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Hepatitis A Virus Vaccination in Persons With Hepatitis C Virus Infection: Consequences of Quality Measure Implementation

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Hepatitis A virus (HAV) superinfection in persons with hepatitis C virus (HCV) infection has been associated with a high mortality rate, and vaccination is recommended. The incidence of HAV is low, and the aim of this study was to determine the mortality risk of HAV superinfection and the consequences of routine vaccination in persons with HCV infection. To determine the mortality risk of HAV superinfection, a meta-analysis including studies reporting mortality in HCV-infected persons was performed. Data were extracted independently by two investigators and recorded on a standardized spreadsheet. The pooled mortality estimate was used to determine the number needed to vaccinate (NNV) to prevent mortality from HAV superinfection. The total vaccine cost was also calculated. A total of 239 studies were identified using a defined search strategy. Of these, 11 appeared to be relevant, and of these, 10 were suitable for inclusion in the meta-analysis. The pooled odds ratio (OR) for mortality risk in HAV superinfection of HCV-infected persons was 7.23 (95% confidence interval: 1.24-42.12) with significant heterogeneity (I^2 = 56%; P = 0.03) between studies. Using the pooled OR for mortality, this translates to 1.4 deaths per 1,000,000 susceptible persons with HCV per year. The NNV to prevent one death per year is therefore 814,849, assuming 90% vaccine uptake and 94.3% vaccine efficiency. The vaccine cost for this totals $162 million, or $80.1 million per death prevented per year. *Conclusion:* These data challenge the use of routine HAV vaccination in HCV-infected persons and its incorporation into clinical practice guidelines. HAV vaccination of all HCV-infected persons is costly and likely to expose many individuals to an intervention that is of no direct benefit. (HEPATOLOGY 2012;56:501-506)

Hepatitis C virus (HCV) infection is an important cause of morbidity and mortality, with an estimated 3.3 million infected persons in the United States.[1] Due to the natural history of HCV infection, the rates of complications related to HCV and subsequent mortality are projected to increase over the next decade.[1,2] In an attempt to reduce mortality, HCV infection has been recognized as an area for quality of care improvement. Quality measures have been developed by the American Medical Association Physician Consortium for Performance Improvement as a driver for quality improvement and mortality reduction.[3,4] In addition to quality measures addressing conventional treatment for HCV, vaccination against hepatitis A virus (HAV) is included.

Several groups have assessed compliance with the quality measure of vaccination against HAV as a measure of quality of care.[5,6] These studies have shown that compliance with this quality measure is low and

Abbreviations: CI, confidence interval; HAV, hepatitis A virus; HCV, hepatitis C virus; NNV, number needed to vaccinate; OR, odds ratio; PCR, polymerase chain reaction.

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the authors each suggested measures to increase compliance. However, the evidence supporting HAV vaccination has not been explicitly addressed and the benefits of vaccination in HCV-infected persons at the current time are not clear. Indeed, reports of an increased risk of death in HAV superinfection of persons with HCV infection are contradictory.[7,8]

The aim of this study was to determine the mortality risk of HAV superinfection in chronic HCV infection and to define the utility of HAV vaccination using incidence and mortality data.

Materials and Methods

We conducted our meta-analysis in accordance with the meta-analysis of observational studies in epidemiology guidelines (Supporting Information).[9] A literature search was conducted using MEDLINE (1948 to October 2011) to identify cohort studies, case-control studies, or cross-sectional studies that reported the mortality of HAV superinfection in persons with HCV infection. Reports of mortality from convenience samples (such as analyses of patients with fulminant hepatic failure only) were excluded. Studies on HAV mortality were identified using the following search terms: hepatitis A, hepatitis C, and hepatitis A superinfection. These search terms were combined with the set operator AND, with studies identified using the term mortality. Reference lists of obtained articles were searched to identify further relevant reports.

Mortality data for HAV superinfection in HCV-infected persons were extracted independently by two investigators (I. A. R. and R. P., Medical Research Council Clinical Research Fellows in Hepatology). Persons coinfected with hepatitis B virus and/or human immunodeficiency virus were excluded. Discrepancies were resolved by consensus. The following data were collected: type of study, years conducted, method of data collection, HAV and HCV diagnostic criteria, the total number of subjects, and the number of deaths attributable to HAV infection. The data were then pooled using a Mantel-Haenszel random effects model to give a conservative estimate of any excess mortality risk in HAV superinfection of HCV-infected persons using Review Manager 5.1.[10] The mortality risk was compared using an odds ratio (OR), with a 95% confidence interval (CI). Heterogeneity between studies was assessed using the I^2 statistic with a cut-off of 50%, and the chi-squared test with $P < 0.10$ used to define a statistically significant degree of heterogeneity.[11] Review Manager 5.1.[10] does not include studies in which there is zero mortality in both groups. To explore the effect of these studies on the estimate of mortality risk, a sensitivity analysis was planned to repeat the meta-analysis with a 0.5 continuity correction[12] using Trial Sequential Analysis.[13] A further sensitivity analysis was performed to assess the role of publication type as an indicator of publication bias. To address confounding by HCV antibody–positive but not chronically infected persons (defined by positive HCV polymerase chain reaction [PCR]), a sensitivity analysis was planned to account for the prevalence of chronic HCV infection (70%[14]) in studies reporting only HCV antibody positivity.

To determine the use of vaccination, we calculated the number needed to vaccinate (NNV), and the vaccine cost per death prevented based on incidence and mortality data as described.[15] The current estimate of the prevalence of HCV infection is 3.3 million persons.[1] Of these, 50% are estimated to be susceptible to HAV infection.[16] To determine the maximum benefit from a vaccination program, we assumed that vaccine coverage would increase to 90% of susceptible individuals and that 94.3% vaccine efficacy[17] would be maintained through administration of two doses to all participants in the program. Vaccine cost was determined to be $54.58 per dose based on an 80%/20% split between private sector ($63.10) and federal contract ($20.82).[18,19]

Results

Mortality Risk of HAV Superinfection. A total of 239 studies were identified using the search strategy outlined. Of these, 11 appeared to be relevant to the study, and of these, 10 studies (including a total of 22,371 persons) were suitable for inclusion in the meta-analysis (Fig. 1). The studies reported the outcomes of cohort studies, population surveillance studies, and the outcomes of HAV outbreaks (Table 1).[20-29] One study including only patients with fulminant liver failure was excluded.

The pooled OR for mortality risk from these studies was 7.23 (95% CI, 1.24-42.12) in HAV superinfection of HCV-infected persons with significant heterogeneity ($I^2 = 56\%$; $P = 0.03$) between studies (Fig. 2). Three studies included in the meta-analysis reported zero mortality in both the HCV-infected and comparison groups. These studies were not evaluable in the initial analysis in RevMan 5.1. The estimation of mortality risk was therefore repeated using a random effects model and a continuity correction. In this analysis

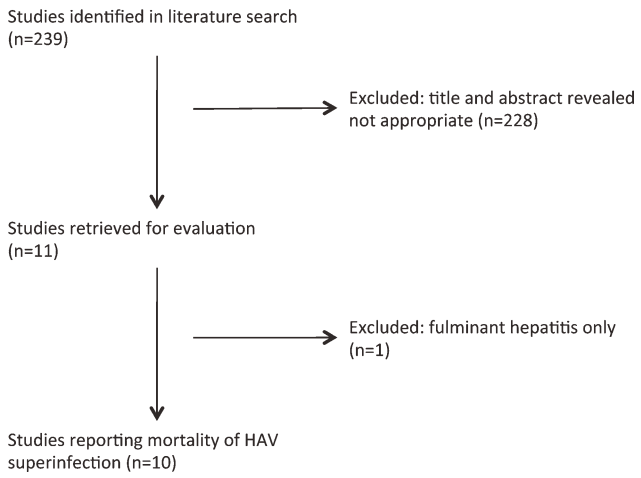

Fig. 1. Flow diagram of studies identified in the systematic review and meta-analysis.

including all 10 suitable studies, the excess mortality risk in HCV-infected persons was similar (OR, 6.88; 95% CI, 1.32-36.01).

The funnel plot of studies included in the meta-analysis suggested publication bias (Fig. 3) in favor of studies reporting increased mortality risk. Indeed, the studies reported as original articles all indicated a substantial increase in mortality (OR, 38.75; 95% CI, 7.33-204.84). In contrast, those reports published as correspondence indicated mortality rates that were not different from the population risk (OR, 0.86; 95% CI, 0.15-4.90).

Due to the nature and timing of the studies identified, many did not establish the presence of chronic HCV infection by PCR. In a sensitivity analysis to address this potential confounding factor where a 70% rate of chronic HCV infection was assumed, no significant effect was observed on the pooled estimate of the increased mortality risk in HAV superinfection (OR, 9.74; 95% CI, 1.79-52.92).

Consequences of HAV Vaccination in HCV-Infected Persons. To understand the relevance of this finding in practice, we examined the current epidemiology of HAV infection in the United States. Data from the Centers for Disease Control and Prevention estimate the incidence to be 2.7/100,000 per year based on extrapolation of actual reports.[30] There are no available incidence data for HCV-infected persons *per se*, although due to concomitant injecting drug use, it might be expected that these individuals are at increased risk. To allow for this likely increased risk we assumed an incidence of HAV superinfection of 5/100,000 in HCV-infected persons. Using a vaccination model where 90% of susceptible individuals receive two doses of HAV vaccine and vaccine efficacy is 94.3% the NNV to prevent one case of HAV in HCV-infected persons per year is 23,565.

The case fatality rate for HAV is known to be low and has been falling in parallel with the incidence of this infection over the last decade. Indeed the latest available data from 2007 show a mortality rate of 0.2/1,000,000 per year (i.e., 34 deaths per year),[31] in the United States population. Using the pooled mortality estimate of a 7.23-fold increased risk the mortality risk of HAV superinfection in HCV-infected persons is 1.4/1,000,000 per year. The NNV to prevent one death is therefore 814,849 per year. Furthermore, the total vaccine cost alone for this program is $162 million, or $80.1 million per death prevented per year.

Discussion

Multiple guidelines recommend HAV vaccination in persons with HCV infection.[32-34] These recommendations have been largely based on a high-profile report of significantly increased relative risk of death in persons infected with HCV[21] and not on the absolute increased risk of death. In this study, we estimated the increased mortality risk of HAV superinfection in HCV-infected persons by meta-analysis. These individuals are at increased mortality risk and are therefore a

Table 1. Characteristics of Studies Included in the Meta-Analysis

Author	Publication Type	Study Design	Data Collection	HAV Diagnosis	HCV Diagnosis	HCV Deaths/Total	Control Deaths/Total
Leino et al.[20]	Correspondence	Outbreak	Retrospective	Serology	Serology	0/75	3/325
Vento et al.[21]	Original	Cohort	Prospective	Serology	PCR	6/17	0/191
Hasle et al.[22]	Correspondence	Outbreak	Retrospective	Serology	Serology	1/101	0/24
Mele et al.[23]	Correspondence	Population surveillance	Prospective	Serology	Serology	0/52	0/5,853
Battegay et al.[24]	Correspondence	Cohort	Prospective	Serology	Serology	0/4	0/3
Helbling et al.[25]	Correspondence	Population surveillance	Prospective	Serology	Serology	0/199	8/4,591
Pramoolsinsap et al.[26]	Original	Cohort	Prospective	Serology	Serology	1/4	0/100
Bianco et al.[27]	Original	Population surveillance	Prospective	Serology	Serology	0/166	1/10,588
Spada et al.[28]	Original	Outbreak	Retrospective	Serology	Serology	2/23	0/22
Deterding et al.[29]	Original	Cohort	Retrospective	Serology	Serology	0/17	0/16

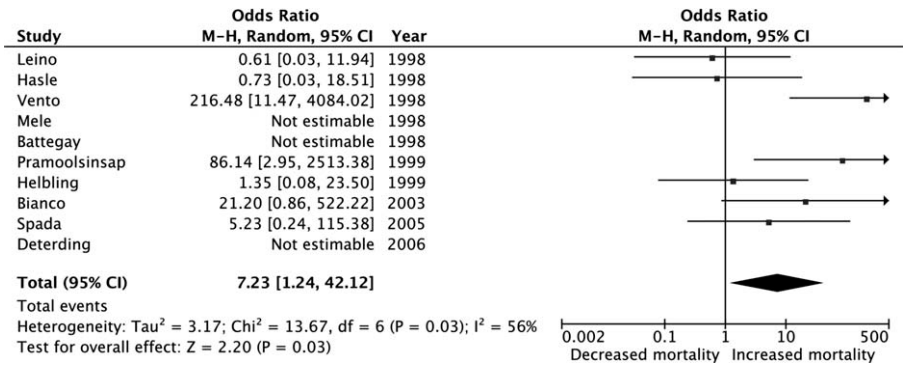

Fig. 2. Pooled OR of mortality risk of HAV superinfection in HCV-infected persons.

potential target group for vaccination. However, the incidence of HAV infection in the United States is falling, and the case fatality rates remain low.[30,35] As a consequence of a combination of low case fatality, we estimate that 814,849 patients need to be vaccinated (at a cost of $80.1 million) to prevent one death per year from HAV in HCV-infected persons.

As with any meta-analysis of observational studies, this analysis has a number of limitations related to the studies that were included. Case fatality rates were low in both the HCV and comparison cohorts, and in three of 10 suitable reports there was no mortality in either group. Chronic infection with HCV measured by PCR was only reported in one study, although using a sensitivity analysis to explore the effect of this confounder there was no significant change in the estimate of increased mortality. Furthermore, there was significant heterogeneity between the studies that may in part be explained by publication bias. To confirm the accuracy of the meta-analysis, the pooled mortality estimate was compared with an analysis of death certificate data in which it was reported that 41% of deaths in HAV infection occur in persons with chronic liver disease.[35] Of these, 40% of deaths occur in persons with concomitant HCV infection (i.e., approximately five deaths per year at 2007 rates). From these data the mortality rate of HAV superinfection in HCV-infected persons is approximately 3/1,000,000 per year and 15-fold higher than the general population. Although this estimate of mortality is numerically greater than that estimated by the meta-analysis, it is within the 95% CIs of the pooled mortality estimate. Using this higher estimate of mortality the NNV to prevent one death each year remains high (392,757, at a cost of $38.6 million per death prevented). Routine collection of HCV status (including HCV PCR) together with information regarding other comorbidities at the time of notification of HAV infection would help to clarify the true mortality associated with HAV superinfection in HCV-infected persons. These data would also allow an assessment of how much of the increased risk is attributable to HCV infection, and how much is attributable to other factors.

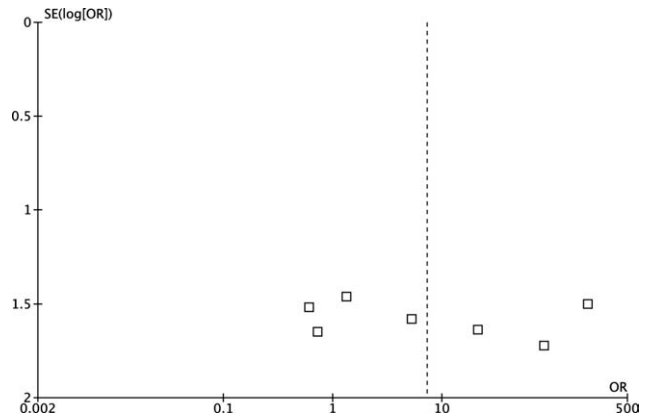

Fig. 3. Funnel plot of studies included in the meta-analysis.

The stimulus for this study was the inclusion of HAV vaccination in the quality improvement program.[3] There is a need to improve the quality of care for persons with HCV infection, because this is a major cause of liver-related morbidity and mortality in the United States. In 2007, there were 6,571 deaths attributed to HCV infection,[31] although this may be an underestimate.[36] Using the pooled estimate of increased mortality risk of HAV superinfection, we can estimate that two to three deaths per year are attributable to HAV superinfection in HCV-infected persons. This translates to one in every 2,190 deaths (0.05%) attributable to HCV infection. Thus vaccination against HAV is unlikely to lead to a significant improvement in mortality in this population.

It was initially suggested that HAV vaccination was not cost-effective[37]; however, two later reports questioned this finding, and cost-effectiveness was established.[18,38] Importantly, the current incidence and mortality rates are significantly lower than when the cost effectiveness studies were performed. For instance, mortality rates have fallen by 75% between 1999 and

2007, suggesting that these analyses may not be representative.[31] Indeed, in these analyses cost-effectiveness was sensitive to changes in incidence. The high vaccine costs presented here suggest that HAV vaccination is not cost-effective given current low mortality rates.

These findings call in to question the utility of vaccinating all persons with HCV infection against HAV in low incidence areas, including the United States.[39] A more practical and less costly approach would be to focus on persons who are at high risk, such as those who are active injecting drug users, homeless, men who have sex with men, or traveling to high-incidence areas in line with current guidance.[34] This would allow resources that are directed at increasing HAV vaccination to be redirected to interventions that show significantly more use, most importantly treating patients with efficacious antiviral medications targeting HCV. This strategy is almost certain to reduce mortality more effectively than HAV vaccination. Without these changes, there is a real risk that the vaccination program targeting persons with HCV infection could indirectly do harm by diverting a small number of patients away from antiviral treatment and toward vaccination.[40] Because only small numbers of HCV-infected persons benefit from vaccination against HAV each year, a focus on vaccination rather than antiviral treatment (where the number of patients needed to treat are much smaller[41]) might deny a clinically significant number from potentially life-saving treatment.

In conclusion, persons with HCV infection are at low risk from mortality due to HAV superinfection in low-incidence areas. HAV vaccination is costly, and only a very small proportion of those vaccinated will benefit. These findings highlight several key issues in the development of both guidelines and quality measures. Firstly, the assessment of the evidence and the benefit of interventions need occur in light of relevant prevalence data. Secondly, changes in prevalence need to be considered when guidelines or quality measures are revised or reassessed. Physicians otherwise run the risk of exposing many patients to interventions that are ultimately of no benefit to them.

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