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Serologic Evidence for Fecal–Oral Transmission of *Helicobacter pylori*

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Abstract. *Helicobacter pylori* infection is among the most prevalent infections in the world and a key cause of gastric diseases; however, its route of transmission remains unclear. This study aimed to assess the potential for fecal–oral transmission of *H. pylori* by leveraging its association with a disease with known etiology. Utilizing serology data from the National Health and Nutrition Examination Survey (NHANES 1999; N = 6,347), the association between *H. pylori* and hepatitis A virus (HAV), a sensitive indicator for fecal–oral exposure, was assessed. Survey-weighted kappa and multiple logistic regression were used to quantify the association between *H. pylori* and HAV after controlling for age, sex, race, poverty, birthplace, crowding, smoking, and alcohol use. Concordant serological results were found among 69.8% of participants (survey-weighted κ = 0.30, 95% confidence interval [CI] = 0.26, 0.35). The adjusted odds of *H. pylori* seropositivity were over two times higher after adjusting for confounders (odds ratio = 2.27, 95% CI = 1.79, 2.87). Results from this study suggest *H. pylori* and HAV infections are strongly associated. Since HAV is primarily transmitted through the fecal–oral route, fecal–oral transmission may be an important pathway for *H. pylori* spread.

INTRODUCTION

Helicobacter pylori infection is one of the most prevalent infections among humans, with seroprevalence estimates as high as 70% worldwide and up to 80% or more in developing countries.[1,2] Although ample epidemiologic research on *H. pylori* exists, there is still uncertainty in how the pathogen is transmitted.[3,4] *Helicobacter pylori* has been hypothesized to spread through various routes, though generally believed to spread from person to person (i.e., not through an intermediary reservoir), either through an oral-to-oral or fecal–oral route.[1–6] For the purpose of this study, we defined fecal–oral transmission as transmission of pathogens in feces from one person to the oral cavity of another person either directly or through contaminated surfaces, food, or water. Prior studies examining the potential for fecal–oral transmission of *H. pylori* yielded mixed conclusions warranting further investigation.[7–12] Better understanding of *H. pylori* transmission is critical in developing primary prevention interventions and reducing reliance on secondary and tertiary prevention efforts that may exacerbate *H. pylori* antibiotic resistance.[13]

Prior studies exploring potential fecal–oral transmission of *H. pylori* have used hepatitis A virus (HAV) seropositivity as an indicator for fecal–oral exposure.[7] Since HAV is transmitted primarily by the fecal–oral route, it is inferred that HAV seropositivity is evidence for prior fecal–oral exposure. The objective of this study is to assess the relationship between fecal–oral exposure, indicated by HAV seropositivity, and *H. pylori* seropositivity among a representative sample of the United States. It is hypothesized that the odds of *H. pylori* seropositivity will be higher among HAV-positive persons than HAV-negative persons. Since individuals of lower socioeconomic status (SES) and minorities are consistently at higher risk for *H. pylori* infection,[14] subgroup analysis of HAV and *H. pylori* infection by SES and race are also explored.

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MATERIALS AND METHODS

A cross-sectional study was conducted to assess the association between HAV and *H. pylori* seropositivity using data from the National Health and Nutrition Examination Survey (NHANES). NHANES is a stratified multistage probability sample of the civilian, non-institutionalized U.S. population, administered by the U.S. National Center for Health Statistics and designed specifically for population health research.[15] Data from NHANES were collected through in-person interviews, clinical examinations, and laboratory testing. NHANES 1999–2000 (NHANES 1999) was the most recent survey cycle to collect *H. pylori* serology and was used in this study.

***H. pylori* and HAV serology.** *Helicobacter pylori* serology was measured among participants aged 3 years and older, using the Wampole Laboratories *H. pylori* IgG enzyme-linked immunosorbent assays (Wampole Laboratories, Cranbury, NJ), intended to detect the presence of IgG antibodies to *H. pylori*.[16] Immune status ratio (ISR) values (range = 0–5.73) were used to categorize serostatus; ISR values < 0.90 were considered negative for *H. pylori*, values between 0.90 and 1.09 were equivocal, and values > 1.09 were positive.[16] Participants with missing (N = 2,472) or equivocal (N = 161) *H. pylori* serology were excluded from analysis. HAV serology was measured in all examinees aged 2 years and older using a solid-phase competitive enzyme immunoassay, and reported as positive, negative, or missing (N = 2,321). Participants missing HAV serology were excluded.

Demographic variables. NHANES 1999 reported race as white, black, Mexican American, or other. Birthplace was dichotomized as U.S./foreign born based on responses to the question "In what country were you born?" An income-to-poverty ratio (family income divided by federal poverty threshold) was used to approximate SES; values were categorized into six levels, from five or greater, representing the highest SES, to < 1 representing the lowest. Household crowding was approximated by number of persons living in each household divided by number of rooms in the household.

HAV immunization status, a potential source of misclassification, was available in NHANES 1999 and categorized as follows: at least 2 doses, less than 2 doses, no doses, and missing. Vaccination values of "Don't Know" or "Refused" were considered missing (N = 368). Smoking status was

categorized as never, current, former, and missing. Current smokers were defined as participants who reported smoking at least 100 cigarettes, 20 cigars, or 20 pipes in their lifetime and reported currently smoking. Alcohol drinkers were defined as those having at least 12 drinks in 1 year.

Statistical analysis. All analyses were survey weighted to account for the multistage sampling design of NHANES 1999. A survey-weighted kappa statistic was calculated to assess the magnitude of agreement between *H. pylori* and HAV seropositivity. The kappa statistic measures the level of agreement between binary variables and accounts for agreement by chance and has been used in prior *H. pylori*/HAV studies to measure serology agreement.[17,18] The "svykappa" package (Lumley T, Auckland, New Zealand) in R (Foundation for Statistical Computing, Vienna, Austria) was used to calculate the survey-weighted kappa.

Survey-weighted multiple logistic regression was used to assess the association between *H. pylori* and HAV after adjusting for a priori chosen confounders (age, gender, race, birthplace, income/poverty ratio, household crowding, smoking, and alcohol consumption) known to be associated with *H. pylori* infection.[1,3,5] Five models were additively fitted. The sequence of modeling was based on variables thought to be most associated (demographics) with *H. pylori* infection to least associated (behavioral). Model 1 included HAV, age, sex, and race as covariates; Model 2 added birthplace; Model 3 added income-to-poverty ratio; and Model 4 added household crowding. Model 5 included smoking and alcohol status but was restricted to participants over the age of 20 years since those under 20 years of age were not asked to provide smoking and alcohol status. A two-tailed Wald test was used to assess statistical significance of HAV ($\alpha = 0.05$) for all estimates. Hosmer–Lemeshow's goodness-of-fit test was used to assess model fit (insignificant P values indicate adequate fit).[19]

Effect modification by race and income-to-poverty ratio were assessed using Model 4 and considered significant at $\alpha = 0.05$ level. Marginal probability plots for *H. pylori* seropositivity with 95% confidence intervals (CI) were generated to visually assess each interaction. All logistic regression analyses and post-estimation tests of fit were done in Stata 12.1 (StataCorp LP, College Station, TX).

Sensitivity analysis. In NHANES 1999, HAV seroprevalence was higher in younger age groups (Figure 1), which may have been caused by uptake of the HAV vaccine made commercially available shortly before the survey. Because HAV serology cannot distinguish between naturally acquired and vaccine-acquired immunity, a sensitivity analysis restricted to participants reporting no HAV immunization was performed.

We also assessed the association between *H. pylori* serology and infections with other transmission modes available in NHANES 1999 using survey-weighted logistic regression. Serology data for sexually transmitted (herpes simplex virus 1 and 2, human immunodeficiency virus [HIV], *Chlamydia*) and other fecal–oral and potentially foodborne (*Cryptosporidium* and *Toxoplasma*) infections were used as indicators for alternative transmission modes. We expected to find an association between the fecal–oral transmitted infections, but not other modes. These analyses were adjusted for age, race, and gender.

RESULTS

There were a total of 9,965 participants in the NHANES 1999 cycle. Excluding participants with missing *H. pylori* and HAV serology reduced the sample to 7,324. Participants under the age of 3 years ($N = 996$) were not required to submit serum for testing and accounted for 27.5% of exclusions. Further excluding participants with missing income-to-poverty ratio, birthplace, and household crowding values reduced the final analysis sample to 6,347 (63.7% of total).

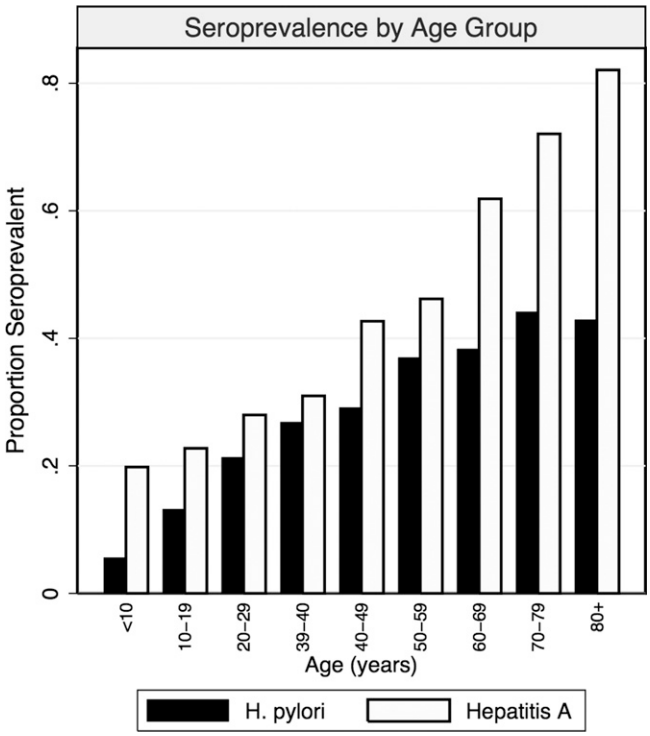

FIGURE 1. Seroprevalence proportions of *Helicobacter pylori* and hepatitis A participants from the 1999 National Health and Nutrition Examination Survey by age group. Includes all participants with reported serology.

About 36% and 25% of the sample were HAV-positive and *H. pylori*-positive, respectively; among *H. pylori*-positive participants, 62.8% were also HAV positive (Table 1). The *H. pylori*-positive participants were older than the *H. pylori*-negative participants and had a greater proportion of non-Hispanic black (17.9% versus 8.3%) and foreign born (30.7% versus 8.7%).

Older age, higher household crowding, being non-white, foreign born, and having lower income levels were strongly associated with being *H. pylori*-positive (all $P < 0.001$) (Table 2). Compared with never smokers, the odds of *H. pylori* seropositivity were slightly elevated among current smokers (odds ratio [OR] = 1.53, $P = 0.004$), and there was little difference in odds between never and former smokers ($P = 0.25$). Alcohol drinkers had 25% lower odds of being *H. pylori*-positive than non-drinkers (OR = 0.75, $P < 0.03$). Drinking and smoking histories were not collected for participants under the age of 19 years (88.6% missing alcohol histories were of those under 19 years of age), so negative associations in the missing categories may be caused by the concentration of non-adults in these groups. The odds of being *H. pylori* positive did not differ by HAV immunization status, indicating vaccination did not influence *H. pylori* seropositivity.

About 15% of participants were both HAV positive and *H. pylori* positive ($N = 1,473$) and 2,826 (54.1%)

TABLE 1

Survey-weighted summary demographics of *Helicobacter pylori*-positive and *H. pylori*-negative participants from the 1999 NHANES included in analysis, United States, 1999–2000

Eligible population	*H. pylori*–	*H. pylori*+	Combined
N (%)	4,234 (74.9)	2,113 (25.1)	6,347 (100)
Age*, mean (SD)	31.57 (17.9)	45.02 (21.2)	36.5 (20.2)
Age category, *n* (%)			
< 19	2,272 (28.8)	594 (9.5)	2,866 (24.0)
20–49	1,166 (49.9)	686 (49.9)	1,852 (49.9)
50–69	489 (15.8)	508 (27.2)	997 (18.6)
70+	307 (5.5)	325 (13.4)	632 (7.5)
Gender, *n* (%)			
Male	2,038 (49.2)	1,079 (49.4)	3,117 (49.3)
Female	2,196 (50.8)	1,034 (50.6)	3,230 (50.7)
Race, *n* (%)			
Non-Hispanic white	1,877 (77.5)	409 (48.5)	2,286 (70.2)
Non-Hispanic black	866 (8.3)	547 (17.9)	1,413 (10.7)
Mexican American	1,174 (5.0)	950 (13.4)	2,124 (7.1)
Other	317 (9.1)	207 (20.2)	524 (11.9)
Foreign born, *n* (%)			
U.S. born	3,714 (91.3)	1,342 (69.3)	5,056 (85.8)
Foreign born	520 (8.7)	771 (30.7)	1,291 (14.2)
Income/poverty, *n* (%)			
≥ 5	620 (22.4)	163 (13.6)	783 (20.2)
3–4.9	844 (25.7)	277 (17.8)	1,121 (23.7)
2–2.9	665 (16.1)	288 (15.8)	953 (16.0)
1–1.9	1,085 (21.5)	642 (25.9)	1,727 (22.6)
< 1.0	1,020 (14.4)	743 (26.9)	1,763 (17.5)
Household crowding†, mean (SD)	0.58 (0.3)	0.60 (0.4)	0.59 (0.31)
Smoking status, *n* (%)			
Never	1,052 (37.4)	764 (41.0)	1,816 (38.3)
Current	380 (15.8)	332 (26.5)	712 (18.5)
Former	530 (18.1)	422 (23.0)	952 (19.3)
Missing	2,272 (28.8)	595 (9.5)	1,867 (24.0)
Alcohol use, *n* (%)			
No	582 (17.7)	505 (27.1)	1,087 (20.1)
Yes	1,313 (51.1)	917 (58.3)	2,230 (52.9)
Missing	2,339 (31.2)	691 (14.6)	3,030 (27.0)
Hepatitis A vaccine, *n* (%)			
At least 2 doses	258 (5.6)	109 (6.0)	367 (5.7)
Less than 2 doses	187 (4.0)	128 (5.9)	315 (4.4)
No doses	3,657 (87.4)	1,795 (84.3)	5,452 (86.6)
Missing	132 (3.1)	81 (3.8)	213 (3.2)
Hepatitis A serology, *n* (%)			
Negative	2,826 (72.2)	640 (37.2)	3,466 (63.5)
Positive	1,408 (27.8)	1,473 (62.8)	2,881 (36.5)
H. pylori serology, *n* (%)			
Negative	–	–	4,234 (74.9)
Positive	–	–	2,113 (25.1)

NHANES = National Health and Nutrition Examination Survey; SD = standard deviation.
*Age in years.
†Persons per room in household.

TABLE 2

Unadjusted odds ratios of *Helicobacter pylori* seropositivity by demographic variables for participants from the 1999 NHANES included in analysis (*N* = 6,347), United States, 1999–2000

	OR	95% CI		*P*
Age*	1.03	1.02	1.03	< 0.001
Age category				
< 19		Ref		
20–49	3.04	2.36	3.93	< 0.001
50–69	5.24	4.03	6.82	< 0.001
70+	7.44	5.52	10.02	< 0.001
Gender				
Male		Ref		
Female	0.99	0.88	1.12	0.87
Race				
White		Ref		
Black	3.43	2.75	4.28	< 0.001
Mexican	4.29	3.40	5.43	< 0.001
Other	3.54	2.75	4.55	< 0.001
Birthplace				
U.S. born		Ref		
Foreign born	4.68	3.79	5.79	< 0.001
Income/poverty ratio				
≥ 5.0		Ref		
3–4.9	1.14	0.83	1.58	0.40
2–2.9	1.62	1.14	2.30	0.01
1–1.9	1.99	1.44	2.76	< 0.001
< 1.0	3.09	2.27	4.20	< 0.001
Household crowding*	1.51	1.07	2.15	0.02
Smoking				
Never		Ref		
Current	1.53	1.18	1.99	0.004
Former	1.16	0.89	1.50	0.25
Missing	0.30	0.23	0.39	< 0.001
Alcohol				
No		Ref		
Yes	0.75	0.58	0.96	0.03
Missing	0.31	0.23	0.41	< 0.001
Hepatitis A vaccine				
At least 2 doses		Ref		
Less than 2 doses	1.37	0.71	2.64	0.33
No doses	0.89	0.55	1.44	0.62
Missing	1.14	0.56	2.32	0.70
Hepatitis A serostatus				
Negative		Ref		
Positive	4.39	3.38	5.68	< 0.001

CI = confidence interval; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio.
*Continuous variable.

were both seronegative. Overall, there was 69.8% serology concordance, which was statistically significant (κ = 0.30, 95% CI = 0.26, 0.35).

The odds of *H. pylori* seropositivity were more than four times higher among HAV-positive participants than HAV negative (OR = 4.39, 95% CI = 3.38, 5.68). After adjusting for age, gender, and race, the *H. pylori*/HAV association attenuated by 41% (OR = 2.57, 95% CI = 2.03, 3.25) (Table 3, Model 1) and attenuated again after adjusting for birthplace (OR = 2.27, 95% CI = 1.79, 2.87) (Table 3, Model 2) with no change in significance. Adjusting for income-to-poverty ratio attenuated the association slightly and including household crowding did not change estimates (Table 3, Model 4). Model 5 resulted in a slight increase in the OR for *H. pylori* seropositivity (OR = 2.30, 95% CI = 1.75, 3.03) (Table 3, Model 5). Among the fitted models, Models 2 (P = 0.53) and 5 (P = 0.23) had the best fit based on Hosmer–Lemeshow's goodness-of-fit test (insignificant P values indicate adequate fit)[19] and reported as preferred estimates. These results were replicated using the same methods with data from the first phase of NHANES III from 1988 to 1991 (Supplemental Table 1), further supporting this association. There was no significant difference in the *H. pylori*/HAV association between survey cycles (i.e., no interaction by survey cycle) (P = 0.93).

The *H. pylori*/HAV association did not differ by poverty subgroup (P = 0.24) indicating no interaction by SES (Figure 2). Similarly, no significant differences in the *H. pylori*/HAV association were observed by race (P = 0.43). As a post hoc analysis, interaction by birthplace was found to be significant (P = 0.048); the odds of *H. pylori* seropositivity was 1.9 times higher in HAV-positives than negatives (OR = 1.91, 95% CI = 1.51, 2.43) among U.S. born, and over five times higher (OR = 5.19, 95% CI = 2.45, 11.00) among foreign born.

TABLE 3

Survey-weighted multiple logistic regression results for *Helicobacter pylori* seropositivity among participants in the 1999 NHANES included in analysis, United States, 1999–2000

	Model 1 (N = 6,342)			Model 2 (N = 6,342)			Model 3 (N = 6,342)			Model 4 (N = 6,342)			Model 5 (N = 3,480)		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
Hepatitis A serostatus															
Negative		Ref			Ref			Ref			Ref				
Positive	2.57	2.03, 3.25	< 0.001	2.27	1.79, 2.87	< 0.001	2.17	1.71, 2.76	< 0.001	2.17	1.71, 2.76	< 0.001	2.30	1.75, 3.03	< 0.001
Age category															
≤ 19		Ref			Ref			Ref			Ref			Omitted	
20–49	3.42	2.47, 4.73	< 0.001	3.08	2.19, 4.32	< 0.001	3.63	2.54, 5.19	< 0.001	3.74	2.58, 5.41	< 0.001		Ref	
50–69	6.02	4.47, 8.11	< 0.001	5.66	4.25, 7.52	< 0.001	7.09	5.26, 9.55	< 0.001	7.55	5.42, 10.52	< 0.001	1.93	1.59, 2.33	< 0.001
70+	7.97	5.38, 11.82	< 0.001	7.74	5.12, 11.70	< 0.001	8.68	5.54, 13.61	< 0.001	9.39	5.84, 15.08	< 0.001	2.63	1.78, 3.87	< 0.001
Gender															
Male		Ref			Ref			Ref			Ref			Ref	
Female	0.91	0.81, 1.03	0.12	0.93	0.83, 1.05	0.23	0.88	0.78, 1.00	0.06	0.89	0.78, 1.01	0.07	0.98	0.85, 1.14	0.81
Race															
White		Ref			Ref			Ref			Ref			Ref	
Black	4.41	3.26, 5.96	< 0.001	4.23	3.06, 5.86	< 0.001	3.63	2.64, 4.98	< 0.001	3.59	2.64, 4.88	< 0.001	3.43	2.54, 4.64	< 0.001
Mexican	4.82	3.77, 6.18	< 0.001	3.82	2.89, 5.06	< 0.001	3.17	2.35, 4.27	< 0.001	3.02	2.33, 3.92	< 0.001	3.52	2.49, 4.97	< 0.001
Other	3.46	2.66, 4.51	< 0.001	2.39	1.75, 3.26	< 0.001	2.03	1.48, 2.78	< 0.001	1.99	1.47, 2.70	< 0.001	2.14	1.61, 2.84	< 0.001
Birthplace															
U.S. born	–	–	–		Ref			Ref			Ref			Ref	
Foreign born	–	–	–	1.97	1.51, 2.58	< 0.001	2.01	1.50, 2.70	< 0.001	1.96	1.42, 2.71	0.001	1.91	1.34, 2.72	0.001
Income/poverty ratio															
≥ 5	–	–	–	–	–	–		Ref			Ref			Ref	
3–4.9	–	–	–	–	–	–	1.26	0.87, 1.82	0.20	1.24	0.85, 1.80	0.248	1.22	0.81, 1.82	0.31
2–2.9	–	–	–	–	–	–	1.44	1.02, 2.04	0.04	1.40	0.97, 2.02	0.066	1.38	0.97, 1.95	0.07
1–1.9	–	–	–	–	–	–	1.61	1.29, 2.01	< 0.001	1.55	1.22, 1.97	0.002	1.35	1.05, 1.72	0.02
< 1	–	–	–	–	–	–	2.89	2.13, 3.90	< 0.001	2.75	1.95, 3.87	< 0.001	2.14	1.48, 3.10	0.001
Household crowding*	–	–	–	–	–	–	–	–	–	1.22	0.86, 1.74	0.248	1.13	0.77, 1.66	0.50
Smoking															
Never	–	–	–	–	–	–	–	–	–	–	–	–		Ref	
Current	–	–	–	–	–	–	–	–	–	–	–	–	2.11	1.59, 2.82	< 0.001
Former	–	–	–	–	–	–	–	–	–	–	–	–	1.38	1.07, 1.78	0.02
Missing	–	–	–	–	–	–	–	–	–	–	–	–		Omitted	
Alcohol															
No	–	–	–	–	–	–	–	–	–	–	–	–		Ref	
Yes	–	–	–	–	–	–	–	–	–	–	–	–	0.93	0.73, 1.18	0.53
Missing	–	–	–	–	–	–	–	–	–	–	–	–	1.18	0.79, 1.78	0.39

CI = confidence interval; NHANES = National Health and Nutrition Examination Survey; OR = odds ratio.

Model 1: hepatitis A + age + gender + race, Hosmer–Lemeshow goodness-of-fit (P = 0.21); Model 2: Model 1 + birthplace, Hosmer–Lemeshow goodness-of-fit (P = 0.53); Model 3: Model 2 + income-to-poverty, Hosmer–Lemeshow goodness-of-fit (P = 0.003); Model 4: Model 3 + household crowding, Hosmer–Lemeshow goodness-of-fit (P = 0.003); Model 5: Model 4 + smoking + alcohol (restricted to 20 years of age and older), Hosmer–Lemeshow goodness-of-fit (P = 0.23).

*Household crowding modeled as a continuous variable (persons per room in household).

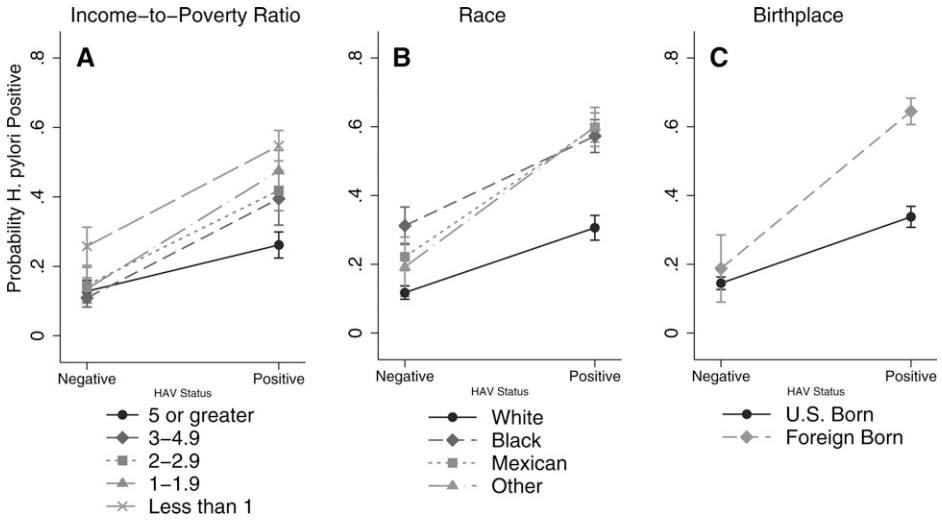

FIGURE 2. Marginal probabilities of *Helicobacter pylori* seropositivity by hepatitis A status for each (**A**) income-to-poverty ratio category, (**B**) race category, and (**C**) birthplace category. There was no significant interaction by income-to-poverty ratio ($P = 0.24$) or race ($P = 0.43$), however interaction by birthplace was found to be significant ($P = 0.048$).

The sensitivity analysis restricted to non-HAV-immunized participants ($N = 5{,}452$) resulted in similar OR estimates from the full sample (OR = 2.32, 95% CI = 1.73, 3.12), indicating little influence of immunization on the estimated *H. pylori*/HAV association. Full results are given in Supplemental Table 2.

In addition to HAV, we found significant positive associations between *H. pylori* and other fecal–oral (*Cryptosporidium*, $P < 0.001$) and potentially foodborne (*Toxoplasma*, $P < 0.001$) infections, but not sexually transmitted (HIV, $P = 0.36$; *Chlamydia*, $P = 0.80$) infections (Supplemental Table 3).

DISCUSSION

After adjusting for confounders, the odds of being *H. pylori* positive were over two times higher among HAV-positive individuals in this analysis, supporting the existence of a strong association between *H. pylori* and HAV. Similar results were also found in the earlier NHANES III sample (1989–1991) indicating this association may persist over time (Supplemental Table 1). Since HAV is primarily transmitted through the fecal–oral route and is a marker for prior fecal–oral exposure, the association between *H. pylori* and HAV found in this study supports the potential for fecal–oral transmission of *H. pylori.*

These results agree with past clinical and observational studies supporting the fecal–oral transmission hypothesis of *H. pylori*.[7,20] Parsonnet and others[10] reported isolating *H. pylori* from human feces in 22% of subjects through induced catharsis. Though not immediately generalizable to human models, Cellini and others[11] demonstrated fecal–oral transmission of *H. pylori* among mice. A recent case–control study among health-care workers found exposure to patient feces increased the risk of *H. pylori* infection and exposure to oral secretions was not associated with *H. pylori* infection, suggesting fecal–oral transmission may be as viable or more viable as a transmission model than oral–oral or gastro–oral transmisson.[12] However, Parsonnet and others[10] reported successful isolation of *H. pylori* from induced vomit (using ipecac) from all infected patients in the their study ($N = 16$) and from air sampled during vomiting from 38% ($N = 6$) and concluded that vomiting (gastro–oral) transmission may be the most viable mode of transmission. As such, fecal–oral transmission may not be the only mode of *H. pylori* transmission.

HAV is not the only pathogen associated with *H. pylori*. Moreira and others[18] reported a significant positive association between *H. pylori* and *Giardia lamblia*—an infection primarily transmitted through the fecal–oral route. In our supplemental analysis, we found positive associations with *Cryptosporidium* and *Toxoplasma*. *Cryptosporidium* is primarily transmitted through the fecal–oral route via contaminated water. *Toxoplasma* is transmitted primarily through infected cat feces. Similarly, past studies have noted cats may become infected with *H. pylori*[21] and that *H. pylori* has also been isolated from cat feces,[22] raising the possibility for zoonotic infection and explaining the association between *H. pylori* and toxoplasma.

Results in this study contrast with prior studies by Chen and others[23] examining a small adolescent population in Taiwan ($N = 91$), Egemen and others[24] in a sample of children in Izmir, Turkey ($N = 102$), Lin and others[25] with a sample of primary school students in Taipei ($N = 289$), and Furuta and others[26] with a clinic-based sample of adults in Japan ($N = 1{,}043$). These studies reported weak nonsignificant associations between *H. pylori* and HAV serology, but were limited in size and scope (all studied non-adult populations, except for Furuta and others) and not generalizable to broader populations. In contrast, our study is the first to use a large nationally representative dataset to study the serologic association between *H. pylori* and HAV, and did find a strong, significant, and consistent association. Another large nationwide study by Stroffolini and others[27] reported a strong association between *H. pylori* and HAV among a sample of 1,695 military students in Italy and concluded the association was driven by higher exposure to poorer regional hygienic conditions.

It is possible that fecal–oral *H. pylori* transmission may be less common in children than in adults and prior studies focusing solely on children may have missed the association.[28] For instance, in a school-based study examining both

kindergarten students and adult teachers, investigators found a significant association between HAV and *H. pylori* seropositivity among teachers, but not students.[29] Further, acute infection with *H. pylori* during childhood is characterized by vomiting and thus gastro–oral transmission may be more common among children.[30] One of the limitations of our study was the high level of excluded children (53.3% of children < 10 years old excluded) due to missing serology, which may have biased OR estimates upward.

Kappa analysis results indicated concordant seropositivity of infections were more likely than chance, but the magnitude of agreement was only fair.[31] These results agree with prior studies reporting low kappa statistics for *H. pylori* and HAV concurrence,[17,18] and have been used to argue against a common mode of transmission.[32,33] However, the low magnitude of agreement between infections may be due to differences in immunologic responses and detection.

HAV IgG antibodies are generally detectable for life, whereas *H. pylori* IgG titers decline to undetectable levels shortly after eradication treatment or infection clearance.[34–37] Although targeted *H. pylori* treatment was uncommon before 1999, use of incidental antibiotics has been found to reduce the prevalence of *H. pylori* infection.[38] Moreover, natural history studies have noted high rates of spontaneous clearance.[39,40] The decline in detectable *H. pylori* antibodies after infection clearance may result in misclassification of true prior *H. pylori* exposure and reduce concurrence with HAV seropositivity. Because *H. pylori* infection is thought to occur early in life and clearance or treatment may occur later in life, this may explain the divergence between *H. pylori* and HAV seroprevalence in older age groups (Figure 1) and the low agreement in positive serology. Prior studies have cited this divergence in seroprevalence as support against a common mode of transmission, but have not considered the differences in immunologic responses.[17,32] There does appear to be high agreement in negative serology between the infections, which has also been reported in prior studies.[18,25]

It has been argued that *H. pylori*/HAV serology studies fail to account for HAV vaccination and that observed associations between the infections are confounded by vaccination.[7] However, HAV vaccination was not widespread during the NHANES 1999 such that this bias was unlikely; furthermore, our sensitivity analyses of the non-immunized sample suggested vaccination had no effect on the association between *H. pylori* and HAV.

Although there was no heterogeneity in the *H. pylori*/HAV association by poverty or race, there was significant interaction by birthplace with odds of *H. pylori* seropositivity being much higher among HAV-positive foreign born than U.S. born. The persistently high burden of infection observed in minority racial and ethnic groups living in the United States is often attributed to low SES, crowded households, and immigration from high burden countries.[41] Indeed, the risk of *H. pylori* infection is generally higher in foreign countries, particularly in developing or low-resource settings.[42] Differential sanitation standards in developing countries may explain the higher rates of fecal–oral transmitted diseases in those countries and the greater risk of exposure and susceptibility to *H. pylori* and HAV infection among foreign-born immigrants in the United States.[43]

The association between *H. pylori* and HAV found in this study provides insight into the potential mechanism of *H. pylori* transmission; the strong, persistent association with HAV supports the possibility that the infections share a common mode of transmission. Since HAV is primarily transmitted through the fecal–oral route, fecal–oral transmission may be an important—but not isolated—pathway for *H. pylori* spread.

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