The Global Challenge of Antimicrobial Resistance

Ramanan Laxminarayan
GARP Regional Meeting, Kathmandu
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?
Substitute for immunization, infection control and water/sanitation

**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
- Influenza pandemic

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

Source: Adapted from Armstrong, Conn et al. (1999).
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 – 0.01
- 0.01 – 0.05
- 0.05 – 0.1
- 0.1 – 0.2
- 0.2 – 0.3
- 0.3 – 0.4
- 0.4 – 0.5
- 0.5 – 1

**3rd Gen. Cephalosporins**

1999–2001

2002–2005

2006–2010

**Proportion of resistant isolates:**

- 0 – 0.05
- 0.05 – 0.1
- 0.1 – 0.2
- 0.2 – 0.5
- 0.5 – 0.75
- 0.75 – 1
- 1 – 1.25
- 1.25 – 1.5
- 1.5 – 1

Note: Data for 2010 available through July.

Percentage of *Staphylococcus aureus* isolates that are methicillin resistant (MRSA) in selected countries, 1999–2014

Depending on the country, resistance to one or more of the following drugs may have been used to test for MRSA: Oxacillin, cefoxitin, flucloxacillin, cloxacillin, dicloxacillin, and methicillin. Intermediate-resistant isolates are included as resistant.

Source: CDDEP 2015
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, fluoroquinolones, 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.
CRE rates in children grew between 2000 and 2012

Logan et al, EID, 2015
Spread of New Delhi metallo beta-lactamase: first detection, by country

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

Select map, trend or chart.

The landing view on the resistance section displays a map with the most recent resistance data. By default, E. coli's resistance is displayed.

Click on a pathogen to explore its resistance.

Antibiotics that have resistance data available are displayed in black. Antibiotic whose data is currently displayed is highlighted in blue.
Resistance rates in various countries on global map
Resistance rates comparison among countries
Where does the burden of resistance lie?
Neonatal sepsis – 421,000 deaths globally
Mortality outcomes are worse in neonates with resistant infections

Neonatal Case fatality rates in India (In Press)

Case fatality ratio (%)

<table>
<thead>
<tr>
<th>Category</th>
<th>Positive</th>
<th>Negative</th>
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<tbody>
<tr>
<td>Culture</td>
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<td>Gram-stain</td>
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<td>Carbapenem resistant</td>
<td>62.3</td>
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<td>ES cephalosporins resistant</td>
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<td>Multi-drug resistant</td>
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<tr>
<td>MRSA</td>
<td>37.2</td>
<td>30.9</td>
</tr>
</tbody>
</table>
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 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 ended the criminal case against a white New York police officer whose chokehold on an unarmed black man led to the man's death, a decision that drew condemnation from elected officials and touched off a wave of protests.

The officers death in July was captured on video and seen around the world. But after examining the footage and hearing from witnesses, including the officer who used the chokehold, the jurors deliberated for less than a day before deciding that there was not enough evidence to go forward with charges against the officer, Donnell Pantaleo, 28, in the death of the man, Eric Garner, 43.

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 maneuver as a take-down move, adding that he never thought Mr. Garner was in mortal danger.

The decision came barely a week after a grand jury found no criminal action in the actions of another white officer, Darren Wilson, who shot and killed 18-year-old Michael Brown, an unarmed 18-year-old black man in Ferguson, Mo.

After the news from Staten Island, a wave of elected leaders renewed calls for Justice Department action, amounting to a financial settlement.

Mr. Garner, in an undated letter, wrote: "If I can't breathe, others shouldn't."

By TIM ARANGO and THOMAS ERDBRINK

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

BAGHDAD — Iranian fighter jets struck extreme targets in Iraq recently, Iranian 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, where Iranian troops are helping Iraq's new government to conduct military operations openly on foreign battlefields rather than covertly and through proxies.

"Superbugs" Kill India's Babies and Pose an Overseas Threat

AMRAVATI, India — A deadly epidemic that could have global implications is quietly sweeping India, and among its many victims are tens of thousands of newborns dying because once-effective antibiotics are no longer working.

These infants are born with bacterial infections that are resistant to most known antibiotics, and more than 15,000 died last year as a result, a recent study found. While that is still a fraction of the annual 800,000 newborn deaths here, the study's authors say that this is just the tip of the iceberg.
Typhoid and para typhoid –
400,000 deaths, 16 million cases
Fig. 1. Distribution of typhoid fever, by age group, at various incidences

- High (>100 per 100,000 per year)
- Medium (10–100,000 per year)
- Low (<10 per 100,000 per year)
Fig. 2. Geographical distribution of typhoid fever
Antimicrobial resistance and management of invasive *Salmonella* disease

Samuel Kariuki\textsuperscript{a,b,*}, Melita A. Gordon\textsuperscript{c,d}, Nicholas Feasey\textsuperscript{d,e}, Christopher M. Parry\textsuperscript{f,g}

**Abstract**

Invasive *Salmonella* infections (typhoidal and non-typhoidal) cause a huge burden of illness estimated at nearly 3.4 million cases and over 600,000 deaths annually especially in resource-limited settings. Invasive non-typhoidal *Salmonella* (iNTS) infections are particularly important in immunosuppressed populations especially in sub-Saharan Africa, causing a mortality of 20–30% in vulnerable children below 5 years of age. In these settings, where routine surveillance for antimicrobial resistance is rare or non-existent, reports of 50–75% multidrug resistance (MDR) in NTS are common, including strains of NTS also resistant to fluoroquinolones and 3rd generation cephalosporins. Typhoid (enteric) fever caused by *Salmonella Typhi* and *Salmonella Paratyphi* A remains a major public health problem in many parts of Asia and Africa. Currently over a third of isolates in many endemic areas are MDR, and diminished susceptibility or resistance to fluoroquinolones, the drugs of choice for MDR cases over the last decade is an increasing problem. The situation is particularly worrying in resource-limited settings where the few remaining effective antimicrobials are either unavailable or altogether too expensive to be afforded by either the general public or by public health services. Although the prudent use of effective antimicrobials,
Resistance is increasing and associated with worse outcomes

- In Kenya, proportion of *S. typhi* in Kenya that are multidrug resistant and resistant to nalidixic acid and with decreased susceptibility to fluoroquinolones had risen from 1% in 2000 to nearly 25% in 2008.
- Fluoroquinolone resistance is increasing in India (44%) and Pakistan (58%).
- Case fatality rates associated with multidrug-resistant *S. typhi* in south Asia are 10% (close to the 12.8% recorded in the pre-antibiotic era) *Lancet Infect Dis* 2005; 5: 481–93
Surgical site infections – over 400,000 deaths
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.
Maternal deaths caused by sepsis – about a tenth of all maternal deaths
Are Institutional Births Institutionalizing Deaths?

SUBMITTED BY JISHNU DAS ON THU, 11/20/2014
CO-AUTHORS: JEFFREY HAMMER

Increasing rates of institutional deliveries place a greater burden on infection standards in health care institutions.
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

- Colorectal surgery
- Caesarean section
- Hysterectomy
- Transrectal prostate biopsy
- Spinal surgery
- Surgical abortion
- Appendectomy
- Total hip replacement
- Pacemaker implantation
- Cancer chemotherapy
- Hip fracture surgery
Malaria – 420,000 deaths
Impact of chloroquine resistance on malaria mortality

Impact de la résistance à la chloroquine sur la mortalité palustre

Jean-François Trape\textsuperscript{a*}, Gilles Pison\textsuperscript{b}, Marie-Pierre Preziosi\textsuperscript{c}, Catherine Enel\textsuperscript{b}, Annabel Desgrées du Loû\textsuperscript{a}, Valérie Delaunay\textsuperscript{c}, Badara Samb\textsuperscript{c}, Emmanuel Lagarde\textsuperscript{b}, Jean-François Molez\textsuperscript{a}, François Simondon\textsuperscript{a}

Risk of malaria mortality in children under 10 went up between two and five-fold in three populations in Senegal following emergence of chloroquine resistance.
Anticipated impact of drug resistance in the near term

- Neonatal sepsis
- Enteric pathogens
- Surgical site infections
- Maternal mortality associated with obstetrics
- Malaria
- Tuberculosis
- HIV
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

Invasive disease caused by non-susceptible Pneumococci, US
Effect of PCV7 introduction on antibiotic prescriptions and ambulatory care visits

Zhou et al, Pediatrics 2008
Effect of PCV7 introduction 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.
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).
Faropenem consumption has increased by 154% since it was approved for use in India in 2010.
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>
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Global availability of colistin

Wertheim et al, JGAR 2013
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.
Antibiotic use for growth promotion and disease prevention
2/3\textsuperscript{rd} of the tonnage of antibiotics sold worldwide are used in agriculture
Numbers of unique β-lactamase enzymes identified since introduction of first β-lactam antibiotics
• 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.
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
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
Global antibiotic consumption in livestock (mg per 10 km$^2$ pixels) 2010

Log10 [(mg/pixel) + 1]

- 0 - 1
- 4 - 5
- 5 - 6
- 6 - 7
- 7 - 8
- 8 - 9
- 9 - 10
- 10 - 11
- No data

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

Van Boeckel et al., PNAS, 2015
Price in USD

- Penicillin: $0.1
- Linezolid: $155

Market Launch:
- Penicillin: 1941
- Linezolid: 2000
Price in USD

- **Penicillin**: $0.1
- **Linezolid**: $155
- **Daptomycin**: $181

**Market Launch:**
- **Penicillin**: 1941
- **Linezolid**: 2000
- **Daptomycin**: 2006
Antimicrobials: access and sustainable effectiveness

EMBARGO
NOVEMBER 18, 2015
[14:00]

“Our intention is to redefine and reposition antimicrobial resistance into a broader and more appropriate context, especially given the new era of sustainable development... Our Series defines two dimensions: sustainable access, as well as sustainable effectiveness.”
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.

©Athens-Clarke County Heritage Room, 2011.
Slides are downloadable @
www.cddep.org

More on the Global Antibiotic Resistance Partnership @

www.cddep.org/garp