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# Molecular epidemiology of *Clostridium difficile* infection in British Columbia, Canada

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# Objectives

- Molecular typing methods for *C. difficile*
- Prevalence & incidence of *C. difficile* infection (CDI)
- Risk factors & sources associated with CDI
- Molecular epidemiology of CDI in British Columbia from recent studies

## *Clostridium difficile* infection (CDI)

- *C. difficile* is becoming the most common pathogen of healthcare–associated (HA) infections
- The epidemiology of CDI is changing

An understanding of *C. difficile* epidemiology is necessary to understand CDI diagnosis and guide infection prevention and control practices



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# THE PAST

# Historical Burden of HA-CDI

1970's: report of severe diarrhea and pseudomembranous colitis associated with clindamycin use in a hospital setting, followed by association with toxin-producing *Clostridium*



Tedesco, Barton, and Alpers (1974) Ann Intern Med

Bartlett, Chang, and Gurwith (1978) N Engl J Med

# Historical Burden of HA-CDI

- The hospital environment is contaminated with *C. difficile* spores that can persist for weeks and are resistant to detergent-based cleaners
- *C. difficile* can be transmitted from patients with CDI and from asymptotically colonized patients through the hands of healthcare workers or contaminated surfaces and objects

Gerding and Lessa (2015) Infect Dis Clin North Am

# Molecular Epidemiology

Evaluation of strain diversity & transmission dynamics

Limitation: no universal, sensitive, reproducible method

- Toxinotyping
  - DNA patterns based on toxin genes
- **Pulsed field gel electrophoresis (PFGE)**
  - DNA pattern based on genome fragmentation by an enzyme
- **Restriction endonuclease analysis (REA)**
  - DNA pattern based on genome fragmentation by an enzyme, more frequent cutting than in PFGE
- **PCR Ribotyping**
  - DNA patterns based on 16S and 23S ribosomal RNA
- Multilocus variable number tandem repeat analysis (MLVA)
  - DNA pattern based on the copy number of parts of a gene

# Historical Burden of HA-CDI

- *C. difficile*: diverse group of organisms
- New strains are frequently introduced to hospitals, some of which result in hospital transmission to multiple patients, whereas most are sporadic and result in few or no transmissions
  - Variations in types geographically and among institutions
  - Variations in types between years and seasons

Gerding and Lessa (2015) Infect Dis Clin North Am



# Historical Burden of HA-CDI

## BI/NAP1/027 emergence in early 2000's

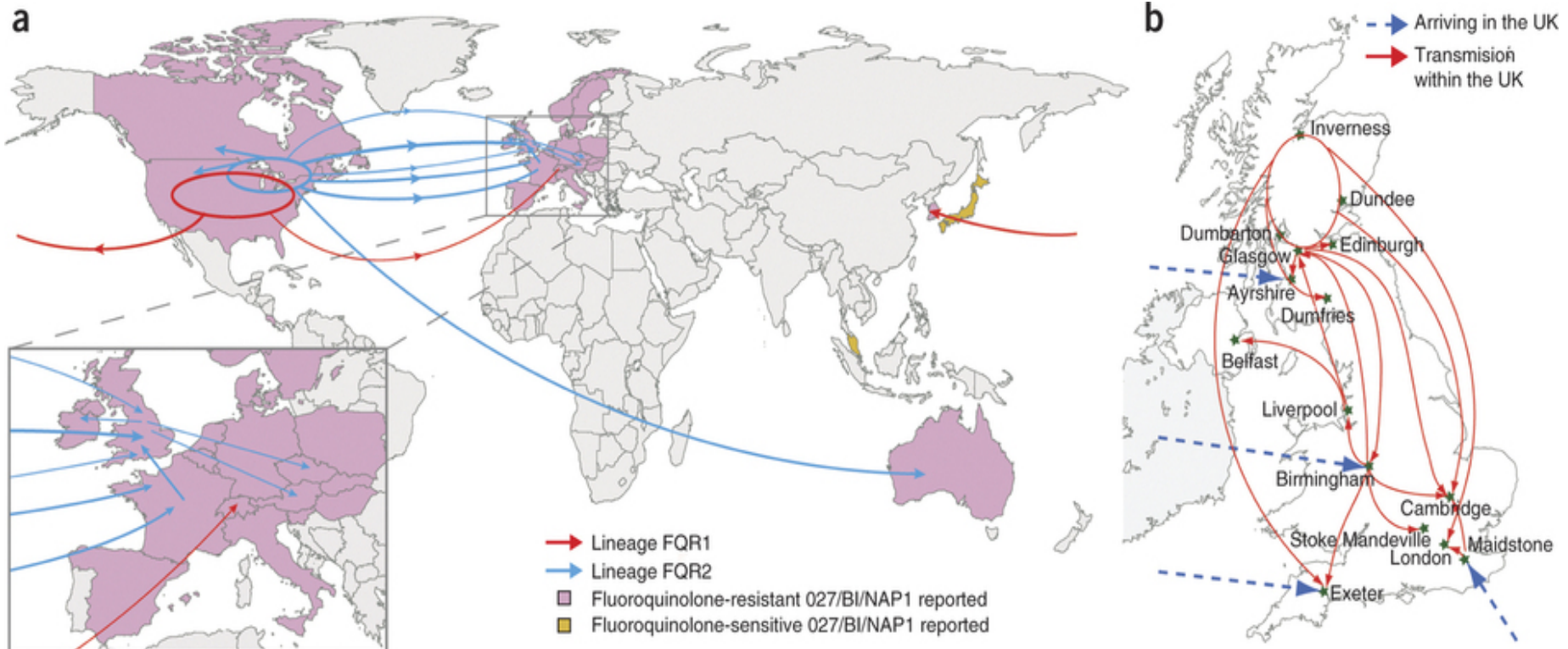
- Increases in CDI incidence, particularly in the Northeast within North America, largely attributed to the emergence of this strain
- North American pulsotype 1 (NAP1) strain is fluoroquinolone-resistant and associated with severe disease and death

Gould and McDonald (2012) Clin Infect Dis  
See, Mu, Cohen et al (2014) Clin Infect Dis  
Rao *et al.* (2015) Clin Infect Dis

# Global Spread of NAP1 *C. difficile*

By whole-genome sequencing & phylogenetic analysis:  
two lineages emerged in North America

He *et al.* (2013) Nature Genetics

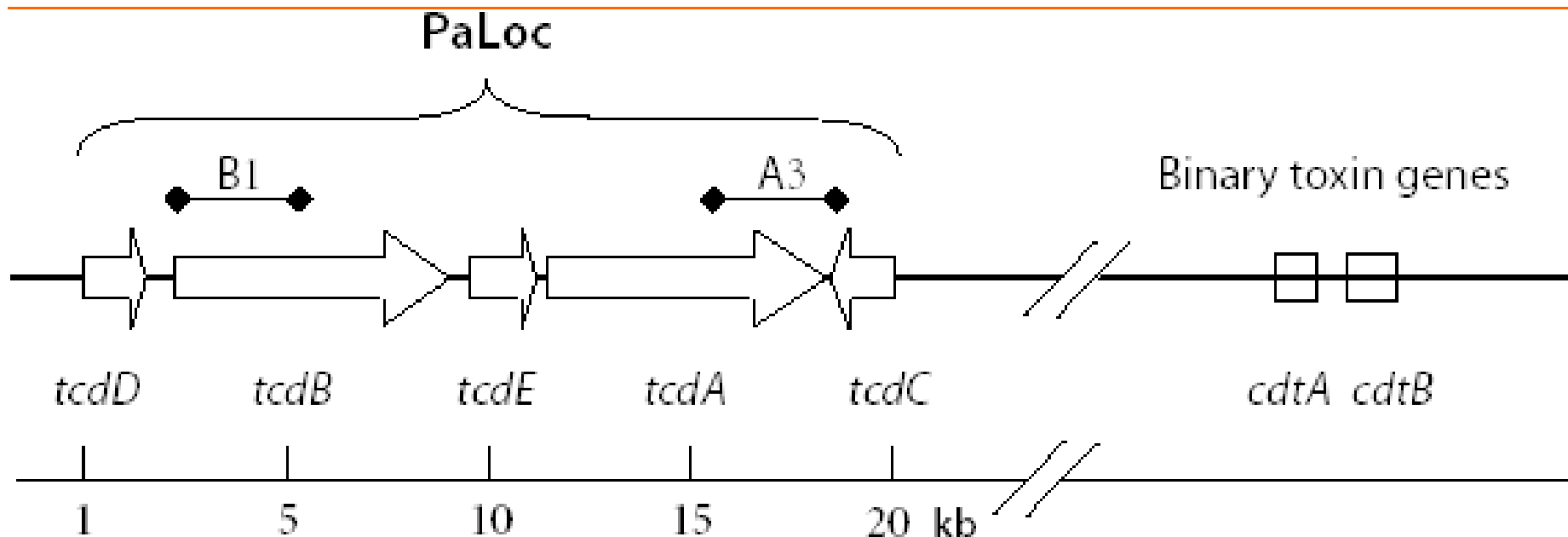


# Characteristics of NAP1 *C. difficile*

Produces toxin A, toxin B, binary toxin, and contains deletions in the repressor of toxins A/B (*tcdC*):

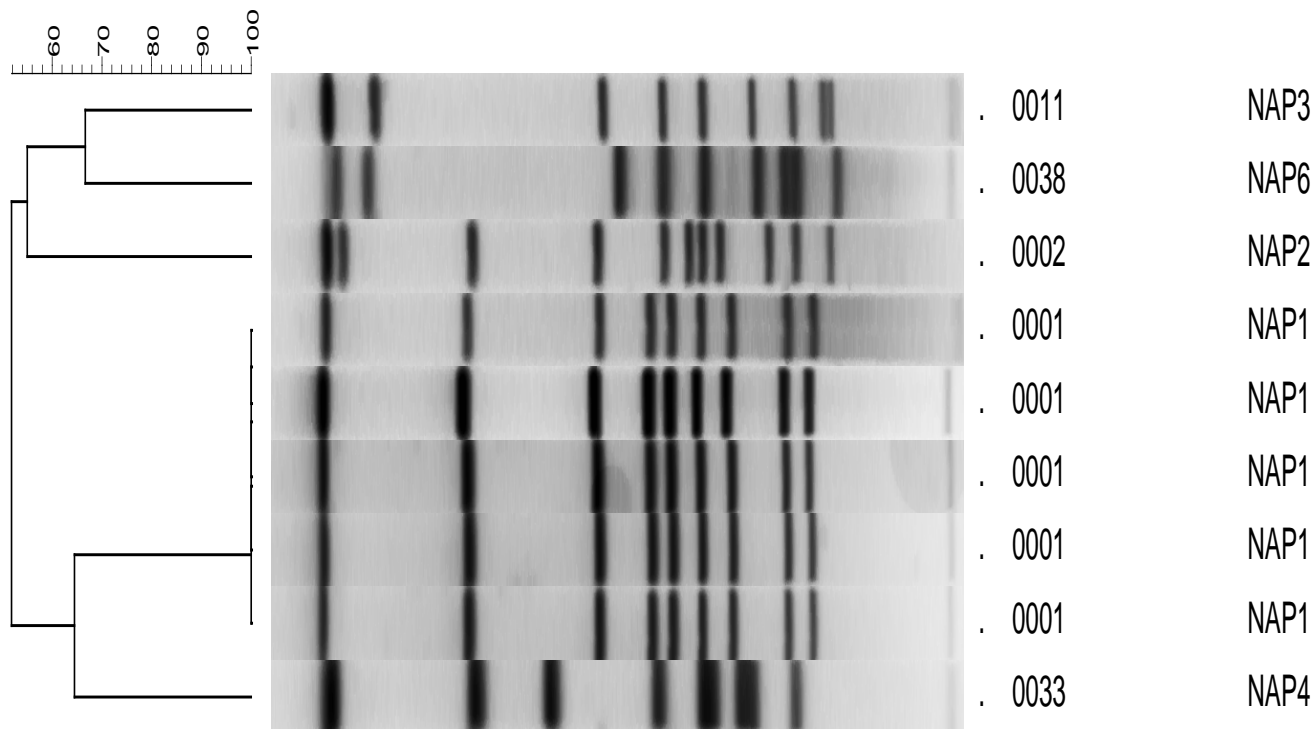
“hypervirulent” strain?

Murray (2009) BMC Infect Dis



# NAP1 *C. difficile* in British Columbia

At BCCDC Public Health Laboratory: DNA fingerprinting by pulsed field gel electrophoresis (PFGE)



# NAP1 in BC: 2008 Molecular Epidemiology Study

From 13 hospital labs & 1 province-wide community lab

- Collected toxin A/B positive stool or isolates in March
- N=341 isolates: 271 (79.5%) and 70 (20.5%), respectively
- **NAP1 designation accounted for 42.7% of isolates**
  - NAP2 for 10.2%, NAP4 for 13.5%, non-NAP for 21.3%

Jassem et al. (2016) Can J Infect Dis Med Microbiol. In press.

In collaboration with BC Provincial Infection Control Network & BC Association of Medical Microbiologists

# 2008 BC-wide Molecular Epidemiology

From 13 hospital labs & 1 province-wide community lab

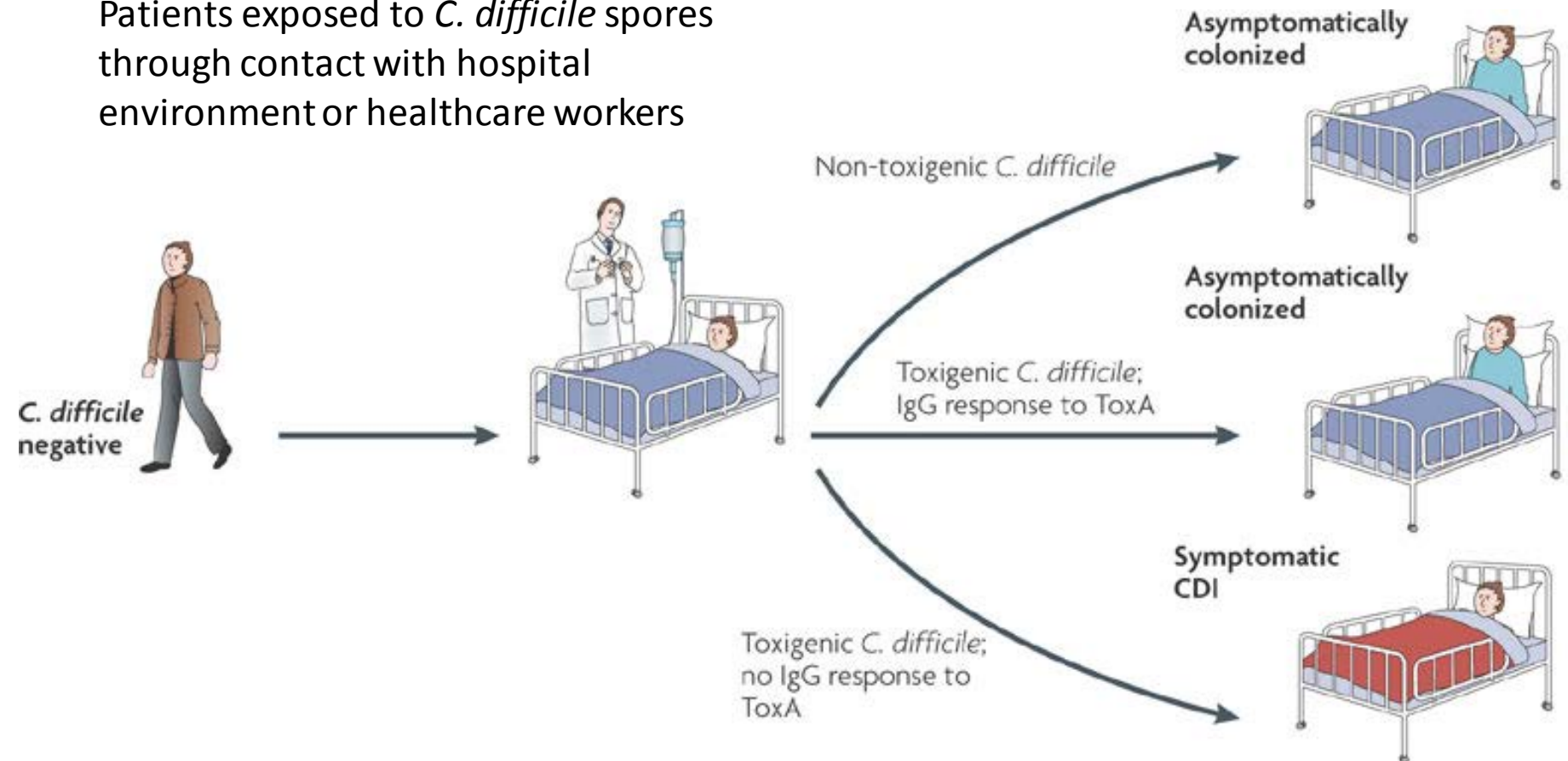
- Mean patient age was 69.3 years (median 77 years)
- **Patients at community sites were 15.4 years younger (mean 57.1 years) than those at hospital sites**
- NAP1 isolates were identified proportionally more at hospital sites (49.6% vs 15.7%), while **community sites had more non-NAP isolates (37.1% vs 17.3%)**

Jassem et al. (2016) Can J Infect Dis Med Microbiol. In press.

In collaboration with BC Provincial Infection Control  
Network & BC Association of Medical Microbiologists

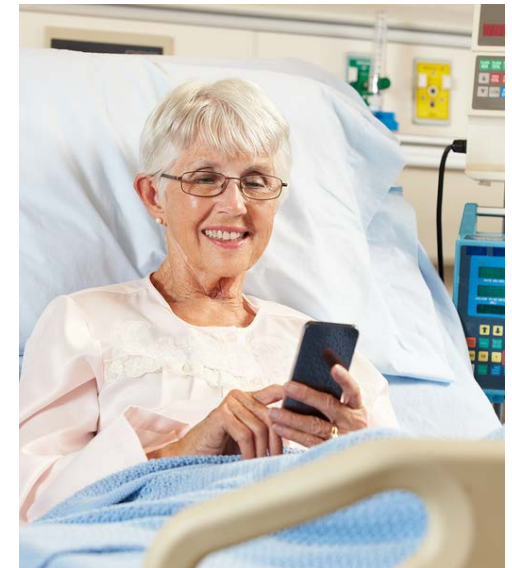
# Established Model for CDI Acquisition

Patients exposed to *C. difficile* spores through contact with hospital environment or healthcare workers



# Risk factors for developing HA-CDI

- Antimicrobial exposure
- Prior hospitalization
- Long duration of hospitalization
- Increased patient age
- Comorbidity
- PPIs and H2 antagonists
- Abdominal surgery



Evans and Safdar (2015) Clin Infect Dis

Gerding and Lessa (2015) Infect Dis Clin North Am

<http://www.illorem.com>





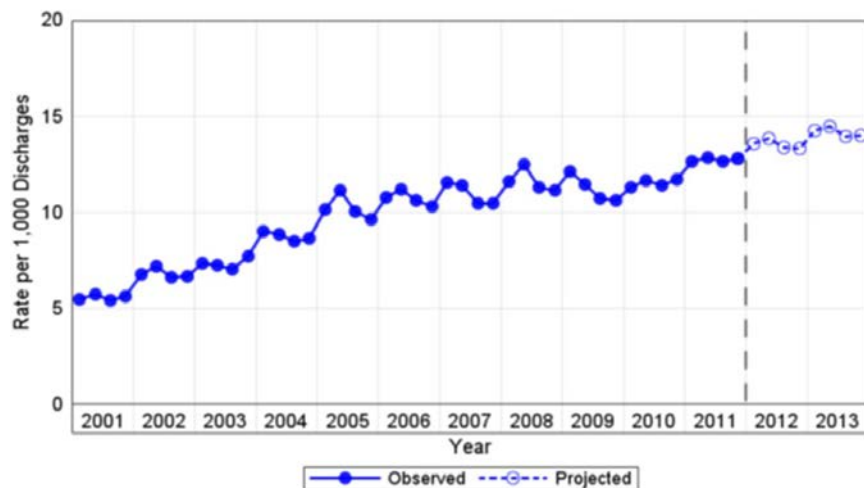
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# THE PRESENT

# Current Burden of HA-CDI in US

- *C. difficile* is the most commonly reported pathogen (12.1% of HAIs in 10 states in one study), surpassing *Staphylococcus aureus*
  - Rates of CDI in US hospitals have increased steadily since 1993 to more than 336,000 in 2009



Magill *et al.* (2014) N Engl J Med  
Lucado, Gould, Elixhauser (2011) US Dept Health Human Services  
Evans and Safdar (2015) Clin Infect Dis

# Current Burden of HA-CDI in Canada

## *Clostridium difficile* Associated Disease (CDAD) Surveillance



**Number of Healthcare-Associated-*Clostridium difficile* infection cases and incidence rate per 10,000 patient days by region**

	Rate per 10,000 patient days							
	Region							
	<i>Western</i>		<i>Central</i>		<i>Eastern</i>		<i>Overall</i>	
	No.cases	Rate	No.cases	Rate	No.cases	Rate	No.cases	Rate
<b>2007</b>	1,180	6.06	1,831	8.22	260	3.95	3,271	6.77
<b>2008</b>	1,060	8.06	1,597	7.36	256	3.86	2,913	7.02
<b>2009</b>	683	6.87	1,401	5.91	161	3.19	2,245	5.80
<b>2010</b>	1,251	6.84	1,266	6.76	155	2.27	2,672	6.09
<b>2011</b>	1,170	6.10	1,910	8.37	101	2.88	3,181	6.99

# Current Burden of HA-CDI in Canada

From 2007 to 2012:

- Overall rates peaked in 2008, then remained stable
- NAP1 strain type were the most dominant type followed by NAP4

2012: estimated 37,900 CDI episodes (27% recurrence)

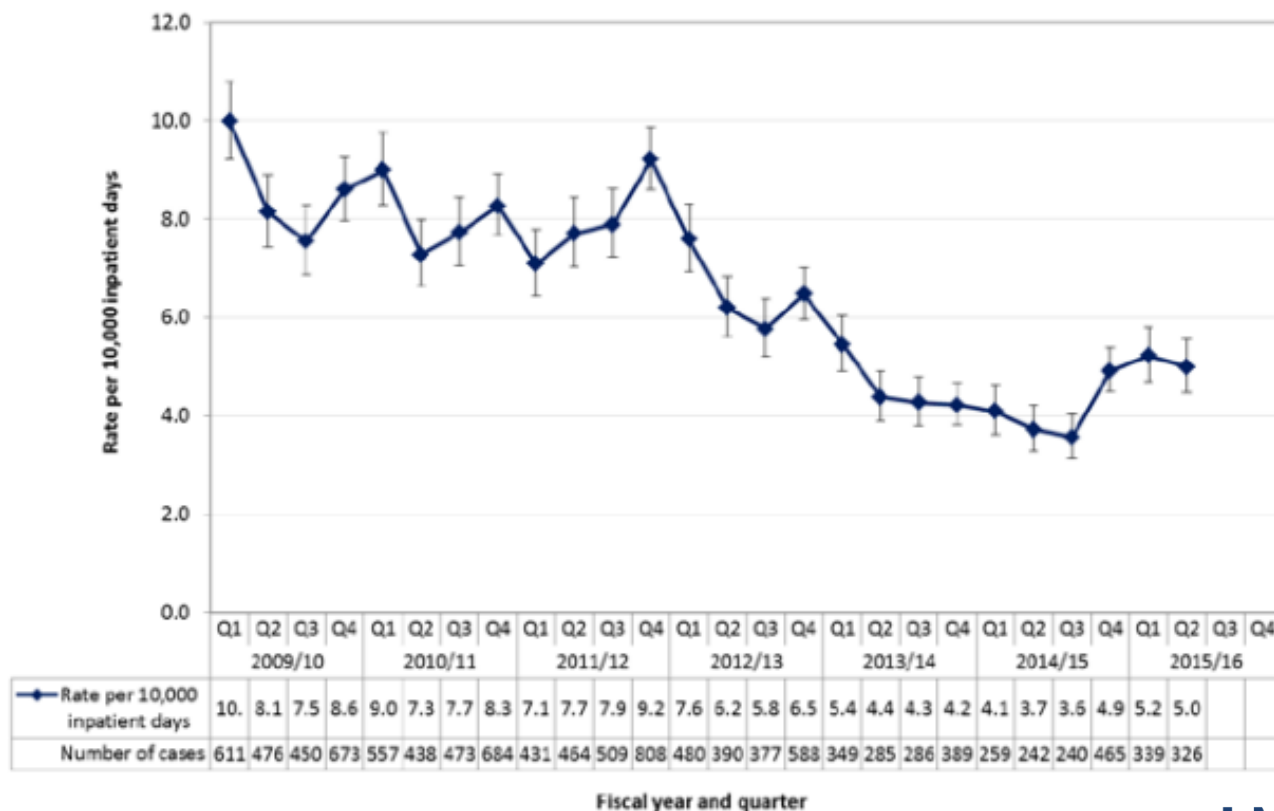
Canadian Nosocomial Infection Surveillance Program (CNISP)  
Healthcare-Associated Clostridium difficile Infections in Canadian Acute-Care  
Hospitals – Surveillance Report January 1<sup>st</sup>, 2007 to December 31<sup>st</sup>, 2012  
Levy *et al.* (2015) Open Forum Infect Dis.

# Current Burden of HA-CDI in BC

- 2,260 CDI cases reported in 2014/15
  - A 4.9% decrease from 2013/14 and the lowest annual number since 2009/10
- Rate of new CDI in 2014/15 was 4.2 per 10,000 inpatient days
  - A 51.2% decrease from 2009/10
- No diagnostic changes in past two years
- Decreases attributed to intervention measures?

# Current Burden of HA-CDI in BC

**Figure 1. Number of new cases and rate of CDI associated with the reporting facility, by fiscal year and quarter, British Columbia<sup>1</sup>**



But...

# Changing epidemiology of HA-CDI

- $\geq 30\%$  of diarrheal deaths in the elderly occur in nonhospital care settings, like **long-term care facilities** (LTCFs)
- Incidence and recurrence rates of CDI in LTCFs are comparable to those of acute-care hospitals
- There have been several outbreaks of CDI in LTCFs
- CDI risk factors in LTCFs are previous antibiotic use and frequent transitions between hospitals and LTCFs

# Community-associated (CA) CDI

- In the 2000's: first reports of CDI in the community
- Incidence of CA-CDI suggested to be increasing across Europe & North America and **occurring in younger (median 53 vs 78 years), healthier persons, with fewer risk factors associated with HA-CDI**
- Patients with CA-CDI are less likely to recur than HA-CDI (10% vs 20%)

CDC (2005) MMWR Morb Mortal Wkly Rep

Dumyati *et al.* (2012) Emerg Infect Dis

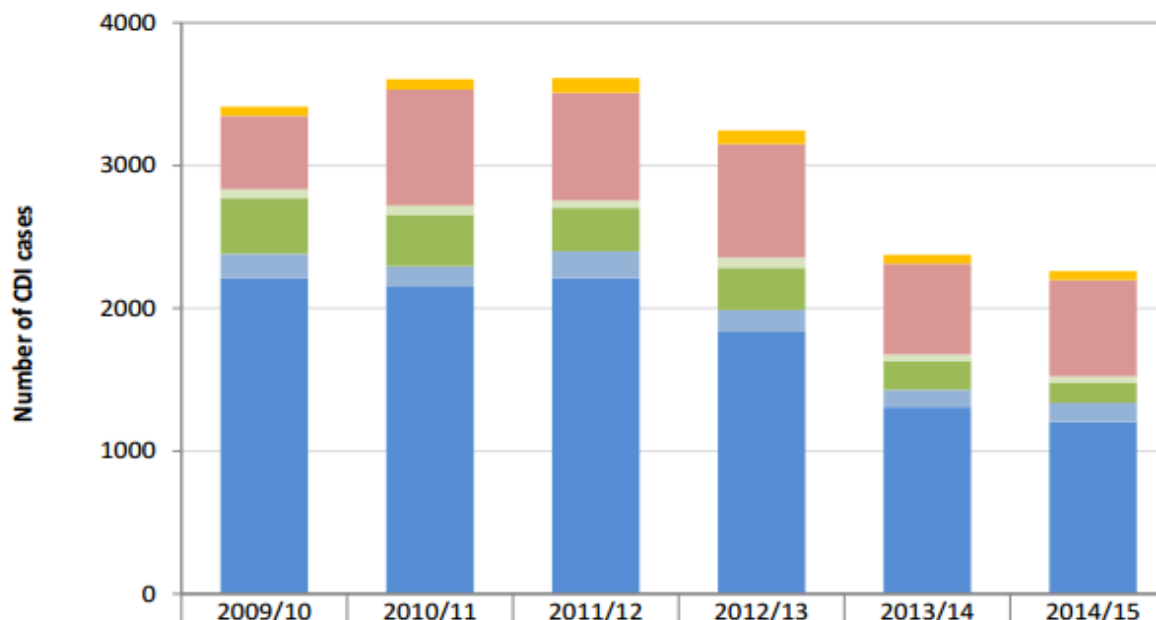
Lessa *et al.* (2012) Clin Infect Dis

Gerding and Lessa (2015) Infect Dis Clin North Am





# Prevalence of CA-CDI in BC

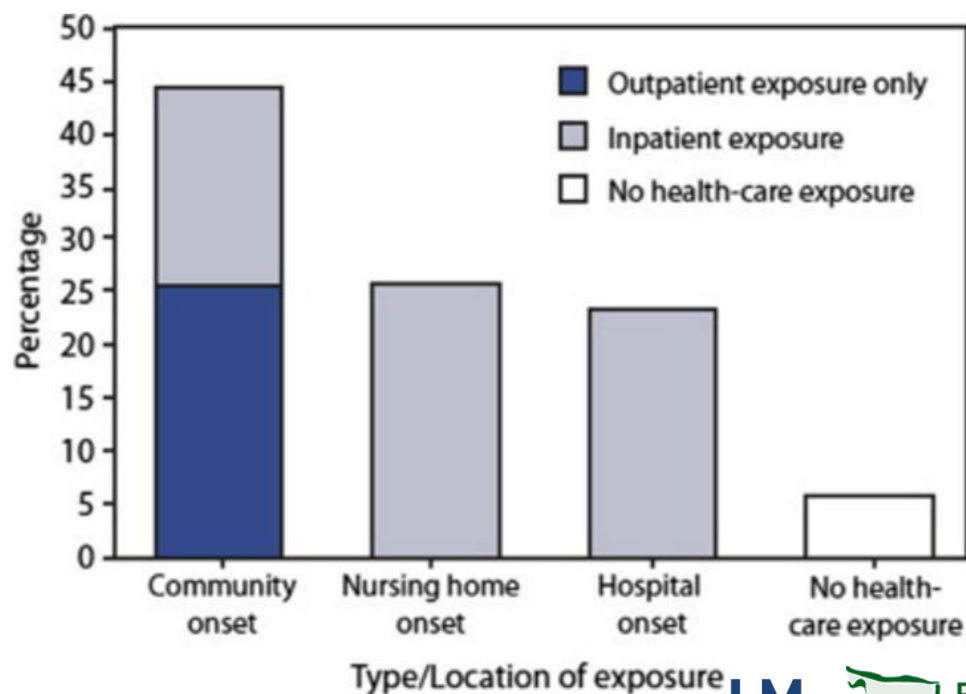


	2009/10	2010/11	2011/12	2012/13	2013/14	2014/15
Unknown	63	72	104	96	63	62
CA	516	812	753	794	636	674
HCA with another facility, relapse	62	63	54	71	46	47
HCA with reporting facility, relapse	390	362	302	297	201	139
HCA with another facility, new cases	171	143	188	153	121	132
HCA with reporting facility, new cases	2,210	2,152	2,212	1,835	1,309	1,206
<b>Total number of CDI cases</b>	<b>3,422</b>	<b>3,604</b>	<b>3,613</b>	<b>3,246</b>	<b>2,376</b>	<b>2,260</b>

# Changing epidemiology of CDI

CDI acquisition is occurring in the outpatient setting and in those with no healthcare exposure

% of CDI cases (n=10,342) by inpatient or outpatient status and type/location of exposure



## Shifts in *C. difficile* strain types

- In some European hospitals the circulation of BI/NAP1/027 strains is decreasing
- **Several countries are reporting emergence of non-BI/NAP1/027 stains**, mostly in healthcare settings
  - Ribotypes 078 (NAP7), 244, 012, 017, 018, 014/20, 106, 015
  - Data on strain types in persons in the community are sparse
  - In North America, still NAP1 dominance?

Goorhuis *et al.* (2008) Clin Infect Dis

Lim *et al.* (2014) Clin Infect Dis

Baldan *et al.* (2015) J Clin Microbiol

Bauer *et al.* (2011) Lancet

Cairns *et al.* (2015) J Clin Microbiol

De Almeida *et al.* (2013) NZ Med J

Quesada-Gomez *et al.* (2015) J Clin Microbiol

Hensgens *et al.* (2009) Euro Surveill

Wilcox *et al.* (2012) Clin Infect Dis

Lessa *et al.* (2015) N Engl J Med

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LABS

## Diversity of *C. difficile*

- *C. difficile* strains are naturally diverse and can evolve rapidly into those with increased pathogenicity
- Epidemic strains result in outbreaks, but then diminish in frequency and are replaced by new types
- New *C. difficile* strains are frequently introduced to hospitals from a large pool of strains

Stabler *et al.* (2006) J Bacteriol

He *et al.* (2010) Proc Natl Acad Sci

Gerding and Lessa (2015) Infect Dis Clin North Am



# 2013 BC Follow-Up Study

Specimens from 1 hospital lab within Island Health

- Collected toxin B positive stools from March-July (n=68)
- Proportion (%) of community-associated inpatient cases:

2008	2009	2010	2011	2012	2013
11.7	17.0	22.0	28.3	34.5	35.6



Jassem et al. (2016) Can J Infect Dis Med Microbiol. In press.

# 2013 BC Follow-Up Study

Specimens from 1 hospital lab within Island Health

- N=68 isolates: 38 (55.9%) HA- and 30 (44.1%) CA-CDI
- **Patients with CA-CDI were 16.2 years younger (mean 58.7 years) than those at hospital sites**
- **The proportion of non-NAP isolates was high in CA-CDI (50.0%) and HA-CDI (39.5%) cases**

Case definitions: medical record review discriminated between inpatients with CA-CDI and HA-CDI. Outpatients and inpatients with CA-CDI were collectively referred to as cases.

# 2013 BC Follow-Up Study

Specimens from 1 hospital lab within Island Health

- **Isolates not matching a NAP type accounted for 44.1%**
  - NAP1 for 11.8%, NAP4 for 22.1%, NAP6 for 11.8%
  - Among no NAPs, no dominant pattern or ribotype
- **Between 2008-13, there was a 28.9% decrease in NAP1 and 20.0% increase in isolates without NAP designation**

# 2013 BC Follow-Up Study

- Taken together, the high proportion of isolates not matching described NAP types among the 2008 community site-collected isolates & the 2013 CA-CDI isolates could relate to a shift of strains from community sources to the healthcare setting
- Therefore, the observed shift in NAP distribution between 2008 and 2013 in the Island Health Authority region could reflect the steady increase in the proportion of CA-CDI inpatient cases identified





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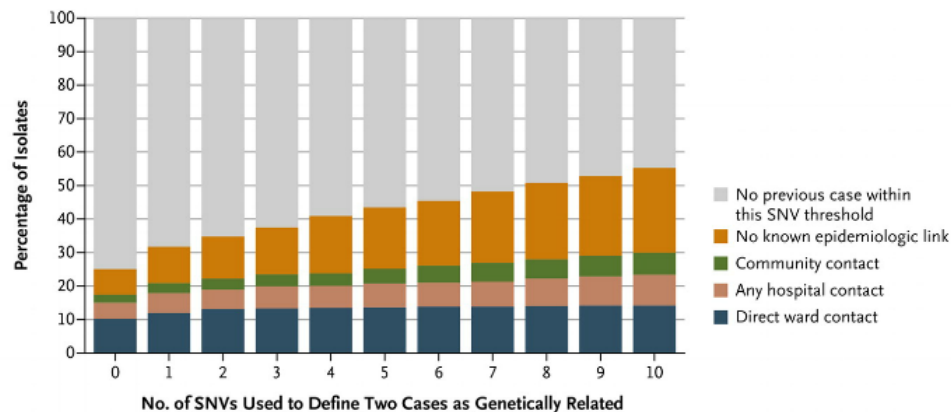
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# THE FUTURE

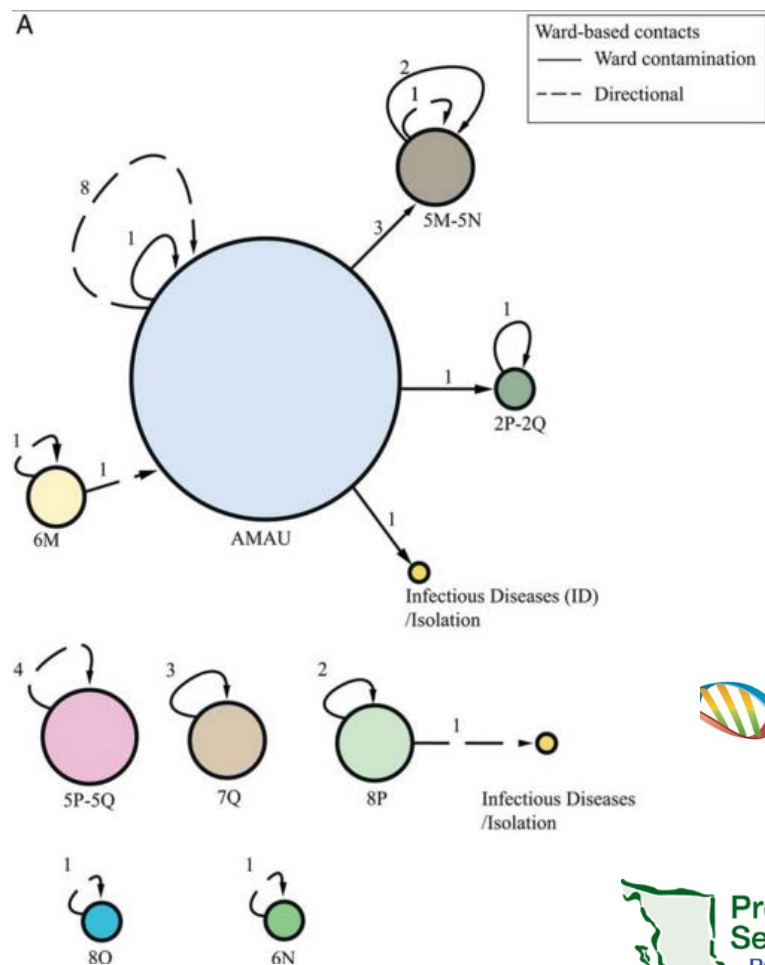
# Role of Whole Genome Sequencing

- WGS: a new method of *C. difficile* molecular typing
  - Most sensitive and specific typing method
- Pairing patient interaction and WGS data, a hospital in the UK found that for non-outbreak cases distinct sources other than symptomatic CDI cases are involved in most (62%) cases of CDI *C. difficile* transmission

Eyre *et al.* (2013) N Engl J Med

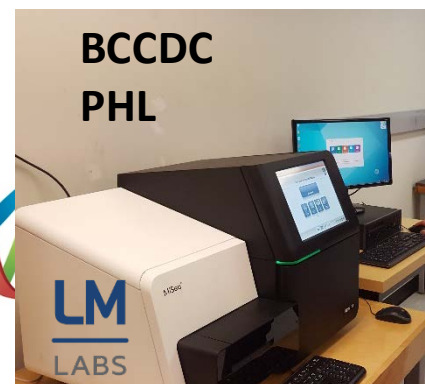


# Role of Whole Genome Sequencing



Study the dynamics of *C. difficile* transmission and CDI recurrence among symptomatic patients

Kumar *et al.* (2015) Clin Infect Dis



# Understanding Sources of CDI

- **Hospital exposures**, including asymptomatic carriers
- **Outpatient health care exposures**
  - Many CA-CDI cases have outpatient health care exposures (doctor/dentist offices, outpatient surgeries, etc) prior to CDI & *C. difficile* has been isolated from environmental surfaces in outpatient clinics
- **Exposure to household members with CDI & infants**
  - Association with increased risk of CA-CDI (infants have a high rate of *C. difficile* colonization)

# Understanding Sources of CDI

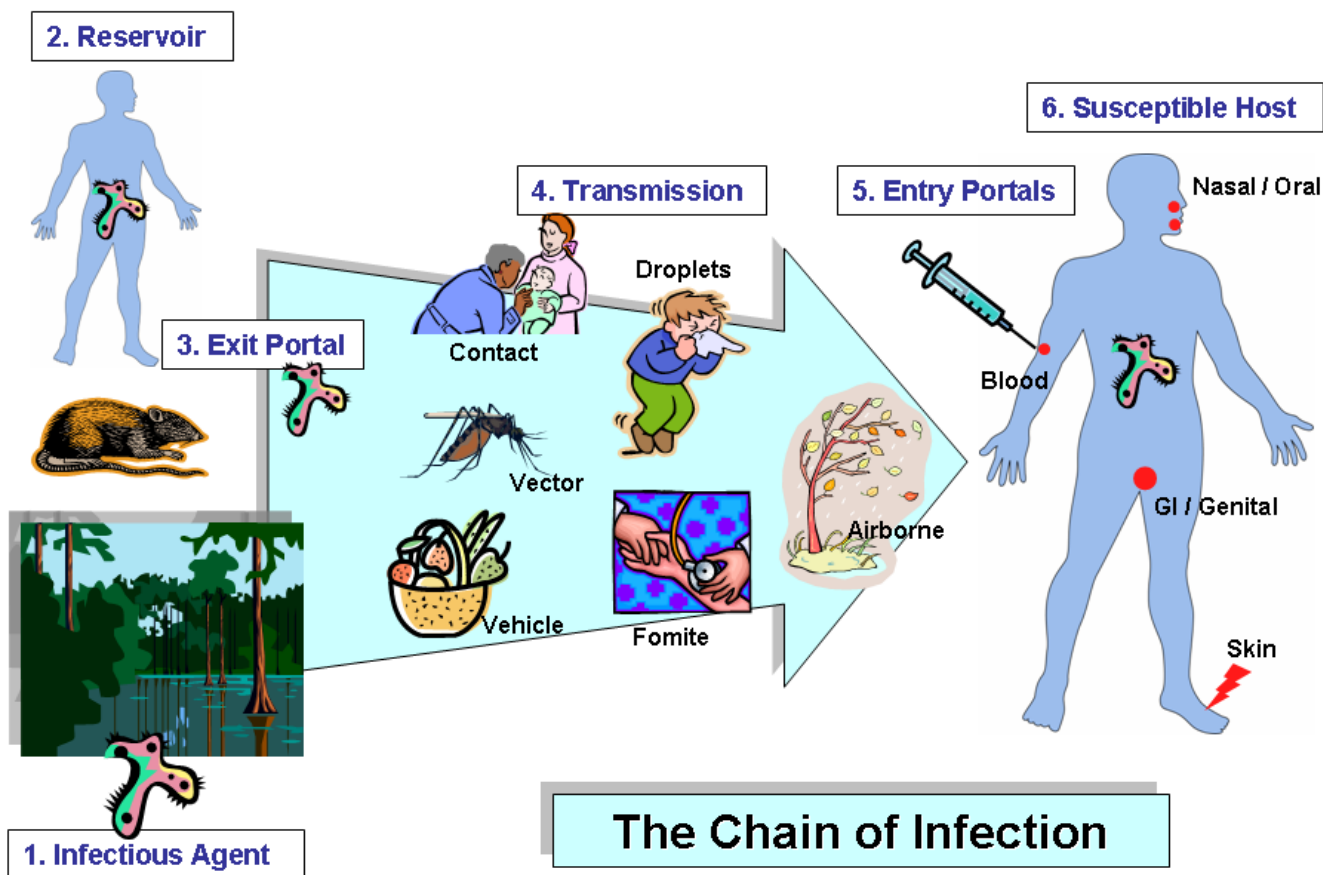
- ***C. difficile* has been isolated from food and animals**
  - Prevalence in retail meats <7%, in vegetables 3-5%
  - Widespread in dogs, cats, pigs, calves, horses, sheep
  - Ribotype 078 (NAP 7) mostly among animal sources
  - WGS showed that farmers and pigs were colonised with identical & nearly identical *C. difficile* clones
- ***C. difficile* has been isolated from soil, sewage, marine sediments, swimming pools, etc.**

# Actual Model of CDI?

+ strain type

Ex. NAP7 in animals

Ex. Toxin A-negative ribotype 017



# Molecular Epid for Prevention of CDI

- It is likely that humans ingest *C. difficile* frequently
- Comprehensive surveillance defining CA- and HA-CDI cases will elucidate sources of acquisition and transmission and identify emerging strains

- Strain description
- Sensitive techniques

## Meet Angus, *C. diff* fighting spaniel

SHARE

He's part of an innovative pilot and our newest weapon in the fight against *C. diff*

February 27, 2015



[www.vch.ca](http://www.vch.ca)

Bomers *et al.* (2012) BMJ

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LABS

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Better health.

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