Drivers of Antibiotic Resistance

Ramanan Laxminarayan
Twitter @CDDEP

Einstein College of Medicine
First reported cases of bacterial resistance against key antibiotics

- **Staphylococcus**: 1950
- **Shigella**: 1962
- **Streptococcus**: 1962
- **Enterococcus**: 1972
- **Enterobacteriaceae**: 1985
- **Pneumococcus**: 1998

**Timeline:**
- 1943: Penicillin
- 1950: Ticarcillin
- 1953: Methicillin
- 1960: Cefazolin
- 1967: Vancomycin
- 1972: Imipenem
- 1985: Ceftazidime
- 1996: Levofloxacin
- 2000: Linezolid
- 2010: Ceftaroline

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

**Proportion of resistant isolates:**
- 0 – .001
- .001 – .01
- .01 – .02
- .02 – .03
- .03 – .04
- .04 – .05
- .05 – 1

**Note:** Data for 2010 available through July.

CRE rates in children grew between 2000 and 2012

Logan et al, EID, 2015
Escherichia coli, Klebsiella spp., and Other Enterobacteriaceae resistant to all six commonly used antimicrobial agents in Malawi.

Musicha et al, *Lancet Inf Dis* 2017

Trends in antimicrobial resistance in bloodstream infection isolates at a large urban hospital in Malawi

Resistant to all six commonly used antimicrobial agents in Malawi
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, fluoroquinolines, clindamycin, 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)

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.
Antibiotic Resistance of *Pseudomonas aeruginosa*

![Bar chart showing antibiotic resistance in different countries](cddep.org)
Resistance of *Acinetobacter baumannii* to Carbapenems

% Resistant (invasive isolates)
Figure 1. Carbapenem- and cephalosporin-resistant Acinetobacter baumannii in the United States: 1999–2012.
Are we overstating the problem of resistance because of measurement bias?
Antimicrobial susceptibility pattern of 361 Streptococcus pneumoniae isolates

Manoharan LID, 2017
Numbers of unique β-lactamase enzymes identified since introduction of first β-lactam antibiotics

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

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.

Global increase and geographic convergence in antibiotic consumption between 2000 and 2015

Eili Y. Klein\textsuperscript{a,b,c,1}, Thomas P. Van Boeckel\textsuperscript{d}, Elena M. Martinez\textsuperscript{a}, Suraj Pant\textsuperscript{a}, Sumanth Gandra\textsuperscript{a}, Simon A. Levin\textsuperscript{e,f,g,1}, Herman Goossens\textsuperscript{h}, and Ramanan Laxminarayan\textsuperscript{a,f,1}

\textsuperscript{a}Center for Disease Dynamics, Economics & Policy, Washington, DC 20005; \textsuperscript{b}Department of Emergency Medicine, Johns Hopkins School of Medicine, Baltimore, MD 21209; \textsuperscript{c}Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205; \textsuperscript{d}Institute of Integrative Biology, ETH Zürich, CH-8092 Zürich, Switzerland; \textsuperscript{e}Department of Ecology and Evolutionary Biology, Princeton University, Princeton, NJ 08544; \textsuperscript{f}Princeton Environmental Institute, Princeton University, Princeton, NJ 08544; \textsuperscript{g}Beijer Institute of Ecological Economics, SE-104 05 Stockholm, Sweden; \textsuperscript{h}Laboratory of Medical Microbiology, Vaccine & Infectious Diseases Institute, University of Antwerp, 2610 Antwerp, Belgium; and \textsuperscript{1}Department of Global Health, University of Washington, Seattle, WA 98104

Eili Y. Klein et al. PNAS doi:10.1073/pnas.1717295115
Global consumption of antibiotics
2015-30 scenario-based forecasts
Daily dosage, bn

## Countries with highest increase in consumption

<table>
<thead>
<tr>
<th>RANK</th>
<th>COUNTRY</th>
<th>2000</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>India</td>
<td>3.2</td>
<td>6.5</td>
</tr>
<tr>
<td>2</td>
<td>China</td>
<td>2.3</td>
<td>4.2</td>
</tr>
<tr>
<td>3</td>
<td>Turkey</td>
<td>0.5</td>
<td>1.4</td>
</tr>
<tr>
<td>4</td>
<td>Brazil</td>
<td>0.5</td>
<td>1.4</td>
</tr>
<tr>
<td>5</td>
<td>Vietnam</td>
<td>0.3</td>
<td>1.1</td>
</tr>
<tr>
<td>6</td>
<td>Pakistan</td>
<td>0.8</td>
<td>1.3</td>
</tr>
<tr>
<td>7</td>
<td>Egypt</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>8</td>
<td>Indonesia</td>
<td>0.3</td>
<td>0.8</td>
</tr>
<tr>
<td>9</td>
<td>Algeria</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>10</td>
<td>Russia</td>
<td>0.6</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Rank according to volume increase; Source: Proceedings of the National Academy of Sciences

Antibiotic use as measured in defined daily doses

Orange: 2000
Red: 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
Carbapenem consumption in the hospital sector in selected European countries, 1997–2013

ESAC-Net 2015
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 1. Workforce of Doctors and Nurses According to Country or Region in 2010.*

<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>
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<tbody>
<tr>
<td><strong>Country</strong></td>
<td></td>
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<td></td>
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<tr>
<td>China</td>
<td>1338</td>
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<td>1,864</td>
<td>2.8</td>
<td>0.97</td>
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<td>1.6</td>
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<td>United States</td>
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<td>756</td>
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<td>Brazil</td>
<td>195</td>
<td>338</td>
<td>1,278</td>
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<tr>
<td>United Kingdom</td>
<td>62</td>
<td>166</td>
<td>626</td>
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<td>South Africa</td>
<td>50</td>
<td>37</td>
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<td><strong>Region</strong></td>
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<tr>
<td>Americas</td>
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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.*9
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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
Figure 1: Total outpatient antibiotic use in 26 European countries in 2002

Goossens et al 2005
Antibiotic Use and Resistance

Source: Sun et al 2012
Seasonality of Prescribing Affects Resistance Rates

Seasonality of Prescribing Not Associated with Viruses

Anthropological and socioeconomic factors contributing to global antimicrobial resistance: a univariate and multivariable analysis

Peter Collignon, John J Beagley, Timothy R Walsh, Sumanth Gandra, Ramanan Laxminarayan

Summary

Background Understanding of the factors driving global antimicrobial resistance is limited. We analysed antimicrobial resistance and antibiotic consumption worldwide versus many potential contributing factors.
Figure 2: *Escherichia coli* resistance levels for fluoroquinolones and third-generation cephalosporins compared with antibiotic consumption.
<table>
<thead>
<tr>
<th></th>
<th>Effect on resistance rate of 1 SD increase in each explanatory variable (logit)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usage (standardised)</td>
<td>-0.88</td>
<td>0.64</td>
</tr>
<tr>
<td>Governance index</td>
<td>-7.89</td>
<td>0.025</td>
</tr>
<tr>
<td>Health expenditure index</td>
<td>-5.54</td>
<td>0.093</td>
</tr>
<tr>
<td>GDP per capita (standardised)</td>
<td>6.62</td>
<td>0.030</td>
</tr>
<tr>
<td>Education index</td>
<td>7.93</td>
<td>0.058</td>
</tr>
<tr>
<td>Infrastructure index</td>
<td>-16.84</td>
<td>0.014</td>
</tr>
<tr>
<td>Climate index</td>
<td>2.01</td>
<td>0.33</td>
</tr>
<tr>
<td>$R^2$</td>
<td>0.54</td>
<td>..</td>
</tr>
</tbody>
</table>

GDP = gross domestic product. $R^2$ = coefficient of determination.

*Table 2: Effect of changes in indices on the resistance of *Escherichia coli* to third-generation cephalosporins and fluoroquinolones*
What are we asking of antibiotics?

**Figure 1.1**

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

- 40 states have health departments
- First continuous municipal use of chlorine in water in United States
- Last human-to-human transmission of the plague
- 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

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**Source:** Adapted from Armstrong, Conn et al. (1999).
Pig Run
Swine output has surged to feed pork-hungry China

Per-capita Pork Consumption
- 45 (kilograms)
- 2020: 40
- 2015: 35
- 1975: 5

Number of Pigs Produced
- 700 (millions)
- 2020: 650
- 2015: 600
- 1975: 100

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>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>77,760</td>
<td>84,240</td>
</tr>
</tbody>
</table>

162,000 of antibiotics used in total

Antibiotics consumed (metric tons) in 2013

In 2013, the global consumption of all antimicrobials in food animals was estimated at 131,109 tons.

Projected to reach 200,235 tons by 2030.

Van Boeckel et al, *Science* 2017
• 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.
The Prevalence of Extended-Spectrum Beta-Lactamase-Producing Multidrug-Resistant *Escherichia Coli* in Poultry Chickens and Variation According to Farming Practices in Punjab, India

Charles H. Brower,1 Siddhartha Mandal,2 Shivdeep Hayer,3 Mandep Sran,4 Asima Zehra,4 Sunny J. Patel,5 Rayneet Kaur,6 Leena Chatterjee,7 Savita Mishra,6 B.R. Das,7 Parminder Singh,8 Randhir Singh,4 J.P.S. Gill,9 and Ramanan Laxminarayan1,9

Brower et al, *Environmental Health Perspectives*, 2017
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
blaNDM-1 was found to be over 20 times greater in the Ganges River during pilgrimage season than at other times of year.
Slides are @www.cddep.org

Thank you