Antimicrobial Stewardship: What Works?

David M. Patrick, MD, FRCPC, MHSc
Disclosures

• I have no commercial conflicts of interest (no honoraria or consultancies)
• I provide policy advice in BC as part of my everyday work
• My research is funded from CIHR, NCCID and BC MoH
• I like jazz, walks on the beach and deep conversation over tapas
“Antimicrobial stewardship should occur across the continuum of healthcare, including acute care, long-term care, and ambulatory care.”

- Ruth Lynfield

But it mustn’t end there ....
Objectives

• To discuss the evidence for interventions to reduce antimicrobial misuse in the community, facilities and in agriculture.
• To discuss means by which such approaches could be more broadly deployed in Canada.
• To discuss the possibility for these and other methods improving utilization in the developing world.
Acknowledgements

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• Jim Hutchinson
• Amee Manges
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• Lynora Saxinger
• Karl Weiss
What To Take Home
(Hospital, Prescriber, Farm)

• Predisposing Factors:
  – Understand the drivers of over-use

• Enabling Factors:
  – Guidelines, interactive education, diagnostics
  – Necessary but not sufficient

• Reinforcing Factors are Required
  – Personalized feedback, e.g. computer assisted
  – Selective use of formulary restriction

• Measure (Iterate)
Drivers of Emergence

• Natural Selection Driven By:
  – antimicrobial use in humans
  – antimicrobials in food production

• Spread of Resistant Organisms
  – Population density
  – Importation
  – Affected by infection control and community hygiene practice

• Concern is not just spread of organisms but of transposable genetic elements conferring resistance
Worrisome Trends in Morbidity

- *Clostridium difficile*
- CA-MRSA
- Resistant enterobacteriaceae (FQ, TMP/SX and ESBL)
- *Neisseria gonorroheae*
- Name your own
We Must Change This

• “Let us therefore brace ourselves to our duties, and so bear ourselves, that if the therapeutic benefit of antimicrobial therapy lasts a thousand years, people will still say, this was our finest hour.”

With DEEP apologies to Winston Churchill
Tools for Reducing Morbidity from Antibiotic Resistant Organisms

• Infection Prevention and Control

• Antibiotic Stewardship: Optimizing our use of antibiotics including reducing unnecessary use
  – The appropriate selection of antimicrobials
  – The appropriate dosing of antimicrobials
  – The appropriate route and duration of therapy
These Foci Are Not New

- 1997 Consensus Conference in Montreal
- Three Core Areas:
  - Stewardship
  - Surveillance of AROs
  - Infection Prevention and Control

AMMI Stewardship Veteran
Host, Agent and Environment Are One

MARINE ENVIRONMENT

Virulent microbes pose threat to orcas

Killer whales inhale deadly pathogens, including antibiotic-resistant bacteria, research shows

BY CRAIG WRECH

SEATTLE

The scientists followed the killer whales by boat, trying to catch the precise moment the animals broke the surface. They, using an eight-metre long pole strung with petri dishes, researchers leaned out and gathered samples of the moist exhaled air that shot like a geyser from each whale’s blowhole.

For four years, a team of researchers gathered these breath samples from the waters off Washington and British Columbia. And by comparing them to surface waters and orca death records, the scientists stumbled upon a trend.

Killer whales — from Puget Sound’s endangered southern residents to the transient whales living hundreds of kilometres offshore — are inhaling bacteria, fungi and viruses once believed to be found only on land.

Some of the pathogens are highly virulent. Some are even antibiotic-resistant.

The discovery comes as researchers also learn that respiratory ailments may be a leading cause of orca deaths, and that leads biologists to a new question:

Killer whales exchange up to 70 per cent of the air in their lungs when they break surface. Scientists say they inhale potentially deadly contaminants at the same time.

So in the mid-2000s, after Puget Sound’s orcas were listed as endangered, most of the time, they just disappeared,” Hanson said. “We were not quite sure, but a few appeared potential.
Other Thinking from “The Dark Side” (Public Health)

1. Communicable diseases are not independent events
   - Neither are colonization events
2. Prevention is better than cure – hard to undo
3. Health promotion theory may apply
4. “The unexamined life is not worth living”
   - Measurement (and its reporting) IS intervention
Metrics of Success

• Rates of Antibiotic Utilization
• Prevalence of AROs and genes
• Gold Standard: Incidence of morbid events associated with AROs
“What Gets Measured Gets Done”
- Lord Kelvin

- Surveillance -> collection and analysis of health-related data, and dissemination to those who will use them in decision-making.

- Standardization is critical and we are just about there
  - Diagnostics – CLSI
  - Morbid Events ICD-9/10
  - Drugs and dosages - ATC, DDD system or Scripts / person-time
“What Gets Measured Gets Done”

- Lord Kelvin

• Our status in Canada?
  – Getting there at community level
  – Hospitals
    • Some have good internal data
    • Few examples of broad publication
    • Point prevalence surveys
    • Risk adjusted figures are possible as a basis for inter-institutional comparison (Ron Polk’s approach applies to DOT, DDD or scripts)
  – Agriculture? *Don’t get me started.*
Figure 8. Total consumption (DDD/1,000 inhabitant-days) and total cost of oral antimicrobials dispensed by retail pharmacies in Canadian provinces, 2009.

Alphanumeric codes represent Anatomical Therapeutic Chemical classes of antimicrobials. DDD = Defined daily dose.

CIPARS 2000-2009 Report
Why Try? The Population Level

- There is ecological, observational and experimental evidence to suggest that populations with lower rates of antibiotic use will generally experience a lower burden of colonization by antibiotic-resistant organisms.

At Institutional Level

Figure 1. Comparison of pooled mean rates of resistance among isolates from adult intensive care unit (ICU) patients (solid bars), non-ICU inpatients (shaded bars), and outpatients (open bars) from 41 U.S. hospitals. CF-PA = ceftazidime-resistant *Pseudomonas aeruginosa*; CF3-ENB = *Enterobacter* species resistant to any third-generation cephalosporin; MR-CNS = methicillin-resistant coagulase-negative staphylococci; MRSA = methicillin-resistant *Staphylococcus aureus*; PIP-PA = piperacillin-resistant *P. aeruginosa*; VRE = vancomycin-resistant enterococci.

## On The Farm

**Table II.**
Prevalence of multiresistant *E. coli* (%)

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<td>6 (14)</td>
<td>9 (22)</td>
<td>1 (5)</td>
<td>7 (15)</td>
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What Works in the Real World?

For:

- The Public
- Prescribers
- Health Care Facilities
- Agriculture

Remember, “Education is Not Enough”? 
Enne VI. Reducing antimicrobial resistance in the community by restricting prescribing: can it be done?
Reasons for Over-Prescribing

• Lack of knowledge – limited coverage in medical schools and lack of formal training
• Influence of senior colleagues
• Inadequate diagnosis or lack of diagnostic facilities
• Incorrect selection, dose, duration and route of administration of drugs
• Compliance with patients’ inappropriate demand or pressure to prescribe antibiotics
• Fear of litigation or adverse outcomes
• Financial gain from pharmaceutical companies in countries where physicians are underpaid, or response to promotional pressures of drug representatives

WHO. The Evolving Threat of Antimicrobial Resistance: Options for Action
What Works for the Public and For Physicians?

• *Infection Prevention and Control*
  – *Community hygiene*
  – *Immunization*
  – *Clean Water*
  – *Food Safety*

• What about Education campaigns?
Community Interventions

- Understand the values, beliefs, and barriers of the target population
- Involve stakeholders from target groups
- Theory-based behaviour models and social marketing show promise
- Multifaceted programs have the best results
Campaigns Aimed at Reducing Utilization in Outpatients

• Review of 22 public education campaigns between 1990 and 2007
  – Europe (16), North America (3), Oceania (2), and Israel (1).
• All campaigns focused mainly on respiratory tract infections and addressed symptoms.
• Most campaigns that were formally evaluated appeared to reduce antibiotic use but the impact on AMR could not be assessed

France

- “Les Antibiotiques C’est Pas Automatique”

- 23% decrease in the use of antibiotics 2002-2007
Physicians

• Guidelines alone may not be enough
• Interactive one on one interventions worked better
• Multifaceted programs work better (e.g. Guidelines plus education PLUS follow-up or supervision (Hawthorne effect)
• Restrictive methods have larger effect than persuasive methods

Guidelines May Work if Well Promoted and Broadly Supported

• Quebec’s education program targeting physicians and pharmacists

• 11 user-friendly guidelines were produced by a group of experts and sent to all physicians and pharmacists in January 2005

• Web distribution, promotion by professional organizations, universities, and experts during educational events

• Acceptance by the pharmaceutical industry

Number of prescriptions per 1,000 inhabitants

Figure 1. Monthly prescribing rates per 1,000 inhabitants for all antibiotics in Quebec and in the other Canadian provinces.

Guidelines dissemination in January 2005

Immediate level change of -4.1 (p=0.002)

Weiss K et al. CID 2011
Relative change in trend -18.2% (95% CI -27.8% to -8.7%)
Theory Based Initiatives: Antibiotic prescribing portraits

- Individualized (anonymous) prescribing portraits to physicians

- DBND has collaborated on 2 antibiotic topics:
  - UTI
  - URTI
Formulary Changes at Pop Level: Australia and Restricted Use of FQ

Figure 3.3 Antibiotic use in Australia (2009–2010) compared to European countries with low use
Priorities in the Community: Must Be Ongoing

• Measurement
  – Get to know your utilization trends / CIPARS)
  – Contribute to compilation and reporting of ARO trends

• Understand sources of demand
  – Study reasons for utilization

• Public education
  – Speak publicly

• Physician education, guidelines and feedback
  – Help design FP audit / feedback strategies

• Formulary decisions at population level
  – Accept committee work for provincial formulary
Health Care Facilities

Mitchell and Webb’s Homeopathic ER
What are Hospitals Using?

- Education
- Guidelines and clinical pathways
- **Prospective audit with intervention and feedback**
- Formulary restriction and pre-authorisation
- Parenteral to Oral antibiotic conversion
- **Computerized decision support** (antibiotic drug use)
Education Alone in Hospital

• Before and after study compared prescribing practices after distribution of an educational handbook versus an order form

• Compliance:
  – Handbook: from 11 ->18%
  – Order Form: rom 17 -> 78%


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<tr>
<th>Strategy</th>
<th>Advantages</th>
<th>Disadvantages</th>
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<tr>
<td>Prospective audit with direct intervention</td>
<td>• May reduce inappropriate antimicrobial use</td>
<td>• Difficulty identifying patients with inappropriate therapy and communicating with prescribers</td>
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<td>and feedback</td>
<td>• May serve an educational purpose to modify future prescribing</td>
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<td>• Allows prescribers to maintain autonomy</td>
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<tr>
<td>Formulary restriction and preauthorization</td>
<td>• May result in immediate and substantial reductions in antimicrobial use and costs</td>
<td>• May increase staffing requirements</td>
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<td>requirements</td>
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<td>• May delay order implementation while approval is obtained from an authorized prescriber, with the potential for adverse patient outcomes</td>
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<td>• May increase use of and resistance of alternative antimicrobial agents</td>
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<td>• Perceived loss of prescriber autonomy</td>
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Audit and Feedback

• Cafino: 22% reduction in use of parenteral broad-spectrum antimicrobials, CDI 2.2 to 1.4 cases per 1000 patient-days, decrease in resistant Enterobacteriaceae.

• Valiquette: Decrease in antimicrobial consumption by 23%, decreased targeted antimicrobial consumption by 54%, CDI infections down by 60%


Prior Authorization

• Lipworth
• Focus on 3rd Gen Cephs
• 86%-97% decrease in use of these agents at both hospitals.
• Prevalence of ESBL-EK decreased by 45% at academic med centre and 22% at community hospital.

Combining Approaches

• Combined audit and feedback AND prior authorization (Philadelphia)
• Found: appropriate antimicrobial selection increased from 32%-90%,
• Cure rate increased from 55%-91%.
• Clinical failure rate decreased from 31%-5%
• Prevalence of resistant pathogens decreased from 9%-1%

Computerized Decision Support

- **RCT:** Existing antimicrobial management team (AMT) using the system in the intervention arm, and without the system in the control arm.
- **Study size:** > 2000 per arm
- **AMT intervened on 16% patients in the intervention arm and 8% in the control arm.** Spent approximately one hour less each day on the intervention arm.
- **Antimicrobial expenditures were $285,812 in the intervention arm and $370,006 in the control arm for a savings of $84,194 (23%) or $37.64/patient.**
- **No significant difference was observed in mortality or length of hospitalization.**

### Other Approaches: Less Strength

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<tr>
<th>Strategy</th>
<th>Advantages</th>
<th>Disadvantages</th>
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| Antimicrobial order forms      | • May reduce inappropriate antimicrobial use  
                              | • May facilitate implementation of guidelines and clinical pathways          | • Potential for inappropriate interruption in therapy due to automatic stop orders |
| Combination therapy           | • May improve clinical outcomes and prevent resistance in certain types of patients and situations | • Often redundant and unnecessary  
                              |                                                                                  | • Insufficient data available demonstrating improved clinical outcomes and prevention of resistance |
| Streamlining or de-escalation of therapy | • Reduces antimicrobial exposure, selection of resistant pathogens, and health care costs | • Prescriber reluctance to de-escalate therapy when cultures are negative and clinical improvement has been observed |
| Dose optimization             | • Tailors therapy to patient characteristics, causative organism, site of infection, and pharmacokinetic and pharmacodynamic characteristics of the antimicrobial agent | • Nursing staff concerns about incompatibilities when prolonged infusions are used based on pharmacokinetic considerations |
| Parenteral-to-oral conversion | • May decrease length of hospital stay and health care costs  
                              | • May reduce the risk of complications from intravenous access              | • Difficulty identifying patients in whom conversion is appropriate |

Antimicrobial Cycling

• Insufficient data to recommend
• Units are not closed systems
• With existing MDR patterns, some classes select for R to others
• Very difficult to design a regimen that eliminates selection
Does stewardship put patients at risk?

- Meta-analysis of 24 studies in Critical Care

*Antibiotic stewardship was not associated with increases in nosocomial infection rates, length of stay or mortality.*

Do Bugs Need Drugs?

Quality Improvement Project for Antibiotic Use in Long Term Care

Project team: Sandra Leung, Mary Carson, Sharon Mitchell, Connie Franchuk, Dr. Mary Hurlburt, Dr. Edith Blondel-Hill

October 2006 - December 2010
Update: Antibiotic Resistance Trends

Percent of uropathogens resistant to ciprofloxacin is correlated with utilization of FQ

Fluoroquinolone utilization

Source: BC Biomedical Laboratories & PharmaNet
1. Antibiotic prescription data from pharmacy

2. Chart review and data extraction

3. Classify prescriptions by diagnosis

4. Evaluate prescription against clinical practice guidelines

5. Intervention
Antibiotic prescriptions by site

- **Site A**
  - Pre-intervention: 2.50
  - Post-intervention: 0.50
  - 18 month follow-up: 1.50

- **Site B**
  - Pre-intervention: 2.00
  - Post-intervention: 1.00
  - 18 month follow-up: 2.00
Priorities for Health Care Facilities Must Be Ongoing

• Measurement
  – *Make sure your health authority can measure what is being used, lobby for people and IT/IM*

• Guidelines
  – *Continue to update guidelines for your peers*

• Prospective audit and limited formulary prescription
  – *Get involved in your hospital / health authority*

• Feedback is essential
  – *New IT/IM should facilitate CDSS/feedback where possible*

• Don’t forget Long Term Care
  – *Extend Stewardship Programs to LTC facilities*
Agriculture: Zoonoses or “Humanoses”?

Figure 4.2 Reservoirs of AMR bacteria causing human infections

[Diagram showing the reservoirs of antimicrobial-resistant bacteria in humans, hospitals, community, and food-producing animals.]
Evidence for foodborne transmission of UTI-causing *E. coli*


**George DB,** **Manges AR.** *Epidemiol Infect.* 2010 Dec;138(12):1679-90.


*E. coli* recovered from retail meat and human infections share common genotypes

Identification of 12 reported outbreaks of UTI

Endemic and epidemic *E. coli* lineages causing UTI

Retail meat consumption and antibiotic resistant UTI infections
WHO Guidance

• Introduce pre-licensing safety evaluation of antimicrobials with consideration of potential resistance to human drugs.
• Monitor resistance to identify emerging health problems and take timely corrective action to protect human health.
• Develop guidelines for veterinarians to reduce the overuse and misuse of antimicrobials in food animals.
• Require obligatory prescriptions for all antimicrobials used for disease control in food animals.
• In the absence of a public health safety evaluation, terminate or rapidly phase out the use of antimicrobials for growth promotion if they are also used for the treatment of humans.
• Create national systems to monitor antimicrobial use in food animals.
Canadian Gaps

- Data on AMR and Utilization
- Regulatory Loopholes
  - Own Use Provision and API
  - Letter on this from CMHOs and CVMHOs
- Fall 2011 Meeting on Stewardship in Canadian Agriculture provides some hope
Figure 1. Temporal variation in resistance to ciprofloxacin in *Campylobacter* isolates from chicken; CIPARS Retail Meat Surveillance, 2003–2010.
Impact of Withdrawal

Figure 4.4 Macrolide use and resistance among *enterococci* in pigs, Denmark

Source: Reproduced from 21 with permission.
The Ceftiofur Story
Transition in Production Poultry

- Voluntary removal of antibiotics from large-scale U.S. poultry farms that transition to organic practices is associated with a lower prevalence of antibiotic resistant and MDR Enterococcus.

Changes Can Happen Rapidly in Agriculture

- Because the population of a given operation may fully turn over
Antibiotic Use in BC Salmon Aquaculture

1995 - 2008

Production is >90% Atlantic salmon (2006 - 2008)

Societal Considerations

- The Consumer Matters
- The Market Matters
- Acting on Loopholes aligns Veterinary field with other health regulation
- Inherent conflict of interest in both prescribing and dispensing needs to be acknowledged
- CCAR died and we are striving to recreate it
- Don’t let that happen to this effort or to CIPARS work
Priorities in Agriculture

• *Work with producers* – *(We need food)*
  – *Keep them advised of changes in priority drug classes*

• To facilitate measurement and tracking
  – *Lobby to close importation loopholes*
  – *Work with producers toward vet oversight and for more infection control to lower demand for antibiotics*

• Think continentally
  – *Work with US colleagues toward common goals*
Summary per John McGowan

Results of Stewardship:
• Improves Patient Outcomes – Still Poor Data
• Improves Patient Safety – Modest Data
• Reduces Resistance – Modest Data
• Reduces Cost – Very Clear
Golden Quadrant from Health Economics

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<th>Decreases Health</th>
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<td>= Don’t Do</td>
<td>= Never Do</td>
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<tr>
<td>Improves Health</td>
<td>= Must Do -&gt; Stewardship</td>
<td>= Should Do</td>
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We Still Need Drug Discovery

• Stewardship may slow down but not stop selection
• Effective stewardship may contribute to commercial failure under current patent laws
• Antibiotics need Discovery Prizes and Special Long-term Patents
• Alternatives to Cidal Antibiotics
• Better exploitation of microbiome and immunity
Think Globally
Unique Issues in Developing World

- Unregulated distribution (and too few MDs)
  - Chile and Mexico may be able to go to Rx only, but this could cause harm elsewhere
- Poor quality supply
- Prevalence of syndromic management

Ergo

• The consumer is more important where MDs are not accessible

• Symptomatic therapy must take into account locally available remedies

• Better diagnostics yes – but look at available resources
Strategies to Reduce Antimicrobial Resistance in Ecuador

Gulzhan Maxutova, Kate McLeod, Kris Vargas, Lisa Wenstob
Figure 1: Model of recommendations for AMR control in Ecuador
In Plain Terms

- Understand community beliefs and adapt low tech messaging to Rx of URTI and diarrhea
- Reinforce guidelines with physicians
- Social determinants of infectious disease spread (water, hygiene etc)
- Gov’t – drug marketing, quality
What To Take Home
(Hospital, Prescriber, Farm)

• Deal with Predisposing Factors
  – Understand the drivers of over-use

• Enabling Factors Are necessary, not sufficient
  – Guidelines, interactive education, diagnostics

• Reinforcing Factors are Required
  – Personalized feedback, e.g. computer assisted
  – Selective use of formulary restriction

• Measure
What Are **You** Going to Do?

Work with “The Happy Few” on your Antimicrobial Stewardship and Resistance Committee
Further Reading Starts Here

- Surveillance of antimicrobial resistance and use
- Rational antimicrobial use and regulation
- Antimicrobial use in animal husbandry
- Infection prevention and control
- Fostering innovations
- Political commitment
- Environmental aspects need to be considered