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Contaminated water as a source of *Helicobacter pylori* infection: A review

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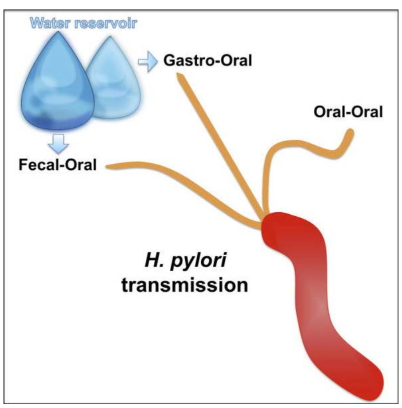
Graphical abstract



Abbreviations: IMS, immunomagnetic separation; PCR, polymerase chain reaction; VBNC, viable-but-non-culturable
Keywords: Epidemiology, Infectious diseases, Climate change, Water crisis

Abstract

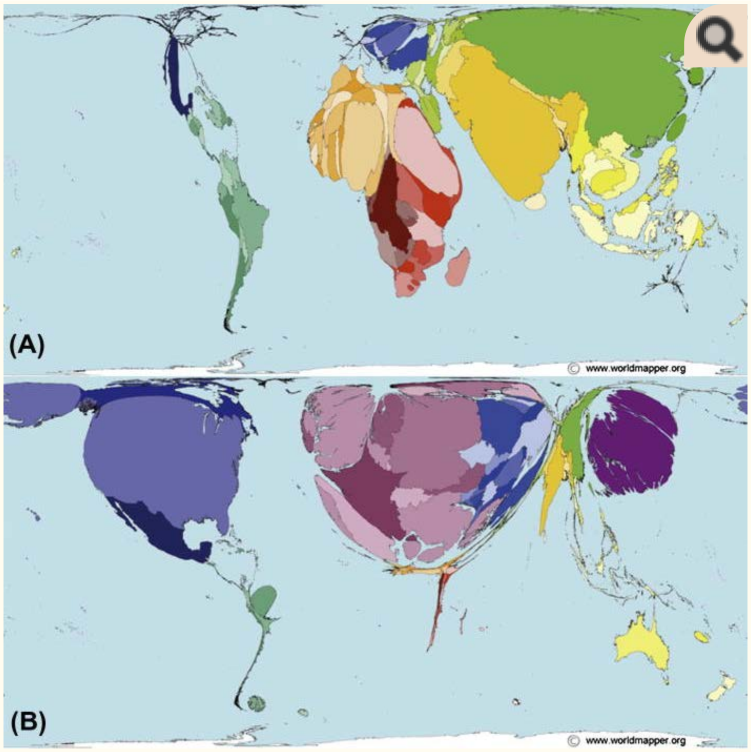
Over the preceding years and to date, the definitive mode of human infection by *Helicobacter pylori* has remained largely unknown and has thus gained the interest of researchers around the world. Numerous studies investigated possible sources of transmission of this emerging carcinogenic pathogen that colonizes >50% of humans, in many of which contaminated water is mentioned as a major cause. The infection rate is especially higher in developing countries, where contaminated water, combined with social hardships and poor sanitary conditions, plays a key role. Judging from the growing global population and the changing climate, the rate is expected to rise. Here, we sum up the current views of the water transmission hypothesis, and we discuss its implications.

Introduction

Water crisis and risk of infectious diseases in the developing world

On July 28, 2010, the General Assembly of the United Nations voted to recognize access to clean water and sanitation as a human right (URL: http://www.un.org/News/Press/docs/2010/ga10967.doc.htm), a long-awaited decision that had been advocated and endorsed by the scientific community [1]. This recent UN resolution came at a time in which water is increasingly becoming at the heart of geopolitical and socioeconomic conflicts, notably in the developing world and in particular as a consequence of climate change [2,3].

In developing countries, many communities lack access to a reliable source of clean water (Fig. 1A) or sanitation services (Fig. 1B) [4]. Instead, those communities find themselves having no other choice but to depend on the surrounding sources of continuously flowing water, such as nearby rivers and streams as their sole everyday water source (Fig. 2A). On the other hand, isolated communities living in low-populated deserted geographical areas, located hundreds of miles away from a nearby river branch or stream, are obliged to rely on municipal water wells as their main supply for drinking and irrigation (Fig. 2B). An alarmingly rising number of those individuals suffer from numerous gastrointestinal tract-related problems [5–8], some of which can be directly linked to *Helicobacter pylori* infection, which can result into chronic infection and even cancer [9,10].



[Fig. 1](#)

Global patterns of (A) percent population without sustainable access to an improved water source (B) percent population with access to sanitation. Cartograms or map projections were downloaded from http://www.worldmapper.org (© Copyright SASI Group, University of Sheffield; and Mark Newman, University of Michigan).

Fig. 2

Example of suboptimal water sources in developing countries. (A) A running water source in Giza, Egypt (Photo credit: Radwa Raed Sharaf); (B) An exposed water well in an Al-Bahariya Oasis, Egypt (Photo credit: Mohamed Mahdy Khalifa).

When waterborne diseases are discussed, acute infections related to diarrhea and malnutrition (e.g., infections by *Vibrio cholerae*, *Escherichia coli*, and *Salmonella enterica*) often come to the front scene [3,11], but it is less common to consider chronic diseases, such as those resulting from *H. pylori* infection, as water-related public health threats. Still, the increase in *H. pylori*-associated gastrointestinal conditions could only raise an obvious question of whether contaminated water is a route of transmission of this pathogen, being a common factor among the infected patients [12]. This question gains particular importance given the continuously changing pattern of human demography expected to redraw the global map of *H. pylori* epidemiology [13].

In this article, we briefly introduce *H. pylori* and its epidemiology, we review evidence suggesting contaminated water as a source of infection with emphasis on recent evidence confirming viability of the bacteria isolated from water sources, and we discuss the potential implications of this route of transmission on global health and health policies.

Helicobacter pylori and its transmission

H. pylori, a bacterium initially observed in 1893 ([14] cited in [15]), has not been recognized as an infectious agent until 1982—in the seminal work of Nobel Laureates, Warren and Marshall [16–18]. *H. pylori* colonizes various regions of the upper digestive system, mainly the stomach and duodenum, causing stomach and duodenal ulcers and certain stomach cancers [9,19,20]. The infection is surprisingly common, and the bacteria are believed to colonize more than half of the world's population [21].

H. pylori bacteria grow only under microaerophilic conditions on rich media [22]. An interesting feature of these bacteria is their ability to adapt to harsh conditions. They are capable of becoming virtually metabolically inactive, with minimal synthesis of DNA and RNA through a conversion from spiral into coccoid forms, offering a survival advantage in cases when chances of survival are slim [23] to none [24,25]. The coccoid form has been further classified into three categories, a dying form, a viable culturable form, and a viable-but-non-culturable state (VBNC), found to be metabolically active but not actively growing [26,27].

The nature of *H. pylori* and its infection niche, the human stomach, suggest ingestion as the most likely means of acquisition of this pathogen [28]. Nevertheless, its specific route of transmission has been widely debated among researchers to be oral–oral, gastro–oral, or fecal–oral (recently reviewed in [13] and [29]).

These three routes of transmission, reviewed elsewhere [13,28], are not mutually exclusive and may all be simultaneously involved in the infection process [30,31]. In this article, we focus on the oral ingestion of contaminated water or water-related items. This route of transmission can be fairly argued [12] since water biofilms have been suggested [27] to provide the bacteria with a protective habitat necessary to endure the water handling process. In addition, groundwater supply, being the sole source of water in many geographic areas, ideally fits into the oral–fecal, and perhaps the gastro–oral, models of infection. By time and throughout their life, inhabitants of those geographic areas consume large volumes, which statistically cause their chances of becoming infected to skyrocket.

Water as a source of infection

The hypothesis of water being a route of transmission of *H. pylori* [7,12,32] is supported by epidemiologic studies that have observed a higher prevalence of *H. pylori* infection [33–35] and a more rapid acquisition rate [36,37] in developing countries, which, in most instances, suffer from problems related to the sanitary distribution of water among the population (Fig. 1).

Evidence supporting the water transmission hypothesis comes largely from two groups of studies: (i) epidemiologic studies showing association between prevalence of *H. pylori* and water-related sources (See Table 1 for landmark studies representing this group) and (ii) studies that detected or isolated *H. pylori* from water sources (Table 2).

Table 1

Example of landmark epidemiologic studies suggesting possible water transmission.

Year published	Location	# Cases	Design/Methods	Mai finding and significa
1991	Peru	407 children (<12 years)	Epidemiologic study using 13C Urea breath test	First repo suggestir water as factor foı *pylori*
2002	Kazakhstan	288 Unrelated healthy individuals	Cross-sectional seroepidemiologic study between May–August 1999	Statistica epidemic evidence water anı poor sanitatioı rather tha ethnicity crowding risk facto for *H. py*

				infection drinking water is t highest r
2008	Japan	224 Children (<6 years)	Three-year follow-up study	In one di using dee groundw the prevalen rate amo children 0%, and children maintain their uninfecte status througho Other dis with nor prevalen rate used water
2012	Malaysia	161 Subjects (including 82 controls)	Case-control study using gastric histology to detect *H. pylori*	Increased of *H. pyl* associate with unsanitar practices Also the of well w and overa poor hyg were associate with a hi risk of infection (OR = 3. 95% CI: 1.76–6.4
2013	Six Latin American countries	1859 adults	Urea breath test	The odds *H. pylori* infection

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correlate with the of indoor plumbing (OR 1.3: 1.8)

Cases: Number of human subjects.

OR: Odds ratio.

CI: Confidence interval.

Refs.: References.

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Table 2

Key studies detecting *H. pylori* in water samples and confirming the water transmission hypothesis.

Year published	Location	Water source	Detection method	fi sig
1993	Maryland, USA	Laboratory microcosms	Autoradiography (to assess viability of VBNC forms)	This prov evid the r activ VBN *pylo* wate supp poss wate rout infe *H. p*
2001	Japan	Tap, well, river, and seawater	Membrane filtration followed by polymerase chain	Dete *H. p* DN

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			reaction	wate
May 2003	Wisconsin, USA	Any	Culture-based method: development of selective medium for *H. pylori*	A se HP-a med deve the i of *H* from micr popu wate prov faste and selec
2003	North Carolina, USA	Fresh water	Membrane diffusion chambers followed by plate counts and Live/Dead Baclight assay	*H. p* pers VBN whic repr publ haza
January 2004	Portugal and United Kingdom	Various	Different culture media and growth conditions	This dem the p of op cultu tech reco *pylo* wate
April 2006	Portugal and United Kingdom	Well	N/A	This sugg dete the p in w desc othe can l to th incre abili *pylo* integ

				biofi unde conc low stres also more selec loca perf mole plate anal the c of *H* drink wate asso biofi
2011	Basra, Iraq	Treated municipal drinking water	Modified Columbia Urea Agar	Succ culti and iden of 1 *pylo* samp
2012	Missouri, USA	N/A	A lanthanum-based concentration method coupled with quantitative real-time PCR	The succ deve dete meth wate with conc of *H* and
2012	Spain	Wastewater	A combination of culture methods following filtration of the samples and molecular techniques, mostly PCR and fluorescent immunohistochemistry	The succ iden pres *pylo* of 4 wast samp

2012	Karachi, Pakistan	Drinking tap water samples	Concentration of samples via membrane filtration and PCR on DNA isolated from residue on membranes	The obta posi in 4(sam] of 5(sam]
2013	Isfahan, Iran	Various water sources including tap water, bottled mineral water from different brands and samples from publicly available water coolers	Culture on supplemented *Brucella* agar followed by Gram staining and biochemical tests. Positive results confirmed by PCR amplification of *ure*C gene	Cult metl succ dete *pylo* out (sam] PCR amp of *ui* was succ 14 s. The sugg PCR cultu nega sam] have forn *pylo* opin coul due pres othe carry bact othe *Heli* spec

Refs.: References.

N/A.: Not applicable.

Water was first suggested as a source of *H. pylori* infection in 1991 by Klein and coworkers, who observed that Peruvian children with an external source of drinking water were more likely to be infected with *H. pylori* than children with an internal source [38]. Subsequently, *H. pylori* cells were detected in the water provided to cities nearby Lima, Peru in 1996 [39] and in municipal water, treated wastewater, and well water in Sweden in 1998 [40]. A few years later, Nurgalieva and coworkers noted that drinking river water was a high risk factor for *H. pylori* infection in Kazakhstan [41]. Accordingly, they stated that transmission of *H. pylori* could be waterborne [41].

Shahamat and colleagues hypothesized that the VBNC form of *H. pylori* persists in water [42], and in a number of studies [36,38,43,44], untreated municipal water was considered as a main cause of the increased *H. pylori* prevalence in the areas subjected to research. Effectively, in 2001, *H. pylori*'s DNA was detected in a Japanese well, whose consumers were infected [45], while a more recent study from Japan suggested river water-associated incidence [46].

The water transmission possibility was studied in depth in a thesis published in 2005, in which Azevedo strongly argues that drinking water can pose a substantial threat of *H. pylori* infection based on the fulfillment of several essential criteria [32]. These criteria include the ability of *H. pylori* to adhere to different materials and to co-aggregate with other bacteria and form complex structures on pipes or other surfaces in contact with water [32]. The notion about the inability of the bacterium to survive alone in running water, but to develop a symbiotic relationship and form complex structures on contact surfaces [47], makes it rational to assume that groundwater is a reservoir for *H. pylori* due to its stagnant nature.

Surprisingly, it is not uncommon to detect *H. pylori*'s DNA in water [48,49]. In fact, Lu and coworkers went as far as culturing the bacteria from the untreated municipal water using immunomagnetic separation (IMS), which was further confirmed by polymerase chain reaction (PCR) and a set of microbiological tests [44]. However, as Azevedo pointed out [32], the improved handling of water in more developed countries, coupled with sanitary conditions, which mandate proper disinfection, has effectively impeded the transmittance of *H. pylori* over the course of the last 20 years [32]. Nevertheless, *H. pylori* was shown to retain its viability in chlorinated water [50,51].

Furthermore, older findings by West and coworkers show that *H. pylori* is capable of survival in different types of aquatic environments under an array of physical variables [52]. West et al. conclude that the bacterium, unlike other pathogens, is unusually tolerant to pH fluctuations [52]. In support of this finding, a study regarding the occupational health hazards, conducted years later (2008) in India, indicated that the sewage and sanitary workers experience a high risk of *H. pylori* infection [53]. This could only be linked to the constant exposure of these workers to contaminated water in their line of work, in the absence of strict regulations and protocols to ensure their safety. In the same study, the author reported a rising blood level of IgG antibodies, targeted against the bacterium, with increased age [53].

In light of accruing evidence from studies published before 2005, Bellack and colleagues suggested a conceptual model for water's role in *H. pylori* transmission. Their model is based on the assumption that humans and animals can be long-term carriers of the bacteria and that they can transfer it to water, which is a short-term reservoir, via the fecal route [12]. Accordingly, their model suggests the requirement for continuous water contamination by human or animal feces with the high likelihood of fecal–oral transmission to humans consuming contaminated water, in which bacteria survive for limited time. However, Bellack's model stopped short at direct evidence of viable bacteria isolated from water sources. Such evidence has lately been available from different sources, where direct isolation of viable *H. pylori* from water has been reported in developing countries, with less optimal water hygiene, suggesting that bacterial isolation is more likely to be successful when the microbial burden is relatively high. Examples include studies in Pakistan [54,55], Iraq [56], and Iran [57] (see Table 2).

Of note, not all investigators support the water hypothesis, and some have actually designed experiments to debunk it. Janzon and coworkers, for example, reported their failure to detect *H. pylori* DNA in water in spite of using a highly sensitive real-time PCR assay and in spite of adopting a series of controls in their study [58]. Although this conflict has not been resolved, it is possible that these contradictions are related to the variability in bacterial load in water samples. After all, "*absence of evidence is not evidence of absence*" (quote attributed to US astronomer Carl Sagan).

Box 1

Culturing bacteria from water samples.

Entrance of *H. pylori* into the VBNC state allows *H. pylori* to persist in water, but the bacteria remain nonetheless difficult to culture [42]. Other investigators attempted to force the bacteria into entering this state within a laboratory setting [59], and despite the great number of viable cells, the culturability declined sharply to less than 10 colony-forming units per milliliter. This could definitely be a strong indication as to what happens under normal circumstances in a real-life setting [59].

What next? From association, detection, and isolation to causation

As noted above, less than a decade ago, the model suggested by Bellack and colleagues for water's role in *H. pylori* transmission [12] seemed quite plausible; yet, there was not enough evidence supporting direct microbial viability. The work of Azevedo [32,47,60] and subsequent published studies on direct microbial isolation (e.g., [56,57]) provided such needed evidence. What remains now is to establish direct causation via well-designed experiments that use water, spiked with *H. pylori*, to cause colonization and/or disease in animal models, fulfilling Koch's postulates for disease etiology [61–63]. One challenge is the choice of appropriate animal model; another is confirming that the initiation of disease is caused by ingested rather than resident *Helicobacter* cells. The latter can be made possible by various methods, ranging from direct labeling to inserting traceable genetic markers in exogenous bacteria by genetic manipulation.

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Water-contaminated infection sources

As a corollary to the water transmission hypothesis, if water is a reservoir of *H. pylori*, then any surface exposed to the contaminated water could potentially act as another source of infection. One clear example is harvested raw fruits and vegetables in rural communities. Those crops pose a threat of being a vehicle for the transmission of *H. pylori*, being contaminated by irrigation water and in some cases municipal water, sought by some as a substitute for organic manure.

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Goodman and coworkers noted this possibility and included the unsanitary habits of the Columbian Andes population as another contribution to the infection pool [43]. These habits range from the use of the open fields when lacking a toilet facility to the late afternoon swimming—as an escape from the surrounding hot climate—in the flowing streams and rivers, considered to be dumping sites for the excess irrigation water. The authors' results are clear-cut: depending on the source of drinking water, whether from a privately owned well, water pumps, or even tap water—as opposed to a nearby stream or river, the risk of infection fits perfectly into place, which was immensely higher in the latter case.

Possible methods of prevention

Knowing the source of infection is a necessary step toward prevention. Salih reports that in recent years, infection with *H. pylori* in the developing countries has declined owing to the increased awareness of the possible root of the problem and recommends boiling water to prevent infection [64]. Nowadays, it is highly advisable to boil water used for drinking, or even for washing hands and dishes. This simple measure is especially recommended for those who lack a trustworthy water purification system within the community, although compliance is not guaranteed. One can only agree that the process of boiling is an effective combating regimen, since a temperature of merely 30 °C was capable of arresting the growth of various strains of the bacterium as reported by Xia and coworkers [65]. In most cases, such practice was initially promoted by the respective health authorities to fight off more serious forms of infections caused by water-borne microorganisms.

Despite this seemingly obvious assumption, earlier findings of Mitchell and coworkers [36] appear to somewhat contradict the effectiveness of boiling water. Mitchell's study included a section of Southern China's population, who were asked to complete a questionnaire. Results indicated a higher prevalence of infection among rural inhabitants, who drank river water as opposed to well water. Surprisingly, most stated that boiling water is included in their everyday routine [36].

Conclusions

In this Review Article, we focused on water as a possible source of transmission of *H. pylori* and discussed some experimental findings indicating the possibility of detecting viable *H. pylori* in water. We recognize that this hypothesis has been challenged [58] and that even if confirmed as a reservoir for *H. pylori*, water may very well be a secondary route of transmission [18,66]. However, given the accruing evidence, it is still important to seriously consider contaminated water as one of the likely candidate sources and deal with it effectively. Ongoing research aims at providing unequivocal evidence of the suggested route of transmission. As soon as this is achieved, efforts can be directed to prevent further infections and properly treat possible transmission vehicles to cut down the number of new cases.

Outlook

The possibility of *H. pylori* transmission through water has its promises and perils. On the one hand, water transmission is preventable by the implementation of necessary measures of hygiene and water sanitation. On the other hand, availability of drinking water is likely to be a crisis in the following decades, and the burden of this crisis falls unequally on developing countries [4,5,67]. The problem becomes even more serious when considering how the climate change is affecting our planet's demography [1,2,67]. Eventual migrations may worsen the situation of the developing countries not only by increasing their populations, but also by rendering the availability of treated potable water even dearer [4,66,68].

On dealing with waterborne infections, one might give priority to infectious diseases with high mortality such as cholera and other diarrheal diseases [3]. However, *H. pylori* causes cancer especially in elder patients and given that life expectancy has increased, and so has poverty, preventing infection-associated cancers (e.g., *H. pylori* and hepatitis C) should be a priority of health organizations in the decades to come.

Conflict of interest

The authors have declared no conflict of interest.

Compliance with Ethics Requirements

This article does not contain any studies with human or animal subjects.

Biographies

Ramy Karam Aziz is an Assistant Professor at the Department of Microbiology and Immunology,

Faculty of Pharmacy, Cairo University. He earned his PhD from the University of Tennessee, USA in 2005. His current research interests are molecular epidemiology, systems biology of microbial pathogens, microbial and bacteriophage genomics/metagenomics, and pharmacomicrobiomics. He published a book and >50 articles in peer-reviewed journals and received several awards, most recently the Egyptian State Incentive Award in 2011 and the World Academy of Science (TWAS) Young Arab Scientist for the year 2010.

Mohammed Mahdy Khalifa is currently a community pharmacist at Bahareya Oasis in Egypt. He earned his MSc degree in 2009 from the Faculty of Pharmacy, Cairo University, for his work on the detection of H. pylori in underground water.

Radwa Raed Sharaf is a graduate PhD student in the virology program at the Division of Medical Sciences, Harvard University. She is currently working in Thorsten Mempel's lab on the cellular dynamics of HIV-infected cells in lymphoid tissues. She earned her MSc degree in 2013 from Charite University in Berlin, for her work on CMV-specific T cells.

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Footnotes