**Vibrio cholerae** non-O1 serogroup (VCNO) bacteraemia is a severe condition with a high case–fatality rate. We report three cases diagnosed in the Netherlands, identified during a national microbiological congress, and provide a literature review on VCNO bacteraemia. A search strategy including synonyms for ‘VCNO’ and ‘bacteraemia’ was applied to PubMed, Medline, Web of Science and Embase databases. The three cases were reported in elderly male patients after fish consumption and/or surface water contact. The literature search yielded 82 case reports on 90 cases and six case series. Thirty case reports were from Asia (30/90; 33%), concerned males (67/90; 74%), and around one third (38/90; 42%) involved a history of alcohol abuse and/or liver cirrhosis. The presenting symptom often was gastroenteritis (47/90; 52%) which occurred after seafood consumption in 32% of the cases (15/47). Aside from the most frequent symptom being fever, results of case series concurred with these findings. Published cases also included rare presentations e.g. endophthalmitis and neonatal meningitis. Based on the limited data available, cephalosporins seemed the most effective treatment. Although mainly reported in Asia, VCNO bacteraemia occurs worldwide. While some risk factors for VCNO were identified in this study, the source of infection remains often unclear. Clinical presentation may vary greatly and therefore a quick microbiological diagnosis is indispensable.

**Introduction**

The genus *Vibrio* is one of the six members of the Vibrionaceae family and includes ten species pathogenic to humans. Probably the most well-known species is *Vibrio cholerae*. Currently, there are over 130 known serogroups based on the presence of somatic O antigens [1,2]. Serogroup O1 and to a lesser extent O139, is notorious for cholera-like outbreaks in form of mild diarrhoea due to toxin-producing VCNO strains but can cause severe extra-intestinal infections such as wound infections and bacteraemia [3,4]. Cases of VCNO bacteraemia are reported in various countries and known risk factors are liver disease/cirrhosis and immunosuppression/immunocompromising conditions [1,3,4]. Sources of infection include seafood and contaminated water [5]. In the Netherlands, VCNO has indeed been isolated from recreational surface water (fresh and brackish) and sporadically from livestock [5,6]. In contrast, a Dutch study from 2010 showed that none of the examined shellfish tested positive for *V. cholerae* [7].

*V. cholerae* is a facultative anaerobic Gram-negative curved or comma-shaped motile bacillus. It can be isolated from blood by using standard culture media such as blood agar [1]. Biochemical properties of this organism include catalase positivity, oxidase positivity, sucrose fermentation and susceptibility for the vibrio-static compound O129. Identification methods are various and include: matrix assisted laser desorption ionization-time-of-flight (MALDI-TOF) analyser (MALDI-TOF, Bruker corporation), VITEK systems (BioMerieux corporation) and polymerase chain reaction (PCR) for 16S and target genes like toxR, ompW and sodB. The non-O1 serogroup can be distinguished from other serotypes by a lack of agglutination with O1-Ogawa and O1-Inaba antigen [1].

In 2013, a patient with a fulminant VCNO sepsis and extensive bullae on the lower extremities was admitted to the Leiden University Medical Centre (LUMC). When searching for literature on VCNO sepsis to help...
determine the source of infection and the optimal treatment strategy, we realised that the available literature appeared to be limited to case reports and small case series. In order to provide evidence for clinicians and public health experts about VCNO bacteraemia we report on a series of three cases and summarise the available literature on VCNO bacteraemia.

Methods

Clinical case reports
During the presentation of the LUMC case at the annual Dutch convention for medical microbiology, we inquired if any of the attending medical microbiologists was aware of additional cases of VCNO sepsis detected in the Netherlands. There is no mandatory notification for VCNO isolates in the Netherlands and VCNO sepsis is rare. Thus, retrieving VCNO sepsis cases detected in the Netherlands was not feasible.

Literature review
In collaboration with an experienced information specialist of the LUMC library, we formulated a search strategy including synonyms for ’V. cholerae non-O1’ and ’bacteraemia’ and applied it to PubMed, Medline, Web of Science and Embase databases (Table 1). Articles published before 15 September 2014 were included. Additional articles were identified by checking the references of relevant articles and duplicates were excluded.

Data of individual case reports were merged and discussed as one patient group. Articles discussing case series were reported separately to prevent overlapping data. Extracted data included: patient demographics, medical history, risk factors i.e. exposure, clinical presentation, laboratory identification method, antimicrobial susceptibility, toxin production, samples cultured, antimicrobial resistance was reported for 10 cases or more, they were reported in this article.

Results

Clinical case reports
In addition to the LUMC case, two additional cases were detected in different Dutch medical centres in 2006 and 2007. A relevant selection of the available data per case is presented; none of the isolates were tested for toxin production. All cases were men and above 50 years of age, with infections during the summer season.

Case 1
Case 1 was a man in his 50s, with a medical history of tuberculosis, chronic obstructive pulmonary disease, depression, marihuana and excessive alcohol use. One day prior to admission, he felt lethargic and developed a painful discoloration on his right ankle. Three days before hospital admission he had walked barefoot along the Dutch shoreline and ate a ready-made tuna salad. Upon admission at the emergency department (ED) he was hypothermic (34.1°C, norm: 36.5 to 37.5), blood pressure was 112/70 mmHg (norm: 120/80), heart rate 115 per minute (norm: 60 to 100), O2 saturation was 90% without additional O2 (norm: 93 to 100). While in the ED he developed circulatory failure.

There were no abnormalities on chest auscultation. Inspection of the lower extremities showed oedema, blue discoloration and large bullae on both lower extremities. The chest X-ray showed patchy bilateral abnormalities of which the differential diagnosis comprised acute respiratory distress syndrome, bilateral pneumonia and pre-existing abnormalities after pulmonary tuberculosis.

Analysis of arterial blood at admission showed severe metabolic acidosis with respiratory compensation: pH 7.24 (norm: 7.35 to 7.45), pCO2 4.5 kPa (norm: 4.5 to 6.0), pO2 2.9 kPa (norm: 10.6 to 13.3), base excess -1.21 mmol/L (norm: -2 to 2), O2 saturation 30% (norm: 94 to 99), glucose 1.3 mmol/L (norm: 3.5
including lungs, spleen, liver and intestine. Vibrio spp. were cultured from several organs but no examination patient died from MOF and sepsis. At post-mortem cans the next day, blood cultures showed C. albicans and Aspergillus fumigatus, but no Vibrio spp. were cultured from several organs including lungs, spleen, liver and intestine.

Microbiology findings
Within 24 hours from presentation at the ED blood cultures and cultures of bullae content grew rod-shaped/curved Gram-negative bacteria which were oxidase-, katalase- and DNase-positive. MALDI-TOF analysis showed V. albensis with a score of 2.0 which corresponds with a secure identification on genus level and probable identification on species level (norm: 2.0 to 2.3). Additional biochemical testing (i.e. API 20E, Biomerieux) indicated V. cholerae. The microorganism did not agglutinate with O1-Ogawa or O1-Inaba antisera, was sensitive to the vibriostatic compound O/129 and was therefore labelled VCNO. This finding was confirmed and supplemented i.e. non-O 139, by the Dutch National Institute for Public Health and Environment (RIVM). In house susceptibility testing by disk diffusion showed ciprofloxacin and co-trimoxazole sensitivity.

Cultures of the tuna salad packaging did not reveal any Vibrio spp.

Case 2
A man in his late 60s with a medical history of heart disease, insulin-dependent diabetes mellitus type II, a cholecystectomy and an aneurysm of the abdominal aorta, presented to the ED with severe diarrhoea. Two weeks earlier, while on one of the Dutch islands, he suffered from severe diarrhoea for two days after having eaten raw herring. There was initial improvement, but the watery diarrhoea recurred and he consulted a general practitioner who referred him to hospital. There was no blood or mucus in his stool. He did not report any surface water contact.

Upon hospital admission, the patient was mildly icteric and had dyspnoea (respiratory rate 29/minute; norm: 12 to 18), lowered O2 saturation of 91% without supplemental oxygen. He was tachycardic (129/minute), blood pressure was slightly elevated (132/92 mmHg) and he had a temperature of 38°C. Aside from abdominal distention, physical examination of the abdomen, heart, lungs and skin on the extremities showed no abnormalities. Ultrasound scan of the abdomen showed no abnormalities except steatosishepatis and liver cysts (4 cm in diameter). The electrocardiogram and abdominal X-ray were normal. The chest X-ray revealed signs of congestive heart failure.

Parameters of the arterial blood analysis were within normal range. Other laboratory findings at admission showed a mild leucocytosis of 14.0 x10^9/L (norm: 4 to 11) and elevated liver enzymes indicating cholestasis. Laboratory results included: Hb 9.0 mmol/L, thrombocytes 226 x10^9/L, CRP 111mg/L (norm: 0 to 10), glucose 12.0 mmol/L (norm: 3.5 to 7.8), sodium 137 mmol/L (norm: 135 to 145), potassium 3.4 mmol/L (norm: 3.5 to 5.0), creatinine 60 µmol/L (norm: 50 to 110), urea 5.3 mmol/L (norm: 2.5 to 7.5), LDH 269 U/L (norm: 0 to 250), ASAT 194 U/L (norm: 0 to 40), ALAT 292U/L, AF251 U/L (norm: 0 to 120), gamma-GT 631 U/L, bilirubin total 90 µmol/L (norm: 0 to 17), bilirubin direct 66 µmol/L.

to 5.5), lactate 11.4 mmol/L (norm: 0.5 to 2.2). Blood analysis showed a leukopenia, a thrombopenia and elevated liver enzymes. Specifically relevant laboratory results were: haemoglobin (Hb) 8.8 mmol/L (norm: 8.5 to 11.0), leukocytes 2.82 x10^9/L (norm: 4.00 to 10.00), thrombocytes 46 x10^9/L (norm: 150 to 400), INR 1.7 (norm: 0.5 to 0.5), C-reactive protein (CRP) 85 mg/L (norm: 0.0 to 0.5), bilirubin 71 µmol/L (norm: 0 to 17), gamma-glutamyltransferase (gamma-GT) 428 U/L (norm: 0 to 55), alkaline phosphatase (AF) 122 U/L (norm: 0-115), aspartate-aminotransferase (ASAT) 194 U/L (norm: 0 to 35), alanine-aminotransferase(ALAT) 68 U/L (norm: 0-45), creatinine was normal.

The putative diagnosis was septic shock due to deep skin infection. Empirical antimicrobial treatment with ciprofloxacin, cefotaxime and selective digestive decontamination with polymyxin E, tobramycin and amphotericin B, was initiated, and the patient was resuscitated, started on vasopressors and admitted to the intensive care unit. Necrotising fasciitis was excluded upon surgical exploration. As VCNO non-O139 was isolated from blood and bullae content on admission day 3, antimicrobial treatment was switched to ciprofloxacin and cefotaxime. Upon the eighth admission day 3, antimicrobial treatment was switched to ciprofloxacin and cefotaxime. With the working diagnosis ‘hospital acquired infection’, gentamicin and flucloxacillin were added.
# Table 1

**Literature search strategy for *Vibrio cholera* non-O1 bacteraemia**

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la: language; MeSH: medical subject headings; TS: title/summary.

* No additional records were retrieved through searching the Medline database after searching the PubMed database.
The diagnosis was sepsis and after obtaining blood cultures, treatment with amoxicillin-clavulanic acid and gentamicin was initiated according to the local sepsis treatment protocol. On the second admission day, the Gram-negative rod was isolated and suspected to be *Salmonella* spp. Treatment was switched to co-trimoxazole. Later that day, as the isolate tested oxidase-positive, the working diagnosis was changed to co-trimoxazole. Later that day, as the isolate tested oxidase-negative, the working diagnosis was changed to *Pseudomonas* spp. and treatment was switched to ciprofloxacin. Ciprofloxacin was continued after the identification of *V. cholerae*. The patient recovered fully, was discharged after five days with oral ciprofloxacin, and returned to his island holiday.

**Microbiology findings**

One day after hospital admission, blood cultures became positive with Gram-negative rods, later identified as *V. cholerae* (Phoenix Automated Microbiology System, BD diagnostics and API E, Biomerieux). The isolate was sent to the RIVM and the biochemical profile, fatty acid analysis and 16S rDNA PCR showed *V. cholerae* non-O1 non-O139. Stool cultures remained negative for *Vibrio* spp.. With standard disk diffusion the isolate tested susceptible to co-trimoxazole, cefuroxime, gentamicin, ciprofloxacin, piperacillin, ceftazidime, meropenem, tobramycin and piperacillin/tazobactam. It was immediately sensitive to amoxicillin, amoxicillin-clavulanic acid, cefazolin and resistant to ceftriaxone.

**Case 3**

A man in his early 70s presented at the ED with general malaise, dizziness, decreased appetite, coughing and dyspnoea that had been lasting for one week. Relevant medical history comprised heart failure and a hepatojenuostomy for chronic cholangitis more than a decade ago. The patient had been having fever, malaise, dizziness, decreased appetite, coughing and dyspnoea that had been lasting for one week. Upon hospital admission, he had a temperature of 39°C, heart rate of 66/minute, blood pressure of 110/70 mmHg and oxygen saturation was normal without oxygen administration. He was disorientated and had trouble concentrating. There were no signs of gastroenteritis or abnormalities on chest examination. No apparent skin lesions were reported.

Arterial blood analysis showed a pH 7.46, pCO2 4.4 kPa (norm: 4.7 to 6.4), bicarbonate 23.1 mmol/L (norm: 22.0 to 29.0), pO2 6.4 kPa (norm: 10.0 to 13.3), base excess -1.0 mmol/L (norm: -3.0 to 3.0), O2 saturation 86%. Analysis of venous blood showed raised inflammatory parameters, impaired renal and liver function tests. CRP 181 mg/L (norm: < 7), leukocytes 10.6 x10^9/L, urea 12.5 mmol/L (norm: 2.9 to 7.5), creatinin 115 umol/L (norm: 01 to 05), AP 336 U/L (norm: 0 to 120), gamma-GT 282 U/L, bilirubin 70 umol/L (norm: 0 to 20), ASAT 132 U/L (norm: 0 to 32), ALAT 104 U/L, glucose 7.9 mmol/L (norm: 0 to 7.8).

The patient was initially empirically treated for sepsis with ceftriaxone and gentamicin, then switched to oral amoxicillin-clavulanic acid. He recovered completely and was discharged after seven days of hospitalisation.

**Microbiology findings**

Within 24 hours after admission, blood cultures grew Gram-negative rods. On TCBS agar, yellow colonies appeared which tested oxidase negative. Identification through API NE (Biomerieux corporation) showed *V. cholerae* (code 7074745, ID 99.0%), which was confirmed with 16S PCR. The isolate’s susceptibility was tested using standard disk diffusion on Muller Hinton agar plates. It was susceptible to amoxicillin, amoxicillin-clavulanic acid, piperacillin, piperacillin-tazobactam, cefoxitin, ceftazidime, meropenem, gentamicin.

Sputum cultures were negative for *Vibrio* spp.. The eel was not examined microbiologically, therefore the source of infection remained unclear.

**Review**

The initial search yielded 163 unique articles and 155 duplicates (Figure 1). Reference checking resulted in identification of two additional unique articles. Of the 165 retrieved articles, 77 were excluded based on title or abstract, leaving 88 articles including 82 case reports [8-89] and six articles reporting case series [90-95].

**Case reports**

The 82 articles retrieved covered 90 patients; 23 (26%) of them were female and the mean age was 49 (0–84) years. Cases were reported worldwide; 22 (25%) were identified in Europe, 19 (21%) in the United States of America, 30 (33%) in the Asian continent and 19 (21%) in the remaining continents. The remaining case characteristics are presented in Table 2 (extraction table for data available from authors upon request).

The most frequently reported symptom was gastroenteritis (51/90; 57%) followed by fever without gastroenteritis (26/90; 29%) and bullae (18/90; 20%). However, also rare presentations such as endophthalmitis and neonatal meningitis were reported. Overall known risk factors such as consumption or handling of seafood or consumption or contact with possibly contaminated water were reported in 45 cases (45/90; 50%). Of the 47 patients (47/90; 52%) presenting with gastroenteritis and no bullae, 15 (15/47) reported prior seafood consumption, five (5/47) reported fishing (possibly implying consumption) and for nine cases (9/47) no exposure data were reported; no information...
on exposure was available for the remaining 18 cases. In five cases (5/90; 6%) authors hypothesised on additional risk factors such as indirect contact with raw seafood e.g. contaminated baby bathwater/bottle (2/5) and administration of the oral *V. cholerae* vaccine (3/5). However, the vaccine contains killed whole *V. cholera* cells with or without recombinant B-sub unit and the nature of the alleged link to VCNO infection was not clarified by the authors. As our case definition of VCNO sepsis included bacteraemia, a positive blood culture was reported for all patients. Additional samples that were positive for VCNO are shown in Table 2. Thirty-one patients died due to their VCNO infection, which results in an overall case–fatality rate of 348 per 1,000 for this selected sample.

For 62 cases (62/90; 69%), susceptibility data of the *V. cholerae* non-O1 isolates were provided (extraction table available from authors upon request). Overall, in vitro resistance was observed to amoxicillin (4/50...
tested (intermediately) resistant, trimethoprim-sulfamethoxazole (4/37), ciprofloxacin (2/24), gentamicin (1/37) and doxycycline (3/38). Antimicrobials to which V. cholerae non-O1 isolates appeared to be susceptible in vitro, without exception, were cephaloridine (n=14 tested), cefuroxime (n=10), cefotaxime (n=14), ceftazidime (n=12), ceftriaxone (n=15), amikacin (n=17) and chloramphenicol (n=33). Toxin production of the isolates was not consistently reported in literature and therefore not included in the analysis.

Case series
Details of the six retrieved case series were extracted and analysed briefly given the selected nature of the sample (Table 2). Altogether, 82 patients with VCNO bacteraemia were retrieved, the majority of reports originating from the Asian continent. As in the three case reports described above, most patients were male. In contrast, fever was the most frequent presenting symptom and risk factors could be identified in only a minority of patients (24/82; 29%).

Overall, the number of cases reported peaked in 1996, 1998, 2007 and 2011 (Figure 2).

Discussion
We presented three cases of VCNO bacteraemia that were identified in the Netherlands between 2006 and 2013 as well as 172 cases from literature occurring between 1980 and 2014. Corresponding with current knowledge, both the recently identified cases and the previously reported ones show that patients are typically male, often have a history of liver/bile duct disease and the presenting symptoms often include gastroenteritis, fever and bullae [1]. The suspected sources while seldom confirmed microbiologically, are commonly fish and surface water. In contrast to previous reports, however, we found that a great variety in clinical presentation does occur, ranging from lethargy to meningitis, endophthalmitis, cough and dyspnoea [1]. Severe outcomes include neurological impairment, lower limb amputation and death. All three Dutch cases presented during summer, the season of recreational activities such as fishing, swimming and of flourishing microorganisms in surface waters due to rising temperatures [96-98].

A major strength of our analysis is that it provides a complete overview of what is known about VCNO bacteraemia, whereas other reports merely describe individual cases or a selection of case reports. The search was formulated by an experienced scientist (MFE) and an information specialist (JS) and articles were provided by the LUMC library which has access to over 9,000 leading (bio-)medical journals. Therefore, we consider that this review includes all relevant published articles published in Dutch and English and provides a complete overview of the available literature on VCNO bacteraemia.

The summary of data on antimicrobial susceptibility provided here may assist physicians in choosing an adequate treatment regimen. The data indicate that administration of a cephalosporin is likely to be the best option when dealing with VCNO bacteraemia. However, an important factor that hinders the extrapolation of our data to clinical practice is publication bias, many authors did not report susceptibility data. This is crucial when evaluating resistance data, as many authors solely reported the susceptibility to antimicrobials administered to the patient in question. Additional relevant data on antimicrobial resistance that may very well have been available to the authors was not published.

After searching current literature for the aetiology of VCNO bacteraemia, we could not reveal why males are affected more frequently than females, but found a similar trend in infections with other Vibrio spp [99]. The role of immunocompromising conditions in acquiring VCNO bacteraemia seems clear and the influence of liver cirrhosis can probably be attributed to high ferritin levels which are required for the metabolism of Vibrio spp [100].

Aside from predisposing conditions and exposure, bacterial virulence may very well play a significant role in the pathogenesis of VCNO bacteraemia. VCNO toxins are being studied and several are known e.g. ctx; large excretion of fluids and electrolytes into the lumen hly; hemolysin, rtxA; actin cross linking, hap; haemagglutinin protease, type 3 and 6 secretion system, nanH; neuraminidase, NAG-ST; heat-stable enterotoxin. The clinical significance of these toxins (e.g. their role in bulla formation, remains yet to be determined [101,102].

In conclusion, VCNO bacteraemia is a disease that can be fatal and poses a threat around the globe especially to patients with a history of alcohol abuse and/or liver cirrhosis. Physicians should be aware of the possibility of VCNO bacteraemia in patients presenting with gastroenteritis, fever or bullae after consumption of or contact with seafood or potentially contaminated water. However, risk factors often remain unidentified, the clinical presentation varies greatly and a quick microbiological diagnosis is indispensable. Cephalosporins are likely the best treatment option for VCNO bacteraemia.

Acknowledgements
We gratefully acknowledge the assistance of Mr. J. Schoones, MA, experienced information specialist at the Walaeus library at the LUMC, with the literature search.

Conflict of interest
None declared.
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47. Laosombat V, Pruekprasert P, Wongchanchailert M. Non-0:1
46. Lalitha MK, Dayal U, Cherian AM. Non-agglutinating vibrio
45. Kontoyiannis DP, Calia KE, Basgoz N, Calderwood SB. Primary
44. Kontoyiannis DP, Calia KE, Basgoz N, Calderwood SB. Primary
43. Kontoyiannis DP, Calia KE, Basgoz N, Calderwood SB. Primary
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