

High Prevalence of Antibiotic Resistance in Enterotoxigenic *E. coli* (ETEC); Minnesota 2000 - 2001

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Enterotoxigenic *E. coli* (ETEC)

Background

- i A leading cause of diarrhea-associated morbidity and mortality worldwide**
- i Has not been considered an important pathogen in the United States**

Pathogenic *E. coli*

i Enterohemorrhagic *E. coli* (EHEC)

i Enteropathogenic *E. coli* (EPEC)

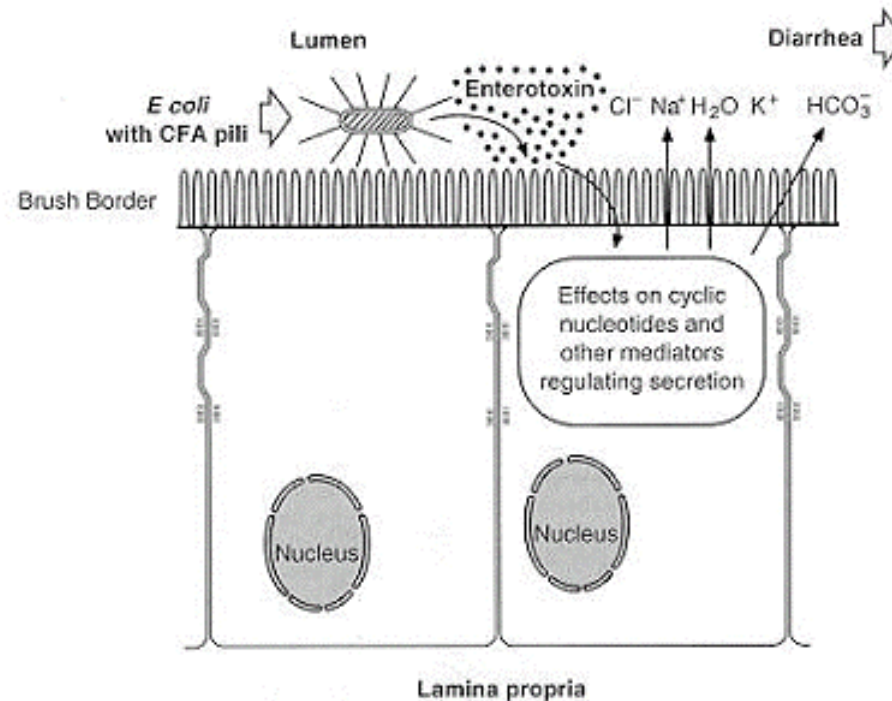
i Enteroinvasive *E. coli* (EIEC)

i Enteroaggregative *E. coli* (EAaggEC)

i Enterotoxigenic *E. coli* (ETEC)

ETEC Pathogenesis: Two Major Enterotoxin Groups

- i Heat stable toxins (ST; 2 subgroups)
- i Heat labile (LT; i cholera-like toxini)

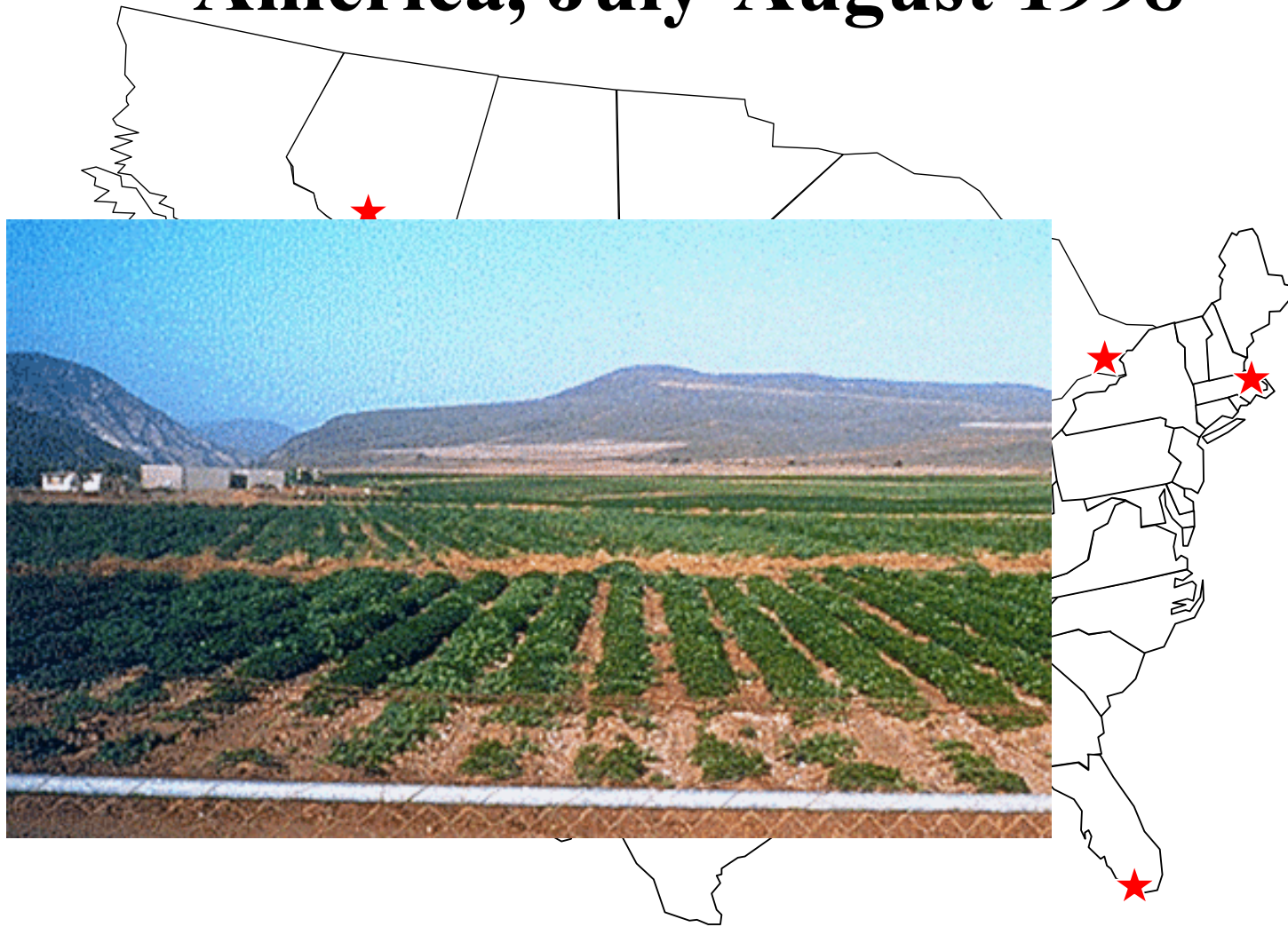


New Concerns about ETEC

- i Increased travel to endemic areas (traveler's diarrhea)
- i Increased import of produce from endemic countries (traveler's diarrhea at home!)



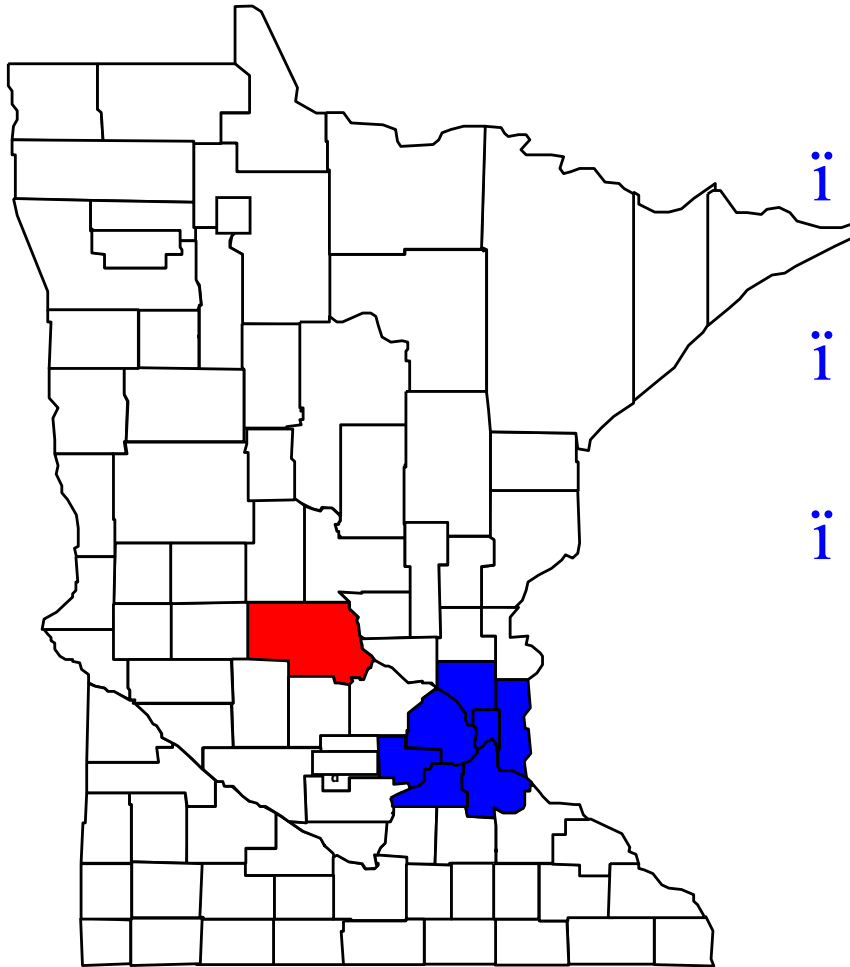
Outbreaks of *Shigella sonnei* Infections Associated with Parsley in North America, July-August 1998



1998 ETEC Outbreaks in Minnesota



Two ETEC Surveillance Sites



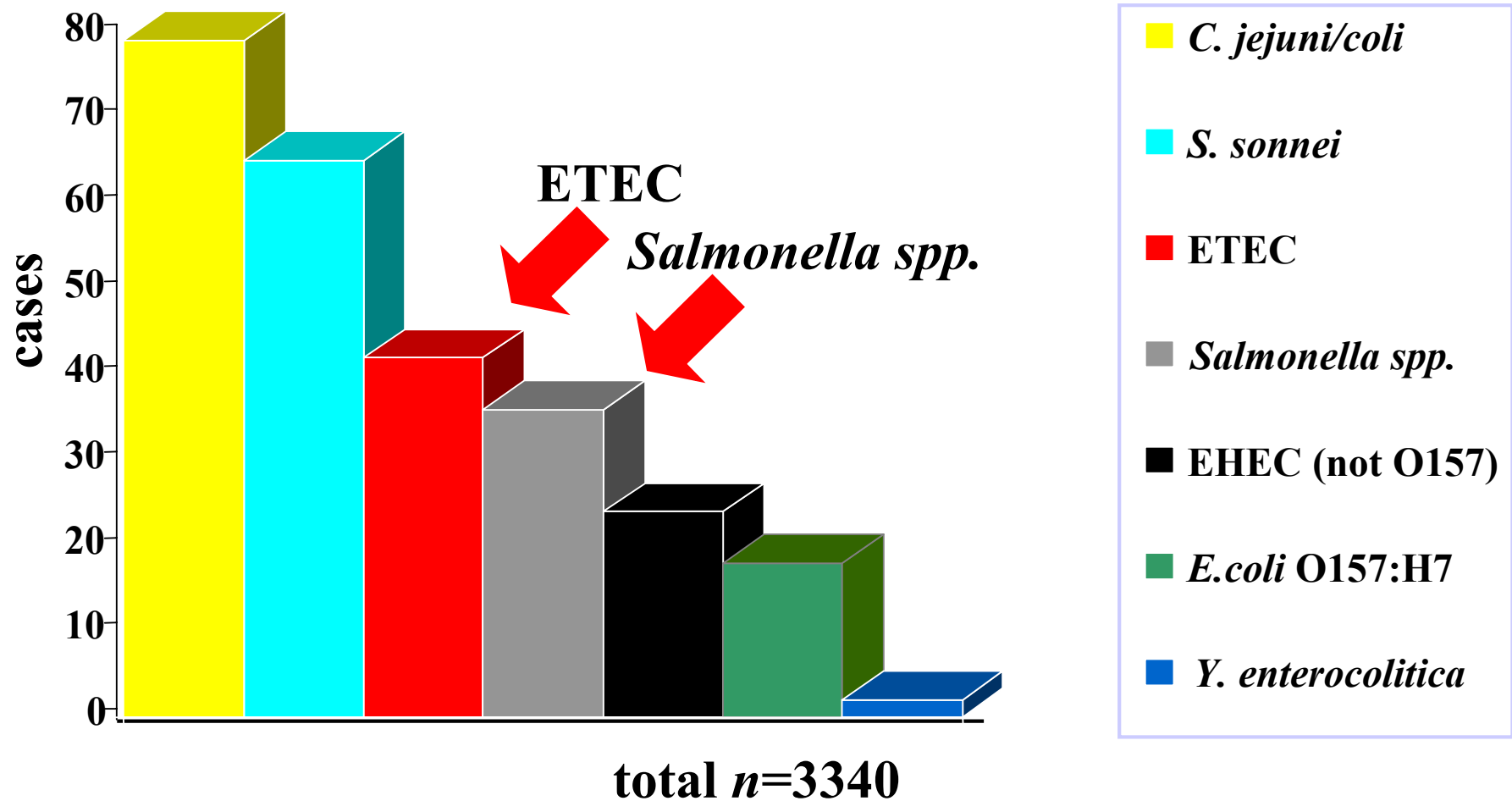
- i A major hospital
(primarily rural) area
- i A major HMO
(primarily urban)
- i Our laboratory
(statewide)

~6,000 samples/yr

~2,000/site/yr

Enteric Bacterial Pathogens in Two Sentinel Surveillance Sites

Minnesota; Jan ñ Sep 2000



Treatment of ETEC

Treatment shortens the duration of illness

i Ciprofloxacin

i Trimethoprim /
Sulfamethoxazole (SXT)

i Doxycycline

Problems with Treating ETEC

- i Testing not available**
- i Treatment largely empiric**
- i Travelers may use prophylaxis or self treat**
- i Susceptibilities to recommended antibiotics not known**

Etiology of Traveler's Diarrhea

ï ETEC

ï *Campylobacter spp.*

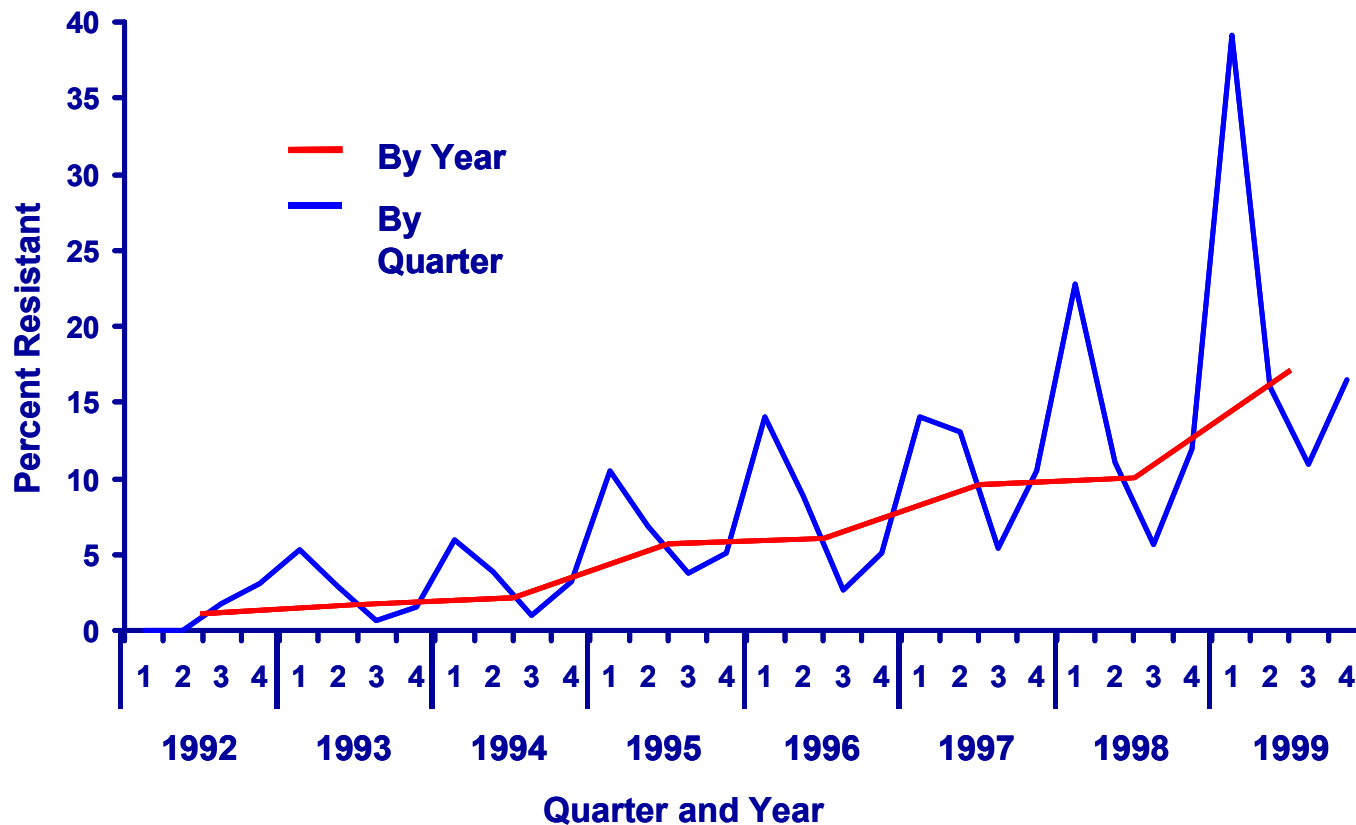
ï *Shigella spp.*

ï *Salmonella spp.*

ï *Giardia lamblia*

Fluoroquinolone Resistance in *Campylobacter jejuni*

Percentage of *C. jejuni* Isolates Resistant to Nalidixic Acid, Minnesota, 1992-1999

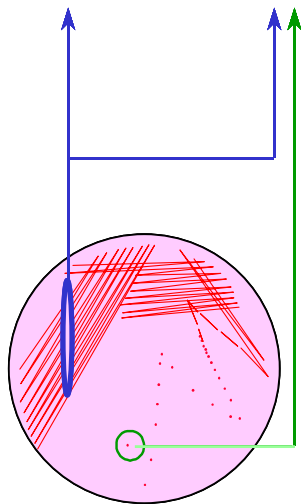


Research Questions

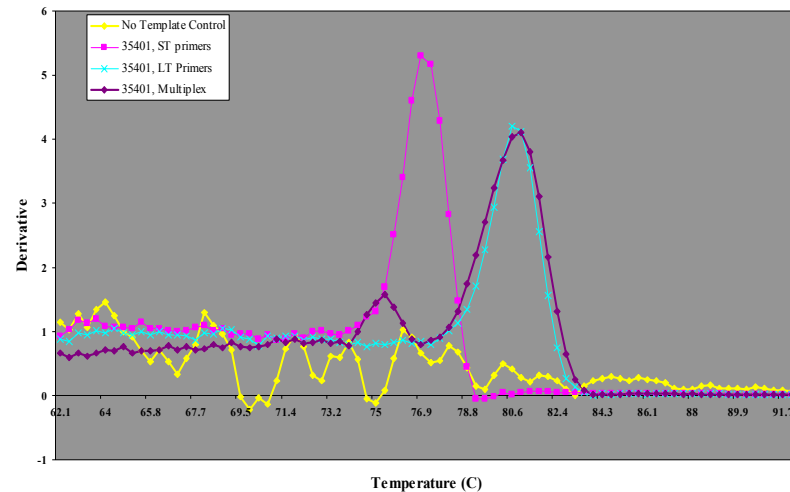
- i Is ciprofloxacin resistance a problem for ETEC?**
- i Are other antibiotics used empirically for traveler's diarrhea likely to be effective against ETEC?**

Methods

i Culture plates from surveillance sites were tested for ETEC ST and LT toxins



Standard PCR



ii Real-time PCR Methods

Methods

- i Culture plates from surveillance sites were tested for ETEC ST and LT toxins
- i Cases were interviewed to determineÖ .
 - ii recent travel history
 - ii antibiotic use before illness
 - ii potential exposures

Methods

- ï Culture plates from surveillance sites were tested for ETEC ST and LT toxins
- ï Cases were interviewed to determineÖ .
 - ï recent travel history
 - ï antibiotic use before illness
 - ï potential exposures
- ï A susceptibility panel was developed

Panel Development: Antibiotics used to treat Traveler's Diarrhea

	CIP	CEF	ERY	AZI	SXT	DOX	FUR
ETEC	X				X	X	
<i>C. jejuni/coli</i>	X		X	X			
<i>Shigella spp.</i>	X	X			X		
<i>Giardia</i>							X
<i>Salmonella</i>	Antibiotic R_x not recommended						

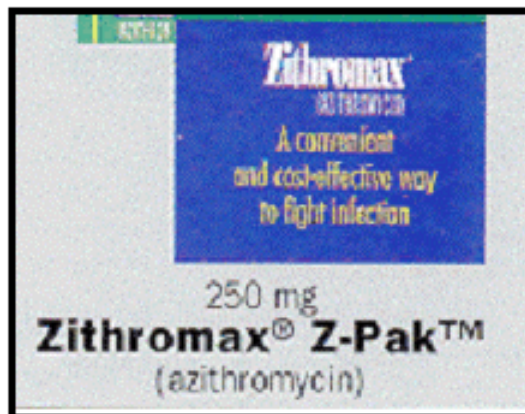
Antibiotic Panel

- ï **Ciprofloxacin**
- ï **Cefixime**
- ï **Erythromycin**
- ï **Azithromycin**
- ï **SXT**
- ï **Doxycycline**
- ï **Furazolidone**

Antibiotic Panel

Macrolides

- ï Used for R_x of traveler's diarrhea because of *Campylobacter spp.* coverage

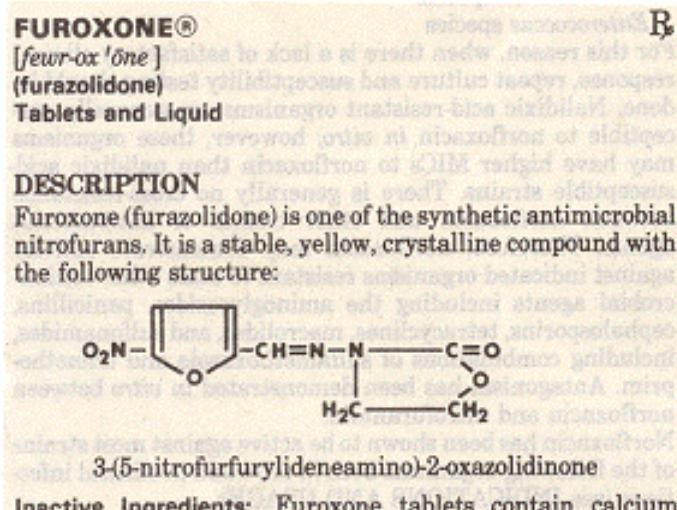


- ï Ciprofloxacin
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- ï **Erythromycin**
- ï **Azithromycin**
- ï SXT
- ï Doxycycline
- ï Furazolidone

Antibiotic Panel

Furazolidone

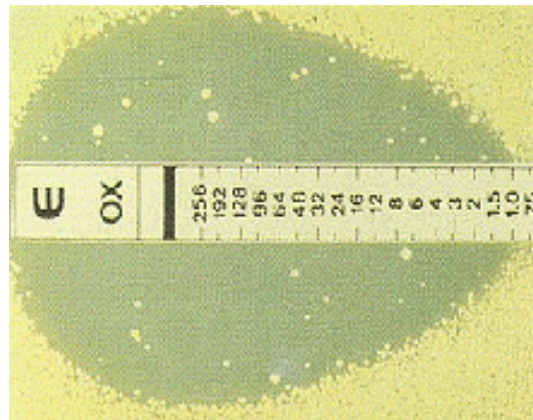
- i Widely used for treatment of *Giardia lamblia*
- i Broad spectrum activity against GI pathogens, including *E. coli* and *Vibrio cholera*



- i Ciprofloxacin
- i Cefixime
- i Erythromycin
- i Azithromycin
- i SXT
- i Doxycycline
- i **Furazolidone**

Microbiology Methods: Antibiotic Susceptibility Testing

- **E TEST**



Nitrofurantoin used as class representative for furazolidone

Macrolide Susceptibility Breakpoints

From NCCLS standards:

<i>interpretation</i>	azithromycin			erythromycin		
	S	I	R	S	I	R
<i>Staphylococcus spp.</i>	<u>≤2.0</u>	4	<u>≥8.0</u>	<u>≤0.5</u>	1-4	<u>≥8.0</u>
<i>Enterococcus spp.</i>	none			<u>≤0.5</u>	1-4	<u>≥8.0</u>
<i>Hemophilus influenzae</i>	<u>≤4</u>		<u>≥32</u>	none		

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<i>Enterococcus spp.</i>	none			<u>≤</u> 0.5	1-4	<u>≥</u> 8.0
<i>Hemophilus influenzae</i>	<u>≤</u> 4	<u>≥</u> 32		none		

Methods: Cases / Isolates

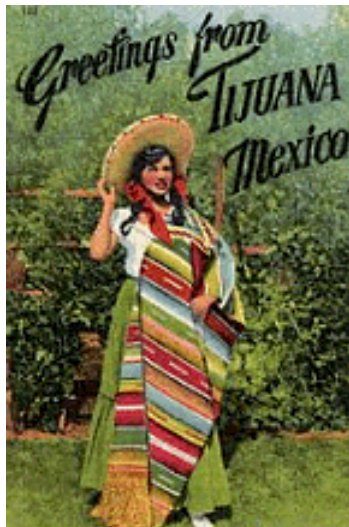
- i All viable ETEC isolates from Jan 2000 through Dec 2001 were tested ($n = 79$)
- i A small set of *Campylobacter spp.* ($n = 20$) and *Shigella spp.* ($n = 20$) were also tested

Results: Cases

- i 107 ETEC cases identified**
- i 79 viable isolates available for testing**
- i 63/79 (80%) of cases interviewed**
- i 40/63 (63%) of interviewed cases reported international travel**

Results: Travel Destinations

- ï Africa (2)
- ï Asia (5)
- ï Caribbean (4)
- ï Central America (4)
- ï Europe (3)
- ï Middle East (1)
- ï Mexico (13)
- ï South America (9)



ï No International Travel

23/63 (37%)



Minneapolis, MN

Results: Antibiotics Used Before Onset of Illness (3 cases)

	When taken	Susceptibility of isolate	Other
DOX	4 weeks before culture	susceptible to DOX	Onset date unknown, no travel
SXT	1 day before culture	susceptible to SXT	
CIP	3 days before culture	susceptible to CIP	

Results: ETEC Susceptibility

n = 79

	sensitive <i>n</i> (%)	intermediate <i>n</i> (%)	resistant <i>n</i> (%)
Ciprofloxacin	78 (99%)	-	1 (1%)
Cefixime	78 (99%)	-	1 (1%)
Erythromycin	11 (14%)	-	68 (86%)
Azithromycin	45 (57%)	31 (39%)	3 (4%)
SXT	59 (75%)	-	20 (25%)
Doxycycline	42 (53%)	2 (3%)	35 (44%)
Furazolidone	75 (94.9%)	-	4 (5%)

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Azithromycin	0 (0%)	0 (0%)	79 (100%)
SXT	59 (75%)	-	20 (25%)
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Campylobacter spp. sample:
All resistant

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n = 79

	sensitive <i>n</i> (%)	intermediate <i>n</i> (%)	resistant <i>n</i> (%)
Ciprofloxacin	78 (98.7%)	0 (0%)	1 (1%)
Cefixime	78 (98.7%)	0 (0%)	1 (1%)
Erythromycin	11 (14%)	5 (6%)	68 (86%)
Azithromycin	45 (57%)	31 (39%)	3 (4%)
SXT	59 (75%)	-	20 (25%)
Doxycycline	42 (53%)	2 (3%)	35 (44%)
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Ciprofloxacin	78 (99%)	-	1 (1%)	
Cefixime	78 (99%)	-	1 (1%)	
Erythromycin	<p><i>Campylobacter spp. and Shigella spp. samples:</i> High levels of resistance</p>			36%
Azithromycin				4%
SXT				25%
Doxycycline	42 (53%)	2 (3%)	35 (44%)	
Furazolidone	75 (94.9%)	-	4 (5%)	

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Erythromycin	<p><i>Campylobacter spp.</i> sample: All sensitive <i>Shigella spp.</i> sample: All sensitive</p>			68 (86%)
Azithromycin				3 (4%)
SXT				20 (25%)
Doxycycline				42 (53%)
Furazolidone	75 (95%)	-	4 (5%)	

Concerns

- i Widespread use of a 3rd generation cephalosporin such as cefixime for empiric therapy of traveler's diarrhea may not be warranted**
- i Although our data suggest that furazolidone may have broad spectrum activity against agents of traveler's diarrhea, there are concerns about potential carcinogenic activity**

Limitations

- i No data are available for individuals successfully treated, but not tested**
- i Results of *Campylobacter spp.* and *Shigella spp.* are suggestive only.**
 - i Small numbers tested**
 - i Not from the same population**
- i Susceptibility testing methods for macrolides not standardized for *E. coli***

Conclusions

- i Of the 3 recommended antibiotics recommended for treatment of ETEC, only ciprofloxacin was $\geq 90\%$ effective**
- i Azithromycin and furazolidone show promise for treatment of ETEC and other agents of traveler's diarrhea**
- i Doxycycline appears to have poor activity against all agents of traveler's diarrhea**

Special Acknowledgements

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² Minnesota Department of Health, Minneapolis MN

