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1   **Review**
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3   **Bacterial zoonoses of fishes: A review and appraisal of evidence for linkages between**
4   **fish and human infections**
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7   David T. Gauthier *

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9   *Department of Biological Sciences, Old Dominion University, Norfolk, Virginia 23529, USA*
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14   *   Corresponding author. Tel.: +1 757 683 3822.
15   *E-mail address:* dgauthie@odu.edu (D.T. Gauthier).

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Highlights

- A variety of bacteria have been described as fish-borne zoonoses in humans.

- Genetic evidence fails to link many supposed piscine zoonoses to human infections.

- Three species and one genus of bacteria are supported as fish-borne zoonoses:

  Mycobacterium spp., *Clostridium botulinum*, *Streptococcus iniae*, *Vibrio vulnificus*.

22

23

Abstract

Human contact with and consumption of fishes presents hazards from a range of bacterial zoonotic infections. Whereas many bacterial pathogens have been presented as fish-borne zoonoses on the basis of epidemiological and phenotypic evidence, genetic identity between fish and human isolates is not frequently examined or does not provide support for transmission between these hosts. In order to accurately assess the zoonotic risk from exposure to fishes in the context of aquaculture, wild fisheries and ornamental aquaria, it is important to critically examine evidence of linkages between bacteria infecting fishes and humans. This manuscript reviews bacteria typically presented as fish-borne zoonoses, and examines the current strength of evidence for this classification. Of bacteria generally described as fish-borne zoonoses, only *Mycobacterium* spp., *Streptococcus iniae*, *Clostridium botulinum*, and *Vibrio vulnificus* appear to be well-supported as zoonoses in the strict sense. *Erysipelothrix rhusiopathiae*, while transmissible from fishes to humans, does not cause disease in fishes and is therefore excluded from the list. Some epidemiological and/or molecular linkages have been made between other bacteria infecting both fishes and humans, but more work is needed to elucidate routes of transmission and the identity of these pathogens in their respective hosts at the genomic level.

41

42   *Keywords:* Bacteria; Zoonosis; Fish-borne; Epidemiology; Molecular biology

Introduction

Bacterial zoonoses of fishes have received increasing attention as new bacterial pathogens have been identified and improved microbiological and molecular methods have enabled identification of fish pathogens in human hosts. Bacterial zoonoses of fishes have been reviewed previously (Ghittino, 1972; Shotts, 1987; Nemetz and Shotts, 1993; Lehane and Rawlin, 2000; Boylan, 2011; Haenen, 2013). Rather than focusing on ground covered by this previous body of work, the present manuscript will examine what is known about the nature of zoonotic associations between bacterial pathogens of humans and fishes, and the evidence for their connections.

The term 'zoonosis' is generally defined as an infection transmissible from animals to humans. The World Health Organization makes a further distinction that zoonosis in its strict sense should be used to describe cases in which vertebrate animals are necessary for maintaining infections in nature, and humans are accidental hosts (PAHO, 2001). This latter definition is contrasted with 'infections-in-common', in which pathogens are acquired by animals and humans from common environmental sources or non-vertebrate organisms. It is not uncommon for infections-in-common, including foodborne infections, to be classified as a form of zoonosis (Haenen et al., 2013), but this to some degree obscures the biology and true epidemiological connections of an infectious association. Many bacteria generally considered as fish zoonoses are facultative pathogens with an environmental niche and often it is not possible to differentiate between infections-in-common and strict zoonoses. The present review will detail what is known about the nature of infections with various bacterial agents in humans and fishes, as well as their transmission routes.

67   When drawing linkages between human and fish infections it is important to

68   determine whether they are caused by the same organism. Most of the existing literature is

69   limited to phenotypic/biochemical descriptions of isolates from fishes and humans, and there

70   is a paucity of information as to whether infections in fishes and humans are caused by the

71   same strains, serotypes, or in some cases, species of bacteria. Use of molecular techniques has

72   improved our ability to determine whether human infections have arisen directly from

73   infected fishes, environmental sources, or through exposure to transiently colonized or

74   contaminated fish products (Table 1). Most bacteria identified as piscine zoonoses by

75   previous authors will be covered in this review, with the addition of *Lactococcus garvieae*,

76   which has not been discussed in previous reviews.

77

78   **Gram positive bacteria**

79   *Clostridium botulinum*

80   *Clostridium botulinum* is commensal in the intestines of marine and freshwater fish

81   species worldwide, and can also be found in environmental sediments and decaying organic

82   matter. A potent paralytic neurotoxin is produced by this bacterium that induces descending

83   paralysis in human beings (Bean and Griffin, 1990). Of the seven recognized botulinum toxin

84   types (A-G), type E is involved in most cases of human disease related to fish consumption,

85   although types A and B are occasionally implicated (Barrett et al., 1977). Disease in fishes

86   due to *C. botulinum* is uncommon and occurs when fishes feed on decaying carcasses that

87   have become anaerobic and thus support growth of the bacterium. The disease is known as

88   'bankruptcy disease' in earthen pond culture of salmonids (Roberts, 2001) and has also been

89   documented as 'visceral toxicosis' of catfish in south eastern USA (Khoo et al., 2011).

90   Human botulism has been associated with consumption of contaminated fish products,

91   notably smoked fish in arctic and northern temperate regions (Hielm et al., 1998; Fagan et al.,

92   2011). Pulsed-field gel electrophoresis (PFGE) and random amplified polymorphic DNA

93   (RAPD) analysis reveal considerable genetic diversity among *C. botulinum* (Hielm et al.,

94   1998) and PFGE has demonstrated links between food and *C. botulinum* genotypes involved

95   in individual outbreaks (Leclair et al., 2006).

96

97   *Erysipelothrix spp.*

98   *Erysipelothrix* spp. include *Erysipelothrix rhusiopathiae*, *E. tonsillarum* (Takahashi et

99   al., 1987) and *E. inopinata* (Verbarg et al., 2004). In non-human animals, the disease caused

100   by *E. rhusiopathiae* is properly known as 'erysipelas', while in humans the disease is referred

101   to as 'erysipeloid'; 'erysipelas' in humans is caused by *Streptococcus* spp., primarily *S.*

102   *pyogenes* and *S. agalactiae*. Human infections with *E. rhusiopathiae* occur via contamination

103   of cutaneous wounds and typically result in localized, painful, self-limiting cellulitis, with

104   purple discoloration and edema ('fish rose') (Reboli and Farrar, 1989; Wang et al., 2010).

105   Systemic infections with *E. rhusiopathiae* in humans are uncommon, but are often associated

106   with endocarditis (Reboli and Farrar, 1989). Among animals, erysipelas is of greatest

107   significance in pigs, in which it causes 'diamond skin disease.' *E. rhusiopathiae* colonizes the

108   mucous coating of fishes, apparently as a commensal, as it has not been reported to cause

109   disease. Zoonotic transmission of *E. rhusiopathiae* to humans occurs among fisheries workers

110   ('fish-handlers disease') (Reboli and Farrar, 1989). Takahashi et al. (2008) performed DNA-

111   DNA hybridization on *Erysipelothrix* spp. from various sources, mainly to classify *E.*

112   *rhusiopathiae* and *E. tonsillarum*, rather than to examine host specificity. Despite the absence

113   of genetic evidence, the link between skin lesions in humans and handling of fishes colonized

114   by *E. rhusiopathiae* support the contention that this bacterium is a zoonotic agent. However,

115   fishes could also be regarded as a mechanical vector, since *E. rhusiopathiae* does not appear

116   to cause disease in fish hosts.

117

118   *Lactococcus garvieae*

119   Among previously described 'group D streptococci', *Lactococcus garvieae* is the most

120   significant fish pathogen and has recently been described as a human pathogen, causing

121   endocarditis, cholecystitis and diskospondylitis (Chan et al., 2011; Kim et al., 2013). *L.*

122   *garvieae* was first isolated from cases of bovine mastitis, initially as *Streptococcus garvieae*

123   (Collins et al., 1983), and has been described from warm water fishes, initially as

124   *Enterococcus seriolicida*, which was subsequently demonstrated to be a junior synonym for *L.*

125   *garvieae* (Teixeira et al., 1996). *L. garvieae* causes serious disease in cultured warm water

126   fishes, typically manifesting as acute hemorrhagic septicemia, with mortality and reduced

127   growth (Vendrell et al., 2006). Human infection with *L. garvieae* has been associated with

128   ingestion of raw seafood (Chan et al., 2011; Kim et al., 2013), seasonal peaks in *L. garvieae*

129   infection in cultured fishes (Wang et al., 2007) and occupational fishery exposure (Aubin et

130   al., 2011).

131

132   RFLP typing demonstrated considerable diversity among *L. garvieae* associated with

133   outbreaks of disease in fishes and lack of similarity between piscine and bovine strains (Eldar

134   et al., 1999). Using PFGE, Vela et al. (2000) observed high genotypic diversity among

135   isolates from fishes, cattle, humans and water, with higher similarities among strains from a

136   given host. There was no similarity between isolates from fishes, including amberjack

137   (*Seriola* spp.) and 'trout', and a range of other species (cattle, pigs, cats, dogs and horses) by

138   PFGE (Kawanishi et al., 2006), nor between isolates from fish and dairy products by RAPD

139   or amplified fragment length polymorphism (AFLP) analysis (Foschino et al., 2008).

140   Comparative genomics of *L. garvieae* isolates did not reveal clear linkages between strains

141   from fishes and other sources (Ferrario et al., 2013), whereas several differences (e.g. adhesin

142   genes) potentially contributing to host specificity have been identified (Miyauchi et al., 2012).

143   The available genetic information points towards separation of human and fish strains, and

144   there is limited epidemiological evidence to support transmission of *L. garvieae* between

145   fishes and humans. Therefore, the status of *L. garvieae* as a fish-borne zoonosis is

146   questionable.

147

148   *Staphylococcus spp.*

149   *Staphylococcus* spp., specifically *S. epidermidis* and *S. aureus*, have been isolated

150   from cultured fishes during disease outbreaks (Kusuda et al., 1976; Baxa et al., 1985), but

151   their pathogenic role is unclear and these bacteria are not generally discussed as agents of fish

152   disease. Nemetz and Shotts (1993) mention a potential human health threat from

153   *Staphylococcus* spp. due to enterotoxin synthesis in spoiled food; however, to date there have

154   been no reports of zoonotic fish-borne infections with *Staphylococcus* spp.

155

156   *Streptococcus spp.*

157   Infection with *Streptococcus* spp. in fishes typically involves Lancefield group B

158   organisms (*Streptococcus agalactiae*) or *Streptococcus iniae*, which does not express

159   Lancefield antigens. *S. agalactiae* is an agent of mastitis in cows and neonatal sepsis in

160   humans. Infection with group B *Streptococcus* spp. has been reported from a wide variety of

161   temperate and warm-water fishes, presenting with hemorrhagic septicemia and, often,

162   neurological signs (Evans et al., 2006). Evans et al. (2008) reported genetic similarity among

163   human neonatal, and piscine and dolphin isolates of *S. agalactiae* from Japan and Kuwait,

164   respectively. However, Pereira et al. (2010) failed to find genetic identity among *S. agalactiae*

165   isolates from humans, fishes and cattle, so currently there is little genetic evidence to

166   implicate Group B streptococci as fish-borne zoonoses.

167

168   *Streptococcus iniae*, originally isolated from the Amazon river dolphin, *Inia*

169   *geofrensis* (Pier and Madin, 1976), has been reported in a variety of piscine hosts (Evans et

170   al., 2006). Weinstein et al. (1997) identified zoonotic infection with *S. iniae* in a disease

171   outbreak in Toronto, Canada, involving nine humans with cellulitis related to handling raw

172   fish (tilapia or unknown species); one patient also had endocarditis, meningitis and arthritis.

173   The PFGE pattern demonstrated an identical strain of *S. iniae* in all nine human patients

174   matching isolates from tilapia in local fish markets, as well as from an outbreak of disease in

175   tilapia in Virginia, USA, in 1993. Two additional human cases were identified retrospectively

176   in Texas, USA, in 1991 and Ottawa, Canada, in 1994 (Weinstein et al., 1997). Zoonotic

177   infections with *S. iniae* have been reported in Southeast Asia, Canada and Hong Kong, and

178   are primarily associated with processing and handling live fishes (Lau et al., 2003; Koh et al.,

179   2004).

180

181   **Acid-fast bacteria**

182   *Mycobacterium spp.*

183   Mycobacteria are the best known zoonotic fish-borne bacterial pathogens, causing

184   granulomatous inflammation of the skin and, occasionally, deeper tissues in humans, known

185   as 'fishermans finger', 'fish tank granuloma, 'fish-fanciers finger' and other similarly

186   descriptive terms. Lesions of this type were first described by Nordén and Linell (1951) and

187   attributed to '*Mycobacterium balnei*' (now *Mycobacterium marinum*) by Swift and Cohen

188   (1962). Disease from fish- or water-borne mycobacterial infection in humans generally takes

189   the form of superficial granulomatous inflammation, usually of the extremities, but may

190   involve deeper tissues, resulting in tenosynovitis, bursitis, arthritis and osteomyelitis (Lahey,

191   2003). Both localized and 'sporotrichoid' forms of the disease are described; the former

192   presents with nodular or ulcerated lesions, while the latter is associated with lymphatic spread

193   (Lewis et al., 2003). The incubation period in humans is variable, but can be protracted,

194   taking weeks to months before symptoms are manifested (Jernigan and Farr, 2000).

195

196   In rare cases, usually associated with immunocompromised patients and/or

197   corticosteroid therapy, disseminated infections may arise, with cutaneous, pulmonary or

198   visceral involvement (King et al., 1983; Ho et al., 2001; Streit et al., 2006). This is of

199   particular concern, since aquatic mycobacterial infections may present symptoms that mimic

200   arthritis or autoimmune disorders, prompting the use of corticosteroids (Barton et al., 1997).

201   Disseminated *M. marinum* infection has also been observed in immunocompetent individuals

202   (Vazquez and Sobel, 1992). Fatalities, although rare, have been reported (Tchornobay et al.,

203   1992; Gould et al., 2004). Antibiotic therapy is generally effective for aquatic mycobacterial

204   infections in humans, although surgical excision of lesions may be required (Lewis et al.,

205   2003; Petrini, 2006).

206

207   In addition to their direct effects, *M. marinum* and other non-tuberculous mycobacteria

208   (NTM) can induce cross-reactivity to skin tests based on purified protein derivative (PPD) of

209   *M. tuberculosis* and *M. avium* (Jolly and Seabury, 1972; Lewis et al., 2003). Interferon release

210   assays have been developed to circumvent false positivity in PPD skin tests, but exposure to

211   some NTM, including *M. marinum*, may generate false positive results with these assays

212   (Kobashi et al., 2009).

213

214   The thermal tolerance of *Mycobacterium* spp. is likely to be involved in their limited

215   ability to infect humans and spread to deeper tissues. Growth of *M. marinum* is restricted to

216   temperatures below 37 °C, limiting most human infections to the distal extremities (Kent et

217   al., 2006). This issue of temperature tolerance is also of relevance to mycobacteria producing

218   mycolactone toxin (MPM), including the human pathogen *Mycobacterium ulcerans* and the

219   closely related fish pathogen *Mycobacterium pseudoshottsii* (Rhodes et al., 2005). Most MPM

220   do not grow at 35 °C and often grow poorly above 30 °C (Ranger et al., 2006), which likely

221   limits transmission to humans. However, apparent zoonotic infections due to MPM have been

222   reported (Chemlal et al., 2002; Williamson et al., 2014).

223

224   Mycobacteriosis affects a wide range of fish species worldwide and most frequently

225   manifests as chronic granulomatous inflammation in viscera and muscles, as well as

226   ulcerative skin lesions (Gauthier and Rhodes, 2009). Piscine mycobacteriosis, historically

227   associated with *M. marinum*, *Mycobacterium fortuitum* and *Mycobacterium chelonae*, is also

228   linked to infections with a wide variety of other mycobacterial species, including

229   *Mycobacterium shottsii* and *Mycobacterium pseudoshottsii* (Rhodes et al., 2003, 2005), and

230   *Mycobacterium salmoniphilum* sp. nov., nom. rev. (Whipps et al., 2007). Mycobacteriosis has

231   a significant impact on aquaculture and ornamental aquaria; with the exception of limited

232   reports of antibiotic treatment, the only treatment option is destruction of infected animals and

233   decontamination of holding facilities.

234

235   Human infections with fish-pathogenic mycobacteria are generally contracted through

236   exposure of wounds and skin abrasions to contaminated water; the disease occurred relatively

237   frequently in users of swimming pools before the widespread use of chlorination (Petrini,

238   2006). Currently, most cases are associated with exposure to aquaria (Aubry et al., 2002), as

239   well as injuries contracted during seafood processing or preparation (Clark et al., 1990;

240   Lawler, 1994).

241

242   There are substantial genetic differences between *M. marinum* isolates from fishes and

243   humans (Ucko and Colorni, 2005). Zebrafish (*Danio rerio*) develop acute disease when

244   inoculated with human isolates of *M. marinum*, but chronic infection when inoculated with

245   fish isolates (van der Sar et al., 2004). Fish isolates of *M. marinum* are infectious for mice,

246   producing footpad and deep tissue infections (Kent et al., 2006). Mycobacterial interspersed

247   repetitive unit (MIRU) typing generally supports the separation of human and piscine isolates

248   of *M. marinum*, but this genetic structuring is not absolute, with some overlap between host

249   groupings (Broutin et al., 2012). Genetic linkages between human infections with *M.*

250   *marinum* and fish sources have been demonstrated using PFGE (Tsai et al., 2007; Slany et al.,

251   2013) and AFLP (Doedens et al., 2008); however in one case, it is likely that exposure was to

252   waterborne *M. marinum* inoculated via a fish spine injury (Tsai et al., 2007).

253

254   A wide range of other NTM reported in humans has also been reported from fishes,

255   especially *M. fortuitum, M. chelonae,* and *Mycobacterium abscessus* (Piersimoni, 2009;

256   Kothavade et al., 2013), but also *Mycobacterium peregrinum* (Pagnoux et al., 1998),

257   *Mycobacterium scrofulaceum* (Ishii et al., 1997) and *Mycobacterium haemophilum* (van

258   Coppenraet et al., 2007). *Mycobacterium* spp. are often presumptively traced back to

259   aquarium or aquarium fish sources using either phenotypic species identification or

260   identification based on housekeeping genes (Pate et al., 2005; Beran et al., 2006; Slany et al.,

261   2012). However, this level of resolution is insufficient to confirm relationships between

262   human and fish infections, given considerable infra-species diversity among the mycobacteria

263   and the high degree of conservation among housekeeping genes. For example, mycobacteria

264   in the *M. marinum* clade, which are > 99% similar to one another at the commonly sequenced

265   16S rRNA locus, include such phenotypically diverse species as the human pathogen *M.*

266   *ulcerans,* extremely slow-growing fish pathogens *M. shottsii* and *M. pseudoshottsii*, and the

267 relatively rapidly growing generalist *M. marinum.* Furthermore, the phenotypically distinct

268 species *Mycobacterium gastri* and *Mycobacterium kansasii* are 100% identical at this locus.

269 Analysis of additional genes, such as *hsp*65 and *rpo*B, allows differentiation of species in

270 most cases, but caution is still necessary in attributing human infections to fish sources based

271 even on multi-locus sequence typing (MLST). This is exemplified by a study in which

272 *Myctobacterium szulgai* was isolated from a human patient, and both aquarium water and fish

273 in the patient's home; PFGE revealed identity between water and human isolates, but the fish

274 isolate was markedly different (Abalain-Colloc et al., 2003).

275

276 *Nocardia spp.*

277   Infection with *Nocardia* spp. in humans is primarily attributed to *Nocardia asteroides*

278 and the closely related species *Nocardia farcinica, Nocardia brasiliensis* and *Nocardia*

279 *otitidiscaviarum*. Nocardiosis in humans manifests in a variety of ways, primarily pneumonia,

280 cutaneous ulcers and wound infections, and occurs more frequently in immunocompromised

281 patients (Lederman and Crum, 2004). Nocardial infections are also observed in fishes, and are

282 attributed to *N. asteroides* (Roberts, 2001) or *Nocardia seriolae* (previously *Nocardia*

283 *kampachi*) (Kudo et al., 1988). To date, no information is available on epidemiological or

284 genetic linkages between piscine and human nocardiosis, and therefore evidence of zoonosis

285 is lacking.

286

287 **Gram negative bacteria**

288 *Aeromonas spp.*

289   *Aeromonas* spp. occur in freshwater habitats worldwide and are implicated in

290 community-acquired and nosocomial infections of humans (Janda and Abbott, 2010). Human

291 infections demonstrate seasonality, with most cases reported in spring and autumn, possibly

292   mirroring increased numbers of pathogenic *Aeromonas* spp. in aquatic environments

293   (Khardori and Fainstein, 1988). *Aeromonas* spp. infections arising from wound exposure have

294   been associated with handling seafood, particularly opening shellfishes (shucking) (Flynn and

295   Knepp, 1987). *Aeromonas salmonicida* is a major pathogen of fishes, causing furunculosis in

296   salmonids and cyprinids, but this species is not reported to be a human pathogen.

297

298   Weir et al. (2012) cite *Aeromonas* spp. as the most common zoonotic bacterium

299   isolated from ornamental fishes; however, among these reports, only a single case study

300   indicated a linkage to human disease, and this was not confirmed by biochemical or genetic

301   testing (Cremonesini and Thomson, 2008). Sukroongreung et al. (1983) examined isolates

302   from outbreaks of disease due to *Aeromonas* spp. in fishes and concomitant cases of diarrhea

303   in humans; most fish isolates were *Aeromonas sobria*, whereas most human isolates were *A.*

304   *hydrophila*, and there was little overlap in biochemical typing between *Aeromonas* isolates of

305   the same species originating from the two hosts.

306

307   *Edwardsiella spp.*

308   The three species recognised in the genus *Edwardsiella* are *Edwardsiella ictaluri*,

309   *Edwardsiella tarda* (synonym *Edwardsiella anguillimortifera*) and *Edwardsiella hoshinae*. A

310   further fish-pathogenic species, *Edwardsiella piscicida,* has been proposed (Abayneh et al.,

311   2013). *E. ictaluri* is a serious pathogen of catfishes (*Ictalurus* spp.), causing enteric

312   septicemia (Hawke et al., 1981), but is not known to infect humans. *E. hoshinae* is typically

313   isolated from reptiles and birds and, although it has been isolated from human feces, its role

314   as an animal or human pathogen is questionable (Janda et al., 1991).

315

316   Human infections with *E. tarda* are characterized primarily by bacterial

317 gastroenteritis, although wound infections and systemic conditions, such as septicemia and

318 meningitis, are also observed, as are extraintestinal infections (Clarridge et al., 1980; Janda

319 and Abbott, 1993). *E. tarda* may be found in the feces of asymptomatic people (Janda and

320 Abbott, 1993). Risk factors for disease include exposure to aquatic environments, as well as

321 to fishes, reptiles and amphibians. *E. tarda* causes hemorrhagic and necrotic disease in

322 marine and freshwater fishes, including *Edwardsiella* septicemia in a variety of species, and

323 'red disease' in eels (Wakabayashi and Egusa, 1973).

324

325   There are few reports linking *E. tarda* from fishes directly to human infections. *E.*

326 *tarda* in a Belgian infant was identical in API (bioMerieux) biotype and antibiotic

327 susceptibility to isolates from an angelfish (*Pterophyllum scalare*) in an aquarium in the same

328 home (Vandepitte et al., 1983). Presumed infection originating from a pet turtle was reported

329 by Nagel et al. (1982), although culture or molecular data supporting the linkage was not

330 provided. Molecular analysis of human and fish isolates of *E. tarda* generally show clear

331 differences (Nucci et al., 2002; Abayneh et al., 2012; Yang et al., 2013). Genomic analysis

332 has indicated that *E. tarda* genotype group EdwGI is most closely related to *E. ictaluri* and

333 contains most fish pathogenic strains, whereas EdwGII contains human and a limited number

334 of fish isolates (Yang et al., 2012). Whole genome comparisons of *E. tarda* from various

335 sources revealed a clear divergence between fish and environmental isolates, but also

336 horizontal gene transfer of a human enteropathogenic virulence factor to a fish isolate

337 (Nakamura et al., 2013).

338

339 Other *Enterobacteriaceae*

340   *Enterobacteriaceae* are ubiquitously distributed in a variety of environmental niches

341   and animal hosts, and a variety of species have been isolated from fishes, including

342   enteropathogenic *Escherichia coli* (Shotts, 1987) and *Salmonella* spp. (Minette, 1986).

343   Isolation generally occurs from intestinal contents or mucous; therefore, it appears that while

344   fishes can transiently harbor a variety of enterobacteria, true infections are not common.

345   Outbreaks of salmonellosis associated with aquaria have been reviewed by Weir et al. (2012).

346   In several instances, identical isolates have been recovered from human and tank water

347   sources, although the role of fishes in maintaining *Salmonella* spp. in contaminated aquaria is

348   unclear. Contamination of fishes and fish products with enterobacteria is a widespread

349   concern in food handling and hygiene practices, and both *Salmonella* spp. and *E. coli* have

350   been linked to foodborne illness, with freshwater fishes or fish products likely serving as a

351   vehicle (Piérard et al., 1999; Terajima et al., 1999; McCoy et al., 2011). However, evidence

352   for these bacteria as strict zoonoses is limited and cases where human infections are linked to

353   fish consumption generally do not provide evidence that infections originated with the fishes

354   and not from another source during food handling.

355

356   Bacteremia due to *Klebsiella pneumoniae* has been reported in conjunction with hand

357   fishing (Reagan et al., 1990); however, plasmid typing of the organism isolated from the

358   blood did not indicate similarity with *K. pneumoniae* in the water where the infection was

359   presumably contracted, and fishes were not sampled in this study. Infection with *Serratia*

360   *marcescens*, a pathogen of humans (Hejazi and Falkiner, 1997), has been reported in white

361   perch (*Morone americana*) (Baya et al., 1992) and a bonnethead shark (*Sphyrna tiburo*)

362   (Camus et al., 2013). However, no association between piscine and human infections with *S.*

363   *marcescens* has been demonstrated.

364

365 *Francisella spp.*

366   *Francisella tularensis* causes tularemia in humans and the related bacterium

367 *Francisella philomiragia* comb. nov. (formerly *Yersinia philomiragia*) has been isolated from

368 cases of human disease (Hollis et al., 1989; Wenger et al., 1989). In view of the high

369 similarity in housekeeping genes, literature concerning the naming of *Francisella* spp. is

370 somewhat confusing and species with standing in nomenclature are in flux (Birkbeck et al.,

371 2011). The current literature appears to have converged on naming fish pathogenic

372 *Francisella* spp. as *Francisella noatunensis* in cold water and *Francisella noatunensis*

373 *orientalis* (syn. *Francisella asiatica*) in warm water species. Human infections with these

374 species have not been reported, and *F. tularensis* or other human-infecting strains likewise

375 have not been isolated from fishes. Since *F. noatunensis* does not survive above 30 °C

376 (Hawke and Soto, 2013), the zoonotic potential of *Francisella* fish pathogens is not supported

377 at present.

378

379 *Leptospira spp.*

380   Fishes may be infected experimentally with *Leptospira* spp. (Davis et al., 2009;

381 Maestrone and Benjaminson, 1962), but natural infections have not been reported.

382 Leptospirosis has been associated with occupations involving fish handling and, especially,

383 fish farming. However, it is probable that, rather than being a fish-borne zoonosis, human

384 infections are attributable to exposure to urine from rodent pests on fish farms, and/or

385 exposure to contaminated water (Gill et al., 1985; Douglas, 1995).

386

387 *Plesiomonas shigelloides*

388   *Plesiomonas shigelloides* has been isolated from a wide range of terrestrial and marine

389 mammals, reptiles, amphibians, birds, fishes and shellfishes (Jagger, 2000). The bacterium

390 appears to be a normal or transient part of intestinal biota in fishes; however, septicemia has

391 been reported (Shotts and Teska, 1989). In two outbreaks of diarrhoea in humans due to *P.*

392 *shigelloides* in Japan, there was limited overlap with serovars collected from environmental

393 sources. Arai et al. (1980) isolated *P. shigelloides* from 10.2% of freshwater fishes and some

394 isolates were the same serovars as found in diarrheic human beings by Tsukamoto et al.

395 (1978). The same serovars were also found in local dogs and cats. Although *P. shigelloides*

396 can infect (or colonize) fishes, evidence for it being a true fish-borne zoonotic is tenuous. *P.*

397 *shigelloides* is frequently isolated from aquaria, and at least one case of human infection has

398 been associated with exposure to aquarium water (CDC, 1989). Hori et al. (1966) linked *P.*

399 *shigelloides* infection in humans with consumption of salted fish. Raw or undercooked

400 shellfish have been implicated in diarrhoea associated with *P. shigelloides* in humans

401 (Brenden et al., 1988; Holmberg et al., 1986; Jagger, 2000), although this may be confounded

402 with concomitant ingestion of local water (Kain and Kelly, 1989).

403

404 *Pseudomonas spp.*

405 *Pseudomonas* spp. are motile aerobic rod shaped bacteria that are common inhabitants

406 of soil and water worldwide. *Pseudomonas fluorescens* is an agent of necrotic and

407 hemorrhagic disease in a variety of freshwater and marine fishes (Austin and Allen-Austin,

408 1985) and is an uncommon agent of human disease (Gershman et al., 2008). *Pseudomonas*

409 *aeruginosa* is a well-known agent of human pneumonia, especially in conjunction with other

410 conditions such as cystic fibrosis, and has been isolated in association with fish viscera

411 (Leung et al., 1992). Zoonotic transmission of these agents from fishes to humans has not

412 been documented.

413

414 *Vibrio spp.*

415   *Vibrio* spp. are widely distributed in marine and estuarine environments and are often

416   referred to as the marine equivalent of aeromonads. A variety of *Vibrio* spp. cause serious

417   disease in wild and cultured fishes, including *Vibrio anguillarum*, the agent of 'red pest' in

418   eels (Roberts, 2001), *Vibrio ordalii*, which causes septicemia in Pacific salmonids (Schiewe et

419   al., 1981), *Vibrio salmonicida*, which causes cold water vibriosis in Atlantic salmon and other

420   fishes (Egidius et al., 1986), and *Vibrio viscosus* and *Vibrio wodanis*, the causative agents of

421   'winter ulcer disease' in Atlantic salmon (Lunder et al., 2000).

422

423   Among *Vibrio* spp. that cause disease in humans, *Vibrio cholerae* is of paramount

424   worldwide health significance, particularly strains which produce cholera toxin. Toxin-

425   producing strains largely belong to the O1 serogroup, but non-O1/O139 serogroup strains

426   may also produce toxins and disease. Non-O1/non-O139 (Farama et al., 2008) and O1 (Blake

427   et al., 1980) strains of *V. cholerae* have been implicated in human disease outbreaks

428   associated with consumption of shellfish and *V. cholerae* has been reported in water used to

429   house or transport ornamental fishes (Smith et al., 2012). However, *V. cholerae* is rarely

430   reported as a disease agent in fishes (Reddacliff et al., 1993) and its role as a fish-borne

431   zoonotic is questionable.

432

433   The most common non-cholera human vibrioses are caused by *Vibrio vulnificus* and

434   *Vibrio parahemolyticus*. These infections are associated with gastroenteritis, septicemia and

435   wound infections in humans, and are of particular concern because of their high case fatality

436   rate (3.6%) relative to other enteric bacteria (Weis et al., 2011). *V. parahemolyticus* causes

437   food-borne illness associated with consumption of shellfish (Drake et al., 2007), but is

438   reported rarely in fishes (Austin and Austin, 2007). RAPD profiling of *V. parahemolyticus*

439   from fish in markets demonstrated overlap with isolates from shellfish sources (Yang et al.,

440   2008); thus, it is unclear whether the *V. parahemolyticus* were derived from fish products or

441   from cross-contamination.

442

443   *Vibrio vulnificus* causes disease in eels (Tison et al., 1982) and other fishes (Li et al.,

444   2006), and has been isolated from the intestinal tract of bottom-feeding fishes (DePaola et al.,

445   1994). Three biotypes of this species are described; biotype 1 is isolated mainly from water

446   and humans, and biotype 2 is isolated mainly from fishes and humans (Amaro and Biosca,

447   1996). Specific polymorphic variants of the type IV pilus gene *pilF* are strongly associated

448   with resistance to human serum and thus potential for human infectivity in all biotypes (Roig

449   et al., 2010). Cohen et al. (2007) demonstrated two major clades of *V. vulnificus* using MLST;

450   most biotype 1 clinical isolates belonged to one clade and also possessed a 33 kb genomic

451   island that may be associated with higher pathogenicity and/or environmental persistence.

452   Pathogenicity for fishes in biotype 2 strains is related to the presence of a 68-70 kb virulence

453   plasmid (Roig and Amaro, 2009). Biotype 2 is further separated into serovars A, E, and I,

454   which are infectious for fishes, but of which only serovar E appears to have zoonotic potential

455   (Fouz et al., 2007). Biotype 3 has been isolated from humans with septicemia and wound

456   infections in Israel and has been postulated to be a hybrid between biotypes 1 and 2 (Bisharat

457   et al., 1999, 2005), although this has been questioned by Cohen et al. (2007).

458

459   *V. vulnificus* biotype 2 septicemia has been reported in a person who had handled eels

460   (Veenstra et al., 1992), and sequencing of virulence genes (*vvhA* and *vvp*) demonstrated

461   overlap between human and eel biotype 2 isolates (Wang et al., 2008). Human isolates of *V.*

462   *vulnificus* biotype 2, serovar E carry identical plasmid profiles to fish strains, including the

463   68-70 kb virulence plasmid (Roig and Amaro, 2009). Linkages between fish and human

464   clinical biotype 3 isolates have also been demonstrated with Variable Number Tandem Repeat

465   (VNTR) analysis (Broza et al., 2009). MLST typing of fish isolates in Bangladeshi

466   aquaculture demonstrated close similarity, but not identity of fish and clinical isolates

467   (Mahmud et al., 2010).

468

469   The current body of literature on genetic similarity between human and fish isolates of

470   *V. vulnificus* is better developed than many other presumptive bacterial zoonoses of fishes,

471   and transmission between fishes and humans appears to be supported, although it is apparent

472   that infections may also be contracted from environmental sources.

473

474   *Vibrio damsela* (Love et al., 1981), now *Photobacterium damselae* comb. nov. (Smith

475   et al., 1991) was first isolated from skin ulcers in damselfish (*Chromis punctipinnis*) and has

476   since been isolated from other fishes, including turbot (*Scophthalmus maximus*), yellowtail

477   (*Seriola quinqueradiata*) and sea bream (*Pagrus auriga*) (Austin and Austin, 2007). *P.*

478   *damselae* infection in humans is primarily associated with skin wounds, leading to necrotizing

479   fasciitis that can be fatal (Morris Jr. et al., 1982; Clarridge and Zighelboim-Daum, 1985;

480   Hundenborn et al., 2013). Two cases of *V. damsela* septicemia in humans have been

481   associated with ingestion of raw fish (Shin et al., 1996; Kim et al., 2009). However,

482   genotypes of human and fish isolates have not been compared, and the degree to which

483   human *V. damsela* infections originate from fishes remains to be determined.

484

485   Additional *Vibrio* spp., including *Vibio hollisae* (*Grimontia hollisae* comb. nov.;

486   Thompson et al., 2003), *Vibrio alginolyticus*, *Vibrio fluvialis, Vibrio furnissii*, *Vibrio harveyi*

487   (syn. *Vibrio carchariae*), *Vibrio metschnikovii* and *Vibrio mimicus*, are associated with

488   disease in fishes and shellfishes, and are also occasionally isolated from cases of human

489   disease, particularly gastroenteritis and wound infections (Austin, 2010). However, direct

490 connections between fish and human infections are tenuous and most cases appear to derive

491 from contamination of wounds with seawater, spoilage of consumed fish and shellfish, or

492 ingestion of raw shellfish.

493

494 *Yersinia spp.*

495   Several members of the genus *Yersinia* cause human disease, including *Yersinia*

496 *enterocolitica*, *Yersinia pseudotuberculosis* and, most notably, *Yersinia pestis*, the cause of

497 bubonic plague. *Yersinia ruckeri* causes enteric redmouth disease (ERM) of salmonids, which

498 is associated with significant aquaculture losses worldwide (Austin and Allen-Austin, 1985;

499 Tobback et al., 2007). A single human case of infection with *Y. ruckeri*, of uncertain clinical

500 significance, has been reported (Farmer et al., 1985). Several other *Yersinia* spp. have been

501 isolated from both fishes and humans, including *Yersinia frederiksenii* and *Yersinia*

502 *intermedia* (Sulakvelidze, 2000), but evidence of fish-borne zoonosis in this group is lacking.

503

504 **Conclusions**

505   A variety of bacteria have been reported as potential fish-borne zoonotic agents, but

506 evidence for zoonotic potential is limited for many of these organisms and few molecular

507 genetic analyses of fish and human strains have been performed. The existing literature

508 supports classification of *C. botulinum, S. iniae*, *Mycobacterium* spp. and *Vibrio vulnificus* as

509 fish-borne zoonoses in the strict sense, i.e. there is substantial epidemiological and molecular

510 evidence for linkages between infections in both hosts. Epidemiological associations suggest

511 zoonotic risks for other fish-associated bacteria; however, some do not cause disease in fishes

512 (e.g. *Erysipelothrix rhusiopathiae*) and more work will be required to link human and fish

513 infections with other bacteria (e.g. *Aeromonas* spp., *E. tarda*, *L. garvieae, P. shigelloides* and

514 *V. damsela*). Other bacterial species either lack significant evidence for epidemiological

515 connections between fishes and humans, have more plausible transmission routes not

516 involving fishes, or are most likely to be transmitted through contamination of food. Further

517 molecular studies examining isolates from fishes and human disease outbreaks would be

518 fruitful in defining epidemiological connections and in determining the zoonotic risk from

519 bacterial fish pathogens.

520

521 **Conflict of interest statement**

522 None of the authors of this paper has a financial or personal relationship with other people

523 or organisations that could inappropriately influence or bias the content of the paper.

524

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1188 **Table 1** Summary of potential agents of fish-borne zoonosis.

1189

Organism	Type	Transmission route	Epidemiological evidence	Molecular evidence
Clostridium botulinum	G(+)	Ingestion	+	+
Erysipelothrix rhusiopathiae	G(+)	Inoculation	+ [a]	-
Lactococcus garvieae (*Enterococcus seriolicida*)	G(+)	Inoculation Ingestion	+	-
Staphylococcus spp.	G(+)	NA	-	-
Streptococcus agalactiae	G(+)	NA	-	(+) [b]
Streptococcus iniae	G(+)	Inoculation	+	+
Mycobacterium spp.	AF	Inoculation	+	+
Nocardia spp.	AF	NA	-	-
Aeromonas spp.	G(-)	Inoculation Ingestion	+	-
Edwardsiella tarda	G(-)	Inoculation Ingestion	+	-
Other *Enterobacteriaceae*	G(-)	Ingestion	+	-
Francisella spp.	G(-)	NA	-	-
Leptospira spp.	G(-)	Ingestion	+ [c]	-
Plesiomonas shigelloides	G(-)	Ingestion	+	-
Pseudomonas spp.	G(-)	NA	-	-
Vibrio damsela	G(-)	Inoculation Ingestion	+	-
Vibrio vulnificus	G(-)	Inoculation Ingestion	+	+
Yersinia ruckeri	G(-)	NA	(+) [d]	-

1190

1191 Strong evidence or evidence from multiple sources is indicated by '+', weak or single reference evidence is

1192 indicated by '(+)' and no evidence (or evidence to the contrary) is indicated by '-'. Epidemiological evidence

1193 includes identification of bacteria by phenotypic/biochemical methods, whereas molecular evidence refers to

1194 demonstration of genetic identity/strong similarity between isolates from human and fish infections. Staining

1195 characteristics are given as Gram positive or negative, G(+) or G(-), respectively, or acid-fast (AF).

1196 [a] *E. rhusiopathiae* is not known to cause disease in fishes, but is a commensal in skin mucus.

1197 [b] Single report (Evans et al., 2008).

1198 [c] Zoonotic transmission via hosts other than fishes appears most likely in this instance.

1199 [d] Single report (Farmer et al., 1985).