**Vibrio cholerae** non-O1 bacteraemia: description of three cases in the Netherlands and a literature review

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**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]. 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 vibriostatic 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.

Retrieved articles were screened based on title and abstract, and exclusion criteria were: *Vibrio* spp. other than *V. cholerae* non-O1, article not available through the journal’s archive/the main author i.e. unanswered email after three months, in vitro data only, environmental samples only, no bacteraemia, no humans, limited clinical data, languages other than English or Dutch. No date limits were applied.

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 aside from blood, treatment and clinical outcome. If 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 development 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 -12.1 mmol/L (norm: -2 to 2), O2 saturation 30% (norm: 94 to 99), glucose 1.3 mmol/L (norm: 3.5
Figure 2

Cases of non-O1bacteraemia reported annually in Europe and worldwide, (n=172 including case reports and case series)

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-O139, by the Dutch National Institute for Public Health and Environment. 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 x10⁹/L (norm: 4 to 11) and elevated liver enzymes indicating cholestasis. Laboratory results included: Hb 9.0 mmol/L, thrombocytes 226 x10⁹/L, CRP 111 mg/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 292 U/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.
<table>
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<th>Unique records</th>
</tr>
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<td>19</td>
</tr>
<tr>
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<td><strong>318</strong></td>
<td><strong>163</strong></td>
</tr>
</tbody>
</table>

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

* No additional records were retrieved through searching the Medline database after searching the PubMed database.
isolate was sent to the RIVM and the biochemical system, BD diagnostics and API E, Biomerieux (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, ceftazidime, meropenem, tobramycin and piperacillin/tazobactam. It was intermediately sensitive to amoxicillin, amoxicillin-clavulanic acid, cefazolin and resistant to ceftriaxone.

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 intermediately 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 hepatojejunostomy for chronic cholangitis more than a decade before presentation. He had not been travelling or swimming, but habitually caught eel in the Ijsselmeer lake that summer and cleaned the eel himself. He did not report having consumed the eel or having had contact with lake water other than taking eel out of fishing nets, or of wounds or lacerations on his hands before his illness.

Upon hospital admission, he had a temperature of 39°C, heart rate of 66/minute, blood pressure of 110/70 mm/Hg 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 0.1 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 *10⁹*/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, ceftoxitin, 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...
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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Dutch cases (n=3)</th>
<th>Literature review</th>
<th>Case reports (n=90)</th>
<th>Case reports (n=82)</th>
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<td>Femalea</td>
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<td>23 (26)</td>
<td>12 (15)</td>
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<td>NR (28–83)</td>
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<td>Europe</td>
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<td></td>
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<td>19 (21)</td>
<td>6 (7)</td>
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<td>12 (15)</td>
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<td>11 (12)</td>
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</tr>
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<td>1 (2)</td>
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</table>

CSF: cerebrospinal fluid; NR: Not reported or insufficient data.

a The sex of one patient (newborn) was not provided.

b Aside from positive blood cultures which were confirmed for all cases.

c Australia, Israel, Kuwait, Lebanon, Mauritius, Ottawa (Canada), Puerto Rico, Qatar, Saudi Arabia.

d AIDS/HIV, chemotherapy, prednisone, neutropenia, non-Hodgkin lymphoma, myelodysplastic syndrome, idiopathic aplastic anaemia, transplant recipient.

e *Vibrio cholerae* vaccine, baby bath/bottle contamination with raw seafood.
tested (intermediately) resistant), trimethoprim-sul-
famethoxazole (4/37), ciprofloxacin (2/24), gentamicin
(1/37) and doxycycline (3/38). Antimicrobials to which
*V. cholerae* non-O1 isolates appeared to be suscepti-
ble in vitro, without exception, were cephalotin (n=14
tested), cefuroxime (n=10), cefotaxime (n=14), ceftazi-
dime (n=12), ceftriaxone (n=15), amikacin (n=17) and
chloramphenicol (n=33). Toxin production of the iso-
lates 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 present-
ing 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 previ-
ous 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 tempera-
tures [96-98].

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

The summary of data on antimicrobial susceptibil-
ity 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 bacterae-
mia. However, an important factor that hinders the
extrapolation of our data to clinical practice is publi-
cation 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 acquir-
ing VCNO bacteraemia seems clear and the influence
of liver cirrhosis can probably be attributed to high fer-
ritin levels which are required for the metabolism of
*Vibrio* spp [100].

Aside from predisposing conditions and exposure, bac-
terial 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-
AET; hemolysin, rtxA; actin cross linking, hap; haemag-
glutinin 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 gas-
troenteritis, fever or bullae after consumption of or con-
tact with seafood or potentially contaminated water.
However, risk factors often remain unidentified, the
clinical presentation varies greatly and a quick microbi-
ological diagnosis is indispensable. Cephalosporins are
likely the best treatment option for VCNO bacteraemia.

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**Conflict of interest**
None declared.


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