What can we do to create more innovative solutions to counteract loss in antimicrobial effectiveness through research and development, new diagnostics and finding new antibiotics?

Panel 4
Marc Ouellette
Jo-Anne Dillon
Gerry Wright
Robert Hancock
Thomas Louie

Innovation in AMR Research and Development in Canada
Marc Ouellette, FCAHS
Scientific Director Institute of Infection and Immunity
Ottawa, Sep 2017
Surveillance-Stewardship-Innovation

ANTIMICROBIAL RESISTANCE AND USE IN CANADA
A FEDERAL FRAMEWORK FOR ACTION

FEDERAL ACTION PLAN ON ANTIMICROBIAL RESISTANCE AND USE IN CANADA
BUILDING ON THE FEDERAL FRAMEWORK FOR ACTION

Tackling Antimicrobial Resistance and Antimicrobial Use
A Pan-Canadian Framework for Action

2014 2015 2017

CIHR Discoveries for life

Surveillance-Stewardship-Innovation

Figure 2: One Health Linkages of Antimicrobial Resistance

Figure 3: Roles and Responsibilities

ROLES AND RESPONSIBILITIES IN CANADA

CIHR Discoveries for life
Research & Innovation Task Group (RITG)

**MANDATE**
To provide advice and recommendations on priority research and innovation activities that will increase scientific knowledge to advance the understanding AMR in humans, animals, agriculture and agri-food, in order to identify faster and effective diagnostics, and new alternative treatments that will preserve the effectiveness of antimicrobials in treating infectious diseases.

<table>
<thead>
<tr>
<th>Name</th>
<th>Role/Position</th>
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<tbody>
<tr>
<td>Dr. Marc Ouellette</td>
<td>Scientific Director, Institute of Infectious and Immunity, Canadian Institutes of Health Research (co-chair)</td>
</tr>
<tr>
<td>Dr. Cheryl Waldner</td>
<td>Professor, Epidemiology, Large Animal Clinical Sciences, Western College of Veterinary Medicine, University of Saskatchewan (co-chair)</td>
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<tr>
<td>Dr. Patrice Allibert</td>
<td>President and CEO, GenePoC</td>
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<tr>
<td>Dr. Reynold Bergen</td>
<td>Science Director, Beef Cattle Research Council</td>
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<tr>
<td>Dr. Eric Brown</td>
<td>Professor, Department of Biochemistry and Biomedical Science, McMaster University</td>
</tr>
<tr>
<td>Dr. Robert Hancock</td>
<td>UBC Killam Professor and Canada Research Chair, Department of Microbiology and Immunology, University of British Columbia</td>
</tr>
<tr>
<td>Dr. Philippe Lappee-Wiens</td>
<td>Assistant Professor of Medical Microbiology and Infectious Disease, University of Manitoba</td>
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<tr>
<td>Dr. Joseph Rubin</td>
<td>Assistant Professor, Veterinary Microbiology Western College of Veterinary Medicine University of Saskatchewan</td>
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<tr>
<td>Dr. Sameeh Salama</td>
<td>Fedora Pharmaceuticals Inc.</td>
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<tr>
<td>Dr. Lakshmi Krishnan</td>
<td>Director, R&amp;D and Program Leader, National Research Council Canada</td>
</tr>
<tr>
<td>Jennifer Van Gerwen</td>
<td>Animal Health Coordinator, Office of the Chief Veterinary Officer, Ontario Ministry of Agricultural, Food and Rural Affairs</td>
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</tbody>
</table>

**Research and Innovation Opportunities for Action:**
- Support a cross-sectoral, multidisciplinary research network to facilitate antimicrobial discovery, best practices, behavioural research and economic and production impacts across sectors and jurisdictions.
- Explore mechanisms to develop the capacity and appropriate infrastructure required to further support the development of human and veterinary medicines and alternative tools.
- Establish a fast-tracked cost-effective process for licensing antimicrobial drugs, alternatives to antimicrobials and new diagnostic tools in Canada to incentivize pharmaceutical investment without compromising safety, efficacy and quality.

**COMPONENT 4: RESEARCH AND INNOVATION**
Responses to AMR must be evidence-based and will require increased knowledge, innovative tools and collaborative approaches to better understand resistance and the development of new treatments and strategies.
III Strategic Plan 2013-2018

Two broad priority research areas

**Priority Research Area 1: Preparing for and responding to emerging threats**
- antimicrobial resistance;
- existing and emerging microbial threats;
- environmental threats;
- vaccine development;
- improved diagnostics.

**Priority Research Area 2: Integrating Infection and Immunity Knowledge in the Control and Prevention of Chronic Disease.**
- Inflammation;
- human microbiome;
- transplantation;
- human immunology and immunotherapy;
- environmental threats;
- Chronic viral infections including HIV/AIDS and hepatitis C.

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**CIHR Response to AMR**

AMR Investments - 2000 to 2016

$249M

Investigator-initiated

$185M

Priority-driven

$64M

5 Year Investment 2010-11 to 2014-15

- Alternative strategies
- Bacterial biology
- Diagnostics
- Epidemiology/Surveillance
- Other organism biology
- New molecules

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### CIHR Strategic Investments

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<tbody>
<tr>
<td>Antimicrobial resistance</td>
<td>19.9 $</td>
<td>19.8 $</td>
<td>17.9 $</td>
<td>18.8 $</td>
<td>20.2 $</td>
<td>96.6 $</td>
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<tr>
<td>Existing and emerging threats</td>
<td>21.9 $</td>
<td>32.2 $</td>
<td>36.5 $</td>
<td>48.7 $</td>
<td>62.8 $</td>
<td>202.0 $</td>
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<tr>
<td>Vaccines</td>
<td>19.2 $</td>
<td>13.3 $</td>
<td>13.9 $</td>
<td>18.0 $</td>
<td>17.6 $</td>
<td>82.1 $</td>
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<td>Inflammation</td>
<td>36.4 $</td>
<td>49.5 $</td>
<td>59.8 $</td>
<td>68.3 $</td>
<td>59.0 $</td>
<td>273.1 $</td>
</tr>
<tr>
<td>Human Microbiome</td>
<td>3.8 $</td>
<td>5.2 $</td>
<td>7.5 $</td>
<td>9.2 $</td>
<td>15.3 $</td>
<td>41.0 $</td>
</tr>
<tr>
<td>Transplantation</td>
<td>15.0 $</td>
<td>17.1 $</td>
<td>20.5 $</td>
<td>20.3 $</td>
<td>20.7 $</td>
<td>93.6 $</td>
</tr>
<tr>
<td>Human immunology and immunotherapy</td>
<td>40.6 $</td>
<td>52.1 $</td>
<td>58.1 $</td>
<td>59.9 $</td>
<td>56.4 $</td>
<td>267.2 $</td>
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<tr>
<td>HIV/AIDS</td>
<td>40.6 $</td>
<td>52.1 $</td>
<td>58.1 $</td>
<td>59.9 $</td>
<td>56.4 $</td>
<td>267.2 $</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>8.6 $</td>
<td>8.5 $</td>
<td>8.6 $</td>
<td>12.6 $</td>
<td>12.1 $</td>
<td>50.5 $</td>
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### AMR Activities

- **AMS Canada**
- **CAHS G7**
- **G20 UNGA**
- **AMS Expert Forum**
- **JPIAMR**
- **Virtual Research Institute**
- **TATFAR**
- **Pan-Canadian framework**
- **Innovation clusters**
- **G20 AMR R&D Hub**
CIHR Actions – International Partnerships

JPIAMR joins forces across nations to fight AMR through effective collaborative actions in areas of unmet needs.

Canada, through CIHR is a participating country in the Joint Programming Initiative on Antimicrobial Resistance (JPIAMR), a consortium of 26 member countries.

CIHR recent Investments in AMR

<table>
<thead>
<tr>
<th>Funding opportunity</th>
<th>Launch Date</th>
<th>CIHR Investment</th>
<th>Funding start date</th>
<th>Topics</th>
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<tbody>
<tr>
<td>JPIAMR InnovaResistance</td>
<td>January 2014</td>
<td>$3.8M for 3 years</td>
<td>January 2015</td>
<td>Innovative approaches to AMR</td>
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<tr>
<td>JPIAMR Transmission Dynamics</td>
<td>January 2016</td>
<td>$2.6M for 3 years</td>
<td>January 2017</td>
<td>Transmission One Health Intervention</td>
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<tr>
<td>JPIAMR Working Groups on AMR</td>
<td>February 2016</td>
<td>$110K for 1 year</td>
<td>January 2017</td>
<td>White papers on priority topics</td>
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<tr>
<td>AMR Point of Care Diagnostics in Human Health</td>
<td>May 2016</td>
<td>$1.39M for 2 years</td>
<td>January 2017</td>
<td>Diagnostics</td>
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<tr>
<td>JPIAMR Prevention and Intervention</td>
<td>January 2017</td>
<td>$3M for 3 years</td>
<td>October 2017</td>
<td>Stewardship One Health</td>
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</table>
Virtual Research Institute (VRI)
A Dynamic Network of AMR Research Facilities

One-Health Approach

AMR Activities

Discoveries for life
What can we do to create more innovative solutions?

PANEL 4

NEW DIAGNOSTICS AND DIAGNOSTIC APPROACHES

Jo-Anne R Dillon PhD FCAFS FRSC
Distinguished Professor and Head, Dep’t Microbiology & Immunology, College of Medicine, University of Saskatchewan
Research Scientist, Vaccine & Infectious Disease Organization –International Vaccine Center, University of Saskatchewan

Antimicrobial Susceptibility Testing (AST)

Effectively use current antibiotics and optimize treatment
Detect emerging resistance
Ascertain mechanisms of resistance to inform the development of new antimicrobial agents
Accurate AST needed for effective antimicrobial stewardship
Evaluate the clonal spread of AMR
  - Presently difficult to achieve in low and middle income countries

Dillon et al Culture 2015 35:1
Detecting Antimicrobial Resistance (AMR): a Global Health Priority

AST Methods:
Broth Dilution, Disc Susceptibility, Agar Dilution, Etest

<table>
<thead>
<tr>
<th>Methodology</th>
<th>Agar Dilution</th>
<th>Etest</th>
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<tbody>
<tr>
<td>Methodology</td>
<td>Difficult, labour intensive</td>
<td>Easier, requires training</td>
</tr>
<tr>
<td>Technology</td>
<td>Technology &gt;40 years old</td>
<td>Reference mostly</td>
</tr>
<tr>
<td>Type of Laboratory</td>
<td>Used primarily in reference laboratories</td>
<td>Reference mostly</td>
</tr>
<tr>
<td>Cost</td>
<td>Technical costs</td>
<td>Unaffordable in many settings. May not be available.</td>
</tr>
<tr>
<td>QA/QC programs</td>
<td>Required but few engage</td>
<td>Required but few engage</td>
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</table>

Challenges for AMR Diagnosis (of Ng) in High-income Countries:
Identification of Pathogens (e.g. STIs) by Nucleic Acid Amplification Testing (NAAT)
No AMR testing done. Molecular testing needed.

Canada: PHAC 2017
PCR-Based Diagnostics of AMR

Performance of Molecular (PCR-DNA sequencing) Assays for AMR:
Can standardization of tests for low and middle income countries be achieved?

<table>
<thead>
<tr>
<th>SNP</th>
<th>Ceftriaxone MIC ≥0.032 mg/L</th>
<th>Cefixime MIC ≥0.032 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Sensitivity</td>
<td>% Specificity</td>
</tr>
<tr>
<td>ponA</td>
<td>98.0%</td>
<td>72.8%</td>
</tr>
<tr>
<td>mtrR</td>
<td>94.6%</td>
<td>80.4%</td>
</tr>
<tr>
<td>porB</td>
<td>93.3%</td>
<td>64.8%</td>
</tr>
<tr>
<td>penA Mosaic</td>
<td>61.1%</td>
<td>99.0%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SNP</th>
<th>Ciprofloxacin MIC ≥1 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Sensitivity</td>
</tr>
<tr>
<td>gyrA S91</td>
<td>100%</td>
</tr>
<tr>
<td>gyrA D95</td>
<td>100%</td>
</tr>
<tr>
<td>pmrC</td>
<td>96.1%</td>
</tr>
</tbody>
</table>

Sensitivity and Specificity of SNP targets on 252 N. gonorrhoeae cultures from Canada
Peterson et al ICM 2015 53:2042; Peterson et al ICM 2015 53:3606
Whole Genome Sequencing (WGS)

Limited number of WGS studies to analyze gonococcal AMR

Advantages: all genetic determinants, including epidemiological typing genes and identification sequences can be ascertained simultaneously

Still relatively expensive, labour intensive and needs expertise; requires specialized analysis

Analyses (phylogenetic trees etc.) are generally not focussed on clinical outcomes at present

Costs are declining and diagnostic-friendly platforms are being developed

Research required to ascertain effects on susceptibility of emerging AMR determinants

Accuracy of Predicted MICs

S, susceptible; I, intermediate; R, resistant; ME, major error; VME, very major error.
Most POC tests must meet ASSURED criteria, i.e. affordable, sensitive, specific, user friendly, rapid, robust, equipment-free, deliverable
- Definition is product oriented and restrictive

**Alternative definition** (Pai et al Microbe 2015, 10:103): Diagnostic testing that will result in a clear and actionable management decision such as when to start treatment
- Goal oriented
- POC is a spectrum of technologies, users and settings
- Not defined by technology but the diagnostic process that leads to a rapid completion
POC tests being evaluated for treatment with ciprofloxacin for many organisms

POC tests for penicillin susceptibility in N. gonorrhoeae?
- Penicillin is used for treating Ng infections in regions of Australia
- Comprehensive molecular testing for penicillin resistance determinants
- A similar test strategy in Saskatchewan (<5% resistance) might allow the use of penicillin in regions with low resistance

Implementation of a Rapid Genotypic Assay to Promote Targeted Ciprofloxacin Therapy of Neisseria gonorrhoeae in a Large Health System

The Future: POC/ WGS-based Diagnostic ID and AST

WGS with portable DNA sequencers (e.g. MinION and others)
Can both a pathogen and its AMR be detected?
- Yes, multiplexing in NAAT and possibly other formats
- Such tests formats could be user- and "field"- friendly

Sample preparation 105 min DNA extraction 30 min Library preparation 15 min
MinION sequencing 60 min Bioinformatic analysis 30 min Results
Bacterial & Resistance genes 1/D

JAC 2017 72:104-114
Other Diagnostic Approaches for AMR under Development

Microfluidic applications

Encapsulation of bacterial cells in micro and nanodroplets with microfluidic manipulation

Leveraging enhanced ultrasensitive detection methods to relay phenotypic information more rapidly

- Mechanical transducers: Atomic force microscopy – mechanical readout of changes to the cell membrane
- Electrochemical sensors – analysis of rRNA and possibly resistance genes
- Electrochemical bacterial phenotyping
- Matrix-assisted laser desorption Time-of-Flight Spectromotry (MALDI-TOF)

Fluorescence In Situ Hybridization (FISH)

Addition of microscopy to various methods

Microfluidics

- Microfluidics: manipulating and controlling fluids, usually in the range of microliters \(10^{-6}\) to picoliters \(10^{-12}\), in networks of channels with dimensions from tens to hundreds of micrometers
- Miniaturizes biological assays
- Gradient microfluidics allows rapid bacterial growth inhibition testing
Rapid AMR Testing and Bacterial Identification: Single Cell Methods

Monitoring Cell Morphology –
High Throughput Agarose Channel Chip
SLAS Tech 2017 22:113-121

AST using Cell Imaging Methods:
Different (POC) Strategies

Microfluidic chip and cell growth monitored by single cell imaging microscopy –AST in 30 minutes
PNAS 2017, 114:9170-9175
Final Thoughts

Many innovations for the rapid and accurate diagnosis of AST
Commercialized strategies with other innovations being actively developed
Standardized AST formats would not require culture and would simultaneously identify pathogens
Molecular/WGS AMR testing in low and middle income countries may be simpler than MIC testing
- Costs of WGS decreasing and becoming competitive
- Bioinformatic platforms can be distributed internationally
- Considerable international standardization and collaboration required

Thank you
Innovation in New Antibiotics

Gerry Wright

Pre-antibiotic era
- Chance discovery
- Synthetic compounds
- Niche applications

Golden Era
- Natural products
- Whole-cell screens
- High success

Med Chem Era
- Synthetic tweaking
- Whole-cell screens
- Broad spectrum
- High success

Resistance Era
- Modern drug discovery
- Target-based
- Broad spectrum
- Zero success

Post–antibiotic Era
- Back to 1900

Why do we need new antibiotics?

- No antibiotics have proven to be resistance proof
- Resistance is ancient
- Resistance is transferred vertically (mother to daughter) and horizontally (cell to cell)
- We cannot overcome evolution

‘Old’ Antibiotics

- Penicillin & streptomycin ushered in the ‘Golden Era’ of antibiotic discovery
- Natural products isolated from other microbes proved highly effective and generally non-toxic
- By the mid 1960s, new antibiotics proved difficult to find
- Next two decades dominated by medicinal chemistry to improve efficacy and overcome resistance
Genomics and target-based drug discovery

- Advent of genome sequencing, structure-based drug design, and combinatorial chemistry promised a new route to antibiotics
- No new drugs

Now what?
Back to the future: Natural Products

- New antibiotics – new sources
- Discarded known antibiotics (narrow spectrum)
- ‘Cryptic’ compounds
- Synthetic biology for novel compounds

Rescuing ‘old’ antibiotics: Antibiotic Adjuvants

- Adjuvants are not antibiotics
- Block resistance
- Enhance antibiotic activity

Innovation Era

- Unconventional discovery
- Antibiotic adjuvants
- In vivo essential targets
- Combinatorial approaches
- Diagnostic development
- Narrow spectrum compounds
- Phage
- Vaccines...
Partnership between:
• Academia
• Private Sector
• Not-for Profit Sector
• Government

www.cain-amr.ca

What Innovations R&D & Diagnostics?

R.E. W. (Bob) Hancock
Department of Microbiology and Immunology
University of British Columbia
Panel 4

Conflicts of Interest: Bob Hancock is the founder of 2 virtual companies ABT Innovations and Sepset Biotherapeutics that are developing new peptides as alternatives to antibiotics and sepsis diagnostics respectively. He consults with many companies re antimicrobials.
Antibiotics are the single most successful medical intervention

- No antibiotics would lead to difficulties with major surgeries, cytotoxic therapy, transplantations, early-term births & even minor injuries.
- Antibiotic resistance
- Dry pipeline; Traditional and genomics-based antibiotic development has not worked well.

When do antibiotics fail?

1. Acquired Resistance (mutations/plasmids etc)
2. Sepsis (~30% death rate; 5-17 million deaths/yr worldwide).
3. Chronic Infections especially biofilms (65% of all infections and very resistant).
4. Individuals with disturbed immune systems (chemotherapy, immunosuppressive disease, genetic diseases, massive injuries or burns).

The last 3 indications are rarely considered when developing new anti-infectives
Alternatives to antibiotics (Adjuncts/Adjuvants)

Antibiotics have saved countless lives and enabled the development of modern medicine over the past 70 years. However, it is clear that the success of antibiotics might only have been temporary and we now expect a long-term and perhaps never-ending challenge to find new therapies to combat antibiotic-resistant bacteria. A broader approach to address bacterial infection is needed. In this Review, we discuss alternatives to antibiotics, which we defined as non-compound approaches (products other than classic antibacterial agents) that target bacteria or any type and engineered bacteriophages; immune stimulation; antimicrobial peptides; innate defence regulators; anti-biofilm peptides.

Diagnostics & Host directed therapies (Sepsis)

Early Sepsis is associated with a diagnostic immune non-responsiveness gene expression signature that demonstrates immune cell reprogramming (cellular amnesia).

The Signature predicts severe sepsis in the emergency ward

Clinical Study

Can we make antibiotics work better in sepsis patients by restoring normal immunity i.e. reversing cell amnesia?
**Vaccines**

The most cost effective Intervention

Reverse Vaccinology

Gene

Bioinformatics

GE³LS

Identify Components

Potential Antigens

Gene Synthesis

Vaccine Testing, Development & Commercialization

Testing in Cattle Animal Models

- **Reverse Vaccinology**
- **Bioinformatics**
- **GE³LS**
- **Identify Components**
- **Potential Antigens**
- **Gene Synthesis**

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**Immune Modulation**

- Successful therapy against infections requires help from the host: immune response

- Immune modulation is highly used in antiviral and anticancer therapy

New immunomodulatory peptides show broad protection in Mouse Model Infections

IDR 1018: VRLIVAVRIWRR-NH₂

Ø

Balb/c mice infected IT with high dose 10⁶ virulent live MTb strain H37Rv.

After 2 months of infection, treatment via IT: 32 µg (~1 mg/kg) peptides every 2 days.

Groups of 5 animals sacrificed after 4 wks of treatment and lung bacilli counted.

Works vs. H37Rv & MDR TB strains.

Bruno Rivas and Rogelio Hernandez Pando, UNA de México

In mice & pigs

PLoS One 2012

Also protect in animal models vs. E. coli, Pseudomonas, MRSA, Salmonella, Klebsiella, Tuberculosis;

Pox & HSV viruses; Sterile inflammation, Malaria, IBD; LPS/hypoxia-ischemia;

→ Wound Healing

Broad Spectrum Anti-Biofilm Activity when added at 0 or 2 days of biofilm formation

Carbenemase K. pneumoniae

Synergy with multiple antibiotics

Peptides lead to rapid degradation of ppGpp (stress signal) in cells

Works in animal models

CAHS FORUM ON ANTIMICROBIAL RESISTANCE SEPT. 14, 2017
Probiotics

- Use of bacteria to prevent infections
- Several mechanisms proposed, e.g. exclusion, immune modulation
- Already used successfully
  - As OTC medicines: *S. salivarius* clinically proven for Strep throat, Halitosis, Chronic sore throat
  - In fecal transplantation for *C. difficile*, and
  - To reduce sepsis (24% → 15%) & enterocolitis (4.6 → 2.5%) in 10,000 premature VLBW babies (similar results in India)
- Consortia of defined bacteria can replace normal microbiota

Phages and Lysins

- Can use consortia of natural phages (Tbli$); phages engineered to utilize common receptors, produce Cas9-CRISPR or toxins; or lysins (enzyme from phages that destroy pathogens; Avacyn).
- Phages self propagate as long as their bacterial hosts survive.
- Several trials underway (some failures).
- More research needed to understand phage biology, create new phages with broader host ranges and detect and engineer lysins.
Conclusions

➢ We need new anti-infectives. Resistance is very complex. And are we doing what is required to overcome all of the situations when antibiotic therapy does not work?
➢ Given our dismal recent success, what if we do not discover new game-changing antibiotics?
➢ Alternatives to Antibiotics provide new hope.

What can we do to create more innovative solutions?

PANEL 4
Replacing Missing Microbes in healthcare:
Probiotics and normal flora components, some or all, for host defense.

• Not enough defense! After 7 decades of antimicrobial use (offense), with infection prevention control, antibiotic stewardship and hand hygiene (defense) to contain spread of AMR, we are losing the war……..

• The value of colonization resistance has barely been utilized in healthcare to limit the spread of AMR. Epithelial surfaces colonized by normal microbiota resist the establishment of pathogenic microbes.

• The perfect storm! Combinations of susceptible hosts, antibiotic exposure, transmission prone health care facilities convert patients into bioreactors to amplify AMR microbes.

Why antibiotics are non-selective, deleterious to the host microbiota, creating ecologic vacuum, favoring pathogens

- intrinsic, high potency / low MICs against pathogens
- elimination pathways: liver inactivation, renal excretion, biliary excretion, intestinal secretion
- Oral antimicrobials are not necessarily safer
- While no MICs available against normal microbiota, in-vivo activity of antimicrobials shown by qPCR reveal 1000 to million fold reductions in normal microbiota
**Bacteroidetes** predominate on the mucosal surface.

**Firmicutes** (major groupings: *Clostridium coccoides*/cluster XIVa and *Clostridium leptum*)/cluster IV [270+ genera]

**Proteobacteria** = Gram Negative
Facultatives are ~1% microbes

Normal Microbiota holds proteobacteria in check!

Antibiotic treatments drive the shift towards pathogen dominance

Multiple colonic biopsies and feces examined by 16S rRNA sequencing

**Ecklund, Bernstein, Relman. Science 2005.**
Multiple colonic biopsies and feces examined by 16S rRNA sequencing
Expansion of proteobacteria in association with impairment of Bacteroidetes and Firmicutes

Healthy normal flora confers protection from acquisition of pathogens. Fidaxomicin, which preserves microflora better than vancomycin is associated with a 5 fold decrease in VRE acquisition during treatment of CDI. Nerandzic & Donskey, CID Aug 2012

Cannon et al, J Antimicrob Chemother in press 09/2017
Establishing the role of components of the microbiome for the prevention and treatment of C. difficile infection.

- **Rec CDI**: Fecal microbiome transplantation whole stool slurry by enema, endoscope, nasojejunal, capsules
- **Modified FMT**: pure microbial preps, microbe ID and recovery
- **Modified FMT via subcomponents of microbiota alone or in combination**
- **Discovery of functional role of microbial Genus / species in host defence / colonization resistance**

- **Specific microbial ‘probiotics’ that restore colonization resistance in a preventative manner in susceptible populations**
Hot spots for Missing Microbes

_reduced alpha and beta diversity of mucosal microbes_

- Intensive care units
- Bone marrow transplant and solid organ transplant units... renal, hepatic
- Medical Surgical services
- C. difficile infection
- Patients with enteric acquisition of AMR organisms: VRE, AmpC, ESBL, CRE, NDM, KPC

Microbe Therapies:

_the to do list_

- Establish the scientific basis of antibiotic stewardship by quantification of the effect of antimicrobial chemotherapy on the host microflora... long overdue.
- Revise the formulary to optimize selectivity of treatment. We have agents we don’t use often enough, use bad agents too frequently, carelessly, unknowingly.
- While low cost drugs might be narrow spectrum, that’s not always the case. eg. Ceftriaxone is inexpensive.
- Probiotics need careful RCTs on larger scale to establish a benefit, yes or no. Many lab and animal studies suggesting protection.
- Out of the FMT studies, the keystone microbial groups / clusters should emerge that would confer colonization resistance.
Where damage to the protective indigenous microbiota is not preventable, where should we focus re-complementation of microbes??

- Intensive care unit ecology, comparative trials on the benefits of maintaining or bolstering the normal microbiota components to prevent ventilator pneumonia, sepsis/bacteremia and multi-organ failure.
- Immunocompromised hosts, particularly leukemia / BMT and solid organ liver> renal transplants, where neutropenia, intestinal dominance by proteobacteria often AMR microbes, leads to translocation, bacteremia and death.
- General medical/surgical patients..more of these, but impact is lower, but persons discovered to persistently harbour AMR organisms
- [Obesity, Autism, NAFLD, IBD, IBS, C.difficile].

In this era of the emergence of pan-antibiotic resistant pathogens, protecting and where damage is done, re-complementing the normal microbiota / microbiome is the largest missing link in the health care.

Health care systems themselves need to invest in self-protection and not depend on funding agencies to do the job for them. Funding agencies can be catalysts however.