Shiga-toxigenic *Escherichia coli* (including O157, non-O157 & HUS)

Investigative Guidelines

March 2018

REPORT WITHIN 1 WORKING DAY

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. To identify outbreaks and potential sources or sites of ongoing transmission.
2. To assess the risk of the case transmitting infection to others, and to prevent such transmission.
3. To educate people about how to reduce their risk of infection.
4. To identify other cases.
5. To better characterize the epidemiology of this infection.

1.2 Laboratory and Physician Reporting Requirements

1. Laboratories and physicians are required to report within one working day of identification/diagnosis. Hemolytic uremic syndrome (HUS) is a clinical diagnosis; physicians must report cases regardless of identification of a specific etiologic agent.
2. Isolates must be sent to Oregon State Public Health Laboratory (OSPHL).

1.3 Local Health Department Reporting and Follow-Up Responsibilities

1. Report all confirmed, presumptive and suspect cases to the Oregon Public Health Division (OPHD) Acute and Communicable Disease Prevention Section (ACDP) (see definitions below) as soon as possible, and no later than the end of the calendar week of initial physician/lab report. Enter information about the case into Orpheus as you gather it during your investigation.
2. Begin follow-up investigation of cases within one working day. Use the STEC/*Escherichia coli* O157 case investigation form, unless it is HUS without antecedent diarrhea (see box page 2). Enter all data into Orpheus as soon as possible, and no later than seven days after the initial report.
3. Ensure that labs forward all patient isolates to the OSPHL for further characterization as required by law. If a suspected O157 isolate is not recovered, the Shiga toxin-positive broth, or specimen, should be forwarded to OSPHL for additional testing.

A Note about HUS Reporting

The requirement for HUS reporting is primarily a roundabout way of finding otherwise unreported STEC infections, and secondarily a way of learning about other potential causes of HUS. A case is de- fined as such by the attending physician—typically a nephrologist or gastroenterologist. (See §2.2.) HUS reports can occur in one of three contexts.

1. Secondary to a confirmed STEC infection: follow-up as for any other STEC case.
2. Secondary to a presumptive STEC infection (see definitions in §3.2): consult immediately with ACDP epidemiologists for current protocols in place to confirm an etiology for these cases; otherwise follow-up as for any other STEC case.
3. Not following any diarrheal illness and not epi-linked to any STEC cases: consult with ACDP epidemiologists. Generally, no specific follow-up is required for these cases by the LHD. Mark them "NOT STEC-related."

The following guidelines generally presume you are investigating STEC-related illness, including O157 and non-O157 serogroups.

2. THE DISEASE AND ITS EPIDEMIOLOGY

2.1 Etiologic Agent

There are hundreds of different *E. coli* serogroups—which (collectively) are ubiquitous in the intestines of warm-blooded vertebrates. These Gram-negative bacteria are classified by their "O" (cell wall) and "H" (flagellar) antigens. [Note that it is a letter "oh", not a zero.] Most *E. coli* serogroups are non-pathogenic. Those that cause human disease are sometimes grouped by pathogenic mechanisms: enterohemorrhagic, enteroinvasive, enteropathogenic, enterotoxigenic, and enteroadherent, although the terms can be misleading. Enterohemorrhagic *E. coli* (EHEC) are now more commonly referred to as Shiga-toxigenic *E. coli* (STEC) or occasionally Vero-toxigenic *E. coli* (VTEC).

Historically, the most common STEC reported has been *E. coli* O157:H7. Less commonly, non-motile O157 organisms (O157:NM, aka O157:H-) occur, which may cause similar illness. Reports of illnesses caused by non-O157 STEC (e.g., O26, O104, O103, O21) have been increasing steadily since 1995 when laboratory tests for detecting these organisms started to become available. Since 2013, more non-O157 than O157 infections have been reported in Oregon each year. Non-O157 STEC can also cause severe illness, but virulence varies by serogroup. Virulence is partially determined by toxins the organism produce—Shiga toxin 1 and Shiga toxin 2. Shiga toxin 2 is more often associated with severe manifestations such as HUS. In Oregon, 13% of reported O157 cases and 2% of non-O157 developed HUS children five years and under are at the greatest risk of developing HUS.

2.2 Description of Illness

Mild, non-bloody diarrheal illness and even asymptomatic infections are common, albeit rarely diagnosed outside outbreak settings. Most diagnosed

cases report bloody stools (62% of Oregon cases), which typically begin 6-48 hours after the onset of non-bloody diarrhea. Diarrhea may be accompanied by abdominal cramps, often quite severe (and sometimes the chief complaint). Nausea and vomiting are also common. Fever is generally absent or low-grade, in contrast to, say, salmonellosis, shigellosis, or campylobacteriosis. Among all reported STEC cases in Oregon, 24% have been hospitalized.

HUS. After 3–10 days, 5%–15% of diagnosed patients may develop hemolytic uremic syndrome (HUS; a combination of microangiopathic hemolytic anemia, thrombocytopenia, and elevated creatinine). Early clinical signs of HUS may include decreased urine output, pallor, and lethargy. Patients with HUS have a variable degree of renal insufficiency that may necessitate dialysis (short- or long-term) or even transplant; there is a greatly increased risk of stroke and other complications. STEC infections are the principal cause of reported cases of HUS in Oregon, particularly for children. Thrombotic thrombocytopenic purpura (TTP), another complication of STEC infection, is very similar to HUS, with prominent neurologic signs (seizures, confusion, etc.); TTP primarily affects adults. Although uncommon, STEC-caused HUS or TTP can occur without antecedent diarrheal illness.

Although the O157:H7 serotype may be more likely to cause hospitalization and HUS, non-O157 STEC infections do result in bloody diarrhea, hospitalization, and HUS. In several small case series, up to 30% of identified non-O157 infections resulted in HUS. Consequently, non-O157 STEC infections should be treated as aggressively as O157:H7 infections. Children with bloody diarrhea should be closely monitored for the development of HUS. If a complete blood cell count with smear, blood urea nitrogen and creatinine are normal 3 days after the resolution of diarrhea, it is unlikely that HUS will develop. See reference information created by Multnomah County to share with health care providers.

2.3 Reservoirs

Cattle are the best characterized reservoir species for STEC. Some 50-80% of cattle herds — both beef and dairy — may be colonized by O157, although on any given day very few animals may test positive. Within a herd, colonization of individual animals (and fecal shedding) is transient. Thus, negative results from herd screening are difficult to interpret. O157 does not cause any illness in bovines, and there is no way known to eradicate it from herds. Wild cervids (deer and elk) are another reservoir, and can also be long-term hosts. Sheep and goats are other potential sources of human STEC infection. There have been a handful of isolations reported from other creatures, including dogs, horses, flies, and seagulls. Environmental reservoirs such as water troughs and cattle feed may be important in maintaining STEC in cattle herds.

2.4 Sources and Routes of Transmission

Fecal-oral. Most human infections are probably foodborne. The infectious dose for O157 is very low — probably <100 organisms. STEC is excreted in the feces of colonized humans and other animals. Undercooked beef (especially

hamburger), other foods cross-contaminated with same, and raw milk are among the most commonly identified sources of infection in common-source outbreaks, reflecting the fact that these foods are essentially always contaminated with cattle manure. Runoff from fields where cattle are grazing, or water that has been contaminated by cattle then used to water crops (e.g., spinach) have been known to cause human illness as well.

Venison is another potential source. Contaminated produce, including lettuce, spinach, alfalfa sprouts, and unpasteurized apple cider are other well-recognized sources. More recently, flour has been implicated as a vehicle of infection. Person-to-person transmission is also common, either directly (especially in day care centers) or indirectly (as in contaminated drinking or recreational water). Infected food handlers are another possible source, although they are rarely identified. Airborne transmission (ingestion of dried manure?) was suggested to have contributed to the Lane County Fair outbreak in 2002.

2.5 Incubation Period

Variable; for O157 almost all within 1–10 days (most commonly 2–6 days).

2.6 Period of Communicability or Infectious Period

The organism is shed in stool for at least the initial period of diarrhea, and variably thereafter. Children typically shed O157 for 2–4 weeks after onset—adults a bit less—but excretion for up to four months has been reported. Long-term carriage has been reported in cattle, but has not been documented in humans. Antibiotic treatment is not known to affect duration of excretion and may increase risk of developing HUS. Shedding of non-O157 strains is not well characterized, but can be prolonged. A study in a day care found shedding of O26 for a median of 29 days, with a range of 15 to 46.

2.7 Treatment

No specific therapy for STEC has been identified that mitigates or shortens illness, and CDC does not recommend antibiotic therapy for patients with suspected STEC infection. Rehydration is indicated, especially when vomiting or diarrhea is severe. In vitro tests of antibiotic susceptibility do not correlate with in vivo efficacy, and most experts recommend no antibiotic therapy. Although (unfortunately) commonly given, sulfa drugs (e.g., Septra® [TMP-SMZ]) are probably contraindicated; some early data suggested that they may increase the risk of developing HUS. Other studies suggest they are probably harmless, but none suggest that they do any good. Anti-motility drugs (e.g., Lomotil®) may also increase the risk of complications. At this writing, we discourage antibiotics and anti-motility drugs. The best treatment is supportive care.

Data from the Foodborne Diseases Active Surveillance Network (FoodNet) found that young children have an increased risk of HUS after *E. coli* O157 infection, while elderly have the highest rate of associated death, regardless of whether they develop HUS. These findings support recommendations that young

children and elderly persons receive aggressive supportive care during early stages of illness due to *E. coli* O157:H7.

3. CASE DEFINITIONS, DIAGNOSIS AND LABORATORY SERVICES

In recent years, reported STEC infections in Oregon have outnumbered *Shigella* infections two to one, and are probably the most common bacterial cause of bloody diarrhea. The diagnosis may be missed if appropriate selective stool culture media and Shiga-toxin assay are not ordered and performed correctly. Accurate and prompt diagnosis is necessary for implementation of appropriate treatment and control measures.

To detect STEC, most Oregon labs culture stools using O157-selective media (typically sorbitol-MacConkey agar, aka SMAC, or chrome agar) and a Shiga-toxin assay, which is CDC's current recommendation to maximize sensitivity. If the O157 culture is positive, the clinical lab sends the isolate to OSPHL for confirmation and subtyping. O157 isolates with an H7 antigen present may be assumed to produce Shiga toxin. If only the Shiga-toxin assay is positive, the clinical lab sends a selective broth to OSPHL for culture and subsequent typing. Currently, OSPHL can detect the most common serogroups: O157, O26, O45, O103, O111, O121, and O145. If an isolate is not from any of these serogroups, it is forwarded to CDC for identification (which may take several months). OSPHL performs PFGE and whole genome sequencing (WGS) on all STEC isolates it receives.

Some Oregon labs only perform one method, either culture with the O157-selective media or the Shiga-toxin assay alone. Doing so may miss STEC cases. If you are concerned, you can ask the lab what methods they use and whether they are able to employ another method. Some healthcare providers may not be aware that they can order that both methods be used. ACDP is working with individual labs to encourage them to perform a culture and, if positive, to send the isolate to OSPHL.

A few labs perform the Shiga-toxin assay directly on stool, which may delay recovery of the organism. It can be difficult for OSPHL to find the STEC organism if they receive a mixed broth, so it is preferable that clinical labs perform the assay on a selective broth to improve recovery of the organism.

Almost all patients with HUS develop antibodies to the O antigen of the bacteria. For culture-negative patients with HUS, you can arrange for a leftover serum sample to be tested for STEC antibodies at CDC. Two to six weeks after onset is the best time to draw (consult with ACDP epidemiologists).

Culturing stool takes time, usually at least 3 days. Often you will receive Shiga toxin results from an assay or PCR before cultures are finalized, and positive specimens should be forwarded to OSPHL for further testing. This means that it can take a week or more to receive all the test results you'll use to determine whether a case ultimately meets the case definition. We recommend you process all Shiga toxin-positive ELRs and begin your case investigation as soon as possible, given the severity of disease than can be caused by STEC.

3.1 Confirmed Case Definition

- For O157, isolation of *E. coli* O157 with evidence of an H7 antigen, evidence of Shiga toxin production, or the presence of a Shiga toxin gene.
- For non-O157 STEC, isolation of *E. coli* with evidence of Shiga toxin production or the presence of a Shiga toxin gene (by assay or PCR). The E. coli serogroup should be characterized at OSPHL or CDC.
- For HUS, physician diagnosis with signs of thrombocytopenia, anemia, and elevated creatinine.

Note: **stool** specimens are generally required; *E. coli* isolated from a urine sample is not an STEC case unless it is a Shiga toxin-producing *E. coli*. Also, when there is a discrepancy, OSPHL results trump private lab results.

3.2 Presumptive Case Definitions

- A person with isolation of E. coli O157 from a clinical specimen without confirmation of H antigen, detection of Shiga toxin or detection of Shiga toxin genes, OR
- Diarrhea (often bloody) and/or abdominal cramps in a person
  - with identification of an elevated antibody titer against a known Shiga-toxin-producing serogroup of *E. coli*, OR
  - with detection of Shiga toxin or Shiga toxin genes in a clinical specimen using a CIDT and no known isolation of *Shigella* from a clinical specimen, OR
  - with detection of *E. coli* O157 or STEC/EHEC from a clinical specimen using a CIDT, OR
  - who is epidemiologically linked to a confirmed or probable case, or is a member of a risk group as defined by public health authorities during an outbreak.
- Absent evidence of another cause, a person with HUS within 3 weeks after an acute diarrheal illness.

3.3 Suspect Case

A person with bloody diarrhea and abdominal pain, no fever or temperature <100.4°F (<38°C), and no other identifiable cause.

3.4 Services Available at the Oregon State Public Health Laboratories

The OSPHL provides enteric pathogen culture, including identification of common Shiga-toxin-producing *E. coli* serotypes (O157, O26, O45, O103, O111, O121, and O145). (see the Lab Test Menu at *www.healthoregon.org/labtests*).

For required specimen submissions for STEC surveillance: If submitting an isolate (preferred), submit stool specimen collected in GN broth. If submitting original material for culture, submit stool specimen in Cary Blair transport media.

During outbreaks: Submit stool in a Cary-Blair transport media, filled to the fill line on the vial. A rectal swab in Cary-Blair transport media is acceptable for infant patients. Store and transport at refrigerator temperatures.

If testing is ordered for test of cure or to remove work or school restrictions, indicate this on the OSPHL Test Request Form to ensure that all specimens are tested. The OSPHL does not routinely test additional specimens submitted if the first specimen is negative.

All specimens must be properly packaged for transport. You may contact the OSPHL with questions about submitting samples.

All STEC isolates are subtyped by pulsed-field gel electrophoresis (PFGE) and whole genome sequencing. Molecular matches may indicate but do not prove a connection, whereas isolates that don't match (by either testing method) presumptively come from different sources.

Serologic tests for antibody levels are available by reference testing in special circumstances; consult with the ACDP epidemiologist for more details.

High-risk food samples can be tested for STEC by reference testing if authorized by ACDP epidemiologists. Food samples should be refrigerated. For more information, see the ACDP website or contact the on-call epidemiologist.

4. ROUTINE CASE INVESTIGATION

Interview all cases and others who may be able to provide pertinent information, and promptly enter data into Orpheus. Make sure you are using *a current form* (from the ACDP web site). Though we try to keep the form up to date, Orpheus has the most updated risk and exposure questions. Interview cases even if you do not have complete test results to determine their case status. In other words, interview and implement control measures even if you only have a Shiga toxin-positive ELR and you are awaiting additional test results. If a patient is determined to be a suspect case after all test results are in, no further investigation is required. If you suspect an outbreak, see §6.

4.1 Identify Source of Infection

Seek information about possible exposures 1–7 days before onset of symptoms. (Longer incubations are possible but not worth pursuing as a matter of routine).

1. Name, diagnosis, phone number, and address of any acquaintance or household member with a diarrheal illness. (Anyone meeting the presumptive case definition should be reported and investigated in the same manner as a confirmed case.)
2. Handling or eating ground beef. Ask about consumption of undercooked hamburger (pink or red), but because of the possibility of cross-contamination, any ground beef consumption is potentially suspect. Get details about any ground beef consumed (stores where purchased, dates of purchase, type of meat [e.g., lean or extra-lean hamburger], and how handled/cooked). Of course, any raw beef is potentially a source of kitchen contamination, but intact cuts of meat sold at retail are unlikely to cause multi-household out- breaks.

3. Consumption of unpasteurized milk including cheese made with unpasteurized milk (e.g., queso fresco, homemade cheese, or other specialty cheese). Identify the brands and sources, and find out when this consumption began. If a commercial raw milk source is named, notify ACDP immediately.
4. Dried meats (particularly home prepared) are another possible source, as is anything related to deer or elk hunting (either consumption, slaughtering, or being around same).
5. Any fresh (not frozen) raw spinach, lettuce, or other leafy greens.
6. Any kind of sprouts, even if eaten as part of a cooked meal.
7. Unpasteurized juice or cider (especially popular in the fall!).
8. Name, date, and location of any restaurant meals.
9. Date, location, and sponsor of any public gathering where the case ate a meal.
10. Occupational exposures: evaluate the potential for exposure to human or animal excreta.
11. Contact with diapered individuals with diarrhea, or children in day care.
12. Recreational water exposures: swimming, playing, or other exposure to lakes, streams, or pools where water may have been swallowed. Don't forget those little backyard wading pools (inflatable cesspools, really,) and the increasingly popular splash pads (aka, public bidets).
13. Contact with livestock, especially cattle. Ask about exposures at petting zoos and county fairs.
14. Travel outside the local area. If part of a group, find out who was in the group, the coordinator, etc.

4.2 Identify Potentially Exposed Persons

1. Contacts - Not important except for persons who have changed diapers of infected persons.
2. Other ill persons - Household and other close contacts of confirmed or presumptive cases should be evaluated; symptomatic contacts should be cultured. Household members with more-or-less concurrent disease are presumptive cases, and should be reported as such on separate forms.

4.3 Environmental Evaluation

Recommended if a commercial food service facility, day care center, or public water source (including recreational water) appears to be implicated as the source of infection. See §6.

5. CONTROLLING FURTHER SPREAD

5.1 Education

Advise individuals on measures to avoid further or future exposures.

1. Avoid eating raw or undercooked meat or poultry, especially hamburger. Hamburger should be cooked to an internal temperature of at least 160°F (70°C). While not foolproof, cooking until there is no red or pink remaining and meat juices no longer are red tinged is better than nothing; best is to use a thermometer.
2. Avoid cross-contamination with meat or other potentially contaminated foods.
3. Wash hands after caring for diapered individuals and after using the toilet;
4. Wash hands after handling pets, fowl, and other animals.
5. Wash hands after handling raw meat, raw poultry, and always before food preparation.
6. Eschew unpasteurized milk and related dairy products. (For diehards, the Extension Service at Oregon State University publishes a bulletin on home pasteurization of small quantities of milk.)
7. Avoid drinking or swallowing untreated surface water. Untreated water should be boiled or otherwise disinfected before consumption.

Cases should be strongly discouraged from bathing in communal facilities (pools, fountains, etc.) until at least 2 weeks after resolution of diarrhea.

5.2 Isolation and Work or Day Care Restrictions

1. Hospitalized patients. Standard precautions are adequate to protect employees and other patients.
2. Work restrictions. Persons should not work as food handlers, school or day care workers, or healthcare workers so long as they have diarrhea. In general, cases with STEC infection, including O157, require two consecutive negative approved fecal specimens collected at least 24 hours apart before returning to school, work or child care.[1] Individuals may continue to be infectious for several weeks, however and should be cautioned accordingly.
3. Case is a Day Care Worker or Attendee. Interview the operator and inspect attendance records to identify other possible cases among staff or attendees in the past two weeks.

   Review food handling and hand washing techniques with the operator and staff.

   Collect fecal specimens from any other attendees or staff with a history of diarrheal illness within the past two weeks.

[1] Work and School restrictions can be waived or modified at the discretion of the local health officer. Also, the county may consider additional restrictions as dictated by the situation (e.g., if a case is known to have poor hand hygiene such as a child recently out of day care (i.e., kindergarten or first grade) or a disabled individual). Finally, because Shiga toxin 1 is rarely associated with HUS, some states do not require that individuals infected with an organism that produces only Shiga toxin 1 adhere to restrictions. In Oregon, hospitalization has been required for 12% of reported STEC cases that produce Shiga toxin 1, indicating that these organisms still cause considerable morbidity.

Cases (including those who are asymptomatic) should be excluded from day care facilities until they have two consecutive negative approved fecal specimens collected at least 24 hours apart.[1]

If more than one case or suspected case is identified among attendees or workers at a day care facility, a thorough inspection of the facility is indicated. Contact ACDP to discuss screening of asymptomatic children.

The facility operator should be instructed to call the LHD immediately if new cases of diarrhea occur.

The day care center should be called or visited once each week for two weeks after onset of the last case to verify that surveillance and appropriate hygienic measures are being carried out.

5.3 Case Follow-up

Stool cultures to document that fecal shedding of the organism has stopped are not routinely indicated, except for the purpose of lifting work, school, or day care restrictions. Please be sure to indicate when specimens are for test of cure if testing is done at the OSPHL. Culture independent PCR tests can be used to test for cure, however, keep in mind that the CIDT might be positive when a culture is negative. If the PCR is negative the person can return to work/school. The importance of proper hygiene must be stressed, however, as excretion of the organism may persist in many cases.

5.4 Protection of Contacts of a Case

The importance of good hand washing should be stressed. There are no formal restrictions or requirements for contacts of cases.

5.5 Environmental Measures

Advice on improving food handling and cleaning of day care environments may be indicated.

6. MANAGING SPECIAL SITUATIONS [4]

Many outbreaks have been described since O157 was first identified as a pathogen in 1982, and they are sometimes quite serious. Non-O157 has also been implicated as the cause of numerous outbreaks since 1995 when testing became available. Media attention can become intense. At even a hint of a common- source outbreak, consult with the ACDP immediately. Active case finding will be an important part of any investigation.

6.1 Outbreaks Linked to Restaurants or Public Gatherings

Likely sources include undercooked meat, cross-contaminated food, or possibly food contaminated by an infected food handler. Any investigation should focus on implicating specific food items and evaluating their method of preparation. Ask about recent illness among food handlers.

6.2 Cases Linked to Raw Milk Consumption or a Public Water Source

Environmental evaluation of the dairy or water source will be a necessary part of any further investigation. Dairy investigations will be conducted in cooperation with the employees of the Food Safety Division, Oregon Department of Agriculture. In addition to ACDP, water source investigations may involve the Drinking Water Program at OPHD or recreational water experts in the OPHD Center for Health Protection.

UPDATE LOG

2018: Updated case definition to reflect CIDT, PCR tests to be probable cases. Updated OSPHL information on specimen submission for test of cure and routine samples. Clarified exclusion of school aged children and Healthcare workers. Added provider letter template used by Multnomah County (June Bancroft)

2015: Updated laboratory testing section and case definitions. Updated information on OSPHL services. Edits throughout to improve clarity. (Kendall Scott)

2002: Original Document