

Antimicrobial Utilization and Stewardship: Human Medicine Perspectives



J Conly MD CCFP FRCPC FACP
Professor of Medicine, Microbiology, Immunology &
Infectious Diseases, University of Calgary
Medical Director, Antimicrobial Stewardship
Alberta Health Services - Calgary and Area

Panacea to Preservation



Disclosures

- Clinical reviewer and co-investigator: CADTH (*C. difficile* and MRSA projects)
- Grants: AI-HS, PHAC, Alberta Health, AHS, Exciton, CIHR
- Speaker or Meeting Participant (last 3 years): Pfizer (new antibacterials), bioMerieux (healthcare infections), Sanofi (*C. difficile* burden of illness), Merck (monoclonal Abs)
- Member: WHO AGISAR, GIPC Network

Objectives

- Outline the frequency and impact of antibiotic use
- Review the general background on antibiotic utilization and stewardship
- Describe the evidence base to support stewardship as a means to improve patient safety and quality of care
- Provide the Canadian context for utilization and stewardship

Antimicrobial Use

- Therapeutic
 - Life threatening situations
 - Potentially life threatening
- Prophylaxis
 - Non-life threatening – easier to alter physician prescribing behaviour
 - Accounts for up to 30% of antibiotic use
- Other
 - Anti-inflammatory, prokinetic, fatigue of chronic lyme

Frequency of Use of Antimicrobials

- Antimicrobials are among the most commonly used class of drugs in Canadian hospitals
- Pharmacy expenditures – represent significant proportion of an institution's total budget
- 55.7% of patients discharged from 323 hospitals in US in 2010 received antibiotics during their hospitalization
- Recent 2015 point prevalence survey Calgary hospitals 30% of patients on antimicrobials

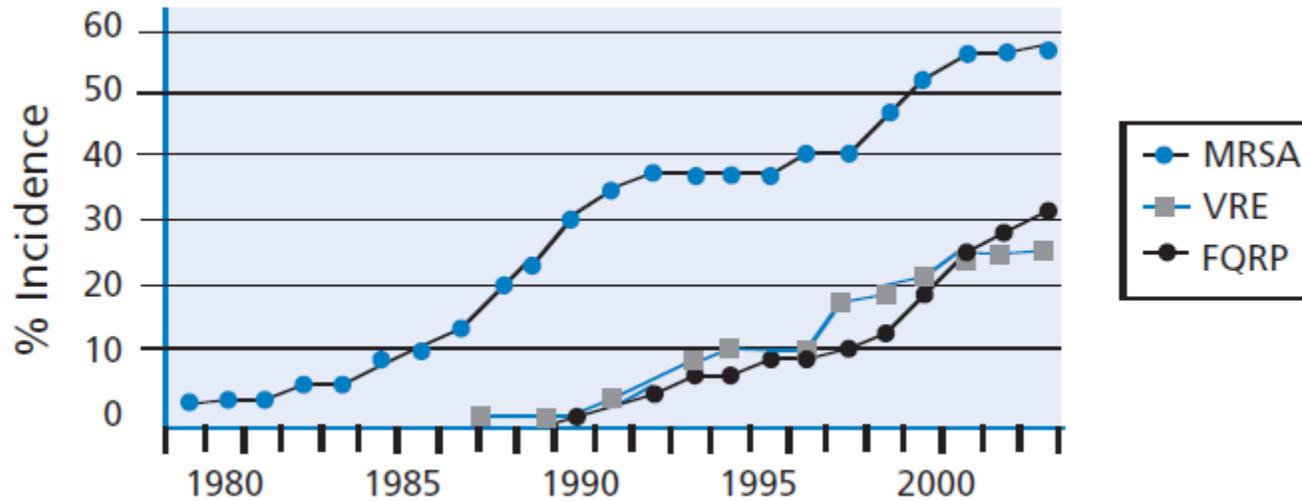
Fridkin et al .Vital Signs: Improving antibiotic use among hospitalized patients. MMWR March 7, 2014 / 63(09);194-200

Nault V et al. Can J Infect Dis Med Microbiol 2008;19(3):237-242

Sabuda D, Rajapaske N, et al AMMI-CACMID Meeting 2016

5 Principles of Antibiotic Resistance

1. Given sufficient time and drug use, antibiotic resistance will emerge – resistance has arisen to every antibiotic.
2. Resistance is progressive – evolving from low levels through intermediate to high levels.
3. Organisms resistant to one drug are likely to become resistant to others.
4. Once resistance appears it is likely to decline slowly if at all.
5. The use of antibiotics by one person affects others in the immediate and extended environments.

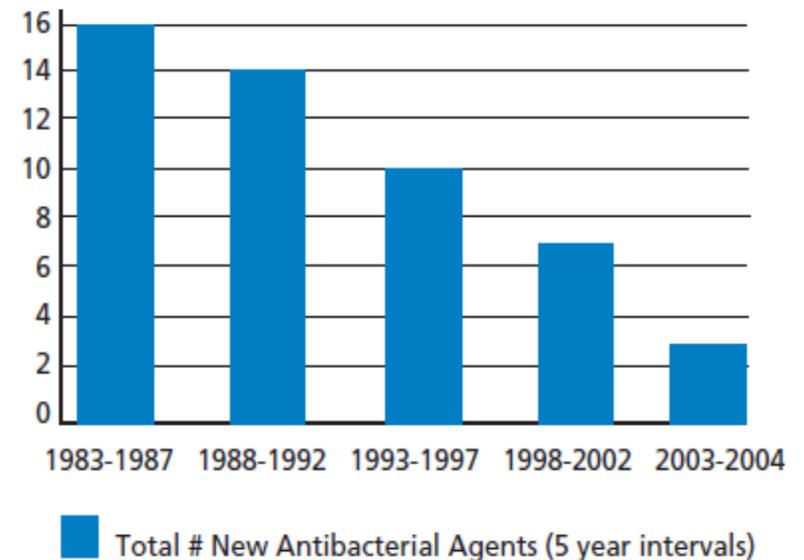


methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and fluoroquinolone-resistant *Pseudomonas aeruginosa* (FQRP). These data were collected from hospital intensive care units that participate in the National Nosocomial Infections Surveillance System, a component of the CDC (US)

Antibiotic resistant organisms are **increasing**. New antibiotic drug development is rapidly **decreasing**.¹

A perfect storm for an infectious disease catastrophe.

Chart 2: Antibacterial Agents Approved, 1983-2004



Source: Spellberg et al., *Clinical Infectious Diseases*, May 1, 2004 (modified)

Common Measures of Antimicrobial Utilization

1. DDD/1000 pt days

- WHO standard; no patient level data; easy to calculate; facilitates intercountry comparisons
- Reference DDDs may not = given dose; not for pediatrics

2. DOT/1000 pt days

- Not affected by changes in WHO reference DDDs; useful for pediatrics; incorporates LOS
- No dosage measure; requires patient level data; undercalls renal dosing

3. LOT/1000 pt days

- Useful for units; requires patient level data

4. Others: COT/LOT ratios; % receiving/admissions; kg used; PDDs

Antimicrobial Stewardship - Definition

“The optimal selection, dosage, and duration of antimicrobial treatment that results in the best clinical outcome for the treatment or prevention of infection, with minimal toxicity to the patient and minimal impact on subsequent resistance.”

Antimicrobial Stewardship - Definition

- In Canada antimicrobial stewardship is considered to be the responsible planning and management of resources in order to prevent and moderate the development of antimicrobial resistance
- May consider from multiple perspectives – clinical, public health, systems, governance
 - human and animal settings

Antimicrobial Stewardship Programs

- **Quality improvement and patient safety**
 - Improve quality of medical care
 - Reduce adverse events and allergies
- **Collateral damage reduction**
 - Prevention of resistance by selection for drug-resistant organisms [ESBLs, MRSA, VRE]
 - *C. difficile*; AAD; unwanted colonization with MDROs)
- **Cost containment**
 - Reduction in antimicrobial costs
 - Clinical and economic burden of antibiotic resistance

Paterson DL Clin Infect Dis 2004;38(Suppl4):S341-S34

Maragakis LL et al. Expert Rev Anti Infect Ther 2008;6:751-763

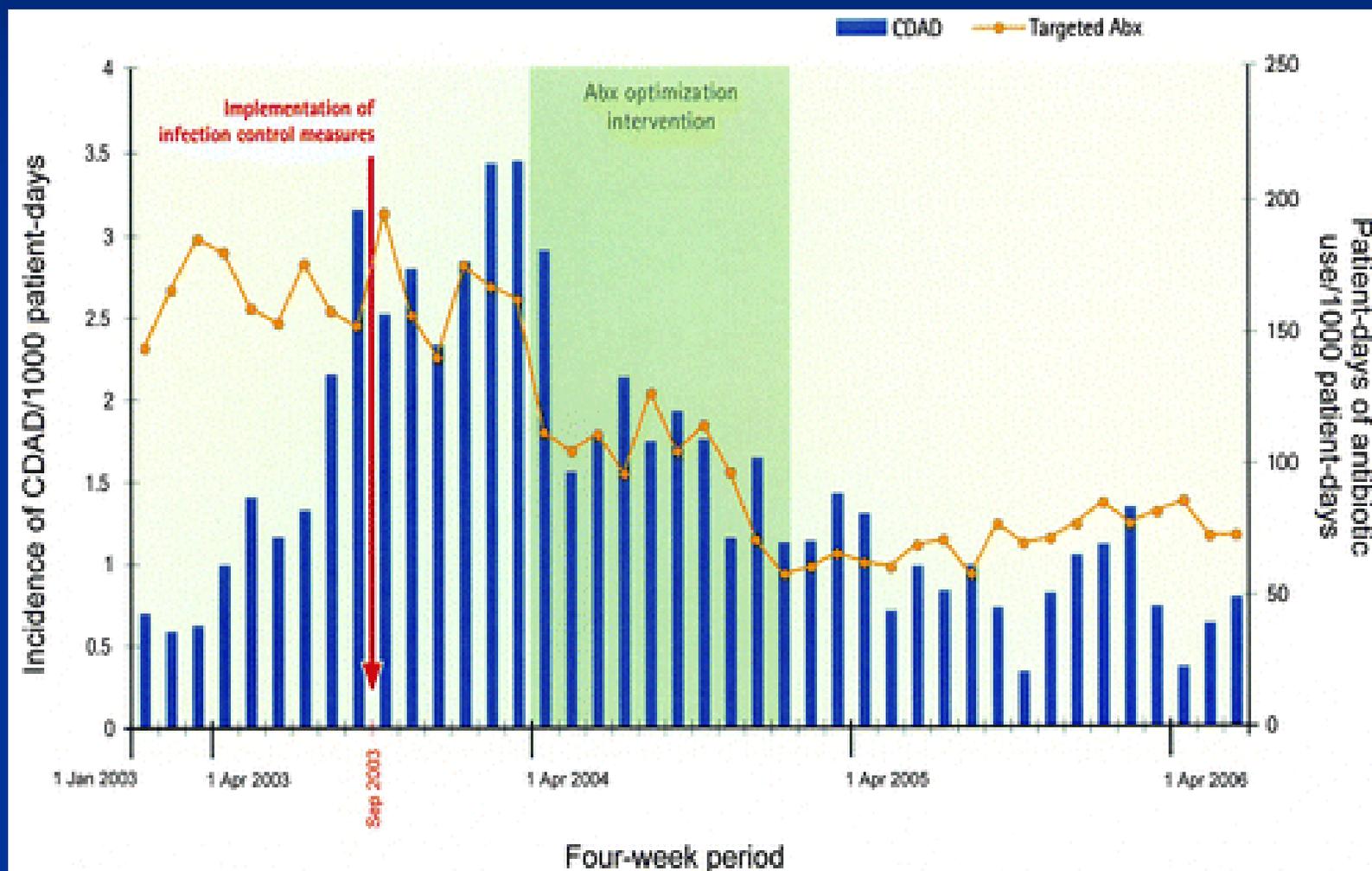
Collateral Damage: Association of Antibiotics with CDAD in Quebec

Table 3: Incidence of hospital-acquired CDAD per 1000 patient-days of use of various classes of antibiotics among all inpatients at the Centre hospitalier universitaire de Sherbrooke

Antibiotic class	Period; incidence per 1000 patient-days of antibiotic use*		
	1999–2000	2001–2002	2003
Narrow-spectrum penicillins	1.4 (28/19908)	1.2 (25/20597)	4.9 (53/10751)
β -lactam/ β -lactamase inhibitors	1.0 (7/7267)	1.3 (17/13419)	5.0 (46/9194)
Cephalosporins			
First-generation	2.3 (30/12779)	2.6 (35/13633)	8.8 (74/8412)
Second-generation	3.9 (55/13984)	2.9 (36/12224)	16.3 (92/5639)
Third-generation	2.7 (18/6786)	4.6 (34/7390)	19.5 (72/3687)
Carbapenems	2.7 (7/2553)	6.7 (15/2248)	7.4 (9/1209)
Aminoglycosides	2.4 (21/8673)	2.2 (18/8230)	6.5 (28/4283)
Quinolones	1.6 (48/29693)	1.2 (36/29375)	9.9 (161/16293)
Clindamycin	4.9 (19/3861)	3.1 (11/3508)	11.7 (22/1880)
Macrolides	1.9 (5/2625)	4.4 (12/2715)	20.0 (33/1649)
Metronidazole	2.0 (20/10092)	1.8 (19/10696)	5.0 (39/7745)
Vancomycin	2.5 (9/3658)	2.4 (10/4137)	5.2 (20/3853)
Cotrimoxazole	0.2 (8/51706)	0.2 (13/54077)	0.5 (11/20287)

*Calculated from numbers in parentheses: the numerator represents the number of patients with hospital-acquired CDAD who received a given class of antibiotic during the 2 months before diagnosis, and the denominator represents the total number of patient-days that this class of antibiotic was used among all inpatients.

Failure of Infection Control Measures - Reduction in CDAD with Targeted Antibiotic Consumption Intervention



Valiquette L et al. Clin Infect Dis 2007;45 (Supl 2):S112-S121

Antimicrobial Stewardship Policies

Persuasive

- Education for prescribers
 - Conferences
- Peer Review
 - Utilization review with feedback
- Tailoring or de-escalation of therapy
- Academic detailing
 - Face to face presentations
- Therapeutic guidelines
 - National, regional, local
- Sequential antimicrobial therapy (IV to oral conversion)
- Computer assisted decision support

Antimicrobial Stewardship Policies

Restrictive

- Cascade susceptibility reporting
- Controlled formulary
- Automatic stop orders
 - IV vs. oral
- Automatic therapeutic interchange
- Restricted antimicrobial agents
 - Approval necessary a priori vs. concurrent review and feedback
- Antibiotic order forms
- Infectious Diseases consultations

Establishing an Antimicrobial Stewardship Program

- Multiple guidelines exist in the literature
 - IDSA guidelines for developing an institutional program to enhance antimicrobial stewardship
Clin Infect Dis 2007;44: 159–177
 - Policy statement on antimicrobial stewardship
Infect Control Hosp Epidemiol. 2012;33:322-7
 - Guidance for the knowledge and skills required for antimicrobial stewardship leaders
Infect Control Hosp Epidemiol. 2014 35(12):1444-51
 - Implementing an antibiotic stewardship program: IDSA evidence based guideline
Clin Infect Dis. 2016 May 15;62(10):1197-202

Components of an Antimicrobial Stewardship Program

■ Minimum Requirements

- Core multidisciplinary team formation
- Formulary with restrictions
- Guidelines relevant to the facility and preauthorization for certain agents
- Measure and monitor antimicrobial use
- Provision of local antibiograms

■ Core and Supplemental Strategies

- **Core:** Formulary restrictions and prospective audit and feedback
- **Supplemental:** education, pathways, de-escalation, iv to oral stepdown, others

Tailoring or De-Escalating Antimicrobials

- Based on natural history of clinical phases of illness
- Acute → Subacute → Convalescent phase
- Empiric antibiotics in acute phase
- Entry to subacute phase about 72-96 hours
- Susceptibilities arrive 48-72 hours
- Timing at Day 3 ideal as process measure to tailor or de-escalate

Pulcini C, Defres S, Aggarwa I, Nathwani D, Davey P. Design of a 'day 3 bundle' to improve the reassessment of inpatient empirical antibiotic prescriptions.

Journal of Antimicrobial Chemotherapy (2008) 61, 1384–1388 doi:10.1093/jac/dkn113

Clinical Benefits of Sequential Antibiotic Therapy

- **Earlier discontinuation of IV**
 - Increased patient comfort
 - Decreased risk of complications
- **Enhanced mobilization**
- **Reduced risk of nosocomial infection**
- **Earlier discharge from hospital**
- **Improved quality of life**

You wouldn't like me
when I'm angry...

Because I always back up
my rage with facts and
documented sources.

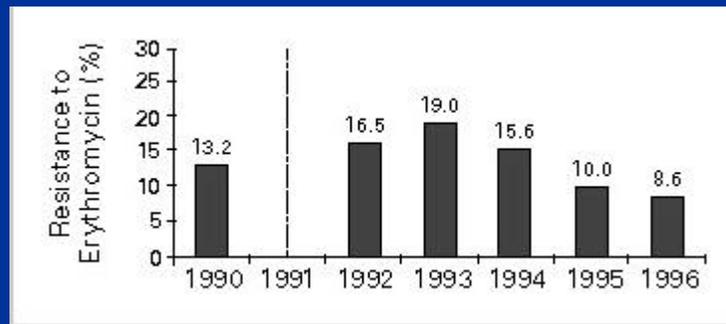
-The Credible Hulk



Evidence Base to Support Antimicrobial Stewardship

■ Reduction in antimicrobial resistance

- Finland's consumption of macrolide antibiotics decreased from 2.40 defined daily doses/1000 inhabitants/day in 1991 → 1.38/1000 inhabitants/day in 1992 ($p=0.007$) and continued to 1996 due to national guidelines.
- With decrease in consumption - ↓ in erythromycin resistance of Gr. A streptococci from throat swabs – 16.5% (1992) → 8.6% (1996)



Seppala H et al. N Engl J Med 1997;337:441-446

Evidence Base to Support Antimicrobial Stewardship

Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis



Emelie C Schuts, Marlies E J L Hulscher, Johan W Mouton, Cees M Verduin, James W T Cohen Stuart, Hans W P M Overdiek, Paul D van der Linden, Stephanie Natsch, Cees M P M Hertogh, Tom F W Wolfs, Jeroen A Schouten, Bart Jan Kullberg, Jan M Prins

Summary

Background Antimicrobial stewardship is advocated to improve the quality of antimicrobial use. We did a systematic review and meta-analysis to assess whether antimicrobial stewardship objectives had any effects in hospitals and long-term care facilities on four predefined patients' outcomes: clinical outcomes, adverse events, costs, and bacterial resistance rates.

Methods We identified 14 stewardship objectives and did a separate systematic search for articles relating to each one in Embase, Ovid MEDLINE, and PubMed. Studies were included if they reported data on any of the four predefined outcomes in patients in whom the specific antimicrobial stewardship objective was assessed and compared the findings in patients in whom the objective was or was not met. We used a random-effects model to calculate relative risk reductions with relative risks and 95% CIs.

Findings We identified 145 unique studies with data on nine stewardship objectives. Overall, the quality of evidence was generally low and heterogeneity between studies was mostly moderate to high. For the objectives empirical therapy according to guidelines, de-escalation of therapy, switch from intravenous to oral treatment, therapeutic drug monitoring, use of a list of restricted antibiotics, and bedside consultation the overall evidence showed significant benefits for one or more of the four outcomes. Guideline-adherent empirical therapy was associated with a relative risk reduction for mortality of 35% (relative risk 0.65, 95% CI 0.54–0.80, $p < 0.0001$) and for de-escalation of 66% (0.44, 0.30–0.66, $p < 0.0001$). Evidence of effects was less clear for adjusting therapy according to renal function, discontinuing therapy based on lack of clinical or microbiological evidence of infection, and having a local antibiotic guide. We found no reports for the remaining five stewardship objectives or for long-term care facilities.

Interpretation Our findings of beneficial effects on outcomes with nine antimicrobial stewardship objectives suggest they can guide stewardship teams in their efforts to improve the quality of antibiotic use in hospitals.

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Lancet Infect Dis 2016

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See Online/Articles
[http://dx.doi.org/10.1016/S1473-3099\(16\)00099-2](http://dx.doi.org/10.1016/S1473-3099(16)00099-2)

Department of Internal Medicine, Division of Infectious Diseases, Centre for Infection and Immunity Amsterdam (CINIMA), Academic Medical Centre, Amsterdam, Netherlands (E C Schuts BSc, Prof J M Prins MD); Scientific Institute for Quality of Healthcare, Radboud Institute for Health Sciences (Prof M E J L Hulscher PhD), Department of Pharmacy (S Natsch Pharm D), and Department of Internal Medicine, Centre for Infectious Diseases (Prof B J Kullberg MD), Radboud University Medical Centre, Nijmegen, Netherlands; Department of Medical Microbiology and Infectious Diseases, Erasmus MC, Rotterdam, Netherlands (Prof J W Mouton MD); Department of Medical

Effects on Mortality of Stewardship Components

De-escalation (Forest Plot)

Prescribing empiric therapy based on guidelines (Forest plot)

Fig. 2 Effect on mortality of de-escalation of therapy based on culture results

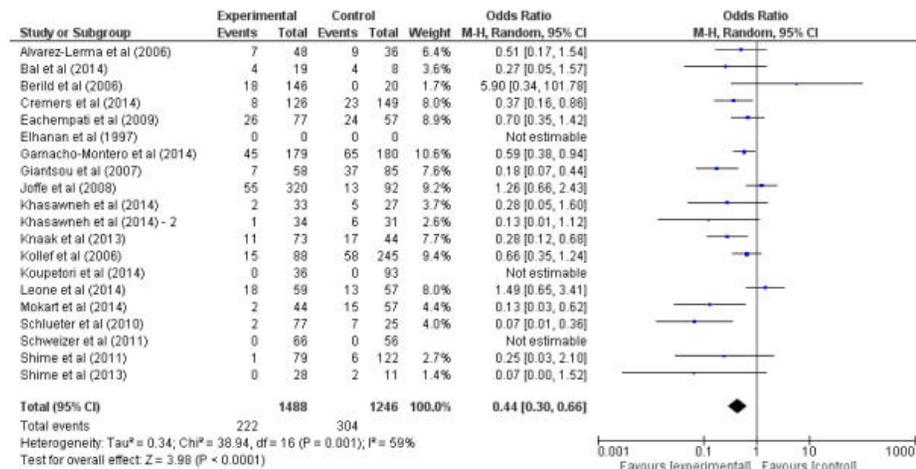
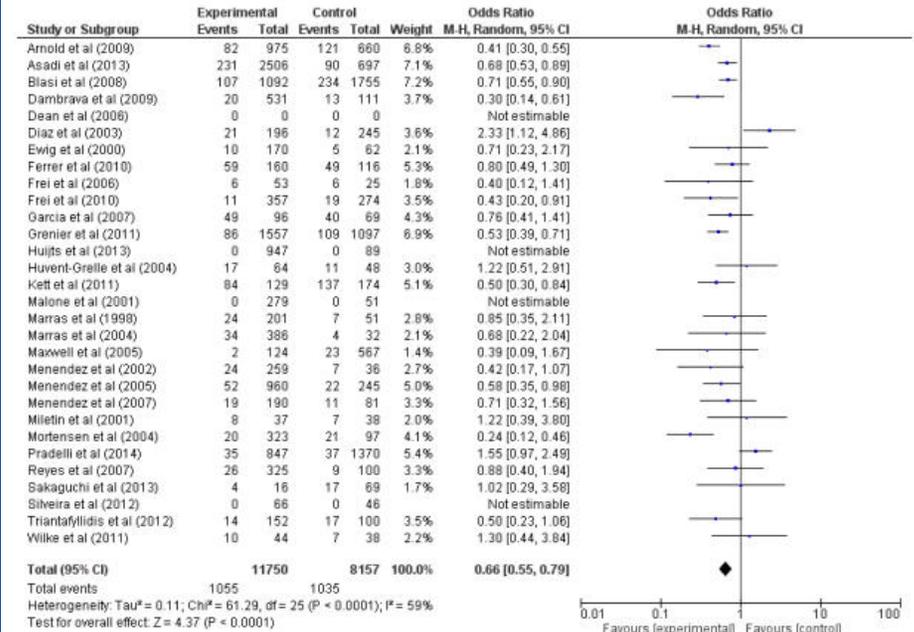


Fig. 1 Effect on mortality of prescribing empiric therapy according to the guideline – CAP



Guideline-adherent empiric therapy RRR for mortality of 35% (relative risk 0.65, 95% CI 0.54–0.80, p<0.0001) and for de-escalation of 56% (0.44, 0.30–0.66, p<0.0001)

Stewardship in ICU-Systematic Review

- Any experimental intervention (any type stewardship) to improve antimicrobial utilization in ICU
- 24 studies met inclusion criteria; 2 de-escalation
3 RCTs, 3 ITS & 18 uncontrolled before-after studies
- Outcomes
 - reductions in antimicrobial utilization (11%–38% DDD/1000 pt-days)
 - lower total antimicrobial costs (US \$5–10/patient-day)
 - shorter average duration of antibiotic therapy, less inappropriate use and fewer antibiotic adverse events
 - stewardship > 6 months associated with ↓ antimicrobial resistance rates and no change NIs, LOS or mortality

De-escalation in ICU

- Cohort study on the safety and impact on in hospital and 90-day mortality of antibiotic de-escalation in patients admitted to the ICU with severe sepsis or shock (n=628)
- De-escalation in 219 patients;
 - By MV analysis, independent RF associated with in-hospital mortality were septic shock, SOFA score the day of culture, inadequate empirical antimicrobial therapy
 - **De-escalation was a protective factor [OR 0.58; 95 % CI 0.36–0.93]**
- Why? Less toxicity; NI; collateral damage

Garnacho-Montero et al. De-escalation of empirical therapy is associated with lower mortality in patients with severe sepsis and septic shock Intensive Care Med (2014) 40:32–40

Effectiveness of Antimicrobial Stewardship Policies

- Based on evidence most effective interventions appear to be restrictive administrative methods including formulary control applied at the institution or provincial level

Antimicrobial Utilization and Stewardship in the Canadian Setting

- Historic issues
- Public Health Agency of Canada initiatives
- Accreditation Canada
- Provincial initiatives
- Local Initiatives

Stewardship in the Canadian Setting

■ Historic overview

- 1997 Canadian Consensus Conference "Controlling antimicrobial resistance. An integrated action plan for Canadians" recommendations
 - establish antibiotic stewardship and antibiotic use teams in all Canadian hospitals by:
 - a. using accreditation standards
 - b. obtaining support from administrative leadership
 - establish antimicrobial use, monitoring, and intervention programs
- 2002 National Policy Conference and 2004 National Action Plan Antimicrobial Stewardship Recommendations
 - obtain, analyze and disseminate data/information on antibiotic use in humans and animals

Stewardship in the Canadian Setting

■ Historic overview

- 2009 Pan-Canadian Stakeholder Consultations on Antimicrobial Resistance
 - develop a universally agreed to definition of stewardship
 - develop a coordinated integrated inter-disciplinary Pan-Canadian approach....
 - develop and promote public and professional awareness of antimicrobial stewardship responsibilities and concerns
- 2014 Senate Briefings; NCCID Report of Antimicrobial Resistance and Antimicrobial Utilization in Canada; Accreditation Canada ROP; Federal Framework for Action
- 2015 Auditor General Report AMR in Canada

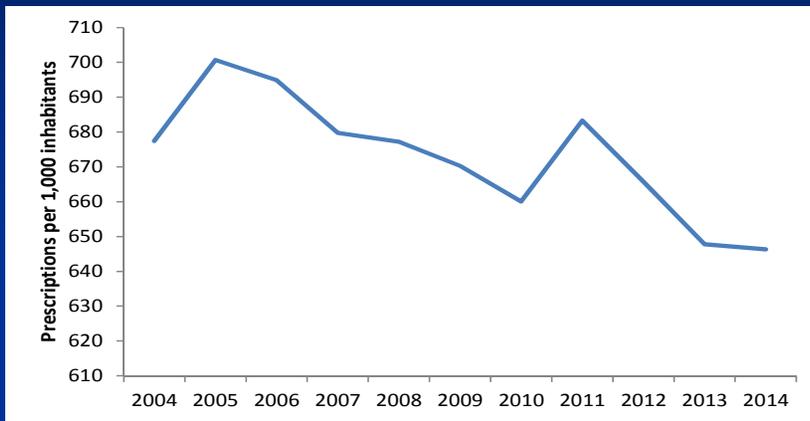
Available AMU Data Canada

- IMS Brogan Products :
 - Canadian Drug Store & Hospital Purchases (CDH)
 - Canadian CompuScript (CSC)
 - Canadian Disease and Therapeutic Index (CDTI)
 - Retail Prescription
- First Nations and Inuit Health Branch (FNIHB)
Non-insured prescription
- CNISP Hospital-based antimicrobial usage

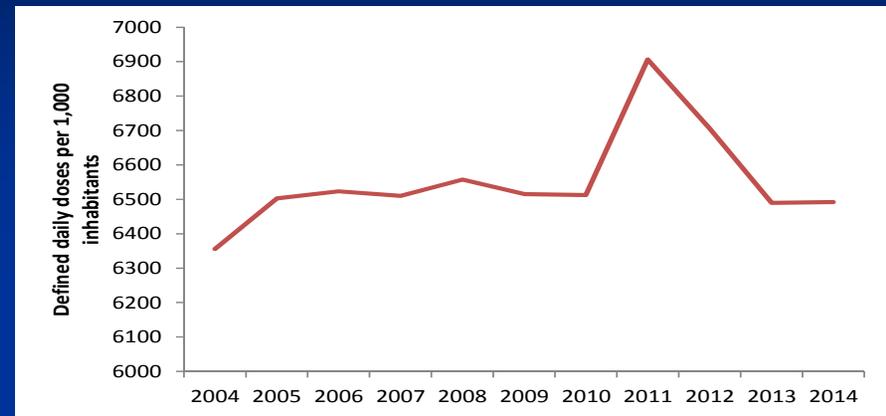
Courtesy PHAC CNISP Kahina Abdesselam

Metrics for monitoring use

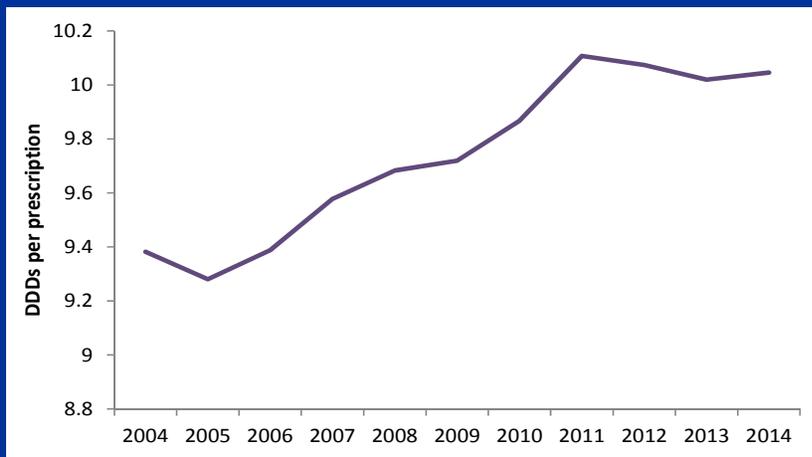
Prescription rates



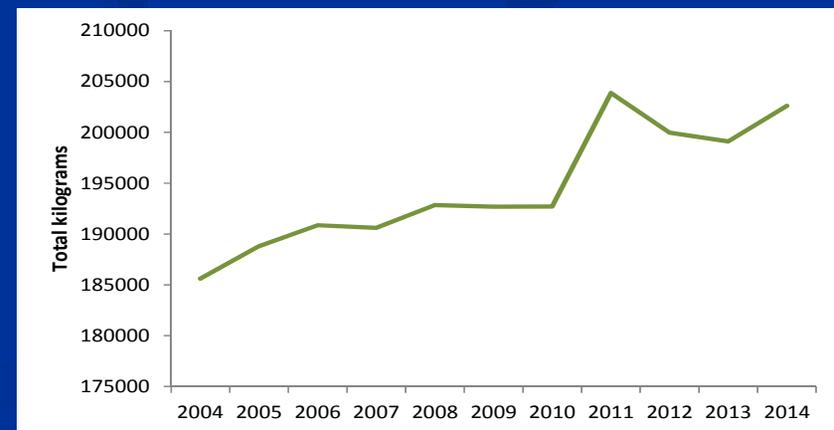
DDD per prescription



DDD rates



Total kilograms of active ingredient



Courtesy PHAC CNISP Kahina Abdesselam

CNISP AMU 2015-16

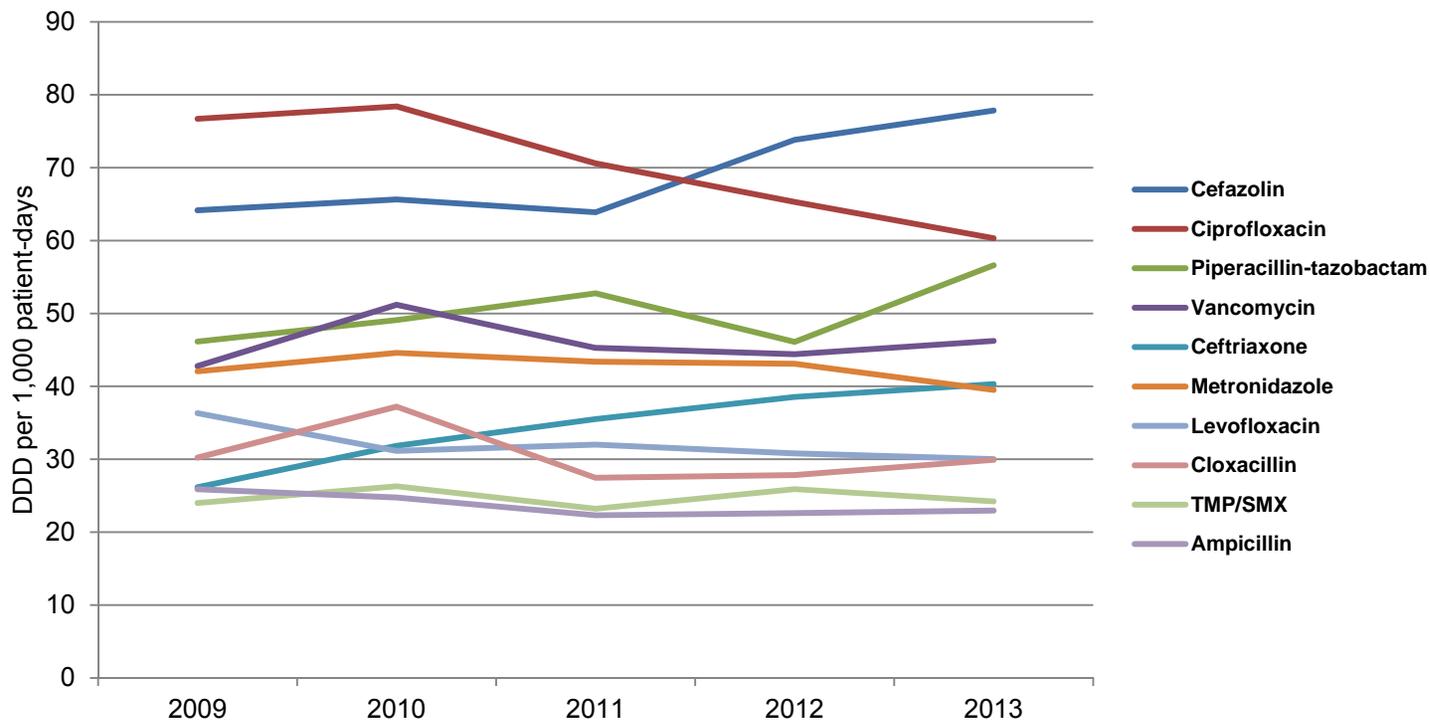
- Approximately 40 sites participating (missing quite a few AMU data)
- 3 pediatrics stand alone participating in 2015 but potentially only 2 participating in 2016
- Variables collected:
 - Antimicrobial
 - Total grams administered or the administered daily dose
 - Bed size
 - Patient days
 - Calendar year
 - Route of administration
 - DOT for pediatric sites

Courtesy PHAC CNISP Kahina Abdesselam

Overall Trend

- Antimicrobial consumption has remained stable over the last 5 yrs but 6% decrease in consumption rate
- Significant Individual drug trend over the last 5 years
 - ↑ 115% Doxycycline
 - ↑ 107% Ertapenem
 - ↑ 64% Clavulin
 - ↓ 37% Cefuroxime
 - ↓ 28% Clarithromycin
 - ↓ 21% Ciprofloxacin
- Antimicrobial consumption based on different categories of bed sizes were not significantly different over the last 5 years
 - > 500 bed size reported 573 DDD per 1,000 patient days; 200 to 500 bed size reported 653 DDD per 1,000 patient days and <200 bed size reported 1,042 DDD per 1,000 patient days

Ten most prescribed antimicrobial by DDD per 1,000 patient-days reported by CNISP participating hospitals between 2009 and 2013 in Canada



Antimicrobial Use Working Group
Canadian Nosocomial Infection Surveillance Program

Courtesy PHAC CNISP Kahina Abdesselam

Accreditation Canada and Stewardship

- Antimicrobial stewardship can accomplish:
 - In combination with a comprehensive infection control program has been shown to limit the emergence and transmission of antimicrobial-resistant bacteria.
 - Studies also indicate that antimicrobial stewardship programs are cost effective, and provide savings through reduced drug costs and avoidance of microbial resistance

Source: Accreditation Canada

A New Accreditation Standard

- Accreditation Canada developed a “Required Organizational Practice” (ROP) under Medication Use on Antimicrobial Stewardship in 2013
 - “The organization has a program for antimicrobial stewardship to optimize antimicrobial use”
 - Applies to all acute care organizations
 - Applicable as of May 2014
 - Organizations should use a tailored approach consistent with their size, service environment and patient population

Source: Accreditation Canada

ROP Tests of Compliance

1. The organization implements an antimicrobial stewardship program
2. The program includes lines of accountability for implementation
3. The program is inter-disciplinary
4. The program includes interventions to optimize antimicrobial use that may include:
 - audit and feedback
 - a formulary with approved indications
 - guidelines and clinical pathways for antimicrobial utilization
 - strategies for streamlining or de-escalation of therapy
 - parenteral to oral conversion of antimicrobials
 - education
 - dose optimization

Provincial Initiatives

■ Ontario

- Public Health Ontario and OHA partnership to focus on stewardship within Ontario hospitals
- Major Consensus Conference planning for stewardship

■ Quebec

- 2011 study from Quebec described the impact of a bundle approach on ambulatory prescribing

■ BC

- Multiple initiatives “Do Bugs Need Drugs”, PharmaNet utilization, BC Clinical Care Management program aims to improve stewardship

■ Alberta

- Alberta wide approach via its 5 zones

Alberta Stewardship Initiatives

Theme:

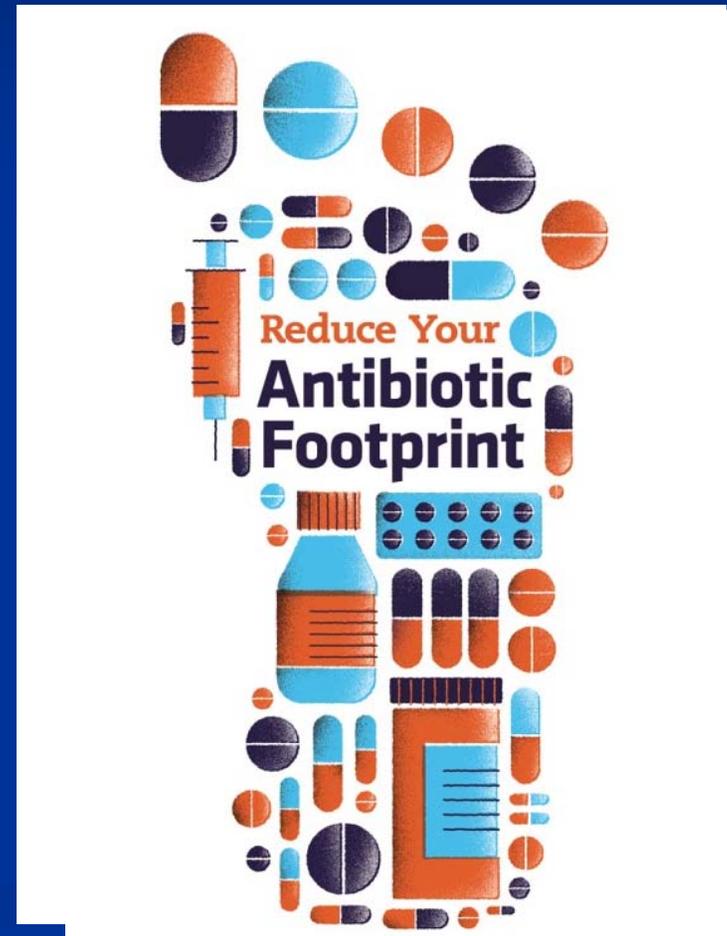
“Reduce Your Antibiotic Footprint”

Current:

- Provincial ASC
- Common formulary and TIs and restrictions
- Zone Committees roll up
- Annual AS report

New:

- Zone Progress Reports
- Zone Initiatives Reports



Reviewed Early/Prescribed Surely

Day 3 Bundle (D3B) for antimicrobials

Reassess initial diagnosis

Review all microbiology results

Tailor antimicrobials; choice & duration

Switch intravenous to oral route

Prospective Audit and Feedback Hospitalist Services

- Re-organization in Pharmacy allowed 4 ID trained pharmacists to conduct daily reviews all new antibiotic starts FMC hospitalists – rounds discussion or note to chart
- Rotation of ID physicians who provide daily discussion of difficult cases
- Evaluation after 1 year revealed 80% acceptance of recommendations (full or partial) and significant improvement de-escalation and conversion to po antibiotics



Spectrum

Get the right drug
for the right bug
at the right dose
and the right duration.



Syndromes



Pathogens



Antimicrobials



info



feedback

*Spectrum*Calgary

- Spectrum is an adaptable and locally tailored antimicrobial stewardship application
- Goals:
 - To educate users on antimicrobial stewardship principles and optimal prescribing through the app experience
 - To improve the appropriate antimicrobial utilization for common infectious syndromes in hospitalized patients in Calgary
 - To expand of the product in scope, location, and media and improve existing content through incorporation of user feedback in an iterative fashion



By Syndrome

Carrier 7:05 PM

[Back](#) **SBP Patient Factors**

SELECT ANY THAT APPLY

Community acquired

Hospital acquired or healthcare associated

Healthcare Associated

Colonized or recent infection with resistant organism (e.g. ESBL or ampC), or recent piperacillin-tazobactam use (<3mo)

Bilirubin > 68 umol/L

Serum Cr > 88 umol/L

Carrier 7:05 PM

[Back](#) **SBP Empiric Rx**

SUGGESTED ANTIMICROBIAL REGIMEN

Piperacillin-tazobactam 3.375g IV q6h

OR

Meropenem 500mg IV q6h

AND

Albumin 1.5g/kg IV at time of diagnosis and 1g/kg IV on day three reduces renal failure and mortality

FOLLOW UP

Patients with SBP should



S P E C T R U M

(your site/region/city...)

- User friendly (above average usability)
- Iterative open source feedback
- iTunes downloadable free app for Spectrum Calgary
- Menus of options for specific site development
 - Base of antimicrobials/pathogens/antibiograms
 - Optional customization of algorithms
 - Optional add local epidemiology
- Future: Android version coming and ICU outcomes evaluation completed and submitted IDSA



Download on the
App Store

s p e c t r u m . m d

**The power to make a difference in stewardship
is in your hands**

