Epidemiology and Economics of Antibiotic Resistance

Eili Y. Klein

February 17, 2016

Health Watch USA Meeting
I. The burden of antibiotic resistance is a growing global threat, but hard numbers are lacking as to the magnitude of the problem
Burden of Antibiotic Resistance in the United States

Estimated minimum number of illnesses and deaths caused by antibiotic resistance*:

At least 2,049,442 illnesses, 23,000 deaths

*bacteria and fungus included in this report

Centers for Disease Control 2013
**Burden by Resistant Pathogen, US**

What is the best measure of burden?

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Infections</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Streptococcus pneumoniae</em></td>
<td>1,200,000</td>
<td>7,000</td>
</tr>
<tr>
<td>Drug-resistant <em>Campylobacter</em></td>
<td>310,000</td>
<td>28</td>
</tr>
<tr>
<td>Drug-resistant <em>Neisseria gonorrhoeae</em></td>
<td>246,000</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Drug-resistant non-typhoidal <em>Salmonella</em></td>
<td>100,000</td>
<td>40</td>
</tr>
<tr>
<td><em>Methicillin-resistant Staphylococcus aureus</em> (MRSA)</td>
<td>80,000</td>
<td>11,000</td>
</tr>
<tr>
<td>Drug-resistant <em>Shigella</em></td>
<td>27,000</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Extended-spectrum β-lactamase producing Enterobacteriaceae (ESBLs)</td>
<td>26,000</td>
<td>1,700</td>
</tr>
<tr>
<td><em>Vancomycin resistant Enterococcus</em> (VRE)</td>
<td>20,000</td>
<td>1,300</td>
</tr>
<tr>
<td>Carbapenem-resistant Enterobacteriaceae (CRE)</td>
<td>9,300</td>
<td>610</td>
</tr>
<tr>
<td>Clindamycin-resistant Group B <em>Streptococcus</em></td>
<td>7,600</td>
<td>440</td>
</tr>
<tr>
<td>Others</td>
<td>23,547</td>
<td>1,380</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2,049,447</strong></td>
<td><strong>23,508</strong></td>
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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

**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

**United States**
- Population: 300m
- >23,000 deaths
- >2.0m illnesses
- Overall societal costs:
  - Up to $20 billion direct
  - Up to $35 billion indirect

Source: ECDC 2007
Source: Pumart et al 2012
Source: US CDC 2013

Global Estimates Not Available
## Measuring the Cost of Resistance

### European Union:

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<th>Extra in-hospital costs</th>
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For the US: If one assumes that there are 2,000,000 ARI per CDC, that $20 billion is an excess cost of $10,000 per infection. (Europe would be €750)
Measuring the Cost of Resistance

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US CDC estimate based on one hospital in which costs for ~1,000 patients with antibiotic resistant infections was estimated to be:
Hospital: $3.4–$5.4 million
Mortality: $7.0–$9.2 million
Lost productivity: $162,624–$322,707
Total: $10.7–$15.0 million
Measuring the Cost of Resistance
Excess costs of resistance by pathogen

<table>
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<tr>
<th>Resistant Organism</th>
<th>Range of Excess Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-resistant <em>Staphylococcus aureus</em></td>
<td>$695 – $29,030</td>
</tr>
<tr>
<td>Vancomycin-resistant <em>Enterococcus</em></td>
<td>$16,711 – $60,988</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>$627 – $45,256</td>
</tr>
<tr>
<td><em>Acinetobacter baumannii</em></td>
<td>$5,336 – $126,856</td>
</tr>
<tr>
<td>Multiple organisms</td>
<td>$9372 – 18,990</td>
</tr>
<tr>
<td>ESBL-producing <em>Enterobacteriaceae</em></td>
<td>$3,658 – $4,892</td>
</tr>
</tbody>
</table>
Unconsidered Costs
Costs of drugs for patients with non-resistant infections

Howard et al 2003
A Growing Problem

Antibiotic Resistance of *Escherichia coli* in United States

<table>
<thead>
<tr>
<th>Year</th>
<th>Aminoglycosides (%)</th>
<th>Aminopenicillins (%)</th>
<th>Fluoroquinolones (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2000</td>
<td>1</td>
<td>1</td>
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<td>2001</td>
<td>2</td>
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<td>2010</td>
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<tr>
<td>2011</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>2012</td>
<td>13</td>
<td>13</td>
<td>13</td>
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Center for Disease Dynamics, Economics & Policy (cddep.org)
A Growing Problem

Antibiotic Resistance of *Klebsiella pneumoniae* in United States

% Resistant (invasive isolates)

- Aminoglycosides
- Carbapenems
- Cephalosporins (3rd gen)
- Fluoroquinolones
- Polymyxins

Center for Disease Dynamics, Economics & Policy (cddep.org)
A Global Problem
Methicillin-Resistant *Staphylococcus aureus*

**FIGURE 1-1**: Percentage of *Staphylococcus aureus* isolates that are methicillin resistant (MRSA), by country (most recent year, 2011–14)

*Source: CDDEP 2015, WHO 2014 and PAHO, forthcoming*
Antimicrobial Resistance Worldwide
More than just antibiotics at risk

Example of mycobacterium:
- **Tuberculosis**
  - Increased morbidity and mortality, increased costs, threatened disease control

Example of parasite:
- **Malaria**
  - Threatened disease control

Example of viruses:
- **HIV and influenza**
  - Threatened disease control
Worldwide Deaths Due to AMR

Source: UK Review on AMR
Economic Cost of AMR

Total GDP loss
$100.2 trillion

Source: UK Review on AMR
II. Increasing incomes are increasing access to antibiotics and saving lives - but they are not a good substitute for public health
Changes in Global Consumption 2000-2010

Antibiotic Consumption is Increasing in Developing Countries

Per Capita Total Antibiotic Consumption

- Pakistan
- India
- China
- Brazil
- French West Africa

Standard Units/1,000 Population

25,000
20,000
15,000
10,000
5,000
0
2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010
Antibiotic Consumption is Increasing in Developing Countries

Per Capita Total Antibiotic Consumption

Standard Units/1,000 Population

2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010

France  USA  Pakistan  Norway  India  China  Brazil  French West Africa
Extended-spectrum macrolide use is highly prevalent in the United States, and increasing in developing countries.
Carbapenem use is increasing in the hospital

Per capita total carbapenem use, hospital sector, 2005-2010

- Standard units per 1000 population
- Countries: Vietnam, China, Norway, USA
But carbapenems are also sold on the retail market.
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?

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

Source: Adapted from Armstrong, Conn et al. (1999).
What are we asking of antibiotics?

Substitute for immunization, infection control and water/sanitation

Source: Adapted from Armstrong, Conn et al. (1999).
III. More antibiotic use is associated with increasing rates of antibiotic resistance
Antibiotic Use and Resistance

Figure 1: Total outpatient antibiotic use in 26 European countries in 2002

Gossens et al 2005
Antibiotic Use and Resistance

Figure 1: Total outpatient antibiotic use in 26 European countries in 2002

Figure 6: Correlation between penicillin use and prevalence of penicillin non-susceptible S pneumoniae

France

Netherlands

Gossens et al 2005
Antibiotic Use and Resistance

Source: Sun et al 2012
IV. Drivers of antibiotic use relate to incentives and behavior of patients, physicians, pharma, payers and healthcare institutions.
Drivers of Antibiotic Use

How do incentives affect antibiotic prescribing?

Patient Expectations/Satisfaction

Patients more likely to get a prescription if they expect antibiotics

Physicians more likely to give a prescription if they believe patient expects antibiotics regardless of patient expectation
Drivers of Patient Expectations

Germs are germs: e.g., bacteria and viruses are the same

Why Not Take a Risk?: e.g., “I don’t know if antibiotics will make me better, but it’s better to be safe than sorry so I should take them”

Others:

Prior Knowledge: “I got better last time I got ABX”

WebMD: “Someone (i.e. internet/friend) told me that antibiotics will make me better”

Trust: "I trust the doctor to give me antibiotics if I am sick (when I need them)"

Seriousness: "If the doctor takes me seriously, they will give me a prescription"

Veni, Vidi, Vici: "Only a prescription is worth the wait"
Why Not Take a Risk?

Motivated by Fuzzy Trace Theory

Status quo: patient is already sick

Two options

1. Stay sick for sure (by avoiding antibiotics)
2. Maybe stay sick; maybe get better (by taking antibiotics)

Getting better is preferred over staying sick, so choose antibiotics

Underlying assumptions:

There is some chance that antibiotics could make them feel better
Antibiotics are essentially harmless to the individual
Drivers of Antibiotic Use

How do incentives affect antibiotic prescribing?

Patient Expectations/Satisfaction

Patient Socioeconomics

Health insurance increases prescribing
Free programs increase antibiotics
Drivers of Antibiotic Use

How do incentives affect antibiotic prescribing?

- Patient Expectations/Satisfaction
- Patient Socioeconomics
- Legal Ramifications
- Physician Remuneration
Hospital Incentives

Antibiotics may be a substitute for infection control

Infection control is often not compensated but longer hospital stays are beneficial to the hospital
Pharmaceutical Incentives

Patents

- Zithromax
- Azithromycin (generic)
Externalities of Antibiotics and how they relate to incentives

Positive Externalities
  Reduce the transmission of disease

Negative Externalities
  The more antibiotics are used, the greater the selective pressure placed on bacteria to evolve

The problem is the absence of economic incentives for individuals/hospitals/companies to take into account the negative impact of their use of antibiotics on social welfare
V. There is no silver bullet for maintaining antibiotic effectiveness. There are tradeoffs to every approach.
So what can we do?

Maintaining antibiotic effectiveness in the long term requires

1. Conservation: Technological, medical, and incentive-based solutions to keep existing antibiotics working
2. Innovation: Develop new antibiotics

But these two approaches are linked in a negative feedback loop. Increased innovation reduces the need for conservation and vice versa.
Conservation

Antimicrobial stewardship
New clinically relevant tests that identify both the cause of an infection and its sensitivity to common antibiotics

Vaccines
Other types of solutions?

Combination therapies that target both essential functions and resistance factors
  Eg. amoxicillin-clavulanate
Repurpose old drugs to optimize dosing levels and the duration, and route of administration
  Eg. optimized dosing of colistin to reduce toxicity and improve efficacy
Prevent resistance by protecting non-target bacterial flora during treatments
Antibiotics as a Natural Resource

The cost of discovering new sources of oil becomes more expensive as the resource is depleted (because harder to find and environmental regulations)

Increased incentives for finding new oil reserves reduces incentives to conserve oil
Antibiotics as a Natural Resource

New antibiotics are likely to cost more than existing ones (because harder to discover and increased regulatory costs)

Subsidies for new drug development discourage efforts to improve how existing antibiotics are used
Dwindling Antibiotic Development

Number of new, FDA-approved antibacterial agents

- 1983-1987: 0
- 1988-1992: 2
- 1993-1997: 4
- 1998-2002: 6
- 2003-2007: 8
- 2008-2012: 10
Once an antibiotic is introduced, resistance is not far behind
Incentives to develop new antibiotics

Decrease cost of development (e.g. tax credits, grants, contracts, liability protection)

- Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) – BARDA partnership

Increase income linked to antibiotics (e.g. extend exclusivity, patent extensions, prizes)

- Under the Generating Antibiotic Incentives Now (GAIN) Act in the United States new antibiotics are given 5 years of additional market exclusivity for designated Qualified Infectious Disease Products
Important questions

Do we need public subsidies for new antibiotic development or will the market respond on its own?
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[Bar chart showing the price in USD of different antibiotics over time, with market launches in 1941, 2000, 2006, and 2010. Penicillin costs $0.1, Linezolid $155, Daptomycin $181, and Sipuleucel-T $31,000.]
Important questions

Do we need public subsidies for new antibiotic development or will the market respond on its own?

What is the impact of public subsidies for new drug development on stewardship?

How can we change the rules of the game to incentivize appropriate use of new (and existing) antibiotics?

How do we balance access with concerns about resistance?
For research, updates and tools on drug resistance and other global health topics, visit:

www.cddep.org

Thank you!