Facile Solutions for A Difficile Problem

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FIELDS INSTITUTE
Thematic Program on the Mathematics of
Drug Resistance in Infectious Diseases
July 6, 2010

A Case

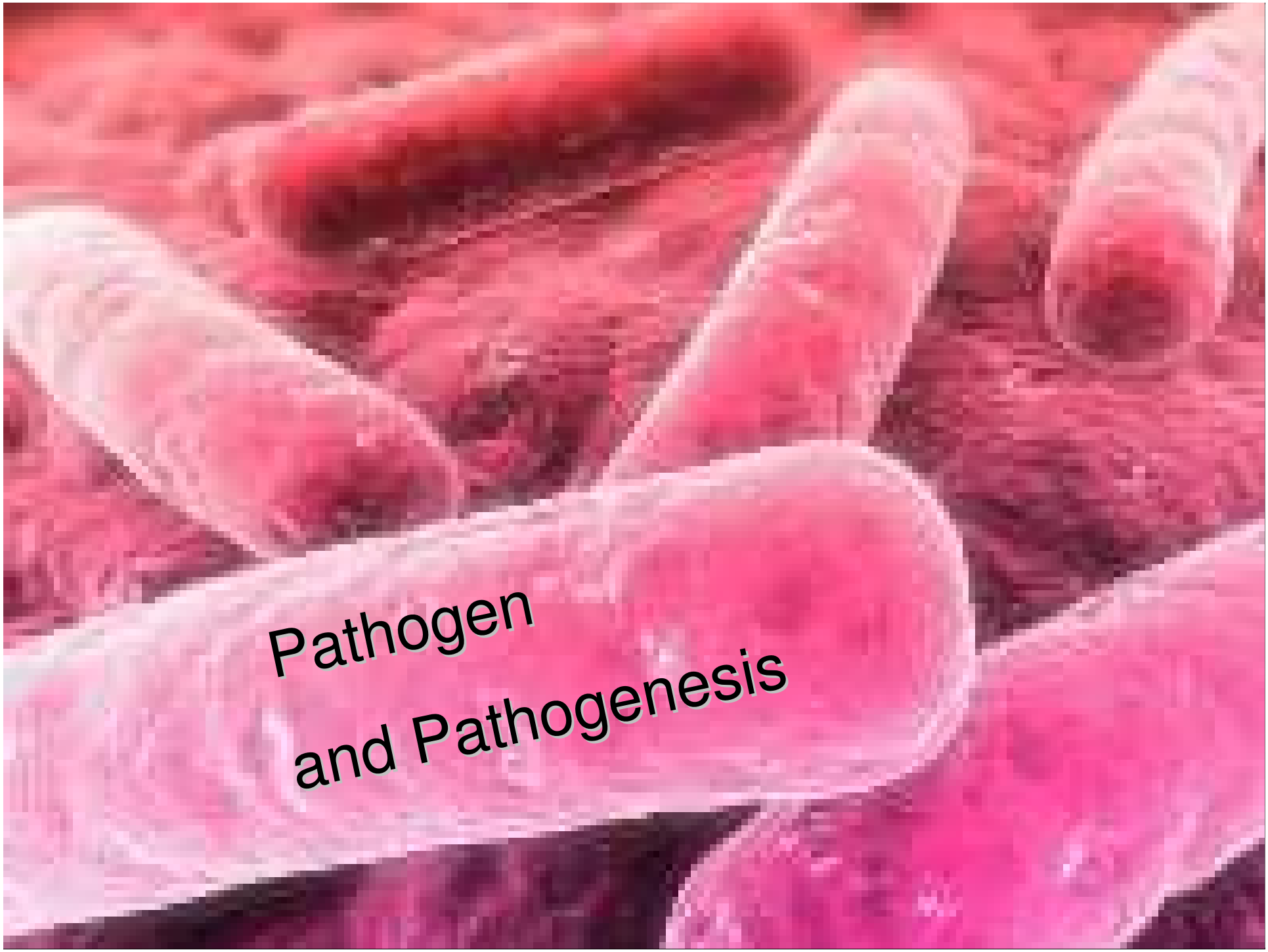
- 44 M
- surgical resection of oral cancer (palate)
- antibiotic prophylaxis
  - cefazolin + metronidazole
- recovering well on ward

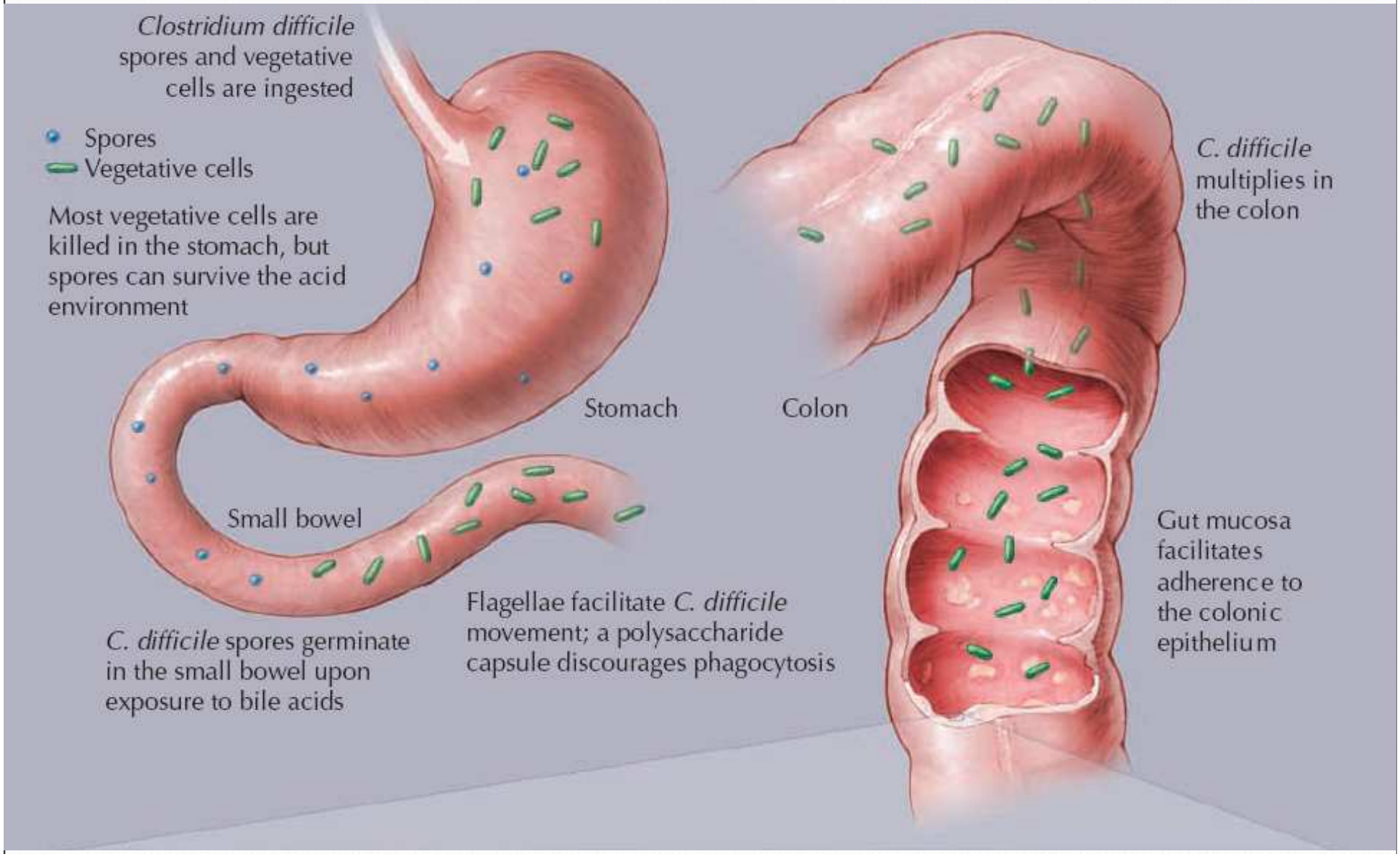
A Case

- post-operative day #6
  - fever, tachycardia, abdominal distension
  - presumed ileus secondary to narcotics
- post-operative day #7
  - subtotal colectomy

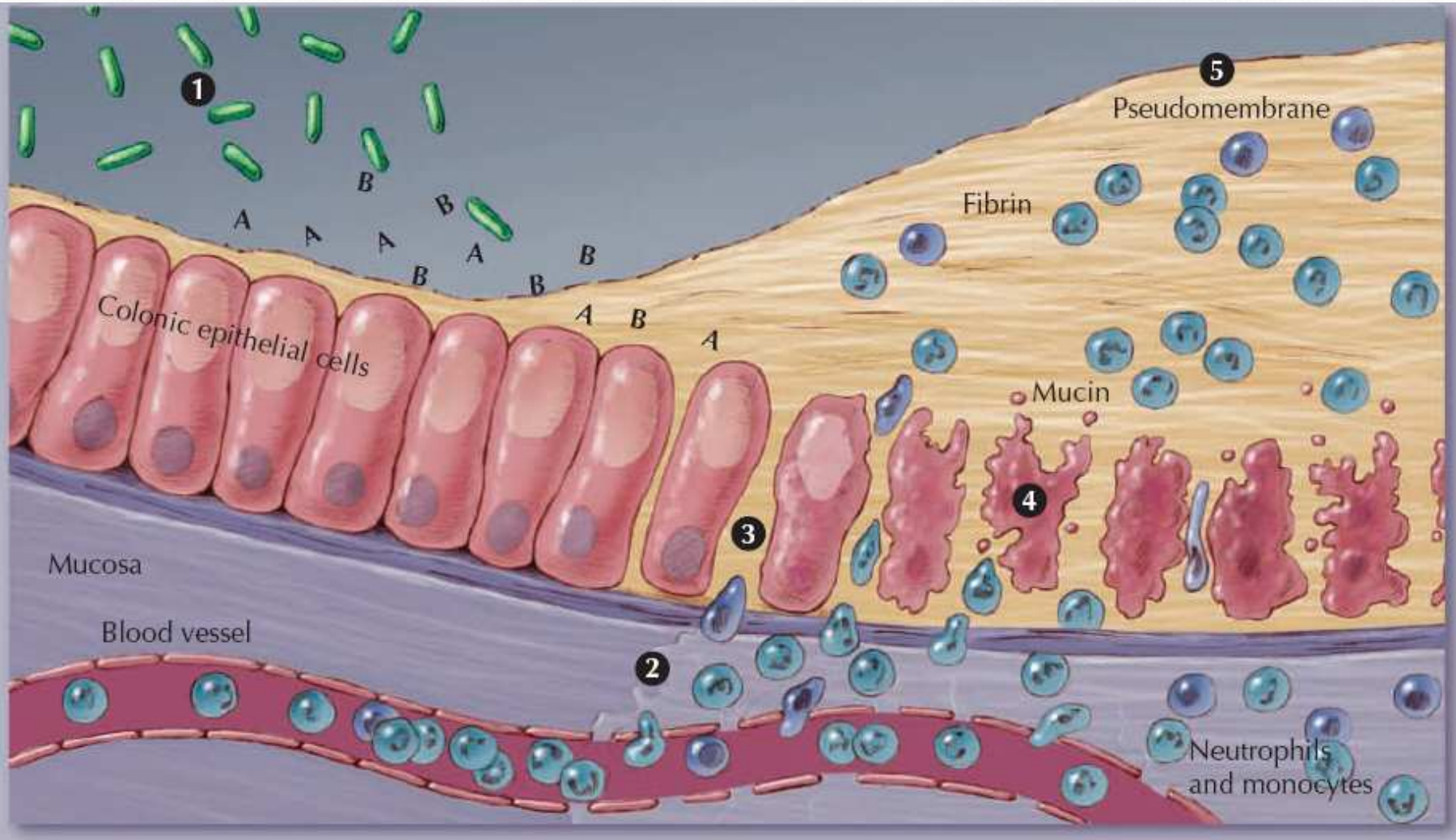
Overview

- Pathogen and Pathogenesis
- Population Burden and Trends
- Treatment
- Prevention


Pathogen
and Pathogenesis



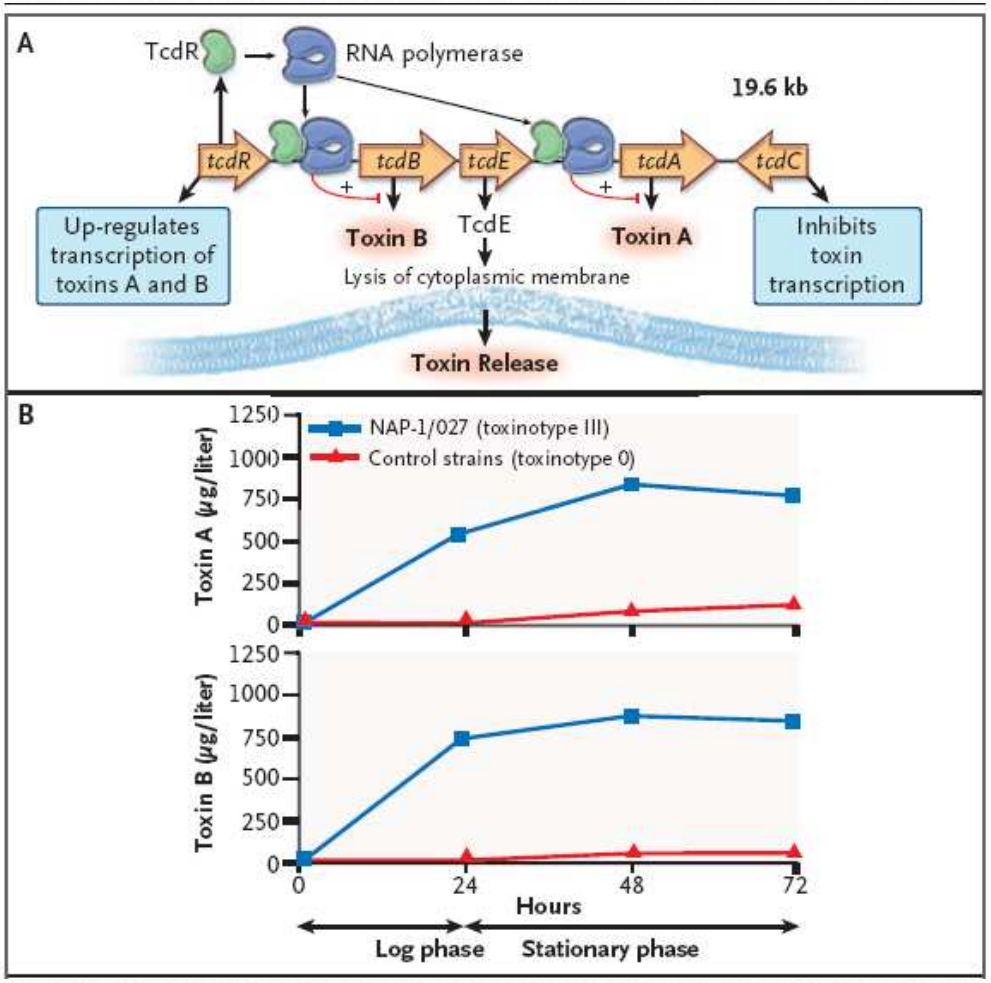
Poutanen *CMAJ* 2004



C. difficile vegetative cells produce toxins A and B and hydrolytic enzymes (**1**). Local production of toxins A and B leads to production of tumour necrosis factor-alpha and proinflammatory interleukins, increased vascular permeability, neutrophil and monocyte recruitment (**2**), opening of epithelial cell junctions (**3**) and epithelial cell apoptosis (**4**). Local production of hydrolytic enzymes leads to connective tissue degradation, leading to colitis, pseudomembrane formation (**5**) and watery diarrhea.

Poutanen *CMAJ* 2004

Emergence of a virulent strain (NAP-1/027)



Kelly *NEJM* 2008

Emergence of a virulent strain (NAP-1/027)

- NAP-1/027 strain associated with
  - 20fold higher toxin production increased severity
  - fluoroquinolone resistance ? ? increased incidence

- "Quebec strain" a misnomer
  - found worldwide
  - responsible for 20-45% of Ontario cases

Martin *JCM* 2008; Simor/CNISP unpublished data

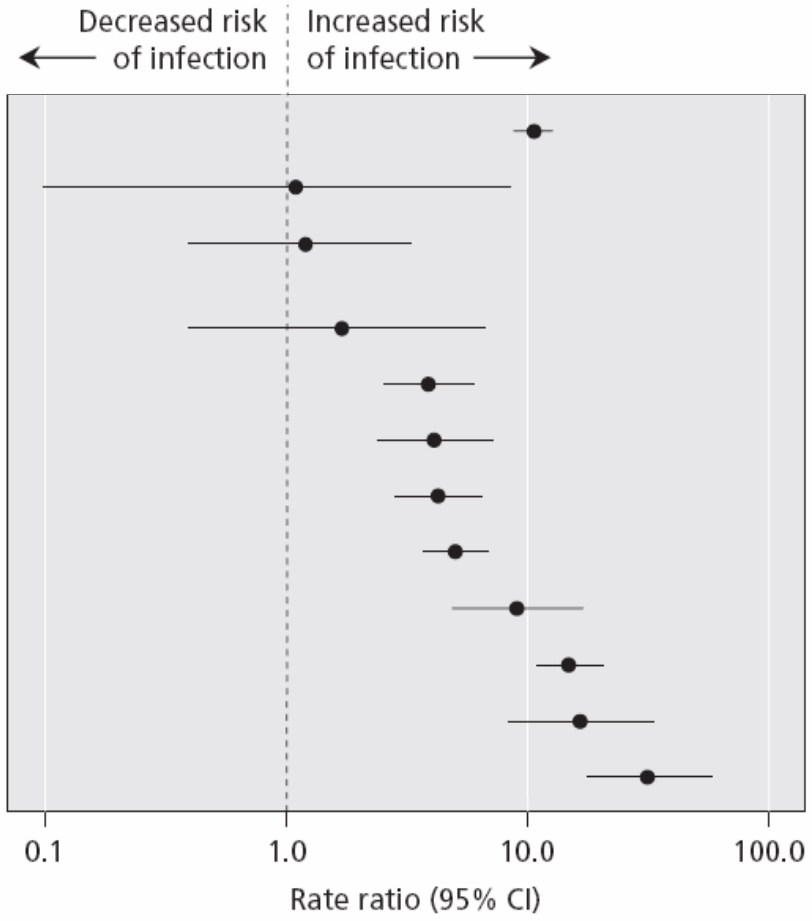
A two-hit hypothesis:

- 1) acquisition of the organism
  - fecal-oral
  - from other infected patients or their environment
- 2) disruption of protective intestinal flora
  - antibiotics
- **(1)+(2)**=nosocomial pathogen
- **(1)+(2)**=reason C.diff included in this theme week

Kelly *NEJM* 2008

Culprit antibiotics

Drug therapy	Adjusted RR (95% CI)
Any antibiotic	10.6 (8.9–12.8)
Tetracyclines	1.1 (0.1–8.6)
Trimethoprim–sulfamethoxazole	1.2 (0.4–3.3)
Other antibiotics	1.7 (0.4–6.8)
Macrolides	3.9 (2.5–5.9)
Levofloxacin	4.1 (2.4–7.1)
Penicillins	4.3 (2.8–6.4)
Ciprofloxacin	5.0 (3.7–6.9)
Moxifloxacin	9.1 (4.9–17.0)
Cephalosporins	14.9 (10.9–20.3)
Gatifloxacin	16.7 (8.3–33.6)
Clindamycin	31.8 (17.6–57.6)



Dial *CMAJ* 2008

Timing after antibiotics

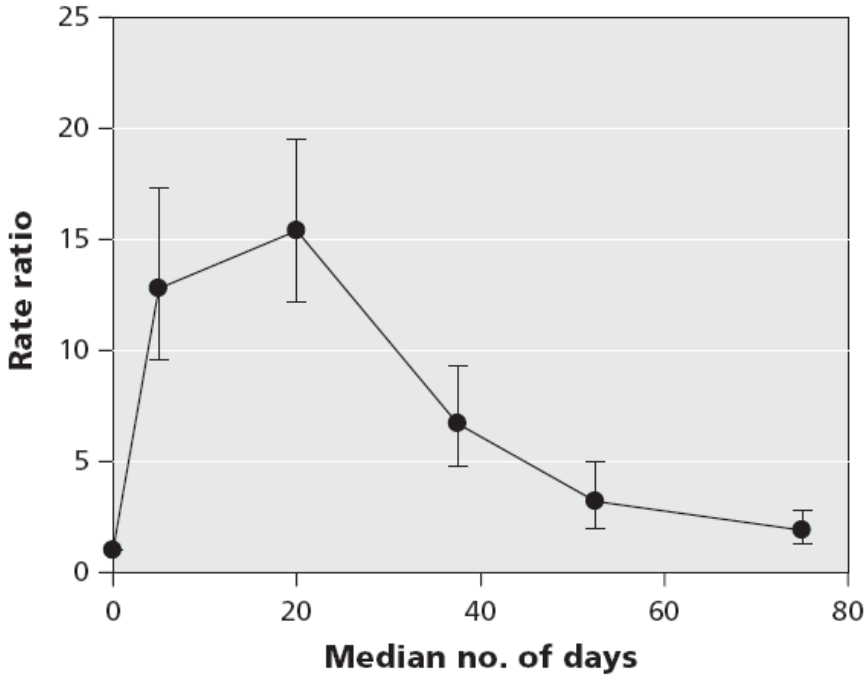
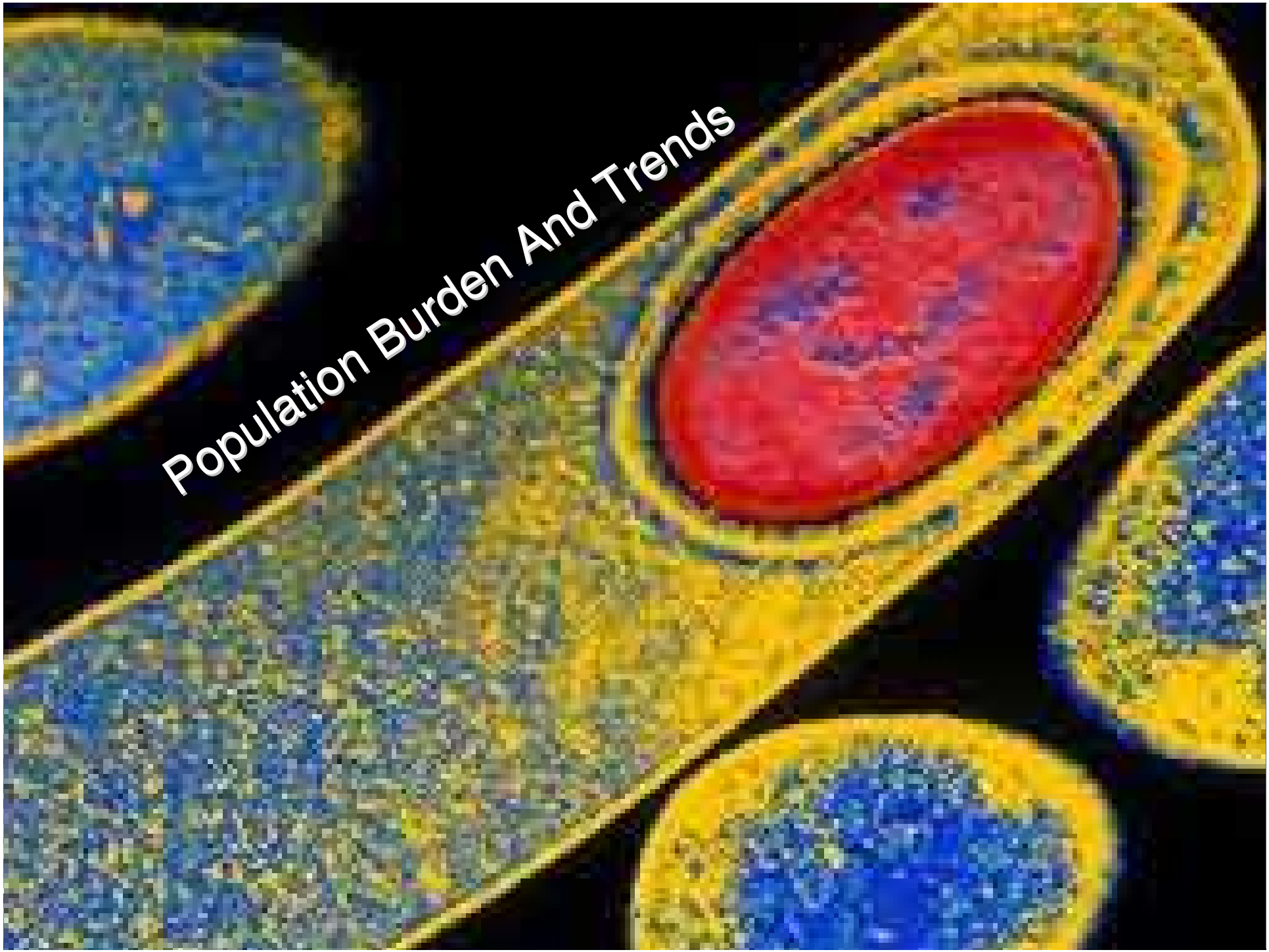


Figure 4: Risk of hospital admission because of *Clostridium difficile* infection as a function of time from most recent antibiotic prescription. Values shown are rate ratios for patients with *C. difficile* infection (n = 836) relative to those without *C. difficile* infection (n = 8360).

Dial *CMAJ* 2008

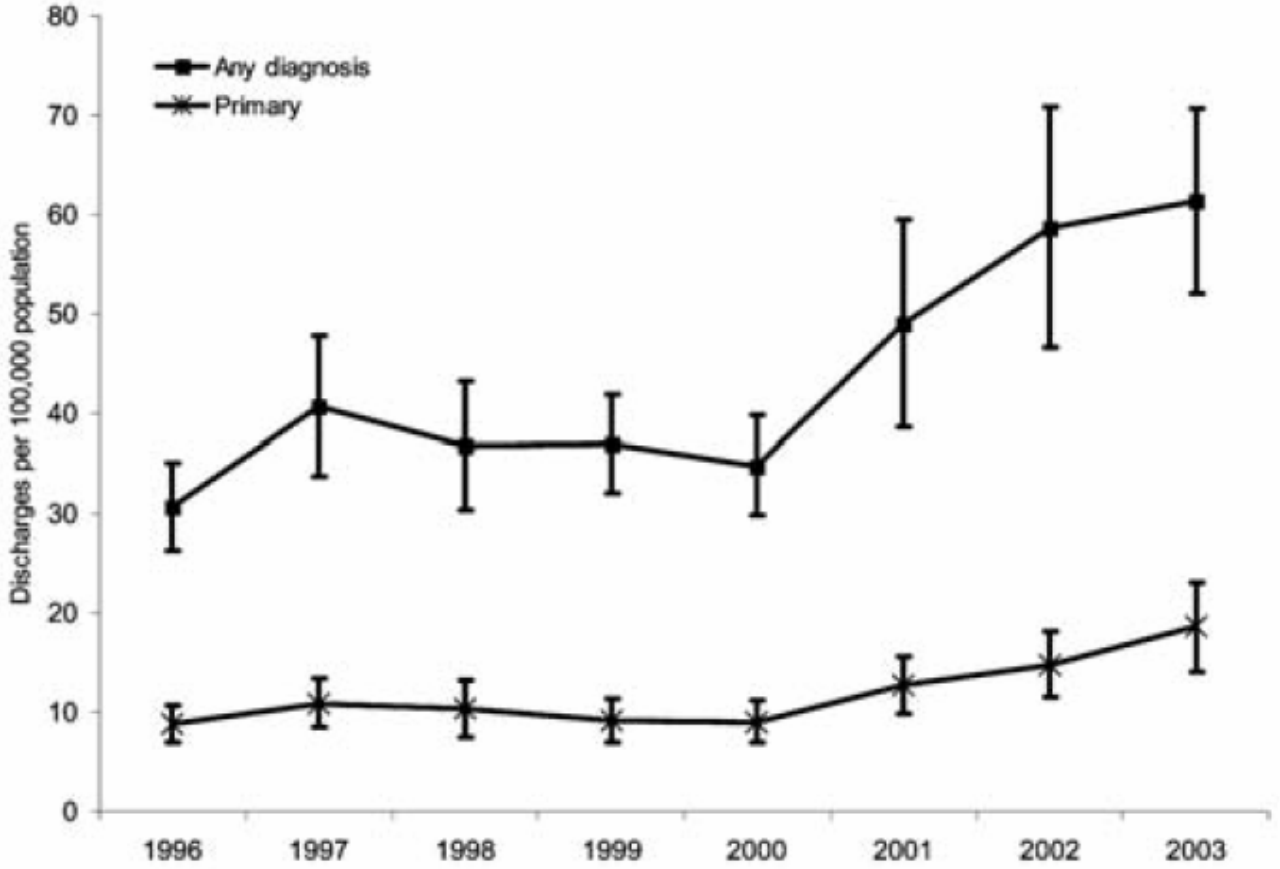

Population Burden And Trends

C.difficile burden

- #1 cause of antibiotic-associated diarrhea
- #1 cause of diarrhea in hospital

Kelly NEJM 2008

Doubling Incidence: U.S. National Statistics



McDonald *EID* 2006

Rising Incidence: The Quebec Story

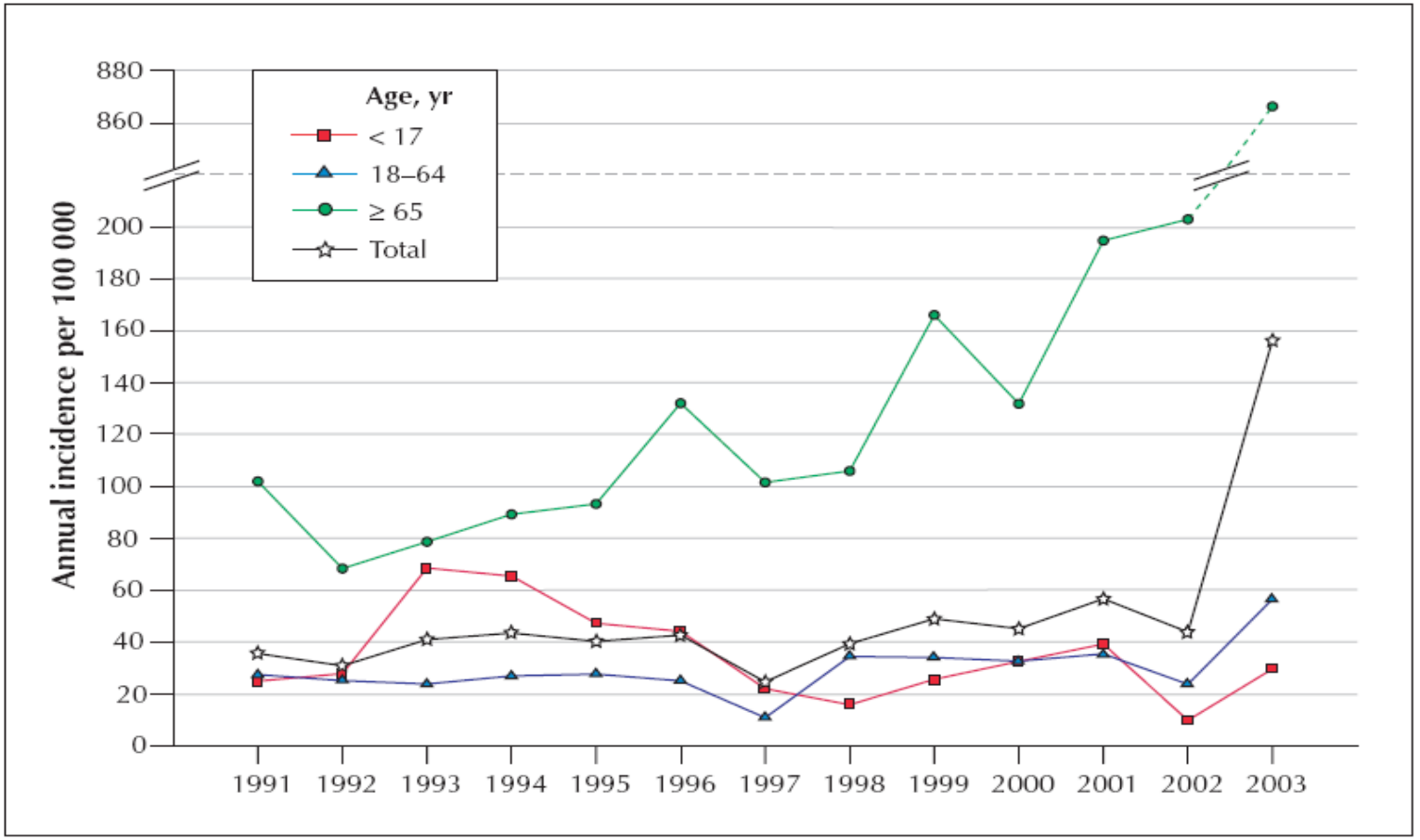


Fig. 1: Annual incidence (per 100 000 population) of *Clostridium difficile*-associated diarrhea (CDAD) in Sherbrooke, Que., 1991–2003.

Pepin *CMAJ* 2006

Table 1. Reported rates of health care–associated *Clostridium difficile* infection (CDI), by province or region, among adults hospitalized in Canadian Nosocomial Infection Surveillance Program hospitals ($n = 1430$).

Hospital location	No. of cases of CDI	No. of hospital admissions	No. of cases per 1000 hospital admissions	No. of patient-days	No. of cases per 100,000 patient-days
British Columbia	128	42,197	3.0	279,911	46
Alberta	153	75,728	2.0	372,966	41
Saskatchewan and Manitoba	67	25,214	2.7	184,153	36
Ontario	666	112,658	5.9	824,658	81
Quebec	282	21,964	12.8	217,507	130
Atlantic Canada	134	30,270	4.4	333,137	40
Total	1430	308,031	4.6	2,212,332	65

29 hospitals, surveillance Nov2004-April 2005

Gravel *CID* 2009

Ontario surpasses Quebec

Incidence and rates of CDAD by province/region

Region	Cases	Admissions	Per 1,000 admissions (95% CI*)	Patient-days	Per 10,000 patient-days (95% CI*)
BC/AB	368	70,773	5.20 (4.67 – 5.73)	432,088	8.52 (7.65 – 9.39)
SK/MB	32	18,190	1.76 (1.15 - 2.37)	119,432	2.68 (1.75 – 3.61)
Ontario	420	76,013	5.53 (5.00 - 6.05)	509,595	8.24 (7.45 – 9.03)
Quebec	151	27,590	5.47 (4.60 - 6.34)	199,701	7.56 (6.36 – 8.77)
Atlantic	107	35,050	3.05 (2.48 - 3.63)	221,023	4.84 (3.92 – 5.76)
Overall	**1,078**	**227,616**	**4.74 (4.45 – 5.02)**	**1,482,485**	**7.27 (6.84 – 7.71)**

* Confidence interval

Simor, communication CNISP results

High attributable mortality of C.difficile colitis

Table 2. Reported mortality rates for adults with health care–associated *Clostridium difficile* (HA CDI) infection who were hospitalized in Canadian Nosocomial Infection Surveillance Program hospitals at 30 days after onset of disease ($n = 1430$).

Hospital location	No of cases of HA CDI	No. of patients who died	Mortality rate per 100 cases	No. of deaths related to HA CDI		No. of deaths attributable to HA CDI per 100 cases
				Directly	Indirectly	
British Columbia	128	22	17.2	1	7	6.3
Alberta	153	14	9.2	1	1	1.3
Saskatchewan and Manitoba	67	10	14.9	1	0	1.5
Ontario	666	108	16.2	7	20	4.1
Quebec	282	64	22.7	20	22	14.9
Atlantic Canada	134	15	11.2	1	1	1.5
Total	1430	233	16.2	31	53	5.7

NOTE. Attributable deaths, deaths directly or indirectly related to HA CDI 30 days after onset; mortality rate, death from all causes within 30 days after onset of HA CDI.

Gravel *CID* 2009

Quadrupling of attributable mortality

- attributable mortality 5.7% (2004-2005)
- attributable mortality 1.5% (1997)

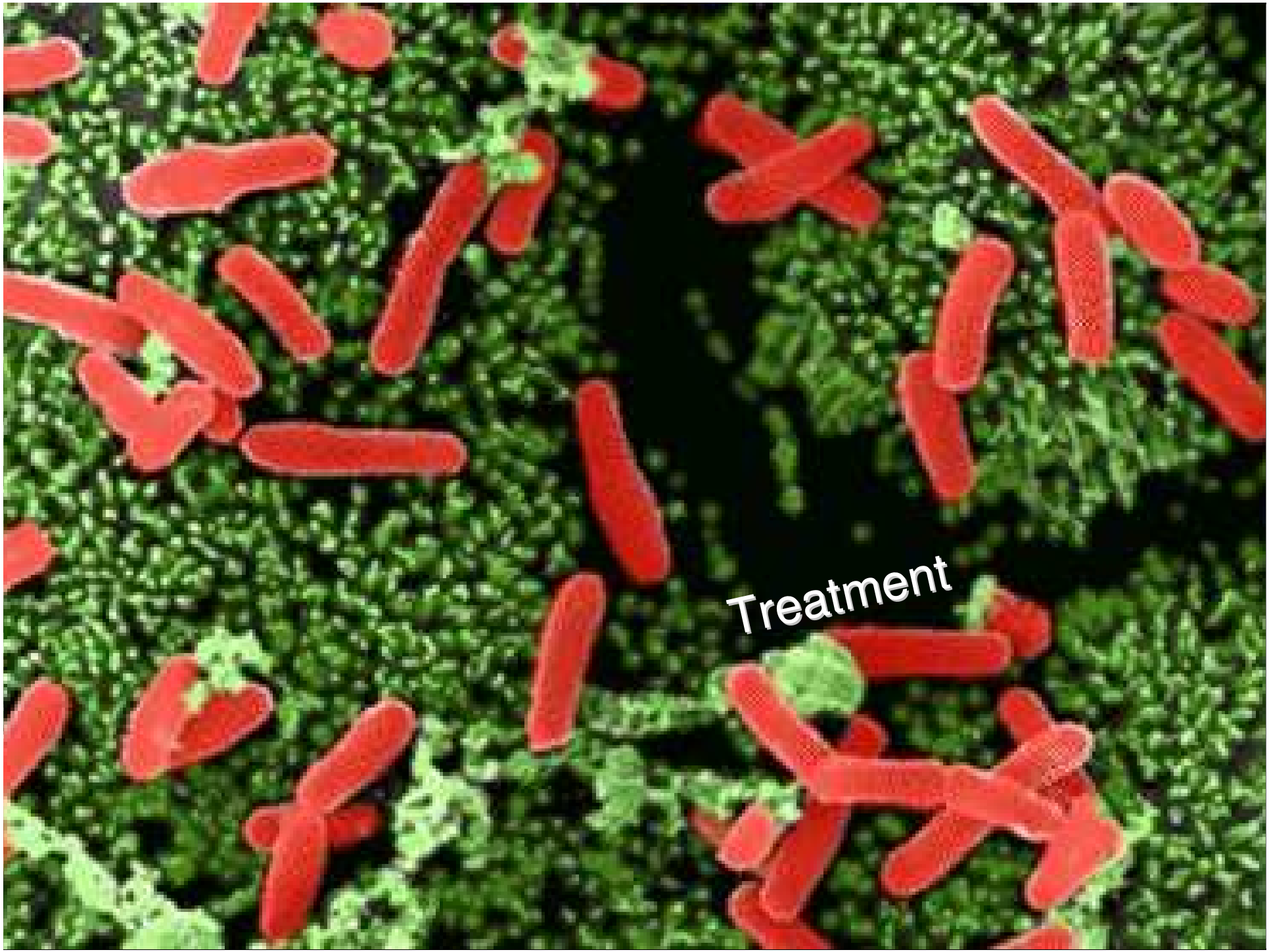
$p<0.001$

Gravel *CID* 2009

C.difficile burden in Ontario

- Ontario Burden of Infectious Diseases (OnBoIDs):
  - administrative databases, and public health databases
  - 2005-2007
- 5,364 cases /yr
- 167 deaths /yr
- 1800 DALYs / yr
- #1 most burdensome GI pathogen
  - no other GI pathogen responsible for >200 DALYs
  - lumped together the other GI pathogens don't add up to 1/4 of Cdiff burden
- #8 most burdensome pathogen in Ontario

OnBoIDs Report: In production (do not quote)


Treatment

Cornerstones of Treatment

- hydration
- stop inciting antibiotics
  - may be sufficient for cure in mild cases
- avoid anti-diarrheal agents
- provide C.difficile specific antibiotics (2 choices)
  - metronidazole
  - vancomycin
- surgery in extreme cases

Treatment: Metronidazole versus Vancomycin

- metronidazole advantages
  - Cheaper:
    - metronidazole $0.80
    - vancomycin po $312
  - reduced risk of selection for vancomycin-resistant *Enterococci (*VRE*)*
  - previous evidence of equal efficacy
- vancomycin advantages
  - less absorption (0 vs 100%) so remains in intestinal lumen at site of infection
  - superior efficacy according to observational evidence eg, Quebec experience
  - superior efficacy according to recent RCT evidence…

A Comparison of Vancomycin and Metronidazole for the Treatment of *Clostridium difficile*–Associated Diarrhea, Stratified by Disease Severity

Fred A. Zar,[1] Srinivasa R. Bakkanagari,[2] K. M. L. S. T. Moorthi,[2] and Melinda B. Davis[1]

[1]University of Illinois at Chicago, Chicago, and [2]Saint Francis Hospital, Evanston, Illinois

Table 2. Rate of cure of *Clostridium difficile*–associated diarrhea by disease severity and treatment.

Disease severity	No. of patients cured/ no. of patients treated (%)			P^a
	Mtz group	Vm group	Total	
Mild	37/41 (90)	39/40 (98)	76/81 (94)	.36
Severe	29/38 (76)	30/31 (97)	59/69 (86)	.02
All	66/79 (84)	69/71 (97)	135/150 (90)	

NOTE. Mtz, metronidazole; Vm, vancomycin.

[a] *P* values were calculated using Fisher's exact test.

Zar *CID* 2007

Treatment:
Vancomycin versus Metronidazole

"There seems to be little doubt that vancomycin is the best drug for patients with severe and complicated C.difficile infection…

…For patients with mild disease, there is some question about the need for an antibiotic, and metronidazole may be the preferred agent when no antibiotic is needed."

Bartlett *CID* 2008

Predictors of Severe C.diff Complications: Sunnybrook retrospective cohort

	Adjusted Odds Ratio	95% CI
Relapse (versus initial) episode	3.1	1.4-6.7
Confusion	1.9	1.0-3.8
Minimum systolic pressure	0.97	0.95-0.98
Elevated WBC	1.04	1.02-1.06
Vancomycin as initial treatment	0.22	0.07-0.74
Other exacerbating antibiotics	3.2	1.5-6.5

A call for mathematical modelling:

"Is Fear of VRE Killing Patients with C.difficile?"

Another Case

- 49 F
  - end stage renal disease (peritoneal dialysis)
  - hospitalized for peritonitis
  - treated with broadspectrum antibiotics
  - day 3 of hospitalization: watery diarrhea
  - stool positive C.difficile

Course of her C.difficile Infection

- Episode 1
  - metronidazole x 10 days
  - symptoms resolve 7 days, recur 5 days post-treatment
- Episode 2
  - metronidazole x 14 days
  - symptoms resolve 7 days, recur 5 days post-treatment
- Episode 3
  - vancomycin x 4 week taper
  - symptoms resolve 2 days, recur 7 days post-treatment
- Episode 4
  - vancomycin x 6 week taper
  - symptoms resolve 2 days … finally cured

Treatment of Relapse

- 1 in 4 patients experience a recurrence
  - reinfection with a new strain
  - relapse with the same strain
    - spores impermeable to antimicrobial treatment
    - germinate to vegetative form up to 6 weeks later

Pepin *CID* 2005; Wilcox *JHI* 1997; McFarland *Am J Gastro* 2002

Relapse does not mean resistance

- resistance to metronidazole and vancomycin is rare
- 258 isolates from Quebec outbreak[1]
  - 0% metronidazole resistance
  - 0% vancomycin resistance
- thousands of isolates have now been tested in Ontario & Canada[2]
  - 0% metronidazole resistance
  - 0% vancomycin resistance
- so, reasonable to retreat with these same medications
- can consider adjunctive therapy

1. Bourgault AAC 2006; 2. Personal communication, A.Simor

Tapered or Pulsed Vancomycin

Tapered or Pulsed Vancomycin

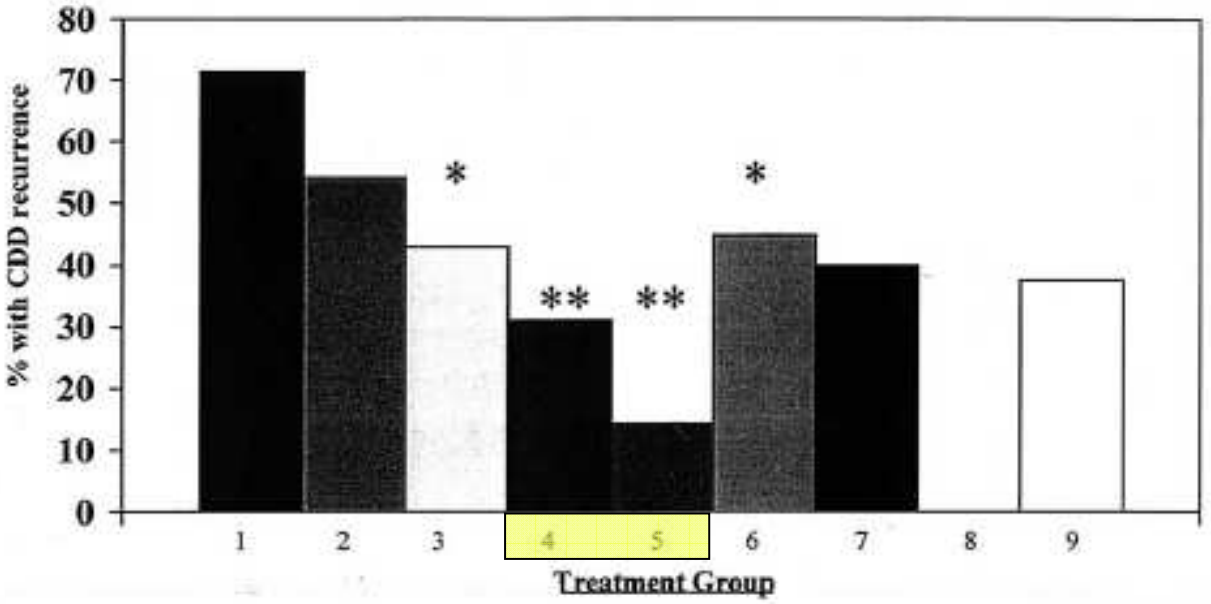


Figure 1. Treatment response in 163 patients with RCDD. 1 = medium dose vancomycin; 2 = low dose vancomycin; 3 = high dose vancomycin; 4 = tapered vancomycin; 5 = pulsed vancomycin; 6 = low dose metronidazole; 7 = medium dose metronidazole; 8 = high dose metronidazole; 9 = miscellaneous. *$0.05 < p < 0.1$, compared to medium dose vancomycin (1 g/day); **$p < 0.05$, compared to medium dose vancomycin (1 g/day).

Probiotics

Saccharomyces boulardii

- a non-pathogenic yeast
- randomized controlled trial
  - n=124 patients with C.difficile, all given vancomycin
    - + *S.boulardii* VS placebo
  - no benefit among patients with first C.diff episode
  - large benefit among patients with second C.diff episode
    - recurrence 35% vs 65% (p=0.04)

McFarland *JAMA* 1994

Saccharomyces boulardii

- BUT
  - no benefit in a 2nd randomized controlled trial
- AND
  - *Saccharomyces* bloodstream infection
    - case reports (60 cases)
    - mortality rate 28%

Surawicz *CID* 2000; Munoz *CID* 2005

Recurrent *Clostridium difficile* Colitis: Case Series Involving 18 Patients Treated with Donor Stool Administered via a Nasogastric Tube

Johannes Aas,[1] Charles E. Gessert,[2] and Johan S. Bakken[3]

150 patients

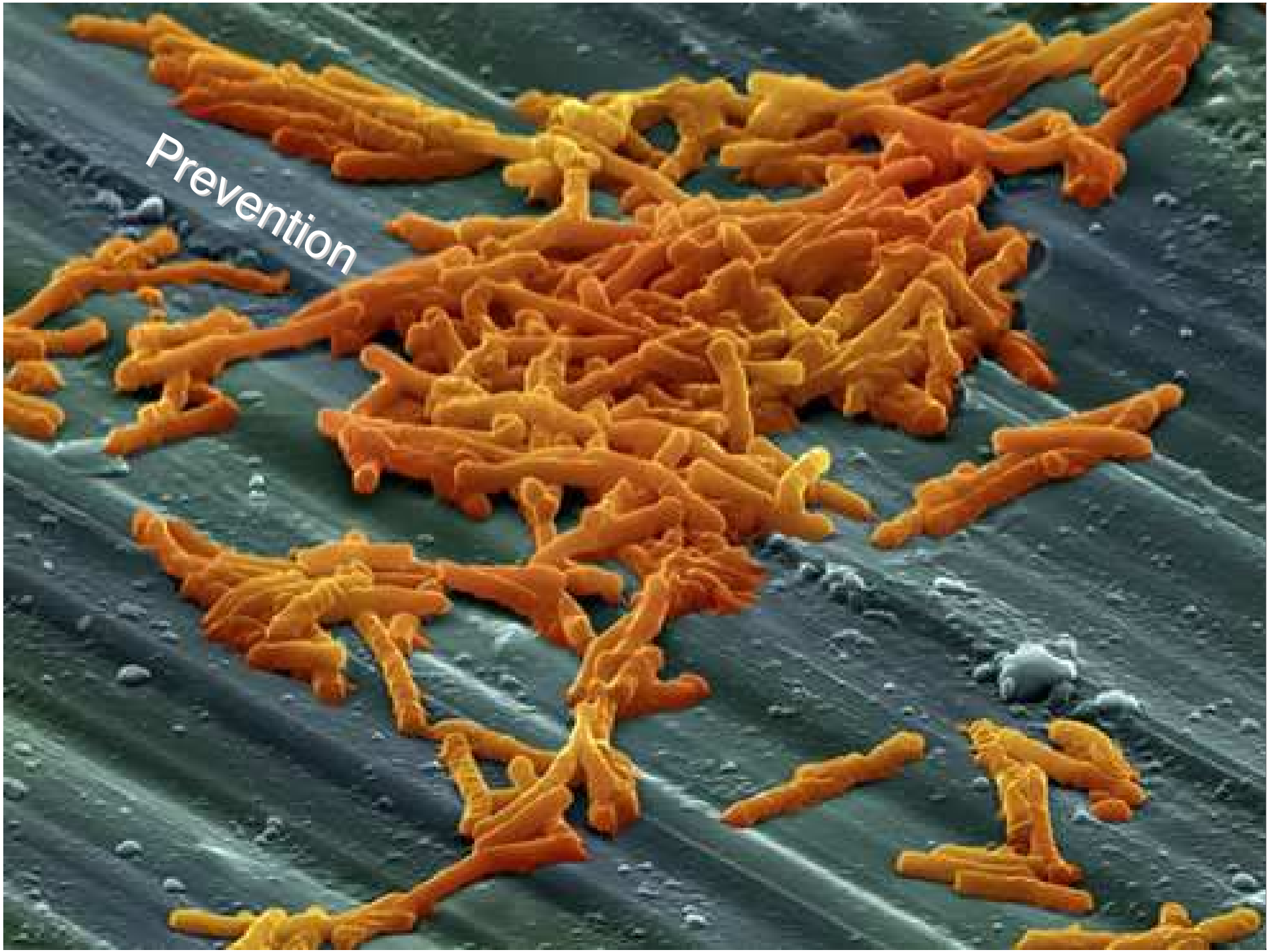
90% success

Table 4. Demographic and clinical information for 18 patients treated for *Clostridium difficile* colitis with stool transplantation (ST).

Patient	Year	Age, years	Sex	Predisposing infection	Antimicrobial agents used before *C. difficile* infection	Antimicrobial courses before ST[a]	*C. difficile* test results before ST, negative/positive[b]	Days from diagnosis to ST	*C. difficile* test results after ST, negative/positive[c]	Outcome
1	1994	61	M	Pneumonia	Cpfx, Clm	3	1/2	73	4/0	Resolution
2	1994	76	F	SBO	Ctri	4	0/3	128	1/0	Resolution
3	1996	76	F	Postoperative wound infection	Amp, Gm	3	1/3	80	0/0[d]	Resolution
4	1996	72	F	Infected BKA	Clex, Cpfx	3	0/3	83	1/0	Resolution
5	1997	58	F	Postoperative wound infection	Cpfx	4	1/3	77	1/0	Resolution
6	1997	65	M	Septic bursitis	Cm, Pen	4	1/4	85	1/0	Resolution
7	1997	88	M	Pneumonia	Ctox	3	1/3	41	0/0[e]	Death
8	1998	79	M	SBO	Amox, Pip	2	0/2	87	0/1[f]	Treatment failure[f]
9	1998	82	F	Pneumonia	Ctri	5	0/5	126	1/0	Resolution
10	1999	83	F	Bronchitis	Clex	2	0/2	25	0/0[e]	Death
11	1999	71	F	Cellulitis	Cpfx, Cm, Pip, TMP-SMZ	3	0/3	57	0/0[d]	Resolution
12	1999	69	F	Chronic osteomyelitis	Ala	3	2/2	81	2/0	Resolution
13	2000	80	F	Urosepsis	Cpfx, Pip	4	0/3	87	1/0	Resolution
14	2000	77	F	Pneumonia	Cpfx	4	0/3	48	1/0	Resolution
15	2000	70	F	Pneumonia	Lev	2	0/2	76	2/0	Resolution
16	2001	71	F	*Helicobacter pylori* gastritis	Tet	7	0/7	497	2/0	Resolution
17	2002	77	M	Leukemia	Vm, Atm, Mtz	6	2/5	114	1/0	Resolution
18	2002	51	F	Crohn colitis	Clex, Pip, Taz	3	0/3	66	1/0	Resolution

Stool transplant Recipe

Stop vancomycin/metronidazole 24-48 hours before procedure.
Continue florastor or other biologics during transplant and for 60 days afterwards
add 50 gms of stool to 200 cc's normal saline in a blender
(the sides of the blenders usually have markings to make measuring the number of cc's easy).
[I do encourage them to try if possible to use "fresh stool" to prevent overgrowth that may be temperature related,
or death of fastidious organisms]
Mix in blender until all liquid (they **throw the blender out when finished, it costs ~35$ at Canadian tire**)
Pour in an enema bag (available at any drug store)
Give enema and patient should hold as long as possible (I tell the patient to lie still as long as possible so that they do not get the urge to defecate)
1 treatment has almost always been enough, but if they feel like the diarrhea is coming back they can repeat.


Prevention

Ontario

NEWS

Ministry of Health and Long-Term Care

ONTARIO LAUNCHES TRANSPARENCY IN PATIENT SAFETY INDICATORS

C. difficile Rates To Be Made Public Beginning September 30th
As McGuinty Government Strengthens Reporting Regulations

NEWS

May 28, 2008
2008/nr-28

The Ontario government is introducing full public reporting on eight patient safety indicators – including Clostridium difficile (C. difficile) – as part of a comprehensive plan to create an unprecedented level of transparency in Ontario's hospitals.

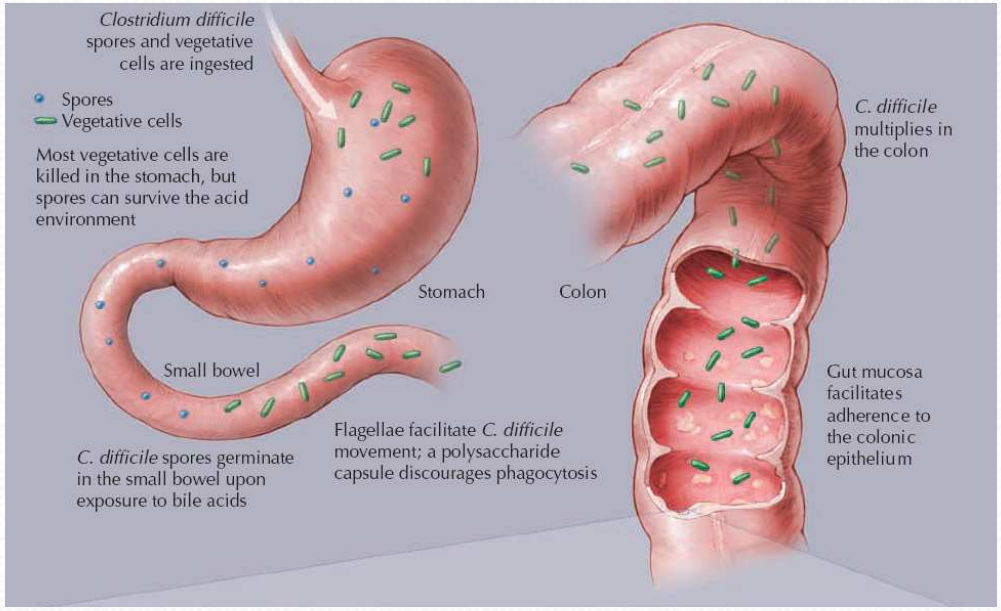
On September 30, 2008, all Ontario hospitals will be required to publicly report on C. difficile rates in their facilities through a public website.

As part of this comprehensive initiative, Dr. Michael Baker, physician-in-chief at the University Health Network, is being appointed Executive Lead – Patient Safety to oversee the government's patient safety agenda. He will build upon initiatives already taken such as the hospital hand hygiene program.

The list of patient safety indicators is:

Patient Safety Indicator	Start Date of Public Reporting
Clostridium difficile (C. difficile)	Sept. 30, 2008
Methicillin-resistant Staphylococcus aureus (MRSA)	Dec. 31, 2008
Vancomycin-resistant Enterococci (VRE)	Dec. 31, 2008
Hospital Standardized Mortality Ratio (HSMR) – mortality rates	Dec. 31, 2008
Rates of ventilator-associated pneumonia	April 30, 2009
Rates of central line infections	April 30, 2009
Rates of Surgical site infections	April 30, 2009
Hand hygiene compliance among health care workers	April 30, 2009

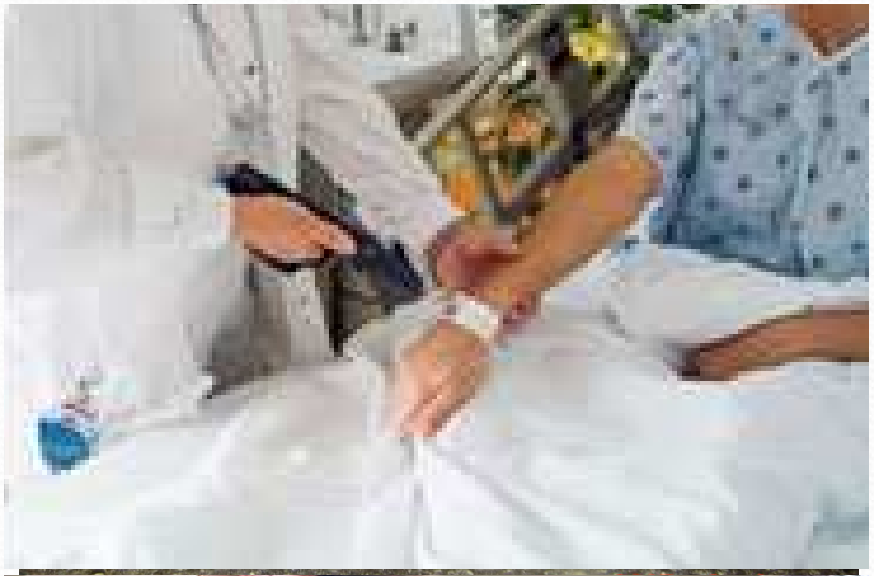
How can hospitals prevent C.difficile?



- decrease transmission
  - hand hygiene
  - gloves, gowns, isolation
  - environmental cleaning
- decrease susceptibility
  - minimize & optimize antimicrobial use

RFID: Radiofrequency Identification

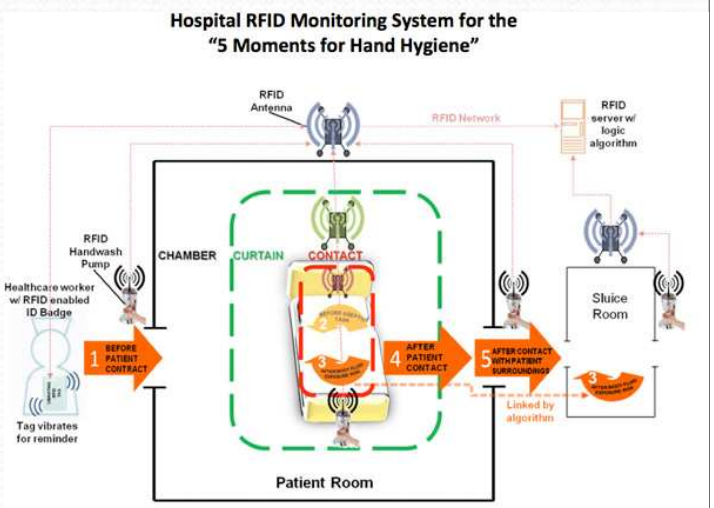
(Sunnybrook & Canadian Aerospace Engineering collaborative innovation…)



RFID and Healthcare:

- The Ultimate Goal (and the Mathematical Modelers' dream)
  - a living laboratory of confidential, de-identified data on the way health care delivery happens

- Pilot study: hand-washing
  - better way of measuring hand washing
  - novel ways of encouraging hand washing



Decreasing Susceptibility: Antibiotic Stewardship

- antibiotics are ubiquitous in hospitals
- much of antibiotic use is unnecessary
- it doesn't take much antibiotic to cause C.diff colitis
- …we need antimicrobial stewardship

Antibiotics are Ubiquitous in Hospitals

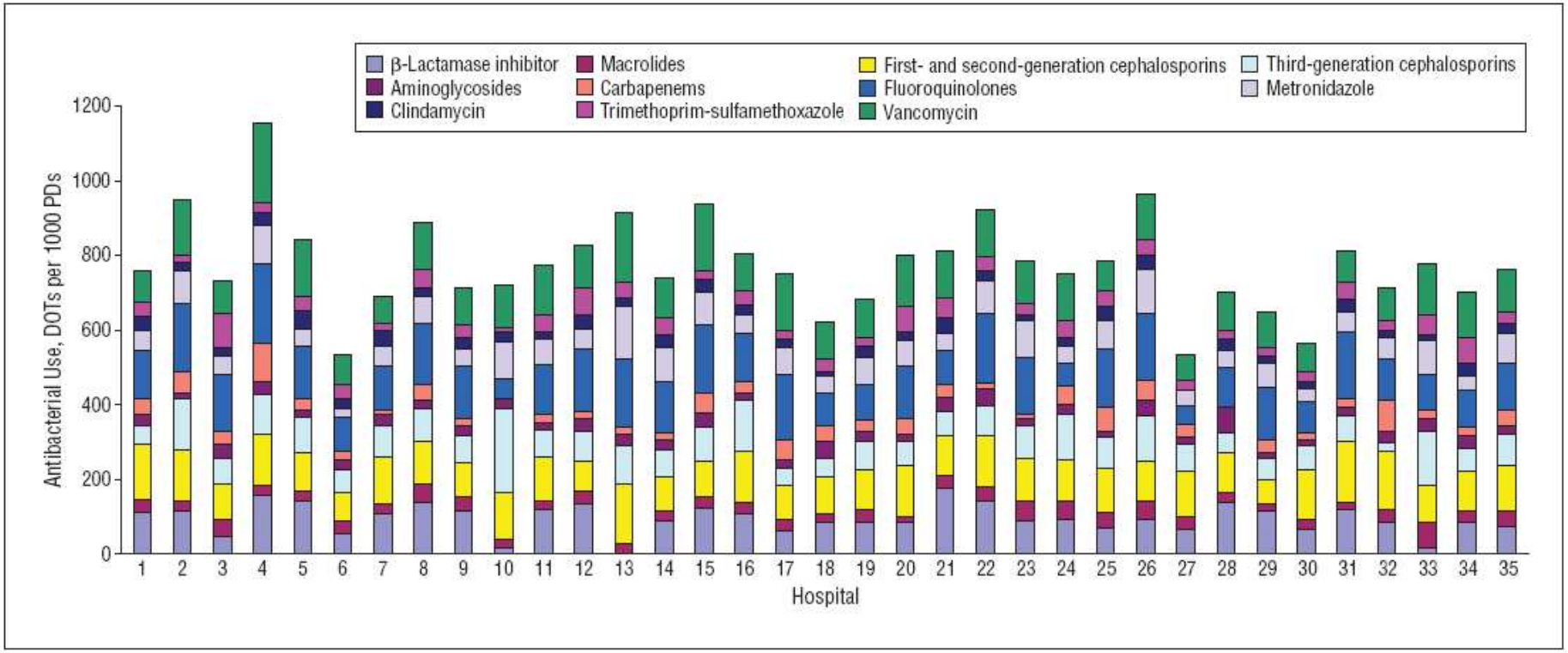


Figure 1. Antibacterial drug use (in days of therapy [DOTs] per 1000 patient days [PDs]) at 35 US academic health centers in 2006. The height of each bar represents the total antibiotic use, and the composition of each bar represents 11 different antibacterial classes. The total use for a single agent reflects the sum of all oral and parenteral dosage formulations.

Pakyz *Arch IM* 2008

Much of Antibiotic Use is Unnecessary

- 2 week study in one U.S. hospital
- 1941 days of antibiotic therapy prescribed
- 576 (30%) deemed unnecessary
- common examples
  - nonbacterial syndromes
  - unnecessary prophylaxis
  - colonization and contamination
  - excessive duration of treatment …

Hecker *Arch IM* 2003

It doesn't take much…

Table 2. Risk of *Clostridium difficile* infection (CDI) according to intensity of antibacterial therapy used during hospitalization.

Variable	No. of surgical procedures	No. of patients who developed CDI	Risk of CDI, no. of cases per 1000 surgical procedures
No antibacterial therapy	389	0	0
Prophylaxis only	5502	40	7.3
Prophylaxis and treatment	2098	55	26.2
Treatment only	378	3	7.9

Carignan *CID* 2008

Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America Guidelines for Developing an Institutional Program to Enhance Antimicrobial Stewardship

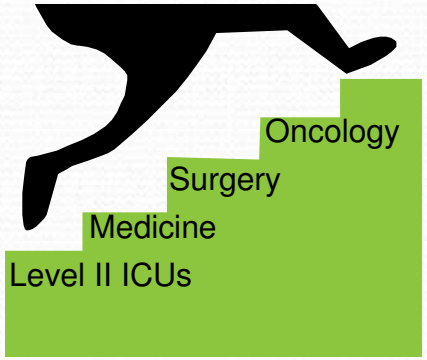
Timothy H. Dellit,[1] Robert C. Owens,[2] John E. McGowan, Jr.,[3] Dale N. Gerding,[4] Robert A. Weinstein,[5] John P. Burke,[6] W. Charles Huskins,[7] David L. Paterson,[8] Neil O. Fishman,[9] Christopher F. Carpenter,[10] P. J. Brennan,[9] Marianne Billeter,[11] and Thomas M. Hooton[12]

[1]Harborview Medical Center and the University of Washington, Seattle; [2]Maine Medical Center, Portland; [3]Emory University, Atlanta, Georgia; [4]Hines Veterans Affairs Hospital and Loyola University Stritch School of Medicine, Hines, and [5]Stroger (Cook County) Hospital and Rush University Medical Center, Chicago, Illinois; [6]University of Utah, Salt Lake City; [7]Mayo Clinic College of Medicine, Rochester, Minnesota; [8]University of Pittsburgh Medical Center, Pittsburgh, and [9]University of Pennsylvania, Philadelphia, Pennsylvania; [10]William Beaumont Hospital, Royal Oak, Michigan; [11]Ochsner Health System, New Orleans, Louisiana; and [12]University of Miami, Miami, Florida

The Answer

- Antimicrobial Stewardship
- multidisciplinary (Infectious diseases physicians and pharmacists)
- core strategies
  - prospective audit and feedback to providers
  - formulary restriction and preauthorization
- key targets
  - broad-spectrum agents
  - intensive care units

Stepped-wedge
randomized controlled trial



MOHLTC
AFP Innovation Award

Dellit *CID* 2008

A call for mathematical modeling:

Where is the greatest yield for prevention…

decreasing transmission

OR

decreasing patient susceptibility?

Spatio-temporal stochastic modelling of *Clostridium difficile*

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- spatio-temporal model of C.diff
- Markov chain Monte Carlo simulation
- validated against 17 mos of data from 2 hospital wards

• halving transmission rates	15% reduction C.diff
• doubling environmental load	3% increase C.diff
• doubling susceptibility	63% increase C.diff

JHI 2008

Hospital Predictors of C.difficile colitis: Natural Experiment in Ontario

- Research Question
  - What hospital characteristics are associated with reduced rates of *C.difficile* colitis?

- Population-based cohort
  - all hospitalizations in Ontario 2002 – 2009
    Canadian Institute for Health Information (CIHI)

    - 8,000,000 admissions
    - 157 hospitals, 228 distinct sites
    - >40,000 cases of *C.difficile*
    - specificity >99%, specificity 88%†

†Scheurer Epi Inf 2007

Hospital Predictors of C.difficile colitis: Natural Experiment in Ontario

- Statistical analysis:
  - multi-level modelling
  - adjust for patient level characteristics:
    - age, comorbidity…

- Hospital Characteristics
  - structures — eg, infection control staffing
  - processes — eg, isolating patients prior to test results
  - implementation strategies — eg, laboratory based alert system

Summary

- C.difficile is already among our most burdensome infections…
- …and incidence and severity are increasing

- C.difficile disease depends on:
  - acquisition of the organism
  - antibiotic depletion of normal intestinal flora
- treatment involves
  - supportive therapy
  - removal of inciting antibiotic agent
  - C.difficile specific antibiotic therapy (vancomycin vs. metronidazole)
  - rarely surgery
- prevention involves
  - minimizing transmission
  - minimizing host-susceptibility
- plenty of uncertainty about how to optimize treatment and prevention