposed by BARDA and EU may encourage new drug development but don’t impact incentives for using drugs appropriately.
• Diagnostics
• Vaccines for Staph and Gram-negative infection
• Bacteriophages
• Probiotics
• Quorum sensing
Price in USD

$ 40,000
$ 20,000
$ 200
$ 100
$ 0.20
$ 0.10
$ 0.1

Penicillin

Market Launch: 1941
Market Launch: 1941

Penicillin: $0.1

Linezolid: $155

Price in USD

$ 40,000
$ 20,000
$ 1000
$ 0.20
$ 0.10
$ 0

0
Seventy-first session
Agenda item 127
Global health and foreign policy

Draft resolution submitted by the President of the General Assembly

Political Declaration of the high-level meeting of the General Assembly on antimicrobial resistance
BLADE OF GRASS IS RESPONSIBLE FOR LOSS OF FOOT

C. W. Jones, athletic director of the Athens Y. M. C. A., yesterday suffered the loss of his right foot, the member having been amputated just above the ankle.

Mr. Jones, it seems, recently was exercising on a plot of grass, dew on a blade of grass cutting him slightly just under the little toe. The cut did not heal as quickly as it should have and medical attention was called, but to no avail. Blood poisoning had set in, and it was imperative that the foot be amputated to prevent the poison spreading further.
Slides are downloadable @ www.cddep.org

Thank you