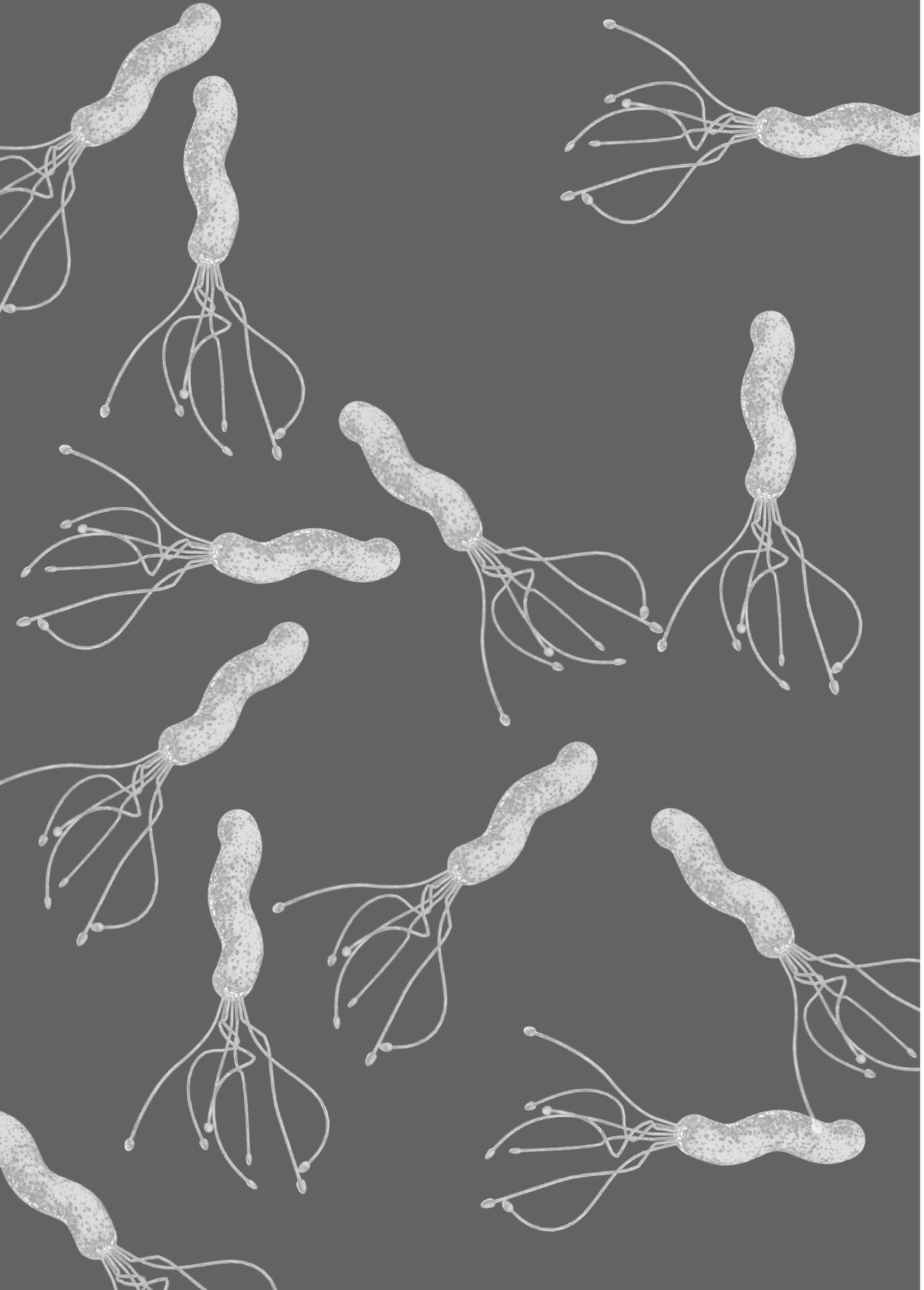
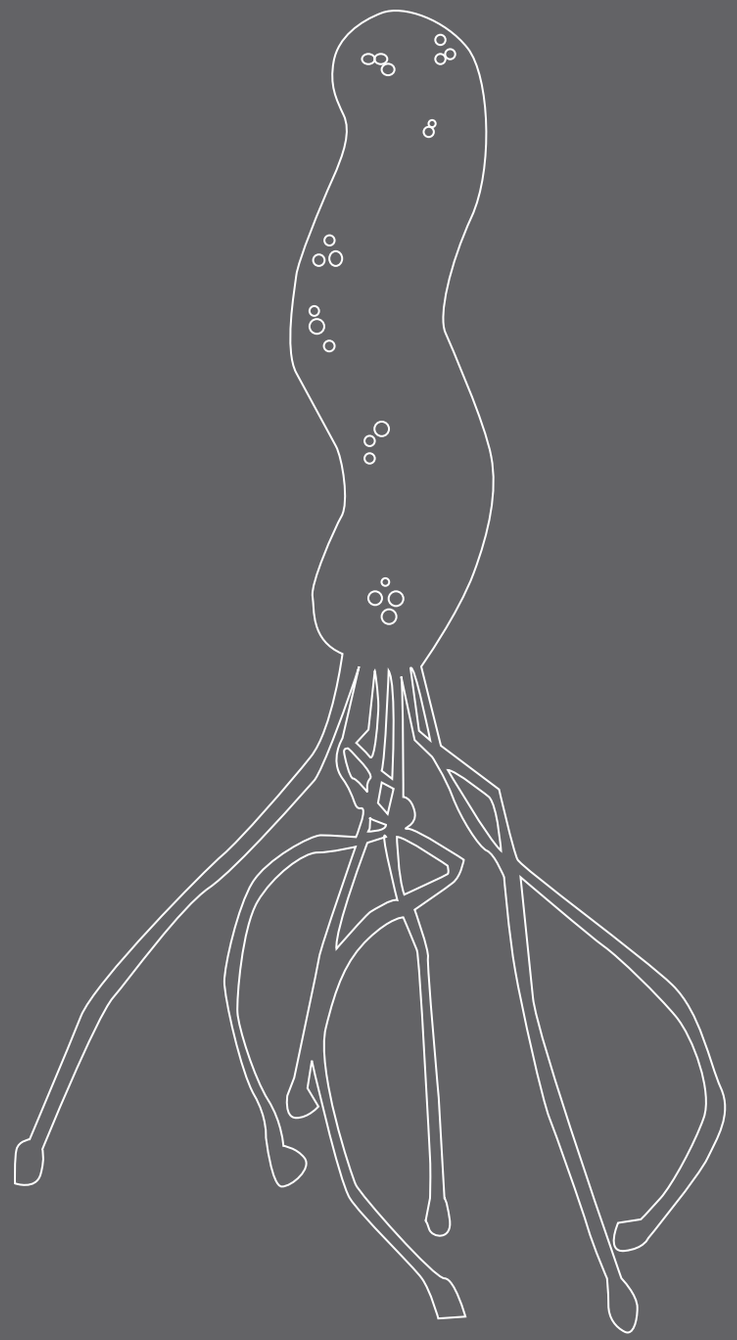


SECTION D

GENERAL DISCUSSION



CHAPTER 8

General discussion, conclusions and topics for further research

ABSTRACT

This chapter discusses the key findings of our research on the prevalence, diagnosis and treatment of *Helicobacter pylori* (*Hp*) infection in children, including some technical aspects on *Hp*-related clinical issues. The final part concerns some aspects of prevention of *Hp* infection and future directions of *Hp*-related research.

8.1 PREVALENCE

Prevalence of *Hp* infection

The prevalence of *Hp* infection varies from 11-70% in Europe to more than 90% in adults in Africa and Asia. This variability is highly related to geography, ethnicity, age and socioeconomic status. The prevalence of *Hp* infection has decreased considerably in the last decades in developed countries [1-4]. Roosendaal *et al* predicted a decrease of the prevalence in Dutch adults between 1940 and 2040 from 50% to less than 20% , based on a decrease of prevalence from 20 to 10% in the 6-15 years age group over 15 years (1978-1993) in the Netherlands [5].

We found a relatively low prevalence in young children (2-4 years of age) in the general Dutch population (1.2%), and a significantly higher prevalence among Dutch children of the same age belonging to ethnical minorities (2.6%) (Chapter 4). A recent study showed that *Hp* prevalence in Dutch children (7-9 years of age) has stabilized between 1993 and 2005 at a level of 9% [6]. This stabilization can be explained in two ways. First, it may be that no further decrease can be expected by improving living conditions and decreasing family size because these have already reached the maximum level attainable. Alternatively, a potential decrease by improvements of these factors may be neutralized, at least partly, by increased immigration of children from high prevalence countries. As a result of this stabilization, colonization with *Hp* is expected to remain common in the coming decades [6]. Notably, more than 90% of the children, investigated in this study, were of Dutch descent, so that the study group does not reflect the current population, of which 21% is reported to be of non-Dutch descent (www.cbs.nl). So, the authors may have underestimated the prevalence of *Hp* among schoolchildren of the general population in the Netherlands.

During the last five years, the number of people from high prevalence countries in Eastern Europe (Poland, Romania, Bulgaria) and Asia and the Middle East (China, Afghanistan, Iran, Iraq), who immigrated into the Netherlands has tripled (www.cbs.nl), which may have a significant influence on the *Hp* prevalence. Since the infection is usually acquired at a young age, it is likely that these immigrants and their offspring have already been infected in the country of origin, and form a risk group for *Hp* infection and its pathology.

After discovering that a group of adopted children that emigrated from Indonesia to the Netherlands tested *Hp*-positive, we decided to investigate the prevalence of *Hp* infection in their country of birth. We expected to find a high prevalence of *Hp* in a crowded district of Bandung (Chapter 6). Interestingly, the prevalence in the young Indonesian children was relatively high (8% for the youngest participants).

However, this could not be confirmed in a follow-up two years later when the prevalence was 0%. Given previous data on the prevalence of *Hp* in Indonesia [7], we speculate that the prevalence of *Hp* infection may differ between various areas in a country. We therefore suggest that before deciding on eradication campaigns in high prevalence countries, the local variation of prevalence should first be monitored.
Apart from the group of children of non-Dutch parents living in the Netherlands (recently immigrated or adopted from abroad), another risk group for *Hp*-infection consists of institutionalized children. The prevalence of *Hp* in residential children with developmental disabilities is reportedly higher than in the general population [8-11]. In the Netherlands the prevalence of *Hp* has been described by Bohmer *et al* in institutionalized persons (N=338, 11-89 year, median age 51 yr), of whom a small number of children [12]. The *Hp* prevalence in these adults was significantly higher (83%) than the prevalence of *Hp* in adults of the general Dutch population (50%).
A third group we have identified to be at risk for severe *Hp* infection are children with immunodeficiencies / X-linked agammaglobulinemia (XLA), because of their proneness to recurrent gastrointestinal infections. Although *Hp* infections in immunocompetent children are limited to superficial infections of the stomach, bacteremia with *Helicobacter* (species) has been found in patients with immunodeficiencies [13,14]. Diagnosis can be delayed by the fact that recognition in standard automatic blood cultures is problematic, since *Hp* germs multiply slowly. Therefore extended culturing after one week of incubation is often applied, if no bacterial growth is observed in the first week. We published a case report and literature review on this topic [15].
In the 10 years database of *Hp*-strains from adults and children at the Leiden University Medical Center, the prevalence of *Hp*-resistance to antibiotics was low, despite dramatically increasing percentages of drug resistance to clarithromycin, metronidazole and amoxicillin reported elsewhere [16-21]. Possibly, the restricted prescription of antimicrobial drugs and the lack of over-the-counter availability of antibiotics in the Netherlands may have contributed to the low prevalence of drug resistance. Intensive surveillance of the resistance patterns will remain important, given the expected changes in the composition of the population in the Netherlands.
With respect to the virulence of *Hp* strains, special attention should be given to children originating from high prevalence countries, for example as a result of adoption or immigration. This group is at increased risk of developing gastroduodenal lesions as they may have been infected with the more virulent strains (CagA positive), that are dominant in these countries. These strains cause more pathology, and at an earlier age [22,23]. In contrast, in the Dutch population CagA positive strains are currently vanishing. Den Hoed *et al* detected CagA-seropositivity

in only 8.2% of the *Hp*-positive Dutch children 6. An earlier Finnish cohort study determined a decline in prevalence of CagA antibodies from 43% to 8% among subjects 14-44 years old over a 21 year period, suggesting that CagA positive strains are disappearing more rapidly than CagA negative strains [24].

Prevalence of gastric and duodenal ulcers

In the prospective multicenter study on the frequency and risk factors of gastric and duodenal ulcers or erosions in European children undergoing an upper endoscopy, we found a frequency of 8.1%, occurring mainly in adolescence. However, *Hp* infection was only detected in 27% of the children with ulcer or erosion (Chapter 5). In an earlier multicenter study on antibiotic resistance of *Hp* in Europe a frequency of 10.4% of ulcers was found in children above the age of 12 years [25]. More ulcers and/or erosions (16.7 to 22%) were found in research centers in Belgium, Italy and Turkey. In all these countries the clinical presentation was similar: clinical symptoms such as epigastric pain, hematemesis, melena and weight stagnation, as well as known chronic diseases such as inflammatory bowel disease (IBD) and rheumatic diseases. If aged above 10 years of age, nocturnal pain was also significantly associated with ulcers [26].
Oderda *et al* reported on *Hp* negative ulcers [27] and highlighted that in countries with a relatively low *Hp* prevalence most ulcers are not associated with *Hp*-infection. So, pediatricians should be aware that gastric and duodenal ulcers in European children, surprisingly, occur more often in *Hp*-negative than in *Hp*-positive children. Therefore, despite the decreasing prevalence of *Hp* in Europe, the frequency of ulcers and/or erosions may still increase due to the increasing prevalence of chronic diseases such as inflammatory bowel diseases (IBD) and rheumatic diseases, as well as the increasing use of drugs, that can cause ulcers as a side-effect (ulcerogenic drugs) in children. The development of gastro-duodenal ulcers is multifactorial, so that many other factors than *Hp*, such as genetic susceptibility, can lead to the development of ulcers.
As mentioned above, the risk of developing peptic ulcer disease (PUD) is higher in pediatric and adult patients that are CagA seropositive or carry CagA positive status. However, not all CagA positive patients develop ulcers, depending on the in situ expressing of CagA. A positive correlation was established between acute and chronic gastritis, bacterial density and CagA-expression. Moreover, Figura *et al* showed that most patients with non-ulcer-dyspepsia harbor both CagA positive and –negative strains [28-31]. For practical reasons, in our study the CagA status of *Hp* or other virulence factors of the bacterium in positive patients with ulcer and/or erosions could not be investigated.

8.2 DIAGNOSIS

In the last decade, much progression has been made in the development of non-invasive diagnostic tools. However, none of these tests are 100% specific and sensitive (Chapter 2) and most tests have been poorly validated in infants below the age of 2 years in low prevalence populations. At the present time the monoclonal stool test is most frequently used, and has an adequate sensitivity and specificity (97-98% and 95-100%, respectively) for the detection of *Hp* [32]. Therefore easily accessible testing of *Hp* has become feasible. The ^{13}C-urea breath test requires special devices and equipment for children, but provides a non-invasive test with an optimal performance, even better for post-treatment control. Serology testing is only useful in epidemiological studies, since this does not discriminate between a past or ongoing infection. The availability of these tests has aroused discussion about the necessity to perform endoscopy in suspected cases versus a test-and-treatment regimen.

Endoscopy versus test-and-treat: implications for the differential diagnosis

Recently, an evidence-based guideline was published for diagnosis and treatment of *Hp* infection in children in Europe and North-America. This guideline recommends endoscopy (including rapid urease testing, histology and/or culture) in all suspected cases, including those with a positive non-invasive test [33]. When used in combination, these tests are still considered "the gold standard" for the diagnosis of *Hp* in children. The main reason for recommending endoscopy is that the symptoms of *Hp* infections are little specific, so that other causes for the symptoms of the child need to be ruled out (e.g. celiac disease, Crohn's disease and gastro esophageal reflux). The added advantage of endoscopy is that other pathologies of the upper gastrointestinal tract can be found, as well as complications of the infection.
However, there are also arguments against endoscopy. First, it is an invasive method that cannot be performed in children without anesthesia or deep sedation. Second, the diagnosis of celiac disease has become easier by recent sensitive antibody-tests, and does no longer require taking duodenal biopsies in selected cases [34]. Third, in children the diagnosis of Crohn's disease is not only based on abdominal complaints, but also on the presence of peri anal alterations (skin tags, fistulas, abcess), extra-intestinal manifestations as mouth ulcers and growth retardation, and a positive family history for inflammatory bowel disease. Fourth, a child suspected for suffering from gastroesophageal reflux, is usually first empirically treated with antacids, proton pump inhibitors or life style intervention before endoscopy is considered.

In our opinion, the decision to perform endoscopy before treatment of *Hp* or not, is dependent on the information obtained at the medical history, physical examination and laboratory investigations. The medical history, given by the child and his/her parents is crucial and should include at least detailed information on the symptoms, family history of gastric ulcers or carcinoma, and country of birth. A thorough examination of the patient, accompanied by laboratory results, is required to assess the likelihood of the various disorders in the differential diagnosis.

Endoscopy versus test-and-treat: implications for the therapeutic strategy

As mentioned above, the recent guideline for children recommends susceptibility monitoring[33] before treatment, implying that endoscopy should always be performed. Theoretically, the obvious advantage is that if the susceptibility for antibiotics is known, the appropriate antibiotics can be administered. However, in our country this would mean that one should have to perform an endoscopy in all cases, as non-invasive susceptibility tests with sufficient diagnostic accuracy are not yet available. While the specificity of PCR in stool is high, the sensitivity is still too low for practical use [35-37]. Susceptibility testing is more important in countries, where high resistance rates of *Hp* play a role, than in our country.
The question is if this general guideline is also applicable for the Netherlands, thus whether a test-and-treat regimen in Dutch children is justified instead of endoscopy and culture with susceptibility testing. This decision should be primarily based on the prevalence of resistance to antibiotics, particularly to clarithromycin. Therefore, it is important to collect information on the patients' previous use of antibiotics, particularly regarding clarithromycin. Current guidelines for adults suggest susceptibility testing only if the resistance rate of *Hp* to clarithromycin is higher than 15-20% [38]. Our study shows that the resistance to clarithromycin in the children was only 6.5% and the resistance to metronidazole 10.4%. As a result of the low resistance rate in children in the Netherlands, we believe that an *Hp* test-and-treat regimen without susceptibility testing is justified as first-line therapy, on the condition that the local and national antibiotic susceptibility of *Hp* are being monitored regularly. Currently, the only way to monitor *Hp* resistance is to analyze databases from centers that perform *Hp* cultures from gastric biopsies.

In conclusion, it seems justified to follow the directive for the adult test-and treat regimen policy, with some exceptions, for example if there are reasons to exclude pathology, or in acute situations (such as hematemesis or melena). In case of one or more risk factors (use of ulcerogenic drugs, family history of ulcers or gastric carcinoma), performing an endoscopy may be necessary to exclude other pathology

and to provide an appropriate treatment and follow-up. In case of eradication failure, susceptibility testing of *Hp* to clarithromycin would be desirable, before a second eradication therapy is applied. Since a non-invasive way of resistance testing (for example by molecular methods in feces) is still not available, in such cases endoscopy is advised.

8.3 TREATMENT

Considering that resistance percentages of *Hp* in the Netherlands are low, the most applied triple therapy (amoxicillin, clarithromycin and a proton pump inhibitor (PPI)) is generally effective in eradicating *Hp*. In case of previous use of clarithromycin, one could consider substituting clarithromycin for metronidazole. If triple therapy does not succeed in the first round, a regimen of amoxicillin, metronidazole and PPI is recommended to cover secondary resistance to clarithromycin. Clarithromycin resistant strains form the main cause of treatment failure, particularly in children [39]. To a lesser extent, this is due to metronidazole resistant strains. In case of a second eradication failure, an alternative regimen (higher doses of the drugs [21], more drugs [40], other drugs (such as bismuth [41] or quinolones [42]), or longer duration of therapy can be considered. A sequential therapeutic scheme, combining a PPI and amoxicillin for the initial five days to reduce the bacterial load and to destroy the bacterial cell wall, followed by a PPI and clarithromycin and metronidazole for the remaining five days, could increase the eradication rate. However, evidence for sequential therapy to be more effective than triple therapy is lacking [43-45]. The downside of these alternative regimens is that they may diminish patient compliance and may increase side effects. As the eradication rate strongly decreases after the first therapy, a well-tailored therapy regimen for children is important.
Recent Italian studies suggest that *Hp* positive immigrants probably should be managed differently from Italian patients [46,47], and possibly this is relevant as well for children in the Netherlands. For example it is unclear if in children of non-Dutch parents efficacy of eradication therapy is lower than in children of Dutch origin, because of worse compliance or by higher antibiotic resistance (Chapter 7).

8.4 PREVENTION

In analogy to the prevention of other infectious diseases, vaccination against *Hp* has been considered. De Vries *et al* calculated that vaccination could possibly be a cost-effective intervention if the prevalence would be higher than 20% [48]. However, these authors exclusively assessed effects 20 years or more after vaccination (such as ulcers and gastric cancer), while pediatricians deal with somatic consequences

(growth, anemia) and cognitive function impairment in children with *Hp* infection [49-51] over a shorter time interval. These effects are particularly worrying in developing countries with a relatively high prevalence.
At present, no *Hp* vaccine has been registered yet, but possible target groups and alternative strategies are being defined. Partly for this reason we assessed the prevalence in young children in the Netherlands in 2006. Due to the low prevalence of *Hp* in the Netherlands, we believe that general preventive measurements, such as vaccination, are not indicated for all children.
In recent years, interest in vaccines has declined, because of publications on adverse effects of *Hp* eradication in adults in developed countries, such as increase of gastroesophageal reflux disease and Barrett's esophagus. Furthermore, it has been suggested that *Hp* eradication may contribute to the obesity epidemic and the increasing prevalence of asthma and allergy. Meanwhile, considerable progression has been made in eradication success rates [52] in developed countries and data on a decline of the prevalence of gastric cancer do also not speak for a vaccination campaign. In high-prevalence countries, however, mass vaccination against *Hp* may be an attractive and practical strategy to eliminate *Hp*-related disease. In some of these countries public health authorities have initiated programs for screening and eradicating of the bacterium.
Thus far, attempts to develop a good (preventive as well as curative) vaccine against *Hp* have faltered for perceptual, practical and financial reasons. Vaccine candidates, delivery routes and adjuvants for preventive and therapeutic strategies were investigated in experimentally infected mice with significant reductions in *Hp* colonization, but only few of these studies achieved complete *Hp* eradication [53]. In humans, few clinical vaccination studies have been performed and the results have been disappointing [52,54]. Moreover, the genetic diversity of *Hp* (sometimes within a single patient) forms a complicating factor. A few years ago, however, a phase 1 study with clinical testing of a vaccine was published with promising results. All healthy non-infected volunteers responded to one or two of the three recombinant antigens (VacA, CagA and NAP) and in 86% of cases the vaccine mounted IgG antibody responses to all of these. Booster immunization after 2 years elicited a strong antibody response to the three antigens in all subjects. The safety of this intramuscular vaccine was satisfactory [55]. However, no further publications on this topic in *Hp* infected persons have been published by the same research group.

8.5 CONCLUSIONS OF THIS THESIS

In this dissertation we present the results of our research on *Helicobacter pylori* infections in childhood, focusing on the prevalence, diagnosis and treatment of the

infection. Our studies were conducted in the Netherlands, Europe and Indonesia. We discuss diagnostic tests, therapeutic regimens, resistance and preventive measurements. We highlight clinical and pathophysiological aspects of the infection and describe which particular strains are prevalent and how transmission occurs. Presently, there are no established correlations between a *Helicobacter pylori* infection and recurrent abdominal pain, gastroesophageal reflux disease or growth retardation. We present data on the prevalence of *Helicobacter pylori* in young infants in the Netherlands and observe that children with at least one non-Dutch parent form a risk group. We assess risk factors in a Europe-wide study on gastroduodenal erosions and ulcers in childhood. In our study, *Helicobacter pylori* infection and gastrotoxic medications were relatively little implicated as etiology of that pathology. The prevalence of *Helicobacter pylori* infection in Indonesian young children is relatively high and points at an early acquisition of the infection. Finally, the resistance of *Helicobacter pylori* to clarithromycin and metronidazole was assessed for adults and children in the Netherlands. Low resistance rates were found, but the resistance in adults is increasing. We conclude that a test-and-treat regimen is justified for the Netherlands.

8.6 TOPICS FOR FUTURE RESEARCH

1. In the Netherlands the prevalence of *Hp* infection in children is low, so screening and treating is probably not useful. Exceptions should be made for identified risk groups. So far, in the Netherlands research in institutionalized individuals has only been carried out in studies on adults, in which some children have been included. We believe that the prevalence of *Hp* should be determined among children in institutions for disabled persons, as they live closely together and possibly part of their abdominal and/or nutritional complaints are caused by *Hp* infection. A gain in the quality of life in those children may be obtained by eradicating *Hp*.
2. Multicenter studies in children with primary or secondary immunodeficiencies are desirable. It is presently unknown what the prevalence is of *Hp* in these children. They often need intensive care nursing and ulcerogenic medication. Scientific studies should be initiated to investigate whether test-and-treat regimen can prevent ulcers and bacteremia in the therapeutic pathway of these children. Within this group of patients particular attention should be drawn to children of non-Dutch parents from high-prevalence countries.
3 In most Dutch children suspected for *Hp* infection a test-and-treat-regimen is justified. Exceptions are children with acute presentations of the disease, such as hematemesis or melena or children with eradication failure. A prospective study on the effects of such strategy should be performed.
4. Regular local surveillance of antibiotic resistance of *Hp* in adults and children is necessary for optimal treatment and prevention of eradication failure and secondary antibiotic resistance.
5. In future Dutch guidelines on treatment of children with *Hp* infection, the choice of antibiotics should be tailored, depending of the development of resistance of *Hp* to clarithromycin and metronidazole in the Netherlands and the resistance rate in the country of birth of the infected children and their parents.
6. The development of a sensitive and specific non-invasive susceptibility test for *Hp* in stool samples would be a significant improvement of the management of children with suspected *Hp* infection before first triple therapy as well as after failure of eradication.
7. Pediatric-based *Hp* research is necessary for our understanding of both clinical and pathophysiological aspects of the infection. Since the prevalence of *Hp* in children of the general Dutch population is low, those studies should ideally be multicenter-based.

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