

# Gut

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## Leading article

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### Transmission of *Helicobacter pylori* infection

*Helicobacter pylori* is one of the world's most common bacterial infections, as more than three quarters of the population of the developing world are infected from an early age. The pattern in the developed world is different, where infection in childhood is less common but with a gradual increase in prevalence with age.<sup>1-4</sup> The mode of transmission of *H pylori* is assuming greater importance as the public health implications of infection become clearer. Understanding the mode of transmission is important as reinfection after eradication of the organism is a particular concern. This review summarises our understanding of the source, transmission, and changing trends of infection, and the implications for reinfection after eradication.

#### Sources of *H pylori* infection

Humans are the sole natural host of *H pylori*, although closely similar organisms have been found in primates.<sup>5</sup> It has never been isolated from the environment, but would be difficult to culture from contaminated sources as it grows more slowly in vitro than most other organisms. *H pylori* DNA has been detected by polymerase chain reaction in Peruvian sewage water.<sup>6</sup> Whether this represents the detection of viable organisms or reflects a lack of specificity is unclear. In vitro experiments have shown that *H pylori* survives for several days in distilled water, saline, and sea water if these are kept cool, but becomes non-culturable after one to three days at room temperature.<sup>7</sup> Whether particulate matter could increase survival time by providing a more favourable local environment is unknown.

It is unlikely that *H pylori* can multiply in the environment, and it seems almost certain that humans are the only source of infection.

#### Route of infection

The ability of the organism to survive in the environment has implications for the transmission of infection. Faeco-oral transmission is not usually a direct interpersonal one but relies on environmental contamination. Oro-oral transmission usually requires direct interpersonal contact.

From its protected niche in the gastric mucosa, *H pylori* could either be transmitted by the oro-oral route with episodes of gastro-oesophageal reflux permitting access to

the mouth, or excreted in faeces. *H pylori* has now been cultured both from the faeces<sup>8</sup> and from dental plaque<sup>9 10</sup> on a small number of occasions, but has been identified by polymerase chain reaction from both sites in a greater number of subjects with infection,<sup>11-13</sup> suggesting that transmission by both routes can occur.

Epidemiological evidence suggests transmission by both routes. The increased rates of infection among children of West African mothers who pre-masticate their infants' food<sup>14</sup> and among Chinese who share eating utensils favours oro-oral transmission. Gnotobiotic beagles who have oro-oral contact transmit *H pylori* to each other.<sup>15</sup> An increased rate of infection, however, among dental workers has not been found,<sup>16</sup> but endoscopists not using gloves have an increased rate of infection.<sup>17</sup> The main epidemiological evidence supporting faeco-oral transmission is the similarity of the seroepidemiology with that of hepatitis A.<sup>18</sup>

#### Clustering of *H pylori* infection: is the family an important source of acquisition?

The absence of an environmental reservoir for *H pylori* suggests interpersonal transmission. Clustering of *H pylori* infection among people living in close proximity to each other has been described in children's institutions<sup>19</sup> and in the family.<sup>20 21</sup> This suggests interpersonal transmission but is consistent with a common environmental source. If there is true clustering of infection within families, then this taken together with the failure to find an environmental reservoir represents powerful evidence for direct or indirect interpersonal transmission.

Interpretation of family studies is not straightforward. Studies of index children have generally shown an increased rate of infection in the families of seropositive children, but there have been no controlled studies for variation in socioeconomic circumstances of the families. Hence the findings may merely represent greater environmental exposure of the index positive children. Studies of the spouses of index adults, on the other hand have generally shown no increased rates of infection. The largest study, among 277 couples in a fertility clinic, which was both the only one with sufficient power to detect modest effects and the only one to control for socioeconomic circumstances, showed no increased rate of infection among the spouses of seropositive index

cases.<sup>22</sup> Two smaller studies have confirmed this finding,<sup>23 24</sup> but one did not.<sup>25</sup> Studies of the children of index adults have given different results,<sup>23-25</sup> but the problems of size of study and controlling for socio-economic circumstances apply to them all. Thus, from family studies so far it is not possible to say whether true clustering occurs.

Evidence of a different type comes from a limited number of DNA and RNA typing studies, which are the only useful typing schemes for epidemiological purposes. There is great variability in the DNA and RNA profiles by restriction endonuclease analysis.<sup>26</sup> The only context in which identical strains may be found by DNA analysis is on separate occasions in the stomach of a subject or in infected family members. *H pylori* is a longlasting infection in its protected niche in the stomach, allowing time for genetic evolution to occur over several decades. Hence finding different strains of organism in two family members may only mean that transmission was not recent. Clonal variants of the same strain of the organism have been found in three generations of a single family,<sup>27</sup> suggesting that the opportunity for genetic evolution of the organism may only be of limited importance.

There are four studies of family members using either DNA or RNA fingerprinting, and they give different results. In the first report by Langenburg of a duodenal ulcer family, seven of eight members had the same strain of *H pylori*. This study only used one restriction enzyme, thus limiting the range of strains that could be detected. In another report, however, of a duodenal ulcer family by Nwokolo using a larger number of restriction enzymes, only three of nine subjects from three generations tested had the same strain.<sup>27</sup> Tee used ribosomal RNA to study seven family groups and found identical digest patterns in members of two families, with variability in strains detected among members of the remaining families, usually husband/wife combinations.<sup>28</sup> In a further study using ribotyping, seven members of three families were studied, with identical isolates being found in mother, father, and son of one family, but different strains in the other two families.<sup>29</sup> Finally, one other report of just two pairs of siblings reported different strains in each.<sup>30</sup>

This evidence does not prove direct interpersonal transmission, but is consistent with spread of infection within the home and also, perhaps more importantly, with acquisition from outside the home. Given that humans are probably the only source of infection, it seems reasonable to conclude that in the developed world at least, interpersonal transmission is occurring, but that the people from whom it is acquired are not restricted to the family.

#### Age of acquisition and risk factors for infection

Two cohort studies suggest that the incidence of infection in adults in the developed world is low, about 0.5% per year.<sup>31</sup> Coupled with a small spontaneous eradication rate, these rates are too low to explain the prevalence of infection among the subjects being studied. This suggests that some sort of birth cohort phenomenon is in operation. Evidence from the follow up of subjects after eradication of infection supports these findings, although reinfection may not be the same as primary infection.<sup>32</sup> A study from the developing world where 20% per year of adults whose infection had been cured were reinfected, suggests that if there were susceptible adults in this environment they would rapidly re-acquire *H pylori*.<sup>33</sup>

We and others have shown a strong association between adult seropositivity and overcrowding in the childhood home independently of father's social class in

the developed world.<sup>3 34</sup> We also showed a strong independent relation with no fixed hot water supply in the childhood home. Adult risk factors in our own cross sectional study for seropositivity at all ages were much weaker than childhood risk factors, suggesting that most British adults acquired their infection in childhood.

The main adult risk factors were the number of children currently living in the home (but not the number who had left home) and marital status. Although the second has a stronger effect than the first it just failed to reach significance because of the small number of unmarried adults.

We studied 40 children of 20 seropositive children identified in this study, but found only one infected based on the <sup>13</sup>C urea breath test,<sup>23</sup> suggesting that children are not the source of their parents infection or that they may be able to spontaneously eradicate infection. This study is also consistent with adults not infecting their children nowadays.

This evidence suggests that in more recent times a larger proportion of those infected are acquiring their infection at a later age, although childhood is still the most important period. Risk factors pertaining to adult life in older adults may be masked by the smaller proportion of susceptible subjects entering adult life.

#### Susceptibility to infection

The prevalence of infection among children in the developed world ranges from 5-15% depending on socio-economic conditions.<sup>1 35-37</sup> It has decreased in the developed world. It may be that environmental contamination has been reduced by improved living conditions and sanitation interfering mainly with faeco-oral transmission, or secondly host susceptibility to infection has diminished, interfering with both faeco-oral and oro-oral transmission.

Hepatitis A, a faeco-orally transmitted disease, has shown the same decline in prevalence as that seen for *H pylori*.<sup>38</sup> Improvements in sanitation and overcrowding have played a part. Epstein-Barr virus, an oro-orally transmitted infection, has shown a different pattern. In the developing world the whole population is infected by the age of 5. In the developed world, as living conditions improve, an increasing proportion are infected in adolescence and young adulthood, from oro-oral contact with the opposite sex, the whole population being infected by the age of 30.<sup>39</sup> The changing pattern may result from decreased family size and diminished contact with other children at a young age. If *H pylori* is oro-orally transmitted, higher rates of infection in young adults would be expected than those seen. The risk factors found in adults, however, pertained mainly to young adults, in whom oro-oral transmission would be expected. If oro-oral transmission is important then changes in host susceptibility may partly explain the decline.

Gastric acid production may play a key part in the transmission of infection. *H pylori* cannot survive for long in an acid environment despite being more acid resistant than other organisms.<sup>40</sup> In the volunteer ingestion study by Marshall,<sup>41</sup> the infecting dose was taken after premedication with cimetidine. Morris could only infect himself with *H pylori* after premedicating himself with cimetidine, having failed to do so without.<sup>42</sup>

Ferrets, whose gastric physiology is similar to humans, are infected by *H mustelae* bearing many similarities to *H pylori* in humans. Forty one per cent of adult ferrets given omeprazole to neutralise the gastric contents had positive faecal cultures compared with 10% of ferrets not given the drug.<sup>43</sup>

A variety of bacterial and parasitic infections suppress gastric acid secretion in humans.<sup>44 45</sup> Malnutrition is also a

recognised cause of reduced gastric acid secretion. A study from the Gambia, where infection is common showed that children had a lower gastric acid secretion than British children, comparable with that of adults taking H<sub>2</sub> antagonists. Although temporary achlorhydria is associated with *H pylori* infection, this is probably not the whole explanation.

Transmission of *H pylori* may have fallen as a result of the general reduction of infection and malnutrition resulting from improved living conditions that have taken place this century, particularly among children, both by decreasing factors that facilitate transmission, as well as decreasing transmission of the organism itself.

## Conclusion

*H pylori* can survive for at least limited periods in the environment, and with humans being the only source of infection, either direct or indirect interpersonal transmission could occur by either the faeco-oral or oro-oral route. The first may be the more important in the developing world and the second in the developed world.

Infection with *H pylori* is declining as living conditions improve. Acquisition is principally in childhood from both inside and outside the home. There is no justification for treating family contacts of subjects receiving eradication therapy, and reinfection after successful eradication is unlikely at least in the developed world.

Further studies in the developed world should concentrate on acquisition in childhood from sources outside the home such as schools.

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