Intrafamilial transmission of Helicobacter pylori infection: a systematical case-control study on 142 families by means of serology and $^{13}$C-urea breath test

Inaugural-Dissertation

zur

Erlangung des Doktorgrades der Medizin
einer
Hohen Medizinischen Fakultät
der Ruhr-Universität Bochum

vorgelegt von
Isabelle Dyrek
aus Loben
( 1999 )
Dekan: Prof. Dr. med. U. Eysel
Referent: Prof. Dr. med. W. Opferkuch
Koreferent: Prof. Dr. med. H. Werchau
Tag der mündlichen Prüfung: 13.07.00
CONTENTS

INTRODUCTION ......................................................................................................................................................... 4
THE AIMS OF THIS STUDY ......................................................................................................................................... 6
METHODS AND PATIENTS ......................................................................................................................................... 7
   I. Epidemiologic part of this study .......................................................................................................................... 7
      1. Collection of data .................................................................................................................................................. 7
      2. Definition of the H. pylori infection state ........................................................................................................... 8
      3. Final study population ......................................................................................................................................... 9
      4. Serology ............................................................................................................................................................ 10
      5. 13 C-urea breath test ......................................................................................................................................... 11
      6. Statistical analysis ............................................................................................................................................. 11
   II. Histopathologic and molecular biologic aspects of this study ........................................................................ 12
      1. Endoscopy and histology ................................................................................................................................. 12
      2. Molecular typing of H. pylori strains .................................................................................................................. 13
RESULTS .................................................................................................................................................................. 15
   1. Characteristics of the study population ............................................................................................................... 15
   2. Intrafamilial spread of H. pylori infection ........................................................................................................ 18
   3. Communicability of H. pylori infection within families: transmission rates to the children ........................................... 26
   4. Childhood H. pylori infection in relation to family size ....................................................................................... 29
   5. Endoscopic and histologic findings ..................................................................................................................... 31
   6. Comparison of DNA fingerprints of H. pylori strains isolated from members of three families ........................................... 34
DISCUSSION ............................................................................................................................................................ 41
SUMMARY ............................................................................................................................................................... 48
REFERENCES ............................................................................................................................................................. 50
ACKNOWLEDGEMENTS .............................................................................................................................................. 62
LEBENSLAUF ............................................................................................................................................................ 63
INTRODUCTION

H.pylori is well established as the causative agent of chronic type B gastritis and an important pathogen in peptic ulcer disease (41). It is also a risk factor for the development of gastric adenocarcinoma (49) and MALT-lymphoma (6). The sources of human infection and the modes of transmission, however, have not been as yet clearly elucidated.

H.pylori infection affects most populations throughout the world, but prevalence rates and age distribution patterns show considerable geographic variations. In developing countries, about 80% of children are already infected by 10 yr of age (23, 25, 45, 59, 60). In Western societies, H.pylori is rare in childhood (8, 52, 57, 65), rises at 0.5-1% per year to reach about 50-60% among elderly people (17, 50,69). The rare occurrence of seroconversion in adults (5, 37, 48, 64) led to the hypothesis that most infections are acquired in childhood and adolescence, and that the increasing prevalence with age probably reflects an age cohort effect, i.e.a gradual decrease in childhood exposure to risk factors over successive birth cohorts. Human and primates have long been considered the only natural hosts of H.pylori. The isolation of this bacterium from a domestic cat (29) raised the possibility of animal-to-human transmission. The low level of seropositivity in cat owners argues, however, against zoonotic infections (2).

No reports exist on the isolation of H.pylori from food or commercial meat products. Waterborne spread through contaminated municipal water supply (36) and transmission through infected housefly excreta (27) or through consumption of raw vegetables (25,31) have been proposed as possible sources of widespread infection in developing countries. In Western populations, apart from ethnic and age-related factors, other important conditions associated with increased risk of contracting H.pylori infection include low socioeconomic level, domestic crowding, lack of running water and sharing of beds during childhood (18, 21, 42, 58, 72). Increased numbers of cases also occur in occupationally exposed endoscopists (39) and nurses (74), as well as in specific closed communities such as in orphanages (56, 70),
institutions for mentally retarded patients (38, 56) or in extremely overcrowded quarters of submarine crews (28). These epidemiological data, together with the repeated isolation of viable and infective bacteria from faecal material and saliva (19, 35, 63, 68) strongly support person-to-person transmission of H. pylori.

The well-known familial tendency of gastritis and ulcer disease led to the question of whether cross infections between family contacts may not be the key mode of transmission of H. pylori. However, most studies on this infection route have involved only a small number of families (3, 4, 12, 22, 59, 71) or have been case reports (14, 44, 46, 47, 53, 54, 16). Larger studies are rare (13, 34, 43, 62), and most of them have relied exclusively on serological evaluation of antibodies to H. pylori, which, however, have often proven to be inaccurate in identifying this infection in children (11, 55, 73). The reported observations in general support the intrafamilial spread of H. pylori, but some investigators reached contrary results (3, 16, 53, 59). In addition, common exogenous sources could not be excluded. As a result, the importance of this transmission route in the epidemiology of H. pylori infection and the infectivity of this organism within families have not been as yet clearly defined.

In order to clarify the potential of intrafamilial spread of this bacterium, we examined the H. pylori infection state by using serology and $^{13}$C-urea breath test in a sample of 142 families selected primarily on the basis of serologic screening in the children. The inclusion of a relatively large number of families with well-defined ethnic and sociodemographic backgrounds permitted - for the first time - to develop an understanding of the infectivity and communicability of this bacterium within families. In some instances, DNA sequences of H. pylori strains isolated from family members were compared in order to ascertain the epidemiologic observations.
THE AIMS OF THIS STUDY

1. The main purpose of this study was to examine the potential for intrafamilial spread of H. pylori infection and, in particular, to evaluate the roles of infected mothers and fathers as possible transmitters of this infection to the children.

2. The second objective of this study was to demonstrate the rate at which exposed children became infected with H. pylori and thus, together with other important factors of direct family environment known to influence the transmission (such as family size, social and ethnic background) to gain first insight into the infectivity and communicability of H. pylori infection within families.

3. Finally, as an understanding of epidemiology is fundamental for strategies directed at a disruption of further transmission, and the prevention of new infections, it was attempted to provide the basis for effective control programmes.
METHODS AND PATIENTS

I. Epidemiologic part of this study

1. Collection of data

The first step of this epidemiologic study was directed at finding cases of childhood H. pylori infection. For this purpose, between November 1994 and January 1997, serum samples obtained from a total of 382 consecutive children aged between 2 and 18 years (median age 8.5 years; 281 were German and 101 were immigrant children), who underwent venipuncture for different indications, were screened for IgG and IgA antibodies to H. pylori by enzyme-linked immunosorbent assay (ELISA). Parallel, demographic information such as age, gender, family size, occupation of the parents, nation, place of birth and duration of residence in Germany as well as clinical data (i.e., presence and frequency of symptoms referable to gastrointestinal tract and family history of ulcer disease, gastric malignancies or gastric surgery) were recorded for each child.

Raised titers of IgG and/or IgA antibodies to H. pylori were found in 25.5 % of the population screened: in 38 (13.5%) of the 281 German children and in 63 (62.4%) of the 101 immigrant children. It was hypothesized that all the children with positive serologic response to H. pylori presumably had had contact with this bacterium, and were either actively infected at the time of this study or had been infected previously. Therefore, whenever a seropositive child was identified, his or her parents, and siblings over the age of 2 years were included in the study. Of the 101 families in whom a seropositive index child was identified, 77 (76.2%) gave their consent and entered into the study. This group comprised all 38 (100%) German families (i.e., 37 mothers, 33 fathers and 32 siblings) and 39 (61.9%) of the 63 immigrant families (i.e., 39 mothers, 36 fathers and 77 siblings). The seropositive index children ranged in age from 3 to 18 years, with a median age of 8.7 years (Germans) and 7.9 years (immigrants).
Families of those seronegative index children whose parents (mainly the fathers) were industrial laborers and/or reported a family history of ulcer disease constituted the control pool. This determination was made as a higher incidence of H. pylori infection among families of lower socioeconomic status or with clinical risk factors contributing to H. pylori infection was to be expected, and because the subjects in the control group were expected to have the same potential to develop the disease as the case subjects. Of the 243 German families with seronegative index children, 160 (65.8%) met the inclusion criteria and 45 (28.1%) of them (i.e., 43 mothers, 34 fathers and 22 siblings) agreed to enter into the study. In the immigrant population, 29 (76.3%) of the 38 control families could be enrolled (i.e., 29 mothers, 26 fathers and 39 siblings). The median age of the seronegative control children was comparable to that of the index children (Germans: 8.0 years, range 3-18 and immigrants: 7.1 years, range 4-15). All of the participating parents and siblings provided a blood sample for the evaluation of IgG and IgA antibodies to H. pylori. In order to identify patients with current bacterial colonisation of gastric mucosa, the serological results were subsequently validated in all participants by using the $^{13}$C-urea breath test.

2. Definition of the H. pylori infection state

In this study, a patient was considered to be actually infected with H. pylori if the result of the $^{13}$C-urea breath test was positive and, concurrently, circulating antibodies to H. pylori were detectable in serum. Seropositive subjects who showed a negative result in the $^{13}$C-urea breath test were reclassified as currently non-infected. In case of negative serology but positive result of the $^{13}$C-urea breath test, the patient was excluded from the study in order to avoid misclassification into the H. pylori positive group.

On the basis of this definition, 26 (33.8%) of the 77 seropositive index children were reclassified as currently not infected on account of the negative result of the $^{13}$C-urea breath test. By contrast, 9 (12.2%) of the 74 children who entered into this study as seronegative
control children showed a positive result in the $^{13}$C-urea breath test and were excluded from the study. Among the family members of the seropositive index children, negative $^{13}$C-urea breath test results were observed in 10 (13.2%) of 76 seropositive siblings and in 17 (12.3%) of 138 seropositive parents. Contrarily, 8 (24.2%) of their 33 serologically negative siblings showed a positive result in the $^{13}$C-urea breath test (such a discrepancy was not observed among their parents). In seronegative control families, 6 (23.1%) of 26 seropositive siblings as well as 14 (17.1%) of 82 seropositive parents were breath test negative, and 5 (14.3%) of 35 seronegative siblings as well as 3 (6%) of 50 seronegative parents were breath test positive. According to the definition, all these family contacts were also either reclassified as currently not infected with H pylori or were excluded from the study. If the H pylori infection state could not be defined in at least one child or in at least one parent, the whole family was excluded (a total of 5 German and 4 immigrant families).

3. Final study population

Ultimately, 78 German and 64 immigrant families were included in the analysis. The study group of German families comprised 141 parents, including 76 mothers and 65 fathers. There were 63 couples, 13 single mothers and 2 single fathers (i.e., 9 of them were single-parent, mother-headed families and in 6 cases only one parent agreed to participation). The age of the parents ranged from 24 to 60 years, with a median age of 38 years. The H pylori infection state was also determined in 128 (92.1%) of their 139 children over the age of 2 years. Their ages ranged from 3 to 20 years, with a median age of 8.2 years. A discrepancy between serology and $^{13}$C-urea breath test was observed in 23 (16.3%) of the 141 parents and in 28 (21.9%) of the 128 children.

The group of 64 immigrant families comprised 122 parents, including all 64 mothers and 58 fathers (3 fathers declined participation, one was excluded according to the definition and in 2 families the father was not present). The age of the parents ranged from 20 to 55 years, with a
median age of 35 years. The H. pylori infection state was also determined in 169 (92.3%) of their 183 children over the age of 2 years (median age 8.5 years, range 3-20). Deviating results of the two diagnostic tests were observed in 8 (6.6%) of the 122 parents and in 14 (8.3%) of the 169 children.

4. Serology

Serum samples were tested for antibodies to H. pylori at The Bioscientia Institute for Laboratory Medicine Ingelheim GmbH (Prof. Dr. med. B. Heicke). Antibodies to H. pylori were measured separately for IgG and IgA by an enzyme-linked immunosorbent assay (ELISA-IgG/-IgA kit, Hycor Biomedical). For the test assay, serum samples (100 µl) diluted in phosphate-buffered saline solution (PBS) 1:100 were incubated with H. pylori antigen-coated microtiter plates. After incubation for 60 minutes at room temperature, the unbound antibodies were washed from the wells three times with BPS containing 0.1% Tween 20, and then 100 µl peroxidase-conjugated anti-human IgG (or -IgA) were added. After incubation for 30 minutes at room temperature, and after repeated washing, 100 µl tetramethylbenzidine (TMB) were added. The reaction was incubated for further 15 minutes at room temperature in the dark. The enzyme conjugate reacted with the substrate, resulting in a color development. The reaction was stopped with 100 µl sulphuric acid (1M H₂SO₄), and the absorbance was read at 450 nm. All assays were performed in duplicate with negative, weakly positive and strongly positive control sera. The test was scored positive for optical density (OD) > 0.20. This assay was validated by comparison with microscopic detection of H. pylori (by Giemsa staining), urease activity in biopsy specimens (CLO-test) and histological findings in a group of 104 adult patients, giving a sensitivity of 92-98% and specificity of 66-96% (according to the report of the laboratory).
5. \(^{13}\)C-urea breath test

After an overnight fast, the weights of the children and their parents were measured and a breath sample was collected for baseline \(^{13}\)CO\(_2\). The participants then received 75 mg of \(^{13}\)C-urea dissolved in 200 ml of non-carbonated mineral water with 5 mg citric acid. A second breath sample was collected 22 minutes after the administration of the substrate. The breath samples were sent in evacuated tubes to the laboratory of the gastroenterological practice in Frankfurt (Dr.H.Bock and Dr.A.Mares), where the \(^{13}\)C concentration of respiratory CO\(_2\) was measured by mass spectrometry. Subjects with enrichment of \(^{13}\)CO\(_2\) in expired breath of 0.25 or more delta units, relative to the excess over baseline (expressed as parts of thousand), were diagnosed as currently infected with H.pylori. In subjects who had previously received antibiotics, the \(^{13}\)C-urea breath testing was performed at the earliest 6 weeks after the antibacterial treatment in order to avoid false negative results due to an intermittent suppression of this organism.

6. Statistical analysis

The statistical evaluation of the data was performed by Dr. S. Lange (Department of Medical Informatics, Biometry and Epidemiology, Ruhr-University Bochum). Families, rather than children, were chosen as units of analysis, because children of the same family are not independent entities. The presence of at least one H.pylori positive child in a family was defined as a binary (yes/no) outcome variable. Apart from a descriptive presentation, logistic regression analysis was used for a simultaneous investigation of explanatory variables.

In logistic regression, the logarithm of the odds is modelled by the regression equation. The odds are the ratio of the probability that an event occurs (p), and of the probability that no event occurs (1-p)(odds = 1/1-p). For example, if the probability of a family with at least one H.pylori positive child is given as 0.2, the odds for a family with at least one infected child
amount to a quarter \((0.2/1-0.2 = 1/4)\). A logistic regression equation is formally given as follows:

\[
\ln \left( \frac{p}{1-p} \right) = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_k x_k ,
\]

where \(x\) denotes the explanatory (predictor) variables and the \(\beta\) denotes the corresponding regression coefficients. The exponential of the coefficients of a logistic regression can be interpreted as odds ratio for the corresponding variable (with the exception of the intercept \(\beta_0\)).

The \(H.pylori\) infection state in the mother, the \(H.pylori\) infection state in the father, the immigrant state and the presence of two or more children in a family were included as explanatory variables in a first model. In a second regression model, the \(H.pylori\) infection state in both the mother and the father was investigated together with the immigrant state and the presence of at least two children in a family. The analyses were also performed separately for the immigrant and German families (hence excluding the immigrant state as an explanatory variable).

**II. Histopathologic and molecular biologic aspects of this study**

1. **Endoscopy and histology**

In order to visualize the extent of gastric mucosal damage, 15 parents and 15 children (8 family groups plus 5 unrelated subjects) in whom serology and the \(^{13}\text{C}\)-urea breath test had yielded positive results were simultaneously examined by upper gastrointestinal endoscopy (Dr.H.Bock and Dr.A.Mares, gastroenterologists, Frankfurt/Main). During endoscopy, one or two biopsy specimens were obtained from gastric antrum and corpus for histologic examination (Prof.Dr.T.Kirchner, Institute of Pathology, University Hospital, Erlangen, or Prof.Dr.H.P. Lange, Institute of Pathology, St.Marcus Hospital, Frankfurt/Main). The presence of gastritis was assessed according to the criteria of The Sydney System (51). The
following parameters were graded on a scale from 0-3: the activity of gastritis (the amount of neutrophilic infiltration), the degree of gastritis (the density of plasmacellular and lymphocytic infiltration), the presence of mucosal atrophy, and the presence of intestinal metaplasia (0 = none, 1 = mild, 2 = moderate and 3 = severe). Mucosal erosions of gastric epithelium were also noted if present. The identification of H. pylori was made on the basis of haematoxylin-eosin or Warthin-Starry silver staining.

2. Molecular typing of H. pylori strains

In 4 children and 6 parents (3 family groups), one additional antral biopsy specimen was taken and immediately sent to the microbiology laboratory for molecular typing of the H. pylori strains (PD Dr. S. Suerbaum, Department of Medical Microbiology and Immunology, Ruhr University, Bochum). Molecular typing was performed by partial nucleotide sequencing of the flaB flagellin gene using a method developed by Suerbaum et al (66). A 531 bp fragment of the flaB gene was amplified by polymerase chain reaction using the oligonucleotide primers OLHPflaB-9 (AAG.GCA.TGC.TCG.CTA.GCG, positions 682-699 of the flaB gene sequence as described by Suerbaum et al (66)) and OLHPflaB-10 (TAA.TGT.CTC.TAG.CGT.CGG, reverse-complement of positions 1195-1212 of the sequence). As a DNA template, genomic DNA was used that was purified from the strains to be analyzed by the QiaAmp kit (Qiagen, Hilden, Germany). The conditions for the PCR reactions were as follows: denaturation for 30 sec at 94°C, annealing at 48°C for 1 min, and extension at 72°C for 1 min. A total of 35 cycles was performed. Subsequently, the PCR product was purified using the QiaQuick kit (Qiagen, Hilden, Germany), and used for non-radioactive PCR cycle sequencing with the ABI Prism Ready kit (Perkin Elmer-Applied Biosystems). 300-500 µg of the double-stranded template were used. Sequencing was performed with the primer OLHPflaB-10. Cycling conditions were as follows: denaturation for 10 sec at 96°C, annealing for 5 sec at 50°C and extension for 4 min at 60°C. 25 cycles
were performed. For the analysis, a stretch of 339 nucleotides that could be read without ambiguities for all strains was used. Strains were only considered identical if all 339 nucleotides were identical.

This study was performed at a suburban pediatric practice. Families participating in the study came from the population of the highly industrialized region southwest of Frankfurt/Main with a known high proportion of immigrants. The majority of the parents examined were industrial laborers. The participants were informed about the aims of the study and about every diagnostic procedure. Before examination, the parents gave informed consent.
RESULTS

1. Characteristics of the study population

During the period of this study, H. pylori infection state was determined both serologically and by means of $^{13}$C - urea breath test in a sample of 142 families selected primarily on the basis of serological screening in children. Table 1 presents the prevalence rates of this infection in index and in control families. Overall, the prevalence of H. pylori infection was significantly higher among the children from immigrant families (69.2%, median age 8.5 years, range 3 - 20) than in German children of comparable age (15.6%, median age 8.2 years, range 3 - 20), and it was associated with an overall higher background rate of this infection in their parents (88.5%; 108 / 122, median age 36 years, range 20-55) as compared to that found in the parents of German children (50.4%; 71 / 141, median age 38 years, range 24 - 60). In both the children and the parents, the prevalence of H. pylori infection was higher in index families than in control families. There were no sex differences in the prevalence rates, neither in the pediatric nor in the adult group studied. The social and demographic characteristics of the population studied are shown in Table 2. The social class distribution of the families, determined according to the profession of the parents (mainly of the fathers), was broadly similar in both study groups: in 57 (73.1%) German families as well as in 52 (81.3%) immigrant families the parents were industrial laborers. The family structure among immigrants differed, however, in an important way from that of the German population: 19 (29.7%) immigrant families comprised four or more children (up to eight), 20 (31.3%) comprised 3 children and the proportion of households with two or fewer children was only 37.5% and 1.6%, respectively. By contrast, the majority of the German families studied included one (29.5%) or two children (48.7%), 17 families had 3 children (21.8%) and there was not a single family with more than three children. The inhomogenous population of immigrants included two well defined ethnic groups of 26 Turkish and 18 Moroccan families.
Table 1. Prevalence of H. pylori infection (as determined by both positive serology and positive $^{13}$C-urea breath test result) in the study population

<table>
<thead>
<tr>
<th></th>
<th>GERMAN GROUP</th>
<th>IMMIGRANT GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total families</strong></td>
<td>78</td>
<td>64</td>
</tr>
<tr>
<td>- of seropositive index children</td>
<td>38</td>
<td>39</td>
</tr>
<tr>
<td>- of seronegative control children</td>
<td>40</td>
<td>25</td>
</tr>
<tr>
<td><strong>Mothers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of infected / Total mothers ( % )</td>
<td>37 / 76 (48.7)</td>
<td>57 / 64 (89.1)</td>
</tr>
<tr>
<td>- in index families</td>
<td>27 / 37 (73.0)</td>
<td>38 / 39 (97.4)</td>
</tr>
<tr>
<td>- in control families</td>
<td>10 / 39 (25.6)</td>
<td>19 / 25 (76.0)</td>
</tr>
<tr>
<td><strong>Fathers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of infected / Total fathers ( % )</td>
<td>34 / 65 (52.3)</td>
<td>51 / 58 (87.9)</td>
</tr>
<tr>
<td>- in index families</td>
<td>23 / 33 (69.7)</td>
<td>33 / 36 (91.7)</td>
</tr>
<tr>
<td>- in control families</td>
<td>11 / 32 (34.4)</td>
<td>18 / 22 (81.8)</td>
</tr>
<tr>
<td><strong>Children</strong> *</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of infected / Total children ( % )</td>
<td>20 / 128 (15.6)</td>
<td>117 / 169 (69.2)</td>
</tr>
<tr>
<td>- in index families</td>
<td>20 / 69 (29.0)</td>
<td>97 / 109 (89.0)</td>
</tr>
<tr>
<td>- in control families</td>
<td>0 / 59 (0)</td>
<td>20 / 60 (33.3)</td>
</tr>
<tr>
<td>- girls</td>
<td>9 / 61 (14.8)</td>
<td>57 / 82 (69.5)</td>
</tr>
<tr>
<td>- boys</td>
<td>11 / 67 (16.4)</td>
<td>60 / 87 (69.0)</td>
</tr>
<tr>
<td><strong>Median age in years ( range )</strong></td>
<td>38 (24 - 60)</td>
<td>36 (20 - 55)</td>
</tr>
<tr>
<td>- parents</td>
<td>8.2 (3 - 20)</td>
<td>8.5 (3 - 20)</td>
</tr>
</tbody>
</table>

* index children their siblings
Table 2. Sociodemographic characteristics of the study population.

<table>
<thead>
<tr>
<th></th>
<th>GERMAN GROUP</th>
<th>IMMIGRANT GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. ( % ) of families with manual occupations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>57 ( 73.1 )</td>
<td>52 ( 81.3 )</td>
</tr>
<tr>
<td><strong>Family size - no. ( % ) of families</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- with 1 child</td>
<td>23 ( 29.5 )</td>
<td>1 ( 1.6 )</td>
</tr>
<tr>
<td>- with 2 children</td>
<td>38 ( 48.7 )</td>
<td>24 ( 37.5 )</td>
</tr>
<tr>
<td>- with 3 children</td>
<td>17 ( 21.8 )</td>
<td>20 ( 31.3 )</td>
</tr>
<tr>
<td>- with 4 to 8 children</td>
<td>19 ( 29.7 )</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity - no. of families</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Turkish</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>- Morrocan</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>- Others *</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td><strong>Place of birth - no. ( % ) of children</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- born in Germany</td>
<td>106 ( 62.7 )</td>
<td></td>
</tr>
<tr>
<td>- born in countries of origin</td>
<td>63 ( 37.3 )</td>
<td></td>
</tr>
</tbody>
</table>

* includes 8 Pakistani, 4 Greek, 3 Albanian, 3 Bosnian and 2 Afghan families
The remaining group of 20 immigrant families consisted of 8 Pakistani, 4 Greek, 2 Afghan, 3 Bosnian, and 3 Albanian families. 63 (37.3 %) of the immigrant children were born in their countries of origin, and 106  (62.7%) were born in Germany. A family history of ulcer disease or gastritis diagnosed endoscopically in first or second degree relatives was present in 16 (20.5%) German families and in 14  (21.9% ) immigrant families.

2. Intrafamilial spread of H.pylori infection

In order to investigate the potential of intrafamilial spread of H.pylori infection, all families participating in this study were classified into four groups according to the H.pylori infection state in the parents: group I included families with both parents infected (Germans n = 21 and immigrants n = 46), group II comprised families with only H.pylori positive mothers (Germans n = 10 and immigrants n = 5), group III consisted of those families in whom the father was infected only (Germans n = 12 and immigrants n = 5) and group IV comprised the families in whom both the mother and the father were H.pylori negative (Germans n = 20 and immigrants n = 2). 15 German and 6 immigrant families could not be classified in any of these groups because of missing data on the H.pylori infection state in either the father or the mother.

The distribution patterns of this infection among the parents, together with the corresponding infection rates in their children are presented in Table 3. The most important finding was that all of the 20 German children as well as all of the 117 children of immigrants, identified as being actually infected with H.pylori, descended from families with at least one infected parent. In contrast to this, no evidence of bacterial colonisation was found in any of the children of whom both parents were H.pylori negative, neither in the German group (children n = 31) nor in the population of immigrants (children n = 5). This indicates strong intrafamilial transmission of the bacterium. In the German study group, at least one childhood infection was found in 9 (42.9%) out of the 21 families in whom the mothers as well the
Table 3. Distribution patterns of H. pylori infection among the parents together with the corresponding infection rates in their children

<table>
<thead>
<tr>
<th>Family group</th>
<th>GERMAN STUDY GROUP</th>
<th>IMMIGRANT STUDY GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) of families with at least one infected child / Total families</td>
<td>No. (%) of infected children / Total children</td>
</tr>
<tr>
<td><strong>Group I</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother + Father +</td>
<td>9 / 21 (42.9)</td>
<td>11 / 36 (30.6)</td>
</tr>
<tr>
<td><strong>Group II</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother + Father -</td>
<td>3 / 10 (30)</td>
<td>5 / 17 (29.4)</td>
</tr>
<tr>
<td><strong>Group III</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother – Father –</td>
<td>1 / 12 (8.3)</td>
<td>1 / 21 (4.8)</td>
</tr>
<tr>
<td><strong>Group IV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother – Father -</td>
<td>0 / 20 (0)</td>
<td>0 / 31 (0)</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother or Father +</td>
<td>2* / 7 (28.6)</td>
<td>3* / 12 (25)</td>
</tr>
<tr>
<td>Mother or Father -</td>
<td>0 / 8 (0)</td>
<td>0 / 8 (0)</td>
</tr>
</tbody>
</table>

** denotes infected / not infected with H. pylori
** includes families with unknown H. pylori infection state in the other parent

* the 3 and the 9 cases of childhood infection (2 German and 6 immigrant families, respectively) implicate exposure to an infected mother.
fathers were infected (in 11 [30.6%] of 36 children) and, similarly, in 3 (30%) out of the 10 families with only H.pylori positive mothers (in 5 [29.4%] of 17 children). By contrast, at least one H.pylori positive child was present in only one out of the 12 families (8.3%) with solely infected fathers (in 1 [4.8%] of 21 children). Analogous trends were observed in the population of immigrants; the proportion of families with at least one H.pylori positive child was higher in the two groups comprising infected mothers (group I: 78.3%; 36/46 and group II: 80%; 4/5) than among families with solely infected fathers (group III: 40%; 2/5). The corresponding infection rates among the children from families in groups I-III were 75.4% (95/126), 62.5% (10/16) and 30% (3/10), respectively.

In order to avoid bias introduced by the occurrence of simultaneous infections among siblings, statistical differences among the above-mentioned family groups were evaluated in the categories defined by presence or absence of at least one H.pylori positive child in a family. The results of logistic regression analysis are presented in Table 4. It measured the effect of H.pylori infection state in the parents in terms of the risk of childhood disease, while taking the higher risk for immigrant children into account, as well as the rising probability of finding an infected child as the number of children living in a family increases. On account of the criterion, by which the outcome variable was defined, age could not be included into this regression model. However, as can be seen in Table 3, the median ages of the children did not vary substantially between the different family groups. The analysis performed for the whole study population revealed strong, and statistically significant association between childhood infection and exposure to an infected mother. For children exposed solely to infected mothers the risk of acquiring H.pylori was not much lower than that estimated for children of whom both parents were infected (OR=0.68, N.S.), whereas children exposed solely to infected fathers were significantly less likely to have this infection than were the children in group I (OR=0.15, 95% CI= 0.03 - 0.6, P= 0.01). A separate consideration of the two study groups,
Table 4. Effect of H. pylori infection state in the parents† on the risk of childhood infection (defined as presence of at least one H. pylori positive child in a family)

<table>
<thead>
<tr>
<th>Family group</th>
<th>Adjusted ‡ odds ratio</th>
<th>95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total study population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group II: Mother + Father –</td>
<td>0.68</td>
<td>0.2 - 2.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Group III: Mother - Father +</td>
<td>0.15</td>
<td>0.03 - 0.6</td>
<td>0.01</td>
</tr>
<tr>
<td>Families with &gt; 2 children</td>
<td>2.3</td>
<td>0.9 - 6.1</td>
<td>0.1</td>
</tr>
<tr>
<td>(vs. families with &lt; 2 children)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immigrant families</td>
<td>5.2</td>
<td>2.0 - 13.7</td>
<td>0.001</td>
</tr>
<tr>
<td>(vs. German families)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>German study group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group II: Mother + Father –</td>
<td>0.47</td>
<td>0.09 - 2.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Group III: Mother - Father +</td>
<td>0.12</td>
<td>0.01 - 1.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Families with 2 children</td>
<td>4.3</td>
<td>0.7 - 25.6</td>
<td>0.1</td>
</tr>
<tr>
<td>(vs. families with 1 child)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Families with 3 children</td>
<td>3.3</td>
<td>0.4 - 28.4</td>
<td>0.3</td>
</tr>
<tr>
<td>(vs. families with 1 child)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immigrant study population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group II: Mother + Father –</td>
<td>0.69</td>
<td>0.05 - 8.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Group III: Mother - Father +</td>
<td>0.26</td>
<td>0.03 - 2.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Families with 3 children</td>
<td>3.0</td>
<td>0.6 - 14.4</td>
<td>0.2</td>
</tr>
<tr>
<td>(vs. families with &lt; 2 children*)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Families with &gt; 3 children</td>
<td>9.5</td>
<td>1.0 - 89.0</td>
<td>0.05</td>
</tr>
<tr>
<td>(vs. families with &lt; 2 children*)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

† estimated by comparison with group I (both parents infected). Families in whom both the mother and the father were H. pylori negative were excluded from the analysis.
‡ adjusted by logistic regression analysis for mutual effects of all family groups listed in the table.
* includes the only one immigrant family with not more than 1 child.
however, showed that the profound effect of infection in the mother on the risk of childhood disease was largely confined to the German study group. In this population, the odds ratio of H.pylori infection for children exposed solely to infected fathers remained nearly unchanged (OR = 0.12), and only the p-value and the confidence interval fell slightly below the significance levels (P = 0.06, 95% CI = 0.01-1.1). Furthermore, consistent with the results obtained in the total study population, the risk of acquiring H.pylori infection in childhood was similar in the two groups of families comprising infected mothers (OR = 0.47, P = 0.4, 95% CI = 0.09-2.5). In the immigrant population, the number of families in groups II and III was too small (n = 5 in each case) to allow for an accurate statistical verification. In comparison with the effect estimated for group II (OR = 0.69), the effect of exposure solely to infected fathers pointed in the opposite direction (OR = 0.26). However, the differences were statistically not significant.

The strength of the correlation between childhood infection and exposure to H.pylori positive mothers in the German study group could also be confirmed in a second analysis, in which the risk of at least one childhood disease in a family was examined in relation to presence versus absence of H.pylori infection in the mother or in the father. This analysis was performed only for those families for whom data on H.pylori infection state were available from both parents. The distribution patterns of childhood infection among infected and non-infected parents are presented in Table 5. The corresponding odds ratios for exposure to an infected mother and for exposure to an infected father (both adjusted for immigrant state, for the number of children per family, and mutually adjusted) are presented in Table 6. In the German study group, at least one infected child was found in 12 out of 31 families comprising H.pylori positive mothers (38.7%), as compared to only 1 out of 32 families in whom the mothers were not infected (3.1%). After adjustment for the above-mentioned effects, the results of logistic regression analysis yielded that exposure to H.pylori positive mothers increased the risk of childhood infection 19.5 times, as compared to absence of infection in the mother (95%
<table>
<thead>
<tr>
<th>H. pylori infection state in the mother</th>
<th>GERMAN STUDY GROUP</th>
<th>IMMIGRANT STUDY GROUP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (%) of families with at least one infected child / Total families</td>
<td>No. (%) of infected children / Total children</td>
<td>Median age (range) in years</td>
</tr>
<tr>
<td>Mother +</td>
<td>12 / 31 (38.7)</td>
<td>16 / 53 (30.2)</td>
</tr>
<tr>
<td>Mother -</td>
<td>1 / 32 (3.1)</td>
<td>1 / 52 (1.9)</td>
</tr>
<tr>
<td>H. pylori infection state in the father</td>
<td>No. (%) of families with at least one infected child / Total families</td>
<td>No. (%) of infected children / Total children</td>
</tr>
<tr>
<td>Father +</td>
<td>10 / 33 (30.3)</td>
<td>12 / 57 (21.1)</td>
</tr>
<tr>
<td>Father -</td>
<td>3 / 30 (10.0)</td>
<td>5 / 48 (10.4)</td>
</tr>
</tbody>
</table>

+ / - Denotes infected / not infected with H. pylori
Table 6. Effect of H.pylori infection in the mother or in the father on the risk of childhood infection *

<table>
<thead>
<tr>
<th>Family group</th>
<th>Adjusted ‡ odds ration</th>
<th>95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total study population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother + (vs. Mother -)</td>
<td>12.3</td>
<td>3.1 - 48.7</td>
<td>0.0003</td>
</tr>
<tr>
<td>Father + (vs. Father -)</td>
<td>2.6</td>
<td>0.7 - 8.8</td>
<td>0.1</td>
</tr>
<tr>
<td><strong>German study population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother + (vs. Mother -)</td>
<td>19.5</td>
<td>2.1 - 179.8</td>
<td>0.009</td>
</tr>
<tr>
<td>Father + (vs. Father -)</td>
<td>3.3</td>
<td>7.1 - 17.0</td>
<td>0.2</td>
</tr>
<tr>
<td><strong>Immigrant study population</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother + (vs. Mother -)</td>
<td>4.8</td>
<td>0.7 - 34.3</td>
<td>0.1</td>
</tr>
<tr>
<td>Father + (vs. Father -)</td>
<td>2.5</td>
<td>0.3 - 19.3</td>
<td>0.4</td>
</tr>
</tbody>
</table>

* Families for whom data on H.pylori infection state were not available from both parents have been excluded from this regression model
† mutually adjusted and adjusted for the number of children living in a family
CI=2.1-179.8, \( P [0.01] \). In contrast to this, infection state in the father did not significantly influence the risk of childhood disease (30.3%, i.e.10 of 33 families with H. pylori positive fathers contained at least one infected child versus 10.0%, i.e.3 of 30 families with H. pylori negative fathers; OR= 3.3, N.S.). In the immigrant study population, the odds ratio of childhood infection for exposure to H. pylori positive mothers was only moderately higher (OR=4.8) than that evaluated for infection in the father (OR=2.5), and the differences were statistically not significant. However, on account of the low number of non-infected mothers and fathers among immigrants (n=7 in each case), no conclusions can be drawn.

Inclusion of the 7 German and 15 immigrant children who were serologically negative for H. pylori but positive for this bacterium on the \(^{13}\)C-urea breath test, would not change any of the results obtained since all these children came from families including an infected mother. Similarly, there were only 2 breath test negative but seropositive children of whom both parents were negative for this bacterium on the two diagnostic tests.

It is also noteworthy that in the German families the frequency of simultaneous infection with H. pylori in both spouses occurring in association with one index-case was high at 48.7% (21/43). As can be seen in Table 3, among the 63 German couples for whom data on H. pylori infection state were available from both spouses, there were on the one hand 20 couples in whom neither parent showed positive result in the \(^{13}\)C-urea breath test and, on the other hand in 21 cases both parents were infected. In 22 cases, a single parent was H. pylori positive. Consequently, transmission between spouses may also play a role in the epidemiology of this infection within family settings. In the group of immigrants, corresponding analysis was not possible because of the high background rate of this infection among the parent generation.
3. Communicability of H. pylori infection within families: transmission rates to the children

The next objective of this study was to gain first insight into the communicability of H. pylori within families. Figure 1 demonstrates the average, and age-related rates of H. pylori acquisition in children exposed to at least one infected parent. The data presented here must, however, be considered a maximum estimate because the control pool consisted of only 28.1% (Germans) and 80.6% (immigrants) of the families initially intended for this study (i.e., with either the social or clinical risk factors contributing to H. pylori infection).

In the group of German families (n=50), H. pylori infection was detected in 20 of the 86 children (23.3%) exposed to an infected parent. The incidence showed a progressive increase with advancing age from 13.8% (4/29) in the youngest age group studied (3-5 years) through 18.2% (6/33) for children at ages 6-10 years, to a high proportion of adolescents aged 11-18 years (41.7%; 10/24). In the group of immigrant families comprising an infected parent (n=62), the overall transmission rate to the children was significantly higher (71.3%; 117/164) than in German families (OR for at least one childhood infection in immigrant families vs German families = 5.2, P [0.001, 95%CI= 2.0-13.7, see Table 4). Although an age-related increase was noticeable, it was much less marked in this population than in German children. Remarkably, in children of immigrants the acquisition of H. pylori infection occurred earlier in life, affecting already 28 (57.1%) of 49 children aged 3-5 years, and in the two older age groups only a slight increase to 72.4% (42/58) and to 82.5% (47/57), respectively, was observed.

As presented in Figure 2, the incidence of childhood H. pylori infection did not vary widely between the two well defined groups of 26 Turkish (67.7%; 42/62) and 18 Morrocan families (81.7%; 49/60) as well as the remaining inhomogenous group of 18 families (61.9%; 26/42) of various other origin (including 8 Pakistani, 2 Afghan, 2 Greek, 3 Albanian and 3 Bosnian
Figure 1. Incidence of *H. pylori* infection in children exposed to at least one infected parent.

- **3-5 years**: 4/29 (13.8%)
- **6-10 years**: 6/33 (18.2%)
- **11-18 years**: 10/24 (41.7%)
- **Total**: 26/66 (40%)

- **German families (n=50)**
- **Immigrant families (n=62)**

- **3-5 years**: 28/49 (57.1%)
- **6-10 years**: 42/58 (72.4%)
- **11-18 years**: 47/57 (82.5%)
- **Total**: 117/164 (71.3%)
Figure 2. Childhood H. pylori infection in relation to ethnic background: comparision between the four study populations.
families). The median ages of the children from these three different ethnic groups were 7.9 years (range 3-20), 9.2 years (range 3-19) and 9.7 years (range 3-16), respectively.

4. Childhood H.pylori infection in relation to family size

As can be seen in Table 4, the results of logistic regression analysis yielded that the odds ratios of at least one childhood infection in a family were higher for households with a great number of children than in smaller families: up to 9.5 for the group of immigrant families comprising four or more children, when measured against those families with not more than 2 children (P=0.05, 95%CI= 0.1-89.0). What is really of interest is the rate at which all children at risk became infected with H.pylori, and how this rate varied in relation to family size (as a surrogate measure of domestic crowding). This relationship is shown in Figure 3. In the population of immigrants, the incidence of childhood H.pylori infection increased continuously from 55.3% (21/38) in families (n= 23) comprising 2 children and 58.3% (28/48) in families (n= 19) with 3 children, through 80% (20/25) in households with 4 children (n=8) to 92.3% (48/52) in those families with five or more children (n=11). As expected, the median ages of the children increased progressively with rising family size from 6.2 years (range 3-15), 8.1 years (range 3-16) and 9.5 years (range 3-19) to 9.9 years (range 3-20), respectively. Correspondingly, in the German population, childhood H.pylori infection was less frequent in families (n=14) including only one child (14.3%; 2/14) than in those families with two (n=25; 25%; 11/44) or three children (n=11; 25%; 7/28). The respective ages of the children were 5.0 years (range 3-12), 8.5 years (range 3-20) and 10.4 years (range 4-20).

In conclusion, children who grew up in large families were at a substantially higher risk for acquiring H.pylori infection by domestic contact than were children from smaller families. However, this conclusion remains statistically unproven. Rising age of the children was an
Figure 3. Childhood H. pylori infection in relation to family size.
indeterminable variable, which might account to some extent for the accumulation of cases among larger families. Otherwise, age (duration of exposure) and family size (e.g. domestic crowding) are not mutually exclusive, and a combination of these two effects is likely. The results provide an additional argument for person-to-person transmission of H. pylori infection within families.

5. Endoscopic and histologic findings

15 H. pylori positive parents and 15 infected children (8 family groups and 5 unrelated participants of this study) underwent upper gastrointestinal tract endoscopy with biopsy sampling. This group comprised 9 children with recurrent abdominal pain, 5 children with clinically silent H. pylori infection, one child with a previous history of a painless duodenal ulcer bleeding (post-treatment follow-up endoscopy), 10 adult patients with a clinical history suggestive of ulcer disease or gastritis (recurrent epigastric pain and periodic nausea/vomiting) and, finally, 5 symptom-free adults. The endoscopic and biopsy results are presented in Table 7. Endoscopic abnormalities were not found in any H. pylori positive child. However, in each case, H. pylori colonisation was accompanied by histological signs of chronic-active inflammation of the gastric mucosa. In the group of adult patients, the endoscopic examination revealed in one patient a markedly stenosed duodenal bulb, and in one further patient a small, active duodenal ulcer. The endoscopic findings in these two patients were accompanied by moderate to severe active antral gastritis on histology. In one further patient, an erythematous antrum and duodenal bulb were visible on endoscopy and, on histology, a severe active antral gastritis with superficial erosions was found. A mild inflammation of both the antrum and corpus portion of the stomach as well as of the duodenal bulb was found in one further patient, and the histologic examination revealed a moderate chronic, severe active antral gastritis. In the remaining 11 adult patients, no abnormalities were noted on endoscopy, but parallel to the pediatric group, H. pylori colonisation in all these
<table>
<thead>
<tr>
<th>Family group/ Patient (age)</th>
<th>Dyspeptic Symptoms †</th>
<th>Detection of H. pylori ‡</th>
<th>Endoscopic Abnormalities</th>
<th>Histologic findings in antral biopsy specimens ††</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fam.A</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother (33)</td>
<td>No</td>
<td>+</td>
<td>+</td>
<td>moderate chronic, moderate active gastritis</td>
</tr>
<tr>
<td>Father (34)</td>
<td>No</td>
<td>+</td>
<td>+</td>
<td>focal atrophy and intestinal metaplasia</td>
</tr>
<tr>
<td>Son (13)</td>
<td>No</td>
<td>+</td>
<td>+</td>
<td>severe chronic, moderate active gastritis</td>
</tr>
<tr>
<td>Son (9)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
<td>moderate chronic, mild active gastritis</td>
</tr>
<tr>
<td><strong>Fam.B</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother (34)</td>
<td>No</td>
<td>+</td>
<td>+</td>
<td>moderate chronic, moderate active gastritis</td>
</tr>
<tr>
<td>Father (35)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
<td>mild chronic, mild active gastritis</td>
</tr>
<tr>
<td>Daughter (15)</td>
<td>No</td>
<td>+</td>
<td>+</td>
<td>moderate chronic, moderate active gastritis</td>
</tr>
<tr>
<td><strong>Fam.C</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother (30)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
<td>moderate chronic, moderate active gastritis</td>
</tr>
<tr>
<td>Father (30)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
<td>moderate chronic, moderate active gastritis</td>
</tr>
<tr>
<td>Daughter (9)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
<td>moderate chronic, mild active gastritis</td>
</tr>
<tr>
<td><strong>Fam.D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother (28)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
<td>moderate chronic, mild active gastritis</td>
</tr>
<tr>
<td>Daughter (9)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
<td>focal atrophy and intestinal metaplasia</td>
</tr>
<tr>
<td><strong>Fam.E</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mother (32)</td>
<td>No</td>
<td>+</td>
<td>+</td>
<td>moderate chronic, severe active gastritis</td>
</tr>
<tr>
<td>Father (32)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
<td>moderate chronic, severe active gastritis</td>
</tr>
<tr>
<td>Daughter (8)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
<td>moderate chronic, severe active gastritis,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>prominent lymphoid follicles</td>
</tr>
<tr>
<td>Fam.F</td>
<td>Mother (31)</td>
<td>No</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
<td>-----</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td></td>
<td>Father (36)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Son (10)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Son (13)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Son (15)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fam.G</td>
<td>Brother (6)</td>
<td>No</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Brother (10)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fam.H</td>
<td>Brother (12)*</td>
<td>No</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Sister (13)</td>
<td>No</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Brother (14)</td>
<td>No</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Unrelated</td>
<td>Male (33)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Male (33)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Male (54)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Male (51)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>Boy (16)</td>
<td>Yes</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

† dyspeptic symptoms include recurrent epigastric or abdominal pain with or without periodic nausea / vomiting.
‡ by (1) ELISA = enzyme-linked immunosorbent assay, (2) $^{13}$C-UBT = $^{13}$C-urea breath test and (3) Warthin-Starry / haematoxylin-eosin staining. A plus (+) sign indicates present, a minus (-) sign absent.
†† the presence of gastritis was assessed and graded according to the criteria of The Sydney System
* a post-treatment follow-up endoscopy in a boy who developed a painless duodenal ulcer bleeding one year ago
subjects was associated with histological signs of chronic-active gastritis. In three patients aged 28, 34 and 54 years, focal atrophy and intestinal metaplasia were noted in the antral mucosa. In both the pediatric and adult group, H.pylori was also visualized in all stained biopsy specimens. A discrepancy between $^{13}$C-urea breath test and staining was observed only in the boy with a previous history of ulcer bleeding; one year after the eradication therapy, the result of the $^{13}$C-urea breath test became negative, but small numbers of H.pylori were still noted on the stained biopsy specimens.

6. Comparison of DNA fingerprints of H.pylori strains isolated from members of three families

Molecular typing was performed for 10 H.pylori strains isolated from family members of 3 different families: 4 strains were isolated from family A (a6 - mother aged 33 years, a3 - father aged 34 years, a1 and a2 - their two sons aged 13 and 9 years, respectively), 3 further isolates were obtained from family B (b1 - mother aged 34 years, b2 - father aged 35 years and b3 - their daughter aged 15 years), and 3 strains were isolated from family C (c3 - mother, c1 - father, both aged 30 years, and c2 - their daughter aged 9 years). They included two Turkish families (families A and C, both of them residing for more than 30 years in Germany) and one German family (family B).

A multiple alignment of the sequences obtained is shown in figure 4A. All sequences could be read without ambiguities. 37 positions of the 339 analyzed were variable (fig. 4B). Only three of these variations were associated with amino acid changes, while 34 of these variable sites were silent. All H.pylori strains isolated from unrelated individuals among these three families possessed unique sequences at the flaB gene fragment. The observed degree of variation as well as the positions of the variable sites were consistent with the data previously obtained with a sample of 100 different H.pylori strains (67). Given the high degree of polymorphism in the flaB flagellin genes, the likelihood that in a small sample such as this...
Figure 4A. Multiple alignment of the partial nucleotide sequences of the H. pylori flaB flagellin gene (339 base pairs) obtained for molecular fingerprinting of the H. pylori isolates.

<table>
<thead>
<tr>
<th></th>
<th>fa1-i.asc</th>
<th>fa2.asc</th>
<th>fa3.asc</th>
<th>fa6.asc</th>
<th>fb1.asc</th>
<th>fb2-iv.asc</th>
<th>fb3.asc</th>
<th>fc1.asc</th>
<th>fc2.asc</th>
<th>fc3.asc</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
</tr>
<tr>
<td></td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
</tr>
<tr>
<td></td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
</tr>
<tr>
<td></td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
</tr>
<tr>
<td></td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
</tr>
<tr>
<td></td>
<td>fa1-i.asc</td>
<td>fa2.asc</td>
<td>fa3.asc</td>
<td>fa6.asc</td>
<td>fb1.asc</td>
<td>fb2-iv.asc</td>
<td>fb3.asc</td>
<td>fc1.asc</td>
<td>fc2.asc</td>
<td>fc3.asc</td>
</tr>
<tr>
<td></td>
<td>TTTAGGCGTT</td>
<td>TTTAGGCGTT</td>
<td>TTTAGGCGTT</td>
<td>TTTAGGCGTT</td>
<td>TTTAGGCGTT</td>
<td>TTTAGGCGTT</td>
<td>TTTAGGCGTT</td>
<td>TTTAGGCGTT</td>
<td>TTTAGGCGTT</td>
<td>TTTAGGCGTT</td>
</tr>
<tr>
<td></td>
<td>AGGGCTTCTT</td>
<td>AGGGCTTCTT</td>
<td>AGGGCTTCTT</td>
<td>AGGGCTTCTT</td>
<td>AGGGCTTCTT</td>
<td>AGGGCTTCTT</td>
<td>AGGGCTTCTT</td>
<td>AGGGCTTCTT</td>
<td>AGGGCTTCTT</td>
<td>AGGGCTTCTT</td>
</tr>
<tr>
<td></td>
<td>ATAATGTCAT</td>
<td>ATAATGTCAT</td>
<td>ATAATGTCAT</td>
<td>ATAATGTCAT</td>
<td>ATAATGTCAT</td>
<td>ATAATGTCAT</td>
<td>ATAATGTCAT</td>
<td>ATAATGTCAT</td>
<td>ATAATGTCAT</td>
<td>ATAATGTCAT</td>
</tr>
<tr>
<td></td>
<td>GGCCACCGGC</td>
<td>GGCCACCGGC</td>
<td>GGCCACCGGC</td>
<td>GGCCACCGGC</td>
<td>GGCCACCGGC</td>
<td>GGCCACCGGC</td>
<td>GGCCACCGGC</td>
<td>GGCCACCGGC</td>
<td>GGCCACCGGC</td>
<td>GGCCACCGGC</td>
</tr>
<tr>
<td></td>
<td>fa1-i.asc</td>
<td>fa2.asc</td>
<td>fa3.asc</td>
<td>fa6.asc</td>
<td>fb1.asc</td>
<td>fb2-iv.asc</td>
<td>fb3.asc</td>
<td>fc1.asc</td>
<td>fc2.asc</td>
<td>fc3.asc</td>
</tr>
<tr>
<td></td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
</tr>
<tr>
<td></td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
</tr>
<tr>
<td></td>
<td>GAACTCACCA</td>
<td>GAACTCACCA</td>
<td>GAACTCACCA</td>
<td>GAACTCACCA</td>
<td>GAACTCACCA</td>
<td>GAACTCACCA</td>
<td>GAACTCACCA</td>
<td>GAACTCACCA</td>
<td>GAACTCACCA</td>
<td>GAACTCACCA</td>
</tr>
<tr>
<td></td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
</tr>
<tr>
<td></td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
</tr>
<tr>
<td></td>
<td>fb1.asc</td>
<td>fb2-iv.asc</td>
<td>fb3.asc</td>
<td>fc1.asc</td>
<td>fc2.asc</td>
<td>fc3.asc</td>
<td>fa1-i.asc</td>
<td>fa2.asc</td>
<td>fa3.asc</td>
<td>fa6.asc</td>
</tr>
<tr>
<td></td>
<td>TGGAGCGTT</td>
<td>TGGAGCGTT</td>
<td>TGGAGCGTT</td>
<td>TGGAGCGTT</td>
<td>TGGAGCGTT</td>
<td>TGGAGCGTT</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
</tr>
<tr>
<td></td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
</tr>
<tr>
<td></td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
</tr>
<tr>
<td></td>
<td>fc1.asc</td>
<td>fc2.asc</td>
<td>fc3.asc</td>
<td>fa1-i.asc</td>
<td>fa2.asc</td>
<td>fa3.asc</td>
<td>fa6.asc</td>
<td>fb1.asc</td>
<td>fb2-iv.asc</td>
<td>fb3.asc</td>
</tr>
<tr>
<td></td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
<td>GGCACAGGGA</td>
</tr>
<tr>
<td></td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
<td>TTGGAGCGTT</td>
</tr>
<tr>
<td></td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
<td>AAGCGAAATC</td>
</tr>
<tr>
<td></td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
<td>ATCAATCGTT</td>
</tr>
<tr>
<td></td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
<td>TTTCTAACAC</td>
</tr>
<tr>
<td></td>
<td>fa1-i.asc</td>
<td>fa2.asc</td>
<td>fa3.asc</td>
<td>fa6.asc</td>
<td>fb1.asc</td>
<td>fb2-iv.asc</td>
<td>fb3.asc</td>
<td>fc1.asc</td>
<td>fc2.asc</td>
<td>fc3.asc</td>
</tr>
<tr>
<td></td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
</tr>
<tr>
<td></td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
</tr>
<tr>
<td></td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
</tr>
<tr>
<td></td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
</tr>
<tr>
<td></td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
</tr>
<tr>
<td></td>
<td>fb1.asc</td>
<td>fb2-iv.asc</td>
<td>fb3.asc</td>
<td>fc1.asc</td>
<td>fc2.asc</td>
<td>fc3.asc</td>
<td>fa1-i.asc</td>
<td>fa2.asc</td>
<td>fa3.asc</td>
<td>fa6.asc</td>
</tr>
<tr>
<td></td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
</tr>
<tr>
<td></td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
</tr>
<tr>
<td></td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
</tr>
<tr>
<td></td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
</tr>
<tr>
<td></td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
</tr>
<tr>
<td></td>
<td>fc1.asc</td>
<td>fc2.asc</td>
<td>fc3.asc</td>
<td>fa1-i.asc</td>
<td>fa2.asc</td>
<td>fa3.asc</td>
<td>fa6.asc</td>
<td>fb1.asc</td>
<td>fb2-iv.asc</td>
<td>fb3.asc</td>
</tr>
<tr>
<td></td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
<td>TGCAATCAGG</td>
</tr>
<tr>
<td></td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
<td>AACCGTGAGA</td>
</tr>
<tr>
<td></td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
<td>GAACCTCACCA</td>
</tr>
<tr>
<td></td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
<td>TTAATGGCGT</td>
</tr>
<tr>
<td></td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
<td>AGAAATTGGG</td>
</tr>
</tbody>
</table>
fa1-i.asc  ACCGTGAATG ATGTGCATAA AAACGACGCT GATGGGAGAT TGACTAATGC
fa2.asc  ACCGTGAATG ATGTGCATAA AAACGATGCT GACGGGAGGT TGACTAATGC
fa3.asc  ACCGTGAATG ATGTGCATAA AAACGATGCT GACGGGAGGT TGACTAACGC
fa6.asc  ACCGTGAATG ATGTGCATAA AAACGACGCT GATGGGAGAT TGACTAATGC
fb1.asc  ACCGTGAATG ATGTGCATAA AAACGACGCT GACGGGAGGT TGACTAATGC
fb2-iv.asc  ACCGTGAATG ATGTGCATAA AAACGATGCT GATGGGAGAT TGATTAATGC
fb3.asc  ACCGTGAATG ATGTGCATAA AAACGATGCT GATGGGAGAT TGATTAATGC
fc1.asc  ACCGTGAATG ATGTGCATAA AAACGACGCT GACGGGAGAT TGACTAATGC
fc2.asc  ACCGTGAATG ATGTGCATAA AAACGATGCT GATGGGAGAT TGATTAATGC
fc3.asc  ACCGTGAATG ATGTGCATAA AAACGACGCT GATGGGAGAT TGACTAATGC

fa1-i.asc  GATAAACTCC GTCAAAGACA GGACGGGCGT GGAAGCGAGC TTGGATATTC
fa2.asc  GATCAACTCC GTCAAAGACA GGACCGGCGT GGAAGCGAGC TTGGATATTC
fa3.asc  GATCAACTCC GTCAAAGACA GGACCGGCGT GGAAGCGAGC TTGGATATTC
fa6.asc  GATAAACTCC GTCAAAGACA GGACGGGCGT GGAAGCGAGC TTGGATATTC
fb1.asc  CATTAATTCC GTCAAAGATC GCACCGGCGT GGAAGCGAGC TTGGATATTC
fb2-iv.asc  CATTAATTCC GTCAAAGATC GCACCGGCGT GGAAGCGAGC TTGGATATTC
fb3.asc  TATTAACTCC GTCAAAGATC GCACCGGCGT GGAAGCGAGC TTGGATATTC
fc1.asc  GATCAACTCC GTCAAAGATC GCACCGGCGT GGAAGCGAGC TTGGATATTC
fc2.asc  GATCAACTCC GTTAAAGATC GCACCGGCGT GGAAGCGAGC TTGGATATTC
fc3.asc  GATCAACTCC GTTAAAGATC GCACCGGCGT GGAAGCGAGC TTGGATATTC

fa1-i.asc  AAGGGCGCAT TAATTTGCAC TCCATTGACG GGCGCGCGAT TTCTGTGCAT
fa2.asc  AAGGACGCAT TAATTTGCAC TCCATTGACG GGCGCGCGAT TTCTGTGCAT
fa3.asc  AAGGACGCAT TAATTTGCAC TCCATTGACG GGCGCGCGAT TTCTGTGCAT
fa6.asc  AAGGGCGCAT TAATTTGCAC TCCATTGACG GGCGCGCGAT TTCTGTGCAT
fb1.asc  AAGGGCGCAT TAATTTGCAC TCCATTGATG GGCGCGCGAT TTCTGTGCAT
fb2-iv.asc  AAGGGCGCAT TAATTTGCAC TCCATTGATG GGCGCGCGAT TTCTGTGCAT
fb3.asc  AAGGGCGCAT TAATTTGCAC TCCATTGATG GGCGCGCGAT TTCTGTGCAT
fc1.asc  AAGGGCGCAT TAATTTGCAC TCCATTGATG GGCGCGCGAT TTCTGTGCAT
fc2.asc  AAGGGCGCAT TAATTTACAC TCCATTGATG GGCGCGCGAT CTCAGTGCAT
fc3.asc  AAGGGCGCAT TAATTTACAC TCCATTGATG GGCGCGCGAT CTCAGTGCAT

fa1-i.asc  GCAGCGAGCG CGAGCGGTCA GGTTTTTGGG GGAGGGAAT
fa2.asc  GCAGCGAGCG CGAGCGGTCA GGTTTTTGGG GGAGGGAAT
fa3.asc  GCAGCGAGCG CGAGCGGTCA GGTTTTTGGG GGAGGGAAT
fa6.asc  GCAGCGAGCG CGAGCGGTCA GGTTTTTGGG GGAGGGAAT
fb1.asc  GCAGCGAGCG CGAGCGGTCA GGTTTTTGGG GGAGGGAAT
fb2-iv.asc  GCAGCGAGCG CGAGCGGTCA GGTTTTTGGG GGAGGGAAT
fb3.asc  GCAGCGAGCG CGAGCGGTCA GGTTTTTGGG GGAGGGAAT
fc1.asc  GCAGCGAGCG CGAGCGGTCA GGTTTTTGGG GGAGGGAAT
fc2.asc  GCAGCGAGCG CGAGCGGTCA GGTTTTTGGG GGAGGGAAT
fc3.asc  GCAGCGAGCG CGAGCGGTCA GGTTTTTGGG GGAGGGAAT
Figure 4B. Variable sites in the partial flaB sequences

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th>111</th>
<th>111</th>
<th>111</th>
<th>112</th>
<th>222</th>
<th>222</th>
<th>222</th>
<th>222</th>
<th>233</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11</td>
<td>335</td>
<td>689</td>
<td>112</td>
<td>225</td>
<td>788</td>
<td>990</td>
<td>001</td>
<td>122</td>
<td>256</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>625</td>
<td>691</td>
<td>640</td>
<td>470</td>
<td>360</td>
<td>739</td>
<td>481</td>
<td>473</td>
<td>902</td>
<td>557</td>
</tr>
</tbody>
</table>

fa1-i  ATA TTT TCC CGA ACA CTA CTG ACC CAG GGG CCT TGC T
fa2  T.. ..C GT. .. GTG TCG .C. C.. .. CA. .. .. ..
fa2  T.. ..C GT. .. GTG TCG .C. C.. .. CA. .. .. ..
fa6  .. .. .. .. .. .. .. .. .. .. .. .. .. .. ..

fb1  T.. .. GT. TTG G.G .CG ..C TT. TCC C.. .T. .. ..
fb2  T.. .. GT. TTG G.G .CG ..C TT. TCC C.. .T. .. ..
fb3  T.G CCC G.. TTG GT. .CG .CT T.. TCC C.. T.. .. ..

fc1  T.. CCC G.T ... ..C. .C. C.. TCC C.. .T. .. ..
fc2  TC. .. .T. ... TTG T.. T.. C.T TCC C.A .TC AAT ..
fc3  TC. .. .T. ... TTG T.. T.. C.T TCC C.A .TC AAT ..

Note: The numbers above the nucleotides indicate the position of the particular variable site in the complete sequence as shown in fig.4A. Dots indicate identity of the particular nucleotide with the one present in sequence fa1-i.
two given strains are identical is extremely small. Two identical strains would indicate that either one patient has been infected from the other or that both have been infected from a common source.

Figure 5 illustrates the phylogenetic distances between the 10 strains. Table 8 shows the distribution of identical H.pylori strains among members of the three families. In family A, mother (a6) and one of the children (a1) harboured identical strains, while the father (a3) and the second child (a2) also had an identical strain, which was, however, distinct from the strain harboured by the other two family members. In family B, the husband (b2) and his wife (b1) had an identical strain, while the daughter (b3) carried a different strain. In family C, the mother (c3) and her daughter (c2) shared the same strain, while the strain of the father (c1) was different. In summary, within each of these families, one or two pairs of individuals carried indistinguishable strains, and all but one child harboured a strain identical to the one in either the mother or the father. These findings strongly support the epidemiological evidence of intrafamilial spread of H.pylori infection.
Figure 5. Phylogramm of the flaB nucleotide sequences obtained for ten different H. pylori isolates from members of families A-C. The sum of horizontal distances represents the phylogenetic distances between the strains.
Table 8. Distribution of identical H.pylori strains within three families: childhood infection

<table>
<thead>
<tr>
<th>Family</th>
<th>Identical strains</th>
<th>Unique strains</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>M (a6) - C (a1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>F (a3) - C (a2)</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>M (b1) - F (b2)</td>
<td>C (b3)</td>
</tr>
<tr>
<td>C</td>
<td>M (c3) - C (c2)</td>
<td>F (c1)</td>
</tr>
</tbody>
</table>

Note: M denotes mother, F denotes father, C denotes children. The letters and numbers in the brackets indicate the corresponding H.pylori isolates.
DISCUSSION

The importance of person-to-person transmission of *H. pylori* infection within families has not been as yet clearly elucidated. There is also no information regarding the rate at which this organism may be spread between family members. Our study differs from other studies on this infection route in that it is a systematical case - control study, carried out in a relatively large sample of 142 families with well defined ethnic and sociodemographic backgrounds. In addition, by using the combination of both positive serology, and positive $^{13}$C-urea breath test result for diagnosis of a current infection, a reliable classification of the *H. pylori* infection state was possible.

The results of our study provide clear evidence for a transmission of *H. pylori* by close person-to-person contact within families. In both the German and immigrant study population, all children infected with *H. pylori* came from families with at least one infected parent and, vice versa, no evidence of current infection was found in any child of whom both parents were *H. pylori* negative. In support of the epidemiologic evidence, genotypic comparison of *H. pylori* strains isolated from 10 members of three families revealed that within each of these families, one or two pairs of individuals carried indistinguishable strains, and that all but one child harboured a strain identical to the one in either the mother or the father. As *H. pylori* shows an unusually high degree of genomic diversity and as almost all bacterial strains isolated from epidemiologically unrelated subjects are genetically heterogeneous (1, 24, 67), these findings strongly support the occurrence of cross infections with *H. pylori* within families. Our previous report on a child with duodenal ulcer bleeding who harboured a strain identical to the one in his two asymptomatic siblings (14), as well as the repeated documentation of identical (4, 44, 54, 71) or at least of clonal variants of the same strain in further families (47) strongly support this conclusion.
Alternatively to the spread of this bacterium from person to person, it could be argued that this clustering of cases within families could relate to common exogenous sources such as food and water. Our study provides some important arguments against the latter possibility. First, the prevalence of H. pylori infection in both the German and immigrant study population was higher in the parent generation than in the children. Secondly, in families where both father and mother were not infected, the children as well were free of infection. Thirdly, the higher incidence of H. pylori infection among children of immigrants correlated well with the higher background rate of this infection among their parents. In addition, the incidence increased with rising family size. Finally, there was a strong correlation between childhood infection and exposure to an infected mother. We observed that children of H. pylori positive mothers were 12.3 times more likely to acquire this infection than were those children whose mothers were not infected (P \( < 0.001 \)), whereas H. pylori infection state in the father did not significantly influence the risk (OR= 2.6, N.S.). Likewise, when we analysed the risk of childhood infection in relation to the H. pylori infection state in both parents, we found, similarly, that childhood infection did not differ significantly between families with only an infected mother, and those with two infected parents (OR= 0.68, N.S.), while, on the other hand, in families where only the fathers were infected, a significantly smaller number of children carried the infection (OR=0.15, P \( < 0.01 \)). This strong correlation between childhood infection and exposure to an infected mother - which has also been reported by Drumm et al (13) and Sedlackova et al (62) - strongly points at the mother as the predominant transmitter of H. pylori to the children. This conclusion implies that person-to-person spread, either directly through close and continuous contact or indirectly through contaminated food and other fomites, is the major mode of transmission of H. pylori infection. In support of this epidemiological evidence, faecal excretion and oral carriage of viable and infective bacteria have been documented by several investigators (19, 35, 68) and, although attempts at
culturering H. pylori from these specimens have been of varied success, these findings indicate that person - to - person transmission may occur. Furthermore, individuals with professional exposure to gastrointestinal secretions, such as nurses (74) and endoscopists (39), exhibit a markedly increased frequency of antibody carriage. This would indicate that indeed, H. pylori is efficiently spread via human secretions.

In apparent opposition to the concept of direct person-to-person transmission, Klein et al (36) postulated that waterborne spread of H. pylori may also be an important vector in the epidemiology of this infection. In this study from Lima, Peru, a close correlation between the source of water supply and the prevalence of childhood infection was reported. Using PCR, the authors were also able to confirm the presence of H. pylori in several samples of drinking water in the same community (32). In principle, the Peruvian study does not contradict our results because water contaminated by human excretions is consistent with the faecal-oral route and, considering the suboptimal sewage disposal practices, waterborne spread may, indeed, play an important role in developing countries such as Peru. Otherwise, H. pylori often assumes coccoid forms in water, and the viability of this form seems to be very restricted (9, 15). Therefore, the importance of this vector continues to remain unclear. In view of our results demonstrating that children of immigrants from high risk countries, most of whom were born in Germany, have infection rates that parallel those of children living in developing countries, direct transmission via infected human secretions appears to be the predominant mechanism of this infection in most areas of the world.

An unexpected finding of our study was the relatively high rate of simultaneous infections among spouses (48.7% in the German study group). As we have shown that most infections are acquired in childhood and adolescence due to intrafamilial spread of this organism, our study strongly supports the so-called "age cohort effect " (5, 37, 48, 64) and indirectly
indicates that most of the parents under study probably had also acquired this infection from their own household contacts in childhood. Nevertheless, the high rate of simultaneous infections among spouses, as well as the isolation of identical bacterial strains in one of the three married couples, suggest that a proportion of the parents may have acquired this infection by transmission between spouses, and that this route of spread may also play a role in the epidemiology of H.pylori within the family setting. This conclusion is supported by Schütze et al (61) who identified in two cases of late reinfection the patients’ spouses as inapparent carriers of an identical strain. That H.pylori infection can occur at all stages in life - in children as well as in adults- is also evidenced by the clustering of this infection among endoscopists, nurses (39, 74) and in specific closed communities such as mentally or physically retarded inpatients (38, 56) or military personnel (28, 33).

Next, along with the identification of the principal source of childhood infection, we were also able to demonstrate the rate at which exposed children became infected with H.pylori, and thus to gain an understanding of the communicability of this infection within families. The data presented here must, however, be considered a maximum estimate because the negative control pool was incomplete, consisting of approximately one third (Germans) to two thirds (immigrants) of the families initially intended for this study (i.e. of those families with either the social and/or clinical factors contributing to the disease). Certainly, the best method for acquiring telling data on the transmission rates would be to determine the percentage of infected children proceeding from the infected parents, but such studies are lacking.

We observed a great disparity in the potential of intrafamilial spread of H.pylori infection between the immigrant and German population. In the group of German families, the overall transmission rate to the children was only 23.3%, and the acquisition of most infections occurred mainly in late childhood or during adolescence ( 41.7% in the age group 11-18
years). In the immigrant population, by contrast, the communicability of H. pylori infection between family members was extremely high. Following exposure to an infected parent, the incidence of secondary infections among the children reached 71.3% on average, and already more than half the children (57.1%) under 6 years of age carried this infection. The reasons for this disparity are not fully understood. Previous studies on prevalence rates in random samples of North American (20, 26), Western European (10) and Australian (30) populations also showed that children of African Americans or immigrants - irrespective of their social backgrounds - were about two to five times more likely to be infected with H. pylori than were Caucasian children residing in the same area. Hypotheses relating to differences in style of living, dietary habits, hygienic practices (20, 26) or, alternatively, to genetic differences in susceptibility for H. pylori infection have been proposed to explain the difference (40). As this disease is apparently spread by close human contact, the striking difference in the family structure between immigrants from less industrialized and Western populations may be an even more important explanation for this disparity. In our German study group, for example, the large majority of the families sampled (78.2%) included two or fewer children and there was not a single family with more than three children. In contrast to this, within the immigrant population studied, the proportion of families with two or fewer children was only 39.1%, and households including four or more children (up to eight) accounted for around one third of this study group (29.7%). Accordingly, under the latter circumstances, H. pylori infection was extraordinarily common, affecting nearly all children exposed to an infected parent (88.3%), whereas in smaller immigrant families, i.e. with two children, the attack rates decreased considerably to 55.3% on average. Certainly, this rate was still twice that estimated for the corresponding group of German families (25%) suggesting that there must be some additional variables responsible for the enhanced communicability of this organism within the group of immigrant families. However, in the latter population such determinatives as birth place in the origin country and conditions associated with displacement, i.e. lodging in multi-family
households or in housing for asylum seekers, may lead to false inferences. In view of these results, although genetics may play a small role, domestic overcrowding and other often correlating factors such as disadvantaged living conditions and deficiencies in personal hygiene doubtlessly play the major role. This conclusion is further supported by previous studies showing a strong correlation between domestic crowding during childhood and H. pylori seropositivity in adult life (18, 21, 42, 58, 72).

The comparatively slow rate at which German children became infected with H. pylori suggests, on the other hand, that in better domestic conditions, i.e. in households with lower density of potentially infectious carriers of H. pylori or with higher standards of hygiene, this infection can not be transmitted as easily, and a long exposure time seems to be necessary in order to establish a persistent colonisation. This would be compatible with the very restricted ecological niche of H. pylori in the human host, which - despite the urease mediated ammonia production allowing this bacterium to neutralise the acidic pH- remains suboptimal for colonisation and for growth of the microorganism. Otherwise, the frequent finding of antibody carriage in breath test negative children from affected families may indicate that minor infections with lower doses of the bacteria presumably occur more often. Certainly, the importance of such a discrepancy remains speculative and false positive serologic results can not be excluded, but there is growing evidence that the conflicting results may also reflect either a healing stage of an acute, self-limiting infection or a current low-grade infection with undetectable bacterial colonisation (26, 37). Graham et al (26), for example, observed in 2 of 12 persistently seropositive subjects, with initially negative results of the $^{13}$C-urea breath test, an extension of bacterial density above the levels scored as positive on repeated urea breath testing. Similarly, the positive $^{13}$C-urea breath test results in absence of serologic responses to H. pylori - a finding that we observed in 7 German and in 15 immigrant children - might
also be attributable to a not fully developed immune response to H.pylori (11, 55), especially when considering the young ages of these children as well as the fact that all of them came from families with infected mothers. If this were the case, our present data might underestimate the infectivity of H.pylori.

In conclusion, as understanding of the epidemiology of H.pylori infection, and of those factors that influence its transmission are essential for effective control measures, the results of our study appear to be fairly relevant. They imply, that in the case of an index patient, investigation and subsequent treatment within the family would be the best approach to effect a long-term cure after eradication therapy and, secondly, that it would also reduce the number of new cases of H.pylori infection. In our opinion, eradication of H.pylori in asymptomatic household contacts would also seem important, because such an inapparent carrier state is associated with potential contagiousness. In view of the early acquisition of most H.pylori infections, and the substantial morbidity and mortality for complications of this disease (7), early identification of "preclinical stages", for example through inclusion of screening for H.pylori infection into the pediatric medical check-ups, appears also a reasonable preventive measure.
SUMMARY

Methods: In order to clarify the potential of intrafamilial spread of H. pylori, the infection state was determined by means of ELISA (Hycor Biomedical) and $^{13}$C-urea breath test in a sample of 142 families (78 German and 64 immigrant families) selected on the basis of serological screening in children. This group comprised the parents and siblings of 77 seropositive index children (m.a. 8.3 yrs, range 3-18) and the relatives of 65 seronegative control children of comparable age (m.a. 7.6 yrs, range 3-18) and social background.

Results: All H. pylori positive children (20 German and 117 immigrant children) came from families with at least one infected parent. Molecular typing of H. pylori strains isolated from 4 children and 6 parents (3 family groups) revealed that all but one child harboured a strain identical to the one in either the mother or the father. Logistic regression analysis yielded a strong correlation between childhood infection and infection in the mother (OR for families with solely infected mothers vs. both infected parents = 0.68, N.S) (OR for exposure to positive mother vs. negative mother = 12.3, P $< 0.001$). By contrast, the infection state in the father had only little effect on the risk of childhood disease (OR for families with solely infected fathers vs. both infected parents = 0.15, P $< 0.01$) (OR for exposure to positive father vs. negative father = 2.6, N.S.). The transmission rate to the children was higher in immigrant than in German families (71.3% vs.23.3%; OR $= 5.2$, P $< 0.001$). Already 57.1% of the immigrant children aged $\leq 5$ years carried this infection. This rate increased steadily from 55.3% in families with 2 children to 92.3% in families with $\geq 5$ children (OR for families with $\geq 4$ children vs. $\leq 2$ children $= 9.5$, P $< 0.05$). In German families, most infections were acquired in adolescence (41.7%). The incidence was also higher in families with 2 or 3 children (25% in each case) than in families with one child (14.3%) (OR for families with 3 children vs. 1 child = 3.3, N.S.).
Conclusions: Children acquire H.pylori infection due to close person-to-person contact within families. Mothers with infection appear to be the predominant transmitter of H.pylori to the children. The disproportionately higher number of children per family (crowded domestic conditions) may, in part, explain the enhanced communicability of H.pylori within the population of immigrant families.
REFERENCES

   DNA diversity among clinical isolates of Helicobacter pylori detected by PCR-based
   RAPD fingerprinting.

   Cat owners risk of acquiring a Helicobacter pylori infection.

3. Ashorn, M., Ruuska, T., Mäki, M., Miettinen, A.
   H. pylori infection in children born to seropositive mothers (abstract).
   Gut 39 (Suppl.2) (1996) A47

   Helicobacter pylori : comparison of DNA fingerprints provides evidence for
   intrafamilial infection.
   Gut 34 (1993) 1348-1350

   The cohort effect and H.pylori.

   Regression of primary gastric lymphoma of mucosa-associated lymphoid tissue type
   after cure of Helicobacter pylori infection.
   Lancet  345 (1995) 1591-1594
7. Blaser, M.J., Chyou, P.H., Nomura, A.
   Age at establishment of Helicobacter pylori infection and gastric carcinoma, gastric ulcer, and duodenal ulcer risk.
   Cancer Res. 55 (1995) 562-565

   The prevalence of Helicobacter pylori-positive serology in asymptomatic children.

9. Bode, G., Mauch, F., Malfertheiner, P.
   The coccoid forms of Helicobacter pylori. Criteria for their viability.

    Häufigkeit der Infektion mit Helicobacter pylori bei Vorschulkindern der Stadt Ulm-eine bevölkerungsbezogene epidemiologische Studie (abstract)

    Immune responses to Helicobacter pylori in children with recurrent abdominal pain.

12. Czkwianianc, E., Bak-Romaniszyn, L., Malecka-Panas, E., Suski, S., Woch, G.
    Prevalence of Helicobacter pylori in children dependently on age and living conditions.
    J. Physiol. Pharmacol. 47 (1) 1996 203-207

13. Drumm, B., Perez-Perez, G.I., Blaser, M.J., Sherman, P.M.
    Intrafamilial clustering of Helicobacter pylori infection.

Bleeding duodenal ulcer in a 12 year old boy as the first symptom of a familial \textit{H. pylori} infection.


Virulence of Coccoid and Bacillary forms of \textit{Helicobacter pylori} in Gnotobiotic Piglets.


Heterogeneous \textit{Helicobacter pylori} isolates from members of a family with a history of peptic ulcer disease.

\textit{Gastroenterology} 111 (3) (1996) 638-647

17. The Eurogast Study Group:

Epidemiology of and risk factors for \textit{Helicobacter pylori} infection among 3194 asymptomatic subjects in 17 populations.

\textit{Gut} 34 (1993) 1672-1676


Growth in infancy, infant feeding, childhood living conditions, and \textit{Helicobacter pylori} infection at age of 70.


Isolation of \textit{Helicobacter pylori} from saliva.


Factors influencing the epidemiology of Helicobacter pylori infection in children.


Helicobacter pylori infection and overcrowding in childhood.

Lancet 339 (1992) 619

22. De Giacomo, C., Lisato, L., Negrini, R., Licardi, G., Maggiore, G.

Serum immune response to Helicobacter pylori in children: epidemiologic and clinical implications.


Use of a urea breath test versus invasive methods to determine the prevalence of Helicobacter pylori in Zaire.


24. Go, M.F., Kapur, V., Graham, D.Y., Musser, J.M.

Population genetic analysis of Helicobacter pylori by multilocus enzyme electrophoresis: extensive allelic diversity and recombinational population structure.


Helicobacter pylori infection in the Colombian Andes: a population-based study of transmission pathways.

Am. J. Epidemiol. 144 (3) (1996) 290-299
   Epidemiology of Helicobacter pylori in an asymptomatic population in the United
   States. Effect of age, race and socioeconomic status.
   Gastroenterol. 100 (1991) 1495 - 1501
27. Grübel, P., Hoffman, J.S., Chong, F.K., Burstein, N.A., Mepani, Ch., Cave, D.R
   Vector potential of houseflies (musca domestica) for Helicobacter pylori.
28. Hammermeister, I., Janus, G., Schamarowski, F., Rudolf, M., Jacobs, E., Kist, M.
   Elevated risk of Helicobacter pylori infection in submarine crews.
29. Handt, L.K., Fox, J.G., Dewhirst, F.E., Fraser, G.J., Paster, B.J., Yan, L.L., Rozmiarek,
   H., Rufo, R., Stalis, I.H.
   Helicobacter pylori isolated from the domestic cat: Public health implications.
   Infect. Immun. 62 (1994) 2367-2374
30. Hardikar, W., Grimwood, K.
   Prevalence of Helicobacter pylori infection in asymptomatic children.
   R.G., Wasserman, S.S., Morris, J.G.
   Seroprevalence of Helicobacter pylori in Chile: Vegetables may serve as one route of
   transmission.
   Helicobacter pylori in the drinking water in Peru.
   Gastroenterology 110 (4) (1996) 1031-1035

   The risk of Helicobacter pylori infection among U.S. military personnel deployed outside the United States.

34. Käding, M., Herrmann, H., Mahner, B., Wiersbitzky, S.K.W.

35. Kelly, S.M., Pitcher, M.C., Farmery, S.M., Gibson, G.R.
   Isolation of Helicobacter pylori from faeces of patients with dyspepsia in the United Kingdom.
   Gastroenterology 107 (1994) 1671-1674

   Water source as risk factor for Helicobacter pylori infection in Peruvian children.
   Gastrointestinal Physiology Working Group.
   Lancet 337 (1991) 1503-1506

   Seroconversion for H. pylori.
   Lancet 342 (1993) 328-331

High prevalence of Helicobacter pylori antibodies in an institutionalized population: evidence for person-to-person transmission.

Am. J. Gastroenterol. 90 (12) (1995) 2167-2171


Helicobacter pylori prevalence in endoscopy and medical staff.

J. Gastroenterol. Hepatol. 9 (1994) 319-324


Helicobacter pylori infection: Genetic and environmental influences. A study of twins.


41. Malfertheiner, P.

Helicobacter pylori in der Ulcuspathogenese.


42. Mendall, M.A., Goggin, P.M., Molineaux, N., Levy, J., Toosy, T., Strachan, D., Northfield, T.C.

Childhood living conditions and Helicobacter pylori seropositivity in adult life.

Lancet 339 (1992) 896 - 897

43. Mitchell, H.M., Bohane, T., Hawkes, R.A., Lee, A.

Helicobacter pylori infection within families.


Antigen recognition during progression from acute to chronic infection with cagA-positive strain of Helicobacter pylori.

Infect. Immun. 64 (4) (1996) 1166 - 1172

Epidemiology of Helicobacter pylori infection in southern China: Identification of early childhood as the critical period for acquisition.


46. Mitchell, J.D., Mitchell, H.M., Tobias V.

Acute Helicobacter pylori infection in an infant, associated with gastric ulceration and serological evidence of intrafamilial transmission.

Am. J. Gastroenterol. 87 (1992) 382-386

47. Nwokolo, C.U., Bickley, J., Attard, A.R., Owen, R.J., Costas, M., Fraser, I.A.

Evidence for clonal variants of Helicobacter pylori in three generations of a duodenal ulcer family.

Gut 33 (1992) 1323 - 1327


Symptoms and risk factors of Helicobacter pylori infection in a cohort of epidemiologists.

Gastroenterology 102 (1992) 41-46

49. Parsonett, J., Friedman, G.D., Vandersteen, D.P., Chan, Y., Vogelman, J.H., Orentreich, H., Sibley, R.

Helicobacter pylori infection and the risk of gastric carcinoma.


50. Pounder, R.E., Ng, D.

The prevalence of Helicobacter pylori infection in different countries.

51. Price, A.B.
   The Sydney System: Histological division.
   J. Gastroenterol. Hepatol. 6 (1991) 209-222

52. Radke, M., Wutzke, K-D., Heine W.
   Prevalence of Helicobacter pylori in asymptomatic children determined by $^{13}$C-
   ureabreath test (abstract).

   Molecular typing of H.pylori strains isolated from siblings and unrelated children
   (abstract).
   Gut 39 (Suppl.2) (1996) A52

   Familial clustering of peptic ulcer disease colonized with Campylobacter pylori of the
   same DNA composition.
   Gastroenterol. 96 (1989) A 409

55. Raymond, J., Kalach N., Bergeret, M.
   Evaluation of a serological test for diagnosis of Helicobacter pylori infection in
   children.

56. Reiff, A., Jacobs, E., Kist, M.
   Seroepidemiological study of the immune response to Campylobacter pylori in
   potential risk groups.
H. pylori and the birth cohort effect: evidence for continuous decrease of infection rates in childhood.

Sarker, S.A., Mahalanabis, D., Hildebrand, P., Rahman, M.M., Bardhan, P.K., Fuchs, G., Beglinger, C., Gyr, K.
Helicobacter pylori in out-patients of a general practitioner: prevalence and determinants of current infection.

59. Helicobacter pylori: Prevalence, transmission, and serum pepsinogen II concentrations in children of a poor periurban community in Bangladesh.

60. Sathar, M.A., Gouws, E., Simjee, A.E., Mayat, A.M.
Seroepidemiological study of Helicobacter pylori infection in South African children.

61. Schütze, K., Hentschel, E., Dragosics, B., Hirschl, A.M.
Helicobacter pylori reinfection with identical organisms: transmission by the patients' spouses.
Gut 36 (1995) 831-833

62. Sedlackova, M., Soucek, A., Dohnalova, A.
Helicobacter pylori infection: familial clustering and transmission
63. Shames, B., Krajden, S., Fuksa, M., Babida, C., Penner, J.L.
    Evidence for the occurrence of the same strain of Campylobacter pylori in the stomach
    and dental plaque.

64. Sipponen, P., Helske, T., Jarvinen, P., Hyvarinen, H., Seppala, K., Siurala, M.
    Fall in the prevalence of chronic gastritis over 15 years: analysis of outpatient series in
    Gut 35 (1994) 1167-1171

65. Staat, M.A., Kruszon-Moran, D.
    A population based serological survey of Helicobacter pylori infection in children and
    adolescents in the United States.

66. Suerbaum, S., Josenhans, C., Labigne, A.
    Cloning and genetic characterisation of the Helicobacter pylori and Helicobacter
    mustelae flaB flagellin genes and construction of H. pylori flaA- and flaB-negative
    mutants by electroporation-mediated allelic exchange.
    J. Bacteriol. 175 (1993) 3278-3288

67. Suerbaum, S., Smith, J.M., Bapumia, K., Morelli, G., Smith, N.H., Kunstmann, E.,
    Dyrek, I., Achtman, M.
    Free recombination within Helicobacter pylori.

68. Thomas, J.E., Gibson, G.R., Darboe, M.K., Dale, A., Weaver, L.T.
    Isolation of Helicobacter pylori from human faeces.
    Lancet 340 (1992) 1194-1195
69. Taylor, D.N., Blase, M.J.

The epidemiology of Helicobacter pylori infection.

70. Vincent, P., Gottrand, F., Pernes, P., Husson, M.O., Lecomte Houcke, M., Turck, D., Leclerc, H.

High prevalence of Helicobacter pylori infection in cohabiting children. Epidemiology of a cluster, with special emphasis on molecular typing.
Gut 35 (1994) 313 – 316


Direct DNA amplification and restriction pattern analysis of Helicobacter pylori in patients with duodenal ulcer and their families.

72. Webb, P.M., Knight, T., Greaves, S., Wilson, A., Newell, D.G., Elder, J., Forman, D.

Relation between infection with Helicobacter pylori and living conditions in childhood: evidence for person to person transmission early in life.
BMJ 308 (1994) 750 - 753


Evaluation of QuickVue, a rapid enzyme immunoassay test for the detection of serum antibodies to Helicobacter pylori.

74. Wilhoite, S.L., Ferguson, D.A.J., Soike, D.R., Kalbfleisch, J.H., Thomas, E.

Increased prevalence of Helicobacter pylori antibodies among nurses.
ACKNOWLEDGEMENTS

I thank Prof. Dr. med. W. Opferkuch, Dr. med. G. Gaida and Dipl.-Biol. D. Gaida for their support and valuable comments during the preparation of this manuscript, Dr. med. H. Bock and Dr. med. A. Mares for endoscopic examinations and biopsy samples, Prof. Dr. med. S. Suerbaum for molecular typing of the H. pylori strains, and Dr. med. S. Lange for statistical analyses.
**LEBENSLAUF**

<table>
<thead>
<tr>
<th>Persönliche Daten</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name:</td>
<td>Isabelle Dyrek, geb.Gaida</td>
</tr>
<tr>
<td>Geburtsdatum, -ort:</td>
<td>21.08.1965, Loben</td>
</tr>
<tr>
<td>Familienstand:</td>
<td>geschieden, 2 Kinder</td>
</tr>
<tr>
<td>Staatsangehörigkeit:</td>
<td>deutsch</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Schul- und Berufsausbildung</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1972 - 1981</td>
<td>Grundschule und Gymnasium in Loben</td>
</tr>
<tr>
<td>1981 - 1985</td>
<td>Gymnasium in Hamburg und Fulda</td>
</tr>
<tr>
<td>10/85 - 02/93</td>
<td>Studium, Medizinische Akademie in Krakau</td>
</tr>
<tr>
<td>08/93 - 10/95</td>
<td>Ärztin im Praktikum in der Kinderarztpraxis Dr.G.Gaida, Flörheim am Main</td>
</tr>
<tr>
<td>04/96 - 08/96</td>
<td>Ärztin im Rahmen des Anerkennungsjahres in der Klinik für Allgemein- und Abdominalchirurgie am Städt. Klinikum Fulda</td>
</tr>
<tr>
<td>seit 09/96</td>
<td>Assistenzärztin in der Kinderarztpraxis Dr.G.Gaida, Flörheim am Main</td>
</tr>
<tr>
<td>05/96</td>
<td>Annahme als Doktorand im Fachbereich Humanmedizin der Ruhr-Universität Bochum</td>
</tr>
<tr>
<td>03/97</td>
<td>Approbation</td>
</tr>
</tbody>
</table>
Medizinische Veröffentlichungen

1. Dyrek, I.
   ichthyosis congenita
   Der Kinderarzt 25 Jg. Nr.7 (1994) 856

2. Dyrek, I., Gaida, G., Bock, H., Mares, A., Gaida, H.
   Blutendes Ulcus duodeni bei einem 12jährigen Jungen als Erstsymptom einer
   asymptomatischen, familiären Helicobacter pylori Infektion.
   Monatsschr Kinderheilk 145 (1997) 897-900

   Potter- Sequenz bei einem Neugeborenen mit beiderseitiger Nierendysplasie aus
   genetischer Sicht.
   Wiadomosci Lekarskie (in Druck)

4. Suerbaum, S., Smith, J.M., Bapumia, K., Morelli, G., Smith, N.H., Kunstmann, E.,
   Dyrek, I., Achtman, M.
   Free recombination within Helicobacter pylori.

5. Dyrek, I., Lange, S., Opferkuch, W., Gaida, G., Gaida, H.
   Intrafamilial spread of Helicobacter pylori infection: a study on 142 families from
   Germany by means of serology and $^{13}$C-urea breath test.
   J. Pediatr. (in Druck)