What is the *Helicobacter pylori* global reinfection rate?

Julie Parsonnet MD

J Parsonnet. What is the *Helicobacter pylori* global reinfection rate? Can J Gastroenterol 2003;17(Suppl B):46B-48B.

Reinfection with any organism is related to the force of infection in the population and on both innate and acquired immunity to infection. Little is yet known about primary immune protection against *Helicobacter pylori*. Some data suggest that children can be recurrently infected, spontaneously eliminating the organism only to be infected again and again until the organism takes hold. This pattern of recurrent infection is not observed in patients who receive eradication therapy for chronic infection. After eradication of infection, the rate of reinfection is probably slightly lower than the primary infection rate in that age group, suggesting some level of acquired immunity. In developed countries, reinfection of adults in unusual, and recurrence usually repesents failure of primary eradicaton rather than new infection. Some cases of reinfection do occur, however. Given that acquired immunity probably varies little from population to population, reinfections will most likely occur in areas where the force of infecton is high, ie, where both the prevalence of infection and the opportunities for transmission are high.

Key Words: Helicobacter pylori; *Incidence; Prevalence; Reinfection; Transmission*

Quel est le taux total de réinfection à *Helicobacter pylori*?

Une réinfection à tout organisme est liée à la force de l'infection dans la population, ainsi qu'à l'immunité innée et acquise à l'infection. On en connaît encore peu sur la protection immunitaire primaire contre *Helicobacter pylori*. Certaines observations laissent suggérer que l'infection peut récidiver chez les enfants, qui élimineraient spontanément l'agent pathogène, pour être ensuite réinfectés à plusieurs reprises jusqu'à ce que l'agent pathogène prenne le dessus. On n'observe pas ce type d'infection récidivante chez les patients qui reçoivent un traitement d'éradication contre une infection chronique. Après l'éradication de l'infection, le taux de récidive est probablement légèrement inférieur au taux d'infection primaire dans ce groupe d'âges, ce qui laisse suggérer la présence d'un certain degré d'immunité acquise. Dans les pays industrialisés, la récidive chez les adultes est inhabituelle et une réapparition de l'infection représente généralement l'échec de l'éradication primaire plutôt qu'une nouvelle infection. Cependant, certains cas de récidive surviennent. Étant donné que le taux d'immunité acquise varie probablement peu d'une population à l'autre, les récidives surviendront très probablement dans des régions où la force de l'infection est puissante, c.-à-d., où la prévalence de l'infection et les occasions de transmission sont élevées.

Since the initiation of *Helicobacter pylori* treatment in the 1980s, concerns have been raised that high reinfection rates might mitigate against *H pylori* treatment. Reinfection has been of particular concern where primary infection rates are also high (ie, in developing countries). In Bangladesh and Brazil, where studies have indicated high annual reinfection rates, investigators have expressed pessimism about long-term treatment benefits (1,2). Even in developed countries such as the United States, reinfection rate has been a concern. Because infection with multiple strains is relatively common, the likelihood of reinfection following treatment is particularly plausible (3). If those who are actively infected can be reinfected, what is to prevent such a phenomenon in recently treated patients? Knowing the reinfection rate provides important data on the natural acquisition of host immunity, providing insights into vaccine development and other immunological therapies. Moreover, from a pathophysiological standpoint, distinguishing reinfection from recrudescence of unsuccessfully treated infection permits us to better delineate the most effective antimicrobial strategies.

The primary incidence rate for *H pylori* is dependent on four factors: the intrinsic transmissibility of the agent, barriers imposed on transmission (these first two factors combine to define the 'force of transmission'), the innate immunity of the host, and the prevalence of infection within the population (4). Of these factors, only the last – *H pylori* prevalence – is known. As predicted, in general, the population prevalence of *H pylori* infection correlates with incidence. Although few incidence studies of adults have been done in high prevalence areas, with rare exception (Table 1), in low prevalence populations, *H pylori* incidence in adults is uniformly low (typically below 0.5% per person year). The best links of prevalence and incidence can be observed in children (Table 1). Where population prevalence of *H pylori* is relatively low, incidence in children is also low. Where population prevalence is high, childhood incidence rates tend to be high. However, there are exceptions to this trend. For example, in Japan, where the prevalence of infection remains high in adults, incident infection in childhood and adulthood is rare (5,6). Thus, prevalence does not necessarily drive transmission within populations. Rather, because the organism itself is not changing, barriers to transmission – either innate to the host or environmental barriers – must arise that disassociate prevalence and incidence.

Given that barriers to transmission may arise in populations over time (eg, improved environmental and household hygiene) and with increasing age (improved personal hygiene, nutritional status or innate immunity), one would expect that the risk for secondary infection in any individual following *H pylori* eradication would be less than their primary risk. This does not mean, however, that a treated individual would be less at risk than a person who has never been infected at all. Having had primary infection may

This article was originally presented at a conference entitled "Helicobacter pylori: Basic Mechanisms to Clinical Cure 2002", sponsored by Axcan Pharma, November 10-14, 2002, Maui, Hawaii
Stanford University School of Medicine, Stanford, California, USA
Correspondence: Dr Julie Parsonnet, Stanford University School of Medicine, Grant Building, Room S156, Stanford University, Stanford, California 94305-5107, USA. Telephone 650-725-4561, fax 650-498-7011, e-mail parsonnt@stanford.edu

TABLE 1
Studies of incidence and prevalence of *Helicobacter pylori* in adults and children

	Incidence calculation		
Adults (reference)	**Years follow-up**	**New infections**	**Incidence (%/year)**
Denmark (17)	11	14/1895	<0.1
The Netherlands (18)	11.5	2/59	0.3
Australia (19)	21	6/86	0.3
Finland (20)	15.0	12/181	0.4
American epidemiologists (21)	8.5	11/278	0.5
Canada (22)	1.5	3/196	1.0
Japan (23)	7.5	5/73	1.0
Okinawa (24)	10	7/64	1.1
Italian aeronautics students (25)	0.8	2/207	1.1
Greek navy recruits (26)	0.7	17/115	22.0
Children			
Finland (27)	12	2/70	0.3
Japan (23)	5.3	5/86	1.1
Sweden (28)	11	40/294	1.7
United States (29)	12	38/171	1.9
United Kingdom (30)	1	4/116	2.7
Taiwan (31)	1.2	6/80	6.4
Bolivia (32)	1.2	44/188	18.0
Ethiopia (33)	2.5	44/67	24.0

TABLE 2
Reinfection rate in recent studies without confirmatory strain fingerprinting

Country (reference)	Number treated	Years follow-up	Annual reinfection rate
Germany (15)	108	2	0
United States (34)	58	4.8	1.0
Japan (peds) (35)	27	1.8	2.4
India (36)	45	1	2.4
Chile (37)	96	3	4.3
Japan (38)	107	2	4.8*
Ireland (peds) (39)	52	2	5.7
Spain (40)	120	1	6.8
Greece (41)	165	1 to 6	7%
Brazil (1)	34	1	7.6
Korea (42)	45	3.5	12.8

**23.1% with cimetidine, amoxicillin, and metronidazole therapy; 1.5% with omeprazole, amoxicillin, metronidazole, and roxithromycin therapy. peds Pediatric subjects*

TABLE 3
Reinfection rate in recent studies with confirmatory strain fingerprinting

Country (reference)	Number treated	Years follow-up	Annual reinfection rate
The Netherlands (14)	173	3.5	0
Japan (43)	377	2	<0.8
China (44)	187	2	1.1*
Austria (45)	18	3.5	3.2
Bangladesh (2)	90	1.5	18%

**Reinfection confirmed by fingerprinting was 0.7%*

indicate continuing host or environmental risk factors that predispose to *H pylori* acquisition. Hence, in the absence of acquired immunity, reinfection rates might be expected to be higher in previously infected patients than in naïve hosts of similar age and socioeconomic status. On the other hand, if *H pylori* infection does induce a protective immune response, previously infected patients may be at lower risk than naïve individuals. Thus, understanding the secondary rates of infection, and being able to compare them with contemporaneous primary rates, provides insights into acquired immunity, innate immunity, and the contribution of environmental barriers to *H pylori* transmission. If the secondary infection rate for a treated population is lower than the primary infection rate expected if the population had been *H pylori* naïve, then there is evidence of acquired immunity suggesting both predisposition to infection and lack of acquired immunity.

Unfortunately, given the importance of the topic, few studies have actually been able to document true reinfection rates. Investigations that have been done fall into two categories: those in which breath test or gastric biopsy indicated reinfection following a period of apparent cure; and those in which genotyping of reinfecting strains was performed. In the last five years, a number of studies of the former type have been performed (Table 2). These studies indicate a considerably higher rate of reinfection than one might expect given the data for primary infection rates in similar areas. Although this finding may lead one to believe that no protective immunity exists and that previously infected patients are at increased risk, there is significant likelihood in this type of study that recrudescence of uncured infection was misclassified as reinfection. The evidence for this type of misclassification comes from several sources. First, studies have documented higher rates of 'reinfection' in patients who receive second-line *H pylori* eradication regimens (7,8) compared with those who receive first-line therapy. Similarly, individuals with high-negative breath tests (9) or continued inflammation at the end of treatment have been found to be 'reinfected' at a higher rate than those with low-negative breath tests or reduced inflammation, again likely indicating failed primary therapy (8). In a 1997 review, Xia et al (10) confirmed the problems with many reinfection studies. Among the factors that caused the greatest discrepancy among studies were inadequacy of the initial test of cure (insensitive tests of cure lead to high 'reinfection' rates) and inadequacy of primary treatment. Most recently, Jeen et al (11) found that eight of 10 patients who had recurrent *H pylori* infection six to 24 months after apparently successful treatment had identical strains by restriction-fragment length polymorphism analysis to the pretreatment strain. Thus, there is considerable evidence that the majority of 'reinfection' represents primary treatment failure. If Jeen et al's figure of 80% recrudescence is applied to the figures in Table 2, it might be deduced that the reinfection rate closely approximates the primary rate in Table 1.

A mere handful of studies have evaluated the reinfection rate using strain fingerprinting techniques (Table 3). As a whole, these studies indicate that the reinfection rate is similar to the primary infection rate in similar populations. Unfortunately, however, even reinfection rates using fingerprinting can yield false results. No diagnostic test for *H pylori* is perfect. Lack of sensitivity of diagnostic tests – which typically have a sensitivity ranging from 85% to 95% – can be misinterpreted as continued treatment success, falsely diminishing the true reinfection rate. Of greater concern, however, are the factors contributing to overestimation of the reinfection rate. For example, coexistence of more than one strain in the stomach can result in regrowth of a strain unidentified at first endoscopy. Some strains, including cag-negative strains and strains carrying resistance to antibiotics, are less likely than others to respond to treatment (12,13). Thus, treatment can successfully eliminate a dominant strain, leaving a less-

dominant strain to regrow. Given the high frequency of multiple infection, this is a plausible hypothesis, although difficult to demonstrate clinically. Another reason for falsely identifying natural reinfection is that a new strain could be introduced by endoscopic means during the study. Such endoscopic transmission has been noted in previous investigations (14).

In summary, reinfection with *H pylori* appears to occur at a similar rate as primary infection in the same population. Reinfection is no higher if family contacts are infected with *H pylori* than if they are not (15,16), and reinfection is not consistently higher in areas of high *H pylori* prevalence than in areas of low prevalence. Thus, reinfection of adults is unusual, even when there is considerable contact with infected hosts. Although several rigorously conducted studies with strain fingerprinting indicate that there may be acquired immunity to infection (reinfection may be somewhat less common than primary infection), the data are not consistent enough to be termed conclusive. Also, despite the relative consistency of fingerprinting studies showing low reinfection rates, one outlier indicates that reinfection can be considerable. In particular, adults in Bangladesh had a high rate of *H pylori* reinfection confirmed by molecular typing (2). Because these results do not conform with other studies – even studies from developing countries – it will be important to dissect the underlying meaning. Is there something in the environment in Bangladesh that makes reinfection particularly likely? Are Bangladeshis innately more susceptible to infection? Was endoscopic transmission of infection occurring? Identifying reasons for this particularly interesting result may be the key to unlocking the true nature of *H pylori* transmission and reinfection.

REFERENCES

1. Della LE, Rohr MR, Moraes M, Siqueira ES , Ferrari AP Jr. Eradication of *Helicobacter pylori* infection in patients with duodenal ulcer and non-ulcer dyspepsia and analysis of one-year reinfection rates. Braz J Med Biol Res 2001;34:753-7.
2. Hildebrand P, Bardhan P, Rossi L, et al. Recrudescence and reinfection with *Helicobacter pylori* after eradication therapy in Bangladeshi adults. Gastroenterology 2001;121:792-8.
3. Jorgensen M, Daskalopoulos G, Warburton V, Mitchell HM, Hazell SL. Multiple strain colonization and metronidazole resistance in *Helicobacter pylori*-infected patients: identification from sequential and multiple biopsy specimens. J Infect Dis 1996;174:631-5.
4. Anderson RM, May RM, Lee PA, Anderson B. Infectious Diseases of Humans: Dynamics and Control. London: Oxford University Press, 1992:27-65.
5. Malaty HM, Kumagai T, Tanaka E, et al. Evidence from a nine-year birth cohort study in Japan of transmission pathways of *Helicobacter pylori* infection. J Clin Microbiol 2000;38:1971-3.
6. Haruma K, Okamoto S, Kawaguchi H, et al. Reduced incidence of *Helicobacter pylori* infection in young Japanese persons between the 1970s and the 1990s. J Clin Gastroenterol 1997;25:583-6.
7. Parsonnet J. The incidence of *Helicobacter pylori* infection. Aliment Pharmacol Ther 1995;9(Suppl 2):45-52.
8. Bell GD, Powell KU, Burridge SM, et al. Reinfection or recrudescence after apparently successful eradication of *Helicobacter pylori* infection: implications for treatment of patients with duodenal ulcer disease. Q J Med 1993;86:375-82.
9. Fraser AG, Schreuder V, Chua LE, Moore L. Follow up after successful eradication of *Helicobacter pylori*: symptoms and reinfection. J Gastroenterol Hepatol 1998;13:555-9.
10. Xia HX, Talley NJ, Keane CT, O'Morain CA. Recurrence of *Helicobacter pylori* infection after successful eradication: nature and possible causes. Dig Dis Sci 1997;42:1821-34.
11. Jeen YT, Lee SW, Kwon SI, et al. Differentiation between reinfection and recrudescence of *Helicobacter pylori* strains using PCR-based restriction fragment length polymorphism analysis. Yonsei Med J 2001;42:41-5.
12. Georgopoulos SD, Ladas SD, Karatapanis S, et al. Factors that may affect treatment outcome of triple *Helicobacter pylori* eradication therapy with omeprazole, amoxicillin, and clarithromycin. Dig Dis Sci 2000;45:63-7.
13. Broutet N, Marais A, Lamouliatte H, et al. cagA status and eradication treatment outcome of anti-*Helicobacter pylori* triple therapies in patients with nonulcer dyspepsia. J Clin Microbiol 2001;39:1319-22.
14. van der Hulst RW, Rauws EA, Koycu B, et al. *Helicobacter pylori* reinfection is virtually absent after successful eradication. J Infect Dis 1997;176:196-200.
15. Knippig C, Arand F, Leodolter A, et al. Prevalence of *H pylori*-infection in family members of *H pylori* positive and its influence on the reinfection rate after successful eradication therapy: a two-year follow-up. Z Gastroenterol 2002;40:383-7.
16. Gisbert JP, Arata IG, Boixeda D, et al. Role of partner's infection in reinfection after *Helicobacter pylori* eradication. Eur J Gastroenterol Hepatol 2002;14:865-71.
17. Rosenstock S, Jorgensen T, Andersen L, Bonnevie O. Seroconversion and seroreversion in IgG antibodies to *Helicobacter pylori*: a serology based prospective cohort study. J Epidemiol Community Health 2000;54:444-50.
18. Kuipers EJ, Pena AS, Van Kamp G, et al. Seroconversion for *Helicobacter pylori*. Lancet 1993;342:328-31.
19. Cullen DJE, Collins BJ, Christiansen KJ, et al. When is *Helicobacter pylori* infection acquired? Gut 1993;34:1681-2.
20. Sipponen P, Kosunen TU, Samloff IM, Heinonen OP, Siurala M. Rate of *Helicobacter pylori* acquisition among Finnish adults: a fifteen year follow-up. Scand J Gastroenterol 1996;31:229-32.
21. Parsonnet J, Blaser MJ, Perez-Perez GI, Hargrett-Bean N, Tauxe RV. Symptoms and risk factors of *Helicobacter pylori* infection in a cohort of epidemiologists. Gastroenterology 1992;102:41-6.
22. Veldhuyzen van Zanten SJO, Pollak PT, Best LM, Bezanson GS, Marrie T. Increasing prevalence of *Helicobacter pylori* infection with age: continuous risk of infection in adults rather than cohort effect. J Infect Dis 1994;169:434-7.
23. Kumagai T, Malaty HM, Graham DY, et al. Acquisition versus loss of *Helicobacter pylori* infection in Japan: results from an 8-year birth cohort study. J Infect Dis 1998;178:717-21.
24. Banatvala N, Kashiwagi S, Abdi Y, Hayashi J, Hardie JM, Feldman RA. *H pylori* seroconversion and seroreversion in an Okinawan cohort followed for 10 years. Am J Gastroenterol 1994;89:1300.
25. Biselli R, Fortini M, Matricardi PM, Stroffolini T, D'Amelio R. Incidence of *Helicobacter pylori* infection in a cohort of Italian military students. Infection 1999;27:187-91.
26. Kyriazanos I, Ilias I, Lazaris G, et al. A cohort study on *Helicobacter pylori* serology before and after induction in the Hellenic Navy. Mil Med 2001;166:411-5.
27. Ashorn M, Maki M, Hallstrom M, et al. *Helicobacter pylori* infection in Finnish children and adolescents. A serologic cross-sectional and follow-up study. Scand J Gastroenterol 1995;30:876-9.
28. Granstrom M, Tindberg Y, Blennow M. Seroepidemiology of *Helicobacter pylori* infection in a cohort of children monitored from 6 months to 11 years of age. J Clin Microbiol 1997;35:468-70.
29. Malaty HM, Graham DY, Wattigney WA, Srinivasan SR, Osato M, Berenson GS. Natural history of *Helicobacter pylori* infection in childhood: 12-year follow-up cohort study in a biracial community. Clin Infect Dis 1999;28:279-82.
30. Patel P, Mendall MA, Khulusi S, Northfield TC, Strachan DP. *Helicobacter pylori* infection in childhood: risk factors and effect on growth. BMJ 1994;309:1119-23.
31. Gold BD, Khanna B, Huang LM, Lee CY, Banatvala N. *Helicobacter pylori* acquisition in infancy after decline of maternal passive immunity. Pediatr Res 1997;41:641-6.
32. Glynn MK, Friedman CR, Gold BD, et al. Seroincidence of *Helicobacter pylori* infection in a cohort of rural Bolivian children: acquisition and analysis of possible risk factors. Clin Infect Dis 2002;35:1059-65.
33. Lindkvist P, Enquselassie F, Asrat D, Nilsson I, Muhe L, Giesecke J. *Helicobacter pylori* infection in Ethiopian children: a cohort study. Scand J Infect Dis 1999;31:475-80.
34. Abu-Mahfouz MZ, Prasad VM, Santogade P, Cutler AF. *Helicobacter pylori* recurrence after successful eradication: 5-year follow-up in the United States. Am J Gastroenterol 1997;92:2025-8.
35. Kato S, Abukawa D, Furuyama N, Iinuma K. *Helicobacter pylori* reinfection rates in children after eradication therapy. J Pediatr Gastroenterol Nutr 1998;27:543-6.
36. Bapat MR, Abraham P, Bhandarkar PV, Phadke AY, Joshi AS. Acquisition of *Helicobacter pylori* infection and reinfection after its eradication are uncommon in Indian adults. Indian J Gastroenterol 2000;19:172-4.
37. Rollan A, Giancaspero R, Fuster F, et al. The long-term reinfection rate and the course of duodenal ulcer disease after eradication of *Helicobacter pylori* in a developing country. Am J Gastroenterol 2000;95:50-6.
38. Seo M, Okada M, Shirotani T, et al. Recurrence of *Helicobacter pylori* infection and the long-term outcome of peptic ulcer after successful eradication in Japan. J Clin Gastroenterol 2002;34:129-34.
39. Rowland M, Kumar D, Daly L, O'Connor P, Vaughan D, Drumm B. Low rates of *Helicobacter pylori* reinfection in children. Gastroenterology 1999;117:336-41.
40. Gisbert JP, Pajares JM, Garcia-Valriberas R, et al. Recurrence of *Helicobacter pylori* infection after eradication: incidence and variables influencing it. Scand J Gastroenterol 1998;33:1144-51.
41. Archimandritis A, Balatsos V, Delis V, Manika Z, Skandalis N. "Reappearance" of *Helicobacter pylori* after eradication: implications on duodenal ulcer recurrence: a prospective 6 year study. J Clin Gastroenterol 1999;28:345-7.
42. Kim N, Lim SH, Lee KH, Jung HC, Song IS, Kim CY. *Helicobacter pylori* reinfection rate and duodenal ulcer recurrence in Korea. J Clin Gastroenterol 1998;27:321-6.
43. Adachi M, Mizuno M, Yokota K, et al. Reinfection rate following effective therapy against *Helicobacter pylori* infection in Japan. J Gastroenterol Hepatol 2002;17:27-31.
44. Mitchell HM, Hu P, Chi Y, Chen MH, Li YY, Hazell SL. A low rate of reinfection following effective therapy against *Helicobacter pylori* in a developing nation (China). Gastroenterology 1998;114:256-61.
45. Schutze K, Hentschel E, Dragosics B, Hirschl AM. *Helicobacter pylori* reinfection with identical organisms: transmission by the patients' spouses. Gut 1995;36:831-3.