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HELICOBACTER PYLORI AND THE BIRTH COHORT EFFECT: EVIDENCE FOR STABILIZED COLONIZATION RATES IN CHILDHOOD

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Abstract

Background—The prevalence of *Helicobacter pylori* has declined over recent decades in developed countries. The increasing prevalence with age is largely due to a birth-cohort effect. We previously observed a decline in *H. pylori* prevalence in 6- to 8-year old Dutch children from 19% in 1978 to 9% in 1993. Knowledge about birth-cohort-related *H. pylori* prevalence is relevant as a predictor for the future incidence of *H. pylori*-associated conditions.

Aim—The aim of this study was to investigate whether the birth-cohort effect of *H. pylori* observed between 1978 and 1993 continued in subsequent years.

Methods—Anti-*H. pylori* IgG antibodies and anti-CagA IgG antibodies were determined in serum samples obtained in 2005/2006 from 545 Dutch children aged 7–9 years who participated in the PIAMA birth cohort. The *H. pylori* and CagA antibodies were determined by ELISAs that have been extensively validated in children, with a 94% sensitivity for *Hp* colonization and a 92.5% sensitivity for colonization with a *cagA*-positive strain.

Results—Of the 545 children (M/F 300/245), most (91.5%) were of Dutch descent. The *H. pylori* positivity rate was 9% (95% CI 6.6–11.4%). The prevalence of CagA antibodies was 0.9% (95% CI 0.1–1.6%). No significant differences were demonstrated in *H. pylori* and *cagA* prevalence in relation to gender or ethnicity.

Conclusion—The prevalence of *H. pylori* in childhood has remained stable in the Netherlands from 1993 to 2005, suggesting a stabilization of the previously decreasing trend in subsequent birth cohorts. This finding may reflect stabilization in determinants such as family size, housing, and hygienic conditions (or offset by day care). If confirmed in other populations in developed countries, it implies that colonization with *H. pylori* will remain common in the coming decades. Remarkably however, the rate of colonization with *cagA*⁺ *H. pylori* strains has become very low, consistent with prior observations that *cagA*⁺ strains are disappearing in Western countries.

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CONFLICT OF INTEREST

Potential competing interests: None.

Keywords

Helicobacter pylori infection; epidemiology; *cagA*; birth cohort effect

INTRODUCTION

Helicobacter pylori resides in the gastric mucosa of a large proportion of the world's population, making it one of the most common bacteria that colonize humans.(1) *H. pylori* is a causative agent of peptic ulcer disease, gastric carcinoma, and mucosa-associated lymphoid tissue-lymphoma (1–3). Over the last decades, the prevalence of *H. pylori* has declined in subsequent birth cohorts in developed countries.(2, 4–6) This is attributed to improvement in socioeconomic standards and possibly antibiotic use. *H. pylori* is mostly acquired during early childhood and colonization generally persists for life in the absence of antibiotic therapy or development of atrophic gastritis (7–9). In industrialized countries the prevalence of *H. pylori* varies between 30% and 40% and increases with age. This observed increase of prevalence with age is largely due to a birth cohort effect, with decreasing colonization rates in subsequent generations. The comparison of prevalence data of cross-sectional adult cohorts at different periods in time demonstrated the existence of a birth cohort effect in the decades after the second World War.(10) This was confirmed by longitudinal cohort studies, showing low acquisition rates in adults.(7) In both 1978 and 1993, we previously determined the prevalence of *H. pylori* in children aged 6 to 8 years and 12 to 15 years old [7]. These data showed a decline in *H. pylori* prevalence in both age groups over the 15-year period from 1978 to 1993. The observed decline was 19 to 9% in 6 to 8 year old children, and 23% to 11% in 12 to 15 year old children.(6) We then predicted scenarios for future population prevalence of *H. pylori*, but it was unknown how the actual prevalence of *H. pylori* developed. This knowledge is relevant as the prevalence of *H. pylori* among children is a predictor for adult diseases, including peptic ulcer disease and gastric cancer.

We therefore performed a study to assess whether the observed decrease in *H. pylori* colonization of 7–9 year old children in the Netherlands continued since 1993.

METHODS

Study population

The study population consisted of Dutch children born in 1996/1997 who participated in the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) birth cohort study, which focuses on risk factors for development childhood asthma and has been described extensively.(11) For this study pregnant women were recruited from the general population in prenatal healthcare clinics and children were prospectively followed from birth. Between 2005 and 2006, blood samples were collected at a regular medical examination of 551 children in the PIAMA study.(12) All children at that time were age 7–9 years. Of the 551 children, there were 6 twins, which we excluded from the analysis. The study protocol was approved by the IRB of the participating institutions and all parents gave written informed consent.

Diagnosis of *H. pylori* carriage

After collection the blood samples were centrifuged and the serum was divided into smaller test tubes, and these tubes were stored at –80 C until use. *H. pylori* IgG antibodies were determined with an enzyme-linked immunosorbent assay (ELISA) that has been validated in children and has been used in previous studies(13). The antigen used in this assay consists of

a preparation of sonicated whole bacteria made from five different clinical *H. pylori* isolates. This ELISA has a sensitivity of 94% and specificity of more than 90% for the detection of *H. pylori*. For each serum sample, an optical density ratio (ODR) was calculated by dividing the optical density of the sample by the mean optical density of the cutoff controls. For each sample, all assays were performed at least in duplicate. Samples were considered negative for *H. pylori* if the ODR was 0–1 and positive for *H. pylori* if the ODR was > 1.0.

CagA ELISA

The ELISA to detect anti-CagA IgG was performed using a recombinant CagA antigen, as described (14). This ELISA has a sensitivity of 92.5% for the detection of a *cagA*-positive strain. The assays were performed on all samples irrespective of *H. pylori* seropositivity. For CagA antibodies, the ODR was calculated in a similar manner. As was the case for the *H. pylori* assay, all assays for CagA were performed in duplicate. Samples were considered negative for CagA if the ODR was 0–0.35 and positive for CagA if the ODR was > 0.35.

Statistical analyses

For continuous variables, mean and standard deviation were calculated. For categorical variables, percentages (with 95% confidence intervals) were provided. Categorical data analysis was conducted using the chi-square or Fisher exact test, performed with Statistical Package for the Social Sciences (SPSS) 15.0. Regression analysis (ANOVA) was performed to test consistency of test results over time and between laboratory operators. The level of significance was set at 0.05. All tests were two-tailed.

RESULTS

Five-hundred and forty-five children (age 7–9 years) were studied (Table 1). Most children (91.5%) were of Dutch descent, 2.5% were of non-Dutch Caucasian descent, 3% were of non-Caucasian descent and in 1.8% of the children data on ethnicity were missing. Seven percent of the children in this cohort had a mother with atopy. Overall, 49 (9%; 95% CI 6.6–11.4%) of 545 serum samples tested positive for IgG antibodies against *H. pylori*, and 5 (0.9%; 95% CI 0.1–1.6%) tested anti-CagA positive. Four of 5 sera with anti-CagA antibodies also tested positive for anti-*H. pylori* antibodies with the general ELISA, and one child tested positive for CagA and negative for *H. pylori* as has been reported previously (15).

No correlation could be demonstrated between *H. pylori* seropositivity and gender, 27 (54%) boys were *H. pylori* seropositive and 23 (46%) girls ($p=0.76$). Forty-five (8.9%) of the 504 children of Dutch descent tested positive compared to 4 (12.9%) of the 31 children of non-Dutch descent ($p=0.46$). Among the 4 *H. pylori*-positive children from non-Dutch descent, one was Caucasian and three were non-Caucasian, corresponding with *H. pylori* positivity rates of respectively 7.1% (1 of 14) and 17.6% (3 of 17). These differences were non-significant ($p=0.61$).

Birth cohort effect

In this study, we found a 9% overall prevalence of *H. pylori* antibodies. This prevalence is similar to the prevalence observed in 6–8 year old Dutch children in 1993 using the same serologic assay (Fig. 1). (10, 13) At that time, the prevalence of *H. pylori* serum antibodies had declined from 19% in 1978 (14 *H. pylori* positive children of 74) to 9% (7 *H. pylori* positive children of 80) in 1993 in Dutch children of Caucasian descent aged 6–8 years. Between 1978 and 1993, the prevalence of *H. pylori* thus decreased by 52% (95% CI 24–71%). The prevalence of 9% in 2005–2006 does not show a further continuation of this trend. Regression analysis (ANOVA) was performed to validate the *H. pylori* and CagA

tests by comparing current results to earlier test results in children. Overall the squared multiple correlation for the *H. pylori* test was high ($R^2 = 0.86$; $p = 0.007$), and for CagA the squared multiple correlation was average, explaining 50% of the variability in outcomes ($R^2 = 0.50$; $p = 0.12$).

DISCUSSION

Colonization with *H. pylori* is still common worldwide (16), even though a major decrease was observed in developed countries over recent decades. It was previously shown that most acquisition occurs in the first five years of life, with colonization status being relatively stable thereafter. As such, the prevalence of *H. pylori* above the age of 5 years may serve as a predictor for the future incidence of associated conditions, in particular peptic ulcer disease and gastric cancer. More recent research suggests that *H. pylori* may simultaneously decrease the risk for esophageal reflux and its sequelae (17), certain atopic conditions (18–19) and perhaps for metabolic conditions such as obesity (18, 20). For this reason, monitoring of the epidemiologic pattern of *H. pylori* prevalence is relevant both from clinical as well as public health perspectives. Prior studies reported a rapid decline in *H. pylori* prevalence in Western countries (16, 21).

In this study, we used an established ELISA test to detect serum antibodies against *H. pylori*, which has been extensively validated in children (13–14, 22–24). This ELISA has been in use since 1988 for the determination of *H. pylori* status in adults and children. We have been using this assay for many years and have previously validated it in Dutch children (6). *H. pylori* gives rise to a systemic and stable IgG antibody response (25), which only decreases after bacterial eradication by antibiotic treatment or by development of atrophic gastritis. In a previous study by our group, the same ELISA test was used to determine the prevalence of *H. pylori* in 6–8 year old Dutch children in 1978 and 1993 (10), showing a marked (52%) decrease in *H. pylori* prevalence between 1978 and 1993. At that time, two models were postulated to predict the future *H. pylori* prevalence. One described a continuous decrease of *H. pylori* among children and young adolescents, continuing the trend observed before 1993. In the second model, a stable *H. pylori* prevalence from 1993 onwards was assumed. Our current data support the second model, since *H. pylori* prevalence rates remained stable at 9% from 1993 to 2005–2006 in 7–9 year old children.

Another Dutch study reported an *H. pylori* prevalence of 1.2% in 1998 in 1258 2 to 4-year old children, using an in-house ELISA technique (2). A plausible reason for the lower *H. pylori* prevalence found in that study was the lower age of the children, as the *H. pylori* prevalence increases with age in early childhood. The ELISA used in that study also had not been validated in children (26–27). Our observation of stabilization of *H. pylori* prevalence in children in a western community needs further confirmation in other populations; however, the observation is plausible. The risk of *H. pylori* colonization in children is related to socio-economic circumstances, such as the number of family members per household, siblings sharing a bed, and bathing facilities (28–32), which changed substantially from the 1940's to the 1980's, in countries like the Netherlands, but have remained relatively stable thereafter. The average number of children per household in the Netherlands decreased from 3.1 in 1940 to 1.6 in 1993, to stabilize to 1.7 in 2005 (33). In contrast, the use of daycare for young children has increased from 6.1% 0–4 year olds before 1990 to 55% in 2005, and the proportion of the population represented by immigrant children with parents with higher *H. pylori* prevalence also has increased (34–37). The relatively small changes in socioeconomic circumstances since 1990 decreasing *H. pylori* acquisition may have been offset by the increased use of daycare and an increased proportion of immigrant children, stabilizing the prior decreasing *H. pylori* prevalence in Dutch children.

The overall *cagA* prevalence of 0.9% is much lower than found in earlier studies (22–23, 38). We previously observed *cagA*⁺ prevalence of 41% among 58 *H. pylori*-positive adults studied in 1992 (7, 22), but in our current study, CagA positivity in *H. pylori*-positive children was 8.2%. In a Finnish population, the proportion of *cagA*⁺ strains as a proportion of the total has declined over time with the overall decrease in *H. pylori* prevalence (38), suggesting that *cagA*⁺ *H. pylori* strains are disappearing faster than *cagA*[−] *H. pylori* strains. A possible explanation could be the increased intensity of antibiotic exposure during childhood (5, 39). Although antibiotic monotherapy has limited (20%–50%) success in eradicating *H. pylori*, the effect of repeated antibiotic regimens during childhood may be substantial (40–42). Evidence that *cagA*⁺ strains are more susceptible to eradication treatment (43), could then explain their more pronounced decline. On the basis of our data and prevalence rates over the last decades, we anticipate that *cagA*⁺ *H. pylori* strains will become rarer in the future and might ultimately disappear at some time point.

Our study was limited by the fact that only 7% of the children in this cohort had a mother with atopy, lower than the prevalence (10–33%) of atopy in Dutch females 20–40 years old (12, 44–45). Such underrepresentation could have led to overestimation of the prevalence of *H. pylori* in Dutch children, given the previously reported negative association between atopy and *H. pylori* (18).

The change in prevalence of *H. pylori* and *cagA*⁺ strains has implications for the incidence of *H. pylori*-associated disorders, including peptic ulcer disease and gastric cancer. Gastric carcinogenesis is complex and multi-factorial, but *H. pylori* colonization rates in childhood can probably predict the occurrence rates of premalignant lesions later in life and thus also gastric cancer rates in different birth cohorts. We previously showed a decline within successive birth cohorts in the incidence of pre-malignant gastric lesions in the Netherlands from 1991 to 2005 (46), presumably resulting from the decline in *H. pylori* prevalence, in particular *cagA*-positive *H. pylori* strains. If *H. pylori* colonization rates remain constant, this may lead to similar trends for *H. pylori*-induced ulcerogenesis and gastric cancer. However, continuing decrease in *cagA*⁺ strains may eventually lead to their total disappearance and related consequences. Nonetheless, this trend needs to be confirmed in other cohorts.

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REFERENCES

1. Bruce MG, Maaroos HI. Epidemiology of Helicobacter pylori infection. *Helicobacter*. 2008; 13 Suppl 1:1–16. [PubMed: 18783514]
2. Mourad-Baars PE, Verspaget HW, Mertens BJ, et al. Low prevalence of Helicobacter pylori infection in young children in the Netherlands. *Eur J Gastroenterol Hepatol*. 2007; 19:213–216. [PubMed: 17301647]
3. Kusters JG, van Vliet AH, Kuipers EJ. Pathogenesis of Helicobacter pylori infection. *Clin Microbiol Rev*. 2006; 19:449–490. [PubMed: 16847081]
4. Banatvala N, Mayo K, Megraud F, et al. The cohort effect and Helicobacter pylori. *J Infect Dis*. 1993; 168:219–221. [PubMed: 8515114]
5. Fawcett JP, Shaw JP, Brooke M, et al. Seroprevalence of Helicobacter pylori in a longitudinal study of New Zealanders at ages 11 and 21. *Aust N Z J Med*. 1998; 28:585–589. [PubMed: 9847945]
6. Roosendaal R, Kuipers EJ, Buitenvoort J, et al. Helicobacter pylori and the birth cohort effect: evidence of a continuous decrease of infection rates in childhood. *Am J Gastroenterol*. 1997; 92:1480–1482. [PubMed: 9317067]

7. Kuipers EJ, Pena AS, van Kamp G, et al. Seroconversion for *Helicobacter pylori*. *Lancet*. 1993; 342:328–331. [PubMed: 8101585]
8. Sipponen P, Helske T, Jarvinen P, et al. Fall in the prevalence of chronic gastritis over 15 years: analysis of outpatient series in Finland from 1977, 1985, and 1992. *Gut*. 1994; 35:1167–1171. [PubMed: 7959219]
9. Veldhuyzen van Zanten SJ, Pollak PT, Best LM, et al. Increasing prevalence of *Helicobacter pylori* infection with age: continuous risk of infection in adults rather than cohort effect. *J Infect Dis*. 1994; 169:434–437. [PubMed: 8106778]
10. Parsonnet J. The incidence of *Helicobacter pylori* infection. *Aliment Pharmacol Ther*. 1995; 9 Suppl 2:45–51. [PubMed: 8547528]
11. Brunekreef B, van Strien R, Pronk A, et al. La mano de DIOS...was the PIAMA intervention study intervened upon? *Allergy*. 2005; 60:1083–1086. [PubMed: 15969692]
12. Brunekreef B, Smit J, de Jongste J, et al. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol*. 2002; 13 Suppl 15:55–60. [PubMed: 12688626]
13. Perez-Perez GI, Dworkin BM, Chodos JE, et al. *Campylobacter pylori* antibodies in humans. *Ann Intern Med*. 1988; 109:11–17. [PubMed: 3288028]
14. Blaser MJ, Perez-Perez GI, Kleanthous H, et al. Infection with *Helicobacter pylori* strains possessing *cagA* is associated with an increased risk of developing adenocarcinoma of the stomach. *Cancer Res*. 1995; 55:2111–2115. [PubMed: 7743510]
15. Romero-Gallo J, Perez-Perez GI, Novick RP, et al. Responses of endoscopy patients in Ladakh, India, to *Helicobacter pylori* whole-cell and Cag A antigens. *Clin Diagn Lab Immunol*. 2002; 9:1313–1317. [PubMed: 12414766]
16. Parkin DM. The global health burden of infection-associated cancers in the year 2002. *Int J Cancer*. 2006; 118:3030–3044. [PubMed: 16404738]
17. Anderson LA, Murphy SJ, Johnston BT, et al. Relationship between *Helicobacter pylori* infection and gastric atrophy and the stages of the oesophageal inflammation, metaplasia, adenocarcinoma sequence: results from the FINBAR case-control study. *Gut*. 2008; 57:734–739. [PubMed: 18025067]
18. Chen Y, Blaser MJ. *Helicobacter pylori* colonization is inversely associated with childhood asthma. *J Infect Dis*. 2008; 198:553–560. [PubMed: 18598192]
19. Linneberg A, Ostergaard C, Tvede M, et al. IgG antibodies against microorganisms and atopic disease in Danish adults: the Copenhagen Allergy Study. *J Allergy Clin Immunol*. 2003; 111:847–853. [PubMed: 12704368]
20. Cho I, Blaser MJ, Francois F, et al. *Helicobacter pylori* and overweight status in the United States: data from the Third National Health and Nutrition Examination Survey. *Am J Epidemiol*. 2005; 162:579–584. [PubMed: 16093294]
21. Rothenbacher D, Brenner H. Burden of *Helicobacter pylori* and *H. pylori*-related diseases in developed countries: recent developments and future implications. *Microbes Infect*. 2003; 5:693–703. [PubMed: 12814770]
22. Kuipers EJ, Perez-Perez GI, Meuwissen SG, et al. *Helicobacter pylori* and atrophic gastritis: importance of the *cagA* status. *J Natl Cancer Inst*. 1995; 87:1777–1780. [PubMed: 7473834]
23. Perez-Perez GI, Bhat N, Gaensbauer J, et al. Country-specific constancy by age in *cagA*+ proportion of *Helicobacter pylori* infections. *Int J Cancer*. 1997; 72:453–456. [PubMed: 9247289]
24. Chodos JE, Dworkin BM, Smith F, et al. *Campylobacter pylori* and gastroduodenal disease: a prospective endoscopic study and comparison of diagnostic tests. *Am J Gastroenterol*. 1988; 83:1226–1230. [PubMed: 3055942]
25. Perez-Perez GI, Maw AM, Feingold-Link L, et al. Longitudinal analysis of serological responses of adults to *Helicobacter pylori* antigens. *J Infect Dis*. 2010; 202:916–923. [PubMed: 20698790]
26. Pena AS, Endtz HP, Offerhaus GJ, et al. Value of serology (ELISA and immunoblotting) for the diagnosis of *Campylobacter pylori* infection. *Digestion*. 1989; 44:131–141. [PubMed: 2628136]
27. Weyermann M, Rothenbacher D, Brenner H. Acquisition of *Helicobacter pylori* infection in early childhood: independent contributions of infected mothers, fathers, and siblings. *Am J Gastroenterol*. 2009; 104:182–189. [PubMed: 19098867]

28. Breuer T, Sudhop T, Hoch J, et al. Prevalence of and risk factors for *Helicobacter pylori* infection in the western part of Germany. *Eur J Gastroenterol Hepatol*. 1996; 8:47–52. [PubMed: 8900908]
29. Brown LM, Thomas TL, Ma JL, et al. *Helicobacter pylori* infection in rural China: demographic, lifestyle and environmental factors. *Int J Epidemiol*. 2002; 31:638–645. [PubMed: 12055167]
30. Nurgalieva ZZ, Malaty HM, Graham DY, et al. *Helicobacter pylori* infection in Kazakhstan: effect of water source and household hygiene. *Am J Trop Med Hyg*. 2002; 67:201–206. [PubMed: 12389948]
31. Rodrigues MN, Queiroz DM, Bezerra Filho JG, et al. Prevalence of *Helicobacter pylori* infection in children from an urban community in north-east Brazil and risk factors for infection. *Eur J Gastroenterol Hepatol*. 2004; 16:201–205. [PubMed: 15075995]
32. Gao L, Weck MN, Raum E, et al. Sibship size, *Helicobacter pylori* infection and chronic atrophic gastritis: a population-based study among 9444 older adults from Germany. *Int J Epidemiol*. 2010; 39:129–134. [PubMed: 19596750]
33. CBS. Livebirths per household in the Netherlands. 2010.
34. De Vries AC, Van Driel HF, Richardus JH, et al. Migrant communities constitute a possible target population for primary prevention of *Helicobacter pylori*-related complications in low incidence countries. *Scandinavian journal of gastroenterology*. 2008; 43:403–409. [PubMed: 18365904]
35. Sherman PM. Appropriate strategies for testing and treating *Helicobacter pylori* in children: when and how? *Am J Med*. 2004; 117 Suppl 5A:30S–35S. [PubMed: 15478850]
36. CPB. Daycare. CPB; 2009. Macro Economic Exploration 2009. 2009
37. E-Quality knowledge center for emancipation fad. Political programs on emancipation/Daycare. 1st: E-Quality. 2010
38. Perez-Perez GI, Salomaa A, Kosunen TU, et al. Evidence that *cagA*(+) *Helicobacter pylori* strains are disappearing more rapidly than *cagA*(–) strains. *Gut*. 2002; 50:295–298. [PubMed: 11839704]
39. McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. *JAMA*. 1995; 273:214–219. [PubMed: 7807660]
40. Blaser MJ. Hypothesis: the changing relationships of *Helicobacter pylori* and humans: implications for health and disease. *J Infect Dis*. 1999; 179:1523–1530. [PubMed: 10228075]
41. Peterson WL, Graham DY, Marshall B, et al. Clarithromycin as monotherapy for eradication of *Helicobacter pylori*: a randomized, double-blind trial. *Am J Gastroenterol*. 1993; 88:1860–1864. [PubMed: 8237933]
42. Rauws EA, Langenberg W, Houthoff HJ, et al. *Campylobacter pyloridis*-associated chronic active antral gastritis. A prospective study of its prevalence and the effects of antibacterial and antiulcer treatment. *Gastroenterology*. 1988; 94:33–40. [PubMed: 3335295]
43. van Doorn LJ, Quint W, Schneeberger P, et al. The only good *Helicobacter pylori* is a dead *Helicobacter pylori*. *Lancet*. 1997; 350:71–72. [PubMed: 9217744]
44. Eduard W, Omenaas E, Bakke PS, et al. Atopic and non-atopic asthma in a farming and a general population. *Am J Ind Med*. 2004; 46:396–399. [PubMed: 15376208]
45. van Pelt, ea. Atopy. *Dutch Journal Clinical Chemistry*. 2000; 25:14–19.
46. de Vries AC, Meijer GA, Looman CW, et al. Epidemiological trends of pre-malignant gastric lesions: a long-term nationwide study in the Netherlands. *Gut*. 2007; 56:1665–1670. [PubMed: 17698860]

Figure 1.
H. pylori prevalence rates in 6–8 yr old children in 1978, 1993 and 2005. Data for 1978 and 1993 from reference (6).

Table 1

Baseline characteristics of the study cohort.

	Overall cohort (n=545)	<i>H. pylori</i>-positive (n=49)
Boy/Girl	300/245 (55/45%)	27/23 (54/46%)
Mean age (SD)	7.9 years (0.62)	7.9 years (0.57)
Ethnicity	92% Dutch (n= 504)	92% Dutch (n=45)
	2.6% Non-dutch Caucasian (n= 14)	2% non-dutch Caucasian (n=1)
	3.1% Non-Caucasian (n=17)	6% non-Caucasian (n=3)
	2.3% unknown (n= 10)	