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Review Article

Zoonotic potential of *Helicobacter* spp.

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Abstract The genus *Helicobacter* contains more than 35 species. *Helicobacter pylori* is the most important in terms of human health. Discovery of these helicobacters gives opportunity to understand the relationship between these bacteria which colonise the animal and human gut and their effect on the host. Infection with *Helicobacter* spp. and the associated diseases in their hosts allow us to study the pathogenic mechanisms. The potential zoonotic pathway for the transmission of *Helicobacter* spp. and epidemiology of this genus, deserve more attention to these emerging pathogens.

Introduction

Helicobacter pylori was discovered in 1982. Over 50% of the world population is infected by this bacterium. *Helicobacter pylori* is the main cause of gastritis, peptic ulcers, and gastric cancer. In 1994, International Agency for Research on Cancer (IARC) categorized *Helicobacter pylori* as a class I carcinogen. Barry Marshall and Robin Warren were awarded with the Nobel Prize in Physiology or Medicine "for their discovery of the bacterium *Helicobacter pylori* and its role in gastritis and peptic ulcer disease", in 2005. The discovery of *H. pylori* increased interest to other spiral bacteria that had been seen in many animal species. Most of these bacteria belong to the genus *Helicobacter*.[1] These non-pylori helicobacters (NPHS) are increasingly being found in human clinical specimens. Thus, their role in human medicine is increasingly documented.

Helicobacter pylori and other *Helicobacter species*

Rappin in 1881 and Bizzozero in 1893 have described spiral shaped bacteria in the stomach of animals, for the first time. Salomon in 1896 reported spiral organisms in the stomachs of dogs and cats. Others have discovered the prevalence of spiral organisms in the stomach of rhesus

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monkeys.[2,3] Helicobacters other than *H. pylori* have been associated with gastritis, gastric ulcers (*Helicobacter suis, Helicobacter felis, Helicobacter bizzozeronii*, and *Helicobacter salomonis*) and gastric mucosa-associated lymphoid tissue lymphoma in humans, like *Helicobacter heilmannii*, which is known to colonize the gastric mucosa of animals.[4,5] Furthermore, some species (*Helicobacter mustelae*, *Helicobacter hepaticus, Helicobacter bilis*) display carcinogenic potential in animals and harbour numerous virulence genes and may cause diseases not only in animals, but also in humans. Recently, Gill et al.,[6] revealed that *H. bilis* and *Helicobacter trogontum* were responsible for abortion in sheep. Importantly, these non-*H. pylori* species, which naturally inhabit mammals (except humans) and birds, have been detected in human clinical specimens. These encompass two gastric (*H. suis* and *Helicobacter baculiformis*) and enterohepatic (*Helicobacter equorum*) groups, showing different organ specificity. Discovery of these helicobacters gives opportunity to understand the relationship between these bacteria which colonise the animal and human gut and their effect on the host. Infection with *Helicobacter* spp. and the associated diseases in their hosts allow us to study the pathogenic mechanisms. To explore different therapeutic regimens to eradicate or prevent helicobacter associated diseases *in vivo* models are being used. The potential zoonotic pathway for the transmission of *Helicobacter* spp. and epidemiology of this genus, deserve more attention to these emerging pathogens.[2] At the moment, the species of the genus *Helicobacter* are more than 35.[7]

Gastrospirillum hominis (*Helicobacter heilmannii*)

In 1987, Dent et al. have described a new species of bacteria in 3/1300 human gastric biopsies. It is the dominant gastric organism in the animal species including pigs, cats, dogs and primates. The first given name of this gastric bacterium is *G. hominis*. It is belonging to the *Helicobacter* genus and has been given the name *Helicobacter heilmannii*. The prevalence of this bacterium is low, ranging from 0.5% in developed countries to 1.2—6.2% in Eastern European and Asian countries. *H. heilmannii* is associated with a range of upper gastrointestinal symptoms. The gastritis observed with *H. heilmannii* infection tends to be less severe than that due to *H. pylori*; infection has been found in association with duodenal ulceration, gastric ulceration, gastric carcinoma and mucosa associated lymphoid tissue (MALT) lymphoma.[1,8] A surprisingly high rate (3.4%) of MALT lymphomas in *H. heilmannii* infected patients was noted by Stolte et al., in 1997.[9] Infection with "*H. heilmannii*" type 1 predominates (80%) and is thought to be acquired from dogs, cats, or pigs. As "*H. heilmannii*" type1 predominates in people, the zoonotic risk posed by dogs and cats is likely small.[10] Other authors have report the case of a 12-year old boy presenting with chronic gastritis caused by *H. heilmannii*. The DNA amplification methods suggest that the boy has been infected by his pet dogs. The patient has been cured by treatment with proton-pump inhibitor and antibiotics (omeprazole, amoxicillin, and clarithromycin). Endoscopic follow-up of the boy has showed a complete cure of gastritis and eradication of the bacterium.[11] Jalava et al.[12] have compared the characteristics of a cultured human "*Helicobacter heilmannii*" isolate with those of other helicobacters found in animals. Infections with this organism may be more frequently associated with MALT-lymphomas. The possibility of zoonotic infection has been discussed. Three species resembling "*H. heilmannii*" have been isolated from dogs or cats-*H. felis, H. bizzozeronii*, and *H. salomonis*.[12] The evidences suggest that "*H. heilmannii*" infection is an example of zoonosis. Dieterich et al.[8] have concluded that human and animal "*H. heilmannii*" strains are closely related and that humans can be infected by more than one "*H. heilmannii*" strain. Sporadic cases of gastric erosion and gastric cancer have also been reported.[8] One of seven species *in Helicobacter heilmannii* is *H. bizzozeronii* that are detected in 0.17—2.3% of the gastric biopsies of human patients with gastric symptoms. Schott et al.[13] recently sequenced the genome of the *H. bizzozeronii* human strain CIII-1, isolated in 2008. They have been performed a comparative genome analysis with *H. pylori,* providing new aspects into the mechanisms of transmission between the primary animal host and humans. They have proposed the hypothesis that the high metabolic versatility and the ability to react to different environmental signals are the basis of the zoonotic nature of *H. heilmannii* infection in humans.[13]

Helicobacter pullorum

Helicobacter pullorum was identified in 1994 by Stanley et al.[14] It was originally cultured from the caeca and livers of broiler and the faeces of humans.[14] *H. pullorum* infection has been linked to vibrionic hepatitis and enteritis in chickens.[14] *H. pullorum* was detected at 100% prevalence in broilers and laying hens from 15 different farms, as well as in a majority of turkeys.[15,16] It is associated with gastroenteritis and hepatobiliary disease in humans and chickens. These findings will also allow future studies in murine models to find out the pathogenic mechanisms for this emerging pathogen.[17] *H. pullorum* has also been isolated from a diarrhoeic psittacine bird, suggesting that pet birds may be a zoonotic risk.[17,18] The emerging technologies in food production explain how new pathogens can establish themselves in the food chain and compromise food safety. The impact of the food technology is analysed for several bacteria, such as *Yersinia, Campylobacter, Arcobacter, Helicobacter pullorum, Enterobacter sakazakii, Mycobacterium avium* spp. *paratuberculosis,* prions related to *vCJD*.[19] *Helicobacter canadensis* closely resembling the enterohepatic zoonotic agent *Helicobacter pullorum*, is one of many new enteropathogens isolated from humans. The clinical importance of this bacterium is not fully established, but it has been isolated from faecal samples of patients with enteritis and from a blood culture of a patient with bacteraemia. The results of this investigation indicate that *H. canadensis* should be considered a probable zoonotic agent. Wild birds are a recognized vector for transmission of zoonotic agents. Faecal contamination of surface water, grazing pastures for production animals, and park areas could all potentially expose humans to infection, as could the consumption of undercooked goose meat.

H. canadensis is widely distributed in nature. These findings show the potential zoonotic pathway for the transmission of *H. canadensis*, the ecology and epidemiology of the bacterium.[20]

H. felis

The majority of *Helicobacter* infections of the canine and feline gastric mucosa are mixed infections of various *Helicobacter* species, including *H. felis, H. bizzozeronii, H. salomonis*. Recently, one additional species was isolated from the stomach of a dog, namely, *Helicobacter cynogastricus*, and one additional species was isolated from the stomach of a cat, namely, *H. baculiformis*. Bridgeford et al.[4] hypothesized that gastric *Helicobacter* species may be a cause of feline gastric lymphoma. *H. felis* has been isolated on artificial media and has experimentally caused gastritis in gnotobiotic dogs. The high prevalence of feline infection is interesting because cats have been implicated as a potential reservoir for human infection by helicobacter-like organisms.[21] EL-Zaatari et al.[22] have investigated whether *H. pylori* infection was common in stray cats. Twenty-five cats have examined for the presence of *H. pylori*. Histologically, the gastric biopsy specimens from all cats have showed large spiral organisms typical of *H. felis* and not *H. pylori*. The helicobacters identified in these samples by PCR have not been cultivable and hence were probably *H. heilmannii*. *H. pylori* infection is uncommon in stray cats and owning pet cats should not be a threat to public health in relation to *H. pylori* infection.[22] De Bock et al.[23] associate *H. felis* infection in humans with severe gastric ulceration. Moreover, the suggestion can be made that the patient contracted *H. felis* from her dog.

Helicobacter canis

Helicobacter-like organisms are frequently found in canine stomachs, but the relationship between such organisms and gastric pathology has not been established. Some such organisms have zoonotic importance.[24] A 78-year-old man with gastric diffuse large B cell lymphoma presented with persistent *Helicobacter canis* bacteraemia while receiving chemotherapy. An examination of his medical history revealed a close exposure to dogs. The patient recovered after 4 weeks of antibiotic therapy. Immunocompromised persons who maintain close contacts with dogs maybe at risk for this infection.[25] *Helicobacter canis* has been associated with hepatobiliary and gastrointestinal disease in dogs, cats, and humans. *Helicobacter canis* was isolated from sheep faeces. These isolates are distinct from other sheep-origin enterohepatic *Helicobacter* species previously isolated. Swennes et al.[26] identified sheep as *H. canis* reservoirs potentially important in zoonotic or foodborne transmission.

Helicobacter cinaedi

Helicobacter cinaedi is associated with gastroenteritis in primates and humans. *H. cinaedi* infection has been reported in Immunocompromised HIV (human immunodeficiency virus-infected) — patients. Prior contact with animals has attracted attention as a possible source of *H. cinaedi* infection. Sugiyama et al.[27] have reported a case of meningitis in an immunocompetent 34-year-old woman who had daily contact with a cat for a month. She has developed acute headaches, fevers, and chills. The etiological agent has been identified as *H. cinaedi* by polymerase chain reaction in cerebrospinal fluid. This is the first adult case of bacterial meningitis caused by *H. cinaedi*.[27] Other authors have reported that *H. cinaedi* infection has been associated with atherosclerosis and atrial arrhythmias. *H. hepaticus* may be associated with hepatobiliary diseases in humans. Perhaps many non-pylori helicobacter spp. will be discovered as human pathogen in the future.[7]

Several such non-pylori helicobacter species isolated from diverse animals' is comprised in Table 1. In brief, *H. pullorum* has been isolated from humans and poultry, *H. canis* from dogs, cats, and humans, *H. cinaedi* from humans, non-human primates, dogs, and hamsters, and *Helicobacter rappini* from dogs, cats, mice, humans, and non-human primates.[2,7,14,17,20,25,26] However, little is known about the specific significance or clinical manifestation of these non-pylori helicobacter species in humans or animals. Most of these non-pylori helicobacter spp. have been suggested to cause MALT lymphoma, peptic ulcer, colitis or gastroenteritis.[8,9,15,18]

Helicobacter pylori — zoopathogen?

Helicobacter pylori is the etiological agent of chronic gastritis, peptic ulcer disease, gastric cancer and MALT-

Table 1 Non-pylori helicobacters and their sources.

Non-pylori Species	Source/clinical importance	Reference(s)
H. marmotae	Prairie dogs	Beisele et al.[28]
H. macacae	Rhesus monkeys, associated with intestinal adenocarcinoma	Marini et al.[3]
Helicobacter magdeburgensis	Mice	Traverso et al.[29]
H. equorum	Foals	Moyaert et al.[30]
H. suis	Pig stomach	Baele et al.[31]
H. bilis, H. canis and *H. cinaedi*	Dogs	Rossi et al.[32]
H. canis, H. bilis and *H. cinaedi*	Cats	
H. cinaedi	Rhesus monkey	Fox et al.[33]

lymphoma, in humans.[34] The route of transmission of this bacterium has not been clearly proved. One of the theories is transmission via raw uncooked milk from animals to humans. Turutoglu et al.[35] have investigated the presence of *H. pylori* in sheep milk. A total of 440 raw sheep milk samples collected from the Burdur region of Turkey have been cultural examined. *H. Pylori* has not been isolated in any sample.[35] The bovine origin of paramyxo virus infections is likely; smallpox comes from camels or from rodents via cattle while mycobacteria and *Helicobacter* infected humans already before the Neolithic. Microbes adapt constantly and quickly to changing environmental situations and transmit into the human population.[36]

In the study of Papiez et al.[37] the *H. pylori* prevalence has reached 97.6% in shepherds, 86% in their family members, but significantly less, 65.1%, in controls without contact with sheep. Considering 100% positive 13C-urea breath test in sheep, it may be reasonable to suggest that *H. pylori* infection in shepherds and their family members originates from sheep and *H. pylori* infection might, therefore, be considered as zoonosis.[37] In several studies, non-human primates were used as models for human *H. pylori* infections. *Macaca mulatta* are commonly infected with *H. pylori*. The rhesus monkey model provides an opportunity to assay the mode of acquisition of *H. pylori*. Socially housed rhesus monkeys rapidly acquire *H. pylori* infection.[4] It is clear that some animals including cats, dogs, sheep, may be transitory infected by *H. pylori*, but their roles in the route of transmission to humans are not proved. In one study *H. pylori* has been demonstrated by PCR methods in the gastric mucosa of laboratory cats but have not been identified in stray cats.[4]

In our study, in Bulgaria, the zoonotic potential was confirmed indirectly. We investigated the risk factors of acquisition and modes of transmission of *H. pylori* infection. The place of residence in childhood and the parent's place of living — village; consumption of uncooked vegetables; the presence of domestic animals; the contact with pets; the consumption of uncooked (unpasteurized) milk (via just milking animal) in childhood; the presence of rodents near or in the houses (the parameters of the impact of animals as a risk factor) — are significantly associated and strong predictors of *H. pylori* seropositivity in Bulgaria.[38,39] In our opinion, *Helicobacter pylori* infection might, in some instances, be considered as zoonosis. It is necessary to prove this causal connection by long-term cohort studies.

Conclusion

Helicobacter pylori is the most important gastric *Helicobacter* in terms of human health. Two other gastric helicobacters, *H. heilmannii* and *H. felis,* also are associated with gastric disease in humans. Some helicobacters naturally colonise the intestinal tract of animals, many of which also colonise humans and are often associated with diarrhoea. Immunocompromised hosts are particularly susceptible to these microaerobic organisms. Some of these enterohepatic helicobacters (*H. pullorum*, *Helicobacter fennelliae, H. canis, H. cinaedi, H. canadensis* and *H. rappini*) have been isolated from diarrhoeic and bacteraemic humans, and may also have zoonotic potential. The detection of *Helicobacter pylori* in animals and their probable transmission in humans as reported in several studies is indicative of its zoonotic credential; however, long-term cohort studies are necessary to link and prove this underlying connection.

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