Epidemic Disease Detectives Hamburg investigating…

An Epidemic of Haemolytic Uraemic Syndrome in Hamburg

Investigation Notebook

Do not look at the materials yet

Work through the Hamburg outbreak scenario by reading the case study thoroughly and exploring its materials.
The grey text boxes in the case study

MX. This is useful information!

point to helpful information and materials provided in this Investigation Notebook.

Can you solve the outbreak?

Modified by Juliane Boenecke, Ralf Reintjes, Ranjeet Dhonkal,
Norbert Georg Schwarz and Dewi Ismajani Puradiredja

Based on a true event

Version: April 2023

M1. Hamburg Map – boroughs and districts

Roughly five million people live in Hamburg's metropolitan region, located in the North of Germany. The city comprises seven boroughs and is subdivided into 104 quarters. It is surrounded by the federal states Schleswig-Holstein to the north and Lower Saxony to the south. Hamburg's main waterway, the Elbe river, connects the city to the North Sea.

M2. Epidemiology of HUS / Epidemic profile in Germany

Haemolytic uraemic syndrome (HUS) is a severe health complication that has been described as a triad of haemolytic anaemia (sudden drop in red blood cells), thrombocytopenia (abnormally low levels of platelets) and kidney dysfunction. HUS remains a leading cause of acute renal injury in children and is increasingly recognized as a cause of renal failure in adults. It often occurs after a gastrointestinal infection caused by *Clostridium*, *Shigella*, Shiga-toxin-producing *Escherichia coli* (STEC), *Salmonella*, *Campylobacter*, *Noro-/Adenovirus* and others (typical HUS). Other non-gastrointestinal infections involve *Streptococcus pneumoniae*, *Coxsackie Virus*, influenza, and HIV, among others (atypical HUS). Most infections are linked to the ingestion of contaminated food or water.

Symptoms of HUS include abdominal pain, vomiting, bloody diarrhoea and weakness, with severe, potentially life-threatening complications such as kidney failure, cognitive impairment and multi-organ failure. Symptoms usually develop one to two weeks after infection (usually 5-10 days). In infected patients, 2-11% develop HUS, with the highest risk in young children. **Diagnosis** is based on the clinical picture, with laboratory tests to evaluate kidney function, red blood cell count and blood or proteins in urine, as well as stool cultures to determine the diagnosis of HUS. **Treatment** of HUS involves supportive care, specifically fluid replacement and renal support, e.g., through blood transfusion, dialysis or plasmapheresis, and treatment of neurological manifestation of the disease.

The **incidence** in the general population, including adults, is approximately 1 to 2 cases in 100,000. In Germany, 50-100 cases of HUS are reported every year, with the highest incidence in children less than five years, according to the National Public Health Department *Robert Koch Institute*. The expected number of HUS cases per day is 0-2 cases.

Suspicion of disease, disease and death from **HUS** are **notifiable** by the treating physician according to § 6 of the IfSG (*Protection against Infection Act*). The *electronic reporting system* in Germany covers standardized data on HUS cases since 2001. Physicians are required to report clinical symptoms of diarrhoea-associated HUS in a patient, including their place of residence, to the corresponding Local Health Department. Case data are then reviewed and sent to the Center for Infectious Disease Epidemiology at the *Institute of Hygiene and Environment* (HU) on a municipal level. Data are further transferred to the Robert Koch Institute (RKI) on a national level.

EDDi * References:

Ullrich S, Bremer P, Neumann-Grutzeck C, Otto H, Rüther C, von Seydewitz CU, Meyer GP, Ahmadi-Simab K, Röther J, Hogan B, et al., **2013**. Symptoms and Clinical Course of EHEC O104 Infection in Hospitalized Patients: A Prospective Single Center Study. PLoS ONE, 8, e55278. DOI: 10.1371/journal.pone.0055278

Hawker J, Begg N, Reintjes R, Ekdahl K, Edeghere O, van Steenbergen JE, **2019**. Communicable disease control and health protection handbook; 4th edition.; Wiley-Blackwell: Hoboken, N.J, 2019; ISBN 978-1-119-32805-6

Frank C, Werber D, Cramer JP, Askar M, Faber M, an der Heiden M, Bernard H, Fruth A, Prager R, Spode A, et al, 2011. Epidemic Profile of Shiga-Toxin-Producing Escherichia coli O104:H4 Outbreak in Germany. N. Engl. J. Med., 365, 1771-1780. DOI: 10.1056/NEJMoa1106483

Kavanagh D, Raman S, Sheerin N, 2014. Management of haemolytic uraemic syndrome. F1000Prime Rep. **2014**, 6. DOI: 10.12703/P6-119.

Tahden M, Manitz J, Baumgardt K, Fell G, Kneib T, Hegasy G, **2016**. Epidemiological and Ecological Characterization of the EHEC O104:H4 Outbreak in Hamburg, Germany, 2011. PLOS ONE, 11, e0164508. DOI: 10.1371/journal.pone.0164508.

M3. HUS – Summary report from the Elbe Clinic since May 1

Patient characteristics, preexisting conditions, symptoms on admission	
Patients	**n = 59**
Mean age (years ± SEM)	39 ± 3
< 5 years	5 (8%)
5-19 years	7 (12%)
20-34 years	20 (35%)
35-49 years	13 (22%)
50-64 years	6 (10%)
65-80 years	5 (8%)
> 80 years	3 (5%)
Male/Female	22/37(38%/62%)
Diarrhoea	59 (100%)
Bloody diarrhoea	55 (94%)
Abdominal pain	52 (88%)
Nausea	32 (55%)
Vomiting	25 (42%)
Fever	6 (10%)
HUS at the time of admission	12 (21%)
Preexisting renal disease	2 (3%)
Preexisting hypertension	9 (16%)
Information: Stool microbiology was requested from all 59 patients	

EDDi * Sources referring to the original outbreak in Hamburg / Germany 2011:

Ullrich S, Bremer P, Neumann-Grutzeck C, Otto H, Rüther C, von Seydewitz CU, Meyer GP, Ahmadi-Simab K, Röther J, Hogan B, et al., **2013**. Symptoms and Clinical Course of EHEC O104 Infection in Hospitalized Patients: A Prospective Single Center Study. PLoS ONE, 8, e55278. DOI: 10.1371/journal.pone.0055278 ***Case numbers and terminologies have been used and modified for teaching purposes***

M4. Laboratory findings from the HU lab in Elbe Clinic patients

Patients' characteristics and stool microbiology	
Patients	**n = 59**
Diarrhoea	59 (100%)
Bloody diarrhoea	55 (94%)
Onset of HUS (Confirmed HUS)	36 (61%)
Shigatoxin 2 positive*	57(96%)
Intimin-gen positive	18 (30%)
Intestinal co-infection	34 (58%)
Norovirus	24 (41%)
Clostridium difficile	25 (42%)
Campylobacter jejuni	1 (2%)
** Microbiology could confirm Shigatoxin 2 produced by Escherichia coli (E.coli) strains in 96% of all 59 patients. No Shigatoxin 1 (Stx 1) has been detected.*	

Report on disease course and complications

Among the 59 hospitalized patients with diarrhoea, 16 improved continuously and could be discharged without symptoms after one week. Forty-three patients developed complications within a maximum of 14 days. The most frequent complication was HUS (36 cases), predominantly seen in women (61%; male/female = 11/25). All HUS patients show symptoms of haemolysis, progressive renal failure and thrombocytopenia. Patients are treated with plasma separation and dialysis in case of renal failure to avoid prolonged kidney failure. In addition, extensive replacement of fluids is applied to treat severe capillary leak syndrome (fluid and proteins leak out of tiny blood vessels into surrounding tissues) with rapid onset seen in all HUS patients. As of May 20, 13 patients developed neurological complications, including epileptic seizure, oculomotor dysfunction, neuropsychiatric syndromes, abnormal involuntary movement disorder (choreatic syndrome), disorientation and others, after 2-11 days past the onset of HUS.

EDDi * Sources referring to the original outbreak in Hamburg / Germany 2011:

Ullrich S, Bremer P, Neumann-Grutzeck C, Otto H, Rüther C, von Seydewitz CU, Meyer GP, Ahmadi-Simab K, Röther J, Hogan B, et al., **2013**. Symptoms and Clinical Course of EHEC O104 Infection in Hospitalized Patients: A Prospective Single Center Study. PLoS ONE, 8, e55278. DOI: 10.1371/journal.pone.0055278 ***Case numbers and terminologies have been used and modified for teaching purposes***

M5. Epidemiology of EHEC / Epidemic profile in Germany

Enterohaemorrhagic Escherichia coli **(EHEC)** is a human pathogenic *E.coli* bacterium that may cause haemorrhagic colitis (bloody diarrhoea), with the potential to result in severe disease, including haemolytic uraemic syndrome (HUS), mainly seen in children, and death. HUS is a severe, life-threatening complication associated with EHEC infection, primarily of serotype O157:H7. However, an infection may also remain asymptomatic or only cause mild symptoms, such as diarrhoeal disease, often accompanied by abdominal cramps and vomiting. The **incubation period** usually ranges from 6 hours to 10 days (most commonly 2-4 days). Usually, about 1/3 of cases are admitted to the hospital. Patients can excrete the organism for 2-62 days (median 5-40 days), potentially being infectious as long as the organism can be detected in faeces.

EHEC belongs to the so-called Shigatoxin-producing *E. coli* (STEC) that shows attaching-effacing effect of enteropathogenic strains (EPEC). The natural reservoirs of EHEC bacteria are ruminants, particularly cattle, but it has also been found in sheep, goats, deer, horses, pigs, rabbits, birds, dogs and flies. **Transmission** may occur primarily through contaminated food (e.g., beef, especially grounded beef, raw salad, fruit, vegetable products) or water, direct contact with animals, secondary faecal-oral spread from infected cases, or occupational exposure, mainly in nursing and laboratory staff. Most cases are sporadic or limited to close contacts. However, even single cases require prompt investigation and control. According to the Robert Koch Institute, about 800-1200 cases are identified annually in Germany. The highest reported **incidence** is seen in children under five, and there is a higher rate in females. Infection usually increases in summer, with a peak often observed in August or September.

Diagnosis is based on stool culture, which is more likely to be successful if obtained within four days after the onset of symptoms. Furthermore, methods exist for examining food, water, environmental and animal samples for contamination. In Germany, the case definition of Shigatoxin-producing E.coli gastroenteritis (without HUS) requires, besides laboratory confirmation, the presence of at least one of the following symptoms: diarrhoea (3 or more loose stools in 24 hours), abdominal cramps, or vomiting. **Treatment** is based on adequate fluid and electrolyte replacement and monitoring of the development of HUS. The use of antibiotics in treating *E.coli* (mainly O157) is usually not recommended and may be associated with an increased risk of developing HUS.

According to § 6 of the IfSG (*Protection against Infection Act*), suspicion of disease, disease, and death from **EHEC infection** is **notifiable** by the treating physician. Furthermore, EHEC detection is notifiable by laboratories according to § 7 IfSG. The *electronic reporting system* in Germany covers standardized data on HUS and EHEC since 2001. Reports are transferred to the Local Health Department. Case data are then reviewed and sent to the Center for Infectious Disease Epidemiology at the *Institute of Hygiene and Environment* (HU) on a municipal level. Data are further transferred to the Robert Koch Institute (RKI) nationally.

EDDi * References:

Hawker J, Begg N, Reintjes R, Ekdahl K, Edeghere O, van Steenbergen JE, 2019. Communicable disease control and health protection handbook; 4th edition.; Wiley-Blackwell: Hoboken, N.J, 2019; ISBN 978-1-119-32805-6.

Frank C, Werber D, Cramer JP, Askar M, Faber M, an der Heiden M, Bernard H, Fruth A, Prager R, Spode A, et al, 2011. Epidemic Profile of Shiga-Toxin-Producing Escherichia coli O104:H4 Outbreak in Germany. N. Engl. J. Med., 365, 1771-1780. DOI: 10.1056/NEJMoa1106483.

Kavanagh D, Raman S, Sheerin N, 2014. Management of haemolytic uraemic syndrome. F1000Prime Rep. 2014, 6. DOI: 10.12703/P6-119.

Tahden M, Manitz J, Baumgardt K, Fell G, Kneib T, Hegasy G, 2016. Epidemiological and Ecological Characterization of the EHEC O104:H4 Outbreak in Hamburg, Germany, 2011. PLOS ONE, 11, e0164508. DOI: 10.1371/journal.pone.0164508.

Burger R, 2012. EHEC O104:H4 IN GERMANY 2011: A large outbreak of bloody diarrhea and haemolytic uraemic syndrome by shiga toxin-producing E.Coli via contaminated food. In: Institute of Medicine (US). Improving Food Safety Through a One Health Approach: Workshop Summary. Washington (DC): National Academies Press (US); 2012. A1. Available from: https://www.ncbi.nlm.nih.gov/books/NBK114499/ (Last access: 2020/11/02)

M6. Case definition in the context of the EHEC / HUS outbreak

Suspected / Possible epidemic case

Any person who developed on or after May 1

(a) STEC diarrhoea defined as an acute onset of diarrhoea or bloody diarrhoea
AND
at least one of the following laboratory criteria:

- isolation of E.coli strain producing *Shigatoxin* (stx2) or harbours stx2 gene
- direct detection of stx2 gene nucleic acid in faeces without strain isolation

(b) STEC HUS defined as haemolytic uraemic syndrome defined as acute renal failure and at least one of the following clinical criteria:

- Microangiopathic haemolytic anaemia (loss of red blood cells through destruction)
- Thrombocytopenia (abnormally low levels of thrombocytes)

Probable epidemic case

Any person meeting the criteria of a possible case of STEC diarrhoea or STEC HUS
AND
during the exposure period of 14 days before the onset of illness, meeting at least one of the following epidemiological criteria

- stay in Germany or any other country where a confirmed case has probably acquired infection
- consumption of food products obtained from Germany
- close contact (e.g., in the household) with a confirmed epidemic case

Confirmed epidemic case

Any person meeting the criteria of a possible case
AND
Isolation of a STEC strain fulfilling epidemiological criteria for a probable case. No STEC serotype has been identified yet.

Exclusion criteria

STEC strains producing Stx1 or being positive for stx1 gene are excluded.

Period of exposure

The duration of exposure has been defined from April 21 onwards. Data on hospitalized cases have been collected from May 1 onwards.

EDDi * Sources referring to the original outbreak in Hamburg / Germany 2011:

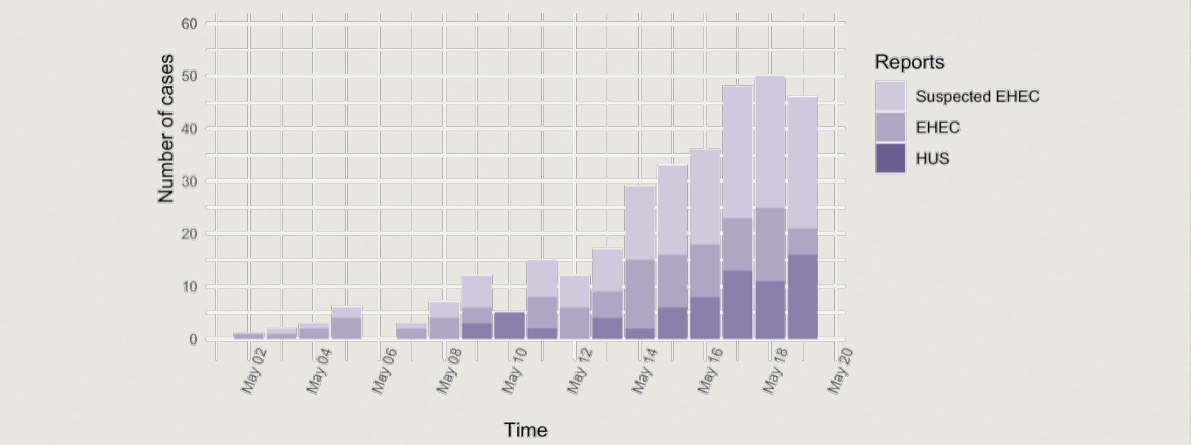
European Centre for Disease Prevention and Control (ECDC), 2011. EU case definition: HUS caused by epidemic strain Shiga toxin 2-producing Escherichia Coli Available online: https://www.ecdc.europa.eu/en/all-topics-zescherichia-coli-ecolithreats-and-outbreaksoutbreak-stec-0104h4-2011/eu-case-definition (Last access: 2019/11/02)

Original case definitions were used to inform the teaching case study

M7. Outbreak Details Hamburg 1st – 20th of May

1 HAMBURG – Case reports Hamburg, as of May 20			
Period	**Suspected EHEC**	**Confirmed EHEC**	**Confirmed HUS**
Week 17: 25th April – 1st May	0	0	0
Week 18: 2nd – 8th May	22	14	0
Week 19: 9th – 15th May	123	63	22
Week 20: 16th – 19th May	180	87	48
TOTAL as of May 20	**325**	**164**	**70**

2 HAMBURG – Epidemiological Curve (as of May 20)

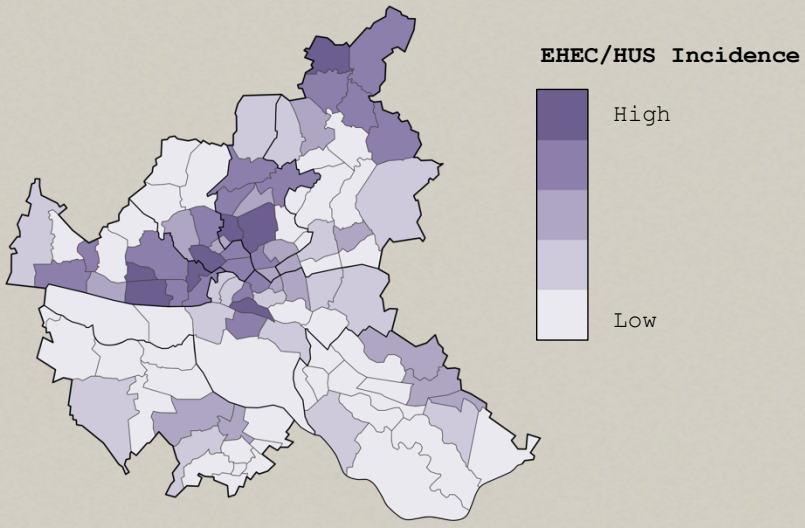


3 HAMBURG – Demographic characteristics					
Report	**N**	**Age**		**Sex (% female)**	**Reported deaths**
EHEC	**164**	**Average = 40.2 years**		61%	0
		< 5 years	9	51%	
		5-19 years	11	49%	
		20-34 years	53	74%	
		35-49 years	48	69%	
		50-64 years	23	64%	
		65-80 years	12	62%	
		> 80 years	8	58%	
HUS	**70**	**Average = 39.2 years**		75%	0
		< 5 years	4	82%	
		5-19 years	8	58%	
		20-34 years	24	77%	
		35-49 years	17	82%	
		50-64 years	9	73%	
		65-80 years	5	65%	
		> 80 years	3	88%	

4 Clinical characteristics	EHEC (n=164)	HUS (n=70)
Reported fever – no. (%)	16(10)	2(3)
Bloody diarrhoea – no. (%)	138(84)	60(86)
Interval between onset of diarrhoea and first presentation of STEC – unit = days	4.1±5.0	4.2±3.2
Stool frequency – no. of stools/day	9.8±9.5	7.6±5.3
Abdominal pain – no. (%)	125(76)	64(91)
Vomiting – no. (%)	25(15)	24(34)
Previous contact with STEC patients – no. (%)	39(24)	13(18)

5 Spatial distribution EHEC/HUS incidence (borough-level, as of May 20)		
Hamburg borough (population est.)	**EHEC/HUS cases (N=234)**	**Incidence per 100,000**
Hamburg-Mitte (301,897)	29	9.61
Wandsbek (436,598)	56	12.82
Hamburg-Nord (311,645)	62	19.89
Eimsbüttel (263,768)	34	12.89
Altona (274,382)	38	13.85
Harburg (166,704)	7	4.19
Bergedorf (129,487)	8	6.18
Hamburg total (1,884,481)	**234**	**12.42**

6 Spatial distribution EHEC/HUS incidences (district-level, as of May 20)



EDDi * Sources referring to the original outbreak in Hamburg / Germany 2011:

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Case data reported in the studies were used to inform the teaching case study

M8. Interviews with hospitalized patients at the Elbe Clinic

Note: *Summary of the interviews with eight hospitalized patients about their regular food choices over the past 25 days*

Patient A: Male, 38 years; Eats a lot of fresh fruits and vegetables regularly, such as apples, strawberries, mushrooms or potatoes; Rarely eats meat (if so, mainly beef and chicken) but lots of cheese; Most of the time he had lunch at his company's canteen, where he prefers salad and desserts.

Patient B: Female, 24 years; Loves all kinds of vegetables and sometimes fruits, such as strawberries, watermelon and grapefruits; Strictly follows a vegan diet with products from the local market: Save the animals, save the planet!

Patient C: Male, 6 years; Recalls having recently eaten a giant Hamburger with fries, which is his favourite meal; His family also had apples, bananas, carrots, tomatoes and spinach, which he didn't like that much.

Patient D: Female, 31 years; Being half-Italian, she regularly eats roasted Mediterranean vegetables, lots of pasta, and sometimes meat and cheese; But never again raw cheese after she got sick in Italy once; She had dinner at her favourite restaurant in Altona a couple of times that serves a variety of burgers and fresh salads.

Patient E: Female, 7 years; Recalls that she ate potatoes, tomatoes, cucumber, cauliflower, some fruits such as apricots and bananas, and sometimes meat; However, she and her mother don't like her father eating raw meat, like Mett on bread rolls; She has never done that.

Patient F: Female, 32 years; Mother of Patient E, follows a healthy diet for her child and husband, with a lot of fresh fruits and vegetables; They sometimes have meat - her husband even raw meat - eggs, and cheese.

Patient G: Male, 61 years; Swears by his diet of local vegetables, eggs, and meat, all from the local market and self-prepared; He hadn't been food sick in ages!

Patient H: Female, 56 years; Wife of Patient G; Follows her husband's dietary habits but strictly avoids eating meat or eggs due to her high cholesterol levels.

M9. Results of the initial case-control study from the Elbe Clinic

Exposures: Consumption of Hamburger meat
Consumption of other under-cooked or raw meat products (e.g., Mett on bread rolls)
Consumption of raw milk or milk products (e.g., raw cheese, cream)
Consumption of salad
Consumption of meals with raw fruits (e.g., fruit salad, desserts)

Cases: 15 patients hospitalized at the Elbe Clinic who developed bloody diarrhoea, EHEC-associated HUS or EHEC gastroenteritis, according to the case definition.

Controls: 17 healthy participants with no signs of bloody diarrhoea, HUS or EHEC gastroenteritis, being members of the same family or household or persons who usually dined with the patients or family

Investigation notes May 21 – Hamburger meat

Contingency Table – Template

Odds Ratio			
		Outcome	
Exposure		ill	not ill
	+	A	B
	–	C	D

$$OR = \frac{A/B}{C/D}$$

Contingency Table – Hamburger meat

		Outcome	
Exposure		ill	not ill
	+	3	8
	–	12	9

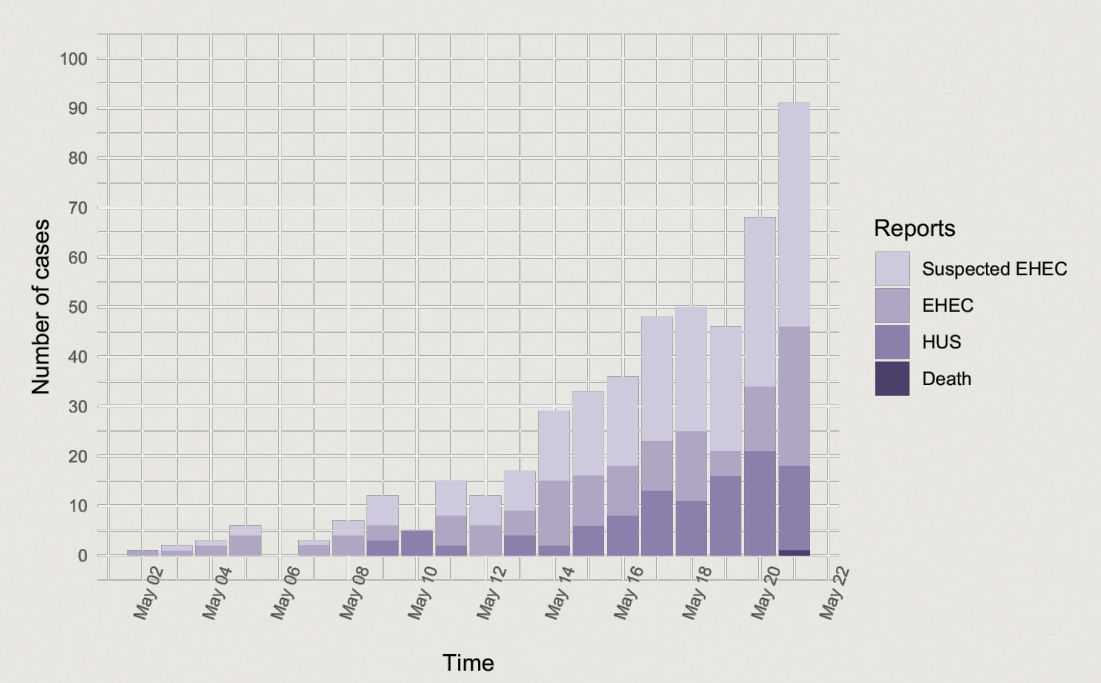
$$OR = \frac{3/8}{12/9} = \frac{0{,}375}{1{,}333} = 0{,}28$$

Investigation notes May 22 – full analysis

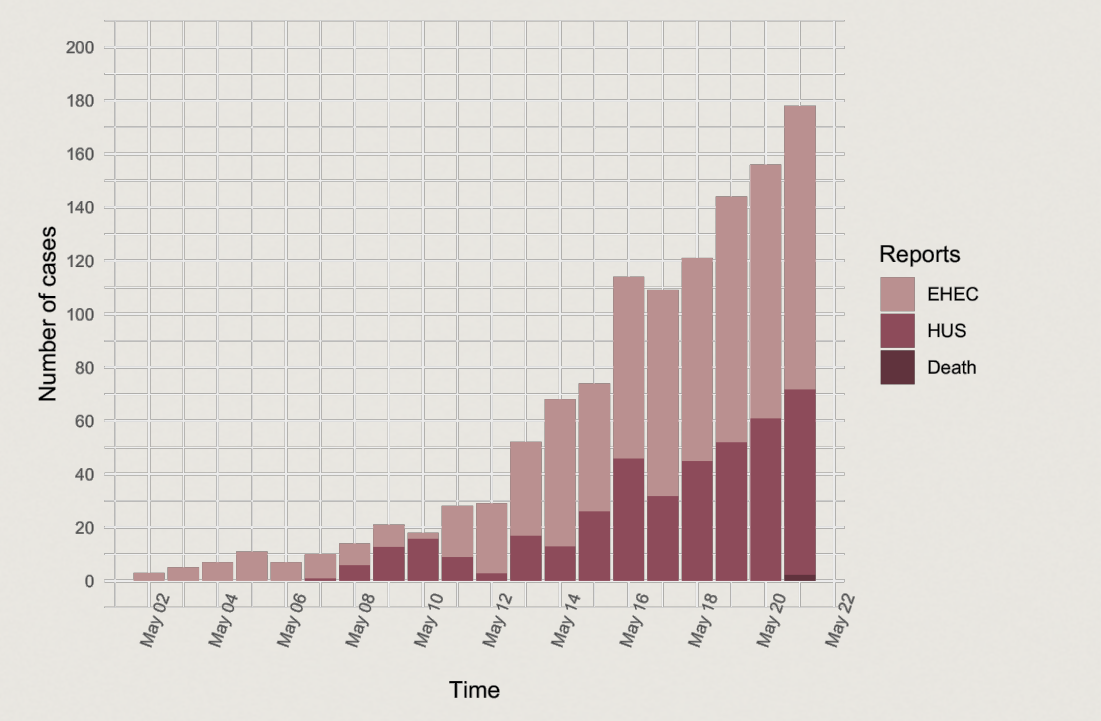
Food items/meals	Cases exposed (no./total no.)	Controls exposed (no./total no.)	Univariable Odds Ratios (95% CI)
Consumption of Hamburger meat	3 / 15	8 / 17	0.28 (0.06-1.37)
Consumption of other under-cooked or raw meat products	4 / 15	12 / 17	0.15 (0.03-0.71)
Consumption of raw milk or milk products	5 / 15	7 / 17	0.71 (0.17-3.03)
Consumption of salads	11 / 15	5 / 17	6.6 (1.4-31.05)
Consumption of meals with raw fruits	9 / 15	5 / 17	3.6 (0.83-15.63)

M10. Outbreak Details Germany, May 1-21

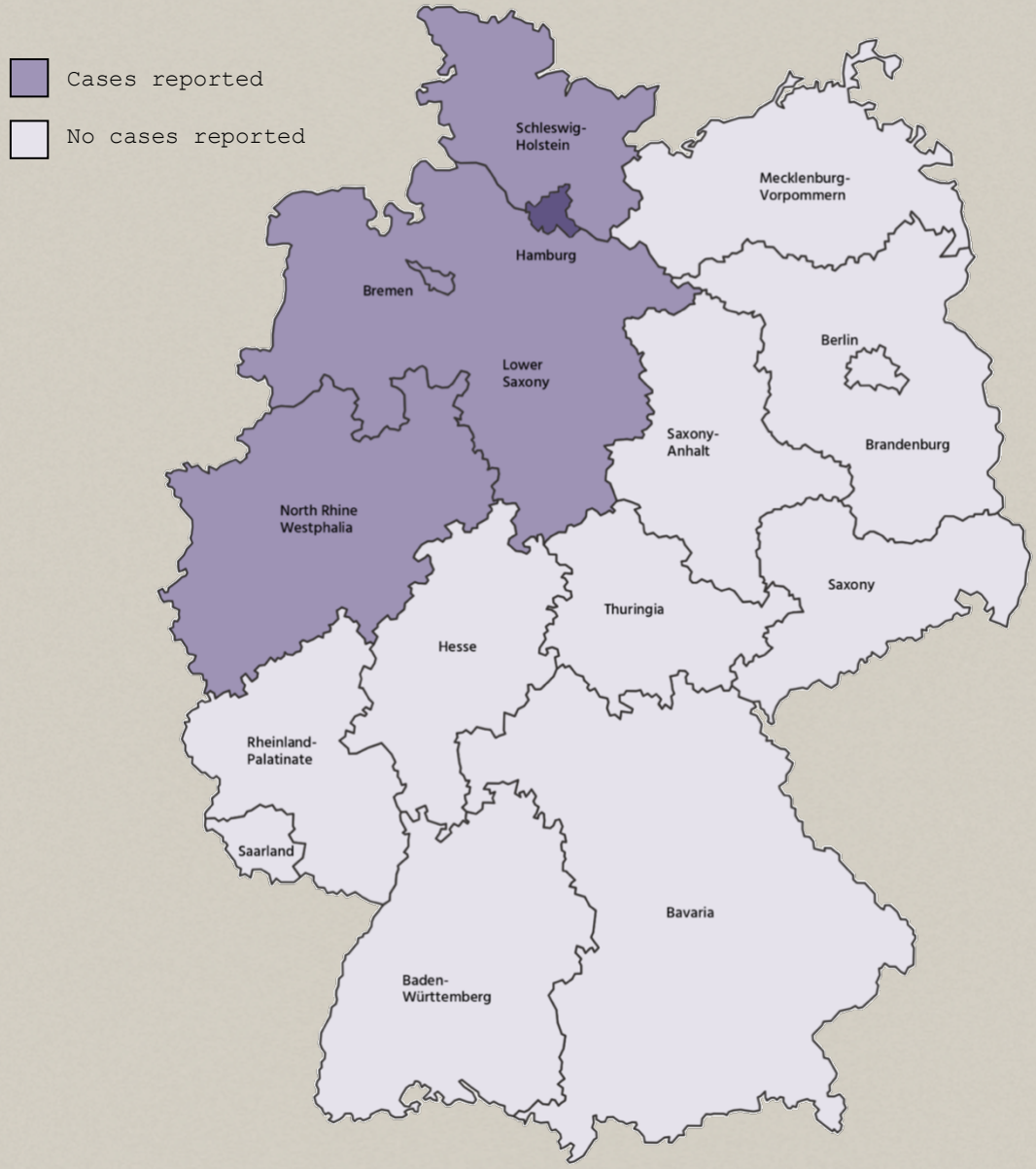
1 EHEC/HUS Epidemiological curve – Hamburg, as of May 21



2 EHEC/HUS Epidemiological curve – Germany, as of May 21



3 EHEC/HUS Outbreak Map – Germany, as of May 21



EDDi * Sources referring to the original outbreak in Hamburg / Germany 2011

Robert Koch-Institut (RKI), 2011. Final presentation and evaluation of epidemiological findings in the EHEC O104:H4 Outbreak Germany 2011. 2011, 45. Online: https://www.rki.de/EN/Content/infections/epidemiology/outbreaks/EHEC_O104/EHEC_final_report.pdf?__blob=publicationFile (Last Access: 2019/11/02).

Frank C, Werber D, Cramer JP, Askar M, Faber M, an der Heiden M, Bernard H, Fruth A, Prager R, Spode A, et al, 2011. Epidemic Profile of Shiga-Toxin-Producing Escherichia coli O104:H4 Outbreak in Germany. N. Engl. J. Med., 365, 1771–1780. DOI: 10.1056/NEJMoa1106483.

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Case data reported in the studies were used to inform the teaching case study

M11. *RECAP* – Overview of epidemiological study designs

Types of observational studies for testing hypothesis

In field epidemiology, two types of epidemiological observational studies are commonly used. An observational study design may be undertaken to investigate a biologically plausible hypothesis of an exposure-disease relationship. For this purpose, standard questionnaires are developed, often based on hypothesis-generating interviews. Observational studies may also involve collecting new data and should consider potential confounding factors. The findings derived from these studies are expected to reveal new or added evidence and inform public health prevention and control.

1 Cohort Studies

This observational study design starts with a cohort of individuals with no signs of a disease or the outcome of interest but different exposure levels. The study approach follows those individuals to observe whether they experience the disease or health condition of interest over time. The individuals will then be compared concerning their different exposure levels to determine whether the exposure may be associated with an increased risk of developing the outcome. Cohort studies can be

Prospective	Enrols participants before they develop the disease or outcome of interest. Participants are then followed to observe whether they experience the disease or health condition of interest over time. The unexposed or group with the lowest exposure usually serves as the comparison group (baseline).
Historical	Enrols participants after they developed the disease or outcome of interest. The population affected is often well-defined. Investigators elicit exposure histories and can compare disease incidence among individuals with different exposures or exposure levels.
Measure of association	Relative Risk (RR) = Ratio of the incidence rate of index subjects to that of control subjects. A RR < 1 provides evidence for a protective effect of the exposure, a RR > 1 for a higher risk of developing the disease or outcome than the non-exposed group. A RR of 1.0 indicates the same incidence rate among the exposed and non-exposed subjects, thus, a lack of association.

2 Case-Control Studies

Unlike cohort studies, the focus of the case-control study approach is the disease or outcome of interest, comparing affected and non-affected individuals. It looks backwards at exposures and exposure levels among individuals to determine whether exposure may be associated with the disease or outcome of interest. In case-control studies, a control group of non-affected individuals must be identified with equal chances and characteristics for exposure as the case group known to be affected by the outcome. Case-control studies are often performed in field epidemiology when cohort studies are impractical.

Measure of association	**Odds Ratio (OR)** = Ratio of the odds of exposure in the outcome group and the non-outcome group. It represents the odds that an outcome will occur given an exposure, compared to the odds of the outcome occurring in the absence of that exposure. An OR of 0 indicates that the exposure does not affect the odds of developing the outcome. In contrast, an OR > 1 provides evidence for higher odds of developing outcome and an OR < 1 with lower odds of developing the outcome compared to the control group.

Comparison of Cohort Study and Case-Control Study Approach in Field Epidemiology

Indicators	Cohort Study	Case-Control Study
Sample Size	Larger	Smaller
Costs	Higher (because of size)	Less
Study time	Short / Long	Short
If outcome is rare	Inefficient	Efficient
If exposure is rare	Efficient	Inefficient
If multiple exposures are relevant	Often can examine	Can examine
If patients have multiple outcomes	Can examine	Cannot examine
Natural history	Can ascertain	Cannot ascertain
Disease risk	Can measure	Cannot measure
Recall bias	Potential challenge	Potential challenge
Selection bias	Potential challenge	Potential challenge
If population is not well-defined	Difficult	Advantageous

Cohort study and Case-control study approach: Measures of association

Cohort study

Relative Risk			
		Outcome	
		ill	not ill
Exposure	+	A	B
	-	C	D

$$RR = \frac{A/(A+B)}{C/(C+D)}$$

Case-control study

Odds Ratio			
		Outcome	
		ill	not ill
Exposure	+	A	B
	-	C	D

$$OR = \frac{A/B}{C/D}$$

EDDi * References:

Deputy Director for Public Health Science and Surveillance, Center for Surveillance, Epidemiology, and Laboratory Services, Division of Scientific Education and Professional Development, **2012**. Principles of Epidemiology in Public Health Practice, Third Edition: An Introduction to Applied Epidemiology and Biostatistics. Lesson 1: Introduction to Epidemiology (Section 5: The Epidemiological Approach). Online: https://www.cdc.gov/csels/dsepd/ss1978/lesson1/section5.html (Last access: 2021/03/12)

Hawker J, Begg N, Reintjes R, Ekdahl K, Edeghere O, van Steenbergen JE, **2019**. Communicable disease control and health protection handbook; 4th edition.; Wiley-Blackwell: Hoboken, N.J, 2019; ISBN 978-1-119-32805-6.

M12. *UPDATE* - Case definition in the context of the EHEC / HUS outbreak

Suspected / Possible epidemic case

Any person who developed on or after May 1

(a) STEC diarrhoea defined as an acute onset of diarrhoea or bloody diarrhoea
AND
at least one of the following laboratory criteria

- isolation of E.coli strain producing *Shigatoxin* (stx2) or harbours stx2 gene
- direct detection of stx2 gene nucleic acid in faeces without strain isolation

(b) STEC HUS defined as haemolytic uraemic syndrome defined as acute renal failure and at least one of the following clinical criteria

- Microangiopathic haemolytic anaemia (loss of red blood cells through destruction)
- Thrombocytopenia (abnormally low levels of thrombocytes)

Probable epidemic case

Any person meeting the criteria for a possible case of STEC diarrhoea or STEC HUS
AND
during the exposure period of 14 days before the onset of illness, meeting at least one of the following epidemiological criteria

- stay in Germany or any other country where a confirmed case has probably acquired infection
- consumption of food products obtained from Germany
- close contact (e.g., in the household) with a confirmed epidemic case

UPDATE: Confirmed epidemic case

Any person meeting the criteria of a possible case
AND
Isolation of a STEC strain serotype O104:H4
OR
Isolation of a STEC strain serotype O104 AND fulfilling epidemiological criteria for a probable case.

UPDATE: Exclusion criteria

All serotypes other than the outbreak strain are excluded. Also, strains producing Stx1 or being positive for stx1 gene are excluded.

Period of exposure

The duration of exposure has been defined from April 21 onwards. Data on hospitalized cases have been collected from May 1 onwards.

EDDi * Sources referring to the original outbreak in Hamburg / Germany 2011:

European Centre for Disease Prevention and Control (ECDC), 2011. EU case definition: HUS caused by epidemic strain Shiga toxin 2-producing Escherichia Coli Available online: https://www.ecdc.europa.eu/en/all-topics-zescherichia-coli-ecolithreats-and-outbreaksoutbreak-stec-0104h4-2011/eu-case-definition (Last access: 2019/11/02)

Original case definitions were used to inform the teaching case study

M13. Canteen-based case-control study

Exposures: Salad consumption, including cucumber, tomatoes and leaf lettuce
Dessert consumption
Fruit consumption
Asparagus consumption

Cases: 28 employees who purchased food in the canteens and developed bloody diarrhoea, HUS or EHEC gastroenteritis, according to the case definition.

Controls: 81 healthy employees who purchased food in the canteens and did not develop bloody diarrhoea, HUS or EHEC gastroenteritis

Results of the canteen-based case-control study

Food item		Total	Cases exposed (no./total no.)	Controls exposed (no./total no.)	Odds Ratios (95% CI)
Salad consumption		109	18 / 28	20 / 81	5.49 (2.18-13.82)
Dessert consumption		109	8 / 28	18 / 81	1.40 (0.53-3.70)
Fruit consumption		109	3 / 28	13 / 81	0.63 (0.16-2.39)
Asparagus consumption		109	4 / 28	19 / 81	0.54 (0.17-1.76)
Gender (♀=1)		109	16 / 28	29 / 81	2.39 (1-5.74)
Age	< 30 years	29	12 / 28	17 / 81	2.82 (1.13-7.08)
	30 - < 40 years	19	7 / 28	12 / 81	Reference value
	40 - < 50 years	33	5 / 28	28 / 81	0.41 (0.41-1.2)
	≥50years	28	4 / 28	24 / 81	0.68 (0.2-2.27)

EDDi * Sources referring to the original outbreak in Hamburg / Germany 2011:

Buchholz U, Bernard H, Werber D, Böhmer MM, Remschmid, C, Wilking H, Deleré Y, an der Heiden M, Adlhoch C, Dreesman J, et al., **2011**. German Outbreak of Escherichia coli O104:H4 Associated with Sprouts. N. Engl. J. Med. 2011, 365, 1763-1770. DOI: 10.1056/NEJMoa1106482
Case data reported in this study were used to inform the teaching case study

M14. A recipe-based restaurant cohort study

List of identified meals

- Garden salad with raw tomatoes, cucumber, lamb's lettuce and sprouts
- Oriental salad with Chinese cabbage, radicchio, iceberg lettuce and sprouts

Study population

- 158 participants who dined at the restaurant during the outbreak period from May 11 till May 16; 34 guests developed bloody diarrhoea, HUS or EHEC gastroenteritis according to the case definition

Results of the recipe-based restaurant cohort study

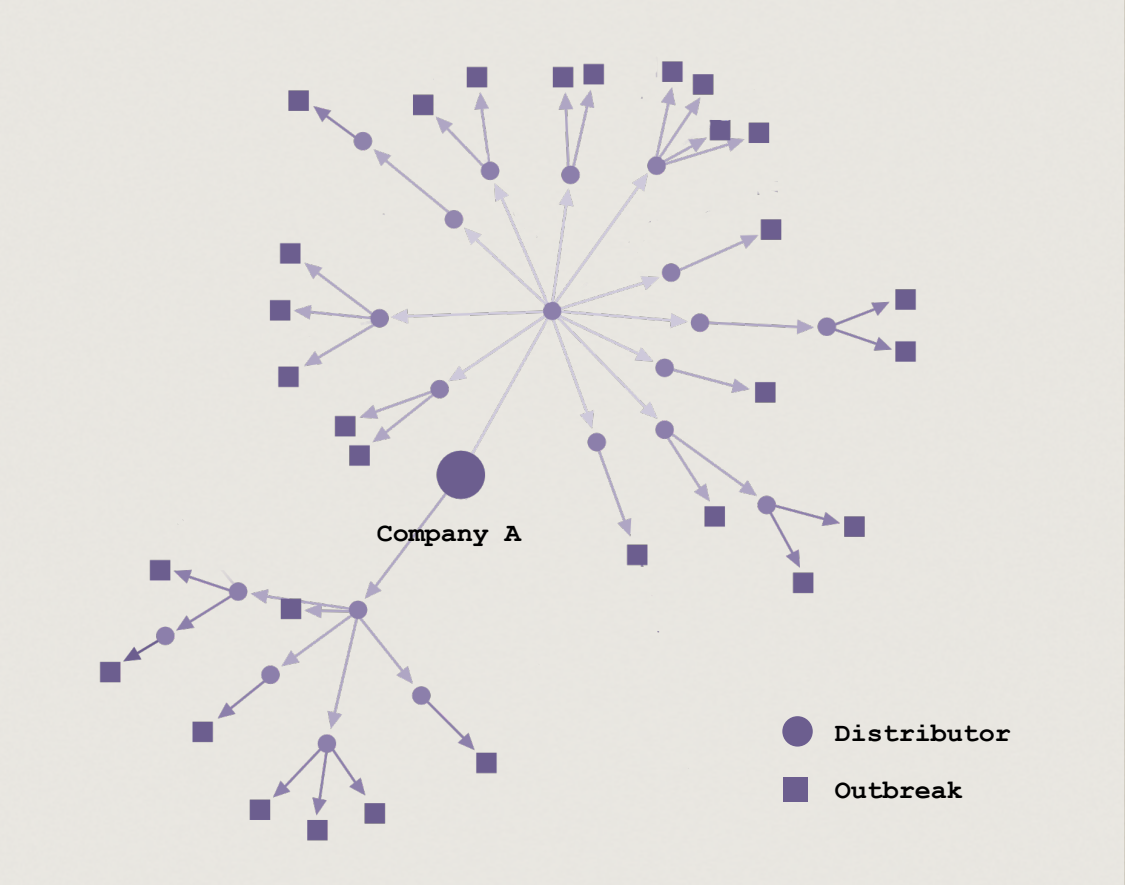
Ingredient	Total	Cases among exposed	Total exposed	Cases among non-exposed	Total non-exposed	RR (95% CI)
Tomatoes	158	13	48	18	110	1.65 (0.88-3.1)
Cucumbers	158	13	48	18	110	1.65 (0.88-3.1)
Sprouts	158	34	118	1	40	11.53 (1.63-81.4)
Lamb's lettuce	158	13	48	18	110	1.65 (0.88-3.1)
Chinese cabbage	158	16	53	14	105	2.26 (1.19-4.28)
Radicchio	158	16	53	14	105	2.26 (1.19-4.28)
Iceberg lettuce	158	16	53	14	105	2.26 (1.19-4.28)

EDDi * Sources referring to the original outbreak in Hamburg / Germany 2011:

Buchholz U, Bernard H, Werber D, Böhmer MM, Remschmid, C, Wilking H, Deleré Y, an der Heiden M, Adlhoch C, Dreesman J, et al., **2011**. German Outbreak of Escherichia coli O104:H4 Associated with Sprouts. N. Engl. J. Med. 2011, 365, 1763-1770. DOI: 10.1056/NEJMoa1106482

Case data reported in this study was used to inform the teaching case study

M15. Results of the traceback analysis – Company A, Lower Saxony



The **trading network** of contaminated sprout products identified 21 distributors (dots) and 30 outbreak clusters (squares) associated with company A (producer A) in Lower Saxony. The network analysis was established by combining backwards and forward tracing.

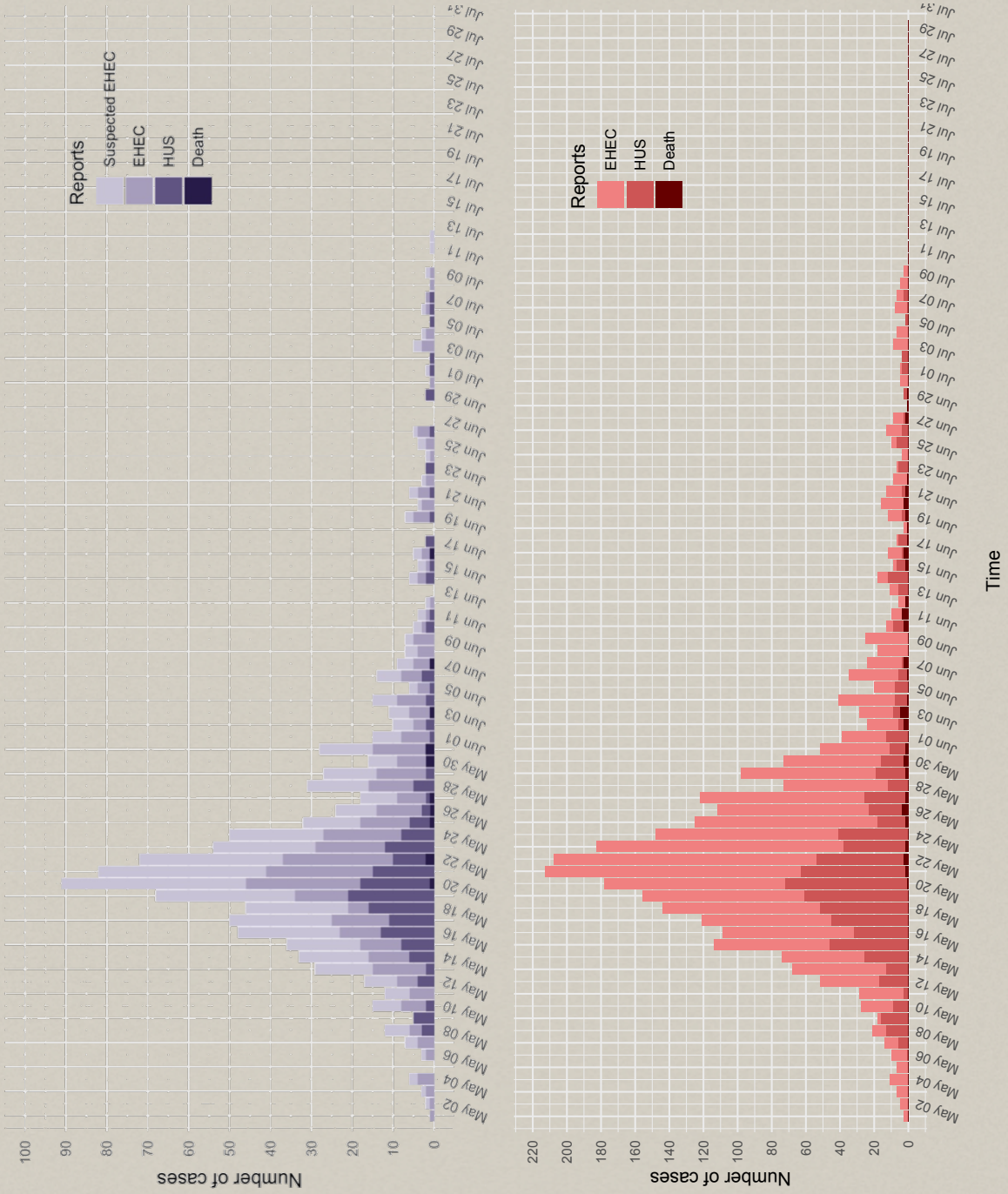
EDDi * Sources referring to the original outbreak in Hamburg / Germany 2011:

Buchholz U, Bernard H, Werber D, Böhmer MM, Remschmid, C, Wilking H, Deleré Y, an der Heiden M, Adlhoch C, Dreesman J, et al., **2011**. German Outbreak of Escherichia coli O104:H4 Associated with Sprouts. N. Engl. J. Med. 2011, 365, 1763-1770. DOI: 10.1056/NEJMoa1106482

Figure 2 of this study was used to inform the teaching case study

M16. Final epidemiological report of EHEC/HUS in Germany and Europe

1 Epidemiological curve – Hamburg (purple) and Germany (red) as of July 31



4 Outbreak reports in Europe and beyond as of July 31

States	EHEC (deaths)	HUS (deaths)
EU		
Denmark	14 0)	9(0)
France	3(0)* + 2(0)**	10(0)**
Greece	1(0)	0(0)
Great Britain	2(0)	5(0)
Luxembourg	1(0)	1(0)
Netherlands	8(0)	3(0)
Norway	1(0)	0(0)
Austria	5(0)	1(0)
Poland	2(0)	3(0)
Sweden	32(0)	17(1)
Spain	1(0)	1(0)
Czech Republic	1(0)	0(0)
TOTAL EU	73(0)	50(1)
Non-EU		
Canada	2(0)	0(0)
Switzerland	5(0)	0(0)
USA	1(0)	4(1)
TOTAL Non-EU	8(0)	4(1)
Overall total	**81(0)**	**54(2)**

* *Cases in connection with a stay in Germany*
** *Cases in connection with the outbreak in France*

EDDi * Sources referring to the original outbreak in Hamburg / Germany 2011:

Robert Koch-Institut (RKI), 2011. Final presentation and evaluation of epidemiological findings in the EHEC O104:H4 Outbreak Germany **2011**. 2011, 45. Online: https://www.rki.de/EN/Content/infections/epidemiology/outbreaks/EHEC_O104/EHEC_final_report.pdf?__blob=publicationFile (Last Access: 2019/11/02)

Frank C, Werber D, Cramer JP, Askar M, Faber M, an der Heiden M, Bernard H, Fruth A, Prager R, Spode A, et al, 2011. Epidemic Profile of Shiga-Toxin-Producing Escherichia coli O104:H4 Outbreak in Germany. N. Engl. J. Med., 365, 1771-1780. DOI: 10.1056/NEJMoa1106483.

Tahden M, Manitz J, Baumgardt K, Fell G, Kneib T, Hegasy G, 2016. Epidemiological and Ecological Characterization of the EHEC O104:H4 Outbreak in Hamburg, Germany, 2011. PLOS ONE, 11, e0164508. DOI: 10.1371/journal.pone.0164508.

Case data reported in the studies were used to inform the teaching case study

References and further reading (1/2)

Robert Koch-Institut (RKI), **2011**. Final presentation and evaluation of epidemiological findings in the EHEC O104:H4 Outbreak Germany 2011. 2011, 45. Online: https://www.rki.de/EN/Content/infections/epidemiology/outbreaks/EHEC_O104/EHEC_final_report.pdf?__blob=publicationFile (Last Access: 2019/11/02).

Frank C, Werber D, Cramer JP, Askar M, Faber M, an der Heiden M, Bernard H, Fruth A, Prager R, Spode A, et al, **2011**. Epidemic Profile of Shiga-Toxin-Producing Escherichia coli O104:H4 Outbreak in Germany. N. Engl. J. Med., 365, 1771–1780. DOI: 10.1056/NEJMoa1106483.

Ullrich S, Bremer P, Neumann-Grutzeck C, Otto H, Rüther C, von Seydewitz CU, Meyer GP, Ahmadi-Simab K, Röther J, Hogan B, et al., **2013**. Symptoms and Clinical Course of EHEC O104 Infection in Hospitalized Patients: A Prospective Single Center Study. PLoS ONE, 8, e55278. DOI: 10.1371/journal.pone.0055278.

Buchholz U, Bernard H, Werber D, Böhmer MM, Remschmid, C, Wilking H, Deleré Y, an der Heiden M, Adlhoch C, Dreesman J, et al., **2011**. German Outbreak of Escherichia coli O104:H4 Associated with Sprouts. N. Engl. J. Med. 2011, 365, 1763–1770. DOI: 10.1056/NEJMoa1106482.

Tahden M, Manitz J, Baumgardt K, Fell G, Kneib T, Hegasy G, **2016**. Epidemiological and Ecological Characterization of the EHEC O104:H4 Outbreak in Hamburg, Germany, 2011. PLOS ONE, 11, e0164508. DOI: 10.1371/journal.pone.0164508.

Burger R, **2012**. EHEC O104:H4 IN GERMANY 2011: A large outbreak of bloody diarrhea and haemolytic uraemic syndrome by shiga toxin-producing E.Coli via contaminated food. In: Institute of Medicine (US). Improving Food Safety Through a One Health Approach: Workshop Summary. Washington (DC): National Academies Press (US); 2012. A1. Available from: https://www.ncbi.nlm.nih.gov/books/NBK114499/ (Last access: 2020/11/02)

Harendza S, **2011**. "HUS diary" of a German nephrologist during the current EHEC outbreak in Europe. Kidney Int. 2011, 80, 687–689. DOI: 10.1038/ki.2011.238.

Hawker J, Begg N, Reintjes R, Ekdahl K, Edeghere O, van Steenbergen JE, 2019. Communicable disease control and health protection handbook; 4th edition.; Wiley-Blackwell: Hoboken, N.J, 2019; ISBN 978-1-119-32805-6.

Salmi IA, Shuaili KA, Metry A, Ismaili FA, Hola A, Hannawi S, **2018**. The Epidemiology of Hemolytic Uraemic Syndrome: Clinical Presentation, Laboratory Findings, Management and Outcomes, 2018. Online: https://symbiosisonlinepublishing.com/hematology/hematology19.php (Last access: 2020/11/02

Askar M, Faber MS, Frank C, Bernard H, Gilsdorf A, Fruth A, Prager R, Höhle M, Suess T, Wadl M, et al., **2011**. Update on the ongoing outbreak of haemolytic uraemic syndrome due to Shiga toxin-producing Escherichia coli (STEC) serotype O104, Germany, May 2011. Eurosurveillance 2011, 16. DOI: 10.2807/ese.16.22.19883-en

World Health Organization (WHO), **2011**. Public Health Review of the enterohaemorrhagic Escherichia Coli Outbreak in Germany; 2011; p. 9. Online: https://www.euro.who.int/__data/assets/pdf_file/0009/144981/EHEC_outbreak_10_June_2011.pdf (Last access: 2020/11/02)

Appel B, **2012**. EHEC outbreak 2011: Investigation of the outbreak along the food chain; Bundesinstitut für Risikobewertung, Eds.; BfR: Berlin, 2012. ISBN 978-3-938163-90-0.

Robert-Koch-Institut (RKI), **2019**. Falldefinitionen des Robert Koch-Instituts zur Übermittlung von Erkrankungs- oder Todesfällen und Nachweisen von Krankheitserregern; 2019. Online: https://www.rki.de/DE/Content/Infekt/IfSG/Falldefinition/Downloads/Falldefinitionen_des_RKI_2019.pdf?__blob=publicationFile (Last access: 2020/11/02)

References and further reading (2/2)

Fatima R, Aziz M, **2019**. Enterohemorrhagic Escherichia Coli (EHEC). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 Jan-. Online: https://www.ncbi.nlm.nih.gov/books/NBK519509/ (Last access: 2020/11/02)

Stark K, **2012**. Epidemiologie des EHEC O104:H4 Ausbruchs Sommer 2011, Deutschland 2012 (Slideshow). Online: https://mobil.bfr.bund.de/cm/343/epidemiologie-des-ehec-o104-h4-ausbruchs.pdf (Last access: 2020/11/02).

Exner M, Hartemann P, **n.d.**. EHEC- Outbreak Management –Learning for the Future – or - „never waste a good crisis" n.d. (Slideshow). Online: https://www.rudolf-schuelke-foundation.com/media-rudolf-schuelke-stiftung/img/Exner_Introduction_Teil-4.pdf (Last access: 2020/11/02)

Manitz J, Kneib T, Schlather M, Helbing D, Brockmann D, **2014**. Origin Detection During Food-borne Disease Outbreaks – A Case Study of the 2011 EHEC/HUS Outbreak in Germany. PLOS Curr. Outbreaks 2014. DOI: 10.1371/currents.outbreaks.f3fdeb08c5b9de7c09ed9cbcef5f01f2

Köckerling E, Karrasch L, Schweitzer A, Razum O, Krause G, **2017**. Public Health Research Resulting from One of the World's Largest Outbreaks Caused by Entero-Hemorrhagic Escherichia coli in Germany 2011: A Review. Front. Public Health 2017, 5, 332. DOI: 10.3389/fpubh.2017.00332.

Rosner B, Bernard H, Werber D, Faber M, Stark K, Krause G, **2011**. Epidemiologie des EHEC O104:H4/HUS-Ausbruchs in Deutschland, Mai bis Juli 2011. J. Für Verbraucherschutz Leb. 2011, 6, 473-481. DOI: 10.1007/s00003-011-0740-1.

European Centre for Disease Prevention and Control (ECDC), **2011**. EU case definition: HUS caused by epidemic strain Shiga toxin 2-producing Escherichia Coli Available online: https://www.ecdc.europa.eu/en/all-topics-zescherichia-coli-ecolithreats-and-outbreaksoutbreak-stec-0104h4-2011/eu-case-definition (Last access: 2019/11/02).

Commission of the European Communities, **2011**. Lessons learned from the 2011 outbreak of Shiga toxin-producing Escherichia coli (STEC) O104:H4 in sprouted seeds; 2011. SANCO/13004/2011. Online: https://ec.europa.eu/food/system/files/2016-10/biosafety-crisis-cswd_lessons_learned_en.pdf (Last access: 2020/11/02)

Deputy Director for Public Health Science and Surveillance, Center for Surveillance, Epidemiology, and Laboratory Services, Division of Scientific Education and Professional Development, **2012**. Principles of Epidemiology in Public Health Practice, Third Edition: An Introduction to Applied Epidemiology and Biostatistics. Lesson 1: Introduction to Epidemiology (Section 5: The Epidemiological Approach). Online: https://www.cdc.gov/csels/dsepd/ss1978/lesson1/section5.html (Last access: 2021/03/12)

EDDi Investigation Notebook - Art Work and Figures

Art Work

"EDDi – Investigation notebook cover" (front page)
"EDDi – STOP sign" [modified] (front page)
"EDDi – Investigation notebook page (right)" (p. I, VI, VIII, XI, XV, XVII, XIX)
"EDDi – Investigation notebook page (left)" (p. VII, X, XII, XVI, XVIII, XX)
"EDDi – Textbook page (left)" (p. II, XIII)
"EDDi – Textbook page (right)" (p. V, XIV)
"EDDi – Paper stack" (p. III, IV, IX, XXI, XXII)
"EDDi – Hamburg Map (districts and boroughs)" (p. I)
created with Affinity Designer (Version 1.9.9 for IPad)
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Epidemiological Maps

"EDDi – Hamburg spatial distribution EHEC/HUS incidences - as of May 20 (p. VIII)
"EDDi – EHEC/HUS outbreak map Germany - as of May 21" (p. XII)
"EDDi – EHEC/HUS trace network analysis" (p. XVIII)
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Epidemiological Curves

"EDDi – EHEC/HUS Epidemiological curve – Hamburg, as of May 20" (p. VII)
"EDDi – EHEC/HUS Epidemiological curve – Hamburg, as of May 21" (p. XI)
"EDDi – EHEC/HUS Epidemiological curve – Germany, as of May 21" (p. XI)
"EDDi – EHEC/HUS Epidemiological curve – Hamburg, as of July 31" (p. XIX)
"EDDi – EHEC/HUS Epidemiological curve – Germany, as of July 31" (p. XIX)
created with R Studio (Version 1.0.136)
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Notice:

The figures and graphs in this teaching case study do not represent real outbreak numbers. They instead are based on the real-world outbreak dynamics of the 2011 EHEC/HUS outbreak in Hamburg, Germany, described in the listed references.

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