



# Emerging Clostridial Infections in the USA



Nothing to Disclose



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*The findings and conclusions in this presentation are those of the author and do not necessarily represent the views of the Centers for Disease Control and Prevention*

# Large clostridial toxins and species



Toxin	Organism	Size (kDa)	Intracellular targets
TcdA	<i>C. difficile</i>	308	Rho, Rac, Cdc42
TcdB	<i>C. difficile</i>	270	Rho, Rac, Cdc42
TcsH	<i>C. sordellii</i>	300	Rho, Rac, Cdc42
TcsL	<i>C. sordellii</i>	270	Ras, Rac, Rap, Ral, (Cdc42) <sup>b</sup>
Tcn $\alpha$	<i>C. novyi</i>	250	Rho, Rac, Cdc42
TcdB-1470 <sup>a</sup>	<i>C. difficile</i> 1470	270	Ras, Rac, Rap, Ral, Cdc42

<sup>a</sup> TcdB-1470 is a hybrid between the TcdB cell entry domains and the TcsL enzymatic domain.

<sup>b</sup> Glucosylation of Cdc42 is strain specific in *C. sordellii*.

# *Clostridium sordellii* and black tar heroin, California, 1999-2000



Patient	Date of onset of symptoms	Pathogen(s) isolated				Disposition at discharge
		Organism 1	Organism 2	Organism 3	Organism 4	
1	14 Dec 1999	<i>Clostridium sordellii</i>	<i>Staphylococcus</i> species	...	...	Alive
2	28 Jan 2000	<i>Bacillus</i> species	...	...	...	Dead
3	30 Jan 2000	$\alpha$ -Hemolytic <i>Streptococcus</i> species	<i>Staphylococcus</i> species	...	...	Alive
4	1 Feb 2000	<i>C. sordellii</i>	<i>Clostridium perfringens</i>	...	...	Alive
5	4 Feb 2000	<i>C. sordellii</i>	<i>Staphylococcus</i> species	...	...	Alive
6	6 Feb 2000	$\alpha$ -Hemolytic <i>Streptococcus</i> species	...	...	...	Alive
7	21 Feb 2000	<i>C. sordellii</i>	<i>C. perfringens</i>	<i>Clostridium beijerinckii</i>	<i>Bacillus</i> species	Dead
8	1 April 2000	<i>C. sordellii</i>	...	...	...	Dead
9	8 April 2000	<i>C. sordellii</i>	$\alpha$ -Hemolytic <i>Streptococcus</i>	<i>Staphylococcus</i> species	...	Dead

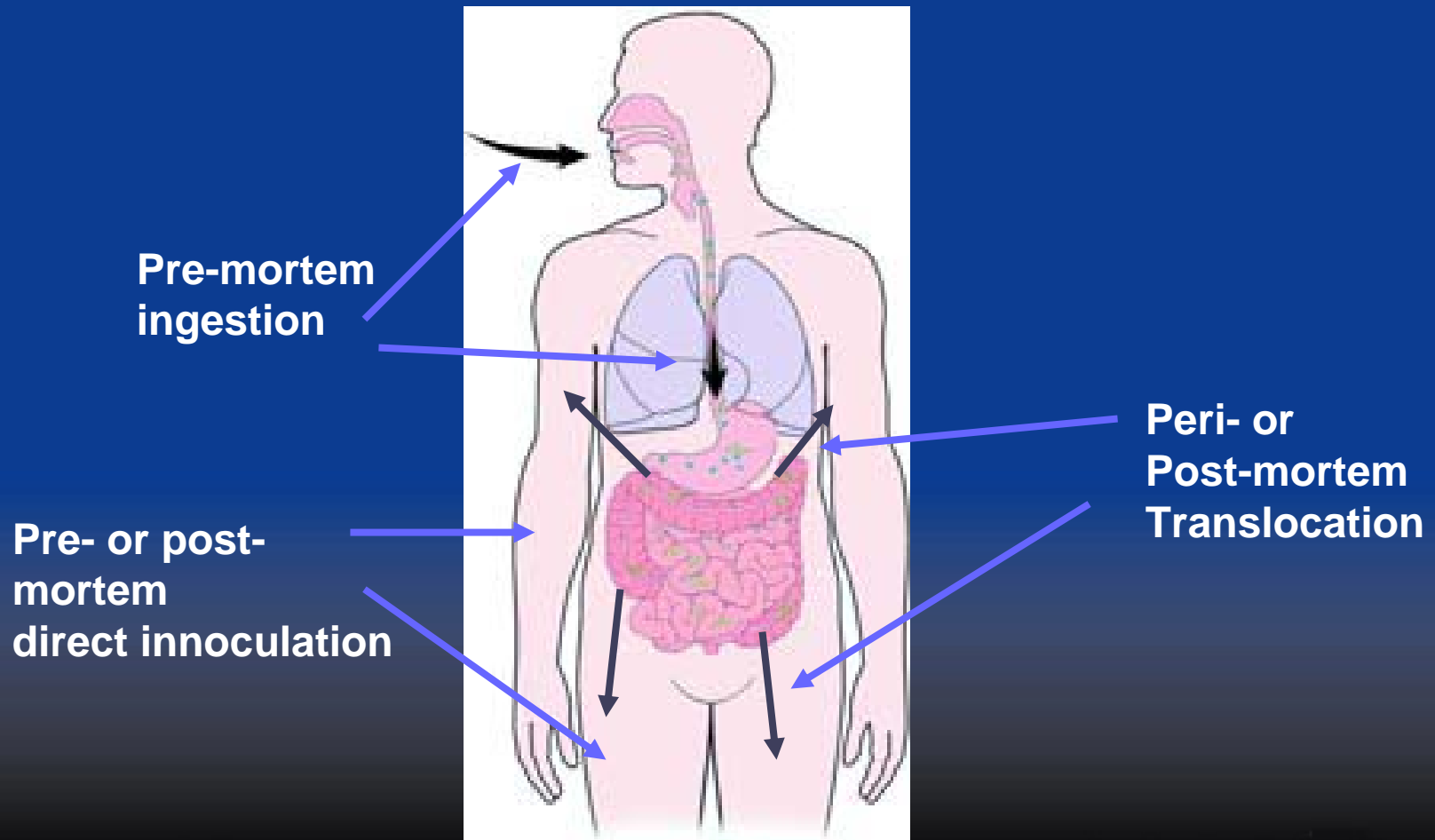
# *Clostridium* spp. infections in tissue allograft recipients (N=14), 1998-2002

- Demographics
  - Median age 32
  - 10 (71%) were male
- Tissues
  - 9 tendon (hemipatellar)
  - 4 bone (femoral condyle)
  - 1 cartilage (medial meniscus)
- Outcomes
  - One death (23 y.o. male)
  - All others required antibiotics, joint irrigation, debridement
  - 10 required allograft removal, 3 required joint replacement
- Microbiology
  - 12 *C. septicum*
  - 1 *C. sordellii*
  - 1 *C. bifermentens*

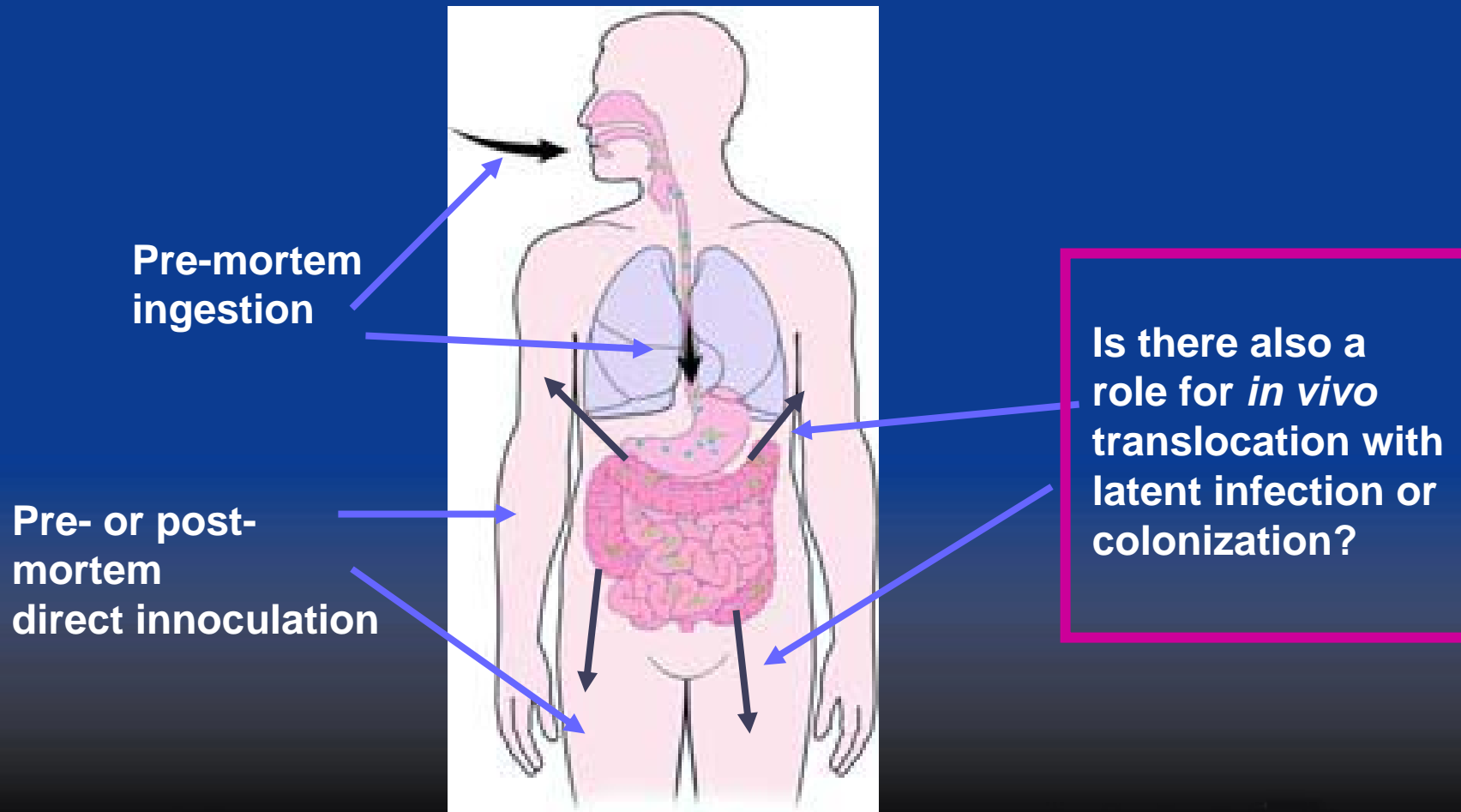
# *Clostridium* spp. infections in tissue allograft recipients and tissue bank A

Type of Tissue	No. of <i>Clostridium</i> Infections/ Total No. of Allografts (%)	Risk Ratio*	P Value
Musculoskeletal tissue			
Tissue Bank A	14/20,152 (0.07)	2898	<0.001
Other tissue banks	0/2,015,428		
Sports-medicine tissues			
Tissue Bank A	14/20,152 (0.07)	85	<0.001
Other tissue banks	0/59,284		
Tendons			
Tissue Bank A	9/16,354 (0.06)	64	<0.001
Other tissue banks	0/54,750		
Femoral condyles			
Tissue Bank A	4/1197 (0.33)	2.6	0.58
Other tissue banks	0/347		
Menisci			
Tissue Bank A	1/2600 (0.04)	—	1.00
Other tissue banks	0/173		

# How do *Clostridium* spp. contaminate human cadavaric (or infect living) musculoskeletal tissues?



# How do *Clostridium* spp. contaminate human cadavaric (or infect living) musculoskeletal tissues?



# Incidence of clostridial contamination in donors' musculoskeletal tissue

- 795 consecutive donor tissues cultured
  - Surgical excision of tissues
  - Samples of blood and bone marrow
- 64 (8.1%) had *Clostridial* spp.
  - 52 blood
  - 37 marrow
  - 30 tissue
  - 8 were positive in tissue only!
  - *C. sordellii* most common!

# Factors associated with clostridial contamination in donors' musculoskeletal tissue

- Death by drowning ( $P=0.02$ )
- Longer interval between death and excision ( $P<0.001$ )
  - Median 16 hours, 10 minutes in cases
  - Median 11 hours, 10 minutes in controls

# Clostridial toxic shock syndrome in medical or spontaneous abortion (n=8), 2001-8

- Characterized by rapidly progressive shock with abdominal pain, hypotension, and tachycardia
- Necrotizing endometritis
- Immunohistochemical stain positive for *Clostridium* spp.
- PCR of formalin fixed tissues positive for *C. sordellii* (n=6) or *C. perfringens* (n=2)
- 7 cases fatal
  - 1 non-fatal, *C. sordellii* infection was negative for Lethal toxin (TcsL)

# Clostridial toxic shock syndrome in medical or spontaneous abortion (n=8), 2001-8

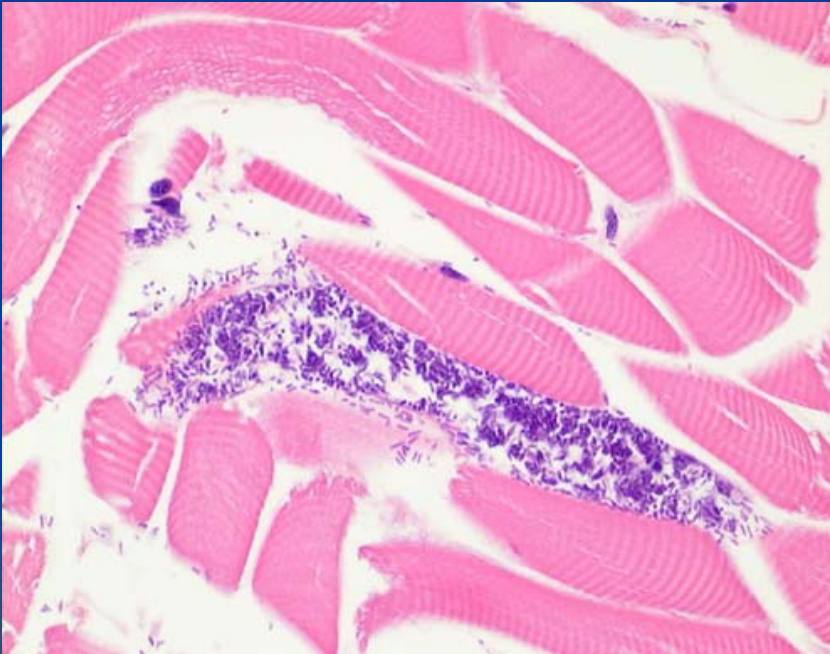
- 6 cases associated with mifepristone and mesoprostol induced abortion
  - 5 with intravaginal mesoprostol
- All 6 *C. sordellii* cases in western U.S. states
  - 5 on pacific coast
  - Not in proportion to regional practice of medical abortion
- *C. sordellii* cases associated with typical:
  - Lukemoid reaction
  - Edema and pleural effusions
  - Hemoconcentration



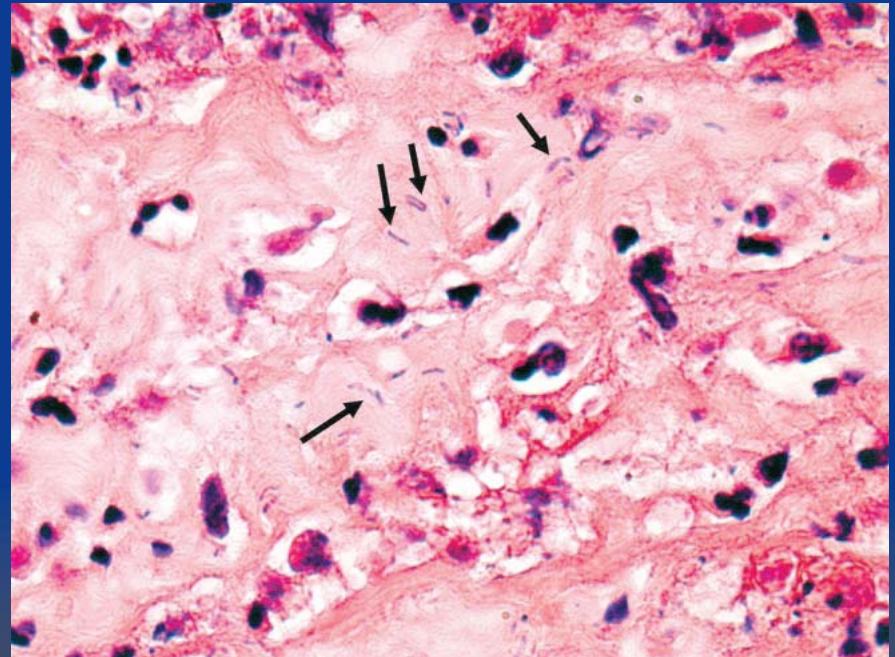
# Where did the *Clostridium* spp. originate to cause necrotizing endometritis?

- Vaginal/Cervical colonization?
- *In vivo* deposition of spores in uterine myometrium?
- Is there a predilection for either of these forms of colonization/latent infection in the western United States?

# Clostridial myonecrosis



Tsokos et al. *Int J Legal Med.* 2007;



Aldape MJ et al. *Clin Infect Dis* 2006; 43:1436–46

# Role for *in vivo* seeding in clostridial myonecrosis: illustrative case

- Healthy 4 y.o. boy with closed transverse fracture of arm
- Placed in cast, sent home
- Returned in 24 hours with pain and swelling
  - Muscle compartment pressures elevated
  - Hand “blackened”
- Volar fasciotomy of superficial and deep compartments
  - Cultures positive for *C. sordellii*
- Condition worsened post-operatively
  - Underwent second limb-sparing surgery
- Patient died with typical *C. sordellii* toxic shock

# Role for *in vivo* seeding in clostridial myonecrosis: illustrative case

- Healthy 37 y.o. man fell off a ladder
- Observed for small skull fracture and intracranial bleed
- Developed intermittent fever and confusion on day 3
  - Blood culture positive for *C. perfringens*
- Rising serum creatinine kinase suggesting myonecrosis
- Complaint of right shoulder pain
  - X-ray: subcutaneous emphysema
- Underwent surgical debridement on day 7 of admission
- Surgical cultures grew *C. perfringens*
- Recovered well post operatively

# Clostridial myonecrosis following closed trauma: illustrative cases



# Evidence for latent clostridial colonization in muscles of horses

- 52 horses undergoing euthanasia for non-infectious reasons
- Aseptic surgical excision of neck muscle
- Anaerobic broth culture of muscle and skin swab (control)
  - 16 *Clostridium* spp. from 10/52 horses
  - 3 *C. perfringens*, 3 *C. sporogenes*, 3 *C. butyricum*, 2 *C. botulinum*, 2 *C. clostridiforme*, 2 *C. histolyticum*, 1 *C. glycolicum*

# Dissemination of *C. novyi* to liver of guinea pigs and sheep

- “Well known” that livers of sheep become
  - “Latently infected” with *C. novyi*
  - Associated with grazing in contaminated fields
- Experimentally fed *C. novyi* spores
  - $1 \times 10^6$  in guinea pigs (N=42)
  - $5 \times 10^6$  in sheep (N=8)

# Dissemination of *C. novyi* to liver of guinea pigs (N=42)

DISTRIBUTION OF *Cl. novyi* TYPE B IN VARIOUS ORGANS IN GUINEA-PIGS AFTER ORAL ADMINISTRATION OF SPORES

		Time after administration of spores (h)						
		2	4	6	12	24	42	72
Number of guinea-pigs containing spores in each organ (6 animals in each group)	Stomach	6	6	6	6	5	3	1
	Small intestine	—	—	3	6	6	3	3
	Large intestine	—	—	—	3	6	5	3
	Liver	—	—	—	—	6	5	6
	Spleen	—	—	—	—	5	5	2
	Mesenteric lymph glands	—	—	—	4	5	1	—
	Peritoneal wash	—	—	—	1	—	—	—
	Heart blood, kidneys and hepatic portal vein	—	—	—	—	—	—	—

— No *Cl. novyi* type B detected

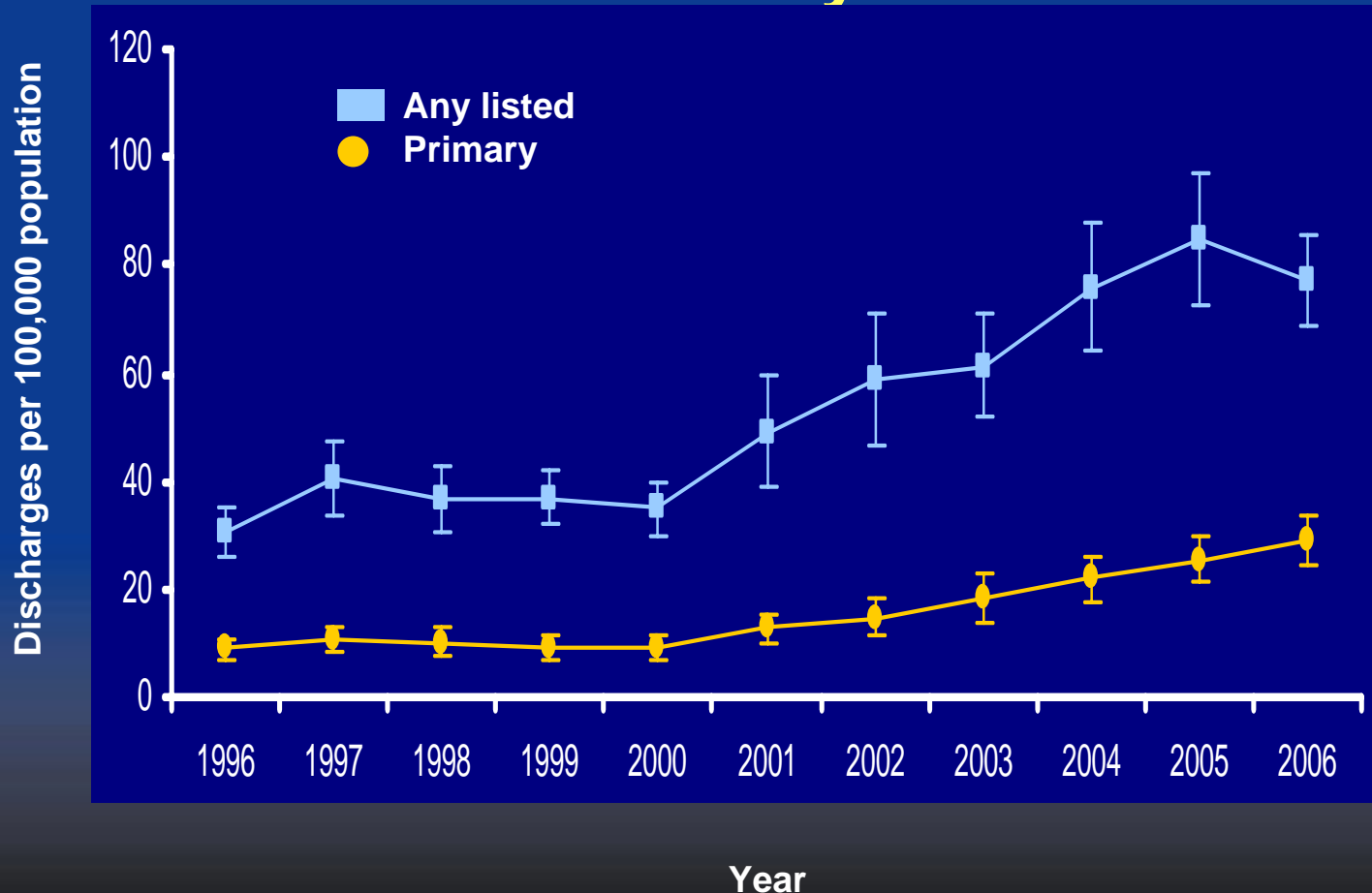
# Dissemination of *C. novyi* to liver of sheep (N=8)

DISTRIBUTION OF *Cl. novyi* TYPE B IN VARIOUS ORGANS IN SHEEP AFTER ORAL ADMINISTRATION OF SPORES

Number of sheep used		1	3	3	1
Time after administration of spores (h)		6	12	24	48
Number of sheep containing organisms in each organ	Rumen, reticulum and omasum	1	1	—	—
	Abomasum	1	3	3	—
	Small and large intestine	—	3	3	1
	Liver	—	—	3	1
	Spleen	—	—	2	1
	Mesenteric lymph glands	—	3	2	1
	Peritoneal wash, heart blood, kidneys and hepatic portal vein	—	—	—	—

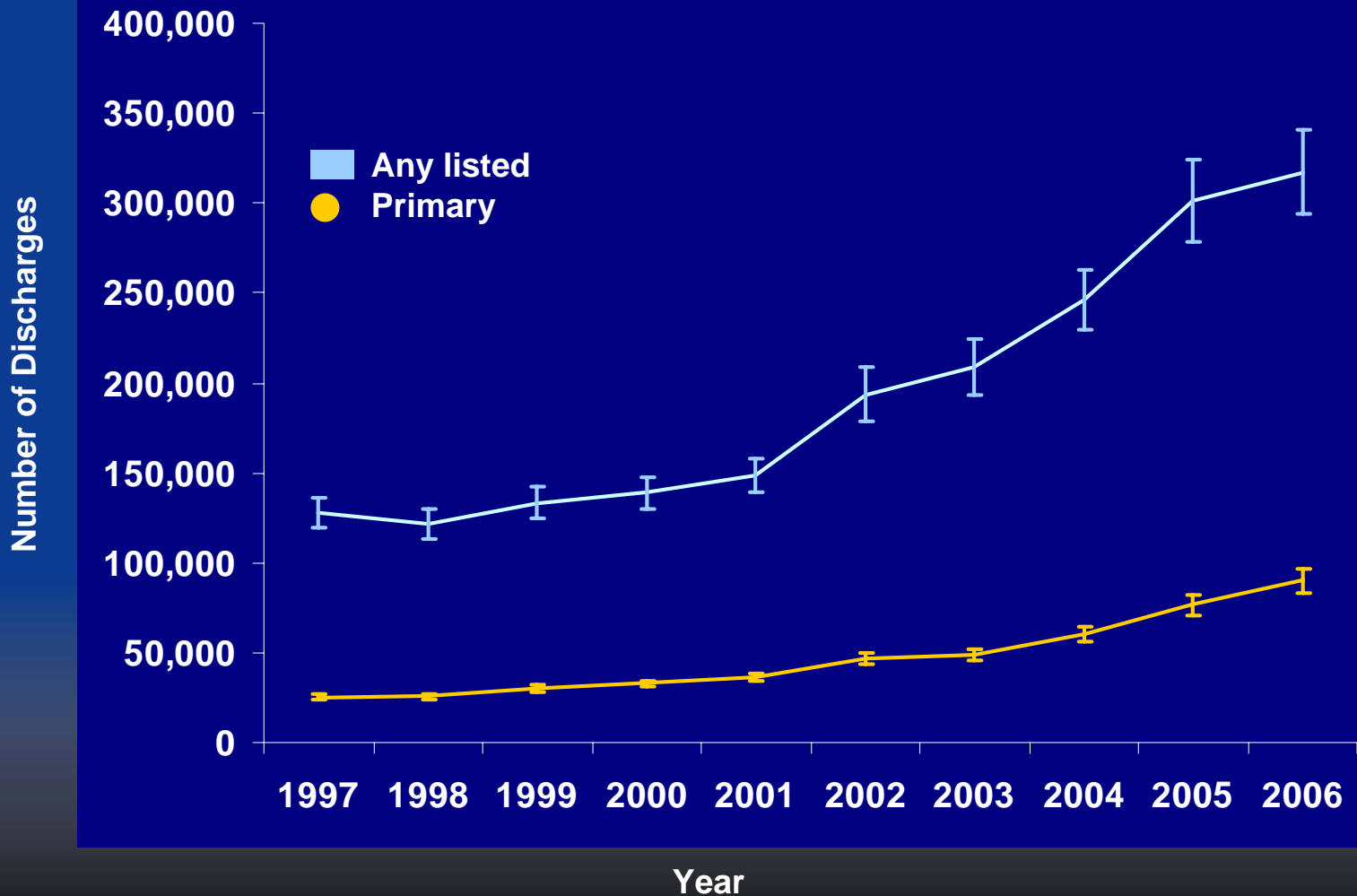
— = No *Cl. novyi* type B detected

# National Estimates of US Short-Stay Hospital Discharges with *C. difficile* as First-Listed or Any Diagnosis, National Hospital Discharge Survey

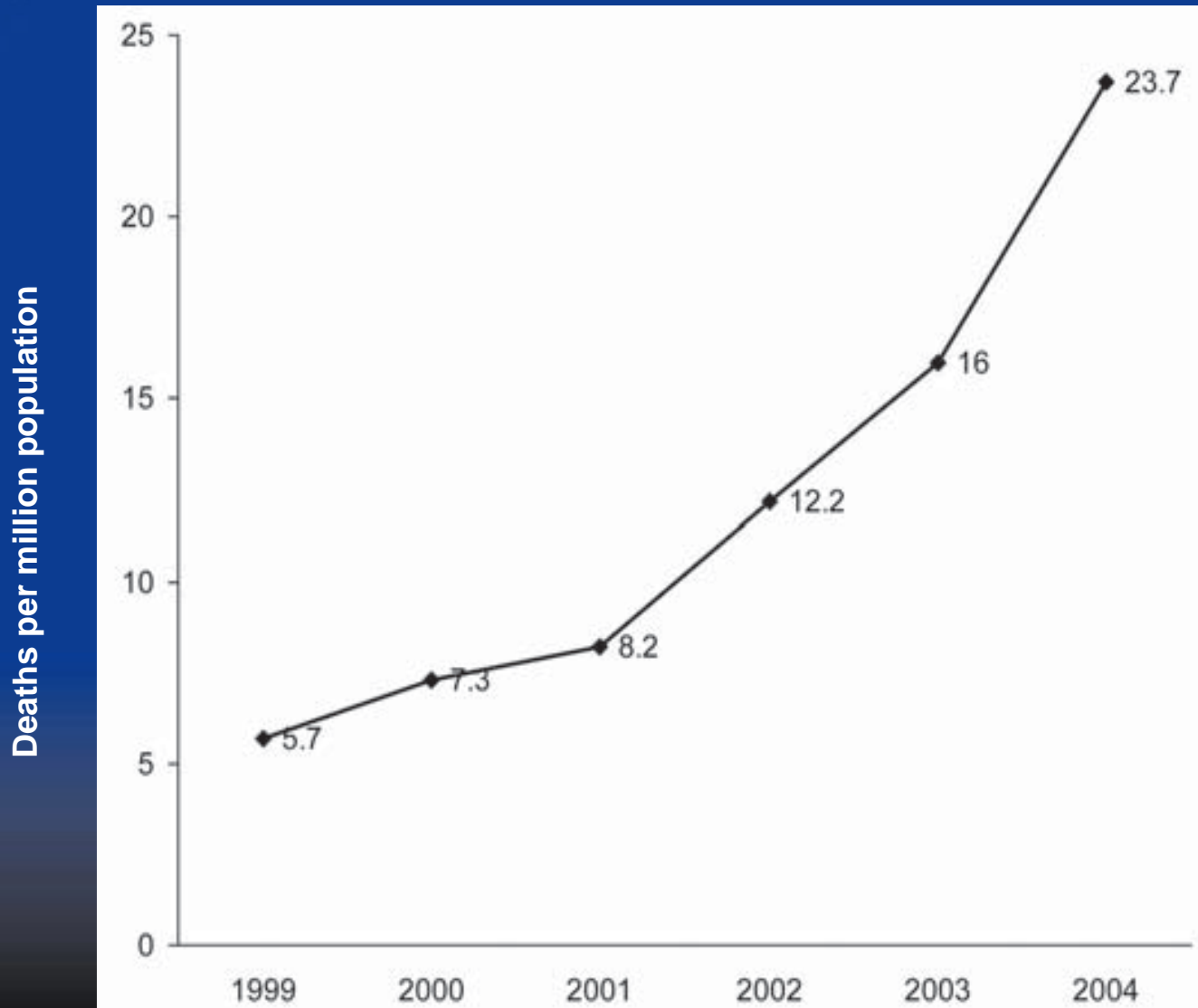


From McDonald LC, et al. *Emerg Infect Dis.* 2006;12(3):409-15 and unpublished CDC data

# National Estimates of US Short-Stay Hospital Discharges with *C. difficile* as First-Listed or Any Diagnosis, National Inpatient Sample



# Yearly *Clostridium difficile*-related mortality by listing on death certificates, United States, 1999–2004.





# Public reporting in Ohio, 2006

## Relative importance of long-term care setting



- Approximately 14,100 cases
  - Hospital onset
    - ~5,000 initial cases; 7–8 per 10,000 patient-days
    - ~1,200 recurrent cases; 1–2 per 10,000 patient-days
  - Long-term care facility onset
    - ~4,800 initial cases; 2–3 per 10,000 patient-days
    - ~3,100 recurrent; 1–2 per 10,000 patient-days



# Outcomes of CDI in setting of endemic disease

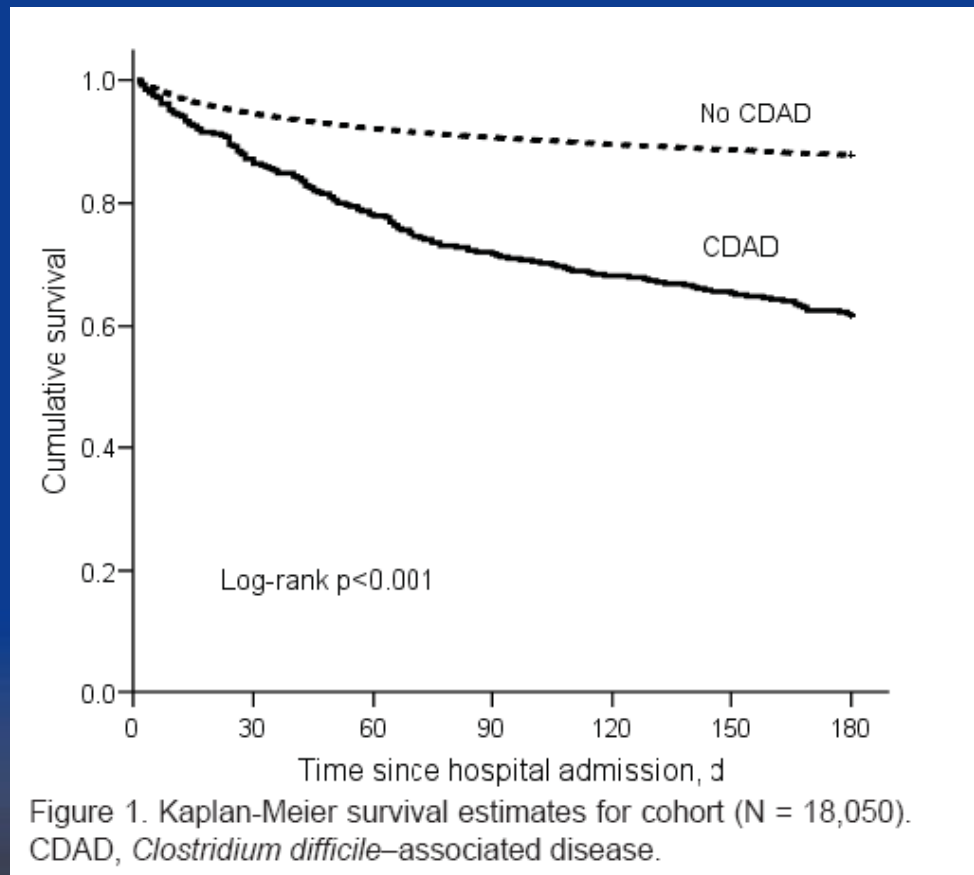


- Excess costs
  - \$2,380 to \$3,240 per index hospitalization
  - \$3,797 to \$7,179 inpatient costs over 180 days of follow-up
- Other outcomes
  - 2.8 days attributable excess length of stay
  - 19.3% attributable readmission (180 days)
  - 5.7% attributable mortality (180 days)
  - More likely discharged to long-term care

Dubberke ER, et al. *Clin Infect Dis*. 2008;46:497-504.

Dubberke ER, et al. *Emerg Infect Dis*. 2008 ;14:1031-8.

# Attributable increased mortality from CDI may extend out many months





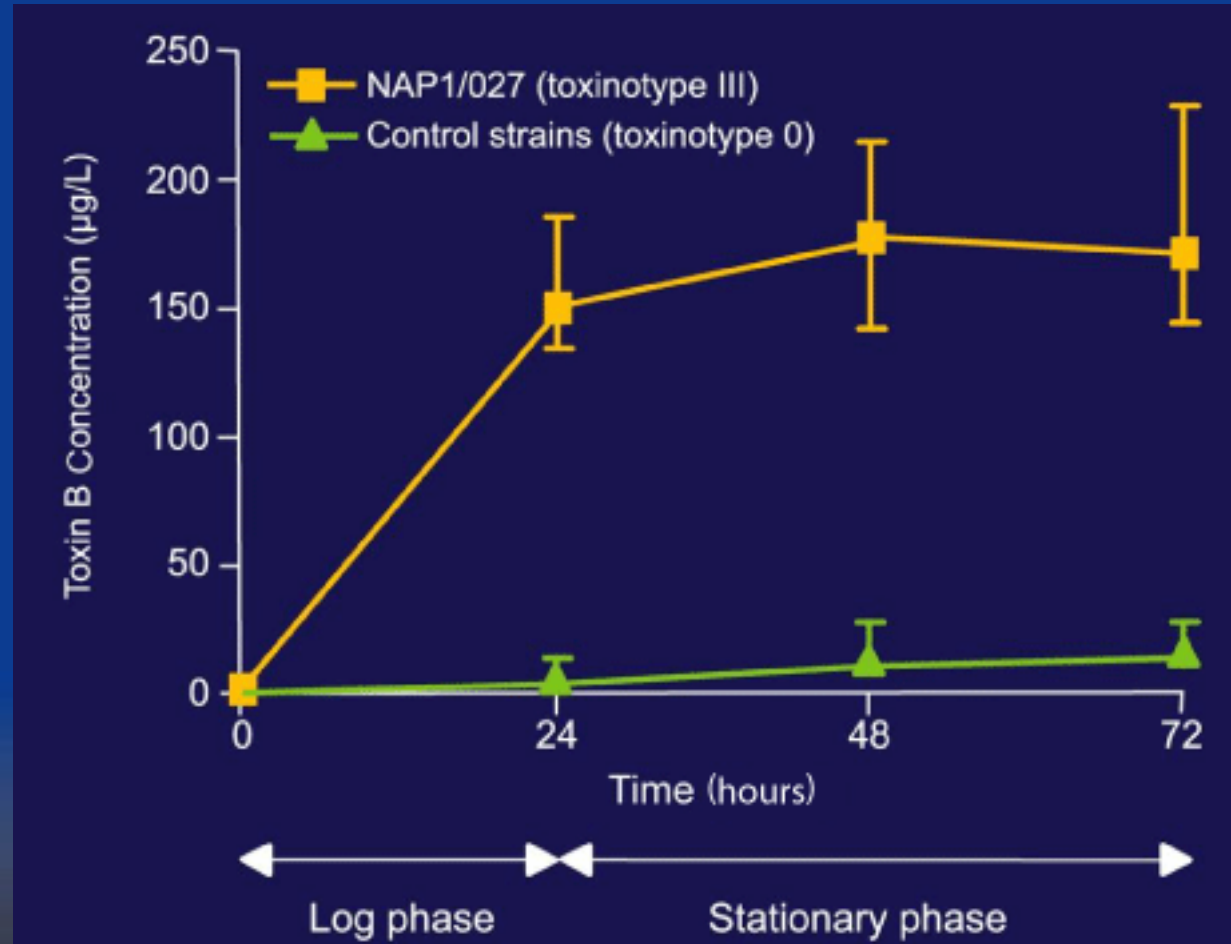
# Current human epidemic strain of *C. difficile*



- BI/NAP1/027, toxinotype III
- Historically uncommon, now epidemic
- Change in behavior coincident with strain becoming more resistant to fluoroquinolones
- Carries extra toxin known as binary toxin
- Polymorphism in toxins A and B regulatory gene (*tcdC*) and increased toxin production *in vitro*

# Increased toxin B production *in vitro*

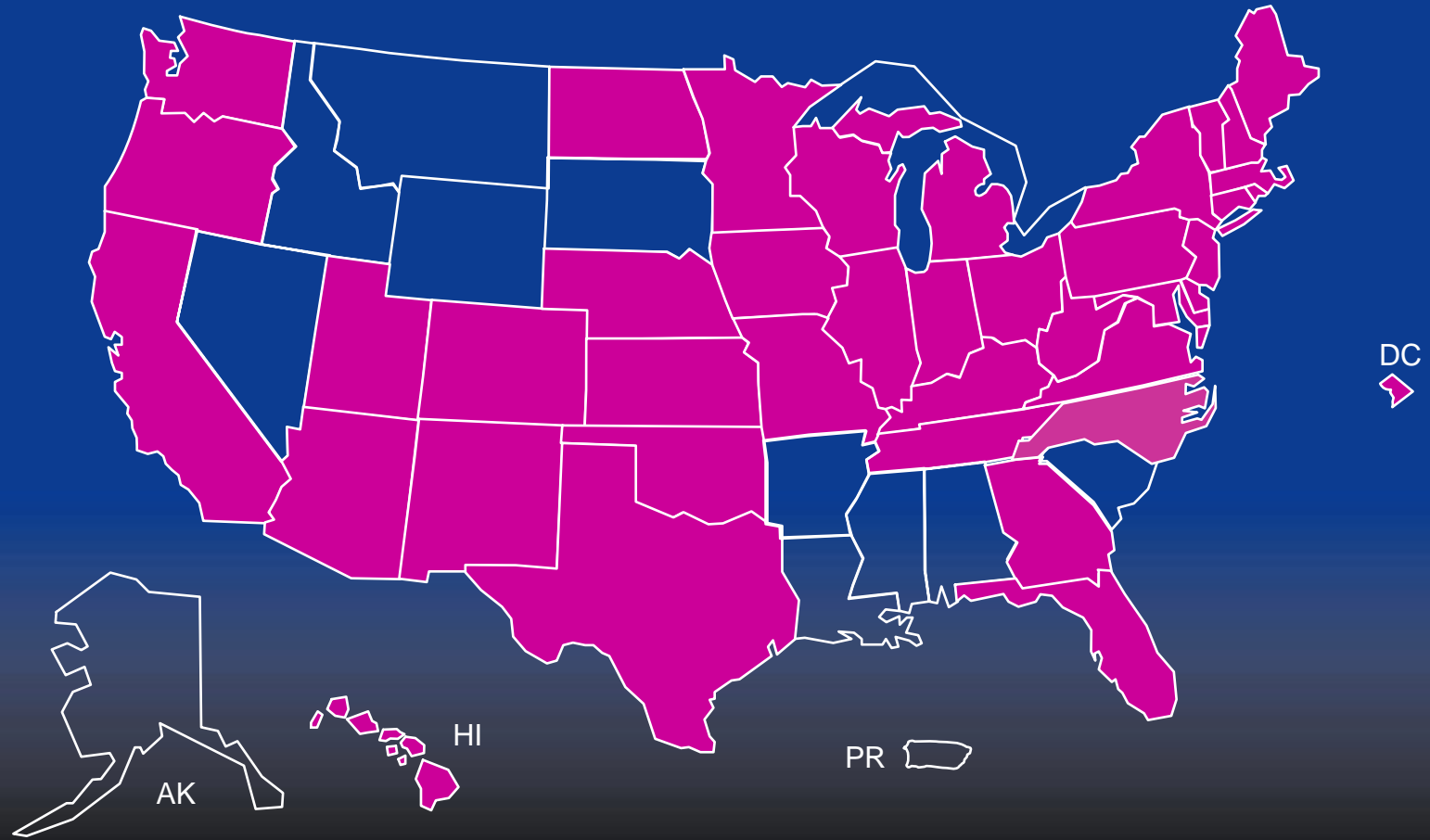
*In vitro* production of toxins A and B by *C. difficile* isolates. Median concentration and IQRs are shown. *C. difficile* strains included 25 toxinotype 0 and 15 NAP1/027 strains (toxinotype III) from various locations.



IQR=interquartile range.

Adapted from Warny M, et al. *Lancet*. 2005;366:1079-1084

# States with BI/NAP1/027 strain of *C. difficile* (N=40), October, 2008



OF HEALTH & HUMAN SERVICES-USA

CDC

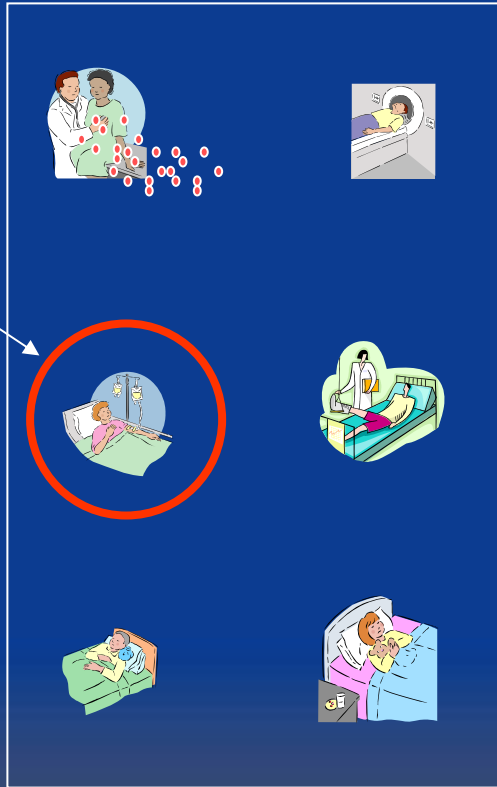
# The epidemiologic forces impacting all multidrug resistant organisms including *C. difficile*



# *C. difficile*-associated disease pressure\* and transmission



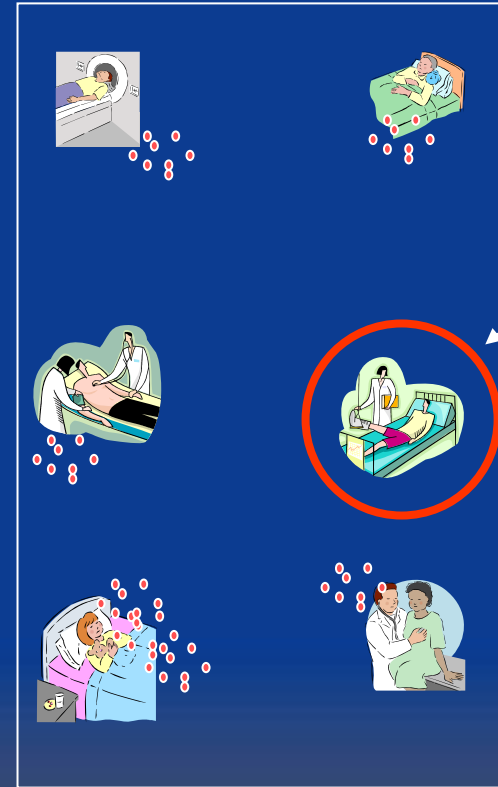
CDAD pressure  
=1 × days in unit



Unit A

Fewer patients with active CDI  
=lower risk of acquiring CDI

CDAD pressure  
=5 × days in unit



Unit B

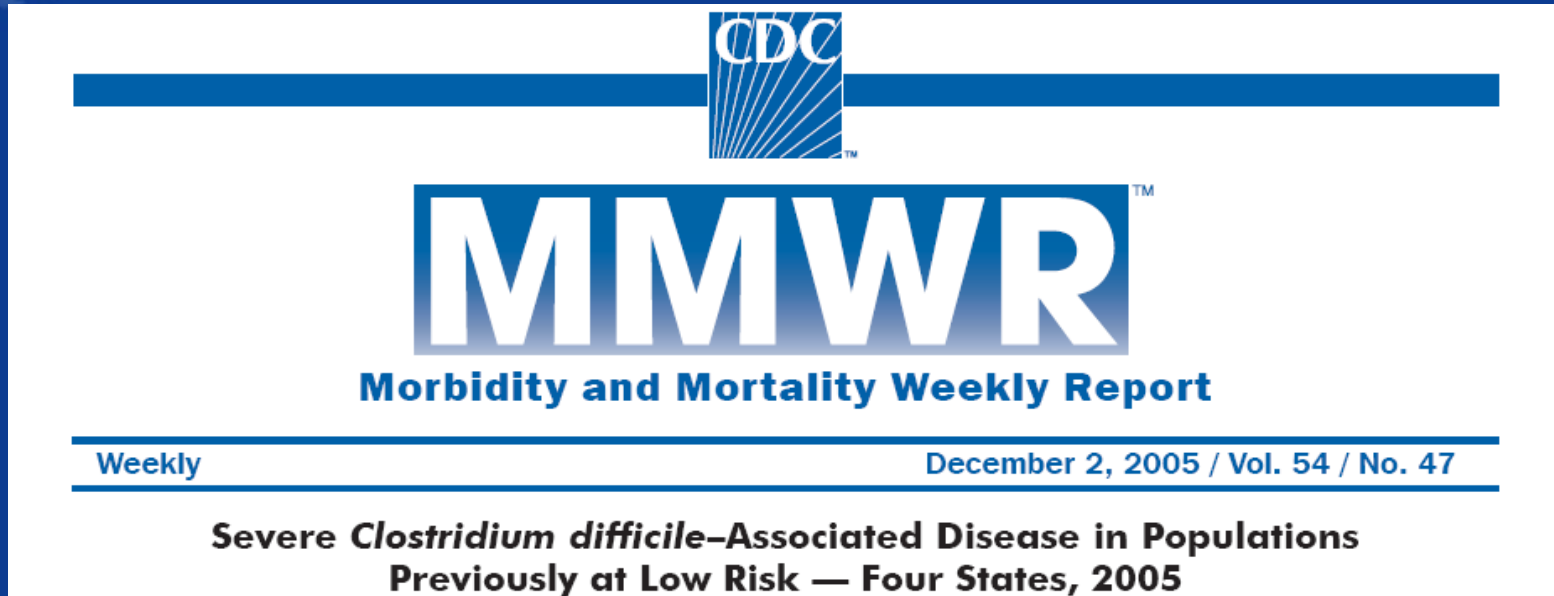
More patients with active CDI  
=higher risk of acquiring CDI

\*Dubberke ER, et al. *Clin Infect Dis*. 2007;45:1543-1549.

# Days of parenteral antibiotic use in U.S. hospitals (N=130), 2002-3

Antibiotic:	Mean days of use ( $\pm$ SD) per 1,000 patient days
Cefazolin	94.3 $\pm$ 27.7
Levofloxacin	74.9 $\pm$ 55.8
Gatifloxacin	52.1 $\pm$ 48.6
Ceftriaxone	62.9 $\pm$ 35.9
Vancomycin	52.7 $\pm$ 26.6
Piperacillin-tazobactam	42.7 $\pm$ 28.5
Metronidazole	32.8 $\pm$ 15.4
Azithromycin	18.0 $\pm$ 14.8
Ciprofloxacin	13.5 $\pm$ 16.3
Clindamycin	22.3 $\pm$ 10.8

# CDI in previously low-risk populations



- 10 Pregnant women
- 23 Generally healthy persons in the community
- Cases without precedent antimicrobial use



# Cases of severe pregnancy-associated CDI

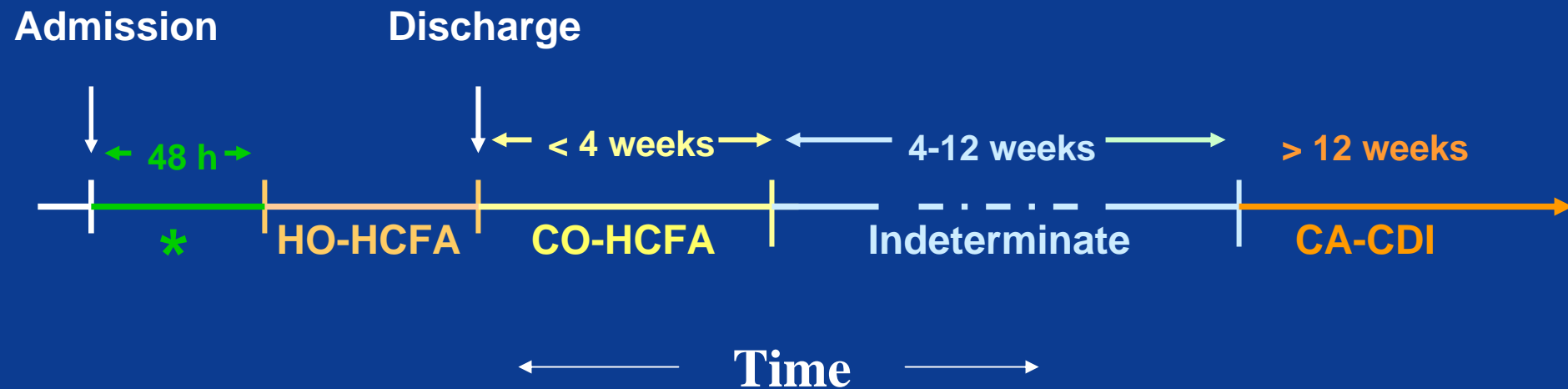


- **10 Cases\***
  - Only three with prior hospitalization
  - One without antimicrobial exposure
  - Six prepartum, three of four postpartum cases within 1 week of delivery
  - Six required intensive care unit for toxic megacolon
    - Two with evidence of NAP1
  - Five required colectomy
  - Three maternal deaths, three fetal losses

Rouphael NG, et al. *Am J Obstet Gynecol.* 2008; Jun;198(6):635.e1-6.

\*Data from Ghai S, Ghai V, Sunderj S. *Obstet Gynecol.* 2007;109(2 Pt2):541-543; and CDC. *Morbid Mortal Wkly Rep.* 2005;54:1201-1205.

# Recommendations for surveillance of *Clostridium difficile* infection



HO: Hospital (Healthcare) onset

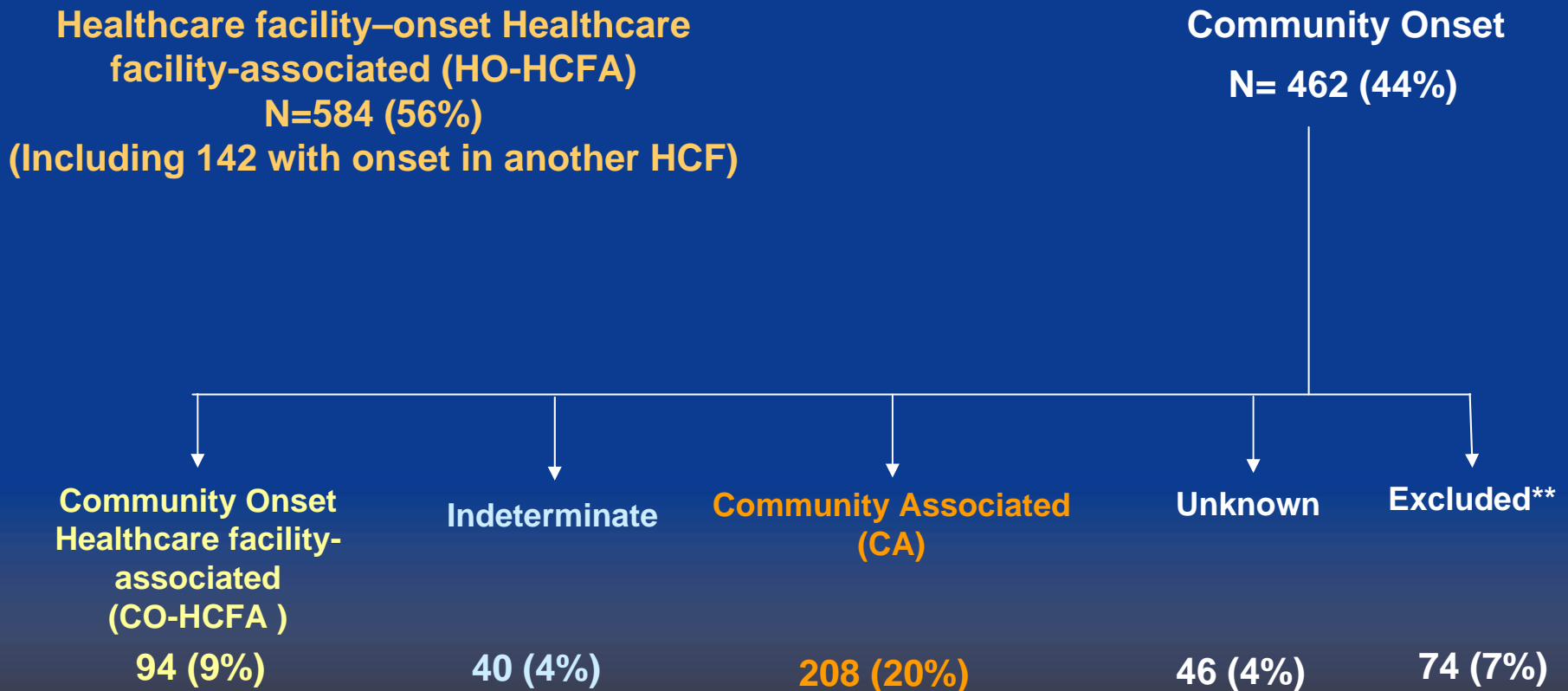
CO-HA: Community Onset Healthcare-associated

CA: Community Associated

\*

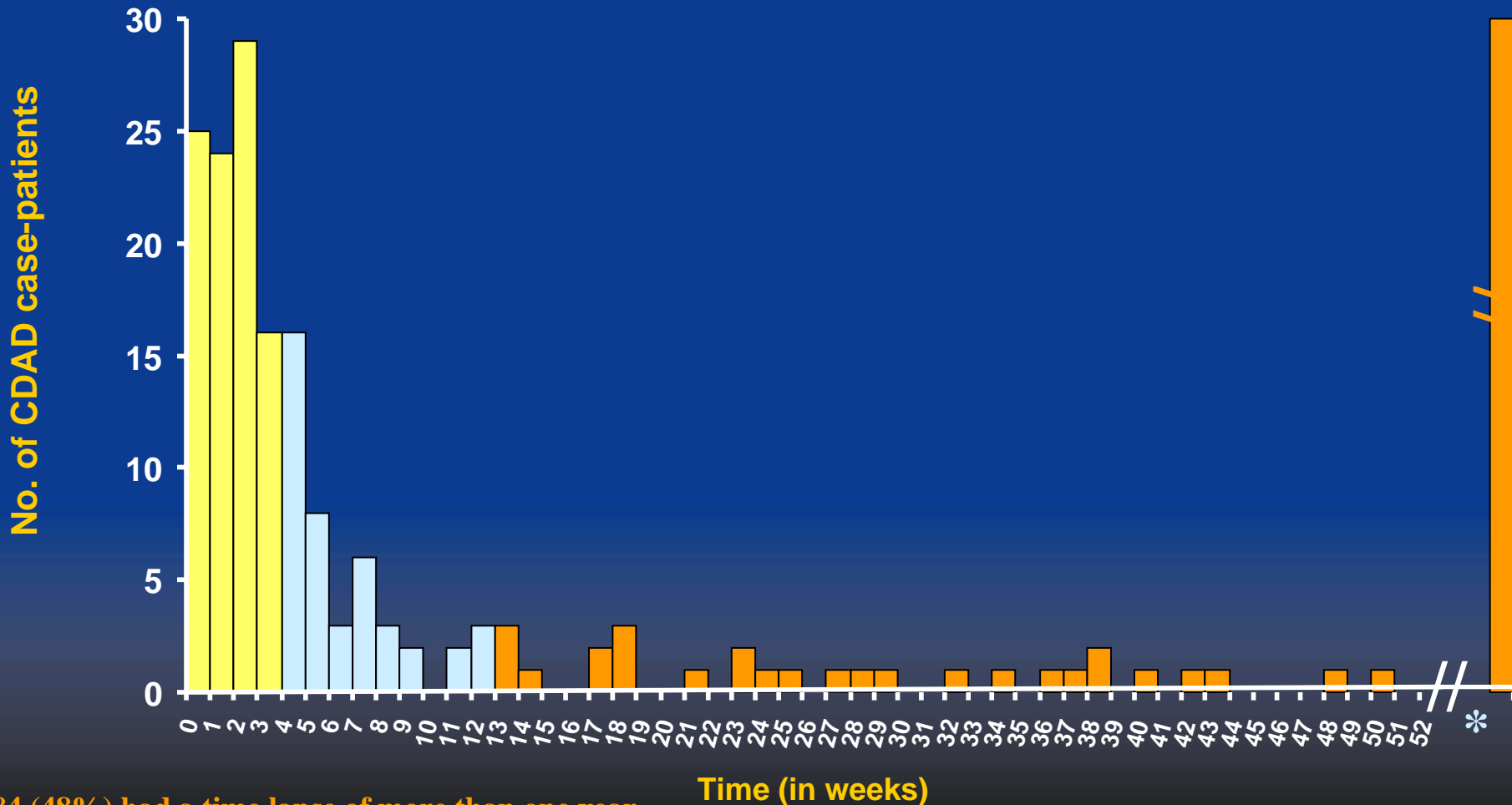
Depending upon whether patient was discharged within previous 4 weeks, CO-HA vs. CA

**Clostridium difficile–associated Disease (CDAD) cases  
N = 1046**



\*\*Excluded:  
Prisoner: 8      Out of State:20      Bone Marrow Transplant: 17      Hemodialysis:29

# Community onset CDI relative to previous discharge, North Carolina, 2005 (N=348)



\* 184 (48%) had a time lapse of more than one year



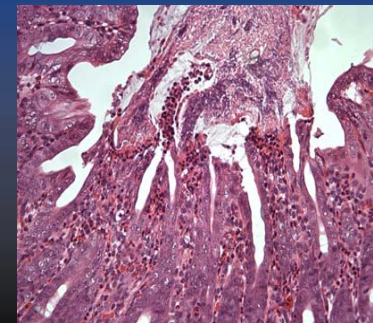
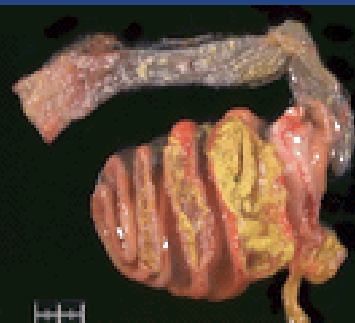
## Surveillance for Community-Associated *Clostridium difficile* — Connecticut, 2006

Characteristic	No.	(%)
<b>Clinical features</b>		
Abdominal pain (n = 222)	169	(76)
Vomiting (n = 221)	50	(23)
Diarrhea <sup>†</sup> (n = 236)	227	(96)
Bloody diarrhea (n = 209)	48	(23)
Fever <sup>§</sup> (n = 203)	56	(28)
<b>Predisposing risk factors</b>		
Previous health-care exposure (n = 214)	63	(29)
Overnight hospitalization or long-term-care facility stay during preceding >3 to 12 months (n = 222)	34	(15)
Day surgery during preceding 12 months (n = 217)	36	(17)
Underlying medical condition (comorbid condition) (n = 220)	147	(67)
Any antibiotic use during 3 months preceding symptom onset (n = 227)	154	(68)
Clindamycin (n = 121)	19 <sup>¶</sup>	(16)
Fluoroquinolones (n = 121)	42 <sup>¶</sup>	(35)
Other <sup>**</sup> (n = 121)	54 <sup>¶</sup>	(45)

# CDI in piglets



- < 7 days of age, “scouring from birth”
  - pasty, yellow colonic contents; constipation; obstipation
- Mesocolonic edema; suppurative foci in colonic lamina propria; volcano lesions
- Apparent increase or emergence around the year 2000
- Little evidence to support link to antimicrobial use

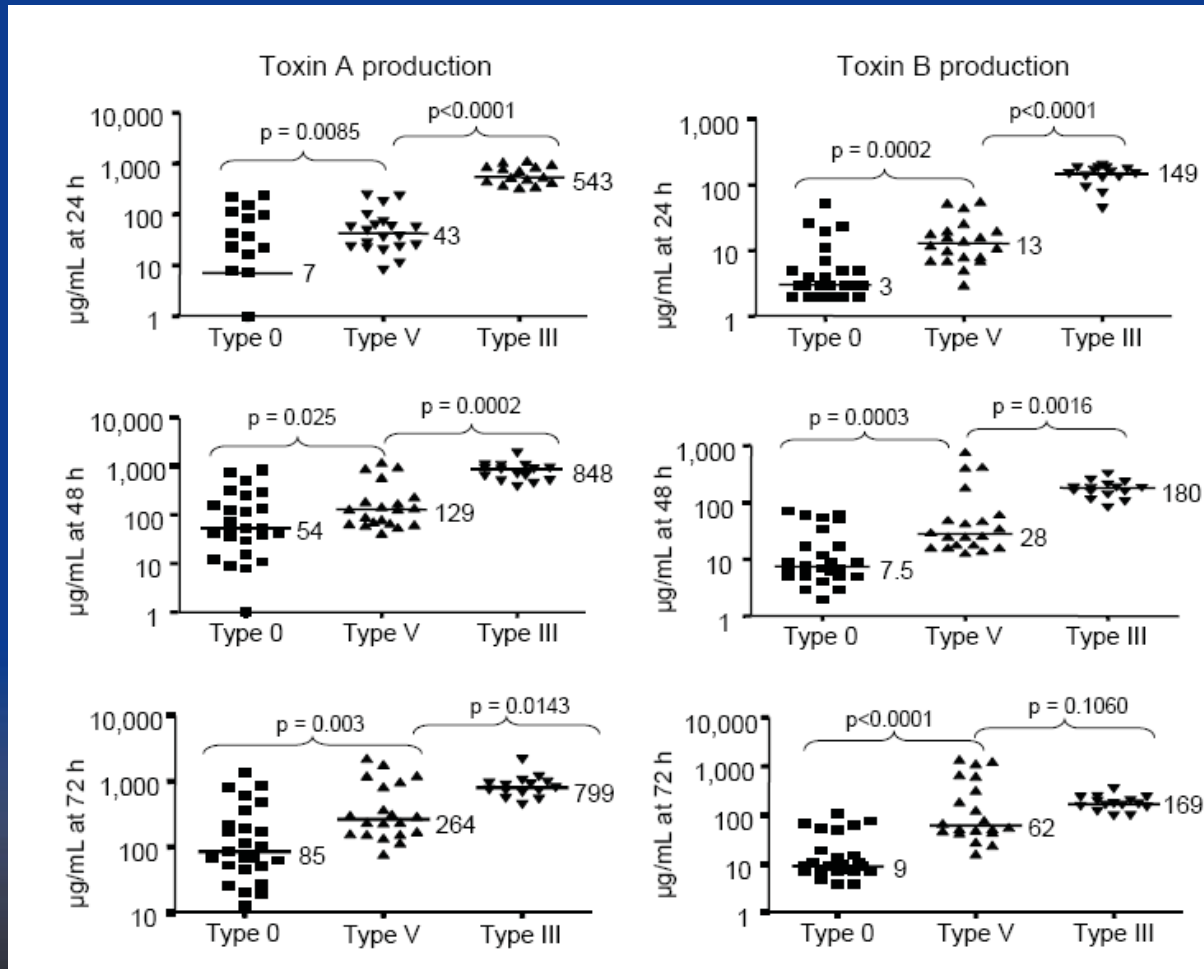


Slide courtesy of J. Glenn Songer

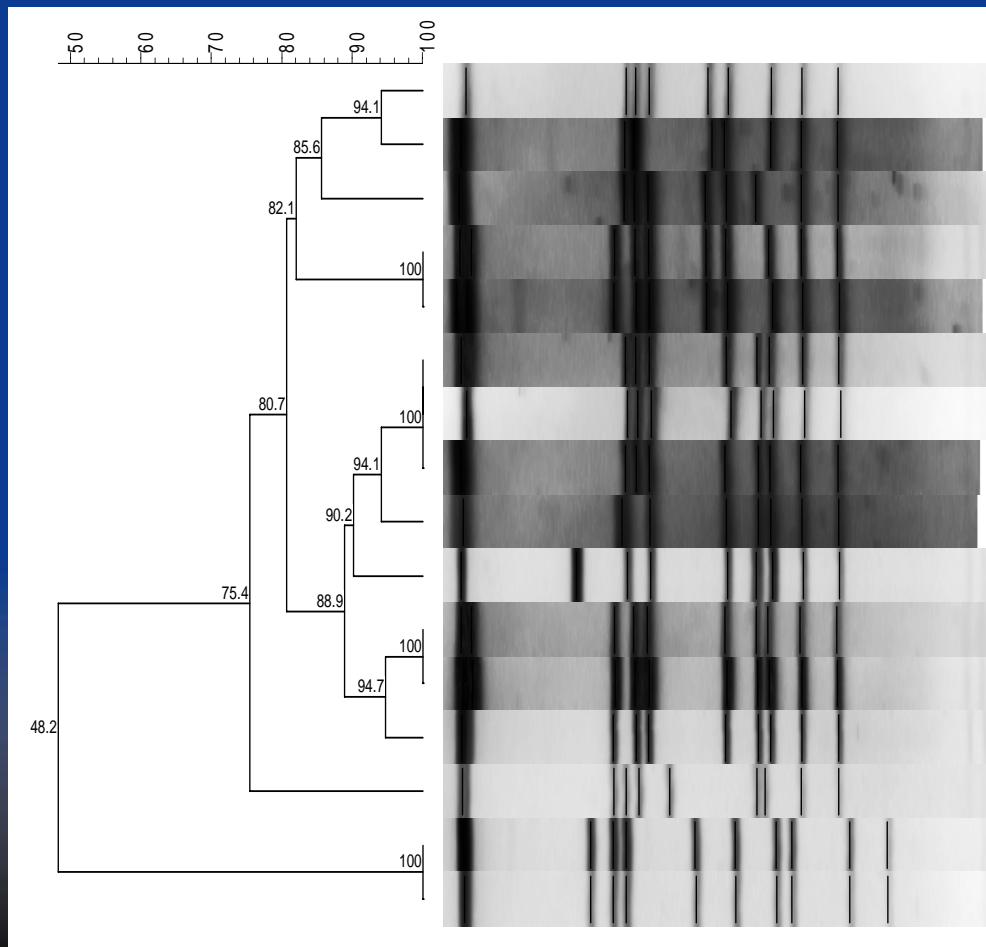
# Epidemic animal strains share characteristics with the human epidemic strain

Characteristic	Human Standard Strains	Human Epidemic Strain	Porcine Epidemic Strains	Bovine Strains
Toxinotype	0	III	V	V
PCR ribotype	001 and others	027	078	078
PFGE pattern	<80% related to NAP1	NAP1	NAP7 & NAP8	NAP7
Binary toxin	—	+	+	+
Deletion in <i>tcdC</i>	—	18 bp	39 bp	39 bp
TcdC protein	233 aa	65 aa	61 aa	61 aa

# Toxin production in BK/NAP7-8/078 (Toxinotype V) relative to other strains



# Human CDI caused by strains similar to animal epidemic strains, 2001–2006



Source	Toxin type	Binary toxin	<i>tcdC</i> deletion
Human	V	+	39 bp
Human	V	+	39 bp
Pig	V	+	39 bp
Pig	V	+	39 bp
Pig	V	+	39 bp
Human	V	+	39 bp
Hosp Env	V	+	39 bp
Human	V	+	39 bp
Human	V	+	39 bp
Human	V	+	39 bp
Human	V	+	39 bp
Pig	V	+	39 bp
Pig	V	+	39 bp
Pig	V	+	39 bp
Pig	V	+	39 bp
Pig	V	+	39 bp

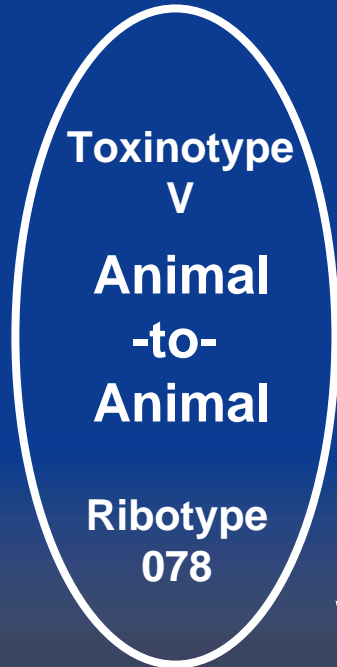
# ToxV (BK/NAP7-8/078) strains; historically rare among hospital isolates, recently more common

<u>Time</u>	<u>Tox V Isolates</u>
Prior to 2001	10/6000
2001-2005	10/600
2006	6/125

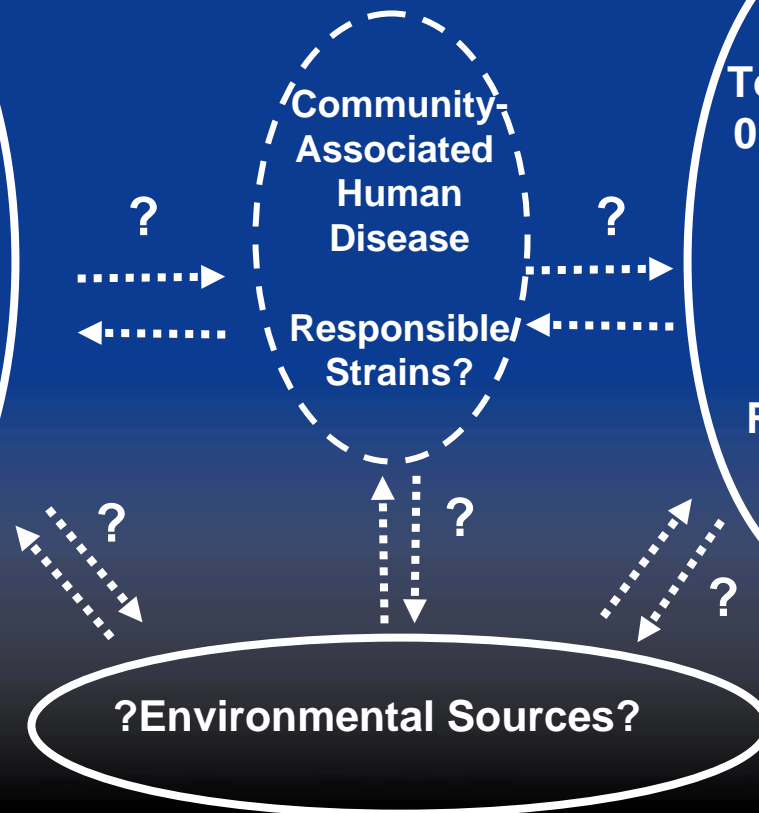
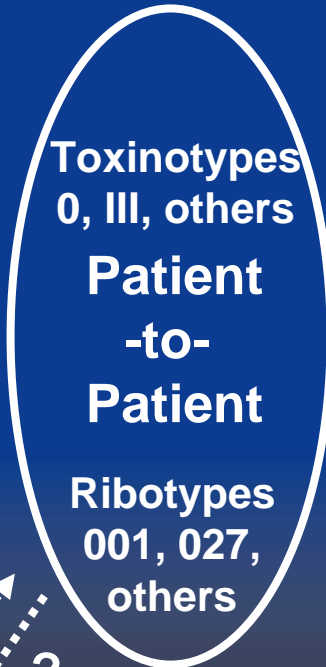


# How should we interpret finding similar *C. difficile* strains in food producing animals and humans?

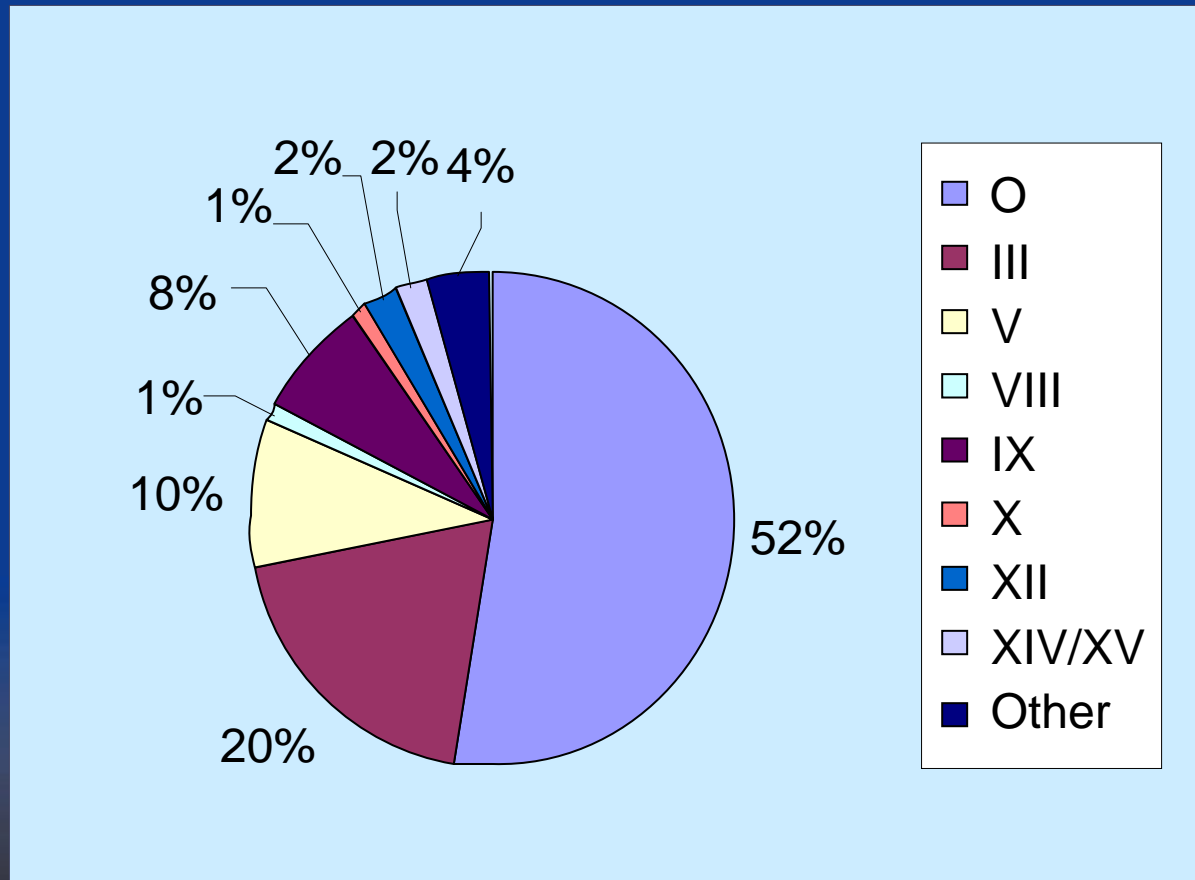
Animal Production  
Facilities



Healthcare  
Facilities



# Toxinotypes represented among CA-CDI isolates, N=92



# Summary



- ***Clostridium* spp. myonecrosis may arise from previously unapparent sources related to low oxygen tension**
  - Allograft related
  - Spontaneous and induced abortion
  - Closed, blunt trauma
- **Rates, mortality, and costs associated with CDI continue to increase**
  - Due to emergence of a hypervirulent, highly fluoroquinolone, resistant epidemic strain
- **CDI becoming more notable in previously low-risk populations**
  - Some without traditional risk factors
- **Ecological evidence for animal to human transmission of *C. difficile***
  - BK/NAP 7-8/078 and other strains?