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Helicobacter – An Emerging New Zoonotic Pathogen

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1. Introduction

The genus *Helicobacter* contains 35 named species and numerous provisionally named species. It is likely that several novel *Helicobacter* species await discovery. Members of this genus are microaerobic, have a fusiform or curved to spiral rod morphology and are motile by flagella that vary in number and location among different species (Vandamme et al., 1990). All known *Helicobacters* live in human and animal hosts, where colonization occurs primarily in the gastrointestinal tract. The type species, *Helicobacter pylori (H. pylori)*, was isolated from the stomach of humans and has been associated with a variety of gastric anomalies including gastritis, peptic ulcer disease, gastric carcinoma, and gastric mucosa-associated lymphoma (Parsonnet, 1998). Like *H. pylori*, other species of *Helicobacter* have also been shown to colonize the stomach and cause disease in animals. Gastric colonizers include *H. felis, H. mustelae, H. acinonychis, H. bizzozeronii, H. heilmannii, H. salomonis*, and a recently isolated novel *Helicobacter* sp. of dolphins (Hodzic et al., 2001). Several species of *Helicobacter* have been identified in rodents, including the species *H. hepaticus, H. bilis, H. muridarum, H. aurati, H. cinaedi, H. cholecystus, H. trogontum, H. rodentium*, and a bacterium morphologically resembling *H. Flexispira* taxon 8 (formerly *Flexispira rappini*) (Hodzic et al., 2001). Evidence is accumulating that especially pigs, dogs, and cats constitute reservoir hosts for gastric *Helicobacter* species with zoonotic potential.

2. History of *Helicobacter* research

The first well-known report of gastric *Helicobacters* was by Bizzozero in Turin in 1893 (Bizzozero, 1893). Bizzozero was a well-known anatomist, famous already for his proof that all dividing cells required cell nuclei (Castiglioni, 1947). In his anatomical observations of the gastric mucosa of dogs, Bizzozero reported "spirochetes" inhabiting the gastric glands (Figura & Orderda, 1996) and even the canaliculi of the parietal cells. In hand-drawn color illustrations, Bizzozero showed gram-negative organisms with approximately 10 wavelengths within the parietal cells and gastric glands. We now know these organisms variously identified as *H. canis*, *H. felis* (Lee et al., 1988), and/or *H. heilmannii* (Heilmann & Borchard, 1991). Bizzozero's work was extended by Salomon, who was able to propagate these spiral organisms in mouse stomachs after feeding ground-up gastric mucosa from cats and dogs to his mouse colony (Salomon, 1896). Salomon's work was a precursor to current studies where the *H. felis*-infected mouse is an important model in vaccine and therapeutic

studies of *Helicobacter* eradication (Chen et al., 1995). Warren had observed patients with spiral organisms on their gastric mucosa since 1979 and had documented the inflammation associated with the bacteria by the time he and Marshall began a concerted attempt to study the organisms in patients with various upper gastrointestinal symptoms. After August 1981, the team studied patients attending for endoscopy and was able to demonstrate the gram-negative bacteria on Gram stains but could not culture them at that time. They tentatively treated one patient with tetracycline and were able to observe a decrease in the number of neutrophils in the gastric mucosa as well as apparent disappearance of the bacteria. They recognized, however, that anecdotal evidence of the bacteria's role in gastric inflammation was of little value and therefore commenced a study in 100 consecutive endoscopy patients to try to culture the bacteria, as well as determine their association with gastritis and/or other clinical syndromes. Initially, they did not focus specifically on the etiology of peptic ulcer disease, although they were aware that gastritis was strongly associated with duodenal and gastric ulcers, as well as with gastric cancer (Warren & Marshall, 1983).

3. Classification of *Helicobacter* species

The genus *Helicobacter* contains 35 named species and numerous provisionally named species. It is likely that several novel *Helicobacter* species await discovery. Members of this genus are microaerobic, have a fusiform or curved to spiral rod morphology and are motile by flagella that vary in number and location among different species (Vandamme et al., 1990). All known *Helicobacters* live in human and animal hosts, where colonization occurs primarily in the gastrointestinal tract. The type species, *H. pylori*, was isolated from the stomach of humans and has been associated with a variety of gastric anomalies including gastritis, peptic ulcer disease, gastric carcinoma, and gastric mucosa-associated lymphoma (Parsonnet, 1998). Like *H. pylori*, other species of *Helicobacter* have also been shown to colonize the stomach and cause disease in animals. Gastric colonizers include *H. felis, H. mustelae, H. acinonychis, H. bizzozeronii, H. heilmannii, H. salomonis*, and a recently isolated novel *Helicobacter* sp. of dolphins (Hodzic et al., 2001). Several species of *Helicobacter* have been identified in rodents, including the species *H. hepaticus, H. bilis, H. muridarum, H. aurati, H. cinaedi, H. cholecystus, H. trogontum, H. rodentium*, and a bacterium morphologically resembling *Helicobacter Flexispira* taxon 8 (formerly *Flexispira rappini*) (Hodzic et al., 2001). A number of *Helicobacter* species may confound experimental data because of their association with disease progressing in various kinds of animals (Chin et al., 2000, Ward et al., 1994, Eaton et al., 1996). *H. hepaticus and H. bilis* were initially reported as pathogens associated with hepatitis and inflammatory bowel diseases (Shomer et al., 1997, Ward et al., 1996), and *H. typhlonicus* caused proliferative typhlocolitis in SCID mice (Franklin 1999). *H. suncus* was isolated from house musk shrews as a pathogenic agent (Goto et al., 2000).

Most routine laboratories apply the same basic biochemical tests for the identification and differentiation of all *Campylobacter*-like organisms and would fail to identify many *Helicobacter* species. Although the number of *Helicobacter* species encountered in human clinical samples is fairly small, the lack of application of highly standardized procedures and the well-known biochemical inertness of *Campylobacter*-like organisms render biochemical identification of all of these bacteria very difficult. Whereas *Arcobacter* strains can be differentiated from *Campylobacter* and *Helicobacter* strains by their ability to grow in air and at low temperature (Vandamme et al., 1991), there are no clear biochemical

characteristics to separate the genus *Helicobacter* from the genus *Campylobacter*. Theoretically, one has to differentiate over 35 validly named species and subspecies, as well as various unnamed taxa. An overview of biochemical and other methods to differentiate *Campylobacter* and *Arcobacter* species was described earlier (Vandamme, 2000). A summary of the characteristics of cultivated *Helicobacter* species shows that discrimination between some species may rely on only one differential feature. Moreover, some species, notably *H. pylori* and *H. acinonychis*, and *H. felis* and *H. bizzozeronii*, cannot be differentiated with conventional phenotypic tests.

4. Clinical sequels of *Helicobacter* infection

Helicobacter pylori (*H. pylori*) is a Gram-negative, spiral-shaped, microaerophilic bacterium that infects the human gastric mucosa (Warren and Marshall, 1983). Chronic infection is thought to be associated with chronic active gastritis, peptic ulcer and gastric malignancies, such as mucosa-associated B cell lymphoma and adenocarcinoma (NIH, 1994). In particular, this organism has been categorized as a class I carcinogen by the World Health Organization (International Agency for Research on Cancer, 1994) and previous studies have confirmed that long-term infection with *H. pylori* induces adenocarcinoma in Mongolian gerbils (Honda et al., 1998; Watanabe et al., 1998). The association between *H. pylori* and gastric cancer has been explained by two possible mechanisms.

Gastric mucosal infection with *H. pylori* is accompanied by infiltration of neutrophils, and activated inflammatory cells are known to produce oxygen radicals (Evans et al., 1995; Ramarao et al., 2000). Oxygen radicals are known as inducers and initiators because they cause direct DNA damage (Clemens, 1991), but the relationship of these radicals with the onset of gastric cancer has not been sufficiently explored. Ammonia/ammonium concentrations increase in the gastric mucosa due to infection with *H. pylori*, and Tsujii et al. have found that ammonia acts as a promoter in a rat model of gastric cancer induced by N-methyl-N-nitro-N-nitrosoguanidine (MNNG) (Tsujii et al., 1992). To consider the association between *H. pylori* infection and the onset of diffuse type of gastric cancer, unlike intestinal type gastric cancer, the process from infection with *H. pylori* through gastric mucosal atrophy, intestinal metaplasia, and development of cancer must be excluded (Correa et al., 1994; Fay et al., 1994). Direct evidence must therefore be found to indicate progression from infection with *H. pylori* through persistent inflammatory cell infiltration resulting in DNA damage by oxygen radicals, point mutations of genes, and finally carcinogenesis.

5. Host ranges of *Helicobacters*

Since *H. muridarum* was first reported in the intestinal mucosal of mice and rats (Lee 1992), additional *Helicobacter* species have been isolated from laboratory animals. Several *Helicobacter* species such as *H. hepaticus* (Fox 1994), *H. muridarum, H. bilis* (Fox et al., 1995), *H. rodentium* (Shen et al., 1997), *Flexispira rappini* (Schauer et al., 1993), *H. typhlonicus* (Franklin et al., 1999) have been identified in rodents. The genus *Helicobacter* contains 24 named species and numerous provisionally named species. It is likely that several novel *Helicobacter* species await discovery. Members of this genus are microaerobic, have a fusiform or curved to spiral rod morphology and are motile by flagella that vary in number and location among different species (Vandamme et al., 1990). All known *Helicobacters* live in human and animal

hosts, where colonization occurs primarily in the gastrointestinal tract. The type species, *H. pylori*, was isolated from the stomach of humans and has been associated with a variety of gastric anomalies including gastritis, peptic ulcer disease, gastric carcinoma, and gastric mucosa-associated lymphoma (Parsonnet, 1998). Like *H. pylori*, other species of *Helicobacter* have also been shown to colonize the stomach and cause disease in animals. Gastric colonizers include *H. felis, H. mustelae, H. acinonychis, H. bizzozeronii, H. heilmannii, H. salomonis*, and a recently isolated novel *Helicobacter* sp. of dolphins (Hodzic et al., 2001). Several species of *Helicobacter* have been identified in rodents, including the species *H. hepaticus, H. bilis, H. muridarum, H. aurati, H. cinaedi, H. cholecystus, H. trogontum, H. rodentium*, and a bacterium morphologically resembling *H. Flexispira* taxon 8 (formerly *Flexispira rappini*) (Hodzic et al., 2001).

6. Transmission of *Helicobacters*

In-depth knowledge of the transmission patterns may constitute important information for future intervention strategies. In the absence of consistent and verified environmental reservoirs, a predominantly person-to-person transmission has been postulated. *H. pylori* infection is associated with poor living conditions, and possible transmission routes are fecal-oral, oral-oral, or gastro-oral, but firm evidence is lacking (Torres et al., 2000). Young children are particularly vulnerable to infection by transmission of *H. pylori* from their infected parents, especially infected mothers (Rothenbacher et al., 1999), and it is generally believed that such transmission is influenced by socio-economic status. However, little is known about how and when maternal transmission occurs during perinatal period, especially whether this occurs before or after parturition. In the present study, we examined these issues in an experimental murine model, Mongolian gerbil model that have been reported as a most optimal laboratory animal model to study *H. pylori in vivo* (Hirayama et al., 1996).

In the previous study, Lee & Kim (2006) examined these issues in an experimental murine model, Mongolian gerbil model that have been reported as a most optimal laboratory animal model to study *H. pylori*. Pregnant Mongolian gerbils, infected experimentally with *H. pylori*, were divided as four groups. Following the experimental design, the stomachs of the mother and litters were isolated and assessed for transmission of *H. pylori* at prenatal period, parturition day, 1-week old age and 3-week old age respectively. Bacterial culture and polymerase chain reaction (PCR) was used to examine the presence of transmitted *H. pylori*. All litters showed no transmission of *H. pylori* during pregnancy and at parturition day. However, they reveled 33.3% and 69.6 % at 1-week old age and 3-week old age respectively by PCR. These results suggested that vertical infection during prenatal period or delivery procedure is unlikely as a route of mother-to-child *H. pylori* infection. It might be acquired *H. pylori* through breast-feeding, contaminating saliva and fecal-oral during co-habitat (Lee & Kim, 2006).

Half of the world's population is estimated to be infected with *H. pylori* and the infection is mainly acquired in early childhood but the exact routes of transmission remain elusive. Infected mothers are generally considered to be the main source of the pathogen (Weyermann et al., 2006; Escobar & Kawakami, 2004; Rothenbacher et al., 2002). The epidemiology of *H. pylori* infection is variable, with prevalence being significantly higher and incident infection occurring earlier in developing countries compared with developed

countries (Frenck & Clemens 2003; Ahuja & Sharma, 2002; Graham et al., 1991). There is an obvious public health impact of *H. pylori* infection and thus, to design targeted and cost-effective prevention strategies, elucidation of the mode of transmission for this bacteria is crucial (Fendrick et al., 1999). It is known that *H. pylori* infection is typically acquired in early childhood and usually persists throughout life unless specific treatment is applied (Crone & Gold 2004). Definitive modes of transmission have not yet been characterized and the principal reservoir appears to be humans. Person-to-person transmission via fecal-oral, oral-oral and gastro-oral routes have been proposed (Mladenova et al., 2006). Numerous studies also indicate low socioeconomic status, including domestic overcrowding in childhood, as major risk factors for higher infection prevalence rates (Frenck & Clemens 2003). Little is known about when and how often maternal transmission of *H. pylori* occurs during perinatal stage. In the previous study, Lee & Kim (2006) examined these issues in an experimental murine model.

The results of the vertical-transmission experiment indicated that vertical transmission of *H. pylori* was not occurred at pregnant and delivery staged. However, they reveled 33.3% and 69.6 % at lactating and weaning stage respectively. Recent epidemiological studies in humans suggest that the acquisition of *H. pylori* occur during childhood. For example, Rothenbacher et al (2000) reported that *H. pylori* acquisition seems to occur mainly between the first and second year of life: that is, after the age of weaning. Our results are in agreement with this report. Also, Rothenbacher et al (2000) reported that infected parents, especially infected mothers, play a key role in the transmission of *H. pylori* within families. Maternal contact behaviour during the breastfeeding period may be responsible for the high frequency of maternal transmission (Kurosawa et al., 2000). Our results also showed that the maternal-transmission of *H. pylori* was not observed during pregnancy and delivery stage, but detected at lactating and weaning stage. On the basis of these findings, vertical infection during pregnancy or at delivery is unlikely as a route of mother-to-child *H. pylori* infection. Lee & Kim (2006) suggested that *H. pylori* infection of transplacental route during pregnancy might not be occurred and that *H. pylori* transmission by discharges of uterine or vagina, obstetric delivery tract, during parturition might not be occurred. It might be acquired *H. pylori* through breast-feeding, contaminating saliva and fecal-oral during co-habitat.

7. Diagnostic methods of *Helicobacters*

To detect *Helicobacter* species, serologic tests (Livingston et al., 1997), the culture method (Russel et al., 1995), and the PCR (Engstrand et al., 1992) have been used. Serologic test may be not available for animal screening because of absence of available species-specific antibodies against *Helicobacter* species. Also, culture assay is labor-intensive. It has been reported that PCR assays is easy and useful method and can be performed even on feces as a noninvasive means of rapidly screening large numbers of animals for *Helicobacter* species (Beckwith et al., 1997). However, those kinds of PCR assays requires multiple assays because of a lot of *Helicobacter* species (Grehan et al., 2002). There is no doubt that a bacteriological culture is the best method for diagnosing a bacterial infection. However, it is not easy to cultivate *Helicobacters* because the specimens are usually obtained from several different locations by biopsy or necropsy. In addition, the sensitivity of the culture-isolation method is low (Hammar et al., 1992). Therefore, a culture is not considered to be the most practical diagnostic method. As a result, the CLO test and staining methods are preferred in

many clinical laboratories. Nonetheless, they also have problems such as accuracy of species-specific identification (Megraud, 1997). PCR which is a specific and sensitive molecular method for detecting *Helicobacter* DNA, can supplement the above methods. However, PCR methods using species-specific primers require multiple assays because of a lot of *Helicobacter* species (Grehan et al., 2002). In this study, the RNA polymerase ß-subunit-coding gene (*rpo*B) was used for the detection of novel *Helicobacter* species by a simple PCR analysis. *rpo*B is an important transcription apparatus in all microorganisms. Because this region is highly conserved, this *rpo*B DNA PCR could be used as a consensus PCR analysis method to detect *Helicobacter* species. Therefore, it is clear that PCR methods targeting a stable gene such as *rpo*B would give more reliable results. Mutiple PCR assays using *Helicobacter* species-specific primers may be considered an expensive, laborious, and thus impractical procedure for many samples in clinical laboratory settings. On the other hand, this consensus PCR can be used alone without multiple assays. Therfore, the cost, which is higher than those of other methods, including culture, will be reduced. *Helicobacter* species may be identified in this single PCR and the presence of a novel species may be detected. Fecal samples may be stored at room temperature for up to a week without affecting the outcome of PCR for *Helicobacter* species (Beckwith et al., 1997). Therefore, monitoring of *Helicobacter* infection could be conducted very easily by this consensus PCR with feces. In the previous study, the consensus PCR using *rpo*B primers was able to detect successfully *Helicobacter* species (Kim & Kim, 2004). A set of primers (HF, 5'-ACTTTAAACGCA TGAAGATAT-3'; and HR, 5'-ATATTTTGACCTTCTGGGGT-3') was used to amplify *rpo*B DNA (458 bp) encompassing the Rif^r region. Amplification of *rpoB* DNAs (458 bp) from *Helicobacter* species PCR products was electrophoresed on a 1.2% agarose gel. The PCR products (458 bp) were observed from the *Helicobacter* species such as *H. felis*, *H. cinaedi*, *H. mustelae*, *H. hepaticus*, *H. pylori* ATCC43504, *H. pylori* ATCC 43579, *H. pylori* ATCC 43619, *H. pylori* ss1, *H. pylori* isolate. There was no amplification from other bacteria such as *E. coli*, *Bacilus subtilis*, *Corynebacterium diphtheriae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Enterococcus faecalis*, suggesting that the primers (HF and HR) are *Helicobacter* specific. This consensus PCR will be useful and effective for monitoring *Helicobacter* species including human and animals and could be used for detection of a new *Helicobacter* species by combination with partial sequencing (Kim & Kim, 2004).

8. Preventive and therapeutic methods of *Helicobacters*

Various pharmacological regimens have been studied in the treatment of *H. pylori* infection. Antibiotics (Fera et al., 2001), proton–pump inhibitors (Park et al., 1996), H_2-blockers (Sorba et al., 2001), and bismuth salts (Midolo et al., 1997) are suggested standard treatment modalities, which are typically combined in dual, triple and quadruple therapy regimens in order to eradicate *H. pylori* infection (Worrel et al., 1998). Some problems may arise upon administration of these eradication regimens, i.e. the cost (Worrel et al., 1998), the efficacy of antibiotics regarding the pH (for instance, amoxicillin is most active at a neutral pH and tetracycline has greater activity at a low pH) (Worrel et al., 1998) and resistance to the antibiotics (Ferrero et al., 2000). However, above 15% of the patients undergoing such drug regimens experienced therapeutic failure (Worrel et al., 1998).

Hence, numerous studies have concentrated on the eradication of *H. pylori* infection using traditional herbal medicines. Garlic and Pteleopsis extracts exhibited weak and modest, respectively, anti-*H. pylori* activity (Germano et al., 1998). Fifty-four Chinese herbs were

screened for anti-*H. pylori* activity, exhibiting *Rheum palmatum*, *Rhus javanica*, *Coptis japonica* and *Eugenia caryophyllata* strong anti-*H. pylori* activity (Bae et al., 1998). Cranberry juice possesses modest anti-*H. pylori* activity (Burger et al., 2000). The anti-*H. pylori* activities of *Aristolochia paucinervis*, black myrobalan and cinnamon were also examined (Gadhi et al., 2001). Anti-*H. pylori* compounds from the Brazilian medicinal plant *Myroxylon peruiferum* have successfully isolated (Ohsaki 1999). Extracts and fractions from seven Turkish plants were also demonstrated to elicit anti-*H. pylori* activity (Yesilada et al., 1999). The leaves, roots and stems of Korean and Japanese wasabi exhibited bactericidal activities against *H. pylori*, having the leaves the highest bactericidal activity (Shin et al., 2004). In addition, some flavonoids and isoflavonoids isolated from licorice such as licochalcone A, licoisoflavone B, and gancaonols have been reported to exhibit inhibitory activities against *H. pylori* (Fukai et al., 2002).

Lee et al (2010) conducted the study of anti-*H. pylori* efficacy with 81 folk medicinal plants. They confirmed that 3 herbal compounds, *Melia azedarach*, *Cinnamomum cassia* and *Magnolia officinalis* showed an antibiotic effect on *H. pylori* infection. It could be a promising native herb treatment for patients with gastric complaints including gastric ulcer caused by *H. pylori*. These results will be able to develop the therapeutics against *H. pylori* infection. *Melia azedarach*, *Cinnamomum cassia* and *Magnolia officinalis* will be useful to treat *H. pylori* infected patients with high therapeutic efficacy and safety (Lee et al., 2010).

9. *Helicobacters* as an emerging new zoonotic pathogen

The genus *Helicobacter* contains at least 24 named species and an additional 35 or more novel *Helicobacters* wait formal naming (Fox, 2002). Members of this genus are microaerobic, have a fusiform or curved to spiral rod morphology and are motile by flagella that vary in number and location among different species (Vandamme et al., 1990). All known *Helicobacters* live in human and animal hosts, where colonization occurs primarily in the gastrointestinal tract. The type species, *H. pylori*, was isolated from the stomach of humans and has been associated with a variety of gastric anomalies including gastritis, peptic ulcer disease, gastric carcinoma, and gastric mucosa-associated lymphoma (Parsonnet, 1998). Like *H. pylori*, other species of *Helicobacter* have also been shown to colonize the stomach and cause disease in animals. Gastric colonizers include *H. felis*, *H. mustelae, H. acinonychis, H. bizzozeronii, H. heilmannii, H. salomonis*, and a recently isolated novel *Helicobacter* sp. of dolphins (Hodzic et al., 2001). The initial interest in animal *Helicobacters* arose from the need for a suitable animal model for studying *H. pylori* infection, and subsequently from an ecological perspective (Fox et al., 1997; Lee et al., 1988). However, there have been recent concerns regarding the potential of animals, notably domestic pets, to be a source of zoonotic *Helicobacter* infection. Dogs and cats used for biomedical research have been occasionally found to harbor *H. pylori* strains (Handt et al., 1995), while *H. felis* has been implicated as a potential human pathogen in a few cases (Wegmann et al., 1991). *H. pylori* has also been found in pet animals, and it can promote gastritis when introduced into specific-pathogen-free cats. The significance of this infection as a cause of gastritis in pet dogs and cats is nevertheless unclear. The main gastric *Helicobacter* species in dogs and cats are primarily *H. heilmannii* (formerly "*Gastrospirillum hominis*") and *H. felis*. These two species are collectively referred to as gastric *Helicobacter*-like organisms (GHLO) because they cannot be distinguished by light microscopy. So far, *H. heilmannii* has not been reliably cultured *in vitro*.

10. Conclusions

Clinical symptoms associated with non-*H. pylori Helicobacters* in humans can be characterized by atypical complaints such as acute or chronic epigastric pain and nausea. Other aspecific symptoms include hematemesis, recurrent dyspepsia, irregular defecation frequency and consistency, vomiting, heartburn, and dysphagia, often accompanied by a decreased appetite. Evidence is accumulating that especially pigs, dogs, and cats constitute reservoir hosts for gastric *Helicobacter* species with zoonotic potential. The recent successes with in vitro isolation of these fastidious microorganisms from domestic animals open new perspectives for developing typing techniques that can be directly applied on gastric biopsies from humans. These techniques should make it possible to determine whether animal and human strains belonging to the same *Helicobacter* species are clonally related.

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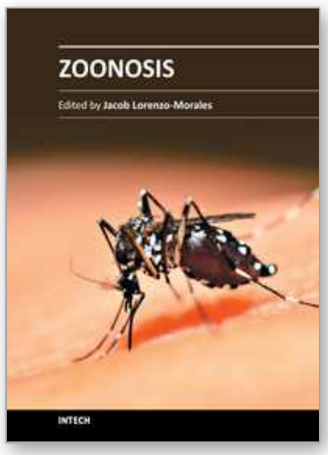

Zoonosis

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Zoonotic diseases are mainly caused by bacterial, viral or parasitic agents although "unconventional agents" such as prions could also be involved in causing zoonotic diseases. Many of the zoonotic diseases are a public health concern but also affect the production of food of animal origin thus they could cause problems in international trade of animal-origin goods. A major factor contributing to the emergence of new zoonotic pathogens in human populations is increased contact between humans and animals. This book provides an insight on zoonosis and both authors and the editor hope that the work compiled in it would help to raise awareness and interest in this field. It should also help researchers, clinicians and other readers in their research and clinical usage.

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