





### Clostridium difficile (CDI) Infections Toolkit

#### Activity C: ELC Prevention Collaboratives

Carolyn Gould, MD MSCR

Cliff McDonald, MD, FACP

**Division of Healthcare Quality Promotion** 

Centers for Disease Control and Prevention

Draft - 12/23/09 --- Disclaimer: The findings and conclusions in this presentation are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.



## Outline



#### • Background

- Impact
- HHS Prevention Targets
- Pathogenesis
- Epidemiology
- Prevention Strategies
  - Core
  - Supplemental
- Measurement
  - Process
  - Outcome
- Tools for Implementation/Resources/References

# SAFER • HEALTHIER • PEOPLE<sup>M</sup>



#### **Background: Impact**





Campbell et al. Infect Control Hosp Epidemiol. 2009:30:523-33. Dubberke et al. Clin Infect Dis. 2008;46:497-504.

- Hospital-acquired, hospitalonset: 165,000 cases, \$1.3 billion in excess costs, and 9,000 deaths annually
- Hospital-acquired, postdischarge (up to 4 weeks): 50,000 cases, \$0.3 billion in excess costs, and 3,000 deaths annually
  - Nursing home-onset: 263,000 cases, \$2.2 billion in excess costs, and 16,500 deaths annually

Dubberke et al. Emerg Infect Dis. 2008;14:1031-8. Elixhauser et al. HCUP Statistical Brief #50. 2008.





#### \*Per 100,000 US standard population

Heron et al. Natl Vital Stat Rep 2009;57(14). Available at <u>http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57\_14.pc</u>





### **Background: HHS Prevention Targets**

 Case rate per 10,000 patient-days as measured in NHSN

- National 5-Year Prevention Target: 30% reduction

• Because little baseline infection data exists, administrative data for ICD-9-CM coded *C. difficile* hospital discharges is also tracked

National 5-Year Prevention Target: 30% reduction

http://www.hhs.gov/ophs/initiatives/hai/prevtargets.html







#### Background: Epidemiology Current epidemic strain of *C. difficile*

- BI/NAP1/027, toxinotype III
- Historically uncommon epidemic since 2000
- More resistant to fluoroquinolones
  - Higher MICs compared to historic strains and current non-BI/NAP1 strains
- More virulent
  - Increased toxin A and B production
  - Polymorphisms in binding domain of toxin B
  - Increased sporulation

McDonald et al. N Engl J Med. 2005;353:2433-41. Warny et al. Lancet. 2005;366:1079-84. Stabler et al. J Med Micro. 2008;57:771–5. Akerlund et al. J Clin Microbiol. 2008;46:1530–3.



#### Background: Epidemiology Risk Factors



Antimicrobial exposure

- Acquisition of C. difficile
- Advanced age
- Underlying illness
- Immunosuppression
- Tube feeds
- ? Gastric acid suppression

Main modifiable risk factors





## **Prevention Strategies**

- Core Strategies
  - High levels of scientific evidence

FEROHEALTHI

 Demonstrated feasibility

- Supplemental Strategies
  - Some scientific evidence
  - Variable levels of feasibility

\*The Collaborative should at a minimum include core prevention strategies. Supplemental prevention strategies also may be used. Most core and supplemental strategies are based on HICPAC guidelines. Strategies that are not included in HICPAC guidelines will be noted by an asterisk (\*) after the strategy. HICPAC guidelines may be found at www.cdc.gov/hicpac





### **Prevention Strategies: Core**

- Contact Precautions for duration of diarrhea
- Hand hygiene in compliance with CDC/WHO
- Cleaning and disinfection of equipment and environment
- Laboratory-based alert system for immediate notification of positive test results
- Educate about CDI: HCP, housekeeping, administration, patients, families

http://www.cdc.gov/ncidod/dhqp/id\_CdiffFAQ\_HCP.html Dubberke et al. Infect Control Hosp Epidemiol 2008;29:S81-92.



- Extend use of Contact Precautions beyond duration of diarrhea (e.g., 48 hours)\*
- Presumptive isolation for symptomatic patients pending confirmation of CDI
- Evaluate and optimize testing for CDI
- Implement soap and water for hand hygiene before exiting room of a patient with CDI
- Implement universal glove use on units with high CDI rates\*
- Use sodium hypochlorite (bleach) containing agents for environmental cleaning
- Implement an antimicrobial stewardship program

\* Not included in CDC/HICPAC 2007 Guideline for Isolation Precautions



#### Supplemental Prevention Strategies: Consider presumptive isolation for patients with > 3 unformed stools within 24 hours

- Patients with CDI may contaminate environment and hands of healthcare personnel pending results of diagnostic testing
- CDI responsible for only ~30-40% of hospital-onset diarrhea
- However, CDI more likely among patients with <u>></u>3 unformed (i.e. taking the shape of a container) stools within 24 hours
  - Send specimen for testing and presumptively isolate patient pending results
  - Positive predictive value of testing will also be optimized if focused on patients with <a>3</a> unformed stools within 24 hours
  - Exception: patient with possible recurrent CDI (isolate and test following first unformed stool)

#### Supplemental Prevention Strategies: Evaluate and optimize test-ordering practices and diagnostic methods

- Most laboratories have relied on Toxin A/B enzyme immunoassays
  - Low sensitivities (70-80%) lead to low negative predictive value
- Despite high specificity, poor test ordering practices (i.e. testing formed stool or repeat testing in negative patients) may lead to many false positives
- Consider more sensitive diagnostic paradigms but apply these more judiciously across the patient population
  - Employ a highly sensitive screen with confirmatory test or a PCR-based molecular assay
  - Restrict testing to unformed stool only
  - Focus testing on patients with <u>></u> 3 unformed stools within 24 hours
  - Require expert consultation for repeat testing within 5 days

Peterson et al. Ann Intern Med 2009;15:176-9.



Supplemental Prevention Strategies: Hand Hygiene – Soap vs. Alcohol gel



- Alcohol not effective in eradicating *C. difficile* spores
- However, one hospital study found that from 2000-2003, despite increasing use of alcohol hand rub, there was no concomitant increase in CDI rates
- Discouraging alcohol gel use may undermine overall hand hygiene program with untoward consequences for HAIs in general

Boyce et al. Infect Control Hosp Epidemiol 2006;27:479-83.

# Supplemental Prevention Strategies:

Product	Log10 Reduction
Tap Water	0.76
4% CHG antimicrobial hand wash	0.77
Non-antimicrobial hand wash	0.78
Non-antimicrobial body wash	0.86
0.3% triclosan antimicrobial hand wash	0.99
Heavy duty hand cleaner used in manufacturing	1.21*
environments * Only value that was statistic	ally better than others

Conclusion: Spores may be difficult to eradicate even with hand washing.

0 H H A I T H

Edmonds, et al. Presented at: SHEA 2009; Abstract 43.





Since spores may be difficult to remove from hands even with hand washing, adherence to glove use, and Contact Precautions in general, should be emphasized for preventing *C. difficile* transmission via the hands of healthcare personnel

Johnson et al. Am J Med 1990;88:137-40.





#### Supplemental Prevention Strategies: Glove Use



#### Rationale for considering universal glove use (in addition to Contact Precautions for patients with known CDI) on units with high CDI rates

- Although the magnitude of their contribution is uncertain, asymptomatic carriers have a role in transmission
- Practical screening tests are not available

EROH

- There may be a role for universal glove use as a special approach to reducing transmission on units with longer lengths of stay and high endemic CDI rates
- Focus enhanced environmental cleaning strategies and avoid shared medical equipment on such units as well





- Supplemental Prevention Strategies: Environmental Cleaning
- Bleach can kill spores, whereas other standard disinfectants cannot
- Limited data suggest cleaning with bleach (1:10 dilution prepared fresh daily) reduces *C. difficile* transmission
- Two before-after intervention studies demonstrated benefit of bleach cleaning in units with high endemic CDI rates
- Therefore, bleach may be most effective in reducing burden where CDI is highly endemic

Mayfield et al. Clin Infect Dis 2000;31:995-1000.

FEROHEAL

Wilcox et al. J Hosp Infect 2003;54:109-14.







- Ensure that environmental cleaning is adequate and high-touch surfaces are not being overlooked
- One study using a fluorescent environmental marker to asses cleaning showed:
  - only 47% of high-touch surfaces in 3 hospitals were cleaned
  - sustained improvement in cleaning of all objects, especially in previously poorly cleaned objects, following educational interventions with the environmental services staff
- The use of environmental markers is a promising method to improve cleaning in hospitals.

Carling et al. Clin Infect Dis 2006;42:385-8.



#### Supplemental Prevention Strategies: Audit and feedback targeting broad-spectrum antibiotics



- A prospective, controlled interrupted time-series analysis in 3 acute medical wards for the elderly in the UK demonstrated the impact of antimicrobial management on reducing CDI.
  - Introduced a narrow-spectrum antibiotic policy
  - Reinforced using feedback
  - Associated with significant changes in targeted antibiotics and a significant reduction in CDI

Fowler et al. J Antimicrob Chemother 2007;59:990-5.



Summary of Prevention Measures

#### **Core Measures**

- Contact Precautions for duration of illness
- Hand hygiene in compliance with CDC/WHO
- Cleaning and disinfection of equipment and environment
- Laboratory-based alert system
- CDI surveillance
- Education

#### **Supplemental Measures**

- Prolonged duration of Contact Precautions\*
- Presumptive isolation
- Evaluate and optimize testing
- Soap and water for HH upon exiting CDI room
- Universal glove use on units with high CDI rates\*
- Bleach for environmental disinfection
- Antimicrobial stewardship
   program

\* Not included in CDC/HICPAC 2007 Guideline for Isolation Precautions



- Core Measures:
  - Measure compliance with CDC/WHO recommendations for hand hygiene and Contact Precautions
  - Assess adherence to protocols and adequacy of environmental cleaning
- Supplemental Measures:
  - Intensify assessment of compliance with process measures
  - Track use of antibiotics associated with CDI in a facility









HO: Hospital (Healthcare)-Onset CO-HCFA: Community-Onset , Healthcare Facility-Associated CA: Community -Associated

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

**†** Onset defined in NHSN LabID Event by specimen collection date

Modified from CDAD Surveillance Working Group. Infect Control Hosp Epidemiol 2007;28:140-5.

### SAFER • HEALTHIER • PEOPLE<sup>M</sup>



# Measurement: Outcome Use NHSN CDAD Module



#### Laboratory-identified MDRO or CDAD Event Exp. Date: 03-31-2

*required for saving				
Facility ID:	Event #:			
*Patient ID:	Social Security #:			
Secondary ID:				
Patient Name, Last: First:	Middle:			
*Gender: M F	*Date of Birth:			
Ethnicity (Specify):	Race (Specify):			
Event Details				
*Event Type: LabID	*Date Specimen Collected:			
*Specific Organism Type: (Check one)				
	siella 🗌 MDR-Acineto	bacter C. difficile		
*Outpatient: Yes No	*Specimen Source:			
*Date Admitted	*Location:	*Date Admitted		
R•HEALTHIER•PEOF				

### Measurement: Outcome Focus on Laboratory Identified (LabID) Events in NHSN

Figure 2. CDAD Test Result Algorithm for Laboratory-Identified (LabID) Events





Measurement: Outcome NHSN Reporting: Definitions



Based on data submitted to NHSN, CDI LabID Events are categorized as:

- Incident: specimen obtained >8 weeks after the most recent LabID Event
- Recurrent: specimen obtained >2 weeks and ≤ 8 weeks after most recent LabID Event



#### Measurement: Outcome NHSN Reporting: Definitions



Incident cases further characterized based on date of admission and date of specimen collection:

- Healthcare Facility-Onset (HO): LabID Event collected >3 days after admission to facility (i.e., on or after day 4)
- Community-Onset (CO): LabID Event collected as an outpatient or an inpatient ≤3 days after admission to the facility (i.e., days 1, 2, or 3 of admission)
- Community-Onset Healthcare Facility-Associated (CO-HCFA): CO LabID Event collected from a patient who was discharged from the facility ≤4 weeks prior to date stool specimen collected

FEROHEALTHI





- Healthcare Facility-Onset Incidence Rate = Number of all Incident HO CDI LabID Events per patient per month / Number of patient days for the facility x 10,000
- **Combined Incidence Rate** = Number of all Incident HO and CO-HCFA CDI LabID Events per patient per month / Number of patient days for the facility x 10,000

\*For a given healthcare facility

SAFER • HEALTH





# **Evaluation Considerations**

- Assess baseline policies and procedures
- Areas to consider
  - Surveillance
  - Prevention strategies
  - Measurement of effect of strategies
- Coordinator should track new policies/practices implemented during collaboration





- Dubberke ER, Butler AM, Reske KA, et al. attributable outcomes of endemic *Clostridium difficile*-associated disease in nonsurgical patients. Emerg Infect Dis 2008;14:1031-8.
- Dubberke ER, Reske KA, Olssen MA, et al. Short- and long term attributable costs of *Clostridium difficile*associated disease in nonsurgical inpatients. Clin Infect Dis 2008:46:497-504.
- Edmonds S, Kasper D, Zepka C, et al. *Clostridium* difficile and hand hygiene: spore removal effectiveness of handwash products. Presented at: SHEA 2009; Abstract 43.





- Elixhauser, A. (AHRQ), and Jhung, MA. (Centers for Disease Control and Prevention). *Clostridium Difficile-Associated Disease in U.S. Hospitals, 1993–2005*. HCUP Statistical Brief #50. April 2008. Agency for Healthcare Research and Quality, Rockville, MD. <u>http://www.hcup-</u> <u>us.ahrq.gov/reports/statbriefs/sb50.pdf</u>
- Fowler S, Webber A, Cooper BS, et al. Successful use of feedback to improve antibiotic prescribing and reduce *Clostridium difficile* infection: a controlled interrupted time series. J Antimicrob Chemother 2007;59:990-5.
- Heron MP, Hoyert DLm Murphy SL, et al. Natl Vital Stat Rep 2009;57(14). US Dept of Health and Human Services, CDC; 2009. Available at <u>http://www.cdc.gov/nchs/data/nvsr/nvsr57/nvsr57\_14.pdf</u>





- Johnson S, Gerding DN, Olson MM, et al. Prospective, controlled study of vinyl glove use to interrupt *Clostridium difficile* nosocomial transmission. Am J Med 1990;88:137-40.
- Mayfield JL, Leet T, Miller J, et al. Environmental control to reduce transmission of *Clostridium difficile*. *Clin Infect Dis* 2000;31:995–1000.
- McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene–variant strain of *Clostridium difficile*. N Engl J Med. 2005;353:2433-41.





- McDonald LC, Coignard B, Dubberke E, et al. Ad Hoc CDAD Surveillance Working Group. Recommendations for surveillance of *Clostridium difficile*-associated disease. Infect Control Hosp Epidemiol 2007; 28:140-5.
- Oughton MT, Loo VG, Dendukuri N, et al. Hand hygiene with soap and water is superior to alcohol rum and antiseptic wipes for removal of *Clostridium difficile*. Infect Control Hosp Epidemiol 2009; 30:939-44.
- Peterson LR, Robicsek A. Does my patient have *Clostridium difficile* infection? Ann Intern Med 2009;15:176-9
- Riggs MM, Sethi AK, Zabarsky TF, et al. Asymptomatic carriers are a potential source for transmission of epidemic and nonepidemic *Clostridium difficile* strains among long-term care facility residents. Clin Infect Dis 2007; 45:992–8.





- SHEA/IDSA Compendium of Recommendations. Infect Control Hosp Epidemiol 2008;29:S81–S92. <u>http://www.journals.uchicago.edu/doi/full/10.1086/59106</u>
   5
- Stabler RA, Dawson LF, Phua LT, et al. Comparitive analysis of BI/NAP1/027 hypervirulent strains reveals novel toxin B-encoding gene (tcdB) sequences. J Med Micro. 2008;57:771–5.
- Sunenshine RH, McDonald LC. Clostridium difficileassociated disease: new challenges from and established pathogen. Cleve Clin J Med. 2006;73:187-97.





- Warny M, Pepin J, Fang A, Killgore G, et al. Toxin production by and emerging strain of *Clostridium difficile* associated with outbreaks of severe disease in North America and Europe. <u>Lancet.</u> 2005;366:1079-84.
- Wilcox MF, Fawley WN, Wigglesworth N, et al. Comparison of the effect of detergent versus hypochlorite cleaning on environmental contamination and incidence of *Clostridium difficile* infection. J Hosp Infect 2003:54:109-14.



### Additional resources



#### SHEA/IDSA Compendium of Recommendations

\$81 INFECTION CONTROL AND HOSPITAL EPIDEMIOLOGY OCTOBER 2008, VOL. 29, SUPPLEMENT 1

SUPPLEMENT ARTICLE: SHEA/IDSA PRACTICE RECOMMENDATION

#### Strategies to Prevent *Clostridium difficile* Infections in Acute Care Hospitals

Erik R. Dubberke, MD; Dale N. Gerding, MD; David Classen, MD, MS; Kathleen M. Arias, MS, CIC; Kelly Podgorny, RN, MS, CPHQ; Deverick J. Anderson, MD, MPH; Helen Burstin, MD; David P. Calfee, MD, MS; Susan E. Coffin, MD, MPH; Victoria Fraser, MD; Frances A. Griffin, RRT, MPA; Peter Gross, MD; Keith S. Kaye, MD; Michael Klompas, MD; Evelyn Lo, MD; Jonas Marschall, MD; Leonard A. Mermel, DO, ScM; Lindsay Nicolle, MD; David A. Pegues, MD; Trish M. Perl, MD; Sanjay Saint, MD; Cassandra D. Salgado, MD, MS; Robert A. Weinstein, MD; Robert Wise, MD; Deborah S. Yokoe, MD, MPH

#### **CDI Checklist Example**

#### Clostridium difficile Infection (CDI) Checklist

Hospital interventions to decrease the incidence and mortality of healthcare-associated C. difficile infections

#### Prevention Checklist

#### · When an MD, PA, NP, or RN suspects a patient has CDI:

- Physician, Physician Assistant, or Nurse Practitioner:
- Initiate Contact Precautions Plus
- Order stool C. difficile toxin testing
- Discontinue non-essential antimicrobials

#### Discontinue all anti-peristaltic medications

- Registered Nurse:
- Obtain stool sample for C. difficile toxin test
- Place patient in single-patient room
- Place Contact Precautions Plus sign on patient's door
   Ensure that gloves and gowns are easily accessible from patient's room
- patient's room
   Place dedicated stethoscope in patient's room
- Remind staff to wash hands with soap and water following patient contact

#### Microbiology Laboratory Staff Person:

 Call relevant patient floor with positive C. difficile toxin test result
 Provide daily list of positive test results for Infection Control

#### Infection Control Practitioner:

- Check microbiology results daily for positive C. difficile toxin results
- Call relevant floor to confirm that patient with positive C. difficile toxin results is in a single-patient room and that the Contact Precautions Plus sign is on the patient's door
- Flag the patient's C. difficile status in the hospital's clinical information system or in the patient's paper chart
- Alert housekeeping that the patient is on Contact Precautions Plus

#### Environmental Services Staff Person:

- Prior to discharge cleaning, check for Contact Precautions Plus sign on the patient's door
- If Contact Precautions Plus sign is on the door, clean the room with a bleach-based cleaning agent
- Confirm for supervisor that bleach-based cleaning agent was used for discharge cleaning for every patient on Contact Precautions Plus

 When an MD, PA, or NP diagnoses moderate CDI: At least one of the following orbital is present diarrhae (6-12 BM3ay), forwar 37-58 % C, WRG 100.00-25 000. or transiv yebbe datable lower

When an MD, PA, or NP diagnoses mild CDI: All of

the following criteria are present: diarrhea (<6 BM/day), no few WBC<15.000, no peritoneal signs, and no evidence of sepsis

Initiate oral metronidazole at dose 500mg every 8

If no clinical improvement by 48-72 hours after

diagnosis, treat patient as moderate CDI

Continue therapy for at least 14 days total and at least 10 days after symptoms have abated

Physician, Physician Assistant, or Nurse

#### Physician, Physician Assistant, or Nurse Practitioner:

Treatment Checklist

Practitioner:

hours

- Initiate oral vancomycin at dose 250mg every 6 hours
   If no clinical improvement by 48 hours, add IV metronidazole at dose 500mg every 8 hours
- Consider obtaining infectious disease consultation
   Consider obtaining abdominal CT scan
   Continue therapy for at least 14 days total and at
- least 10 days after symptoms have abated

#### When an MD, PA, or NP diagnoses severe CDI: At

Aest one of the following oriteria is present: diarrhea (>12 BM/day), fever >38 5°C, WBC >25,000, hemodynamic instability, marked & continuous addominal pain, lieus, absence of bowls isounds, evidence of sepsis, or intensive care unit level of care required

#### Physician, Physician Assistant, or Nurse Practitioner:

- Obtain immediate infectious disease consultation
   Obtain immediate general surgery consultation
   Obtain abdominal CT scan
- Initiate oral vancomycin at dose 250mg every 6 hours together with IV metronidazole at dose 500mg every 6 hours

Following consultation with general surgery regarding

its use, consider rectal vancomycin Ask general surgery service to assess the need for

sk general surgery servic colectomy

Dubberke et al. Infect Control Hosp Epidemiol 2008;29:S81-92. Abbett SK et al. Infect Control Hosp Epidemiol 2009;30:1062-9. viden: MD-medical dodor, PA-physician assistant, ND-mans prodilector, RN-mpileter nane, BM-bowl novement, VBD-while blocd call court, DT-computed tomography, ND PTGU RF 3. Clostridium difficile infection checklist at Brieham and Women's Hospital.





### **Additional Reference Slides**

- The following slides may be used for presentations regarding CDI.
- Explanations are available in the notes section of the slides.

#### Supplemental Prevention Strategies: Rationale for Soap and Water: Lack of efficacy of alcohol-based handrub against *C. difficile*

Interventions compared		Mean log reduction (95% CI),
Intervention 1	Intervention 2	log <sub>10</sub> CFU/mL
Warm water and plain soap	No hand hygiene	2.14 (1.74-2.54)
Warm water and plain soap	Alcohol-based handrub	2.08 (1.69-2.47)
Cold water and plain soap	No hand hygiene	1.88 (1.48-2.28)
Cold water and plain soap	Alcohol-based handrub	1.82 (1.43-2.22)
Warm water and plain soap	Antiseptic hand wipe	1.57 (1.18-1.96)
Warm water and antibacterial soap	No hand hygiene	1.51 (1.12-1.91)
Warm water and antibacterial soap	Alcohol-based handrub	1.46 (1.06-1.85)
Cold water and plain soap	Antiseptic hand wipe	1.31 (0.92-1.71)
Warm water and antibacterial soap	Antiseptic hand wipe	0.94 (0.55-1.34)
Warm water and plain soap	Warm water and antibacterial soap	0.63 (0.23-1.02)
Antiseptic hand wipe	No hand hygiene	0.57 (0.17-0.96)
Antiseptic hand wipe	Alcohol-based handrub	0.51 (0.12-0.91)
Cold water and plain soap	Warm water and antibacterial soap	0.37 (-0.03 to 0.76)
Warm water and plain soap	Cold water and plain soap	0.26 (-0.14 to 0.66)
Alcohol-based handrub	No hand hygiene	0.06 (-0.34 to 0.45)

Oughton et al. Infect Control Hosp Epidemiol 2009;30:939-44.

### Supplemental Prevention Strategies: Hand Hygiene – Alcohol Hand Rub Use 2000-2003



FIGURE 1. Use of alcohol hand rub by healthcare workers, in liters per 1,000 patient-days, per quarter, 2000-2003.

Boyce et al. Infect Control Hosp Epidemiol 2006; 27:479-83.





FIGURE 2. Number of patients with 1 or more tests positive for *Clostridium difficile* toxin per 1,000 patient-days, 2000-2003.

Boyce JM et al. Infect Control Hosp Epidemiol 2006; 27:479-83.



Supplemental Prevention Strategies: Universal Glove Use



#### Role of asymptomatic carriers? Rationale for universal glove use on units with high CDI rates



Riggs et al. Clin Infect Dis 2007;45:992-8.

# SAFER • HEALTHIER • PEOPLE<sup>™</sup>



#### Supplemental Prevention Strategies: Environmental Cleaning



#### How Much Can be Achieved via Environmental Decontamination?



Mayfield et al. Clin Infect Dis 2000;31:995-1000.



#### Supplemental Prevention Strategies: Environmental Cleaning



Assess adequacy of cleaning before changing to new cleaning





#### Supplemental Prevention Strategies: Audit and feedback targeting broadspectrum antibiotics



