Hepatitis E, Helicobacter pylori, and peptic ulcers in workers exposed to sewage: a prospective cohort study

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Abstract

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Methods: 332 workers exposed to sewage and a control group of 446 municipal manual workers (participation: 61 %) entered a prospective cohort study with clinical examination and determination of antibodies to H. pylori and HEV (immunoglobulins G and A or G and M, respectively). Survival curves were examined with log rank tests and Cox regressions. Travelling to endemic areas, socioeconomic level, age, country in which childhood was spent, number of siblings, and personal protective equipment were considered as the main confounding factors.

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Keywords: Hepatitis E, Helicobacter pylori, sewage
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Conclusions: These results do not support the hypothesis of sewage as a source of occupational infection for H. pylori or HEV in sewage workers trained for this job with available personal protective equipment and working in a region with good sanitation.
Main messages

The incidence of clinical hepatitis E and peptic ulcer disease is not increased in workers exposed to sewage.

The seroconversion rates due to the contact with the virus of hepatitis E or the bacterium H. pylori are not increased in sewage workers.

Policy implications

In this population trained to work with waste water, having personal protective equipment at its disposal and working in a non endemic area, no increased risk of infection with the virus of hepatitis E or H. pylori was found. This may not hold true in endemic regions where other genotypes of the hepatitis E virus are circulating.
Hepatitis E (HE) is a viral hepatitis with mostly benign course and low case fatality rate in the general population (about 1 %), with the exception of pregnant women. Helicobacter pylori (H. pylori) is the main cause of peptic ulcer disease and stomach cancer. Both pathogens have been found in sewage. Consequently, compensation and prevention of HE, peptic ulcer disease and possibly stomach cancer in workers exposed to sewage must be considered.

In a previous cross sectional study, the prevalence of peptic ulcer disease or hepatitis E and the seroprevalence of H. pylori and HE were not increased in workers exposed to waste water compared to non exposed subjects. However, a cross sectional design may give too optimistic results because diseased workers do not work or have left the workplace. Furthermore, incidence rates are more reliable than prevalence rates to examine the temporal relationship between exposure and disease and the prospective design allows for using each subject as his/her own control. Therefore, a follow-up of a previous cross sectional study in sewage workers was conducted to confirm the results of the original cross sectional investigation. The endpoints were the incidence of clinical HE, peptic ulcer disease, and seroconversion rates.
SUBJECTS AND METHODS
A detailed description has been given with the results of the baseline examination, so only the main aspects will be briefly summarized here.

Subjects
All workers exposed to sewage in the Canton of Zurich (Switzerland) had the opportunity to participate, whereas potential control subjects (garbage collectors, gardeners, workers maintaining waterways, public transport workers, and forestry workers) were approached one by one and invited to participate until enough control subjects were recruited. The workers were included in the study only after they had given written consent. Overall, 778 subjects were included in the baseline examination (participation: 61 %): 355 and 423 workers were from waste water and control plants, respectively (participation 90 and 49 %, respectively). Exposure to sewage during the whole working life was assessed for each job separately and whenever exposure defined by the plant differed from individual occupational history misclassifications were corrected to be sure that no subject from the control group has any exposure to sewage and conversely. Ultimately, 332 and 446 workers were included for follow-up as currently exposed and non exposed to waste water, respectively.

Participation was associated with Swiss nationality (66.2 v 47.5 %) and slightly younger age (median: 44 v 47 years) but not with gender (p > 0.4; \( \chi^2 \) test). The lower participation in controls was associated mainly with two plants (participation rate: 15 and 21 %). When these were excluded the rate rose to 79 %. Thus, some statistical analyses were re-run without these plants. Some immunological results are missing because of blood sampling was not accepted or possible or for organizational reasons.

Methods
This prospective cohort study conducted in the Canton of Zurich consisted of a baseline and four annual follow-up examinations. The baseline medical examination took place between June 2000 and July 2002, the 5th examination between August 2004 and May 2006. As a general rule, examinations were planned at one-year intervals but could be advanced or postponed because of holiday, illness, or increased workload. The minimal interval between two consecutive examinations was six months. As the plants did not regularly inform us about workers leaving the plant we were not able to organize a final examination on time. Therefore, as soon as we knew that a worker had left, he (she) was contacted to complete a short checklist to get some insight into the reasons of leaving. In particular, information was collected to record possible medical reasons for leaving. After three unsuccessful attempts by phone and/or by mail workers were declared missing.

Each physician examined both exposed and unexposed subjects and the coding of the answers was reviewed during the whole study by the same occupational health practitioner. Divergences were resolved by checking again information and discussing codes with the examining physicians. At each follow-up examination workers were asked whether their physician had diagnosed a liver or stomach disease since the last examination. Blood transfusion was asked at the final examination to take into account such transmission of HEV. Peptic ulcer and liver diseases were defined on the basis of clinical history, gastritis on the basis of biopsy data reported by the patient. Socioeconomic level, “country of childhood”, alcohol consumption and \( \gamma \)-glutamyltransferase (GGT) activity were assessed at baseline, smoking was assessed at baseline and at the last examination, travel to endemic areas was assessed yearly as described previously. Use of personal protective equipment was assessed at baseline. Suitable gloves and adequate masks were defined as personal protective equipment worn for at least 50 % of the working time and adequate for work with waste water (i.e. leather gloves permeable
to water were not considered as suitable). Furthermore, masks had to be maintained correctly. Exposure was assessed individually at all five examinations with the same questionnaire and defined by four indicators: exposure to sewage during follow-up (yes/no), duration of exposure during follow-up (weeks), occurrence of splashes during follow-up (never exposed to sewage, never more than 20 splashes of raw sewage in any job, at least one job with more than 20 splashes), and exposure to raw sewage during follow-up (never exposed, exposure ≤ 5 times monthly or more than 5 times monthly in at least one job). Changes in occupational duties were taken into account in the exposure assessment.

All immunologic determinations were carried out in the Clinical Immunology Unit (University Hospital, Zurich) according to the manufacturer’s instructions and with a quality control. Analyses were done in batches and the laboratory did not know the exposure status. The same methods were used during the whole follow-up. The limit values recommended by the manufacturer and in use in the University Hospital were used. Immunoglobulin G antibodies to H. pylori (H. pylori IgG) and immunoglobulin A antibodies to H. pylori (H. pylori IgA) were determined with enzyme linked immunosorbent assays (ELISA) (Synelisa H. pylori (IgG) Abs, Pharmacia and Upjohn, Germany; Quanta Lite H. pylori IgA ELISA, Inova Diagnostics Inc., California, USA). Test results below 10 and 20 U/ml for H. pylori IgG and IgA, respectively, were considered negative. A questionable seroconversion was defined by antibody titres in a range including the cut off plus 10% (the inter-assay coefficient of variation given by the manufacturer). Antibodies (IgG/IgM) to HEV were determined with an ELISA using rDNA as an antigen (ORF3 and part of ORF2) (Abbott Laboratories, Abbott Park, IL 60064, USA). Every positive result for antibodies to HEV is based on a duplicate determination. Regarding HEV borderline results were classified as positive for statistical analyses. As seropositive subjects were not followed up, seroreversion rates could not be calculated.

Data analyses
The normality of the distribution was tested and logarithmic transformations done if necessary or non parametric tests used. Survival was defined as the time between the baseline examination and the occurrence of seroconversion, the end of exposure to waste water, or the end of follow-up, whichever came first. Three survival times (antibodies to HEV, H. pylori IgG, H. pylori IgA) were calculated for each worker and examined with log-rank tests and Cox regressions, which included the variables from the final model presented by Jeggli et al. Cox regression used the option “exact” for ties handling and age was included as a time-dependent covariate. Sensitivity analyses looked after an informative censoring by considering either all censored cases as having seroconverted at the time of censoring or all censored cases as having remained seronegative until the highest follow-up duration (270 weeks). All calculations were done with SAS statistical software (version 8.2; SAS Institute Inc., Cary, NC, USA).
RESULTS
Median interval was 60 (n=700), 46 (n=676), 52 (n=642), and 52 (n=603) weeks between the first and second, second and third, third and fourth and fourth and fifth examinations. The shortest and longest total length of follow-up was 8 and 270 weeks, respectively (median: 196 weeks).

Figure 1 summarizes reasons for non participation and loss to follow-up. Table 1 summarizes the characteristics of the subjects. At baseline, there were several statistically significant differences between groups: age, gender, education level, nationality, country of childhood, smoking status (but not pack-years), duration of follow-up, and GGT activity (but not alcohol consumption) (0.0001 < p < 0.02). All possible risk factors were considered in the Cox regression although the differences were mostly too small to be viewed as clinically relevant for H. pylori or HE. Importantly, participation until the end of the study was associated with "job change because of any health problem" [12 (21%) versus 44 (79%) in participants and non participants, respectively; p < 0.0001]. However, job changes during follow-up were associated with seroconversion neither for HEV nor for H. pylori (p ≥ 0.3; Fischer’s exact test) and no job changes occurred because of hepatitis or liver disease. One single sewage worker left the follow-up because of early retirement due to a perforated peptic ulcer, but this was not an incident case (a first bleeding episode because of peptic disease had already occurred 10 years before the beginning of the follow-up). Women left the study during follow-up slightly more often than men (p=0.06). No further difference between those participating and non participating till the end of the follow-up appeared with respect to the other variables listed in table 1 (p>0.4) and the lifelong duration of exposure to sewage was similar in those exposed at baseline, whether they participated or not till the end of the follow-up (p=0.1). Four workers changed location once during follow-up, one single worker was in the same plant at the beginning and the end of the follow up but worked in the meantime for two years in another sewage plant.

According to occupational history, number of sewage-exposed jobs of the workers exposed at the beginning of the follow-up was one to five (number of subjects and median duration in years were 332 and 8, 92 and 6, 25 and 5, 5 and 4, and 1 and 0.5 for the current and the 1\textsuperscript{st}, 2\textsuperscript{nd}, 3\textsuperscript{rd}, and 4\textsuperscript{th} prior sewage-exposed job, respectively).

Sewage plant workers must follow a training, most waste water workers have a 5-year training (“Klärrwerkermeister”), and courses remind them about the importance of hand washing and personal protective equipment. Each plant has a shower unit, which is much used. Work clothes are always used, wearing of gloves and mask is given in table 1. Goggles, if any, are used primarily in the plant laboratory.

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the subjects at the beginning of the follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure to waste water</td>
</tr>
<tr>
<td>no (n = 446)</td>
</tr>
<tr>
<td>yes (n = 332)</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>42 (16-68)</td>
</tr>
<tr>
<td>46 (17-66)</td>
</tr>
<tr>
<td>Male gender</td>
</tr>
<tr>
<td>417 (94)</td>
</tr>
<tr>
<td>331 (100)</td>
</tr>
<tr>
<td>Education level</td>
</tr>
<tr>
<td>low</td>
</tr>
<tr>
<td>104 (24)</td>
</tr>
<tr>
<td>39 (12)</td>
</tr>
<tr>
<td>middle</td>
</tr>
<tr>
<td>323 (73)</td>
</tr>
<tr>
<td>290 (87)</td>
</tr>
<tr>
<td>high</td>
</tr>
<tr>
<td>15 (3)</td>
</tr>
<tr>
<td>3 (1)</td>
</tr>
<tr>
<td>Nationality</td>
</tr>
<tr>
<td>Swiss</td>
</tr>
<tr>
<td>342 (77)</td>
</tr>
<tr>
<td>302 (91)</td>
</tr>
<tr>
<td>Other countries</td>
</tr>
<tr>
<td>104 (23)</td>
</tr>
<tr>
<td>30 (9)</td>
</tr>
<tr>
<td>Country of childhood</td>
</tr>
<tr>
<td>Switzerland</td>
</tr>
<tr>
<td>332 (74)</td>
</tr>
<tr>
<td>299 (90)</td>
</tr>
</tbody>
</table>
### Table 2. Seroconversion and clinical endpoints

<table>
<thead>
<tr>
<th>Exposure to waste water</th>
<th>no</th>
<th>yes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Seroconversion / person-year</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatitis E</td>
<td>0.01</td>
<td>0.01</td>
</tr>
<tr>
<td>H. pylori IgG</td>
<td>0.10</td>
<td>0.11</td>
</tr>
<tr>
<td>H. pylori IgA</td>
<td>0.18</td>
<td>0.15</td>
</tr>
<tr>
<td><strong>Incidence of clinical endpoints (person-years)</strong>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>peptic ulcer</td>
<td>0</td>
<td>0.0008</td>
</tr>
<tr>
<td>gastritis</td>
<td>0.005</td>
<td>0.002</td>
</tr>
<tr>
<td>eradication</td>
<td>0.008</td>
<td>0.002</td>
</tr>
</tbody>
</table>

* Absolute number of cases was: 0 and 1 for peptic ulcer, 7 and 2 for gastritis, and 12 and 3 for eradication in non exposed and exposed workers, respectively (p > 0.1; Fisher’s exact test). Seven workers were diagnosed with both gastritis and eradication.

667 workers were seronegative for HE at the beginning of the follow-up and had at least one follow-up determination. During follow-up no clinical HE was diagnosed and seroconversion was found in 26 subjects with identical incidence rates in both exposed and non exposed workers (table 2). Twenty-five subjects had undoubtedly positive titres; in only one single case seroconversion was based on a borderline finding (as the subject left after seroconversion, no further determination was available). In 24 subjects seroconversion was without clinical symptoms. In two further patients, liver disorders were noted but no diagnosis of HE was made (one case of hepatitis B and one subject with pathological liver enzymes found at a check-up). Thirteen of the 26 seroconverters had never been in endemic areas and...
no association was found between seroconversion and travel to endemic areas (p > 0.6; χ² test). Survival did not differ between sewage and control workers (figure 2) for any exposure indicator (p ≥ 0.4). None of the two subjects with blood transfusion during follow-up seroconverted. Wearing personal protective equipment had no statistically significant effect (p > 0.6).

Regarding H. pylori, no differences appeared with respect to clinical endpoints either (table 2). Regarding H. pylori IgG and IgA, valid follow-up data were available for 395 and 534 subjects seronegative at baseline, respectively and seroconversion occurred in 125 and 242 subjects, respectively. Incidence rates were very close in control and exposed subjects (table 2). Survival curves and hazard ratios (HR) from Cox regression (figures 2 and 3) did not disclose any statistically significant effect of exposure to waste water (p > 0.2 for all four exposure indicators and both antibody classes). After excluding subjects with questionable seroconversion, the number of seroconverters decreased markedly to 93 and 162 for anti-H. pylori IgG and IgA, respectively but this exclusion did not alter the results of survival analyses. In the Cox regression no independent variable was associated with seroconversion in a significant and consistent way for both IgG and IgA antibodies. Specifically, shift work and personal protective equipment had no statistically significant effect (p > 0.2) and no dose-response relationship was found. Smoking habits at the end of follow-up (instead of baseline) did not alter the results either.

None of the six sensitivity analyses looking for informative censoring showed an increased seroconversion rate in sewage workers for any of the three serological outcomes. Excluding the workers from both plants with very low participation did not alter the results either.

Most recent European studies on H. pylori seroconversion assessed seroconversion rates in “%/year” in a population made only of participants with valid results at a baseline and a follow-up examination (no survival curves were calculated). Thus, a subgroup selected in a similar way was drawn from the whole study population to calculate seroconversion rates in “%/year”. This subgroup comprised all subjects having participated both in the first and the last examination, with valid results at both time points, seronegative at baseline, and having a follow-up > 4 years. This subpopulation had been followed for a median time of 4.5 years (range: 4.01 – 5.10 years; first and last examination mostly in 2000 and 2005, respectively). The seroconversion rates were 6.8 and 10.8 %/year for H. pylori IgG and IgA, respectively, and decreased to 5.8 and 8.2 %/year after excluding subjects with questionable seroconversion. In all four comparisons exposure to waste water had no effect on survival (p ≥ 0.3).
DISCUSSION
This is the first prospective cohort study having examined the incidence of HE and peptic ulcer disease as well as the incidence of antibodies to HEV and H. pylori in a large group of sewage workers. The purpose was to examine the hypothesis that sewage workers were at increased risk of HEV and H. pylori infection as both agents have been found in sewage. 

These results from the Canton of Zurich (Switzerland), a non endemic country, are in line with recent findings from England. Indeed, 26 workers seroconverted but a clinical diagnosis of HE was made in none of these subjects. Thirteen of the 26 workers had never been in endemic areas, which suggests that the hepatitis E virus circulates in Switzerland as well. However, contrary to the hypothesis, none of the four indicators of exposure was associated with seroconversion. At first glance, this finding seems at variance with the results of Vaidya et al and El Esnawy. However, Vaidya et al examined sewage workers in India, an hyperendemic area, where the possibly more virulent genotype 1 is prevailing in humans. Furthermore, the virus titres in sewage may be much higher in India allowing for the infectious dose to be reached more easily. Thus, the different findings may represent two different clinico-epidemiological forms of HE. As Egypt is also an endemic area the increased prevalence found by El-Esnawy may be explained by the same cause.

Peptic ulcer disease in sewage workers has been hitherto examined in two cross sectional studies with inconclusive results. In the present cohort, the incidence of peptic ulcer disease did not differ between the exposed and the control group. This finding agrees well with the odds ratio (OR) of 1.4 (95% confidence interval (95%CI): 0.31 – 6.1) reported by Friis et al. in Swedish sewage workers and with the OR of 0.72 (95%CI: 0.32 – 1.61) from the baseline examination of this cohort and does not support an increased risk of clinical peptic ulcer disease in this population.

At baseline the H. pylori IgG seroprevalence was lower in the exposed than in the non exposed group. It was suggested that unknown bias or residual confounding most likely explained this decreased prevalence. The results of the cohort study support this hypothesis and agree well with the findings on H. pylori IgG from Sweden and from a preliminary Belgian study. Overall, the available evidence, although still limited, does not confirm an increased risk of H. pylori infection in workers exposed to sewage although the bacterium can be identified in wastewater. Possible explanations are the occurrence in water of the coccoid form that is not able to colonize human stomach and too low an infectious dose.

The lack of association is unlikely to be explained by a selection bias at baseline, although 488 eligible workers did not enter the study. Indeed, they were more often foreigners, a subgroup with a fairly high H. pylori seroprevalence in this study. As the workers not entering the study came mainly from two control plants, their inclusion should have rather increased the seroprevalence of H. pylori in the control group and, therefore, their inclusion would not have increased risk in sewage workers. The lack of association cannot be explained by ill workers leaving the plant either. Indeed, job changes during follow-up were not associated with seroconversion for HEV or for H. pylori, hepatitis or liver disease or incident peptic ulcer. Furthermore, subjects participating and non participating until the end of the study were well comparable regarding important characteristics associated with H. pylori seroprevalence (age, education, nationality, country of origin, etc.).

The results of this study do not support the hypothesis that sewage workers were at increased risk of HEV and H. pylori infection. Further studies are needed to confirm this finding and to investigate the reasons for the different findings between the present study and previous studies.
childhood) and lifelong duration of exposure to sewage was similar in both groups. Finally, as few workers changed location during follow-up, a bias because of a high turnover causing misclassifications in exposure is unlikely too.

This study was planned as a comparison of survival curves, whereas most other European studies based on serologic results determined seroconversion rates in %/year for the subpopulation having valid results at two points in time, i.e. without considering cases lost to follow-up. In a comparable subpopulation, the seroprevalence rates were consistent with those of these studies. However, the range is very wide (0.08-22 %/year) although possible differences associated with time period or areas were limited by study selection (studies eligible for comparison were fully published original papers having been conducted in Europe and published between 2000 and 2007 26 27 28 29 30 31). Besides possible genuine differences in transmission of H. pylori between areas, test kits, 32 large differences in the selection procedure of the population and the proportion of cases lost to follow-up probably play a role. Indeed, selection of the population influences the test performances 32 and cases lost to follow-up may not be comparable to participants, which modifies the results. 31 Moreover, including or excluding borderline cases may have a non negligible effect on the seroconversion rates as found in this study and reported by Rosenstock et al 31 and Kuipers et al. 33 However, as serology was not repeated after seroconversion, it was not possible to examine survival curves with different cut offs. The difference in seroconversion rates between H. pylori IgG and H. pylori IgA is likely due to the less good diagnostic performances of the IgA-based tests. 32

The study has some limitations. With respect to H. pylori seroprevalence, the study was designed to be capable of detecting a small relative risk, whereas the power necessary to detect the clinical endpoints could not be assessed meaningfully at the beginning of the study. Indeed, the rate of infection with H. pylori in industrialized countries has decreased substantially in the last decades and eradication has greatly reduced the recurrence and duration of peptic ulcer disease. Therefore, to consider a possible bias due to treatment the cases of gastritis and eradication were also recorded. The data show no trend towards more cases of clinical endpoints in the exposed group (table 2), which is reassuring. However, a lack of power cannot be definitely excluded and results might have been different with more subjects and/or a longer duration of the study.

The use of personal protective equipment is difficult to assess accurately and was based on the baseline interview only. Repeated objective assessments would have been better but may cause a surveillance bias and are very labour-intensive. The main limitation is that the Canton of Zurich is not an endemic area and has good sanitation. Therefore, the results of the study may not be applicable to endemic areas or regions with less good sanitation.
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Conflict of interest. All authors: no conflicts.

Figure 1. Flow chart showing reasons for non participation
Figure 2.: H. pylori IgG: survival distribution function
Figure 3.: H. pylori IgA: survival distribution function
REFERENCES


1266 eligible subjects

- 470 declined participation
- 18 not examined (organisational reasons, sick leave)

778 entered the study (participated in the baseline examination)

- 9 refused further examination
- 132 left (other employer)
- 34 without final examination (organisational reasons, sick leave, or retirement)

603 participated during the whole study

**Figure 1** Flow chart showing reasons for non participation
**Figure 3**  H. pylori IgG: survival distribution function
Figure 4  H. pylori IgA: survival distribution function as supplement