Introduction

During the past 15 years, we have observed a worldwide dissemination of infections caused by CTX-M extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae [1]. These infections are associated with increased mortality, morbidity, health care costs, and the need for broad-spectrum antibiotics [2]. Community-acquired urinary tract infection (CA-UTI) is the most common infection caused by ESBL-producing Enterobacteriaceae [1]. There is limited knowledge regarding the clinical epidemiology of these infections [1,3]. Most studies have focused on health care related infections and associated risk factors. Moreover, these studies have largely been based on information from medical records. Thus, information on possible risk factors not regularly noted in those records is sparse [4–20]. A large multinational survey of infections caused by ESBL-producing Enterobacteriaceae identified age ≥65 years, male sex and recent use of cephalosporins as independent risk factors for CA-ESBL infections [3]. However, the authors expressed a poor predictive value of their chosen model.

The present study was conducted in Norway. The yearly Norwegian nationwide antimicrobial resistance surveillance programme has shown a very low prevalence of infections caused by ESBL-producing Enterobacteriaceae [21]. A prevalence of 1.6% ESBL-positive UTI in the Norwegian population was estimated for 2011. The prevalence is slowly increasing. A country with low prevalence of infections with ESBL-producing bacteria is well suited to identify risk factors for acquisition of ESBL, and a nationwide prescription database makes Norway suitable for the study of antibiotic use in detail [22]. Based on these advantages and patient interviews we aimed to investigate whether patients with ESBL-positive CA-UTI have a different frequency of risk factors of CA-UTI as compared to patients with ESBL-negative CA-UTI.

Materials and Methods

Design and Study Population

A case-control study was conducted at the Department of Medical Microbiology, Vestre Viken Hospital Trust situated in a mixed urban, suburban and rural area in the South-Eastern part of Norway. Our two laboratories analyse samples from in- and outpatients in an area comprising four hospitals and approximately 450,000 inhabitants (source population). The inclusion period was from February 2009 to April 2011.
The eligible population constituted all patients ≥18 years old with a urine culture yielding *E. coli* or *K. pneumoniae* >10,000 CFU/ml. The following exclusion criteria were used: i) patients who had lived in Norway for <1 year, ii) were unable to answer our questionnaire, iii) had previously diagnosed infection caused by ESBL-producing bacteria, and iv) patients with health care associated UTI (i.e., hospitalized or residing in a nursing home for >24 hours during the last 31 days).

The study population consisted of all patients willing to participate with ESBL-positive UTI (case group) and randomly selected patients with ESBL-negative UTI (control group) (Figure 1).

The patients received written information and were invited to participate by ordinary mail. Non-responders were contacted twice. Acceptance was given by returning a signed consent form.

**Ethics statement.** The study was approved by the Regional Committee for Medical and Health Research Ethics in South-Eastern Norway (reference number: 2009/2037 BS-08901b).

**Data Collection**

Urine cultivation and bacterial identification were performed using ChromID CPS3 agar and the VITEK-2 system (both BioMerieux, Marcy l’Etoile, France). Antimicrobial susceptibility testing and interpretations including ESBL screening were performed using VITEK-2 or agar disc diffusion method according to EUCAST recommendations and clinical breakpoints [23].

Isolates resistant to cefpodoxime, cefotaxime or ceftazidime were selected for confirmatory ESBL testing using the E-test system (AB-Biodisk, BioMerieux). ESBL genotype analysis was performed using PCR for *blaCTX-M* detection and group assignment, as described [24]. Isolates negative for *blaCTX-M* were analyzed using conventional *blaTEM* and *blaSHV* PCR and sequencing, as described [25].

**Statistical Analysis**

This case-control study was analysed using a pragmatic strategy, which means that priority was not given to a specific hypothesis. Univariate analyses were performed using Student’s *t* test, Pearson’s chi-square test or Fisher’s exact test when appropriate. The association between potential risk factors and infection caused by ESBL-producing *E. coli* or *K. pneumoniae* was quantified by odds ratio (OR) with 95% confidence interval (CI). Any variable with a *p* < 0.15 from the univariate analysis was considered a candidate for the multivariate model. A manual backward stepwise...
elimination procedure using a multivariate logistic regression model was performed to identify independent risk factors. Multivariate analyses were preceded by estimation of correlation between risk factors. Evaluation of the predictive accuracy of the models was assessed by calibration and discrimination. Calibration was evaluated by the Hosmer and Lemeshow goodness-of-fit test. A statistically non-significant Hosmer and Lemeshow result (p>0.05) suggests that the model predicts accurately on average. Discrimination was evaluated by analysis of the area under the ROC curve. We defined acceptable discriminatory capability as an area under the ROC curve greater than 0.7 [27]. Two-tailed ROC curve. We defined acceptable discriminatory capability as an area under the ROC curve greater than 0.7 [27]. Two-tailed

Results

Approximately 28,000 urine samples from 15,000 unique patients were submitted to our department during the inclusion period. A total of 359 (1.3%) samples yielded ESBL positive E. coli (n = 342) or K. pneumoniae (n = 17). After exclusion 171 subjects with ESBL UTI were invited to participate (case group). Also, 439 randomly selected control patients were invited to participate (Figure 1).

Relevant background characteristics of the participants are presented in Table 1. The cases and controls were in large similar.

Table 1. Demographic and clinical characteristics of the study population with and without ESBL positive urinary tract infection.

| Variable                             | ESBL positive (n = 100) | ESBL negative (n = 190) | Crude OR | 95% CI     | p          |
|--------------------------------------|-------------------------|-------------------------|----------|------------|------------|
| Age in years, mean ± SD              | 55±19                   | 64±17                   |          |            | <0.001     |
| Female gender                        | 88 (88%)                | 168 (88%)               | 0.96     | 0.45–2.0   | 0.92       |
| Number of household members, mean ± SD| 2.4±1.3                 | 2.1±1.1                 |          |            | 0.09       |
| Pets in household                    | 30 (30%)                | 44 (23%)                | 1.4      | 0.82–2.5   | 0.20       |
| Infection caused by Klebsiella pneumoniae | 5 (5%)                 | 13 (7%)                 | 0.72     | 0.25–2.1   | 0.54       |
| Hospitalization past year            | 21 (21%)                | 34 (18%)                | 1.2      | 0.66–2.2   | 0.52       |
| Recurrent UTI                        | 17 (17%)                | 47 (25%)                | 0.62     | 0.34–1.2   | 0.13       |
| Charlson index score ≥3              | 11 (11%)                | 25 (13%)                | 0.83     | 0.39–1.8   | 0.64       |
| Pulmonary disease                    | 13 (13%)                | 25 (13%)                | 0.99     | 0.48–2.0   | 0.98       |
| Rheumatic disease                    | 9 (9%)                  | 33 (17%)                | 0.47     | 0.21–1.0   | 0.05       |
| Malignancy                           | 6 (6%)                  | 9 (5%)                  | 1.3      | 0.45–3.7   | 0.64       |
| Diabetes mellitus                    | 12 (12%)                | 9 (5%)                  | 2.7      | 1.1–6.8    | 0.02       |
| Gastrointestinal disease             | 14 (14%)                | 29 (15%)                | 0.90     | 0.45–1.8   | 0.76       |
| Cardiac disease                      | 13 (13%)                | 31 (17%)                | 0.76     | 0.38–1.5   | 0.44       |
| Renal dysfunction                    | 7 (7%)                  | 10 (5%)                 | 1.35     | 0.50–3.7   | 0.56       |
| Hepatic dysfunction                  | 1 (1%)                  | 1 (1%)                  | 1.90     | 0.12–31    | 1.00       |
| Cerebrovascular disease              | 2 (2%)                  | 10 (5%)                 | 0.36     | 0.08–1.7   | 0.23       |
| Urinary catheter at any time during past year | 15 (15%)        | 25 (14%)                | 1.1      | 0.56–2.2   | 0.74       |

*Data are presented as the absolute number of patients with percentages in parentheses with the exception of age and household members, which is listed as mean value ± standard deviation (SD).
*Some variables have missing values (number of missing patients in parentheses): Household members (2), Charlson comorbidity index score (8) Pulmonary disease (2) Rheumatic disease (1), Malignancy (2), Diseases of the gastrointestinal tract (1), Cardiac disease (4), Renal dysfunction (1), Hepatic dysfunction (1), Cerebrovascular disease (2), Urinary catheter (6).
*Excluding the time period from 24 hours to 31 days before the urinary sample was taken. No patient had resided in a nursing home without being hospitalized in the time period.
*To quantify the number of UTIs for each patient in the preceding year, the number of prescriptions of three antimicrobial agents—trimethoprim, mecillinam, and nitrofurantoin—were counted. In Norway, these agents are first choices for UTI treatment and are not used for other infections. Recurrent UTI was defined as ≥3 UTIs during the past year.

doi:10.1371/journal.pone.0069581.t001

ESBL Genotyping

PCR and sequence analyses showed that 65%, 30%, and 5% of the ESBL isolates belonged to the CTX-M group 1, CTX-M group 9 and SHV group 5/12, respectively. TEM-type ESBLs were not detected.

Antibiotic Use and Antibiotic Resistance

Data on antibiotic use are presented in Table 2. More than 90% of the participants reported that they had completed all prescribed courses of antibiotics received during the past 5 years. Antibiotic use was more prevalent in the study population (59% during the past three months before the infection) than in the age-adjusted general Norwegian population (29% during the past year) – (data from the Norwegian Prescription Registry [22]). This difference was mainly due to increased use of antimicrobials used to treat UTIs in the study population.

In general, ESBL-producing isolates expressed more co-resistances compared to non-ESBL strains. For cases and controls the proportion of non-susceptible strains were 59% and 13% for ciprofloxacin, 78% and 24% for trimethoprim, 35% and 4% for gentamicin, 4% and 2% for nitrofurantoin and 4% and 3% for mecillinam, respectively.
Risk Factor Analysis

The results of the univariate analyses on risk factors are presented in Table 3. Travelling to Asia, Middle East or Africa up to 2 years in the past, recreational swimming, eating dinner at restaurants and close occupational contact with humans were identified as significant risk factors for ESBL UTI. Interestingly, frequent consumption of fish meals (Figure 2), infrequent bath or shower and digestive problems seemed to have a protective effect.

The results of the multivariate analyses are presented in Table 4. Patients with an ESBL positive UTI had travelled 21 times more to Asia, Middle East or Africa during the past 6 weeks than patients with a non-ESBL UTI, and this was the strongest predictor for ESBL UTI. Travel to the same areas in the period from 6 weeks to 24 months in the past was to a lesser degree associated with ESBL UTI (OR 2.3, 95% CI: 1.2–4.4, p = 0.017). The variables regarding (time since) travel abroad were also analysed as continuous variables but this did not influence the results. Recreational freshwater swimming was identified as an independent risk factor, and patients with ESBL UTI had swum twice as frequent in freshwater as patients with ESBL negative UTI.

Previously known risk factors such as recent antibiotic use and diabetes mellitus were also identified as independent risk factors. Age and weekly fish meals were found to be putative protective factors.

The final multivariate model was applied to participants with infection caused by *E. coli* only and this did not change any trends in the results (data not shown).

The Hosmer and Lemeshow goodness-of-fit test was not significant indicating a satisfactory fit of the model ($X^2 = 5.64$, df = 8, p = 0.69). The area under the ROC curve was 0.83 (95% CI: 0.79–0.88) indicating a good discriminative ability between ESBL-positive and ESBL-negative patients.

Discussion

This is to our knowledge the first population-based study to identify risk factors for acquisition of CA-ESBL infections in a low prevalence country. International travel was identified as the most important risk factor for ESBL positive CA-UTI in this study. Most travel-associated ESBL UTIs occurred during the first six weeks after returning home. This observation is consistent with previous studies and adds new information about the time course between colonization during travel and actual infection [5,28,29]. The area associated with the highest risk (Asia, Middle East and Africa) corresponds well with areas previously associated with a high rate of colonization in returning travellers [28]. This observation contrasts a recent French study. Nicolas-Chanoine and co-workers did not identify travelling abroad for ESBL-positive urinary tract infection with increasing number of fishmeals per week. Control for the variables: Travelling to Asia, Middle east or Africa, Use of fluoroquinolones the past 90 days, Use of β-lactams except mecillinam the past 90 days, Diabetes mellitus,Recreational freshwater swim past year and age. Reference category: eating ≤1 fishmeal per week. doi:10.1371/journal.pone.0069581.g002

**Table 2.** Comparison of the antibiotic usage during the last 90 days prior to inclusion in the study population with and without ESBL positive urinary tract infection.

| Antimicrobial agents* | ESBL positive (n = 100) | ESBL negative (n = 190) | Crude OR | 95% CI | p |
|-----------------------|------------------------|------------------------|----------|--------|---|
| No antibiotic past 90 daysb | 38 (38%) | 80 (42%) | 0.84 | 0.51–1.4 | 0.50 |
| Mecillinam | 15 (15%) | 45 (24%) | 0.57 | 0.30–1.1 | 0.08 |
| Macrolides | 7 (7%) | 5 (3%) | 2.8 | 0.86–9.0 | 0.12 |
| Tetracyclines | 5 (5%) | 6 (3%) | 1.6 | 0.48–5.4 | 0.52 |
| Fluoroquinolones | 14 (14%) | 3 (2%) | 10 | 2.84–36 | <0.001 |
| Nitrofurantoin | 8 (8%) | 16 (8%) | 0.95 | 0.39–2.3 | 0.90 |
| Trimethoprim or trimethoprim/sulfamethoxazole | 16 (16%) | 42 (22%) | 0.67 | 0.36–1.3 | 0.22 |
| β-lactams except mecillinamc | 18 (18%) | 18 (9%) | 2.1 | 1.0–4.2 | 0.04 |
| - Phenoxymethylpenicillin | 11 (11%) | 12 (6%) | 1.8 | 0.78–4.3 | 0.16 |
| - Aminopenicillin | 3 (3%) | 6 (3%) | 0.95 | 0.23–3.9 | 1.0 |
| - Cloxacillin | 3 (3%) | 1 (1%) | 5.8 | 0.60–57 | 0.12 |
| - Cephalexin | 4 (4%) | 2 (1%) | 3.9 | 0.70–22 | 0.19 |
| Methenamine hippurate | 2 (2%) | 15 (8%) | 0.24 | 0.05–1.1 | 0.04 |

*Number of subjects who had used at least one dose in the past 90 days.

bSix cases and 17 controls received an antimicrobial agent at the day before the urinary sample only.

cPenicillin, amoxicillin, cloxacillin or cephalexin (some patients used more than one type).

doi:10.1371/journal.pone.0069581.t002
**Table 3.** Univariate comparison of risk factor exposition in the study population with and without ESBL-positive urinary tract infection.a

| Variableb | ESBL positive (n = 100) | ESBL negative (n = 190) | Crude OR 95% CI | p     |
|-----------|-------------------------|-------------------------|-----------------|-------|
| Travel destinations abroad within the past 6 weeksc | | | | |
| - America or Oceania (including Japan) | 0 (0%) | 1 (1%) | 0.65 | 1.00 |
| - Asia, Middle East or Africa | 23 (23%) | 2 (1%) | 6.5–122 | <0.001 |
| - Europe | 11 (11%) | 13 (7%) | 1.7 | 0.72–3.9 | 0.22 |
| Travel destinations abroad between the previous 6 weeks to 24 monthsc | | | | |
| - America or Oceania (including Japan) | 13 (13%) | 17 (8.9%) | 1.5 | 0.71–3.3 | 0.28 |
| - Asia, Middle East or Africa | 39 (39%) | 36 (19%) | 2.7 | 1.6–4.7 | <0.001 |
| - Europe | 67 (67%) | 108 (57%) | 1.5 | 0.93–2.6 | 0.09 |
| Travel destinations abroad between the previous 24 months to 5 yearsc | | | | |
| - America or Oceania (including Japan) | 10 (10%) | 15 (7.9%) | 1.3 | 0.56–3.0 | 0.54 |
| - Asia, Middle East or Africa | 26 (26%) | 38 (20%) | 1.4 | 0.79–2.5 | 0.24 |
| - Europe | 55 (55%) | 92 (48%) | 1.3 | 0.8–2.1 | 0.29 |
| Recreational swimming past year | | | | |
| - In seawater | 68 (68%) | 98 (52%) | 2.0 | 1.2–3.3 | 0.01 |
| - In freshwater | 26 (26%) | 30 (16%) | 1.9 | 1.0–3.4 | 0.04 |
| - In swimming pool | 53 (53%) | 78 (41%) | 1.6 | 0.99–2.6 | 0.05 |
| - Usually submerges head during recreational swimming | 41 (41%) | 56 (30%) | 1.6 | 0.97–2.7 | 0.06 |
| Eating habits | | | | |
| - Number of fish meals per week, mean ±SD | 2.1±1.1 | 2.7±1.4 | 0.67 | 0.54–0.83 | <0.001 |
| - Number of meat meals per week, mean ±SD | 3.5±1.4 | 3.3±1.3 | 1.1 | 0.94–1.3 | 0.22 |
| - Organic food ≥1/week | 24 (24%) | 40 (22%) | 1.2 | 0.66–2.1 | 0.58 |
| - Dinner at a restaurant ≥2/month | 29 (29%) | 28 (15%) | 2.4 | 1.3–4.3 | 0.003 |
| - Prefers meat well done | 33 (34%) | 74 (40%) | 0.77 | 0.46–1.3 | 0.33 |
| Close occupational contact with humansd | 29 (29%) | 31 (17%) | 2.1 | 1.2–3.7 | 0.01 |
| Bath or shower ≥2 times/week | 12 (12%) | 44 (23%) | 0.46 | 0.23–0.92 | 0.03 |
| Oral/dental health problems | 13 (13%) | 28 (15%) | 0.85 | 0.42–1.7 | 0.65 |
| Digestive problems (constipation or diarrhoea) | 25 (26%) | 75 (40%) | 0.51 | 0.30–0.87 | 0.01 |

aData are presented as the absolute number of patients with percentages in parentheses with the exception of fish and meat meals, which is listed as mean value ± SD.

bSome variables have missing values (number of missing patients in parentheses). Usually submerges head during recreational swimming (7), Organic food (7), Dinner in restaurant (2), Prefers meat well done (8), Close occupational contact with humans (6), Bath or shower (3), Digestive problems (6).
cOnly trips lasting > 24 hours are included.
dSelf-reported close occupational contact with humans.

doi:10.1371/journal.pone.0069581.t003

**Table 4.** Independent risk factors of ESBL positive community acquired urinary tract infection identified using multivariate logistic regression analysis.

| Variable | Level | Adjusted OR | 95% CI | P     |
|----------|-------|-------------|--------|-------|
| Travelling to Asia, Middle East or Africaa | yes/no | 21 | 4.5–97 | <0.001 |
| - During the past 6 weeks | yes/no | 2.3 | 1.2–4.4 | 0.017 |
| Use of fluoroquinolones the past 90 days | yes/no | 16 | 3.2–80 | <0.001 |
| - Between the previous 90 days to 24 months | yes/no | 5.0 | 2.1–12 | <0.001 |
| Use of β-lactams except mecillinam in the past 90 days | yes/no | 3.2 | 1.0–11 | 0.051 |
| Diabetes mellitus | yes/no | 2.1 | 1.0–4.3 | 0.040 |
| Recreational freshwater swim past year | yes/no | 0.89 | 0.82–0.97 | 0.014 |
| Age | 5 year increase | 0.68 | 0.51–0.90 | 0.008 |

aData are presented as the absolute number of patients with percentages in parentheses with the exception of fish and meat meals, which is listed as mean value ± SD.

bSome variables have missing values (number of missing patients in parentheses). Usually submerges head during recreational swimming (7), Organic food (7), Dinner in restaurant (2), Prefers meat well done (8), Close occupational contact with humans (6), Bath or shower (3), Digestive problems (6).
cOnly trips lasting > 24 hours are included.
dSelf-reported close occupational contact with humans.

doi:10.1371/journal.pone.0069581.t004
Risk Factors for ESBL in Urinary Tract Infection

>14 days during the past 6 months as a risk factor for an ESBL-positive (blaCTX-M-15) infection in hospitalized patients [6]. In our study, travelling abroad for >14 days was a strong predictor of ESBL UTI when using blaCTX-M-1 -positive infections as an endpoint (data not shown). It is likely that the importance of travel as a risk factor will differ between the French hospitalized population and the Norwegian non-hospitalized population in our study. Also, the proportion of ESBL-producing clinical isolates of Enterobacte-



References
1. Pitout JD, Laupland KB (2008) Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis 8: 159–166.
2. Rottier WC, Ammerlaan HS, Bonen MJ (2012) Effects of confounders and intermediates on the association of bacteraemia caused by extended-spectrum

3. Ben-Ami R, Rodriguez-Bano J, Arslan H, Pitout JD, Quentin C, et al. (2009) A multinational survey of risk factors for infection with extended-spectrum beta-

4. Doi Y, Park YS, Rivera JL, Adams-Haduch JM, Hingee A, et al. (2013) Community-associated extended-spectrum beta-lactamase-producing Escherichia coli infection in the United States. Clin Infect Dis 56: 641–648.
5. Laupland KB, Church DL, Vidaekevich J, Mucenski M, Pitout JD (2008) Community-onset extended-spectrum beta-lactamase (ESBL) producing Esch-

E. coli O157:H7

E. coli

Enterobacteriaceae

E. coli

K. pneumoniae

REFERENCES

Acknowledgments
We thank Anne Fritzvold, Bjørg Haldorsen and Carina Thilesen for their excellent technical assistance and the Norwegian Prescription Database for good service.

Author Contributions
Conceived and designed the experiments: A. Søraas A. Sundsfjord PAJ. Performed the experiments: A. Søraas. Analyzed the data: A. Søraas A. Sundsfjord IS CB PAJ. Wrote the paper: A. Søraas A. Sundsfjord IS CB PAJ.

Risk for ESBL UTI when using study, travelling abroad for ESBL-positive bacteria [3,7,8,11,31]. We found that recent use compared to most penicillins [33].

Moreover, mecillinam has a selective activity against Gram-negative bacteria and is more stable against ESBL hydrolysis compared to most penicillins [33].

Recreational swimming in freshwater was identified as an independent risk factor for ESBL UTI. ESBL-producing bacteria like E. coli have been detected in environmental water [34–36]. Furthermore, outbreaks of E. coli O157:H7 have been linked to swimming in contaminated freshwater [37]. Swimming may therefore be a risk factor for intestinal colonization with E. coli with ESBL and any subsequent UTI may be caused by a newly acquired ESBL-producing strain from the water [38]. This finding highlights a possible link between environmental pollution and antimicrobial resistance, but will have to be substantiated before any conclusions can be drawn [39].

Interestingly, eating fish was associated with a reduced risk of ESBL UTI (Figure 2). Each weekly fish meal reduced the risk of an ESBL-positive infection with about 30%. It is clear that eating habits influence the microbial flora in the gut [40]. However, whether eating fish may affect the resistance pattern of the gut microbial flora and potentially lower the risk of ESBL UTI remains speculative and eating fish may be a marker of a more fundamental risk factor not measured.

Retail chicken meat has recently been implicated as a possible source of ESBL-colonization [41]. We did not specifically investigate this possible risk factor, but ESBL-producing bacteria have only very rarely been found in the Norwegian food chain [42].

In our study, patients infected with an ESBL-producing E. coli or K. pneumoniae were significantly younger than the control patients. In two studies with similar design but including hospitalized patients, no association between age and ESBL-positive infection was found [8,43]. This suggests that the epidemiology of ESBL infections differs in Norway or among non-hospitalized patients.

Limitations
Limitations include the possibility of selection bias due to non-participation and a potential problem with differential misclassification of exposure because the interviewers were not masked to the status of the patient being a case or a control. To minimize the latter the questionnaires were sent to the participants in advance and interview training was given.

We did not use the Friedman criteria for health care acquired infections and thus patients with health care system contact during the past 2–3 months and patients catheterized the past month were included for analysis [44]. Excluding these patients (n = 30) did, however, not change any trends in the results (data not shown).

Finally, our study may overestimate the use of antibiotics as a risk factor since patients in the control group, with susceptible bacteria, may be less likely to have used antibiotics. This is because non-ESBL E. coli and K. pneumoniae are more susceptible to antibiotics than ESBL-producers, and recently treated patients with such susceptible strains are therefore less likely to show up in the control group [45].

In summary, we have addressed the knowledge gap concerning risk factors for CA-UTIs caused by ESBL-producing bacteria [3]. Previously suspected risk factors for ESBL UTI have been supported and possible new ones uncovered. Our study shows that the predictive antimicrobial resistance pattern in uropathogenic E. coli is heavily influenced by the country the patient has recently visited [28,46]. Thus, information on recent travel is important when treating patients with serious infections that may involve this organism. Physicians in low-prevalence countries should consider ESBL when treating UTI in patients who have visited countries in Africa, The Middle East or Asia during the past six weeks [28,46].

An association between recreational swimming and ESBL UTI was detected. Further investigation to examine the possible negative impact of environmental pollution with ESBL-producing Enterobacteriaceae seems warranted.

Finally, eating fish regularly was associated with a protective effect against ESBL UTI. If this is confirmed in other studies, an interesting link between diet and infection has been established.

Limitations include the possibility of selection bias due to non-participation and a potential problem with differential misclassification of exposure because the interviewers were not masked to the status of the patient being a case or a control. To minimize the latter the questionnaires were sent to the participants in advance and interview training was given.

We did not use the Friedman criteria for health care acquired infections and thus patients with health care system contact during the past 2–3 months and patients catheterized the past month were included for analysis [44]. Excluding these patients (n = 30) did, however, not change any trends in the results (data not shown).

Finally, our study may overestimate the use of antibiotics as a risk factor since patients in the control group, with susceptible bacteria, may be less likely to have used antibiotics. This is because non-ESBL E. coli and K. pneumoniae are more susceptible to antibiotics than ESBL-producers, and recently treated patients with such susceptible strains are therefore less likely to show up in the control group [45].

In summary, we have addressed the knowledge gap concerning risk factors for CA-UTIs caused by ESBL-producing bacteria [3]. Previously suspected risk factors for ESBL UTI have been supported and possible new ones uncovered. Our study shows that the predictive antimicrobial resistance pattern in uropathogenic E. coli is heavily influenced by the country the patient has recently visited [28,46]. Thus, information on recent travel is important when treating patients with serious infections that may involve this organism. Physicians in low-prevalence countries should consider ESBL when treating UTI in patients who have visited countries in Africa, The Middle East or Asia during the past six weeks [28,46].

An association between recreational swimming and ESBL UTI was detected. Further investigation to examine the possible negative impact of environmental pollution with ESBL-producing Enterobacteriaceae seems warranted.

Finally, eating fish regularly was associated with a protective effect against ESBL UTI. If this is confirmed in other studies, an interesting link between diet and infection has been established.

Acknowledgments
We thank Anne Fritzvold, Bjørg Haldorsen and Carina Thilesen for their excellent technical assistance and the Norwegian Prescription Database for good service.

Author Contributions
Conceived and designed the experiments: A. Søraas A. Sundsfjord PAJ. Performed the experiments: A. Søraas. Analyzed the data: A. Søraas A. Sundsfjord IS CB PAJ. Wrote the paper: A. Søraas A. Sundsfjord IS CB PAJ.
6. Nicolas-Chazaine MH, Jarlier V, Robert J, Alet G, Drieux L, et al. (2012) Patient’s origin and lifestyle associated with CTX-M-producing Escherichia coli: a case-control study. PLoS One 7: e30498.

7. Colodner R, Rock W, Chazan B, Keller N, Guy N, et al. (2004) Real-time TaqMan PCR for rapid detection and typing of genes encoding extended-spectrum beta-lactamases. J Antimicrob Chemother 53: 410–417.

8. Nicolas-Chanoine MH, Jarlier V, Robert J, Arlet G, Drieux L, et al. (2012) Antibiotic resistance genes in the antibiotic-resistant Enterobacteriaceae of environmental samples. PLoS One 7: e30498.

9. Friedman ND, Kaye KS, Stout JE, McGarry SA, Trivette SL, et al. (2002) Antimicrobial resistance and integrons of extended-spectrum beta-lactamase (ESBL)-producing enterobacteria. J Clin Microbiol 40: 1401–1407.

10. Steel CM, Crespo-Figuero LS, Bachiller-Luque P, Dominguez-Gil GM, Gomez-Nieto A, et al. (2012) Incidence of intake of oral, intravenous, or nasogastric nutrition in patients at the University of Minnesota Medical Center, Fairview. Am J Infect Control 35: 606–612.

11. Birkent CI, Luzlam HA, Woodford N, Brown DF, Brown NM, et al. (2007) The profile of gut microbiota and weight gain in humans. Future Microbiol 7: 91–105.

12. Birkent CI, Luzlam HA, Woodford N, Brown DF, Brown NM, et al. (2007) Real-time TaqMan PCR for rapid detection and typing of genes encoding CTX-M extended-spectrum beta-lactamases. J Med Microbiol 56: 52–55.

13. Birkent CI, Luzlam HA, Woodford N, Brown DF, Brown NM, et al. (2007) Extended-spectrum beta-lactamase-producing clinical isolates of Escherichia coli and Klebsiella pneumoniae in Norway. J Clin Microbiol 45: 199–205.

14. Samadpour M, Stewart J, Steingart K, Addy C, Louderback J, et al. (2002) Community-onset bacteremia due to extended-spectrum beta-lactamase-producing Escherichia coli among travelers to the Indian subcontinent in New Zealand. Clin Infect Dis 47: 689–692.

15. Kleinbaum DG, Klein M (2010) Assessing Discriminatory Performance of a Binary Logistic Model: ROC curves. In: Kleinbaum DG, Klein M. Logistic Regression. A Self-Learning Text. Third edition. In: 346–386.

16. Kleinbaum DG, Klein M (2010) Assessing Discriminatory Performance of a Binary Logistic Model: ROC curves. In: Kleinbaum DG, Klein M. Logistic Regression. A Self-Learning Text. Third edition. In: 346–386.

17. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

18. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

19. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

20. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

21. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

22. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

23. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

24. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

25. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

26. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

27. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

28. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

29. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

30. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

31. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

32. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

33. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

34. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

35. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

36. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

37. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

38. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

39. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

40. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

41. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

42. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

43. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.

44. Williams I, Whitehead M, Ilett KF, Sevdalis N, Bailey V, et al. (2009) Evaluation of the Marshall scoring system for predicting mortality. Med Care 47: 104–113.