



Meeting Report

Nordic Meeting on detection and surveillance of VTEC infections in humans

Copenhagen 7-8 May 2007

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(Statens Serum Institut) and the meeting participants

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PURPOSE OF THE MEETING

The meeting was an informal work-shop where representatives from national governmental institutes from the Nordic countries shared their experiences and discussed joint challenges and various topics related to detection, handling and control of human VTEC infections. The meeting aimed at:

- increasing the knowledge of the situation in the other countries
- strengthening the collaboration between the Nordic countries
- strengthening the Nordic network of professionals working with VTEC
- establishing common recommendations for surveillance and outbreak preparedness concerning VTEC.

The main topics were:

- National outbreak/event surveillance systems: design, experiences, evaluations and improvements; requirements for systems on the Nordic level.
- Laboratory diagnostic procedures and capacity in the different countries.
- Outbreak investigation: The national institutes' responsibilities and tasks; recent examples; the experiences from different questionnaires.

The meeting was held at Statens Serum Institut in Copenhagen 7-8 May 2007 and this report prepared afterwards. The meeting was co-sponsored by the Nordic Council. Personnel costs, including the cost of preparing this report, was paid by the participating institutes and institutions. The meeting was organised as a result of initial consultations between the countries done in connection with the Nordic meeting on Epidemiological Intelligence held in Oslo 4-5 December 2006.

The recommendations agreed upon by the group of Nordic VTEC experts are summarised in the conclusions.

INTRODUCTION

Verocytotoxin-producing *E. coli* (VTEC) are defined as: *E. coli* with the presence of *vtx* gene(s) and/or production of Verocytotoxin. The gold standard test is the Vero cell assay in which culture supernatants from *E. coli* strains are added to Vero cells (African Green monkey kidney cells) in tissue culture and observed for apoptotic cell death for up to 4 days (7). Presently, this method is challenged by various PCR methods for *vtx* genes and by commercially available EIA methods for toxin production. Detection of *vtx* genes may be complicated by the existence of at least 4 *vtx1* subtypes a-d (including 7 *vtx1* variants), and 7 *vtx2* subtypes, a-g (including more than 60 *vtx2* variants). Furthermore, there is some evidence that VTEC strains associated with outbreaks and human disease may lose the phage-encoded *vtx* gene(s) and the diagnosis may therefore under some circumstances be based on an individual evaluation based on specific typing-analysis of isolates (2). DNA fingerprinting methods such as Pulsed-Field Gel Electrophoresis (PFGE) and Multi-Locus VNTR (Variable Number of Tandem Repeats) Analysis (MLVA), and also phenotypic typing methods are used in order to establish the relationship to known VTEC clones.

VTEC is often associated with bloody diarrhoea, but there is a wide clinical spectrum in the association between specific subtypes of VTEC and the clinical outcome. Bloody diarrhoea has been shown to be associated with an increased risk of developing severe sequelae such as acute renal failure (Haemolytic Uraemic Syndrome, HUS) and neurological impairment such as paralysis. HUS is a serious and often life-threatening condition and up to 50% of patients with HUS may develop long term renal damage or blood pressure related complications. It is therefore important to reduce the risk of transmission in outbreaks as well as from person to person. Children in the age group 2-6 are at significantly increased risk of developing HUS. Furthermore, children are at an all together increased risk of acquiring a VTEC infection, and the infection is most often domestically acquired. The infectious dose is very small increasing the risk of person-to-person transmission. Carriers preparing food or working with vulnerable groups (children in day-care, hospitalised patients, the elderly etc) are often quarantined regardless of the specific VTEC type.

The presence of the *E. coli* attaching and effacing gene, *eae*, (and a series of related genes which together code for a specific pathogenic mechanism) together with a specific subtype of *vtx2* (*vtx2a*) seems to be more strongly associated with serious disease (8). However, absence of in the *eae* gene (and related genes) does not necessarily limit the potential to cause serious human disease. In Germany, variants of the *vtx2d*-activatable subtype in *eae* negative VTEC has been found to be significantly associated with the ability to cause severe disease such as HUS (1).

The natural reservoir for VTEC is ruminants and transmission from animal husbandry, petting zoos and visiting farms have occurred in all Scandinavian countries. The prevalence of VTEC in the animal reservoir is very high, yet the pathogenic potential of specific subtypes seems to vary and needs to be further elucidated. Presence of the *vtx2e* subtype has not been significantly associated with human disease and *vtx2e* positive strains are probably not human pathogens.

REASONS FOR DETECTION AND SURVEILLANCE OF VTEC

Correct diagnosis

The clinical symptoms of VTEC infection are similar to those of infection with other intestinal pathogens such as *Campylobacter* spp., *Clostridium difficile*, *Salmonella enterica*, *Shigella* spp. and *Yersinia enterocolitica* infections. Furthermore the symptoms of a VTEC infection may resemble those of other diseases such as appendicitis, colitis ulcerosa, ischaemic colitis, ileocoecitis, pseudomembranous colitis, intussusception (intestinal invagination) and Crohn's disease. Exclusion of other serious disease is essential because the wrong diagnosis could lead to wrong treatment. As an example, a patient with VTEC infection might be operated on suspicion of appendicitis thus increasing the risk of complications.

Early detection

Early detection will minimise the risk of developing HUS. The sooner supportive treatment is initiated the better the prospects for complete recovery of the patient. The earlier the treatment, the better are the chances of minimizing the risk of sequelae in relation to HUS. Early detection will also reduce and prevent transmission. In addition, early detection will increase the chance of timely recognition of outbreaks.

Outbreak detection

Timely detection of an outbreak followed by investigation of the source and instalment of control measures will limit the number of affected people and reduce the risk of serious disease to those exposed. Furthermore, the knowledge gained from past outbreak incidents is very important when trying to avoid future outbreaks.

Management

At present, the majority of patients and carriers with VTEC are quarantined from institutions or excluded from work regardless of the specific VTEC type. However, subtyping and serotyping of a specific isolate will give some indication of the potential pathogenicity and ability to cause outbreak. Thus, a differentiation in the quarantine regulations based on subtypes of VTEC may be implemented in future management of VTEC infected patients and carriers.

Treatment

Antibiotic treatment of children with VTEC O157 infection has been thought to increase the risk of HUS (13), but this has not been shown to be the case for adults and it remains controversial. In Denmark, patients who experience serious work-related problems due to prolonged, asymptomatic carriage of non-O157 VTEC are successfully treated with antibiotics according to virulence profile and serotype (6).

Epidemiology

The isolation and detailed characterisation of VTEC isolates combined with epidemiological information of age, gender, clinical features and travel is essential for surveillance and for management of patients:

- Trends over time may be monitored and new virulence types discovered as they appear and not when it is too late.

- The association of specific types and subtypes to disease can be evaluated and control, management and treatment of patients can be adjusted to the observed.
- Efforts and control plans to reduce disease burden can be focused on the most prevalent or virulent types.

WORKING GROUPS

Two working groups were formed during the workshop. The groups collected information on the current practices in the Nordic countries concerning detection, surveillance and outbreak detection. This information is presented here, structured into two parts: Detection and Epidemiology.

The working groups collected information on the current status of detection and surveillance and control in each of the five Nordic countries. This information is presented below.

RESULTS FROM THE DETECTION WORKING GROUP

The detection working group primarily focused on the ability of primary diagnostic laboratories to adequately detect VTEC as this is a prerequisite for all further actions taken by public health officers and clinicians.

The group collected information on three topics of methodology, structured into a series of four tables (see below), the headlines of which were:

1. Sampling criteria for examination for VTEC.
2. Laboratory detection methods for VTEC in humans and in animals.
3. Capacity to detect VTEC and routine clinical criteria.
4. External Quality Assurance (EQA) programmes.

Sampling criteria

Sampling criteria, *i.e.* which patients should be examined for VTEC, are not standardised in any of the four countries and often based on individual assessments. Written guidelines are present in all four countries but not necessarily followed or not up to standard.

An inventory of sampling criteria has been done in Sweden but not in the other three countries. In general, the below listed clinical categories are examined for VTEC.

DETECTION Table 1. Sampling criteria

Sampling criteria for examination for VTEC shown as generalised clinical categories by country.

Clinical category	Norway	Sweden	Denmark	Finland
BD	Y	Y	Y	Y
HUS	Y	Y	Y	Y
Link to VTEC	Y	Y	Y	Y
Acute diarrhoea, Age	-	<10yrs	<7 yrs	N
Persistent diarrhoea	N	N	Y	Risk group
Travel	N	N	Y	N
Hospitalised	Y	N	Y	Y

BD: Bloody diarrhoea; HUS: Haemolytic uraemic syndrome; Y: Yes; N: No

Note: Individual differences occur in all Nordic countries and between regions. Detection methods are often based on local, individual assessments

Laboratory detection methods for VTEC

DETECTION Table 2. Humans

Primary detection methods for human isolates. Approximate numbers of primary clinical laboratories.

Country	Norway n ^a = 22	Sweden n = 29	Denmark n = 15	Finland n = 26
Method				
Slide agglutination for O157	All (22)	6	1	26
Slide agglutination of highly relevant O groups	7	1	7	0
Fermentation of sorbitol	22	29	0	26
Gene detection (PCR & DNA hybridization)	6	9	4	1 ^b
Phenotypical detection Verocell assay	0	0	1	0
EIA	1	1	2	3
Serology ^c	1	0	0	0

^a Total number of county or regional primary diagnostic laboratories.

^b PCR for primary faecal cultures in addition to isolates. Many laboratories use commercial polyvalent antisera and refer positive strains to the national reference laboratory.

^c Only used at the national reference laboratories, in special outbreak situations.

DETECTION Table 3. Animals

Primary detection methods for animal isolates.

Number of public or state laboratories. There may be private laboratories, capable of performing analyses for VTEC.

Country	Norway n = 3	Sweden n = 1	Denmark n = >5	Finland n = 5
Method				
IMS for O157	4	1	≥5	5
IMS of other relevant O groups	4 ^a	1 ^a	≥5	1
Slide agglutination for O157		1	≥5	5
Slide agglutination of highly relevant O groups		1	≥5	1
Fermentation of sorbitol	4	1	≥5	5
Gene detection (PCR & DNA hybridization) ^d		1 ^b	1	2
Phenotypical detection Verocell assay	^c	0	1 ^c	0
EIA		0	1 ^c	0

^a O26, O103, O111 and O145.

^b One laboratory performs additional PCR specific for O121.

^c Not as a routine assay.

^d PCR as screening for virulence factors in animals is not very informative as many animals regularly are positive for these factors.

Capacity to detect VTEC and routine clinical criteria

DETECTION Table 4. Capacity

Capacity of primary laboratories to detect non-O157 VTEC and routine clinical criteria for testing.

	Norway	Sweden	Denmark	Finland
Brief description of the capacity of primary laboratories to find non-O157, and testing-routines (in routine panel or specific criteria for testing)	All clinical labs use the SMAC plate and can detect <i>E. coli</i> O157 with agglutination kits. 3 main labs have PCR and the capacity to detect non-O157. The smaller labs which do not have PCR can send isolates to the more well-equipped labs for testing by PCR on suspicion of non-O157 VTEC.	All labs testing for VTEC (9 labs) do PCR on primary cultures. Attempts to isolate VTEC are from positive samples. Isolation frequency 60-80%. Criteria for testing differ between counties with 1-4 criteria per county. Most commonly used criteria are suspicion by the general practitioner, bloody diarrhoea and patient being a child.	Laboratories testing samples from about 50% of the Danish population use molecular detection methods (PCR or dot blot hybridisation) targeting the verocytotoxin genes, followed by slide agglutination and typing. Most of the remaining laboratories use slide agglutination of suspect colonies, with OK-antisera against the most common VTEC serotypes. At a few laboratories verocytotoxin-specific ELISA detection is used. None of the labs use SMAC plates.	Four university hospital labs have capacity to screen VTEC non-O157 bacteria with VT-toxin detection kits (Premier EHEC, Genotype EHEC). All clinical labs use the SMAC plate, and can detect <i>E. coli</i> O157 with agglutination kits. In addition, all clinical labs can send suspected primary stool cultures for further testing to a commercial clinical-lab-service that uses VT-toxin detection and PCR-based methods (<i>vtx1</i> , <i>vtx2</i>) for VTEC (including non-O157). Moreover, with specific criteria, clinical labs can send primary stool cultures to KTL, Enteric Bacteria Laboratory (EBL) for testing for VTEC non-O157 by PCR (<i>vtx1</i> , <i>vtx2</i> , <i>eae</i> , <i>ehly</i> , <i>saa</i>).
Are serum tests used routinely in HUS cases?	No, but we're currently considering to implement this for culture negative samples.	No	No (used if culture negative, but not routinely).	No
Is there a national reference laboratory for VTEC?	Yes	Yes	Yes, (national ref lab for enteric pathogens). Also WHO <i>Escherichia coli</i> laboratory. Both at SSI.	Yes- at KTL

External Quality Assurance (EQA) programmes and protocols

Accreditation is not introduced in all primary clinical diagnostic laboratories.

Generally, clinical microbiological laboratories (some only in Norway) participate in the NEQAS organised by Colindale and/or External Quality Assurance in Laboratory Medicine in Sweden (EQUALIS) or in Finland (Labquality). However, none of these have specific focus on VTEC and it should be explored whether the Nordic Council could fund special VTEC ring trials in one of these settings.

Norway

Written guidelines for the detection of VTEC O157 have existed since 1996 and are under revision to include all VTEC. Four ring trials per year on all microbiological aspects. The most recent ring trial of VTEC was followed by a consensus meeting with bacteriological reports in 1996.

Sweden

Ring trials include sending out specimens and inventory. Written guidelines with a reference method exist.

Denmark

There is no Danish EQA programme. The Danish Microbiological Society (DSKM) has written guidelines, but the choice method and clinical sampling scheme is determined by the regional clinical microbiological laboratories.

Finland

All clinical microbiology laboratories need to be licensed statutorily by the State Provincial Offices. In order to get a licence to investigate human stool samples for VTEC, a laboratory has to participate in at least four annual ring trials, planned (each including more than one specimen) for these investigations. Most labs participate in UK-NEQAS (one stool sample/month) and in Labquality (a set of stool specimens) every third month.

Regional differences therefore occur in all four countries and detection of VTEC is very patchy and generally under-diagnosed.

RESULTS FROM THE EPIDEMIOLOGY WORKING GROUP

The epidemiology (EPI) working group primarily focused on surveillance of disease, the ability to find outbreaks and how to respond to outbreaks besides the management of sporadic and outbreak related cases of VTEC.

The group collected information on five topics, structured into a series of five tables (see below), the headlines of which were:

- 1.** Infections with VTEC and HUS.
- 2.** Reporting and surveillance of VTEC.
- 3.** Case management.
- 4.** Outbreak management.
- 5.** Past registered outbreaks.

For each topic a brief description of the situation in each of the five Nordic countries is presented in a separate column in the tables. Although Iceland didn't participate in the meeting, core information was collected via personal information to Dr. Gudrun Sigmundsdottir.

EPI Table 1. Infections with VTEC and HUS

	Norway	Sweden	Denmark	Finland	Iceland
Incidence of VTEC since 2000 (annual number of cases per 100,000 population)	0.2 to 0.4 before 2006. 1.1 in 2006	<u>Total incidence:</u> 2000 1.1 2001 1.1 2002 1.4 2003 0.8 2004 2.2 2005 4.3 2006 2.9 <u>Domestic incidence:</u> 2000 0.7 2001 0.7 2002 1.2 2003 0.6 2004 1.2 2005 3.3 2006 2.0	2000 1.1 2001 1.7 2002 2.6 2003 2.4 2004 3.1 2005 2.8 2006 2.7	0.2 to 0.4	0.3 to 1.6
No of HUS cases (since 2000)	<div> <div>non-</div> <div>O157 O157</div> </div> 2000 - - 2001 - - 2002 - 1 2003 1 1 2004 - - 2005 1 2 2006 2 10	<div> <div>non</div> <div>O157 -O157</div> </div> 2000 2 2 2001 6 3 2002 13 4 2003 4 1 2003 6 1 2005 7 5	<div> <div>Not</div> <div>notifiable</div> </div> 2000 2001 7 2002 4 2003 3 2004 5 2005 6 2006 3	No information available	0
Frequency of the main O-groups diagnosed in 5-year period from 2002-2006	<u>O157:</u> 39% (45/115) <u>O103:</u> 27% (31/115) <u>O26:</u> 9% (10/115) <u>O145:</u> 5% (6/115)	<u>O157:</u> 40% Main non <u>O157 O-groups:</u> O121, O26, O103, O91, O128, O145, O146	<u>O157:</u> 19% (141/751) <u>O103:</u> 13% (100/751) <u>O26:</u> 9.2% (69/751) <u>O146:</u> 6.8% (51/751) <u>Orough:</u> 6.5% (49/751)	<u>O157:</u> 50% (47/94) <u>O103:</u> 14% (13/94) <u>O145:</u> 7% (7/94) <u>O26:</u> 7% (7/94)	No information available
Number of out-breaks 2002-2006 (not including small household and day-care clusters)	2	9	3	1	1

EPI Table 2. Reporting and Surveillance of VTEC

	Norway	Sweden	Denmark	Finland
Is VTEC notifiable by diagnostic laboratory?	Yes	Yes	Yes	Yes
Is VTEC notifiable by treating physician?	Yes	Yes	Yes	Yes
Is HUS notifiable?	Yes	No	Yes	No
Are VTEC strains referred to the national reference centre?	Yes, required	Yes, but not required (almost 100% of isolated strains are referred representing ~70% of cases)	Yes, but not required (voluntary system, almost 100% of strains are referred)	Yes, required
Which case definition is used for VTEC?	Case definition is currently under revision	Infection with "EHEC". Currently working on new case definitions	VTEC isolated from stool or urine specimen	VTEC isolated from stool specimen
Which case definition if used for HUS?	None. Will use the EU case-definition when it is ready	None	None	None
No of data systems in place for management of notification data	One database	One database	Two databases (lab DB and clinical DB)	One database
Laboratory notification, mode and timeliness requirements	Electronic (20%) and paper (80%) required on daily basis	Electronic, required on daily basis	Paper (fax, letters); required on weekly basis	Electronic (90%), required on daily basis
Clinical notifications, mode and timeliness requirements	Paper, required within 24 h (in reality this is not fulfilled)	Electronic, required within 24 h	Paper, required 'as soon as possible' (in reality notifications are not sufficiently timely to allow for outbreak detection)	Paper, required within one week
Average delay in reporting cases to the national level	From date of illness-onset to reporting=19 days From date of sampling to reporting=17 days Until genotyping results: Add 3 days	Average delay in 2006 sporadic notifications (n=241) from date of sample collection to date of notification in SmiNet-2: 5.8 days. Average delay from time of diagnosis to clinical notification: 14 days	Based on 418 interviewed cases, median no of days from onset to sample received in lab was 21 (range quite large). With diagnostics, referral of strains (up to 1 wk) and subsequent typing, delay may be considerable.	Median delay from sample date to NIDR database 11.5 to 13 days in 2003-2005.
Proportion of HUS cases diagnosed with VTEC: Culture/serum	Before 2006 ob; only culture. During ob: 4 w Ab	Unknown	Unknown	Unknown

Note, in Iceland VTEC cases are notifiable, both clinically and by laboratory. HUS cases are not notifiable.

EPI Table 3. Management of VTEC cases

	Norway	Sweden	Denmark	Finland
Description of the infectious control measures and follow-up procedures that are routinely used when sporadic VTEC/HUS cases are diagnosed?	The medical officer ("kommunelege") is phoned from FHI to discuss the case. If not travel related: interviews are generally done on all HUS cases and many EHEC cases. Advice on how to handle the situation exists in a specific document.	Trace back investigation by the county medical officer responsible for communicable diseases. When a case has a farm contact the animals are sampled for VTEC.	GPs and Medical Officers are phoned from SSI. Advice is dependent on sero/virulence profile.	If contact with farm animals, Finnish food safety authority is informed.
Are cases routinely interviewed using a standardised questionnaire?	All non-travel-related cases should be interviewed regarding possible exposures.	Fifty percent of the County Medical Officers interview all domestic cases to find the source of infection.	Interviews were performed from 1997 to 2005. Presently, only information regarding bloody diarrhoea, HUS and foreign travel is collected.	All cases are interviewed to find suspicious food items or contact with farm animals or travel abroad.
Do recommendations on contact screening exist?	No, not if contacts are asymptomatic. It is often done though.	Varies between counties. Often sampling of all family contacts. If case in day-care an investigation is launched in consultation with the county medical officer.	Yes, SSI recommends <u>not</u> screening asymptomatic persons.	In general, no contact screening is recommended.
Do recommendations on sampling from food, animals, water or the environment exist?	Yes. If suspected that animals are the source of human infection relevant animals are sampled. Sampling of food, water etc may also be done as trace back.	Yes, see notes. If suspected that animals are the source of human infection relevant animals are sampled. Sampling of food, water etc may also be done as trace back. Sampling of animals may also be performed at visiting farms or petting zoos if deemed necessary.	Yes, these matters are decided based on the circumstances.	No routine recommendations.
Are there guidelines for control of VTEC among certain groups of people?	Guidelines exist for control of VTEC in day-care centres, hospitals and for food workers.	Guidelines exist for control of VTEC in day-care centres.	Guidelines exist for control of VTEC in day-care centres, hospitals and for food workers.	Guidelines exist for control of VTEC in day-care centres, hospitals and for food workers.
What are the control measures?	Cases are not allowed to go to work or kindergarten.	Infected children should not be in day-care.	Cases are not allowed to go to work or day-care.	Cases are not allowed to go to work or day-care.
Which groups are affected?	Children and staff in kindergartens, food handlers and health care workers where they take care of immunocompromised people.	Children in kindergartens.	Children and staff in day-care systems, food handlers and health care workers and staff in homes for the elderly.	Children and staff in day-care systems, food handlers and health care workers.
How many negative faeces samples are required before a person is considered negative for VTEC?	5 negative samples.	No fixed rules.	2 negative samples.	3 negative samples.

Material concerning sampling from food, animals, water or the environment:

Sweden

Rapport från Livsmedelsverket, Statens Jordbruksverk, Statens veterinärmedicinska anstalt, Smittskyddsinstitutet, Socialstyrelsen och Naturvårdsverket. Verotoxinbildande E.coli- VTEC-bakteriers smittvägar, förekomst samt risker för folkhälsan http://www.smittskyddsinstitutet.se/upload/Publikationer/riskprofil_ehec_2007.pdf.

Sweden

Föreskrift om förebyggande åtgärder avseende zoonoser (Regulation on preventive measures concerning zoonoses) (SJVFS 2003:71, K112).

Sweden

Regulation on preventive measures concerning zoonoses (SJVFS 2003:71, K112).

Sweden

Handlingspolicy avseende kontroll av humanpatogen verotoxinbildande Escherichia coli - utarbetad av Statens veterinärmedicinska anstalt, Statens jordbruksverk, Livsmedelsverket, Smittskyddsinstitutet och Socialstyrelsen. (Document with written guidelines by five authorities representing the human-, food- and veterinary side, new revision of the document will start in autumn 2007)

Material concerning visiting farms:

Denmark

www.foedevarestyrelsen.dk/Foedevaresikkerhed/Tilberedning_hygijne/Personlig_hygijne/Vask_haender_efter_kontakt_med_dyr.htm

Legal regulation (Bekendtgørelse om besøgslandbrug): <https://www.retsinformation.dk/Forms/R0710.aspx?id=6949>

EPI Table 4. Management of outbreaks

	Norway	Sweden	Denmark	Finland
SOP* for handling outbreak alerts at national level	Yes, to some degree	No, but are working on that now	No. Started project that may produce SOPs	No
Have national outbreak investigation guidelines been produced?	Yes	No (started to work on one)	Yes (under revision now)	No written guidelines exist for outbreak investigation. General guidelines for taking human specimens in outbreaks, and also for investigation of food samples in outbreaks.
Logging of outbreaks	Yes	Yes, new system just started.	No. Started project that hopefully produce log mechanism.	Yes (start at time of alert)

* Standard operation procedure

Outbreak investigation guidelines as pdf files:

Norway

<http://www.fhi.no/dav/9CA787E011.pdf>.

Denmark

www.food.dtu.dk/Admin/Public/DWSDownload.aspx?File=Files%2fFiler%2fZoonosecentret%2fPublikationer%2fUdbrudsmanual%2fUdbrudsmanual_endelig.pdf.

EPI Table 5. VTEC outbreaks registered 2001 – 2007

Year	Country	No cases	No HUS	Place	Source	Contributing factors/com-ments	Strain	Reference
2001	FI	3	0	Southeastern Finland	Imported kebab-meat	Insufficient heating of the meat	O157:H7	(4)
2002	SE	28	9	Skåne	Cold-smoked sausage	VTEC found in the sausage	O157:H7	(9)
2002	SE	11		West Coast	Water/beach	No positive samples from the environment		
2004	SE	17		Västra Götaland	Not known	Suspected from a school where participants of the Gothia Cup dined.	O157, VT1+VT2	
2005	SE	135	10	West Coast	Lettuce	Contaminated with irrigation water from a polluted creek	O157 VT2	(12)
2005	SE	2	0	Jönköping	Cold-smoked game sausage	Identical VTEC in sausage and human samples		
2005	SE	8	0	Jönköping	Unpasteurised milk	Identical VTEC in cows and human samples		
2005	SE	4		Stockholm	Suspected sandwich			
2005	SE	4		Halland	Not known	Party		
2005	DK	25	0	Sealand	Pasteurised organic milk from one specific dairy	Unclear, pasteurisation conditions may not have been stringent enough.	O157: H-, vtx1+, vtx2+, eae+, pt8	(5)
2005	DK	5	0	North Sealand (Egely outbreak)	Goats in 'petting zoo'	Insufficient hygienic barriers	Several, dominant: O157, vtx2+, eae+	None
2006	NO	17	10	Nation-wide	Sausage		O103:H25 vtx1-, vtx2+, eae+	(10)
2006	SE	3		Skåne	Suspected Gyrus			
2006	SE	10		Skåne	Suspected vegetables	Different kindergartens in the same municipality had lunch together.	O157	
2007	DK	20	0	Nation-wide (primarily Århus and Inner Cph county)	Batch of 19,000 organic, fermented, cured, beef sausages.	Fermentation fault and/or heavily contaminated raw product.	O26:H11, vtx1+, eae+, vtx2-	(3)
2007	IS	9	0	Nation-wide	Imported lettuce	Associated with Dutch outbreak occurring at the same time.	O157, pt8	(11)

RECOMMENDATIONS

The working groups discussed the measures needed to react to the threats imposed by the infection. VTEC infections constitute an emerging problem and national institutions are expected to be able to conduct state-of-the art detection methodology, efficient modern surveillance and a rapid response in outbreak situations. The current measures in place in the countries were evaluated in this light. Current measures were to a large degree viewed as being sufficient to live up to the requirements, but in some areas room for improvement were seen and in some instances current control measures were seen as clearly inadequate. On several issues the outcome of the discussions could be summarised as a series of recommendations. However, as different circumstances and cultures in different countries don't always allow for uniform requirements, these recommendations were divided into two different levels: Optimal recommendations and minimal requirement recommendations; the latter being less ideal than the first but still seen as acceptable in order to manage these infections at the public health level.

Detection working group

Sample criteria for examination for VTEC

The optimal goal would be that all diarrhoeal stool specimens should be examined for all VTEC.

Sub-optimally, these minimal recommendations should be followed:

Examination for VTEC in the following high priority groups:

- Bloody (actual or anamnestic) diarrhoea (all age-groups)
- HUS, clinically verified or suspected
- Epidemiological link to VTEC-case
- All diarrhoea in children <7 years
- Abdominal cramps
- Laboratory associated case with unknown aetiology, i.e. negative for all other enteropathogens (salmonella, campylobacter, yersinia etc, and parasites and vira)
- Serious symptoms, especially in the elderly and immunocompromised patients
- Diarrhoea in patients in contact with ruminants (petting zoo, visiting farms)
- Diarrhoea in persons consuming raw animal products (fermented sausages, unpasteurised milk etc.) or raw vegetables and fruits (suspected of having been in contact with animal products, organic fertilisers, manure, contaminated soil or water)
- Professionals working with food that will be served or distributed without further heating.

Note: Significant proportions of HUS cases are preceded by non bloody diarrhoea. Urinary tract infections may also precede HUS.

Other reasons for VTEC detection may include:

- Epidemiological follow up or clarification
- Biopsies or autopsies.

Laboratory detection methods for VTEC

Methods should be able to detect all human pathogenic VTEC regardless of serotype or phenotype. Rather than recommending a specific method, the working group decided

that the best results would be obtained if the detection methods were tested in regular ring trials.

External Quality Assurance (EQA) programmes

Accreditation of all primary clinical diagnostic laboratories should be mandatory. This should include testing of laboratories in regular ring trials.

Epidemiology working group

Notification systems

Reporting of cases and strains

In order to be able to detect outbreaks in a timely and efficient manner, thereby hopefully being able to prevent the occurrence of new cases, the working group recommended that:

- Reporting from the laboratory should be done electronically and immediately (at least the same day)
- Clinicians should report on illness immediately (the same day); suspect HUS cases in particular should be reported
- Strains should be sent immediately (the same day) from the primary laboratory to the reference laboratory (or typing laboratory).

The working group agreed on the following minimal requirements:

- Reporting should be done electronically within 48 hours
- Clinicians should report HUS cases immediately (the same day)
- Strains should be sent at least twice a week from the primary laboratory to the reference (or typing) laboratory.

Furthermore, the working group notes that there is currently no clear-cut case definition of VTEC associated HUS. Agreement on a case definition is a prerequisite for an efficient notification system.

Case management

Case interviews

The working group recommended that:

All cases are interviewed using a structured questionnaire. The data are collected at the national level. These interviews are used for the detection of local point source outbreaks (events, amusement parks, resorts). It may be beneficial to use a web-based harmonized Nordic version of a questionnaire.

The working group also agreed that:

Interviews of cases are dispensable if efficient real-time typing molecular typing of strains is in place. However, interviews are generally of good use for case management at the local level.

Contact tracing/screening

Only symptomatic family members or children in day-care systems should be tested. This is done in order to restrict the 'quarantine' measures to symptomatic cases. How-

ever, there could be circumstances where testing of asymptomatic persons may be indicated to avoid serious consequences (e.g. HUS cases).

Restrictions on cases (in order to prevent further person-to-person transmission)

The working group noted that practice currently varies considerably from country to country. It was recommended that: Patients belonging to special risk groups should stay at home until they test negative even after symptoms have ended. The most important of these groups are staff and children in day-care systems and food handlers who are in contact with food served without being heat-treated. In general two negative samples (taken on separate days) are required and sufficient to lift the sanctions, although three negative samples can also be asked for. There may be national social or economical factors that needs to be taken into consideration. The responsibility for imposing and lifting these sanctions should therefore depend on a judgment in the concrete situation (performed by the medical officer).

Sampling from food, animals, water or the environment

The working group recommended that sampling is performed on suspicion. If it is suspected that food products or animals are the source of human infection (sporadic or outbreak) relevant foods and/or animals should be sampled or other samples collected. The sampling scheme should be designed so that there is a good probability of determining if the bacteria was present or not. Sampling of food, water etc may also be used as a supplement in the trace-back of human infection.

Sampling may be particularly valuable in certain high prevalence regions: it can give information for example about survival of the pathogens on farmland or pasture, risk of spread by using manure as fertilisers; risk of spread if a stream leads to a swimming area or a beach and if cattle are grazing up-stream etc. Such information may lead to new recommendations or a change of previous recommendations of potential control measures.

The working group agreed that the optimal requirements should be in line with what is described above. The working group furthermore agreed on the following minimal requirements: Sampling need only be done if HUS cases occur or when investigating outbreaks. However, in the case of visiting farms, petting zoos or kindergartens with animals it is always important to sample animals/environment in order to determine the risk of transmission. National guidelines concerning visiting farms etc should exist and be adhered to. In order for the above to work in practice, it is of course necessary that established routes of contact between the human-, food-, and veterinary sectors exist.

Outbreaks

The working group recommended that:

- Standard operating procedures are made concerning the handling of VTEC outbreaks
- An interview call-centre is established at the central epidemiological institution in each country
- The Nordic countries cooperate in order to produce adequate trawling questionnaires which can be used (with modifications) in all countries
- Trawling questionnaire interviews are initiated when there are two cases with the same strain and no obvious connection between the cases.

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LIST OF ABBREVIATIONS

BD	–	Bloody diarrhoea
DFVF	–	Danmarks Fødevareforskning (Danish Food and Veterinary Institute, presently called food-DTU)
ECDC	–	European Center of Disease Control
EVIRA	–	Elintarvikeurvallisuuvirasto (Finnish Food Safety Authority), Finland
FHI	–	Folkehelseinstituttet (National Institute of Public Health), Norway
FSA	–	Food Safety Authority
FVST	–	Fødevarestyrelsen (Food and Veterinary Administration), Denmark
GP	–	General practitioner
HUS	–	Haemolytic uraemic syndrome
KTL	–	Kansanterveyslaitos (National Public Health Institute), Finland
NVI	–	Norwegian Veterinary Institute
SMI	–	Smittskyddsinstitutet (Swedish Institute for Infectious Disease Control), Sweden
SOP	–	Standard operation procedure
SSI	–	Statens Serum Institut (National institute for infectious diseases), Denmark
SVA	–	Swedish Veterinary Institute
EQA	–	External Quality Assurance
VTEC	–	Verocytotoxin-producing <i>E. coli</i>

APPENDIX 1

List of participants in the workshop

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APPENDIX 2

Nordic Workshop on VTEC/STEC, Copenhagen 7-8 May 2007

Work plan and agenda

The issues covered during the workshop have been divided into different themes. The work form will alternate between brief national presentations, round-table discussions and discussions in sub-groups. The minimum outcome of the meeting will be a small report containing results from the meeting, including a set of basic guidelines for the handling of VTEC infections and ideas for future cooperation among the Nordic countries.

Theme 1: Diagnostic of VTEC

Monday afternoon: National presentations and group work. Tuesday morning: Discussion

Theme 2: Surveillance of VTEC

Monday afternoon: National presentations and group work. Tuesday morning: Discussion

Theme 3: Issues relating to VTEC outbreak investigations

Tuesday morning/afternoon: Presentations and discussion

Theme 4: Scientific projects concerning VTEC

Tuesday afternoon: Presentations and discussion

Practical information

The meeting room is in building 23 at the SSI. When you arrive you need to register at the gate. Ask where building 23 is. One of the organisers will probably be in the room also Monday morning. Otherwise, if you arrive early, ask for the offices of Steen or Flemming.

We have organised dinner Monday evening and lunch for Tuesday, but not lunch Monday. If you arrive early you are of course very welcome to use the SSI cantina together with the locals.

Tuesday afternoon we will go to a new meeting room, the old library in the directors 'villa', bld 33. The restaurant for Monday night is called COFOCO, the address is Værnedamsvej 10 in Vesterbro, not far from the hotel. We need to be there at 6 pm.

Monday 7th

13.00	Meeting begins, brief welcome
13.00 - 14.30	Diagnostics
13.00 - 13-15	Norway
13.15 - 13-30	Sweden
13.30 - 13.45	Finland
13.45 - 14.00	Denmark
14.00 - 14.30	Discussion: Differences and similarities
14.30 - 16.00	Surveillance
14.30 - 14.45	Denmark
14.45 - 15.00	Norway
15.00 - 15.15	Sweden
15.15 - 15.30	Finland
15.30 - 16.00	Discussion: Differences and similarities
16.00 - 17.00	Discussion about diagnostics and surveillance in two to four groups
18.00	DINNER

This day will be about the two major themes: diagnostics and surveillance. The purpose of the brief national presentations is to let everyone know what the situation is in each country. The purpose of the group discussions is to reach consensus about how diagnostics and surveillance should be orchestrated in our countries. Each participant should decide if they prefer to be in the diagnostics or surveillance group. The groups are expected to present a sing-and-dance act Tuesday morning presenting the results of the discussions.

Diagnostics

The focus is on diagnostics of human patients.

The national presentations may seek to answer the following questions:

- Which laboratory methodology for detection of VTEC is in use?
- Are there regional differences in procedures?
- Who decides which procedures should be used?
- Which procedures exist for selection of samples for analysis for VTEC?
- Who decides this?

In the sub-group, these questions are revisited and discussed in more detail. Which methods are acceptable? How important is it to be able to diagnose VTEC relative to other diseases? Which types of VTEC should we be able to find? What is the role of the national institutes or reference labs in diagnostics and in planning of the diagnostic strategy? Which patients are tested? What are the selection criteria for examining stool samples for VTEC? May our countries benefit from cooperation concerning these matters? Should we seek to produce common guidelines? Will it make any difference?

Surveillance

This topic encompass both human and veterinary/food surveillance.

The questions answered in the national presentations may include:

- Structure of the reporting system on human cases
- Surveillance systems for animals
- Surveillance systems for food
- Typing of isolates for surveillance purposes (human and vet/food)

In the surveillance group, again these questions may be discussed in more detail. Are clinical cases, lab cases or HUS cases notifiable? What is the purpose of the surveillance systems apart from outbreak detection? How well do the notification systems work in terms of timeliness and completeness? Which types of outbreaks do they detect? Which types of outbreaks should they be able to detect? Are there sufficient systems for the detection of VTEC in animals or food? Is there good knowledge about national animal reservoirs? Which sub-typing systems are in place and are they used on a regular and timely basis (serotyping, virulence-gene typing, vtx2 gene sub-typing, PFGE, MLVA)? Do productive working conditions between different national and regional agencies exist? Are isolates or sub-typing information exchanged between different institutes? May our countries benefit from cooperation concerning these matters? Should we seek to produce common guidelines?

In addition questions concerning risk assessment and risk management may be discussed. Risk assessment questions might include: Which VTEC should be regarded as human pathogen types (depending on the presence of the vtx and eae genes or sero-groups)? And does it make a difference if the strains are found in patients or carriers, food or animals?

Risk management questions might include: What kind of infectious control measures are in place in each country concerning the finding of VTEC in various institutions or settings such as: child care institutions, food productions facilities (e.g. restaurants), hospitals, visiting farms?

Do they make sense? Should others be implemented?

Tuesday 8th

9.00 - 10.30 Diagnostics & surveillance continued

9.00 - 9.45 Sub-group discussions continued

9.45 - 10.30 Presentation of group work (all together)
Results of discussions in the diagnostics group
Results of discussions in the surveillance group

10.30 - 10.45 Coffee break

10.45 - 14.00 Outbreak investigations
5-15 min presentations: Finland
Denmark
Norway
Sweden

11.30 - 12.00 Discussion. What may we learn from each other.

12.00 - 12.30 LUNCH

12.30 Transfer to new meeting room, library in bld 33.
Guided tour in WHO coli lab, if time permits
13.00 - 14.00 Outbreak investigations discussions continued

14.00 - 16.00 Scientific projects concerning VTEC

5-15 min presentations Sweden
Finland
Denmark
Norway

15.00 - 16.00 Discussion of projects with a possible aspect of collaboration among the Nordic countries

16.00 - 16.30 Final words. Where do we go from here? Future work?

16.30 End of meeting

Tuesday morning we begin by wrapping up the discussions from Monday followed by presentations of what conclusions were reached. Hereafter it will be about the two last themes: outbreaks and cooperation among the countries on scientific projects.

Outbreaks

The purpose of this session is not to go into details with past outbreaks, but to focus on what we have learned from outbreaks and how the handling of VTEC outbreaks might differ from other food-borne outbreaks. In the national presentations, please emphasise the lessons learned from past experiences.

Points for discussion: By which routes may VTEC outbreaks be discovered? Are there special procedures in use for VTEC outbreaks because they are seen as particularly serious? Will the national public health institute always be involved? Who has authority in outbreaks? Are there special (or any) standard operating procedures when it comes to VTEC outbreaks, special trawling questionnaires etc? Norway may have given extra thoughts to these matters, has there been recent changes to the way Norway consider to handle outbreaks in the future and how may the other countries learn from Norway? Any thoughts on risk foods, ready-to-eat foods, beef/sheep sausages?

Scientific projects concerning VTEC

It would be nice if each country could briefly summarise recent as well as on-going projects concerning VTEC.

Points for discussion: Are there plans to start new major projects in any of the countries? Are there projects, future or running, that involve more than one of the Nordic countries? Are there ways in which we might benefit from cooperative projects? It would be good if we at the meeting could outline such projects and form sub-groups that could continue with the development of the projects after the meeting.

Group photo, 8 May 2007



