ECDC RAPID RISK ASSESSMENT

Outbreak of Shiga toxin-producing *E. coli* (STEC) in Germany

Update 14 June 2011

Source and date of request

Request from the European Commission's Directorate-General for Health and Consumers (DG SANCO, Unit C3) on 24 May 2011. Initial Rapid Risk Assessment on 25 May 2011, updated 27 May 2011.

Public health issue

Unusual increase of Shiga toxin-producing *Escherichia coli* (STEC) infections in Germany, with patients presenting with haemolytic uremic syndrome (HUS) and bloody diarrhoea.

Consulted experts

ECDC acknowledges the contributions from a large number of experts from different public health institutes in Germany and other countries, particularly those that were affected and reported cases.

Stockholm, June 2011

Disease background information

Shiga toxin-producing *E. coli* (STEC) is a type of pathogenic *Escherichia coli* strains capable of producing Shiga toxins. The strains are also known as verotoxin- or verocytotoxin-producing *E. coli* (VTEC). Virulent strains among this pathotype are also called enterohaemorrhagic *E. coli* (EHEC) and can cause illness ranging from mild intestinal disease to severe kidney complications. There are around 250 different *E. coli* O serotypes producing Shiga toxin, of which over 100 have been associated with human disease. While the serotype O157:H7 is considered as clinically the most important, up to 50% of STEC infections are caused by non-O157 serotypes.

The incubation period ranges from three to eight days. The typical presentation of infections with STEC is acute gastroenteritis, often accompanied with mild fever and sometimes vomiting. The diarrhoea is in most cases mild and self-limiting and most people recover within five to seven days. Around 15% of children diagnosed with STEC O157 infection develop the severe complication of haemolytic uremic syndrome (HUS). This proportion is usually much lower among adults. HUS is a serious and sometimes deadly complication. The complete clinical picture of HUS is characterised by acute renal failure, haemolytic anaemia and thrombocytopenia. Typically, it is preceded by diarrhoea, often bloody. The severity of STEC diarrhoea is determined by several factors, including the *E. coli* serotype, the patient's age and the infecting dose. Children under the age of 5 years are at higher risk of developing haemolytic uremic syndrome when infected, and infants are at increased risk of death from dehydration and septicaemia.

Transmission of STEC infection mainly occurs through contaminated food, water or contact with animals, even though person-to-person transmission is also possible among close contacts (families, childcare centres, nursing homes, etc).

The treatment of STEC infections is mainly based on rehydration. Antibiotic treatment is controversial as certain antimicrobial drugs may activate Shiga toxin release and, therefore, cause clinical deterioration with a potential evolution to HUS.

STEC infections in humans are under epidemiological surveillance in the EU. In 2009, there were 3 573 reported cases of STEC infections, of which about half were caused by the *E. coli* O157:H7 serotype. A total of 242 HUS cases were reported in 2009.

Event background information

On 22 May 2011, Germany reported through the EWRS a significant increase in the number of patients with HUS and bloody diarrhoea caused by STEC. An urgent inquiry was launched through the EPIS platform on 24 May.

The causative agent was identified as Shiga toxin 2a-producing *E. coli* serotype O104:H4. This very rare serotype was previously reported in a few STEC and HUS cases but never in foodstuffs. The outbreak strain possesses an unusual combination of virulence factors of STEC (*stx2* gene positive) and presence of *aat*, *aggR* and *aap* genes, typical for Enteroaggregative *E. coli* (EAggEC). EAggEC infections are usually associated with prolonged watery diarrhoea, particularly among children and travellers to developing countries. This hybrid STEC/EAggEC pathotype appears to have only been reported very rarely. It has been described in strains of serotype O111:H2 causing a small outbreak of HUS in children in France.

In addition, the 2011 outbreak strain is multidrug-resistant and produces a CTX-M-15 extended spectrum beta-lactamase (ESBL). PFGE results of O104:H4 outbreak-associated clinical isolates from patients in Germany and Denmark showed indistinguishable or closely related pulsed field gel electrophoresis (PFGE) patterns. Detailed information on the outbreak strain characteristics can be found at the Robert Koch Institut (RKI) website[1]. The outbreak strain serotype O104:H4 has never been reported in food or animals and the combination of virulence factors suggests that the strain is rather of human than animal origin. ECDC has published background information of STEC/VTEC strains[2] with special reference to O104:H4 serotype reported from humans and food in the European Union.

Since 2 May and as of 13 June 2011, 817 cases with haemolytic syndrome (HUS) have been reported, including 781 in Germany. HUS cases have also been reported in Austria (1), Denmark (8), Netherlands (4), Poland (2), Spain (1), Sweden (17) and United Kingdom (3). Among these, 23 have died. In addition 2 508 non-HUS cases have been reported in the EU/EEA Member States, including 2 447 in Germany. Among the non-HUS cases, 13 have died. In total, 36 people affected by STEC infection (23 with HUS and 13 non-HUS) are confirmed to have died. Thirty-five deaths are from Germany and one from Sweden. Of all HUS cases, 69% were female and 88% were 20 years old or older.

[1] http://www.rki.de/cln_145/nn_467482/DE/Content/InfAZ/E/EHEC/EHEC__Diagnostik.htm

[2] Technical report Shiga toxin/verotoxin-producing *Escherichia coli* in humans, food and animals in the EU/EEA, with special reference to the German outbreak strain STEC O104, published on 9 June 2011 and available from: http://ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=685

Most cases are from, or have a history of travel to, the North of Germany (mainly Hamburg, Northern Lower Saxony, Mecklenburg-Western Pomerania and Schleswig-Holstein). For three cases, their exposure can only be explained due to their contact with a previous case coming from or who visited Germany (Denmark, Poland and Norway).

On 26 May, the Hamburg Institute for Hygiene and Environment informed about isolation of STEC from two samples of cucumbers originating from Spain that eventually were confirmed to be a different serotype than the outbreak strain. On 27 May, based on epidemiological evidence suggesting that the disease was associated with the consumption of raw vegetables (particularly cucumbers, tomatoes and lettuce) the Robert Koch Institut and German Federal Institute for Risk Assessment (BfR) issued an advice to the public to avoid the consumption of these vegetables[3].

In Germany, three stakeholders have collaborated at the federal level in the investigation of the outbreak: the Robert Koch Institute (public health), the Federal Institute for Risk assessment (BfR) (food-related risk and food sampling), and the Federal Office of Consumer Protection and Food Safety (BVL) (trace back studies in food chain). In addition, food safety and public health authorities have performed extensive investigations at the states level.

The Robert Koch Institute has performed epidemiological studies that include case-control studies, meta-analyses of all case control studies, cohort studies and further investigations of clusters. Details of all investigations and results are available[4].

The investigations in Germany were focused on five clusters based on confirmation of cases as part of the outbreak and availability of exposure information. The traceback investigated exposure to open markets, distributors and producers. The Ministry of Food, Agriculture, Consumer Protection and Regional Development in Lower Saxony has done investigations on STEC/HUS cases and their food exposure history. Based on the results, the evidence suggests that the consumption of several types of sprouts from a local producer is associated with the STEC/HUS outbreak. Progressively during this week, further evidence has been accumulating and sprout food chain has been linked to 33 out of 55 clusters. On Friday 10 June 2011, the three federal institutes published a joint statement with recommendation to abstain from eating sprouts[5]. At the same time, the ban for cucumbers, tomatoes and lettuce was lifted.

Hundreds of samples have been taken from the suspect sprout farm, including sprouts, seeds, water and environmental samples, but so far the pathogen STEC O104:H4 has not been found in any of the samples from the farm. Raw sprouts retrieved in an open bag from the household of a family with EHEC infection were found to harbour the outbreak EHEC strain O104:H4[6].

RKI has established syndromic surveillance in acute/emergency units in hospitals for incoming patients with bloody diarrhoea. This serves as an important tool for monitoring any potential reoccurrence of the outbreak.

ECDC threat assessment for the EU

The 2011 German outbreak strain isolated from humans is of pathotype STEC/EAggEC and serotype O104:H4, a very rare *E. coli* genotype and phenotype.

The STEC outbreak reported from Germany is the second largest STEC outbreak reported in history worldwide. The biggest outbreak occurred in Japan, affecting over 6 000 school children. It was epidemiologically associated with radish sprouts.

While HUS, caused by STEC infections, is usually observed in children under 5 years of age, in this outbreak 88% of cases are 20 years or older, with around two thirds being women. This may be explained by growing interest in organic food and consumption of sprouts in Germany.

The outbreak has been limited to an exposure history in northern Germany. There has been no indication that the implicated food has been distributed outside of Germany. Three secondary cases, at least, have been identified among travellers to Germany from other countries (Poland, Denmark and Norway).

Although the source of the outbreak is still under investigation, sprouts originating from a specific farm in northern Germany have been indicated by the German authorities as the most likely vehicle of infection.

The number of new cases is declining and the outbreak seems to be waning. However, close monitoring of new suspected cases of STEC in Germany and in the rest of Europe is of outmost importance to rule out the presence of the pathogen in the food chain.

[3] http://www.rki.de/cln_109/nn_205760/DE/Home/Ergebnisse__EHEC.html

[4] http://www.rki.de/cln_178/nn_217400/DE/Content/InfAZ/E/EHEC/epi__frageboegen/ehec__epidemiolgischeStudien-Text.html

[5] http://www.rki.de/EN/Home/homepage__node.html

[6] http://www.bfr.bund.de

Conclusions

This STEC outbreak is unusual in its magnitude, gender, age distribution, STEC strain implicated and clinical picture of cases. Particular pathogenic characteristics of the *E. coli* strain involved may be responsible for these specific features. This hypothesis requires further study.

The exposure has been limited to Germany. All cases having occurred outside of Germany had an exposure in Germany during the exposure period, except three cases that may have acquired the disease through person-to-person transmission (in Denmark, Norway and Poland).

During the recent days, and accounting for the delay in reporting, there is a clear decreasing trend of STEC or HUS cases reported. This may be related to the warning given in north Germany on 22 May 2011 to avoid the consumption of raw vegetables and the adherence of the population to this advice. An alternative or complementary hypothesis is the possibility of a point source or a vehicle of contamination no longer active.

It is important to highlight that persons working in the food chain at all levels (from production to catering), as well as consumers, should be very strict with personal hygiene (hand washing) when handling food. Thorough washing of raw vegetables, and peeling if possible, is still very relevant, to avoid exposure to this or other enteric pathogens.

This outbreak shows how epidemiological evidence can orient food investigations and this should be accompanied with quick traceability studies to identify the source. Sprouts are not an unusual source of outbreaks of *E. coli,* when reviewing the literature. The pathogen has not been identified by the microbiological tests done in any of the samples taken at the farm identified through the traceback studies, but isolation of enteric pathogens from seeds or sprouts is difficult. Furthermore, it is also possible that contamination has been limited and the implicated batch responsible for the outbreak has been consumed.

Since it is possible that the original source of the contamination at the local sprout producer came with the dry beans and seeds used for sprouting, German authorities have now also issued a health warning for citizens not to make their own sprouts at home[7].

The outbreak highlights the need to have good preparedness in place in every EU/EEA country so that this highly virulent STEC pathogen can be quickly identified in the laboratories.

ECDC continues to monitor closely this event, in collaboration with the concerned Member States, the European Food Safety Authority (EFSA), the European Commission and the World Health Organization (WHO).

Contact

support@ecdc.europa.eu

References

Centers for Disease Control and Prevention. Outbreaks of *Escherichia coli* O157:H7 infection associated with eating alfalfa sprouts – Michigan and Virginia, June-July 1997. Morb Mortal Wkly Rep 1997;46:741-4.

Ethelberg S, Smith B, Torpdahl M, et al. Outbreak of non-O157 Shiga toxin-producing *Escherichia coli* infection from consumption of beef sausage. Clin Infect Dis 2009;48: e78-81.

Ferguson DD, Scheftel J, Cronquist A, Smith K, Woo-Ming A, Anderson E, et al. Temporally distinct *Escherichia coli* 0157 outbreaks associated with alfalfa sprouts linked to a common seed source – Colorado and Minnesota, 2003. Emerg Infect Dis 2005 Jun;133(3):439-47.

Heymann DL (Ed.). Control of communicable diseases manual. 19th edition. Official report of the American Public Health Association, 2008:181-6.

Janet C, Moehle-Boetani, et al. *Escherichia coli* O157 and Salmonella infections associated with sprouts in California 1996-1998; Ann Intern Med 2001;135;239-247. Available from: http://www.annals.org/content/135/4/239.full.pdf+html

Johnson KE, Thorpe CM, Sears CL. The emerging clinical importance of non-O157 Shiga toxin-producing *Escherichia coli*. Clin Infect Dis 2006;43:1587-95.

[7] http://www.bfr.bund.de

Mellmann A, Bielaszewska M, Köck R, et al. Analysis of collection of hemolytic uremic syndrome-associated enterohemorrhagic *Escherichia coli*. Emerg Infect Dis 2008;14:1287-90.

Ministry of Health and Welfare of Japan, National Institute of Infectious Diseases and Infectious Disease Control Division. Verocytotoxin-producing *Escherichia coli* (enterohemorrhagic *E. coli*) infection, Japan, 1996–June 1997. Infectious Agents Surveillance Report 1997;18:153-4.

Morabito S, Karch H, Mariani-Kurkdjian P, Schmidt H, Minelli F, Bingen E, et al. Enteroaggregative, Shiga toxin-producing *Escherichia coli* O111:H2 associated with an outbreak of hemolytic-uremic syndrome. J Clin Microbiol. 1998 Mar;36(3):840-2.

Schaffzin JK, Coronado F, Dumas NB, et al. Public health approach to detection of non-O157 Shiga toxin-producing *Escherichia coli*: summary of two outbreaks and laboratory procedures. Epidemiol Infect 5 May 2011;1-7 (Epub ahead of print).

Taormina PJ, Beuchat LR, Slutsker L. Infections associated with eating seed sprouts: an international concern. Emerg Infect Dis Sept-Oct 1999;5(5).

Watanabe Y, Ozasa K, Mermin JH, Griffin PM, Masuda K, Imashuku S, et al. Factory Outbreak of *Escherichia coli* O157:H7 Infection in Japan. Emerg Infect Dis May-June 1999; 5(3). Available from: http://www.cdc.gov/ncidod/eid/vol5no3/pdf/watanabe.pdf