The Coming Crisis in Antibiotics

Ramanan Laxminarayan
European Parliament Conference
June 2017
First reported cases of bacterial resistance against key antibiotics

- **Staphylococcus**
  - 1943: Penicillin introduction
  - 1968: First resistant case reported
- **Shigella**
  - 1959: Tetracycline introduction
  - 1968: First resistant case reported
- **Streptococcus**
  - 1950: Methicillin introduction
  - 1962: First resistant case reported
- **Enterococcus**
  - 1960: Vancomycin introduction
  - 1979: First resistant case reported
- **Enterobacteriaceae**
  - 1972: Imipenem introduction
  - 1988: First resistant case reported
- **Pneumococcus**
  - 1985: Ceftazidime introduction
  - 1998: First resistant case reported

Bars represent the amount of time taken for bacteria to develop resistance after market introduction.

Red year = First resistance case reported
Green year = Market introduction

Penicillin was in use prior to its market introduction in 1943.

Antibiotic resistance is ancient

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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 microbes1,2. 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 antibiotics3. 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 recognized4,6. 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
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, cloxacillin, 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)

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: 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
Percentage of carbapenem-resistant *Klebsiella pneumoniae*, 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: 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.
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>
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<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>
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<tr>
<td><strong>Klebsiella spp (n=169)</strong></td>
<td></td>
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</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>
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<tr>
<td>MDR</td>
<td>91/169 (54%)</td>
<td>52/91 (57%)</td>
<td>43/78 (55%)</td>
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<td><strong>Escherichia coli (n=137)</strong></td>
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<td>ES cephalosporins</td>
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<td>40/64 (63%)</td>
<td>43/73 (59%)</td>
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<tr>
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<td>21/137 (15%)</td>
<td>12/21 (57%)</td>
<td>71/116 (61%)</td>
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<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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<tr>
<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>
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<td>19/21 (90%)</td>
<td>34/47 (72%)</td>
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<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
**NEW YORK TIMES**

**U.S. and Iran Both Attack ISIS, But Try Not to Look Like Allies**

**By Tim Arango and Thomas Erbrink**

Baghdad — Iranian fighter jets struck extremist targets in Iraq recently, Iran and American officials have confirmed, in the latest display of Tehran’s new willingness to conduct military operations openly on foreign battlefields rather than covertly and through proxies.

The shift stems in part from Iran’s deepening military role in Iraq against the Islamic State group, a�ands of which are in Syria and Iraq, where Tehran and Washington find themselves fighting the same enemy in an increasingly complex conflict.

While there is no direct coordination between Iran and the United States, there is a de facto nonaggression pact between the two nations.

**‘Superbugs’ Kill India’s Babies And Pose an Overseas Threat**

**By Ganesh R. Harris**

AMRAVATI, India — A deadly epidemic that could have global implications is quietly spreading in India, and among its many victims are tens of thousands of newborns dying because of a nosocomial bacteria, a type of bacteria that spreads in medical settings.

These infants are born with bacteria and other infections that are resistant to most antibiotics, and the disease has no known cure.

More than 500,000 newborns died last year as a result, according to the World Health Organization.

This epidemic is growing, and it could spread to other countries, the WHO said.

**NEW YORK OFFICER FACING NO CHARGES IN CHOKEHOLD CASE**

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

**By DAVID GOODMAN and AL BAKER**

A Staten Island grand jury on Wednesday ended the investigation into the death of Eric Garner, an unarmed black man who died in police custody.

The grand jury found that no charges should be filed against the officer involved in Garner’s death.

The decision was made after the grand jury reviewed the evidence presented in the investigation.

**LATE EDITION**

Today, a milder day, with some clouds, high 42. Skies mostly clear, rain tomorrow, mostly cloudy, chilly, high 43. Weather map is on Page B16.
Absolute risk reduction (ARR) of infection with antibiotic prophylaxis in common surgical procedures and blood cancer chemotherapy in the USA

Number of additional infections per year in the USA under a 30% decreased efficacy of antibiotic prophylaxis

Surgical site infections

- There are 92 million surgeries in low-income countries each year
- 5.5 million surgical site infections or SSIs (6 per 100 procedures) – about a third of all healthcare associated infections
- SSIs are the leading cause of infection in settings with limited resources
- Mortality rate from SSI Rates of mortality from surgical site infections are 3% in the US and between 8 and 20% in low-income countries
- Between 400,000 and a million deaths from SSIs each year with an increasing number caused by resistant pathogens.
Bacterial diseases are still major killers in developing countries because of lack of access to antibiotics

O’Brien et al, Lancet 2009
What are we asking of antibiotics?

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

- Influenza pandemic
- 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).
Population without access to improved sanitation, by MDG region 2012

Source: WHO/UNICEF 2014
Global antibiotic consumption 2000 to 2010: an analysis of national pharmaceutical sales data

Thomas P Van Boeckel, Sumanth Gandra, Ashvin Ashok, Quentin Caudron, Bryan T Grenfell, Simon A Levin, Ramanan Laxminarayan

Summary
Background Antibiotic drug consumption is a major driver of antibiotic resistance. Variations in antibiotic resistance across countries are attributable, in part, to different volumes and patterns for antibiotic consumption. We aimed to assess variations in consumption to assist monitoring of the rise of resistance and development of rational-use policies and to provide a baseline for future assessment.
Percentage change in antibiotic consumption per capita 2000–2010*, by country

Source: Van Boeckel et al. 2015 (adapted; based on IMS MIDAS)

*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).
Total antibiotic consumption in selected countries, 2000 and 2010

Van Boeckel et al. 2014 (based on IMS MIDAS)
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
Pig Run
Swine output has surged to feed pork-hungry China

Per-capita Pork Consumption
45 (kilograms)

Number of Pigs Produced
700 (millions)

Source: Bloomberg data
Drug Binge

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

<table>
<thead>
<tr>
<th></th>
<th>Humans</th>
<th>Animals</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>77,760</td>
<td>84,240</td>
<td>162,000</td>
</tr>
</tbody>
</table>

Antibiotics consumed (metric tons) in 2013


Bloomberg
- Total consumption in China - 92700 tons in 2013,
- 54000 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.
CONTAMINATION OF SURFACE, GROUND, AND DRINKING WATER FROM PHARMACEUTICAL PRODUCTION

JERKER FICK, †HANNA SÖDERSTRÖM, †RICHARD H. LINDBERG, †CHAU PHAN, †MATS TYSKLIND, †and D.G. JOAKIM LARSSON‡
†Department of Chemistry, Umeå University, Linnaeusväg 6, SE-90187 Umeå, Sweden

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
### 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>
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<tbody>
<tr>
<td>1994</td>
<td>Meropenem</td>
<td>Carbapenem</td>
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<td>AstraZeneca</td>
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<tr>
<td>1999</td>
<td>Moxifloxacin</td>
<td>Fluoroquinolone</td>
<td></td>
<td>Bayer</td>
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<tr>
<td>2000</td>
<td>Linezolid</td>
<td>Oxazolidinone</td>
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<td>Telithromycin</td>
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<td>Balofloxacin</td>
<td>Fluoroquinolone</td>
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<td>Choongwae Pharma</td>
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<td>Iclaprim</td>
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<td>2012</td>
<td>Bedaquiline</td>
<td>Diaryquinolinel</td>
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</table>

Fig. 3. Antibiotic pipeline for the past 20 years.
Incentives for new antibiotics, as proposed by BARDA and EU may encourage new drug development but don’t impact incentives for using drugs appropriately.
Price in USD

Market Launch: 1941
Price in USD

- Penicillin: $0.1 (Market Launch: 1941)
- Linezolid: $155 (Market Launch: 2000)
- Daptomycin: $181 (Market Launch: 2006)
Price in USD

- Penicillin: $0.1, Market Launch: 1941
- Linezolid: $155, Market Launch: 2000
- Daptomycin: $181, Market Launch: 2006
- Sipuleucel-T: $31,000, Market Launch: 2010
Slides are downloadable @ www.cddep.org

Thank you