What Must Be Done Next: Prioritizing Immediate Actions

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Lonnie King, DVM, MS, MPA, DACVPM
Emeritus Professor and Dean
College of Veterinary Medicine
The Ohio State University
AMR is an Exceptionally Complex Problem

“When one tugs at a single thing in nature, he/she finds that it is attached to the rest of the world.”

- John Muir (Naturalist)
Transmission of Resistance
Multiple Domains of One Health

- Horizontal and vertical
- Within species
- Across species
- Environmental
- Food
- Water
- Multiple human settings
- Attribution
For every complex problem there is an answer that is clear, simple, and wrong.

H. L. Mencken
The Critical Need for Immediate Actions

Potential loss of momentum/urgency – can easily be overtaken by other circumstances/crises
Avoid “paralysis by analysis” – about 200,000 articles is enough knowledge to take action
Budget climate may not be conducive in near future
Leverage building collaboration across One Health domains – an improving relationship
“When it is all said and done; much more gets said than done” – well founded truism
“Culture will eat strategy for lunch”! True aphorism; can action be embedded into culture and sustained
Recommendations To Combat Antibiotic Resistance

- Appropriate Use of Antibiotics in Animal Agriculture
- Effective Global Coordination
- Strong Federal Leadership
- Effective Surveillance and Response
- Improving Stewardship Programs
- Economic Incentives to Develop Antibiotics
- New Antibiotics
- Fundamental Research
- Fundamental Research
National Action Plan to Combat AMR Bacteria

1. Slow the emergence of resistant bacteria and prevent the spread of resistant infections (stewardship)
2. Strengthen national One Health surveillance
3. Advance the development and use of rapid and innovative diagnostic tests to ID and characterize resistant bacteria
4. Accelerate basic and applied research for new antibiotics, vaccines and other therapeutics
5. Improve global capacity and collaboration
<table>
<thead>
<tr>
<th>Positive Steps and Activities</th>
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<tbody>
<tr>
<td><strong>Global attention – G-20; UN; WHO</strong></td>
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<td><strong>Responses to FDA Guidance</strong></td>
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<td><strong>One Health emphasis</strong></td>
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<td><strong>Improved dialogue</strong></td>
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<td><strong>U.S. CARB national plan</strong></td>
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Establishing Priorities by Importance and Time Frames

Tier 1 – activities that meet established criteria and can be delivered immediately or in the very short term (6 months)

Tier 2 – critical needs and activities that can be delivered in mid term (1-3 years)

Tier 3 – also important activities but delivered on a longer term basis (3-5 years and longer)

If possible and depending on resources, the activities within these tiers should be concurrent and not sequential. All the activities should be prioritized, measurable and adaptive depending on results.
Criteria for Prioritization

1. Number of Animals involved - impact
2. Costs and ROI
3. Feasibility and Practicality
4. Evidence-based
5. Ease of acceptance and overcoming barriers
6. Implementable/scalable
7. Win-Win-Win – improving one health domains
8. Can be accomplished immediately or in a relatively short term for Tier 1 actions
9. Accelerate positive outcomes and usable results
Tier 1 Priority Actions

**Stewardship**
- Establish using key elements
- Implement and build on existing quality assurance programs

**Awareness, Education and Communication**
- National leadership and attention
- Model curriculum
- Make issue personal and relevant
- Impact from things you care about

**Infection Prevention**
- Health Management Programs
- Vaccines
Tier 1 Priority Actions

National Institute for Innovation, Policy and Research

- Create either at university or within a public agency (USDA)
- Public-private-partnership
- National portfolio of activities

Changing Business Model

- Counter market failure for new drugs – push and pull incentives
- Delinking model – use vs payment
Stewardship

Stewardship is a commitment to always use antibiotics only when necessary to prevent or treat disease, to choose the right antibiotic, and to administer them with the right dose, for the right period of time, and using the right route of administration in every case.

The result is optimizing clinical outcomes while minimizing unintended consequences such as toxicity, selection of pathogens and emergence of resistance. Past efforts implementing stewardship programs in hospitals have been shown to be effective, improve results and reduce health costs.
CDC’s Core Elements of Hospital Stewardship
Outpatient antibiotic usage rates by region, 2010

Northeast: 830
Midwest: 868
West: 638
South: 936

National rates: 258 million courses (833/1000 population)

Source: LA Hicks et al. *NEJM* 2013; 368:1461.
Figure 2
Outpatient Antibiotic Prescribing by Provider Specialty, 2013
Percent of antibiotic prescriptions

- Primary care physicians: 45%
- Nurse practitioners and physician assistants: 18%
- Dermatology: 3%
- Dentistry: 9%
- Surgical specialties: 8%
- Emergency medicine: 5%
- OB-GYN: 3%
- Other: 9%

Source: Centers for Disease Control and Prevention.
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Behavior: Issues of Prescribing

Emotional, social, biased, fast and automatic
Increasing Rx use: time pressure/decision fatigue
Influence of patient’s satisfaction survey (Yelp report)
Bias toward over-treatment; “Just to be safe”
Perception of patient’s demand for antibiotics
CMS payments to hospitals – based on stewardship
Direct education not too impactful on stewardship
Structural Animal Health Planning – Netherlands 3 yr
“Ikea Principle” – need bottom-up not just top-down; cognitive bias and value for products we create
Evidence that Stewardship Can Work

Interventions:
1. Suggested alternatives – computer pop-ups
2. Accountability justification – rationale on charts
3. Peer comparisons – “top performer”

Benefits – decreasing costs and resistance; improved outcomes and patient-focused

Hospital “playbooks” – flexible; apply core elements

Meta-analysis (32 large studies (Baur) – stewardship associated with 51% reduction in MDR gram-neg pathogens; most effective when combined with infection control plans
Awareness, Education and Communication

Compelling evidence to act – e.g. McNeil Report
National Leadership and messaging – create a high profile social issue; e.g. HIV; clean water; tobacco
Model curriculum – multiple levels and sites
Make personal and socialize; security at risk
Add voices beyond health: policy, economics, social sciences
Counter potential loss of sense of urgency
Unified concept based on shared interests
AMR difficult to understand – simplify; less science
The Deadly Impact of No Action
Jim McNeill Report (UK)

From 700,000 deaths/yr today to 10,000,000 in 2050
Global costs estimated to be $100 trillion/yr in 2050
Developing world would be hit the hardest
Up to 50% of human antibiotics are used unnecessarily or inappropriately (CDC estimate)
U.S. illnesses currently estimated at 2.25 million and 37,000 deaths; $20-35 billion excess healthcare costs; $35 billion loss of productivity and 8 million additional hospital days; estimated to cost between $18-29K extra per patient
UK Five Year Antimicrobial Resistance Strategy
2013 to 2018

Information resources also need to be strengthened to support health professionals, their patients, animal keepers and the public, so that all understand the value and importance of antibiotics to society. This will only be achieved if human and veterinary health professionals work more closely with their patients and animal keepers, before deciding if an antibiotic is really needed and, in the event that it is, which one is most appropriate. This is in line with the aims of the global ‘One-Health’ approach which spans people, animals, agriculture and the wider environment.

Professor Dame Sally C. Davies  
Chief Medical Officer  
Chief Scientific Adviser  
Department of Health

Nigel Gibbens  
Chief Veterinary Officer  
Department for Environment Food and Rural Affairs

On behalf of the Chief Medical Officers and Chief Veterinary Officers in Northern Ireland, Scotland and Wales.
Infection Prevention

- Sanitation and hygiene
- Biosecurity and infection control
- Health Management – ventilation, weaning age, farm traffic, non-drug additives
- Improve the host immune response
- Re-conceptualize bacteria – good vs bad
- Environmental risk reduction
- Build on existing practices: quality assurance, etc. and can be combined with food safety
- Effective vaccine timing and delivery
- More than reducing antibiotic use but cost savings as well
- Transportation strategies
Create and fund Institute (USDA) to support research across species with an emphasis on immunology and vaccine development; assist in education at various levels; provide for key field studies to conduct, evaluate and create DB of efficacy studies on alternative products (PACCARB – Sept. 2017)

Create a university-based research organization (URO) to coordinate research, educational and outreach programs to address AMR(2015):
(Recommendation from APLU-AAVMC Task Force

Both emphasized PPP; national coordination; inter-professional work and One Health as foundation
National focus and leadership on this critical issue
Avoiding duplication
Establishing a national priority and portfolio of action
Would include AMR issues for companion animals
Easier to fund and support as a collaborative and not just competitive model
Should have a One Health foundation
Would work best as a public-private-partnership
Needs strong support from public and human health
Innovation, experimentation and scale up
Changing the Business Model for Producing New Antibiotic

**Push Incentives**: R&D support; reduced regulatory burden; and, extending market exclusivity

**Pull Incentives**: balancing the cost of new antibiotics with effective stewardship and the need to use less. The real value in antibiotics is likely not using them. Some pull models are: premium price model; market entry reward model; insurance model; NPV ($100M) – revenue over lifetime combining total costs with demand and revenues. E.g. CARB-X

The decision is an immediate action not drug devel.

Innovation and change in animal ag business model; recovering the new costs of rearing L/S and poultry.
## Prioritization of Actions

<table>
<thead>
<tr>
<th>Actions</th>
<th>Timeline</th>
<th>Cost</th>
<th>Scalability Feasibility</th>
<th>Evidence Based</th>
<th>Impact</th>
<th>Barriers</th>
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<tbody>
<tr>
<td>Stewardship</td>
<td>Immediate, ST</td>
<td>🟥⬛</td>
<td>YES</td>
<td>+++</td>
<td>HIGH</td>
<td>Behavioral, Standardization, Regulatory</td>
</tr>
<tr>
<td>Awareness, Education &amp; Communication</td>
<td>Immediate, ST</td>
<td>🟥⬛</td>
<td>YES</td>
<td>++</td>
<td>MEDIUM</td>
<td>Leadership, University Support</td>
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<tr>
<td>Institute</td>
<td>Decision for Funding, ST</td>
<td>🟥⬛</td>
<td>Possible with partnering</td>
<td>++</td>
<td>MEDIUM</td>
<td>Cost Leadership</td>
</tr>
<tr>
<td>Infection Prevention</td>
<td>Immediate, ST</td>
<td>🟥⬛</td>
<td>YES</td>
<td>+++</td>
<td>HIGH</td>
<td>Producer Costs</td>
</tr>
<tr>
<td>Business Model</td>
<td>Decision to Change, ST Implement, MT</td>
<td>🟥⬛</td>
<td>Possible</td>
<td>+</td>
<td>LOW &amp; HIGH</td>
<td>High Cost, High Return, Public Funds?</td>
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Tier 2 Priority Actions

**R & D**
- Alternatives for antibiotics
- Host response
- Horizontal transmission
- Diagnostics

**One Health Surveillance**
- Data from all 3 One Health Domains

**Field Studies to Measure Effectiveness**
- FDA Guidance and VFD – proof of concept
- Infection Prevention effectiveness
- Stewardship measures/comparisons
- Longitudinal baseline studies
Research

- Expand fundamental research relevant to developing new antibiotics and alternatives to treat bacterial infections
- Develop alternatives to antibiotics in agriculture and opportunities and methods to build host resistance/immunity vaccines; monoclonals; phage therapy; small molecules; natural products; probiotics
- Improve the fundamental understanding of AMR and dynamics of horizontal and vertical transfer
- Need for research and study designs to measure success; do the FDA guidance work? Evidence/metrics for change
- Testing the success of on-farm infection prevention actions
- Linking studies with microbiome and metagenomic research at the One Health level
• Need for research in the social and behavior sciences
• Studies to determine the success of stewardship programs and their sustainability
• Basic research and understanding of AMR should involve interdisciplinary teams and not just medicine and integrate with federal partners
• Research is needed to better understand the role of our environment in the development and distribution of resistant organisms
Tier 3 Priority Actions

Global Integration and Cooperation
- Collaborate with international agencies
- Share information and best practices

Basic Research
- Microbiome Studies
- Co-selection factors of resistance
- Environmental role and interventions

New Antibiotics
- Important but long term time horizon
## Barriers and Concerns to be Addressed

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<thead>
<tr>
<th>Loss of momentum</th>
<th>Metrics – what gets measured gets done</th>
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<tr>
<td>Leadership</td>
<td>Consensus of action</td>
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<td>Relevance/personalized and non-scientific communications</td>
<td>Costs to animal health</td>
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<td>Accountability</td>
<td>Antibiotic-free vs judicious use: consumer competitive space</td>
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<td>Incorporating companion animals</td>
<td>Burden of disease measure: to be included</td>
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<td>Behavior modification</td>
<td>Sustainable funding</td>
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Difficult But Necessary Reconciliations

Does antibiotic use correlate directly to resistance?
Commitment to developing new antibiotics vs. implementing stewardship programs to reduce use
Rapid and substantial increase in livestock/poultry globally with more antibiotic use in developing world
Profound crisis yet without a “public face”; abstract
“Mencken solution” – “connexity” – difficult to plan and implement solutions which may also be complex
Reducing the use of antibiotics vs reducing the need
Reducing antibiotics vs. reducing resistance
Understanding/appreciating societal benefits
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<tbody>
<tr>
<td>1.</td>
<td>Creating a real sense of urgency</td>
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<td>2.</td>
<td>Creating a powerful enough guiding coalition</td>
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<tr>
<td>3.</td>
<td>Establishing a clear and compelling vision</td>
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<td>4.</td>
<td>Communicating the vision (10 X more than believe)</td>
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<td>5.</td>
<td>Removing obstacles and empowering others</td>
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<td>6.</td>
<td>Planning and achieving short term wins</td>
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<td>7.</td>
<td>Not declaring victory too soon</td>
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<td>8.</td>
<td>Anchoring change in organizational culture</td>
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