REVIEW

Hepatitis A in workers exposed to sewage: a systematic review

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Abstract

***Objectives*—To assess whether the scientific literature supports the hypothesis that workers exposed to sewage are at higher risk of hepatitis A (HA).**

***Methods*—All original papers reporting epidemiological studies published in English, French, or German which reported on the risk of HA infection in workers exposed to sewage were eligible. They were identified by several methods and each original paper was assessed independently with a checklist by two people. Studies were classified according to the strength of their design. Non-eligible studies were also examined to assess the impact of publication bias. If the risk estimates diverged widely, causes for heterogeneity were assessed. A distinction was made between seroprevalence studies based on subclinical HA (defined only by the presence of anti-HA antibodies) and clinical HA.**

***Results*—17 eligible studies were identified. No indication of an increased risk of clinical HA could be found. For seroprevalence the studies with the strongest design suggested a slightly increased risk of subclinical HA with an odds ratio (OR) <2.5. Heterogeneity was considerable and precluded a meta-analysis. Considering non-eligible studies would still decrease the OR.**

***Conclusions*—The systematic review does not confirm an increased risk of clinical HA in workers exposed to sewage. An increased risk of subclinical HA cannot be excluded but the association between seropositivity and exposure to sewage was not strong and became still weaker if publication bias was taken into account.**

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Keywords: hepatitis A; sewage; systematic review

Main messages

- Studies on the incidence of clinical hepatitis A (HA) do not show an increased risk in workers exposed to sewage.
- Seroprevalence studies may show a moderately increased risk of subclinical HA infection.
- Results of seroprevalence studies may be flawed by several methodological factors.

Policy implications

- Systematic HA vaccination of every worker exposed to sewage will have little effect on the incidence of clinical HA.
- Vaccination of the heavily exposed workers may be of value but this has hitherto not been demonstrated.

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The prevalence of hepatitis A (HA) as defined by the presence of antibodies against HA virus (anti-HAV antibodies) increases with age and is inversely related to socioeconomic level.[1–5] The disease used to occur mainly in childhood, when it is mostly (70% of children <6 years of age) asymptomatic. As a result of better hygienic conditions,[6–8] children are nowadays less often infected. The disease is usually symptomatic among older children and adults, with jaundice occurring in more than 70% of patients. Adults are incapacitated for 4–6 weeks.[9] Eleven per cent to 22% of people with HA are admitted to hospital, and the case fatality rate is 1.8% in those older than 50.[5]

The transmission of the disease occurs by the faecal-oral route. Thus, sewage workers might be at risk of HA through aerosols,[10–14] smoking, and eating. Younger sewage workers may now be at greater risk of HA than the older ones as they often have not been infected during childhood.

Opinions on the need to vaccinate sewage workers diverge widely. Whereas some authors recommend a systematic vaccination because of the increased risk found in sewage workers[1 8 15–21] others do not consider vaccination necessary.[5 22 23] Some occupational health specialists just recommend immunisation for "maintaining labor peace",[24] or to prevent litigation costs,[25 26] or only after evaluating the specific epidemiological situation.[27] The reasons for these differences are unclear and because no systematic review analysing the literature could be found, a systematic review was conducted. The purpose was to see whether the scientific literature supports the hypothesis

Table 1 Cross sectional studies: criteria considered for classification

(*a*) Exposure assessment:
At least two exposure surrogates were used—for example, (1) duration of exposure and (2) intensity, frequency, or probability of exposure
Influence of misclassifications assessed or at least discussed
(*b*) Main outcome measures:
Definition of the type of immunoglobulins determined for assessing seroprevalence
Definition of the term "clinical" hepatitis A
(*c*) Biases:
Exclusion of vaccinated people*
Distinction between hepatitis A occurring before and after beginning of employment
(*d*) Confounding factors:
At least consideration of the three following variables: age, travelling in endemic areas, socioeconomic status (defined according to education, income, or another recognised classification system)
If present consideration of locally important confounding factors—for example, consumption of shellfish
(*e*) Control group:
The selection and the composition of the control group must exclude important flaws capable of introducing a bias

*If no information on vaccination could be found, the period during which the study was conducted—or if not indicated the year of publication—was used as an indicator of the probability of vaccination. A vaccination was considered as very unlikely if the study was performed before 1992.

that workers exposed to sewage are at higher risk of HA.

Methods

All original studies that were published in English, French, or German and that assessed the risk of HA in workers exposed to sewage were sought with several methods. A Medline search (Ovid software, 1966–99) was conducted (*a*) with text words ($=truncation symbol): drainag$ and hepatitis; (sew$ or sanita$) and hepatitis A; (*b*) with MeSH terms: sanitation or waste products and hepatitis or hepatitis A; drainage and hepatitis A; (*c*) with hepatitis A as MeSH term and sew$ as text word. All MeSH terms were "exploded" and the literature search was carried out again after completing the review. Secondly, the data base of the Unit of Occupational and Environmental Medicine (based on a manual search in *Current Content Life Sciences* 1200 and in journals for occupational health; period 1986–99) was used. Thirdly, the bibliography of each article included in the review was checked. Finally, two specialists in the field were asked for further (unpublished) literature**.** Both peer reviewed and non-peer reviewed journals were included.

Because letters, abstracts, and governmental reports did not usually offer a full account on a survey, this type of reference was not eligible. However, as non-publication in scientific journals may also be due to publication bias, clues to "grey" areas in the literature were searched for. The studies not published in English, French, or German were dealt with in a similar way but the source of information was restricted to the abstract or the figures and tables. To make comparisons between eligible and non-eligible literature easier the second is presented in a separate section of the tables. The impact of non-eligible literature is assessed in the discussion by comparing strength of design and results with those of published studies.

Each article was independently assessed by two occupational physicians with a checklist considering period and place, study design, eligibility criteria, selection and characteristics of the study population, exposure assessment, definition of outcome, biases, and confounding factors. Divergences were resolved by consensus. In cases of duplicate studies information from all publications was taken into account. No eligible studies were excluded on the basis of this assessment.

Firstly, the studies were classified according to the strength of their design (in order of decreasing strength: cohort, case-control, cross sectional, and case reports or series). Secondly, it was attempted to single out the most convincing studies and to assess an overall risk estimate based on those studies only. The quality criteria defined four categories ranging from 1 (not very convincing) to 4 (very convincing) (table 1 and table 2). Owing to the number of studies in each design stratum this could be done for the cross sectional studies only. If the risk estimates diverged widely, causes for heterogeneity were assessed.

The appraisal of the study characteristics raised some problems regarding vaccination, exposure definition, and risk estimates.

Whether HA vaccine was used at the time of the study is often not known either because it is not stated in the publication or because the study was carried out before the introduction of a vaccine. If no information on vaccination could be found, the period during which the study was conducted—or if not indicated, the year of publication—was used as an indicator of the probability of vaccination. A vaccination was considered as very unlikely if the study had been performed before 1992.

For this review an exposed worker was defined as a worker exposed to sewage. It was not possible to define the exposure more precisely with respect to minimal duration of employment, exposure intensity, frequency, or type. Indeed, exposure has mostly not been assessed objectively and the tasks of the workers are often described only very briefly. Thus, the use of a standardised terminology was not

Table 2 Definition of the categories used for classifying cross sectional studies

Category	*Definition (according to the criteria listed in table 1)*
4	Criteria (*a*–*e*) are all met.
3	Criteria (*a*, *b*, and *d*) are met; criteria (*c* or *e*, or both) are only partly met
2	(*a*) Exposure assessment at least qualitatively—for example, job name only (*b*) Criterion (*b*) is met (*d*) Only one or two of the four most important confounding factors considered (*c* and *e*) These criteria may or may not be met
1	Still less comprehensive than category 2

Table 3 Studies with clinical outcome

Reference	*Definition of outcome*	*Results Comments*
Eligible studies		
Lerman *et al* (1999)[28]	Clinical HA in 1993–4	HA patients retrieved from three sources: (1) cases reported to the local health district offices (HA is a notifiable disease in Israel); (2) reports from laboratories (IgM); (3) discharges from general hospitals. 85% Of the cases were confirmed serologically.
Brugha *et al* (1998)[29]	Clinical diagnosis of viral hepatitis	The company records showed no cases of viral hepatitis in the 5 years before the study.
Trout *et al* (2000)[33]	History of jaundice or hepatitis in the past	History of hepatitis more frequent in exposed (12%–13%) than in control subjects (0%–1%).
	Definition of hepatitis: NI	Difference hardly interpretable because of differences in age, sex and socioeconomic levels between the four subgroups. Moreover, no distinction between time before and after beginning employment was done and no good association between anti-HAV antibodies and clinical history was found.
DeSerres *et al* (1995)[35]	History of jaundice and hepatitis	No case of jaundice after the beginning of employment was found.
Schlosser and Roudot-Thoraval (1995)[36]	History of jaundice	History of jaundice not more frequent in the exposed group. No distinction between jaundice before and after beginning employment.
Heng *et al* (1994)[37]	Hospital admission because of acute HA after start of work in the sewage treatment plant.	No control group
Skinhoj *et al* (1981)[38]	History of "jaundice or liver disease unrelated to gall bladder disease"	11Episodes of jaundice reported. Eight cases occurred before present occupation (three sewer workers, three gardeners, two clerks). Three cases in sewer workers but none in the control groups occurred during their current employment
Khuder *et al* (1998)[39]	Occurrence of jaundice or HA 1995–1996. Self administered questionnaire	No case of jaundice or HA recorded in either group
Ross *et al* (1998)[44]	Diagnosis of HA reported by consultants in communicable diseases control (n=116).	No cases occurred in sewerage workers
Non-eligible studies		
Clark *et al* (1984)[45]	Continuous collection of self reported illness data	Both workers who seroconverted reported hepatitis symptoms at a time consistent with the period in which the seroconversion occurred (the number of seronegative workers at the beginning of follow up was 249).
PHLS working group (1991)[15]	Cases of HA (interview and salivary IgG and IgM)	Sources for identification of HA cases were apparently (*a*) notifications made by medical practitioners and (*b*) voluntary laboratory reports. No increased risk in sewage workers was found according to Maguire[60]
Tornberg and Ronne (1997)[48]	Notified cases of HA	HA is a mandatory notifiable disease in Denmark The authors wrote that sewage workers "may be particularly at risk although the risk is still low".

NI=no information was found in the publication.

possible and the terms used by the authors of the respective study had to be used in the tables.

If no risk estimates were reported, crude odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated with the information available in the paper (program Epi Info; Center for Disease Control; Atlanta, GA, USA).

Results

The literature search identified 17 eligible studies: one historical prospective,[28] 15 cross sectional,[29–43] and one descriptive.[44] They were conducted between the end of the 1970s and 2000 in eight countries, primarily European ones (10 studies). Two were carried out before 1992, the year used as an approximate surrogate for the introduction of vaccination. No randomised control trials and no case-control studies were identified. The same literature search identified five non-eligible studies: one cohort (research report),[45] one case-control (no published full account),[15] two cross sectional, and one descriptive (published in Italian, Greek, and Danish, respectively).[46–48] They were conducted between 1975 and 1998 in five countries (four in Europe). At least three studies were carried out in part before 1992, the year used as an approximate surrogate for the introduction of vaccination. Despite several attempts one paper[49] could not be obtained and it is not known whether it would have been eligible.

Table 3 summarises the results related to clinical HA, and the main characteristics of all studies are presented in a detailed table found on the online version of *Occupational and Environmental Medicine*.

Two main end points have been considered: clinical hepatitis and seropositivity.

CLINICAL HEPATITIS A

The historical prospective, the descriptive, and seven cross sectional studies used clinical HA as the outcome measure (table 3). The historical prospective, the descriptive study and the cross sectional studies by DeSerres *et al*[35] and Brugha *et al*[29] recorded no excess cases of HA. By contrast, three cases of jaundice during current employment were reported by Skinhoj *et al*[38] in the exposed group but none among the control group. As the available information is very limited no definitive conclusions could be drawn from four studies[33 36 37 39] (table 3).

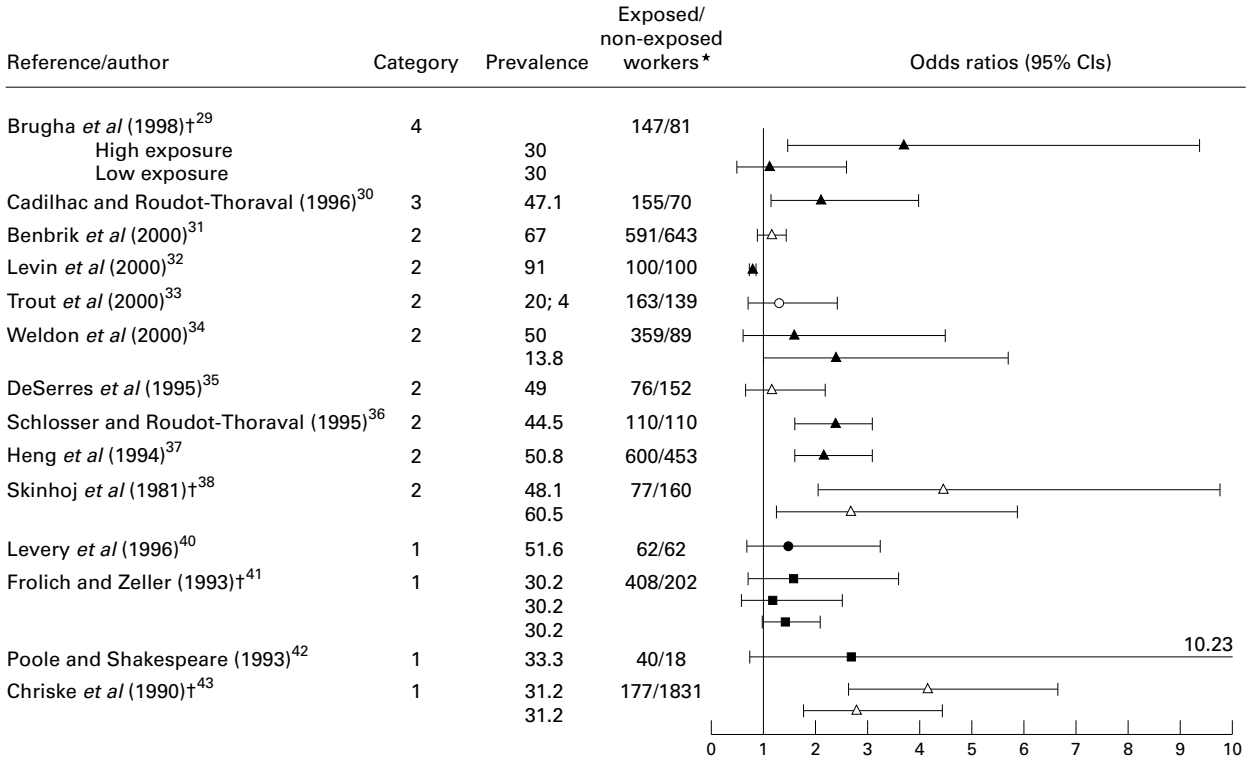

*Figure 1 Cross sectional seroprevalence studies: ORs (95% CIs), and prevalence rates of seropositive subjects in the control groups. Closed triangles=adjusted ORs (95% CIs), (variables considered for adjustment not identical in all studies); closed squares=crude ORs (only crude ORs were given in the publication); open triangles=crude ORs (95% CI) calculated with the data available in the publication (no OR given by the authors); open circle=adjusted prevalence ratio (95% CI); closed circle=subjects matched on age, sex, and socioeconomic level; prevalence=prevalence rates of seropositive subjects in the control group(s). *Study population entered in the seroprevalence study. †More than one main OR given in this study.*

Excluding those four studies left five studies using three different designs. All these studies but one were negative and the increased risk reported by Skinhoj *et al*[38] may also be explained by chance (increased risk based on three cases) or bias. Thus, the hypothesis of a more frequent and more severe HA in unimmunised sewage workers is not supported by these results. The non-eligible studies[15 45 48] are in line with this conclusion (table 3).

SEROPREVALENCE STUDIES

All eligible studies having determined seroprevalence were cross sectional. These 14 studies included 3065 exposed workers and 4110 control subjects. Importantly, the size of the control group was largely determined by one single study with 1831 control persons.[43] Regarding seroprevalence the 20 main comparisons yielded imprecise risk estimates ranging from 0.8 to 4.5 (figure 1). Whereas one study reported a significantly decreased OR[32] non-significantly increased ORs were found in 10 comparisons,[29 31 34 35 40–42] and definitely increased ORs (>3) were reported three times.[29 38 43] In five other comparisons weaker but significant ORs of 2.2 to 2.8 were found.[30 36–38 43] In one study non-significantly increased prevalence ratios were reported.[33] As these large differences in risk estimates suggested some heterogeneity, the influence of study population, confounding factors, exposure characteristics, definition of outcome measure, time period, and study quality was examined.

COMPARABILITY OF THE MAIN FEATURES OF THE CROSS SECTIONAL SEROPREVALENCE STUDIES

Prevalences of anti-HA antibodies ranged from 4% to 91% across the control groups of the different studies. It is not possible to know whether the control groups were actually a representative sample of the general population or whether these differences were due to selection bias. Indeed, information on participation rates and representativeness are rather scarce (extra table on the online version of *Occupational and Environmental Medicine*). In the few studies that included two control groups, an influence of the selection of the control group on the ORs was evident.[34 38 42] However, there was no clear association between seroprevalence in control subjects and ORs across studies. Indeed, OR >3.5 (n=3), of 2.2 to 2.4 (n=4), and 1.2 (n=3) were associated with prevalences ranging from 30% to 48%, 14% to 51%, and 30% to 67%, respectively.

For confounding variables, age and sex may not have been comparable in the control and exposed groups of three studies.[41–43] Only three studies[29 30 33] out of 14 considered the three essential confounding variables (age, travelling in endemic areas, socioeconomic level) but they used different approaches making direct comparisons difficult. There was no obvious relation between methods used for controlling variables and risk estimates (fig 1).

Similar considerations apply to vaccination and a meaningful analysis after stratifying according to vaccination was not possible

because the necessary information was too scarce (web table).

That differences in exposure levels impact on the risk estimates is suggested by the findings of Brugha *et al*[29] and to some extent by those of Chriske *et al*[43] but this hypothesis could not be tested. In a few cases[29 30] a semiquantitative exposure assessment was done by managers or workers. In some other investigations the exposure was characterised by duration of employment.[35–38] However, the definition differed between studies or was unclear (duration of employment in the present plant only or during the whole working life). Finally, job name as the only exposure surrogate in some reports[41–43] is probably too simple an indicator. Indeed, exposure sources were very different: work with raw sewage,[29] workers maintaining the flow of a section of a river polluted with waste water,[41] subjects working in the system of sewers, laboratory workers,[36] gully cleaners, cesspit emptiers, etc.[42] The composition of and the processes used to treat sewage are generally unknown. No objective exposure assessments were made in any cross sectional study. Therefore, it was not possible either to stratify the studies according to exposure or to test a dose-response relation. Moreover, this issue was further complicated by misclassifications of exposure. Indeed, in some plants the workers carried out several tasks with and without exposure and were moving in and out of high risk jobs. It is currently hardly possible to assess the combined effect of difference in exposure level and misclassifications on the ORs.

Differences in sensitivity and specificity of the test kits or different definitions of a positive test result might explain some divergences. Unfortunately, methodological indications are scarce or even absent in some studies[35 36 41 43] and a stratification according to the method of determination of anti-HAV antibodies was impossible.

A decrease of the prevalence of HA infection with time is unlikely to explain the differences of ORs during the past 10 years. The prevalences ranged from 4% to 91% and 30% to 50% for the periods 1995–9 and 1990–4 respectively).

No useful information appeared from the case series and case reports.[24 64–72]

FURTHER LITERATURE

Several studies, the titles of which suggested that they could include useful indications[2 17 73–81] and recommendations of medical boards and books,[1 5 15 21 82–87] were also examined for further literature. Several reviews[6 8 16 18 19 23 26 27 63 68 71 88–98] were found but the interpretation of the older reviews was made difficult by the lack of a serological diagnostic test or of reliable statistical data. It should be stressed however, that the reviews by Dixon and McCabe,[88] Safety Committee-California Water Pollution Control Association,[71] Clark *et al*,[89] and Clark and Linnemann[68] do not suggest a strongly increased risk of HA in sewage workers.

Discussion

A major question is whether the selection procedure has excluded studies quite different from those meeting the eligibility criteria and whether there is some indication of publication bias. The exclusion of the two cross sectional seroprevalence studies which found either decreased[46] or increased risk,[47] would hardly have modified the results. Indeed, there was no difference pertaining to study design, exposure assessment, outcome measure, and results from the abstracts of these investigations. The same holds true for the descriptive study by Tornberg and Ronne.[48] By contrast, the exclusion of the cohort[45] and the case-control study[15] suggests an important publication bias. Indeed, both studies had a design stronger than the cross sectional one and included large study populations. Moreover, PHLS has conducted investigations of HA outbreaks and an increased risk of occupational exposure to sewage was not found[15] (the PHLS report summarises extremely briefly both one case-control study which should have been negative according to Maguire[60] and some additional investigations). Consequently, risk estimates calculated only on the basis of investigations published as a full account in scientific journals may represent an overestimation.

Thus, the risk of clinical HA is not increased in workers exposed to sewage, a conclusion supported by both eligible and non-eligible studies. By contrast, the results for subclinical HA, as defined by seropositivity, are somewhat confusing and we were unable to identify a single factor explaining the disparity of the ORs. However, prevalence rate of anti-HA antibodies in the general population, vaccination policy, lack of adjustment for important confounding variables, and differences in levels of exposure to sewage seem to be reasonable explanations. The respective impact of each factor is likely to vary from one study to another and the overall effect is extremely difficult to assess. Altogether, the analysis of the studies, having adjusted at least for age and socioeconomic level, suggests that the exposure effect does not completely disappear after adjusting but that ORs are generally below 2.5 with the possible exception of heavily exposed subgroups. However, these risk estimates should be viewed with caution even if risk estimates of this magnitude may provide evidence of causal association. Indeed, risk estimates below 3 may be due to biases or confounding variables, which occurred fairly often (web table). Moreover, all studies on subclinical HA were cross sectional, a design not capable of controlling for seropositivity before employment. Finally, it is very disturbing that the only study with a stronger design[45] obviously conflicts with these conclusions.

Dose-response relations were often not examined, non-significant, or difficult to interpret (details can be found on the online version of *Occupational and Environmental Medicine*). Moreover, misclassifications of exposure have probably confused the relation by either non-differential misclassification or combinations of misclassification and bias. Whereas

non-differential misclassification reduces OR towards the null value a combination of bias and misclassification may increase the OR if a high seroprevalence actually due to socioeconomic level, country of origin, or travelling to endemic areas is falsely attributed by erroneous exposure assessments to heavy exposure.

No meta-analysis was done. Indeed, an overall OR could be misleading as meta-analysis cannot correct for biases or lack of consideration of confounding factors. Furthermore, a meta-analysis stratifying according to exposure level would have answered one of the most important questions, that of the dose-response relation, but this was not possible.

These results do not suggest that all sewage workers have to be systematically vaccinated against HA. Indeed, no clue to an increased risk of severe clinical infection was found, and no endemic outbreaks with severe course of HA among sewage workers were reported. As a dose-response relation was found in the best cross sectional study[29] this finding could be seen as supporting a dose-response relation and, thus, vaccination might be discussed for those workers heavily exposed to sewage. However, this conclusion refers to subclinical HA only and is based on a very limited set of data.

These results suggest that further research should use a cohort design (strength of the design), select the control population very carefully (immunisation and confounders), pay more attention to power (precision of the estimate), and define exposure levels accurately. Further cross sectional studies are unlikely to give new useful information especially because of the limitations of this study design.

To summarise, evidence suggesting an increased risk of HA in sewage workers is based on seroprevalence data from cross sectional studies and not on the incidence of clinical HA. The ORs of about 2 suggested by the most reliable cross sectional studies are in a range compatible with the effect of biases or confounding factors, and publication bias might suggest values higher than those actually occurring. These conclusions are based mainly on investigations from Europe and North America and may not be generalisable to populations of workers with quite different natural immunity.

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Table 3. Study populations and results of the seroprevalence studies.

Reference Country Time period †	Study design ‡	Study population §	Exposure surrogate ¶ Outcome	Prevalence and risk estimate ‖	DRR, MA ** Comments
Study populations and results of the eligible studies. *					
Lerman et al. (1999) [28] Israel 1993-1994	HP	1130 patients with clinical HA in a labour force of about 3,700,000 Standardised incidence ratios calculated using 2 standard populations R: 681 lost cases of similar gender and age. No specific information on vaccination available.	Belonging to occupational group “cleaning and sewage workers” (n=59,480) clinical HA identified in 1993-1994.	SIR: 0.88 and 0.95 (99%CI: 0.38-2.03 and 0.38-2.42, with standard population 1 and 2, respectively)	DRR: NA. Exclusion criteria were age less than 18 y, contact with a family member suffering from HA; travelling to hyperendemic area before the occurrence of the disease, being a tourist, prisoner, and soldier on active duty. MA: age, gender, ethnicity, and time of immigration to Israel controlled for. Israel is a country endemic for HA.

Table 3. continued

Brugha et al. (1998) [29] United-Kingdom (London area) 1995-96	CS 4	E: 147 high risk employees from the 3 main drainage depots and 3 large sewage treatment works C: 81. Age (all participants): 39 (NI) Probably males. P: 85 and 68 % in E and C, respectively. Exclusions and V: see comments.	Exposure to raw sewage (according to manager) ED, EI, EF (frequency of splashes; structured questionnaire) IgG clinical diagnosis of viral hepatitis	E: 46 % (sewerage workers) C: 30 % ORs: raw sewage some of the time: 1.14 (0.50-2.59) raw sewage most of the time: 3.73 (1.48-9.37)	DRR: increase (n.s.) in seropositivity with exposure risk as defined by manager (46, 40, 29, 30 % in sewerage workers, flushers and fitters, electricians and supervisors, and unexposed workers, respectively). Increasing OR with frequency of exposure: see OR. MA with numerous confounding factors (travelling in endemic areas, age, socio-economic level, etc.) Lost cases unlikely to have caused a major bias. 13 participants secondarily excluded (10 vaccinated subjects and 3 with ambiguous test results). Exposure to raw sewage most of the time may represent a subgroup with particularly high exposure.

Table 3. continued

Cadilhac and Roudot-Thoraval (1996) [30] France (Val de Marne) 1993	CS 3	E: 155 sewage workers Age: 85.2 % older than 29 y. 125 M (80.6 %). C: 70 employees from the same firm. Age: 90 % older than 29 years. 19 M (27 %). P (E +C together): 82 %. R: NI Exclusion of immunized subjects: NI	CO ED (about 10 ± 8) EF (3 grades) “total specific antibodies”	E: 60 % C: 47.1% OR: 2.15 (1.15-4.00)	DRR: no DRR found in multivariate analysis. The seroprevalence of anti-HAV antibodies was very similar in the 3 subgroups defined by EF. Detailed MA: age, gender, educational level, number of siblings, travelling in endemic areas as well as occupational exposure (qualitative indicator, EF, and ED). Two other papers refer to the same population (Cadilhac and Roudot-Thoraval [50 51]). The publication by Schlosser and Roudot-Thoraval (see below) might include part of the same population.

Table 3. continued

Benbrik et al. (2000) [31] France (City of Paris) 1995-1996	CS 2	E: 201 sewage workers and 390 water-purification station workers. Age: 41 and 39 (23-59 and 20-60) respectively. M only C: 643 administrative workers. Age: 42.5 (21-63) M only. Education level, country of birth, V: see comment. Overall P: 85.5 %. R: NI	CO ED Occupational risk factors (“soiled earth”, “floating corpses”, etc.) total antibodies (IgG and IgM)	E: 71 % C: 67 % OR(*): 1.17 (0.91-1.50)	DRR: not explored in a MA. MA: factor analysis identified 5 subgroups (non-exposed workers and 4 subgroups of exposed workers). No clear subgroup-specific patterns of occupational risk factors appeared. Results very descriptive (no a priori hypothesis tested in a logistic regression model). No clear definition of the types of non-occupational and occupational risk factors (for example “floating corpses”). Education level and country of birth differed between both groups. Vaccination status recorded but not included in multivariate analysis.

Table 3. continued

Levin et al. (2000) [32] Israel 1996-1997	CS 2	E: 100 sewage workers Age 42.7 (22-67) M only R: NI C: 100 controls matched for age, sex, education, and smoking V: NI	CO EF: daily exposure in 63 % of the cases ED (0.5-35) IgG	E: 82 % C: 91 % OR: exposure to sewage removed from the logistic regression except seniority (see DRR)	DRR: no association with frequency of exposure or use of protective equipment. Increased seniority predicted less seropositivity with an adjusted OR of 0.8 (0.7-0.9). MA: age, education, smoking, seniority, exposure frequency, and several indicators of protective equipment considered in the analysis Israel is a country endemic for HA

Table 3. continued

Trout et al. (2000) [33] U.S.A. (Ohio) 1998-1999	CS 2	E: 163 workers (waste-water treatment plant and wastewater maintenance) Age: 46-47 (23-74) F: 2-3 %. A 2nd plant could not be surveyed. C: 139 workers (recreation centres, electrical workers) Age: 38-39 (20-63). F: 40 and 4%, respectively P: 74-88 % R: NI All workers unimmunized	CO EI (no further information) Saliva IgG Prevalence of jaundice or hepatitis	E: 18 and 31 % in treatment plant and maintenance workers, respectively. C: 20 and 4 % in recreation centres and electrical workers, respectively. Adjusted prevalence ratios (95%CI): 1.3 (0.7-2.4)	DRR: no significant DRR. MA: models including occupational factors (exposure, protective equipment, hygiene) as well as age, gender, travelling in endemic areas, education, income, race, household contact, foreign birth. Large differences (up to 20 times) between some sub-groups regarding gender, race, income, and education were found. Thus, crude prevalence rates are hardly comparable. Adjusted prevalence ratios calculated with multivariable regression models. The authors could not account for the low prevalence in electrical workers (however this subgroup was younger and had a higher income).

Table 3. continued

Weldon et al. (2000) [34] U.S.A (Texas) 1996-1997	CS 2	E: 359 wastewater workers. Age: 41.2 (NI) M: 88.4 %. Hispanic: 18.9 %. C: 89 drinking water workers. Age: 41.3 (NI). M: 89.3 %. Hispanic: 27 %. P: “approximately 65 - 85 %”. R: convenience sample. V: see comment	CO EI ED EF IgG and IgM	E: 28.4 % E, Hispanics: 57.4 % E, non-Hispanics: 21.6 % C: 23.6 % C, Hispanics: 50 % C, non-Hispanics: 13.8 % OR: 1.6 (0.6-4.5) in Hispanics and 2.4 (1.0-5.7) in non-Hispanics	DRR: OR for employment in the wastewater industry for more than 7 y and for skin contact with sewage at least once a day of 1.9 (1.1-3.6) and 1.8 (1-3.3), respectively. MA: travelling to endemic areas not mentioned. In the model used for assessment of DRR ethnicity was no longer considered. V: anti-HAV negative participants with a history of HA vaccination not excluded from analysis (anti-HAV assay not always capable of detecting the low levels of anti-HAV that may accompany vaccine-induced immunity).

Table 3. continued

DeSerres et al. (1995) [35] Canada (Quebec City area) 1993	CS 2	E: 76 sewer workers P: 75% of all municipal sewer workers (Quebec City area) Age: 41 (28-64) (74M/2F) all born in Canada. R: those who refused did not differ from participants by age and ED. C: 2 outpatients undergoing lipid testing pro worker (matched on age and sex). P, R, V: see comments.	ED at this work (10; 1-30) Ig type: NI history of jaundice and hepatitis	E: 54 % C: 49 % OR(*): 1.20 (0.67-2.17)	DRR: no association of seropositivity with ED; MA: socio-economic level and travelling to endemic areas not considered R of C group: C “assumed to represent a valid sample of the overall population”. V: no subject had been vaccinated according to DeSerres [52].

Table 3. continued

Schlosser Roudot-Thoraval (1995) [36] France (region of Paris) Before 1995	CS 2	E: 110 workers exposed to sewage (made of 4 subgroups with different exposure types). C: 110 workers from the same firm matched on age (±5y) and education. Age: 36.5 (20-58). M: 79 %. R, P: NI. Exclusion of immunized workers: NI	CO ED (10.3; 1-36) IgG or total antibodies history of jaundice	E: 60.9 % C: 44.5 % OR: 2.4 (1.6-3.1)	DRR: not tested in an MA with confounding variables. MA: travelling to endemic areas not considered. Gender was not a matching criterion. (21 % female workers). Three other publications or abstracts refer to the same population (Schlosser and Roudot-Thoraval [53 54], Roudot-Thoraval and Schlosser [55]). No new original data in a further letter (Schlosser and Roudot-Thoraval [56]).

Table 3. continued

Heng et al. (1994) [37] Singapore 1992-1993	CS 2	E: 600 sewage workers P: 77 % of those deployed in Singapore. R: NI. Age: 20-≥50. M: 95 %. Chinese: 36.3 %, Indians: 29.5 % C: 453 subjects attending routine health checks. Age: 20-≥50. F: 66.2 % Chinese: 92.3 % Indians: 3.5 %. P, R: NI. All subjects unimmunized.	ED in current job total Ig (IgG and IgM)	E: 72.7 % C: 50.8 % OR: 2.2 (1.6-3.1) hospital admission because of acute HA	no DRR in multivariate analysis MA: age, sex, ethnic group, past medical history and educational level considered. Shellfish consumption not included although it may have been an important confounding variable (Goh et al., [57 58]). Older age, lower socio-economic level, longer duration of employment, higher frequency of illness collected in the Indian sewage workers who were hardly represented in the control group

Table 3. continued

Skinhoj et al. (1981) [38] Sweden (Copenhagen) Before 1981	CS 2	E: 77sewer workers Age: Md 44 (21-65). M only C1: 81 gardeners C2: 79 clerks (matching: age, sex, duration of employment). All subjects were municipality workers P: 96 % (E, C1, C2). No information on the third control group (street workers). V: before 1992.	ED in this plant Md: 9 (1-36) EF Probably total IgG jaundice or liver disease unrelated to gall bladder disease	E: 80.5 % C1: 60.5 % C2: 48.1 % OR(*): 2.70 (1.24-5.91) compared with C1 4.46 (2.06-9.75) compared with C2	DRR: no association between prevalence rates of anti-HAV antibodies and ED or EF after adjusting for age. MA: unclear information; socio-economic status and travelling in endemic areas not considered.

Table 3. continued

Khuder et al. (1998) [39] U.S.A. (Ohio) 1995-1996	CS 1	E: 150 wastewater treatment workers age: 43.7 (SD: 9.1) 130 M. P: about 62 % (30-100 %). R: NI. C: 54. Age: 44.9 (SD: 8.2). 52 M. P: similar to E group. R: NI. V: see comment	high vs low exposure risk (2/3 vs.1/3) ED: 14.1 (SD: 8) Jaundice/HA (self-administered questionnaire)	NA OR: NA	DRR and MA: inapplicable Unclear whether the immunity of control and exposed workers was comparable before employment. Nothing is known about socio-economic level, travelling to endemic areas, seropositivity, and vaccination No anti-HAV antibodies determined.

Table 3. continued

Levery et al. (1996) [40] France (region of Touraine) 1993-1994	CS 1	E1: 47 workers (“heavily exposed”, i.e. work in sewers, septic tanks, and /or with cleaning pumps). E2: 15 workers (“less exposed”, i.e. sewage works). Age: 36 (20-57). M only. P: 77.5 %. R: NI. C: 62 subjects matched according to age, sex, and socio-economic status. V: NI.	ED (≤ 5 and > 5) EI (“heavily” and “less exposed”, respectively). anti-HAV anti-bodies (type unknown)	E: 61.3 % C: 51.6 % OR(*): 1.48 (0.68-3.23)	DRR: “heavily” exposed workers with > 5 y exposure more often seropositive than their controls (92.3 vs 61.5 %, respectively). MA: further counfounders searched for but not used in in an MA Relative risks were calculated whereas ORs would have been more appropriate and have given less or non-significant results. Power rather low for subgroups analyses according to age classes. The paper by Levery et al. [59] is an abstract referring to the same population

Table 3. continued

Frolich and Zeller (1993) [41] Germany (Dortmund - Duisburg) 1992	CS 1	E: 408 sewage exposed employees (3 subgroups; age: 40.8, 41.1, 40.3; SD: 9.6, 9.9, 12.3). Probably M. P: NI C: 202 subjects from the same plant. Age: 40 (SD: 10.5). Probably M. P: NI. Workers from endemic regions excluded. All subjects unimmunized.	CO total Ig (IgG and IgM)	E: 37.7 % C: 30.2 % COR: see under comment	DRR: not explored (exposure defined qualitatively). No matching (gender, socio-economic level) and no MA Non-significant ORs in all 3 subgroups: 1.41 (0.96-2.09), 1.20 (0.56-2.51), 1.58 (0.69-3.62), for workers on the sewage treatment area (n=332), workers on the pumping station, and workers maintaining the flow of a section of a river, respectively. Confidence intervals calculated on the basis of the data presented by the authors.

Table 3. continued

Poole and Shakespeare (1993) [42] United Kingdom (West Midlands) Before 1993	CS 1	E: 40 sewage workers Age: 42.2 (21-58). Probably M. P: 100 %. C: 18 road workers. Age: 38.7 (20-62). Probably M. P: NI. "No subject vaccinated in the previous 6 months"	CO IgG	E: 57.5 % C: 33.3 % COR: 2.71 (0.74-10.23)	DRR: not explored. MA: no MA with age, travelling to endemic areas, and social class. The authors reported a COR of 2.6 (1.04-6.51) by comparison with another control group. However, road workers were specifically selected to take into account age and social class of the potentially exposed workers (Maguire [60]) and the selection of the second control group may have been biased (Poole and Calvert [61]). Another paper refers to the same population (Shakespeare and Poole [62]).

Table 3. continued

Chriske et al. (1990) [43] Germany (Cologne) Before 1990	CS 1	E1: 93 sewer workers. P: 67.8 %. R: NI. E2: 84 workers from sewage treatment works. P: 93.3 %. E1 and E2: age: NI (21-65), gender: NI, German workers only. C: 1831 persons recruited from the general population. Age: NI (21-65). Gender, P, and R: NI. V: before 1992	CO anti-HAV anti-bodies (type: NI).	E1: 65.6 % E2: 56.0 % C: 31.2 % OR(*): E1: 4.20 (2.65-6.66) E2: 2.80 (1.76-4.45)	DRR: not explored. MA: no MA. Gender was not a matching criterion. The data presented by Hofmann et al. [63] are taken from this study and not from an independent study population.

Table 3. continued

Ross et al. (1998) [44] United Kingdom October 1996-September 1997	RS	1037 cases of occupationally acquired infectious diseases Age and gender both specified for only 600 cases R: probably non-representative study population V: NA.	occupation and industry (standard classification) diagnosis of HA made by consultants	no case in sewerage workers	DRR and MA: NA No overlap with the study reported by the PHLS working group (1991) (see above) Comparison with other surveillance schemes suggests differential underreporting of eligible cases and added an estimated total of 257 cases.

Table 3. continued

Study populations and results of the non-eligible studies.

Clark et al. (1984) [45] U.S.A. (Memphis, Cincinnati, Chicago). 1975-1978	Cohort (and CS ana-lyses)	E: 339 workers (sewer maintenance, sewage and activated sludge treatment). C: 185 subjects (highway maintenance, water treatment plant, gas and electric public utility). Exact gender and age distribution: NI. P, R: NI. V: before 1992.	CO ED (with 2 subgroups less than 75 months and 75 and more). Air and waste-water monitoring. anti-HAV anti-bodies (type NI) every quarter and illness data	Seroconversion in 1/180 exposed and 1/69 non-exposed worker who were initially seronegative (exact duration of follow-up for these subjects: NI).	DRR and MA (tested in cross-sectional analyses): exposure effect (defined qualitatively or by ED) n.s. in MA including age, race, and socio-economic index ($0.15 \leq p \leq 0.6$).

Table 3. continued

PHLS working group (1991) [15] England and Wales (1990-1991)	CC	3000 cases and controls V: NA	Indicator of exposure: NI Interview Salivary IgG and IgM	No increased risk in sewage workers was found according to Maguire [60].	No further information available. A later full account of the study results was announced in this paper. However, the corresponding publication could not be located.

Table 3. continued

Salano and Copello (1998) Genoa [46] Before 1998	CS	E: 126 (maintenance of sewage network; waste water treatment plant (3 exposure subgroups). M: NI. C: general population. V: NI.	3 exposure subgroups hepatitis A markers	Decreased risk in exposed workers especially in those aged less than 30 years (see comment) OR: NI	Seroprevalence > 80 % in all three age classes in control group (< 31, 31-40, > 40 y). In exposed group seroprevalence was about < 5, 25, and 78 % in the same age classes.

Table 3. continued

Arvanitidou et al. (1998) [47] Greece (Thessaloniki) before 1998	CS	E: 167 (M and F) P: 82.2 %. C: apparently no non-exposed group V: NI.	ED EI anti-HAV antibodies	E: 93.4 % (100 % over 50 y) no OR in abstract.	DRR: prevalence von anti-HAV antibodies of 100 % in the "highest occupational risk group"; effect of duration of employment was n.s. Several confoundig variables were considered. MA: ?. No further information available in the abstract

Table 3. continued

Tornberg and Ronne (1997) [48] Denmark 1980-1995	RS	3790 cases of HA notified between 1980-1995. V: NA.	notified cases of HA.	average incidence: 4.6/100,000 population per year

* Studies are classified according to strength of their design. General abbreviations are: Md, median; NI: not indicated in the publication; NA: not applicable; n.s.: statistically non-significant; SD: standard deviation.
† Before "year of publication": indicates that no indication on exact time period could be found
‡ CC: case-control study; CS: cross-sectional study (numbers indicate the rank as described in table 2); HP: historical prospective; RS: reporting scheme.
§ E: exposed; C: controls; population size represents the number of subjects having actually been included (lost cases excluded); age: mean age (range) if not otherwise indicated; M: male; F: female. P: participation rate; R: representativeness of the study population; V: vaccination; " before 1992": see methods.
¶ CO: current occupation/job (is mostly a qualitative exposure indicator only); ED: exposure duration in years (mean and range if not otherwise indicated), EI: exposure intensity; EF: exposure frequency.
‖ Prevalence: prevalence rates of anti-HAV positive workers. SIR: standardised incidence ratio; OR: adjusted odds ratios and 95 % confidence interval. If no adjusted OR were given crude OR (COR) as reported by the authors are presented. Otherwise, crude ORs (OR(*)) were calculated on the basis of the data available in the publication (see methods).
"Adjusted" means adjustment for the set of confounding variables considered by the authors. However, the models used for adjustment were not always comparable. If the authors calculated several ORs, all the main ORs are indicated.
** DRR: dose-response relationship; MA: multivariate analysis.