Tackling Antibiotic Resistance: A Global Priority

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Disclosures

• Adjudication Committee – NIH
• Data Monitoring Committee
  — Actelion
• Editor
  — ID Clinics of North America
  — Antimicrobial Agents and Chemotherapy
• Treasurer, Infectious Diseases Society of America
• Member, ID Board and ID Test Writing Committee, American Board of Internal Medicine
• Voting Member, Presidential Advisory Council on Combating Antibiotic Resistant Bacteria (PACCARB)
Have We Returned to the Pre-antibiotic Era? Recent Case

71 year old lady with laryngeal cancer post laryngectomy, chemotherapy and radiation in 2012, COPD on home oxygen, and recent admission for tracheobronchitis now transferred from rehabilitation with fever, flank pain and respiratory failure

— Cured of cancer
Have We Returned to the Pre-antibiotic Era?
Recent Case

History:
- 12/2015 Cough, sputum production with acute on chronic respiratory failure
- She had no fever, chills or other constitutional symptoms
- Evaluation for viruses, other infections negative
- Blood and sputum cultures grew GNR ultimately identified as MDR *K. pneumoniae*, + metallo-carbapenemase
- Did well, cleared blood cultures, did not need re-intubation
- Treated for 2 weeks with
  - IV tigecycline
  - IV colistin
    - inhaled colistin
- January, 2016 switched from colistin IV/inhaled to IV minocycline
Have We Returned to the Pre-antibiotic Era?
Recent Case

Admitted with pneumonia again in late January and in May

She presented with respiratory failure and tracheobronchitis along with a urinary tract infection

- Discharged on a 5 day course of levofloxacin
- Sputum and urine cultures subsequently grew a carbapenemase-producing *Klebsiella pneumoniae*
- 4 days later, she was found to have an increased oxygen requirement
- ER: reports feeling very tired, still has urinary symptoms (dark, foul-smelling, with right flank pain), T 38.5°C, increased oxygen requirements
- Urine culture $\geq 100,000$ CFU/mL *Klebsiella pneumoniae*, + Carbapenem resistance, MDR organism
Have We Returned to the Pre-antibiotic Era?
Recent Case

Culture Urine $\geq 100,000$ CFU/mL *Klebsiella pneumoniae*, + Carbapenem resistance, multidrug resistant (MDR) organism

Resistant to:

- Ampicillin
- Ampicillin/sulbactam
- Piperacillin/tazobactam
- Cefazolin
- Cefoxitin
- Ceftazidime
- Ceftriaxone
- Cefepime

- Meropenem
- Amikacin
- Gentamicin
- Tobramycin
- Ciprofloxacin
- Nitrofurantoin
- Trimethoprim/Sulfa
- Ceftolozane-tazobactam
- Ceftazidime-avibactam
Have We Returned to the Pre-antibiotic Era? Recent Case (continued)

After discussion re: limited options, predictable renal, neurological and other toxicity, patient and her family decided on hospice care
Case

47 year old female school teacher presents with pain upon urination, lower abdominal pain

- Started on standard oral therapy - ciprofloxacin

Two days later she comes back and appears ill with new chills, nausea and back pain

- High fever, exam notable for new right flank tenderness
- Urine shows signs of infection
- Labs: elevated white blood cells with left shift

Therapy advanced to guideline therapy for pyelonephritis; she looked well enough to go home

- One dose IV ceftriaxone, then oral TMP/SMX

http://cid.oxfordjournals.org/content/52/5/e103.full.pdf+html
Case continued…
Two days later

Substantially worse, acutely ill, high fever, low BP, requires hospitalization for intravenous hydration as unable to eat or drink; 2 episodes of vomiting

- Exam – T 38.7, BP 90/60, elevated HR, ill appearing, mild distress due to pain; worsening right flank tenderness
- Despite antibiotic therapy, urine culture grows > 100,000/mL *K. pneumoniae*
- *K. pneumoniae* identified as ESBL+
  - Resistant to ciprofloxacin, ceftriaxone, TMP/SMX

- Admitted to hospital and treated with imi/meropenem
  - Drugs of choice for ESBLs
Have we returned to the pre-antibiotic era?

Maybe so…

- mcr-1/mcr-2
  - Transmissible (plasmid) colistin resistance
  - Already associated with KPC; true MDR/XDR possible
- We should be scared
- Forced to use drugs with extremely limited/negative data – e.g.,
  - Inhaled/parenteral colistin
  - Fosfomycin for ESBL infections
  - Tigecycline for MDR infections (despite warning re: death)
- Infection prevention, stewardship, surveillance of paramount importance
  - Progress is being made through CARB, WHO, others

Infections With 'Nightmare Bacteria' Are On The Rise In U.S. Hospitals

MARCH 05, 2013  2:56 PM ET

CDC: Deadly drug-resistant bacteria on rise in U.S. hospitals

Water Research

Volume 37, Issue 8, April 2003, Pages 1685-1690

Antibiotic resistance of E. coli in sewage and sludge


Occurrence of Antibiotic-Resistant Uropathogenic Escherichia coli Clonal Group A in Wastewater Effluents

Laura A. Boczek, Eugene W. Rice, Brian Johnston and James R. Johnson

Carbapenem-Hydrolyzing GES-5-Encoding Gene on Different Plasmid Types Recovered from a Bacterial Community in a Sewage Treatment Plant

Delphine Girlich, Laurent Poirot, Rafael Szczepanowski, Andreas Schlüter, and Patrice Nordmann

Laura A. Boczek US EPA
And we now face a global crisis

- CDC 2013
- Other reports are similar (ECDC, WHO, CDDEP)
In the United States, each year we have

23,000 deaths/year ≈ One jumbo jet crash every week
Global Deaths Attributable to AMR Every Year by 2050

www.amr-review.org
Cost of AMR

- Deaths
  - 25,000/year in the United States
  - 500,000/year globally
- Costs
  - US health care costs $20 billion/year
- Lost productivity
  - $3.5 billion/year in the US
  - €1.5 billion/year in the EU
Impact of Antibiotics on Mortality

Antibiotics caused US deaths to decline by ~220 per 100,000 in 15 years

Sulfa

Penicillin

All other medical technologies reduced deaths by ~20 per 100,000 over the next 45 years

# Power of Antibiotics

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pre-Antibiotic Death Rate</th>
<th>Death With Antibiotics</th>
<th>Change in Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community Pneumonia¹</td>
<td>~35%</td>
<td>~10%</td>
<td>-25%</td>
</tr>
<tr>
<td>Hospital Pneumonia²</td>
<td>~60%</td>
<td>~30%</td>
<td>-30%</td>
</tr>
<tr>
<td>Heart Infection³</td>
<td>~100%</td>
<td>~25%</td>
<td>-75%</td>
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<tr>
<td>Brain Infection⁴</td>
<td>&gt;80%</td>
<td>&lt;20%</td>
<td>-60%</td>
</tr>
<tr>
<td>Skin Infection⁵</td>
<td>11%</td>
<td>&lt;0.5%</td>
<td>-10%</td>
</tr>
</tbody>
</table>

*By comparison...treatment of heart attacks with aspirin or clot busting drugs⁶ -3%*

Antibiotics for Cellulitis Save More Lives Than Aspirin or Streptokinase for Myocardial Infarction!

<table>
<thead>
<tr>
<th>Disease</th>
<th>Death No Treatment</th>
<th>Death With Treatment</th>
<th>Reduction in Death</th>
<th>NNT to Save a Life*</th>
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</thead>
<tbody>
<tr>
<td>Cellulitis</td>
<td>11%</td>
<td>0.3%</td>
<td>&gt;10%</td>
<td>9</td>
</tr>
<tr>
<td>MI†</td>
<td>12%</td>
<td>9%</td>
<td>3%</td>
<td>33</td>
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</tbody>
</table>

*Spellberg et al. Clinical Infectious Diseases 2009

*Number of patients Needed to Treat (NNT) to save a life

†From ISIS-2 Study published in 1988 in Lancet 2:349-60
Antibiotics and Medical Progress

Ability to control infection is critical to other advances in medicine including:

— Neonatal care
— Transplantation
— Chemotherapy
— Immunosuppression
— Complex and routine surgery
  • Joint replacement
— Obstetric care
— Intensive care interventions
Antibiotics
A limited resource

- Increasing antibiotic resistance
- Overuse of antibiotics
- Poor access for many LMIC
- Dry antibiotic pipeline

Spellberg, B. et al. Clinical Infectious Diseases 2008; 46 (2):155-64
Emergence of antibiotic resistance threatens ability to control infection

“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.”

Sir Alexander Fleming, 1945

4. Sir Alexander Fleming, Nobel Lecture, December 1945
Emergence of Antibiotic Resistance

Spread of VRE Healthcare Environment

C. A. Arias and B. E. Murray.
Global Spread of VRE

Overuse of Antibiotics
Community Antibiotic Prescribing Rates per 1000 Population — United States, 2014

Lowest state: 501 per 1000

Highest state: 1,285 per 1000

Dr. Lori Hicks, CDC; Data: IMS Health Xponent
http://www.cdc.gov/getsmart/community/programs-measurement/measuring-antibiotic-prescribing.html
What We Know about U.S. Outpatient Antibiotic Use

- The U.S. uses lots of outpatient antibiotics compared to other countries
- There is a lot of geographic variability within the U.S.
- There is a lot of unnecessary use, especially for respiratory conditions, in doctors’ offices and emergency departments

What We Don’t Know and are Working to Address

- Where there are opportunities to improve antibiotic use in dental offices, retail clinics, and urgent care centers
What We Know about U.S. Nursing Home Antibiotic Use

- Up to 70% of residents receive an antibiotic each year
- Estimate 40-75% of antibiotic use in inappropriate or unnecessary
  - Lack national data

What We Don’t Know and are Working to Address

- What’s being used?
- For what indications?
- In what types of nursing home patients?

http://www.cdc.gov/longtermcare/prevention/antibiotic-stewardship.html
Global Antibiotic Prescribing
CDDEP

**Figure 1.6**

Antibiotic prescribing rates for the United States and other countries

- **Sources:** Canada, Australia, and United States, 1994 (McManus, Hammond et al. 1997); Russia, 1998 (Cizman, Beovic et al. 2004); Australia, 2002 (National Prescribing Service 2005); European countries, 2004 (Goossens, Ferech et al. 2003).
- **Note:** DDD=defined daily doses, a standardized measure of antibiotic consumption.

https://www.cddep.org/tool/antibiotic_prescribing_rates_country/
Global antibiotic consumption grew 30% between 2000 and 2010. Growth is driven mostly by countries such as South Africa and India, where antibiotics are widely available over the counter and sanitation in some areas is poor.

https://www.nature.com/news/dramatic-rise-seen-in-antibiotic-use-1.18383; CDDEP
Use/Overuse in Animals

• > 60,000 tons of antimicrobials used in animals globally/year
  — Therapy
  — Prevention/growth promotion
• 40 countries have policies to limit use of antimicrobials in livestock
• Major differences between species
  — Pork, beef, poultry (chickens/turkey)
  — Companion animals
Major use of antibiotics on plants

Bacterial spot of peach and nectarine (Xanthomonas arboricola pv. pruni)

~15% of quantity of antibiotics
~6,000 kg annually
Three sprays on 15% of acreage

Fire blight of pear and apple (Erwinia amylovora)

~85% of quantity of antibiotics
~29,500 kg annually

Pear: Three sprays on 45% of acreage
Apple: One spray on 18% of acreage

Intervene if fire blight risk high: warm temperatures coincide with open flowers in orchards with recent history of disease.

Virginia Stockwell, PACCARB presentation, June, 2016
Carbapenem-resistant isolates of apparent fecal origin including numerous *bla*<sub>NDM-1</sub> positive pathogens

Prof David W Graham, PACCARB June, 2016
Observations

- Antibiotic use and regionally poor water quality drive the global spread of AR
- Developed countries are complacent because of locally clean water
  - AR is massively discharged in wastes where management is limited
  - International travel (human, wildlife) spreads local AR to global scales

Prof David W Graham, PACCARB June, 2016
AMR
Problem of Access to Antimicrobials

- Low and Middle Income Countries
- Unacceptably high mortality due to untreated infection
- Access = major priority for WHO and other global agencies
Antibiotic Discovery

Figure 1. Discovery of new classes of antibiotics.

No New Classes to Treat Gram Negative Bacilli For 4 Decades

Courtesy J.G. Bartlett
Rate of New Antibacterials Approved by US FDA Over 30 Years

Antibiotic resistance: Global Priority

2014: WHO Global Report on Surveillance
- Very high rates of resistance observed for common bacteria that cause healthcare associated and community-acquired infections in all WHO regions
- Significant gaps in surveillance
- Urgent need to strengthen collaboration on global surveillance to address antimicrobial resistance (AMR)

May 2015
- World health assembly endorses global action plan to tackle AMR

September 2016
- 193 countries sign UN Declaration to take action on AMR, reaffirming their commitment to develop national action plans on AMR, based on the global action plan.

Combating Antimicrobial Resistance: Policy Recommendations to Save Lives

Infectious Diseases Society of America (IDSA)*

Clinical Infectious Diseases 2011;52(S5):S397–S428

IDSA PUBLIC POLICY SUPPLEMENT ARTICLE

BAD BUGS, NO DRUGS

As Antibiotic Discovery Stagnates ... A Public Health Crisis Advances

10x '20

Ten new ANTIBIOTICS by 2020
IDSA Calls to Action on AMR

- **Bad Bugs, No Drugs. As Antibiotic Discovery Stagnates … A Public Health Crisis Brews**
  - Infectious Diseases Society of America. July 2004
- **Bad Bugs Need Drugs: What’s in the Development Pipeline? An Update from the Antimicrobial Availability Task Force of the Infectious Diseases Society of America**
  - *Clin Infect Dis* 2006; 42: 657-68

**Bad Bugs, No Drugs: No ESKAPE! An Update from the Infectious Diseases Society of America**

Helen W. Boucher,1 George H. Talbot,2 John S. Bradley,3 4 John E. Edwards, Jr,5 6 7 David Gilbert,8 Louis B. Rice,9 10 Michael Scheld,11 Brad Spellberg,5 12 and John Bartlett12

1 Division of Geographic Medicine and Infectious Diseases, Tufts University and Tufts Medical Center, Boston, Massachusetts; 2 Talbot Advisors, Wayne, Pennsylvania; 3 Division of Infectious Diseases, Rady Children’s Hospital San Diego, and 4 University of California at San Diego, San Diego; 5 Division of Infectious Diseases, Harbor—University of California at Los Angeles (UCLA) Medical Center, and 6 Los Angeles Biomedical
Status of IDSA 10 x ‘20 Initiative

Progress, but unmet needs remain, all of these drugs have gaps, and we remain at high risk
Combating AMR: Multiprong One Health Approach

One Health

- R&D
- Prevention
- Research
- Stewardship
- Access
- Surveillance
- ID Workforce
One Health

- Human medicine
- Veterinary medicine
- Environmental health
- Ecology
- Public health
- Molecular and microbiology
- Health economics
- Translational medicine
One Health History - Founders Veterinary Epidemiology and One Medicine-One Health

Sir Calvin Schwabe
1927-2006

Dr. James H. Steele
1912-2013

Prof Emeritus
UT School of Public Health

Source: CDC, 2011
Organizations working on One Health

- World Health Organization (WHO)
- Food and Agriculture Organization (FAO)
- World Organization for Animal Health (OIE)
- One Health Initiative
- US Centers for Disease Control
- EcoHealth Alliance
Tripartite Alliance
AMR Review May, 2016
“The O’Neill Report”

- Recommendations across 10 areas
- Most aim to reduce demand for antimicrobials
  - Vaccines
  - Alternatives to antibiotics
  - Diagnostics
- Need a global workforce!

[Tackling Antimicrobial Resistance on Ten Fronts diagram]

https://amr-review.org/
Progress on Antimicrobial Resistance
United States Policy

- President Obama’s Executive Order (9/18/14)
- President’s Council of Advisors for Science and Technology (PCAST) Report
- National Strategy from White House
  - Combating Antibiotic Resistant Bacteria (CARB)
NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

MARCH 2015
CARB National Action Plan

Five Goals:

1. Slow the Emergence of Resistant Bacteria and Prevent the Spread of Resistant Infections
2. Strengthen National One-Health Surveillance Efforts to Combat Resistance
3. Advance Development and Use of Rapid and Innovative Diagnostic Tests for Identification and Characterization of Resistant Bacteria
4. Accelerate Basic and Applied Research and Development for New Antibiotics, Other Therapeutics, and Vaccines
5. Improve International Collaboration and Capacities for Antibiotic Resistance Prevention, Surveillance, Control, and Antibiotic Research and Development
Setting National Targets: Outpatient Antibiotic Prescribing

47 million unnecessary antibiotic prescriptions per year

INITIAL ASSESSMENTS OF THE NATIONAL ACTION PLAN FOR COMBATING ANTIBIOTIC-RESISTANT BACTERIA

MARCH 2016

PACCARB
Presidental Advisory Council on Combating Antibiotic-Resistant Bacteria
Recommendations:

- Fully embrace One Health approach
- Lead Federal champion of CARB initiative
- Coordination of federal response
- Resource allocation
- Development of critical partnerships
- Economic incentives for developing(deploying new diagnostic, preventative and therapeutic tools

<table>
<thead>
<tr>
<th>Human Health</th>
<th>Incentives to Develop</th>
<th>Animal Health</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Provide additional funding for the development of new product pipelines for vaccines that prevent viral or bacterial syndromes that drive antibiotic use.</td>
<td><strong>Vaccines</strong></td>
<td>Develop and fund a National Policy and Innovation Institute under USDA whose main functions will include the following:</td>
</tr>
<tr>
<td>2. Optimize the interactions among sponsors, regulatory agencies (such as FDA), and use policy committees (e.g., the ACIP).</td>
<td></td>
<td>Supporting basic research on immunology across species for the development of vaccines.</td>
</tr>
<tr>
<td>3. Incentivize the uptake of vaccines by influencing behavior, such as reimbursement to ensure “first-dollar coverage.”</td>
<td><strong>Diagnostics</strong></td>
<td>Promoting educational programs for veterinarians on the use and interpretation of diagnostic tests.</td>
</tr>
<tr>
<td>4. Include the development of a concomitant AST as part of any new antibiotic funding (or funding for new antibiotics).</td>
<td></td>
<td>Providing resources to conduct, evaluate, and create a database of efficacy studies of alternative products.</td>
</tr>
<tr>
<td>5. Provide financial support for diagnostic manufacturers to bring new tests to market.</td>
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<tr>
<td>6. Continue funding for clinical trial networks with common rules or shared IRBs.</td>
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<tr>
<td>7. Develop new economic models (pull incentives) for therapies to support the currently available push incentives.</td>
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*The comprehensive list of PACCARB recommendations, including the top 10 listed here, begins on page 4.

**Abbreviations:** ACIP, Advisory Committee on Immunization Practices; AST, antimicrobial susceptibility test; FDA, U.S. Food and Drug Administration; IRB, institutional review board; USDA, U.S. Department of Agriculture.

TUBERCULOSIS: A GLOBAL PRIORITY FOR RESEARCH

FIVE REASONS WHY

1. Tuberculosis (TB) is the number one global infectious disease killer today, causing 1.8 million deaths per year. Drug-resistant TB is the most common and lethal airborne AMR disease worldwide today, responsible for 250,000 deaths each year.

2. Patients with multidrug-resistant TB (MDR-TB) need complex and prolonged multidrug treatment with costly, highly toxic, and much less effective second-line medicines. There is a limited number of second-line medicines to treat MDR-TB and only 52% of patients are successfully treated globally.

3. In about 50% of MDR-TB patients worldwide, treatment regimens are already compromised by second-line drug resistance. Treatment of extensively drug-resistant disease (XDR-TB) is successful in only one in three patients at best.

1 MDR-TB = multidrug-resistant tuberculosis, that does not respond to at least isoniazid and rifampicin, the two most effective drugs.
ANTIBIOTIC RESISTANCE THREATS
in the United States, 2013

Urgent Threats
- *Clostridium difficile*
- Carbapenem-resistant Enterobacteriaceae (CRE)
- Drug-resistant Neisseria gonorrhoeae

Serious Threats
- Multidrug-resistant Adinobacter
- Drug-resistant Campylobacter
- Fluconazole-resistant Candida (a fungus)
- Extended spectrum β-lactamase producing Enterobacteriaceae (ESBLs)
- Vancomycin-resistant Enterococcus (VRE)
- Multidrug-resistant Pseudomonas aeruginosa
- Drug-resistant Non-typhoidal Salmonella
- Drug-resistant *Salmonella* Typhi
- Drug-resistant *Shigella*
- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Drug-resistant *Streptococcus pneumoniae*
- Drug-resistant tuberculosis

Concerning Threats
- Vancomycin-resistant *Staphylococcus aureus* (VRSA)
- Erythromycin-resistant Group A *Streptococcus*
- Clindamycin-resistant Group B *Streptococcus*
Three categories according to urgent need for new antibiotics:

**Critical priority**
- *Acinetobacter baumannii*, carbapenem-resistant
- *Pseudomonas aeruginosa*, carbapenem-resistant
- *Enterobacteriaceae*, carbapenem-resistant, ESBL-producing

**High priority**
- *Enterococcus faecium*, VRE
- *Staphylococcus aureus*, MRSA, VISA/VRSA
- *Helicobacter pylori*, clarithromycin-resistant
- *Campylobacter* spp., fluoroquinolone-resistant
- Salmonellae, fluoroquinolone-resistant
- *Neisseria gonorrhoeae*, cephalosporin-resistant, fluoroquinolone-resistant

**Medium priority**
- *Streptococcus pneumoniae*, penicillin-non-susceptible
- *Haemophilus influenzae*, ampicillin-resistant
- *Shigella* spp., fluoroquinolone-resistant
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><em>Acinetobacter baumannii</em>, carbapenem-R</td>
<td>Critical</td>
<td>Serious (MDR)</td>
<td>Yes</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em>, carbapenem-R</td>
<td>Critical</td>
<td>Serious (MDR)</td>
<td>Yes</td>
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<tr>
<td><em>Enterobacteriaceae</em>, carbapenem-R, 3rd-gen cephalosporin-Resistant (ESBL+)</td>
<td>Critical</td>
<td>Urgent (carbapenem-R)</td>
<td>Yes</td>
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<tr>
<td><em>Enterococcus faecium</em>, vancomycin-R</td>
<td>High</td>
<td>Serious (VRE)</td>
<td>Yes</td>
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<tr>
<td><em>Staphylococcus aureus</em>, methicillin-R, vancomycin-I/R</td>
<td>High</td>
<td>Serious (MRSA)</td>
<td>Yes</td>
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<tr>
<td><em>Helicobacter pylori</em>, clarithromycin-R</td>
<td>High</td>
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<td></td>
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<tr>
<td><em>Campylobacter</em> spp., fluoroquinolone-R</td>
<td>High</td>
<td>Serious (drug-R)</td>
<td></td>
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<tr>
<td><em>Salmonella</em> spp., fluoroquinolone-R</td>
<td>High</td>
<td>Serious (drug-R)</td>
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<tr>
<td><em>Neisseria gonorrhoeae</em>, 3rd-gen cephalosporin, fluoroquinolone-R</td>
<td>High</td>
<td>Urgent (drug-R)</td>
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<tr>
<td><em>Streptococcus pneumoniae</em>, penicillin-NS</td>
<td>Medium</td>
<td>Serious (drug-R)</td>
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<td><em>Haemophilus influenzae</em>, ampicillin-R</td>
<td>Medium</td>
<td></td>
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<tr>
<td><em>Shigella</em> spp., fluoroquinolone-R</td>
<td>Medium</td>
<td>Serious</td>
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<td><em>Clostridium difficile</em></td>
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<td><em>Candida</em> spp. fluconazole-R</td>
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<td>Serious (Flu-R)</td>
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<td><em>M. tuberculosis</em></td>
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<td>Serious (drug-R)</td>
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<td>Group A <em>Streptococcus</em></td>
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<tr>
<td>Group B <em>Streptococcus</em></td>
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<td>Concerning (clindamycin-R)</td>
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</tbody>
</table>
**8 new classes of antibiotics**

**5 Non Traditional Approaches**

**10 New Targets**

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## CARB-X Portfolio

The CARB-X portfolio comprises 18 early stage R&D projects investigating 8 new classes of antibiotics, 5 non-traditional antibiotics, 10 new molecular targets and a rapid diagnostic to determine the type of drug-resistant bacteria that is causing an infection.

<table>
<thead>
<tr>
<th>Company/Research Team</th>
<th>Project</th>
<th>New Class</th>
<th>Novelty*</th>
<th>Non-traditional</th>
<th>New Target</th>
<th>Project description</th>
<th>Urgency/Priority**</th>
<th>Bacteria Targeted / Stage of Early Development</th>
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<tr>
<td>Achaogen</td>
<td>AKAO-LpxC</td>
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<td>✔️</td>
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<td>✔️</td>
<td>Bifunctional immunotherapy</td>
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<td>✔️</td>
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<td>✔️</td>
<td>Recombinant lysin protein</td>
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<td>Debiopharm</td>
<td>Debio 1453</td>
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<td>✔️</td>
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<td>✔️</td>
<td>Narrow-spectrum inhibitors of Pabi</td>
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<td>Neisseria, Gram-negative</td>
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<td>Eligiochem</td>
<td>Helical AMP</td>
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<td>✔️</td>
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<td>Helical Antimicrobial Peptide</td>
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<td>Eretis Therapeutics</td>
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<td>Oral Gram-negative combination</td>
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<td>Forge Therapeutics</td>
<td>FG-LpxC</td>
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<td>Iterum</td>
<td>Sulopenem</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
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<td>Oral and IV penem</td>
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<td>Microbix</td>
<td>T3SS Inhibitor</td>
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<td>✔️</td>
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<td>✔️</td>
<td>Virulence modifier</td>
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<td>Oppilotech</td>
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<td>✔️</td>
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<td>Targets synthesis of LPS</td>
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<td>Reck Pharma</td>
<td>NBTI</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>Dual-acting topoisomerase inhibitor</td>
<td>✔️</td>
<td>Acin. + P. aeruginosa + Enterobacteriaceae</td>
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<td>✔️</td>
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<td>Potentiator</td>
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<td>✔️</td>
<td>✔️</td>
<td>Next-generation tetracycline</td>
<td>✔️</td>
<td>Acinetobacter + Enterobacteriaceae</td>
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<td>VC Bio</td>
<td>VC Bio-01</td>
<td>✔️</td>
<td>✔️</td>
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<td>Antibody-drug conjugate</td>
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<td>Pseudomonas aeruginosa</td>
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</tbody>
</table>

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A portfolio of ~20 antibacterial candidates

Private sector approach to funding/portfolio management

A minimum of 2 candidates progress to clinical development

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*Novelty* indicates whether the project is novel to CARB-X.

**Urgency/Priority** indicates the level of urgency and priority for funding.

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POC Diagnostic

The Development Stage

- Feasibility Demonstration
- Optimization and Preparation for Development
- Product Development
- System Integration and Testing

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“Scientists developing promising new antibiotics in India, Ireland, France, Switzerland, the US and UK are to share up to $17.6m to speed treatments for the world's deadliest superbugs”

The seven projects supported include:

- Five potential new class antibiotics for Gram-negative bacteria
- Potential new treatment for drug-resistant gonorrhea
- New molecule targeting a superbug causing serious infections in cystic fibrosis patients
- Phase 1 clinical trial of a new oral broad-spectrum antibiotic"
CARB-X funding for global scientists racing to discover new antibiotics to treat superbugs

https://www.eurekalert.org/pub_releases/2017-07/wt-cff072417.php
Public-Private Partnerships and Other Global R&D Efforts

- The European Union (EU) Innovative Medicines Initiative (IMI) -- NewDrugs4BadBugs
  - Knowledge sharing at pre-competitive research stage
  - Goals: better networks of researchers, more fluid trial designs and incentives for companies
  - IMI will provide $149.6 million, private companies will contribute $144.1 million for first phase
- GARDP/DNDi established May 2016 (WHO/DNDi)
  - Sept ’17 - 5 countries+Wellcome+others pledged €56.5 mil
- Diagnostics prizes
  - £10 mil Longitude Prize (UK); $10 AMR Diagnostic Challenge (US)
- Global R&D Hub (German leadership)
- UK & China joint R&D venture (tot £17 mil)
Market Entry Rewards Needed to Establish a Pull Incentive

- Antibiotics are one of the only class of drugs whose use diminishes utility overtime

- How do we ensure antibiotics are available while not driving inappropriate use?

- Market Entry Rewards models seek to uncouple profit of antibiotics from the number of units sold
  - Allow a reasonable return on investment (ROI)
  - Can build in provisions for stewardship and conservation

August 2016

September 2017
Market Entry Rewards

- Revenues delinked from consumption
- Consumption directed by public health policy, no sales and marketing costs
- Price at cost which enables global access
Other Pull Incentives

- Priority Review Vouchers (PRV)
- Transferrable IP Rights (TIPR)
- Lump sum Market Entry Reward
Call on governments to work with them to develop new and alternative market structures that provide more dependable and sustainable market models for antibiotics, and to commit the funds needed

- Provide appropriate incentives (coupled with safeguards to support antibiotic conservation) for companies to invest in R&D to overcome the formidable technical and scientific challenges of antibiotic discovery and development

- These include mechanisms to ensure that
  - pricing of antibiotics more adequately reflects their benefits
  - novel payment models that reduce the link between the profitability of an antibiotic and the volume sold
  - An integral part of these models is a reduced need for promotional activity by companies

- 85 companies, 9 industry associations 18 countries; [http://amr-review.org/industry-declaration]
Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating AMR – 3 Areas

• Reducing the development of drug resistance
  – Stewardship; including principles set out by the World Health Organization (WHO) Global Action Plan on antimicrobial resistance (AMR), and via improved education of clinicians…extends to promoting judicious use of antibiotics in livestock, as part of a ‘one health’ approach

• Increasing investment in R&D that meets global public health needs
  – Commitment to continuation and extension of collaborative initiatives between industry, academia and public bodies to improve R&D

• Improve access to high-quality antibiotics for all
  – Commitment to supporting initiatives aimed at ensuring affordable access to antibiotics in all parts of the world, at all levels of income

http://amr-review.org/industry-declaration
United Nations High Level Meeting on AMR – September 2016

• 4th High Level Meeting for infectious diseases
• Reaffirmed WHO Global Action Plan on AMR
• Priorities
  — Innovation of novel therapeutics and diagnostics
  — Ensuring access to current and future treatments and diagnostics
  — Improving surveillance systems
    • Antimicrobial use
    • Antimicrobial resistance
  — Developing metrics to assess progress
UN Declaration: Global Governance Responses

- WHO, FAO and OIE to finalize a global development and stewardship framework
- Establish the **Interagency Coordination Group on Antimicrobial Resistance (IACG)**
  - co-chairs: UN Deputy Secretary-General and the Director-General of the WHO
  - Mandate: to provide practical guidance for ensuring sustained effective global action to address AMR
  - Founded on 17 March 2017, incorporating 27 organisations and 15 independent experts
  - Three conveners: Professor Junshi Chen, Professor Dame Sally Davies and Ms Martha Gyansaa-Lutterodt
Interagency Coordination Group on Antimicrobial Resistance (IACG)

• First meeting in New York on 2–3 May 2017
• Adopted a Framework for Action, based on over 150 interviews
  — establishes a comprehensive view on 14 different issues mapped against the SDGs and the WHO’s Global Action Plan (GAP) on AMR
  — presents five levers that can help address them
Interagency Coordination Group on Antimicrobial Resistance (IACG)

Five primary objectives:

1. Support implementation of UNGA Political Declaration and the GAP and link them to the SDGs by advocating for action against AMR at the highest political level

2. Coordinate mapping of the actions being taken towards achieving measurable results, and to identify opportunities for collaboration, as well as gaps, redundancies and duplication

3. Promote, plan and facilitate collaborative action to align activities so that gaps are closed and resources optimally distributed

4. Explore feasibility of developing global goals and ambitions related to AMR for UN agencies, component members and, where appropriate, other stakeholders, for priorities set out in the declaration

5. Report regularly on progress/IACG meetings and issue a full report to the Secretary-General during the 73rd session of the UNGA
May, 2017, Meeting of the G20 Health Ministers - Recommendations

- National Action Plans based on One Health approach “well underway” by 2018
- Raise awareness of AMR through prevention and stewardship campaigns as part of balanced approach to addressing the five objectives of the WHO Global Action Plan on AMR
- Act to strengthen infection prevention and control measures
- Promote participation in the WHO global “Save Lives: Clean Your Hands” campaign
- Foster R&D for priority pathogens and TB via Global R&D Hub (Germany)
- Promote development, support implementation of antimicrobial stewardship programs to reduce inappropriate antibiotic consumption by humans and require that antibiotics must be prescribed/dispensed by domestically certified health professionals

May, 2017, meeting of the G20 Health Ministers - Recommendations

- Strengthen One Health approach within the G20
- Reactivate R&D pipeline through incentive mechanisms that avoid the reliance on high price/volume combinations
- Promote prudent and responsible use of antimicrobials
- Support ongoing initiatives, examining push and pull mechanisms that take into account needs of all countries and stress the need for a better coordination of existing initiatives
- Build on the work of existing product development partnerships and funding initiatives such as the Global Antibiotic Research and Development Partnership (GARDP), launched May 2016 by the WHO and the Drugs for Neglected Diseases initiative (DNDi), UNITAID, the Joint Programming Initiative on AMR (JPIAMR), Combating Antibiotic Resistance Bacteria Biopharmaceutical Accelerator (CARB-X), Innovative Medicines Initiative (IMI), the TB Alliance for new anti-tuberculosis medicines

WHO Progress

- Established GLASS
  - Global Antimicrobial Resistance Surveillance System
    - First call for data: April ‘16-July ‘17
- Tripartite organizations (WHO/FAO/OIE) developing joint monitoring and evaluation approach
- Expert meeting on indicators for monitoring/evaluation of country/global efforts
- Expert meeting on workforce and AMR education
  - Established subcommunity on Health Workforce AMR Education & Training
  - 91 educational tools available
WHO country self-assessment on NAPs

- 151/195 WHO member states responded
  - 85% countries developing or have NAPs
  - 52% fully developed NAP addressing full One Health spectrum
  - 52% LMICs national-level measures in place on IPC in human healthcare; 7% in animals/foods
  - 19% multisectoral AMR action plan with monitoring
  - 5% multisectoral AMR action plan that has been implemented with $$$ and monitoring
Progress in Animal AMR Industry/Non-profits

- Gates Foundation, World Veterinary Association, AAVMC
- Natural Resources Defense Council, consumer groups Sept 2016
  - Graded top 25 US restaurant chains re: meat raised with antibiotics
  - 9 passed assessment; Panera and Chipotle exemplary
  - Tyson, McDonalds, KFC, Taco Bell, Burger King all pledged to cut down or cut out antibiotics in food animals
AMR Call to Action – Berlin 2017
Wellcome Trust, UK, Ghanian Thai Govts

- AMR is now recognised at highest political levels
  - High-level UNGA meeting September 2016
  - Renewed commitments - G20 Health Ministers’/G20 Leaders’ Declaration, May/July 2017
- Political rhetoric not consistently translated into action
  - Progress in just 1/3 priority areas in 2016 AMR Review
- AMR poses a threat to all in today’s interconnected world, and is deeply tied up with the achievement of the Sustainable Development Goals (SDGs), universal health coverage and health security
- Call to Action on AMR builds momentum towards concrete and tangible actions by acting as the first step to an effective and coordinated response that transcends borders
- Community present at the Call to Action on AMR and beyond must support and input into the work of the IACG to achieve these goals
AMR: A Global Priority

- Human Health
- Animal Health
- Environmental Protection
- National and Global Security
AMR: A Global Priority
Future Goals

- Coordinate AMR and TB activities
- Facilitate multinational research networks
- Promote research that leads to improved use of existing antibiotics while maintaining access
  - Global stewardship
- Advance “push” and “pull” incentives for antimicrobial therapeutics, diagnostics and vaccines
- Secure an expert infectious diseases workforce to address AMR
- Make AMR activity map publicly available
- Create a mechanism to facilitate collaboration and sharing of resources and knowledge
Thank You!

- Antimicrobial Resistance Committee, IDSA
- Cesar Arias
- Sara Cosgrove
- James Hughes
- Amanda Jezek
- Ramanan Laxminarayan
- Kevin Outterson
- John Rex
- George Talbot
Helpful Resources

- Wellcome Trust Wellcome.ac.uk
- www.amr-review.org
- Pew Charitable Trust www.pewtrusts.org
- WHO 2017 PPL (aka, Priority Bacterial Pathogens List)
- CDC 2013 Threat List
- ESKAPE