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, BC MoH and the BCCDC Foundation
Objectives

• To overview the issue of antibiotic resistance
• To discuss the scope of stewardship and its intimate relationship to infection control
• To overview elements of stewardship with proven efficacy in communities, hospitals and on farm
What To Take Home

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

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

• Reinforcing Factors are Required
  – Personalized feedback, e.g. prospective audit & feedback, computer assisted if possible
  – Selective use of formulary restriction

• What gets measured, gets done
• Does overuse of antibiotics cause bacteria to mutate or otherwise acquire resistance genes?
NO!

Mutation (or acquisition of new genes) is only the first of two steps in evolution.

Natural selection accounts for the survival of resistant organisms when antibiotics are in greater use.

"Mutation is random; natural selection is the very opposite of random" – Richard Dawkins

Worrisome Trends in Morbidity

- Resistant gram negatives causing UTI
- CA-MRSA
- Clostridium difficile

Resistant gram negatives causing UTI
Drivers of Emergence

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

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

• Concern is not just spread of organisms but of transposable genetic elements conferring resistance
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
Other Thinking from Public Health

1. Communicable diseases are not independent events
   • *Neither are colonization events*

2. Prevention of emergence is better than dealing with it as a fait accompli

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

| Number of antibiotics resistant | Turkeys  
\( (n = 43) \) | Broilers  
\( (n = 45) \) | Laying hens  
\( (n = 20) \) | Turkey farmers  
\( (n = 45) \) | Broiler farmers  
\( (n = 42) \) | Laying-hen farmers  
\( (n = 20) \) | Turkey slaughterers  
\( (n = 45) \) | Poultry slaughterers  
\( (n = 39) \) |
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Enne VI. Reducing antimicrobial resistance in the community by restricting prescribing: can it be done?
Physician CME
Pharmacist CEU
Grade Two
Daycare
Seniors
Employee Groups

Public Health
Occupational Health
Continuing Care
Infection Control
Dentists
Dental Assistants CE
Post-secondary Students

Translations
Print Materials
Website
TV ad
Transit Ads
Figure 1: Overall antibiotic daily consumption rates from 1996 to 2010
Figure 2: Overall antibiotic daily consumption rates in children from 1996 to 2010
Update: Antibiotic Use by Indication

Prescriptions/1000 population/day

- Acute otitis media
- Acute pharyngitis
- Acute sinusitis
- Lower UTI
- Acute Bronchitis

Source: PharmaNet & MSP linked data
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.
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

Formulary Changes at Pop Level: Australia and Restricted Use of FQ
Other Theory Based Initiatives: Antibiotic prescribing portraits

- Individualized (anonymous) prescribing portraits to physicians
- DBND has collaborated on 2 antibiotic topics:
  - UTI
  - URTI
Priorities in the Community

- Measurement
- Understand sources of demand
- Public education – ongoing
- Physician education, guidelines and feedback – ongoing
- More thought into formulary decisions at population level - ongoing
Health Care Facilities

Mitchell and Webb’s Homeopathic ER
To Show Hospital Purchase Data
Total oral and injectable antimicrobials purchased by Canadian hospitals and dollars spent in 2011
What are Hospitals Using For Stewardship?

• 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 vs. Order Form

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

Compliance with Guidelines


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

• 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 Can Facilitate Reinforcement

- Makes it possible to achieve the same ends more efficiently

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.**

Priorities for Health Care Facilities

• Measurement
• Awareness of Guidelines
• Prospective audit and limited formulary prescription
• Feedback is essential – CDSS where possible
• Don’t forget Long Term Care
• Sustained Effort is Required
Agriculture:
Zoonoses or “Humanoses”? 

Figure 4.2 Reservoirs of AMR bacteria causing human infections

Schematic overview of some of the most important antimicrobial resistant pathogens and the overlap between the different reservoirs. As indicated some pathogens are strictly confined within the human reservoir, whereas others have a mainly or partly animal reservoir.

Source: Reproduced from⁶⁶ with permission
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
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.

Antibiotic Use in BC Salmon Aquaculture

Antibiotic Use in BC Salmon Aquaculture 1995 - 2008

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

Priorities in Agriculture

• Work with Industry – We need food
• Close the Loopholes
• At least have all use visible and measured, if not prescribed
• Think continentally
## Golden Quadrant from Health Economics

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<td>= Must Do -&gt; Stewardship</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
Back to PRECEDE/PROCEED?

After L. Green
What To Take Home
(Hospital, Prescriber, Farm)

• Deal with Predisposing Factors
  – Understand and address 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
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
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