# Shiga Toxigenic *E. coli*: a fully emerged, still underappreciated pathogen

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# Disclosures

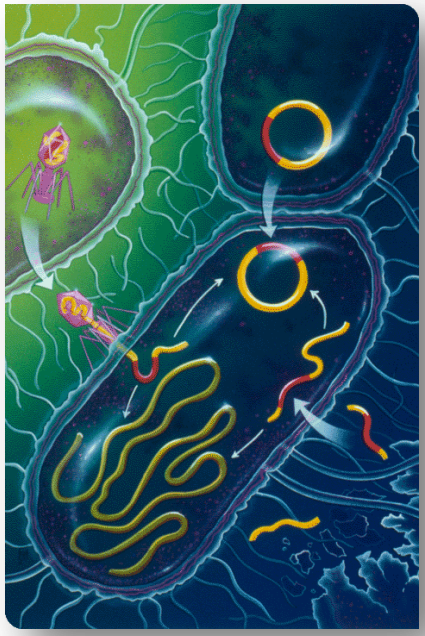
- Speaking fees/honorarium – Meridian Biosciences
- Honorarium – Biofire Diagnostics
- Research reagents – BioGX
- Research reagents - Alere

# Objectives

- Summarize the key features of STEC and the illnesses associated with infection
- Evaluate their laboratory methods to determine if their current practice meets the guidelines and recommendations for testing
- Evaluate their laboratory's ability to detect emerging strains of STEC

# Pathogenic *E. coli*

- Enteropathogenic *E. coli* (EPEC)
- Uropathogenic *E. coli* (UPEC)
- Enterotoxigenic *E. coli* (ETEC)
- Enteroinvasive *E. coli* (EIEC)
- Extraintestinal pathogenic (ExPEC)
- Enteroaggregative *E. coli* (EAggEC)
- Shigatoxigenic *E. coli* (STEC/EHEC/VTEC)



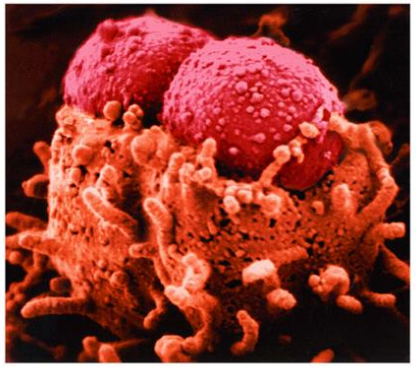
# What's in a name?

- STEC = shiga toxigenic *E. coli*
  - Toxin name is shiga-like toxin
- VTEC = verotoxigenic *E. coli*
  - Attributed to early cytotoxic effects seen in Vero cells (antiquated name)
- EHEC = enterohaemorrhagic *E. coli*
  - Attributed to blood loss from the bowel

# STEC


- First isolated in 1982
- Infectious dose 10-50 cfu
  - 3-8 day incubation period (dose dependent?)
- Media-worthy: several prominent foodborne disease outbreaks worldwide
  - Multiple deaths, significant healthcare dollars
- Conventionally serotyped by:
  - “O” lipopolysaccharide and “H” flagellar antigens

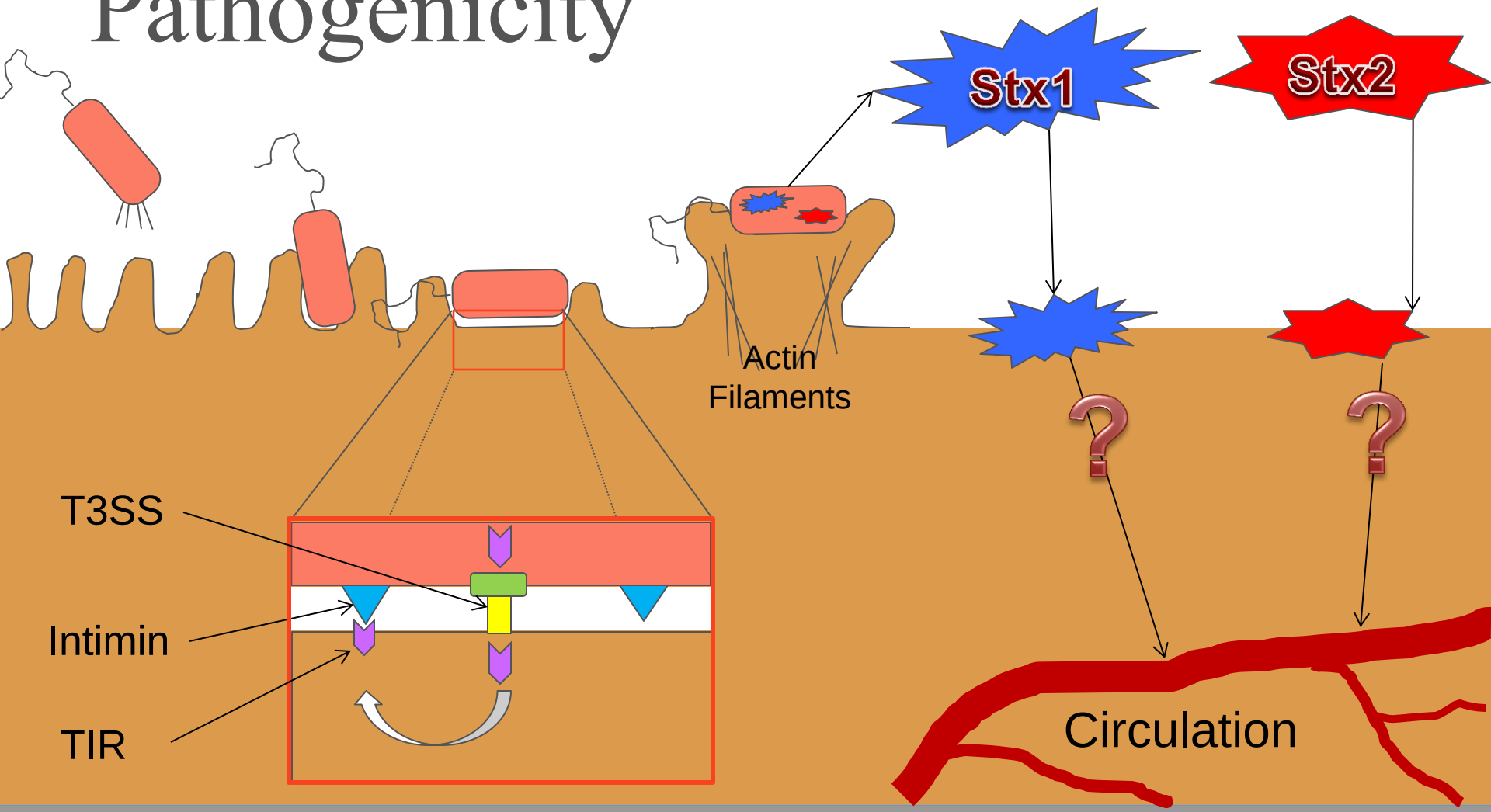
# What is STEC?



Nature Reviews | Microbiology

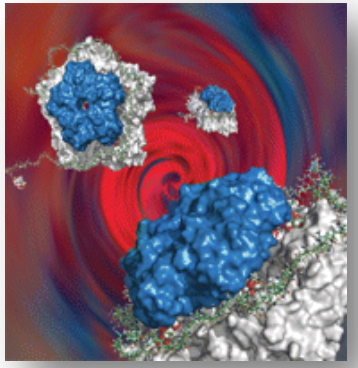
- Normal *E. coli*...
  - Considered of ungulate origin
  - Two phage-encoded shiga-like toxins
    - Stx1 – analogous to *Shigella dysenteriae* shiga toxin
    - Stx2 – unique toxin to STEC (~50% similar to Stx1)
  - LEE pathogenicity island
    - *eae* (Intimin)
    - TIR (transmembrane intimin receptor)
    - Type 3 secretion system
    - Attachment/Effacement lesions

# Pathogenicity



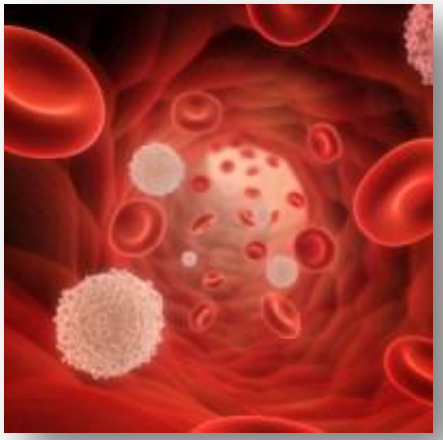
# Shiga toxin function

- Toxins enter circulation → kidney
- Subunit B binds globotriaosylceramide ($Gb_3$) receptor
  - Kidney >>> intestinal epithelium
  - Bovine lack vascular receptors
- Subunit A cytotoxic to cells
  - Inactivates ribosomes → renal cell death



# Hemolytic Uremic Syndrome (HUS)

- Glomerular endothelial cells swell & detach
- 2º activation of platelet & coagulation cascade initiated
  - Fibrin deposition → narrowing capillaries → RBC shearing
    = microangiopathic hemolytic anemia
  - Platelet consumption → thrombocytopenia
  - Restricted blood flow → renal failure



# Patient symptoms

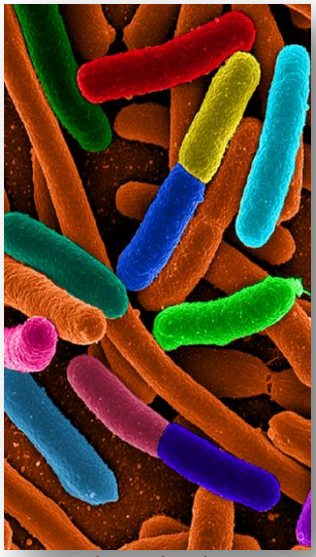
- Severe acute diarrhea +/- blood
- Afebrile
- ~8% of infections lead to HUS
- More complications in elderly & children
  - 10-15% of Peds develop HUS
  - Majority of patients >65 are hospitalized
- Children often require dialysis
- Early/aggressive IV isotonic volume expansion

# Therapy/Managment

- Antibiotic therapy is controversial
- Phage induction by Quinolones, TMP-SXT, β-lactams
  - S.O.S. response induces phage promotor expression = ↑ Stx production
- Antimotility agents may increase disease severity
- Supportive care is the gold standard
- Standard contact precautions

# STEC - serotypes

- 150+ disease assoc. serotypes
  - O157:H7 most commonly reported in USA
  - O26:H11 second most
  - Other virulent types also reported


www.the-scientist.com

- Typing for outbreak investigations

- Testing for toxin is the logical progression toward proper testing & comprehensive reporting

# Perceived degree of severity

- O157 Stx2
- O157 Stx1/2
- Non-O157 Stx2
- Non-O157 Stx1/2
- Stx1 any serogroup

- Stx2 +
- Stx 1/2
- Stx1

- Serogroup correlation may still be a biased phenomenon

# New guidelines

- 2009 MMWR guidelines: CDC/APHL recommend toxin detection plus culture for O157
  - Adoption has been slow and voluntary
- CAP - none
- Dec. 2012: JCAHO mandates shiga toxin detection for all stool specimens submitted for diarrheal illness

**EFFECTIVE July 1, 2013**

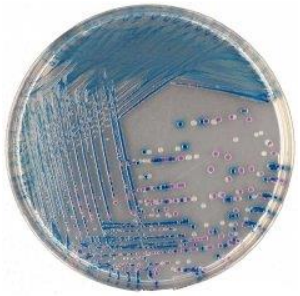
**Element of Performance for QSA.04.06.01**

A 6. All stool specimens from patients diagnosed with acute community-acquired diarrhea are simultaneously cultured for O157 Shiga toxin-producing Escherichia coli (STEC) on selective and differential agar and assayed for non-O157 STEC with a test that detects Shiga toxins or the genes encoding these toxins.

This is NOT voluntary, and typically CAP follows JCAHO…so stay tuned!

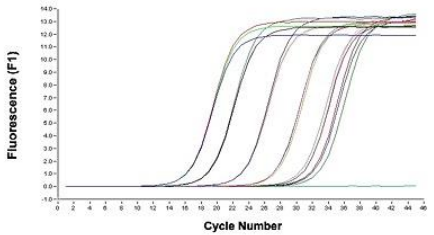
# Lab testing

- Culture

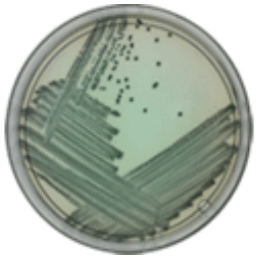


- EIA or Immunochromatographic detection of toxin


- PCR for *stx1* and *stx2* genes



# Culture



- Culture conditions select for O157
  - Sorbitol MacConkey +/- cefixime & tellurite (CT-SMAC)
  - CHROMagar® O157
  - Rainbow® O157 agar
- Results in <24 hours
- Cannot detect other STEC
- May detect shiga toxin negative O157 *E. coli*
- Can fail to recover O157 STEC
- Further contribute to a reporting bias when used alone

# EIA/Immunochromatography

- Detects toxin in sample
- High sensitivity
- No serogroup bias
- Cross react w/ *S.dysenteriae* toxin
- May not detect toxin subtypes
  *e.g.* $Stx2_d$ & $Stx2_e$*
- Variable specimen type




*Willford *et al*. *J Food Prot,* 2009

# Test performance

- Agreement with reference methods (per package inserts/510(k))

| | Immunocard ® STAT! EHEC[1] | Duopath® Verotoxin[1] | ProSpecT® EHEC[2] | Premier™ EHEC[2] | Shiga Toxin Quik Chek®[2] |
|---|---|---|---|---|---|
| Direct Stool | - | - | 87% | 78.9/95.8% | 98%/99.9% |
| Broth Enrichment | 89.1/99.7% | - | 92/100% | 100/97.9% | - |
| Colony testing | 100/99.7% | 99.5/97.5% | - | - | - |

[1] Premier EHEC as reference method
[2] Cytoxic culture as reference method

# EIA vs Immunochromatography

Factors to consider

- Laboratory model
  - Central vs satellite
- Cost
- Test volume
- Specimen preferred (enriched or raw?)



# Enriched stool vs raw?

- Quik Chek claims equivalent performance to enriched stool using direct from stool testing on LFA
  - Performed Quik Chek on all Pos. EIA specimens

- N= 5687 EIA performed: June 18, 2013 – July 16, 2014
  - 26 EIA positives **(0.46% positivity)**
  - 19 LFA positives

- 5 discrepant specimens arbitrated by PCR

# Discrepant resolution

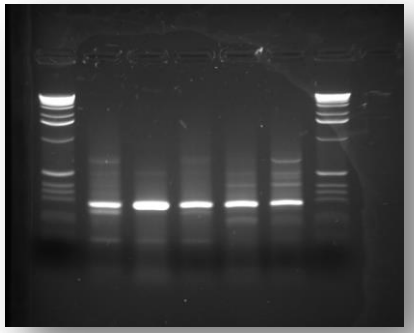
| EIA enriched | Quik Chek | PCR | EIA repeat enriched | Quik Chek enriched | PCR enriched | Final resolution |
|---|---|---|---|---|---|---|
| + | - | - | - | - | - | Negative for Shiga toxin, EIA false Pos |
| + | - | **Stx2** | + | **Stx2** | **Stx2** | Positive for Stx2, STEC |
| + | - | - | + | - | **Stx2** | Positive for Stx2, STEC |
| + | - | **Stx1** | - | - | **O157+** | Positive for Stx1, O157 STEC |
| + | - | **Stx2** | - | - | **Stx2** | Positive for Stx2, STEC |

Couturier et al. Manuscript in preparation, Poster presentation ASM 2015

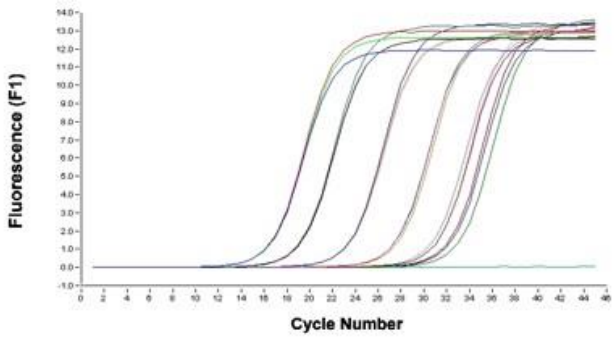
# Conclusion

- Stool enrichment with EIA detected 4 additional positive specimens that LFA could not detect
  - EIA detected one false positive, however LFA was not applied to all specimens received
- 25 true STEC positive specimens during our study period were detected by EIA using manufacturer's recommendations, only 21 detected by LFA
- At such a low prevalence (0.46%) this is an unacceptable performance loss; enrichment is recommended

# PCR



- Historically non-standardized
- Flexible throughput
- Better performance from enrichment culture
- Can screen single colonies
- Detect and identify each shiga toxin gene
  - Can design to detect *stx1/2* subtypes
- Indirect evidence of toxin
  - Expression?

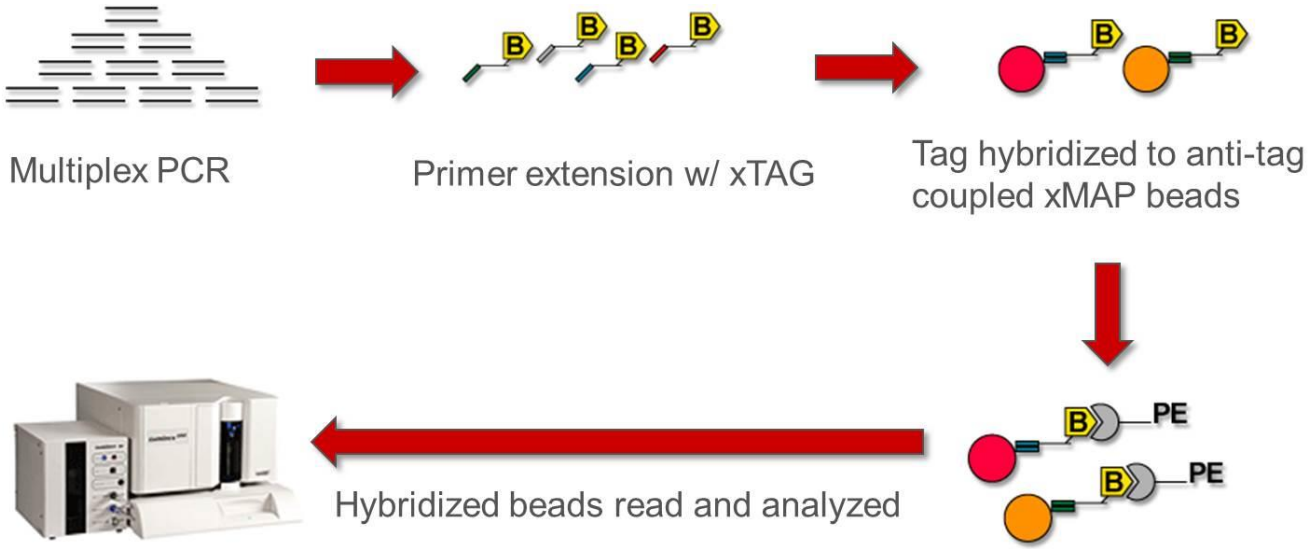


# FDA cleared methods for stx1/2

- Luminex™ Gastointestinal Pathogen Panel
- Prodesse® Progastro ® SSCS
- BioFire® FilmArray™ Gastrointestinal Panel
- Nanosphere Verigene® Enteric Pathogens Test
- BD MAX™ Enteric Bacterial Panel

# Luminex™ Gastointestinal Pathogen Panel

- Detect 11 GI pathogens
- Frozen stool: samples cannot be cultured
- High throughput, batch runs, complicated assay, 5+ hour TAT



# Published studies

- Navidad et al. *J Clin Micro* 2013.
  - 94% (28/30) sensitivity vs EIA and LDT PCR

- Claas et al. J. Microbiol Biotechnol 2013
  - 901 stools
  - STEC detection
    - 15/16 vs culture for O157
    - 8/8 vs EIA
      - » 1 False positive by Luminex
      - » 5 False negative by Luminex (unresolved)

# Prodesse® Progastro ® SSCS

- Detect *Salmonella, Shigella, Campylobacter*, and *stx*1 & *stx*2
- Frozen stool or Cary Blair preserved stool (allows for culture)
- High throughput, complicated assay, batch runs, 4 hour TAT

Extraction: Biomerieux NucliSENS easyMAG system

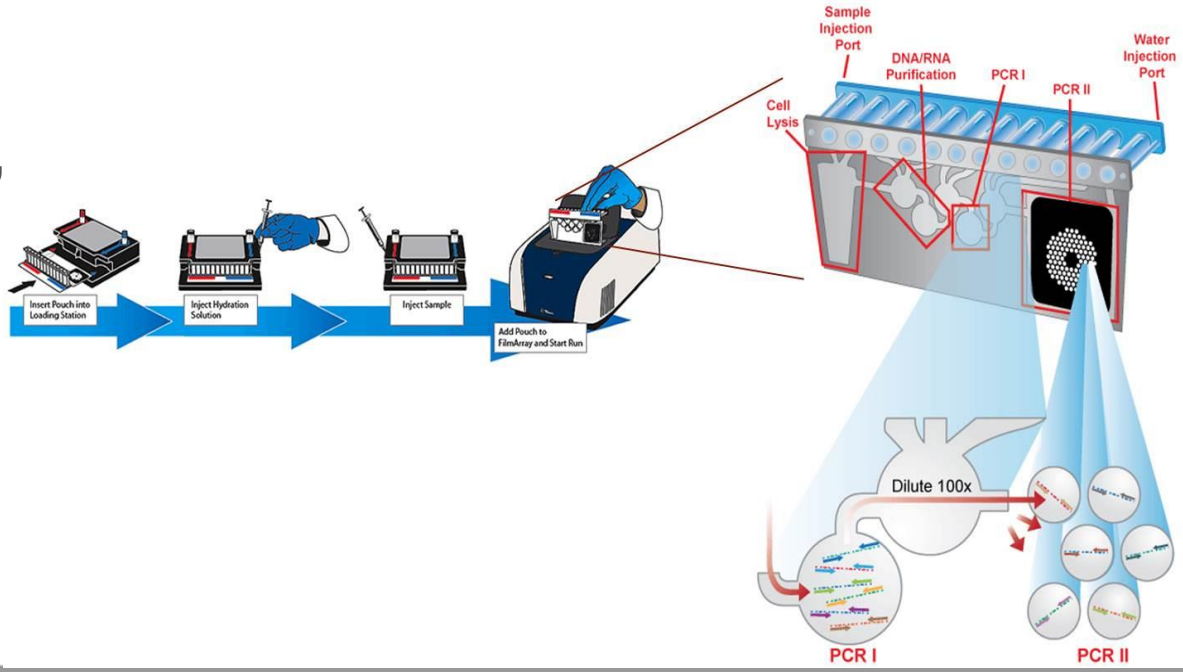

Amplification:
Cepheid Smart Cycler II

# Published study

- Buchan et al. *J Clin Micro* 2013.
  - 100% specificity (17/17), 99.9% specificity
    - 1 false positive stx (initially 9…8 resolved)
    - EIA/Cx only 54% sensitive compared to sequence confirmed specimens

# BioFire® FilmArray™ Gastrointestinal Panel

- Detects 22 pathogens/targets
- Cary Blair stool: can be cultured
- Low throughput,
  random access,
  very simple method,
  ~1 hour TAT

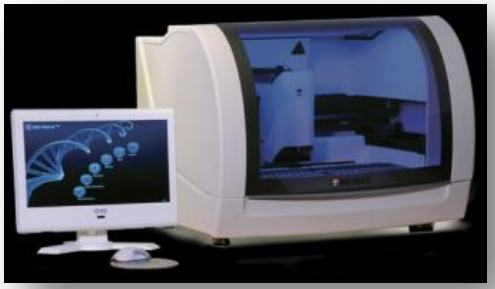


# Published study

- Buss et al. J. Clin Micro. 2015. 53(3).
- Detected 38 STEC versus 33 on comparator PCR method
  - “5 false positives” (N=1556 samples total)

# BD MAX™ Enteric Bacterial Panel

- Detects *Salmonella, Shigella, Campylobacter,* and *stx*1 & *stx*2
- Fresh unpreserved stool or Cary Blair: can be cultured
- Variable throughput, simple method, ~2.5 hour TAT



# Published study

- Harrington et al. J. Clin Micro. 2015. 53(3).
- Detected 85 STEC versus comparator PCR method or EIA/culture
  - 8 false positives after resolution (N=2437 samples total)

# Nanosphere Verigene® Enteric Pathogens Test

- Detects 7 pathogens/targets
- Cary Blair stool: can be cultured
- Variable throughput, random access, simple method, ~2 hour TAT

- No publications to date!

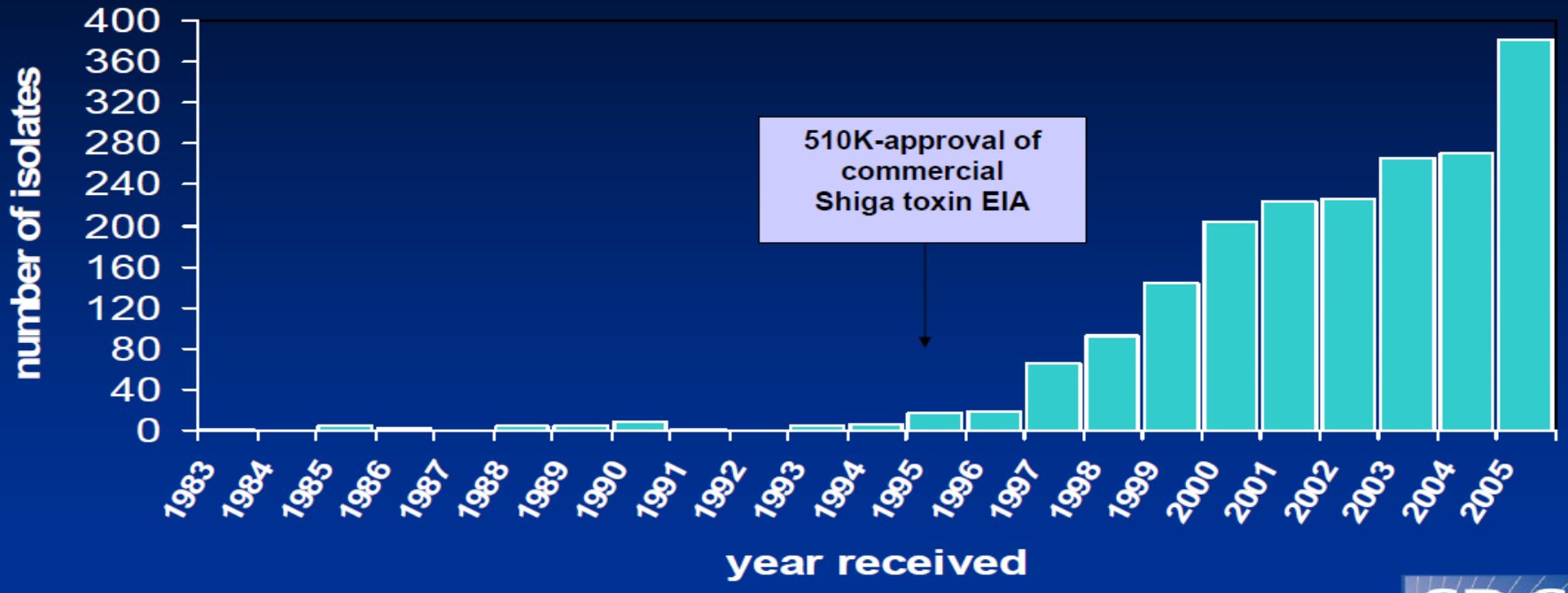

# So many methods…

How should a lab test for STEC?

# Strategies for detecting STEC

| Method | Detect all STEC | Detect non-toxigenic O157 | Comments |
|---|---|---|---|
| O157 Culture only | NO | YES* | • Must reflex to PHL to confirm toxin<br>• Contributes to biased reporting |
| O157 culture, toxin detection based on criteria (*e.g.* – bloody diarrhea, age <5 or >60, summer months, HUS, ruminant/farm exposure) | NO | YES | • Will detect some additional STEC, but not all<br>• Must reflex to PHL to confirm toxin<br>• Contributes to biased reporting |
| O157 culture + Toxin detection | YES | YES | • Provides recognizable name on preliminary report |
| Toxin detection reflex positive to O157 culture | YES | NO* | • Delayed ID of O157 if present<br>• Need to educate physicians as to importance of Stx detection |
| Toxin detection w/rapid submission to PHL | YES | NO* | • Delayed ID of O157 if present<br>• Need physician education as to importance of Stx detection<br>• May lead to broad appreciation of Stx vs serotype |

# 1,945 Isolates of Non-O157 STEC Serogrouped by CDC, 1983-2005




*CDC, unpublished data*

CDC
Centers for Disease Control and Prevention

With permission from Dr. Roberta Carey

# Increased reporting of non-O157 EHEC in Washington

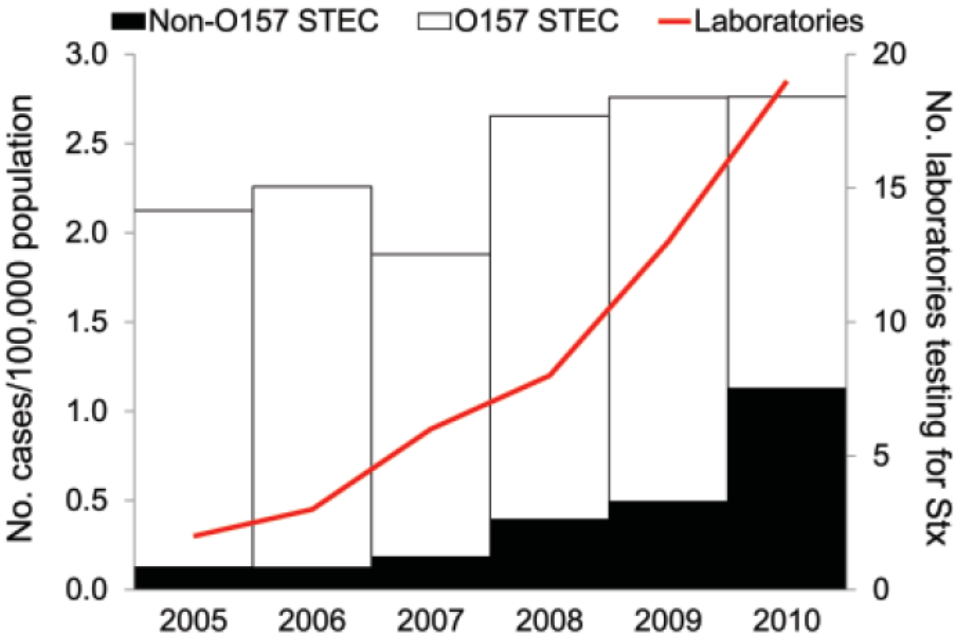
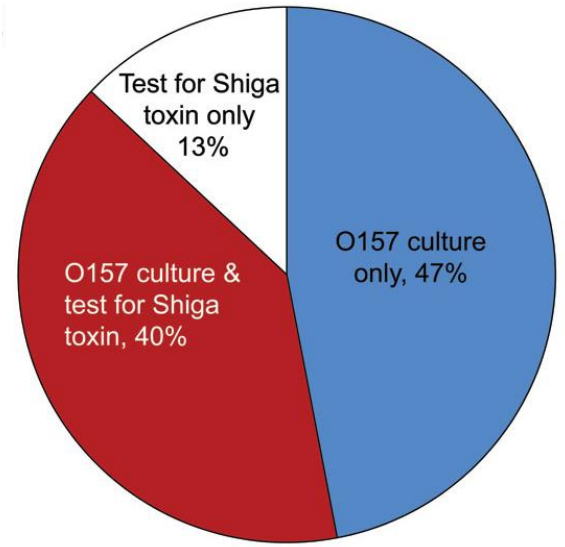



Figure 1. Rate of reported O157 and non-O157 Shiga toxin (Stx)–producing *Escherichia coli* (STEC) infections and number of laboratories performing Stx testing by year, Washington State, USA, 2005–2010.

Specimens tested




Stigi *et al*. *EID*, 2012

# Stool tested by PCR, submitted for viral enteritis

N= 2725 (2006-2008)

- 38 Stx+ specimens
- Cx pos.
  O157 (3) vs non-O157 (12)
- Previous outbreak strains
  O26:HNM, O26:H11,
  O103:H25, O121:H19,
  O145:HNM

TABLE 2. Shiga-toxigenic *E. coli* isolated from patient stool from Alberta and Northern Territories

| Yr | Serotype | Patient age | *stx* type(s) | Stool appearance |
|---|---|---|---|---|
| 2007 | O26:H11 | 83 yr | $stx_1$ | Liquid, brown |
| | Orough:H11 | 3 yr | $stx_1$ | Liquid, brown |
| | O11:H30 | 3 yr | $stx_1$ | Liquid, brown |
| | O157:H16 | 2 yr | $stx_1/stx_2$ | Solid, brown |
| | O6:H16/O103:H25 | 31 yr | $stx_1$ | Liquid, brown |
| 2008 | O145:HNM | 8 mo | $stx_1$ | Liquid, tan |
| | O26:HNM | 13 yr | $stx_1$ | Liquid, brown |
| | O69:H11 | 52 yr | $stx_1$ | Solid, brown |
| | O26:H11 | 6 mo | $stx_1$ | Liquid, yellow |
| | Orough:HNM | 16 mo | $stx_1$ | Semisolid, brown |
| | O121:H19 | 10 yr | $stx_1/stx_2$ | Liquid, brown |
| | O157:H7 | 48 yr | $stx_1/stx_2$ | Liquid, brown |
| | O157:H7 | 3 yr | $stx_1/stx_2$ | Liquid, brown |
| | O103:H25 | 16 yr | $stx_1$ | Semisolid, brown |

# Comprehensive detection

N= 2328 (2009-2010)

- 21 Stx+ identified
- 8, O157:H7 (5 bloody)
- 13, Non-O157 (5 bloody)
- Culture only method (8/21 detected)
- Criteria-driven and culture-only methods would underdiagnose

| *E. coli* serotype | Age (yr) | Stool sample description |
|---|---|---|
| O157:H7 | 5 | Liquid |
| O157:H7[a] | 23 | Liquid, bloody, mucoid |
| O157:H7 | 26 | Mucoid, bloody |
| O157:H7 | 37 | Liquid |
| O157:H7 | 66 | Bloody, liquid |
| O157:H7 | 15 | Blood speckled, liquid |
| O157:H7 | 22 | Bloody, liquid |
| O157:H7 | 51 | Liquid |
| O26:H11 | 3 | Liquid |
| O6:H2 | 20 | Bloody, liquid |
| O111:HNT | 21 | Bloody, mucoid |
| O5:HNM | 28 | Liquid |
| O111:HNM | 34 | Bloody |
| O103:H25[a] | 45 | Mucoid |
| O121:H19 | 54 | Liquid |
| O111:HNM | 57 | Liquid |
| O121:H19 | 17 | Semiformed |
| O121:H19 | 17 | Liquid |
| O5:HNM | 21 | Liquid, bloody |
| O145:HNM | 21 | Bloody, liquid |
| ONT:H25 | 34 | Mucoid |

Chui *et al.* *J Clin Micro* 2012

# Review

- Testing for shiga-toxins is necessary for comprehensive detection of STEC: non-O157 are a significant proportion of infections
- Sporadic nature of these infections paired with outbreaks demands constant surveillance through incorporation into routine testing
- Number of infections overall is still underappreciated based on current testing practices

# Infamous outbreaks

| Year | Serotype | Source | Location | Cases | HUS | Deaths |
|---|---|---|---|---|---|---|
| 1993 | O157:H7 | Jack in the Box hamburgers | US Northwest | Several 100 | 3 | 4 (children) |
| 1996 | O157:H7 | Odwalla apple juice | NW US/Canada | 65 | 13 | 1 (16 mo) |
| 2000 | O157:H7 | Public Water Supply | Walkerton, Ontario | ~2500 | 24 | 7 |
| 2006 | O157:H7 | Bagged spinach (CA) | 26 states | 199 | 31 | 3 |
| 2008 | O111:HNM | Country Cottage Buffet | Oklahoma | 341 | 17 (9 children) | 1 |

http://www.cdc.gov/ecoli/outbreaks.html

# Recent outbreaks

| Year | Serotype | Source | Location | Cases | Hospitalized | HUS | Deaths |
|---|---|---|---|---|---|---|---|
| 2009 | O157:H7 | JBS Swift Beef Co/Fairbanks Farms Beef | 8 states | 26 | 19 | 5 | 2 |
| 2009 | O157:H7 | Nestle Raw cookie dough (flour) | 30 states | 72 | 34 | 10 | 0 |
| 2010 | O145 | Shredded romaine lettuce | 5 states | 30 | 12 | 3 | 0 |
| 2011 | O157:H7 | Romaine lettuce | 10 states | 60 | 30 | 2 | 0 |
| 2012 | O126 | Jimmy John's clover sprouts | 11 states | 29 | 7 | 0 | 0 |

http://www.cdc.gov/ecoli/outbreaks.html

# Recent outbreaks

| Year | Serotype | Source | Location | Cases | Hospitalized | HUS | Deaths |
|---|---|---|---|---|---|---|---|
| 2012 | O157:H7 | Organic spinach/spring mix blend | 5 states | 33 | 15 | 2 | 0 |
| 2013 | O121 | Frozen food products | 19 states | 35 | 9 | 2 | 0 |
| 2013 | O157:H7 | Ready-to-eat salad (sold @ Trader Joe's) | 4 states | 33 | 11 | 2 | 0 |
| 2014 | O121 | Raw clover sprouts Evergreen Fresh Sprouts (Idaho) | 6 states | 19 | 8 | 0 | 0 |

http://www.cdc.gov/ecoli/outbreaks.html

# Recent outbreaks

| Year | Serotype | Source | Location | Cases | Hospitalized | HUS | Deaths |
|---|---|---|---|---|---|---|---|
| 2014 | O157:H7 | Ground beef Wolverine Packing Co. | 4 states | 12 | 7 | 0 | 0 |
| 2015 | O26 | Chipotle Mexican Grill | 14 states | 60 | 22 | 0 | 0 |
| 2015 | O157:H7 | Costco Rotisserie chicken salad | 7 states | 19 | 5 | 2 | 0 |
| 2016 | O157 | Alfalfa sprouts Jack & The Green Sprouts | 2 states | 11 | 2 | 0 | 0 |

http://www.cdc.gov/ecoli/outbreaks.html

# Source and cause summary

Major outbreaks since 2009
(advent of broad toxin testing adoption):

- Produce vs Meat = 9 vs 4
- O157 vs non-O157 = 8 vs 5

Non-O157 likely still underreported

- Pre 2009: 5 O157 vs 1 non-O157

The worst case scenario

# THE 2011 O104:H4 GERMAN STEC OUTBREAK

# Timeline of events - 2011

- May 23rd – Robert Koch Institute reports unusual number of HUS & bloody diarrhea attributable to STEC
  - Samples first detected May 8th
- May 24th – WHO contact Danish *E. coli* network after German patient diag/w STEC
  - Isolate typed as O104:H4 & positive for shiga-toxin production ($Stx_{2a}$)
  - Subsequent German samples all type as O104:H4
- May 26th – Spanish cucumbers implicated in outbreak by PCR
- May 30th – O104:H4 specific PCR developed in Germany
- June 6th – whole genome sequence assembled & released
- June 10th – O104:H4 detected on fenugreek sprouts by PCR

Mellmann *et al*. 2011, PLoS One: 6(7).

# The final numbers (*circa* July 22)

- Total diagnosed infections: 4075
- HUS cases: 908 cases
  - 22.3% (atypical)
  - 34 deaths (3.7 % fatal)
- Non-HUS cases: 3167
  - 16 deaths (0.05% fatal)
- Sporadic cases in Europe, US, & Canada

| Country | HUS | | STEC | |
|---|---|---|---|---|
| | Cases | Deaths | Cases | Deaths |
| Austria | 1 | 0 | 4 | 0 |
| Canada | 0 | 0 | 1 | 0 |
| Czech Republic | 0 | 0 | 1 | 0 |
| Denmark | 10 | 0 | 15 | 0 |
| France | 7 | 0 | 10 | 0 |
| Germany | 857 | 32 | 3078* | 16 |
| Greece | 0 | 0 | 1 | 0 |
| Luxembourg | 1 | 0 | 1 | 0 |
| Netherlands | 4 | 0 | 7 | 0 |
| Norway | 0 | 0 | 1 | 0 |
| Poland | 2 | 0 | 1 | 0 |
| Spain | 1 | 0 | 1 | 0 |
| Sweden | 18 | 1 | 35 | 0 |
| Switzerland | 0 | 0 | 5 | 0 |
| UK | 3 | 0 | 4 | 0 |
| USA | 4 | 1 | 2 | 0 |
| Total | 908 | 34 | 3167 | 16 |

# Atypical presentation

- Median age of patients with HUS, 42 y.o.
- HUS distribution:
  - 2% < 5 y.o. vs normally 69%
  - 88% of HUS cases were in adults (20X normal)
- Bloody diarrhea (adults 91% vs children 64%)
- Severe neurological symptoms (48%, 104/217)
- Many received Abx (mero, azithro, rifaximin, tigecycline)
  - Outcome data pending; carbapenems and rifampin were recommended in some cases
- Person-to-person??

Frank *et al*. 2011, NEJM: 365(19).
Magnus *et al.* 2012. *Brain*, Apr. 26 (Epub)

# Strain characteristics

- The German STEC is not actually STEC!!
- Screening PCR found genes for the aggregative adhesin locus of EAggEC
- All biochemical profiles similar for EAggEC & less for STEC
- Genome sequence suggests EAggEC was phage-transduced w/ Shiga-toxin bacteriophage

# A strange duck

- Intimin-negative – rare for STEC
  - Typically don't cause HUS in children
- O104:H4 is a rare serotype for Stx production
- Encodes antibiotic determinants
  - TEM-1 broad spectrum β-lactamase
  - CTX-M-15 ESβL also confers cefepime resistance
- Because shiga-toxin is major factor, strain has been termed an STEC

Frank *et al*. 2011, NEJM: 365(19).
Mellmann *et al*. 2011, PLoS One: 6(7).

# Not as unique as we thought

- Review of unpublished data from PulseNet & EU Surveillance Network
- Stx2+ O104:H4 in databases
  - 2001 – 2 patients w/HUS, Germany (EAggEC/STEC)
  - 2004 – 1 patient (no clinical Hx), France
  - 2005 – 1 HUS, Korea
  - 2009 – 2 HUS, Republic of Georgia (EAggEC/STEC)
  - 2010 – 1 severe diarrhea, Finland (EAggEC/STEC)

# The Forgotten French experience

- 1995, small outbreak of HUS linked to O111 STEC/EAggEC strain ($Stx_{2a}$+)
- 1º children
- Severe disease & ↑ HUS
- Suggests this combination may be more potent for disease


Boudailliez. 1997, Pediatr Nephrol: 11(1) 36-39.

# All Quiet on the Western Front

- Outbreak diminished per mid-July 2011
- Largest & deadliest STEC outbreak in history
- Food inspection agencies reviewed processes
  - Egyptian sprout seeds implicated
- Multinational effects - 16 nations w/ cases

# How would labs fare in this outbreak now?

| Method | Detect EAggEC/STEC emerging pathogen??? | Comments |
|---|---|---|
| O157 Culture only | No | • Miss all infected patients! |
| O157 culture, toxin detection based on criteria (*e.g.* – bloody diarrhea, age <5 or >60, summer months, HUS, ruminant/farm exposure) | Maybe | • Symptoms were atypical<br>• Most patients were >5 and <60<br>• Many children non-bloody<br>• Ruminant/farm exposure absent<br>• Severe cases without HUS<br>• BUT, all were summer, and many adults were bloody… |
| O157 culture + Toxin detection/PCR | **YES** | • Toxin is unchanged, will detect<br>• No delay |
| Toxin/PCR detection reflex positive to O157 culture | **YES** | • Toxin is unchanged, will detect<br>• No delay |
| Toxin/PCR detection w/rapid submission to PHL | **YES** | • Toxin is unchanged, will detect<br>• No delay |

# Key Points

- Not a seasonal illness – occurs year round
- Geographically unpredictable
- Bloody diarrhea – poor universal predictor of STEC
- >60% of sporadic cases and 40% of outbreaks are non-O157
  - Must screen for shiga toxins or genes
- Prevention of HUS only achievable 3-4 days after onset of illness
  - Delays are critical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