Where are we today with *Helicobacter pylori* infection among healthy children in Saudi Arabia?

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Abstract

Background/Aims: The available studies on *Helicobacter pylori* (*H. pylori*) prevalence among healthy asymptomatic population across Saudi Arabia suffers from significant limitations. We conducted this large population-based study to estimate the *H. pylori* seropositivity rate among apparently healthy children in Saudi Arabia, using anti-*H. pylori* immunoglobulin A (IgA) and IgG serology tests, and to study the influence of *H. pylori* infection on growth.

Materials and Methods: We conducted a cross-sectional study to screen apparently healthy school aged Saudi children (aged 6–15 years), attending primary and intermediate schools in Riyadh between 2014 and 2016, for *H. pylori* seropositivity by checking for the presence of anti-*H. pylori* IgG and IgA antibodies in serum specimens.

Results: Out of 3551 serum specimens, 1413 cases tested seropositive for *H. pylori* organism (40%): 430 (12.2%) were both IgG and IgA positive, 212 (6%) and 771 (21.7%) cases showed isolated positivity for IgG or IgA, respectively. Male gender, older age, lower levels of socioeconomic status (SES), and family members >10 were significantly associated with *H. pylori* seropositivity. The proportion of participants with short stature was significantly more in the *H. pylori* seropositive group than the seronegative group (OR1.249, confidence interval [1.020–1.531], $P = 0.033$). There was no significant association between *H. pylori* seropositivity and gastrointestinal symptoms.

Conclusion: The prevalence of *H. pylori* seropositivity among apparently healthy Saudi children (40%) is intermediate compared with that in developed and developing countries. The Saudi pediatric population shows a predominant IgA-type immunological response to *H. pylori* infection.

Keywords: Epidemiology, *Helicobacter pylori*, prevalence, Riyadh, short stature, socioeconomic status

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INTRODUCTION

The prevalence rates of *Helicobacter pylori* (*H. pylori*) infection vary from country to country depending on socioeconomic status (SES) and development stage. The prevalence of *H. pylori* infection is approximately 50% worldwide and is as high as 80–90% in developing countries.[1] The cumulative life-time risk of developing

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a peptic ulcer is 10% to 15% and 0.5% to 1% risk of developing gastric carcinoma (GC).[2] Acquisition of the infection occurs mostly in early childhood;[3] therefore, a better understanding of the epidemiology and the risk factors associated with *H. pylori* infection in the pediatric population is important in clarifying the natural history and complications of the infection, and programming eradication strategies.

The prevalence rate of *H. pylori* in Saudi Arabia was reported to be in the range of 50–80% among symptomatic patients with dyspepsia, abdominal pain or in patients undergoing endoscopic procedures.[4-10] The available information on *H. pylori* prevalence among apparently healthy populations across Saudi Arabia is vastly inadequate. Few "community"-based studies were conducted in the healthy Saudi population from the different regions of the country and most of these studies were among adults,[11-18] reporting a prevalence rate that ranged between 23 and 67%. The single study from Riyadh, Saudi Arabia, was conducted in 1989 and included 134 children only.[11] These studies suffered from several major limitations related to small sample size, nonrandom selection of the study population, and inappropriate study settings. These limitations led to significant selection bias and inadequately powered studies that affected the precision of the results and made these studies nonrepresentative of the general Saudi population.

These facts prompted us to design a large population-based study to determine the prevalence rate of *H. pylori* seropositivity among apparently healthy Saudi pediatric population via serologic screening of a large randomly selected study sample of school-aged children in Riyadh city. In addition, we aimed to study some aspects of *H. pylori* infection during childhood that were not investigated before in Saudi Arabia, like the influence of *H. pylori* infection on growth and the utility of the combined use of anti-*H. pylori IgA* and anti-*H. pylori IgG* antibodies (Abs) in screening for *H. pylori* infection.

MATERIALS AND METHODS

Study design and setting
This is a cross-sectional population-based study to screen apparently healthy school aged Saudi children (aged 6–15 years) of both sexes, attending primary and intermediate schools in Riyadh between 2014 and 2016, for *H. pylori* seropositivity by checking for the presence of anti-*H. pylori* IgG and IgA Abs in serum specimens. Riyadh is a new and well developed city that, in less than 5 decades, expanded from a population of 5,000 to

almost 5 million people with Saudis constituting 75% of the population. The Saudi community is tribal but belong to Arab ethnicity. Saudi Arabia has shown significant industrial and educational development over the past decades. Riyadh is the most representative city of all Saudi population because of its high rate of immigration from different parts of the country which make its inhabitants share similar demographic and sociocultural lifestyles, and dietary characteristics with those of whole population of Saudi Arabia.

Study population
The details of the methodology of the celiac mass screening study, from which the study population for the present study was selected, has been described elsewhere.[19] In brief, a total of 104 schools (61 primary schools and 43 intermediate schools; 53 male schools and 51 female schools) were randomly selected from the five "administrative" geographic regions of Riyadh city (North, South, East, West, and Center) using probability proportionate sampling procedure. Parents of 7930 students (mean age 11.22 ± 2.62 years) signed the informed consents and accepted to participate in the mass screening study. The 5 mL blood specimen collected from each student was centrifuged at 2000 RPM for 10 minutes and plasma was separated, given a code number from 1 to 7930, and stored at -80°C until analysis. Out of the 7930 serum specimens, we selected the odd-numbered specimens for *H. pylori* serology testing.

Study procedures
Data collection
A health advocator in each school distributed envelopes to all students. Each envelop contained the following: 1) an informed consent form, and 2) a questionnaire to collect data on demographics, gastrointestinal (GI) symptoms, and SES. All students whose parents signed the informed consent underwent measurement of growth parameters prior to blood collection. The SES of students was measured by collecting data on four main indicators: parents' educational level, family income, habitation, and parents' jobs. We used a point scale of 1–20 as follows: educational level, 6 points; family income monthly, 6 points; type of residence, 4 points; type of work, 4 points. An overall score of ≤5 from a maximum of 20 defined the low SES, 6–10 as lower middle SES, and 11–15 as higher middle SES, and >15 as high SES. Participants were categorized into six educational levels: postgraduate degree (6 points), university graduate (5 points), high school graduate (4 points), intermediate school graduate (3 points), primary school graduate (2 points), and illiterate (1 point). Monthly family income was graded as follows: US $ >8000 (6 points),

US $ 5000 - 8000 (5 points), US $ 2500 - 5000 (4 points), US $ 1500 - 2500 (3 points), US $ <1500 (2 points), and no income (1 point). The habitation was categorized into four types: Palace (4 points), Villa (3 points), apartment (2 points), small traditional house (1 point). Occupation of parents was classified as: trader/businessman/professional (4 points), office clerk (3 points), worker (2 points), and unemployed (1 point).

Serology evaluation

The serum specimens were analyzed for the presence of anti-*H. pylori* IgG and IgA antibodies by enzyme-linked immunosorbent assay (ELISA), according to the manufacturer's instructions. This method has been validated and extensively used in research on *H. pylori* infection in children.[20,21] The ELISA test used was QUANTA Lite *H. pylori* IgA and the QUANTA Lite *H. pylori* IgG kit (Inova Diagnostics, Inc., USA) with a sensitivity and specificity of over 90%. The cutoff value for positive IgA or IgG antibody to *H. pylori* was set at ≥25 units, negative at ≤20 units, and equivocal if the value ranges between 20.1 and 24.9 units. If the value remained equivocal after repeat testing, the result was reported as equivocal. A specimen with positive *H. pylori* IgA and/or IgG was reported as positive for *H. pylori* infection. A negative result indicated no IgA or IgG antibodies to *H. pylori*.

Ethical consideration

This study was approved by the institutional review board (number 11-066) and the Ministry of Education in Saudi Arabia. All study participants, or their legal guardians, provided informed written consent prior to study enrollment. The study was conducted according to the ethical guidelines of the Declaration of Helsinki.

Statistical analysis

Categorical variables, such as gender, region, SES, and other variables are presented in frequencies and percentages, whereas continuous variables such as age, weight, height, and body mass index (BMI) are expressed as mean ± standard deviation (S.D). Independent sample *t*-test was used to test mean significant differences between positive and negative *H. pylori* group with study characteristics. Chi-square/Fisher's exact test was used when the cell expected frequency was less than five and was applied to determine the significant relationship between categorical variables. A binary logistic regression was used to ascertain the most important significant risk factors/predictors between positive and negative *H. pylori* patients. A *P*–value <0.05 two-tailed was considered as statistically significant. All data was analyzed through statistical package SPSS 22 (SPSS Inc., Chicago, IL, USA).

RESULTS

General characteristics of the study cohort

We used a representative sample of 3965 serum specimens from an existing population-based biorepository of archived 7930 serum samples. Among these, 3953 were suitable for serology testing and 12 samples were inadequate. Out of the 3953 samples, 402 showed equivocal results (36 were equivocal for both IgG/IgA *H. pylori*, 296 equivocal for IgA-*H. pylori* only, and 70 equivocal for IgG-*H. pylori* only) and were excluded from the analysis. Thus, a total of 3551 samples showed seropositive or seronegative results and constituted our study cohort [11.25 ± 2.5 years; females = 1834 (51.6%) and males = 1717 (48.4%]. Table 1 shows the general characteristics of the 3551 participants including their demographics, distribution among the five geographic regions of Riyadh, distribution among the 4 levels of SES, number of family members, frequency of gastrointestinal symptoms, and age groups.

Seroprevalence of *H. pylori* infection

The overall seropositivity of *H. pylori* in this cohort was 40% (1413 *H. pylori* +ve specimens): 212 samples (6%) were *anti-H. pylori* IgG+/IgA−, 771 (21.7%) were *H. pylori* IgG−/IgA+, and 430 (12.2%) were both IgG+/IgA+. The overall *H. pylori* IgG +ve was 18.2%. The uninfected participants (*n* = 2138) constituted the control group. In the *H. pylori* IgG+/IgA+ group, the titer of *H. pylori* IgA was significantly higher than the titer of IgG Abs across all age groups except at age 10 years [Supplementary Table 1]. The mean level of IgA-Abs titer in the *H. pylori* IgG+/IgA+ group was 53.96 ± 36.24 units versus a titer of 43.10 ± 23.07 units of IgG-Abs in the isolated *H. pylori* IgA+ group. Comparison of the two isolated *H. pylori* positive groups (Isolated IgG+ versus isolated IgA+) [Supplementary Table 2] revealed no gender difference but significantly younger age of the isolated IgA+ group. Although the IgG and IgA Abs were detected in all ages, the rate of IgA seropositivity was significantly greater at ages 8 and 9 years, while the IgG seropositivity was significantly greater at age 14 years.

Risk factors for *H. pylori* seropositivity

The grades of the socioeconomic status of the total study cohort (*n* = 3551) in each region in Riyadh city are shown in Table 2. The low and lower middle SES predominated in the center and south of Riyadh (85.7% and 60%, respectively) as compared to the east and north of Riyadh (40% and 17.5%, respectively) [*P* value <0.001]. This pattern of distribution was also maintained among the 1413 *H. pylori* positive cases [Table 3].

Table 1: General characteristics of the study population (*n*=3551)

Variable	Study cohort (total number=3551)
Gender F:M†	1834 (51.6%)/1717 (48.4%)
Age (Mean±SD)	11.25±2.589
Region	
Center	421 (11.9%)
East	1108 (31.2%)
North	738 (20.8%)
South	464 (13.1%)
West	794 (22.4%)
Unknown	26 (0.7%)
Symptoms	
Poor appetite	752 (21.2%)
Abdominal distension	278 (7.8%)
Diarrhea	220 (6.2%)
Constipation	350 (9.9%)
Abdominal pain	877 (24.7%)
Vomiting	193 (5.4%)
Socioeconomic class	
Low socioeconomic status	279 (7.9%)
Lower middle socioeconomic status	1320 (37.2%)
Higher middle socioeconomic status	1604 (45.2%)
Higher socioeconomic status	348 (9.8%)
Socioeconomic indicators	
Father's Education	
Unknown	52 (1.5%)
Illiterate	231 (6.5%)
Primary	499 (14.1%)
Intermediate	543 (15.3%)
High school	1071 (30.2%)
Bachelor	916 (25.8%)
Doctorate/Master	239 (6.7%)
Mother's Education	
Unknown	59 (1.7%)
Illiterate	428 (12.1%)
Primary	567 (16.0%)
Intermediate	564 (15.9%)
High school	911 (25.7%)
Bachelor	972 (27.4%)
Doctorate/Master	50 (1.4%)
Family income ($)	
Unknown	160 (4.5%)
No income	181 (5.1%)
<1,500	611 (17.2%)
1,500-2,500	1037 (29.2%)
2,500-5,000	1067 (30.0%)
5,000-8,000	327 (9.2%)
>8,000	168 (4.7%)
Type of residence	
Unknown	56 (1.6%)
Traditional house	430 (12.1%)
Apartment	1153 (32.5%)
Villa	1891 (53.3%)
Palace	21 (0.6%)
Number of family members	
≤5	887 (25.0%)
6-10	2282 (64.3%)
≥11	382 (10.8%)
Age (yrs)	
6 yrs	89 (2.5%)
7 yrs	202 (5.7%)
8 yrs	330 (9.3%)
9 yrs	364 (10.3%)
10 yrs	418 (11.8%)
11 yrs	454 (12.8%)

Contd...

Table 1: Contd...

Variable	Study cohort (total number=3551)	
12 yrs	470 (13.2%)	
13 yrs	414 (11.7%)	
14 yrs	413 (11.6%)	
15 yrs	397 (11.1%)	
H. Pylori serology results		
IgG positive and IgA negative	122 ⌉	
IgG positive and IgA weakly positive	90	
IgG negative and IgA positive	645 ⊢	35%
Both IgG + IgA positive	430	
IgA positive and IgG weak positive	126 ⌋	
IgG weak positive	70 ⌉	
IgA weak positive	306 ⊢	10.4%
Both IgA + IgG weak positive	36 ⌋	
Both IgA + IgG negative	2138 (54%)	

†M=male, F=female

Table 4 shows the comparison of the *H. pylori* positive and *H. pylori* negative groups. No significant association was observed between gastrointestinal symptoms and seropositivity status. Male gender, older age, central and southern regions of Riyadh, lower levels of SES, and family members >10 were significantly associated with *H. pylori* seropositivity. Subanalysis of the SES indicators revealed that parents with educational level below high school, monthly family income US $ <2500, living in traditional house with limited space were risk factors for *H. pylori* seropositivity, while participants with higher income, higher education levels had significantly lower likelihood of having *H. pylori* seropositivity.

Table 5 shows the distribution of the 1413 *H. pylori* positive individuals stratified according to the geographic area in Riyadh, SES, and age of participants. The *H. pylori* positivity was significantly higher in the central region of Riyadh (53.2%) where the majority of the residents belong to a low or lower middle SES (85.7%) [Table 2], followed by the Southern region. *Helicobacter pylori* seroprevalence was significantly affected by SES; the highest seroprevalence (52%) was observed among participants from the low SES and was lowest (30.5%) among high SES participants. Multiple regression analysis revealed that lower family income US $ <2,500; 1.5 [1.256–1.784] *P* < 0.001) and low educational level below intermediate school [OR = 1.83, *P* < 0.001] were the two most important contributing factors to seropositivity of *H. pylori* organism. By age, *H. pylori* positivity increased in a nearly linear fashion from 21% at age 6 years to 54% at 15 years of age [Figure 1] and the average increase per year was 3.3%. This linear increasing pattern of distribution was also maintained among the 642 *H. pylori* IgG positive cases when the prevalence of *H. pylori* increased from 11.2% at age 6 years to 31.2% at 15 years of age.

Table 2: Stratification of the socioeconomic status by the region in the study cohort (*n*=3551)

| Socioeconomic status	Study cohort (*n*=3551)†					
	Center (*n*=421)	South (*n*=464)	West (*n*=794)	East (*n*=1108)	North (*n*=738)	*P*
Low socioeconomic status (*n*, %)	112 (26.6%)	59 (12.7%)	57 (7.2%)	43 (3.9%)	7 (0.9%)	<0.001
Lower middle socioeconomic status (*n*, %)	249 (59.1%)	217 (46.8%)	343 (43.3%)	377 (34%)	123 (16.7%)	<0.001
Higher middle socioeconomic status (*n*, %)	55 (13.1%)	171 (36.9%)	369 (46.5%)	552 (49.8%)	444 (60.2%)	<0.001
Higher socioeconomic status (*n*, %)	5 (1.2%)	17 (3.7%)	24 (3.0%)	136 (12.3%)	164 (22.2%)	<0.001

†26 Participants had unknown region

Table 3: Stratification of the socioeconomic status by the region in the *H. pylori* positive cases (*n*=1413)

Socioeconomic status	*H. pylori* positive cases (*n*=1413)†					
	Center (*n*=224)	South (*n*=225)	West (*n*=309)	North (*n*=245)	East (*n*=399)	*P*
Low socioeconomic status (*n*, %)	63 (28.1%)	30 (13.3%)	25 (8.1%)	2 (0.8%)	24 (6.0%)	< 0.001
Lower middle socioeconomic status (*n*, %)	136 (60.7%)	113 (50.2%)	147 (47.6%)	56 (22.9%)	139 (34.8%)	<0.001
Higher middle socioeconomic status (*n*, %)	24 (10.7%)	76 (33.8%)	132 (42.7%)	141 (57.6%)	190 (47.6%)	< 0.001
Higher socioeconomic status (*n*, %)	1 (0.4%)	6 (2.7%)	5 (1.6%)	46 (18.8%)	46 (11.5%)	< 0.001

†26 Participants had unknown region
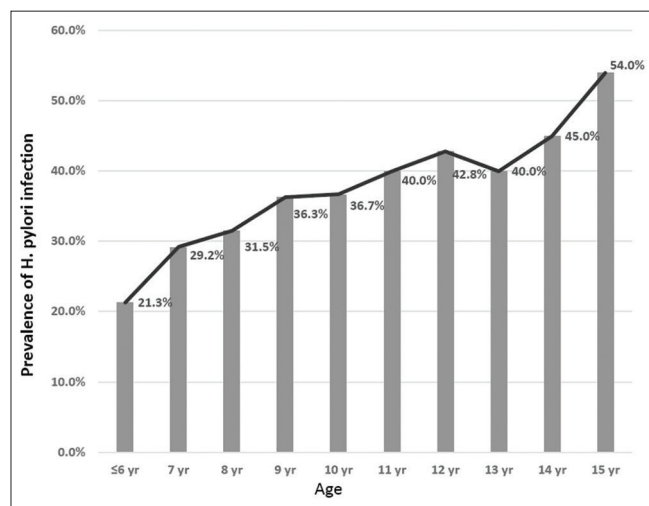
Figure 1: *H. pylori* positivity among the total study participants (=3551) according to age

Impact of *H. pylori* seropositivity on growth

The proportion of participants with short stature was significantly more in the *H. pylori* seropositive group than the seronegative group (13.6% versus 11.2%, OR 1.249, CI [1.020–1.531], *P* = 0.033). After controlling for SES, we did not find significant differences in the *H. pylori* positive and *H. pylori* negative groups (*P* value = 0.151, OR [95% CI] = 1.162 [0.946 – 1.428]). The frequency of underweight (<3rd percentile), BMI (<3rd percentile), and the mean weight, height, and BMI for age z-scores were not different between the infected and uninfected groups.

DISCUSSION

Our study is important for two main reasons: (a) the sample size was very wide and the study was properly designed allowing a more precise estimate of *H. pylori* seroprevalence, and (b) it provides further insight on the epidemiology of *H. pylori* infection in the heart of the Arabian Peninsula, an area that has shown significant modernization over the past few decades. We report several important findings. The sero-prevalence of *H. pylori* among apparently healthy Saudi children (40%) demonstrated here, using both IGA and IgG serology tests, is intermediate compared with that in developed (<30%) and developing countries (>50%).[22-24] Considering only the *H. pylori* IgG Abs testing, which was the only serology method used in the previous seroepidemiology studies in Saudi Arabia, the seroprevalence of *H. pylori* organism among apparently healthy Saudi children has dropped significantly from 40 - 50% in 1989 to 18.2% in the present study which is relatively a low rate compared with developing countries.[11] Another important and unique finding was the large percentage of *H. pylori* infected apparently healthy Saudi children (54% of the total 1413 cases) who have shown isolated IgA-immune response against *H. pylori* organism as compared to 0–7% in different ethnicities.[22,25-28]

Our study confirms and extends evidence obtained from several studies worldwide that *H. pylori* is strongly associated with lower SES, measured as a lower family income, lower educational level, and poor housing leading to poor living conditions and sanitation, and crowding of family members.[23] Furthermore, the *H. pylori* infection rate varies in Riyadh city based on the region studied, the Central and Southern regions with the highest proportion of lower SES had significantly the highest rates of *H. pylori* seropositivity (48–53%) as compared to the north and east regions (30–33%) where higher levels of SES predominate (*P* < 0.001). The epidemiology of *H. pylori*

Table 4: Comparison of the *H. pylori* positive and *H. pylori* negative groups

Variable	*H. pylori* positive (n=1415)	*H. pylori* Negative (n=2138)	OR [95% C.I]	P
Gender F:M[†]	682 (48.3%)/731 (51.7%)	1152 (53.9%)/986 (46.1%)	1.252 [1.095-1.433]	0.001
Age (Mean±SD)	11.70 2.56	10.96 2.56	0.894 [0.870-0.918]	< 0.001
Region				
Center	224 (15.9%)	197 (9.2%)	1.86 [1.513-2.278]	< 0.001
East	399 (28.2%)	709 (33.2%)	0.79 [0.685-0.918]	0.002
North	245 (17.3%)	493 (23.1%)	0.7 [0.59-0.83]	< 0.001
South	225 (15.9%)	239 (11.2%)	1.5 [1.237-1.831]	<0.001
West	309 (21.9%)	484 (22.6%)	0.96 [0.814-1.124]	0.575
Unknown	11 (0.8%)		1.11 [0.509-2.425]	0.795
Symptoms				
Poor appetite	284 (20.1%)	468 (21.9%)	0.9 [0.761-1.059]	0.194
Abdominal distension	108 (7.6%)	170 (8.0%)	0.96 [0.745-1.232]	0.721
Diarrhea	97 (6.9%)	123 (5.8%)	1.21 [0.917-1.59]	0.182
Constipation	128 (9.1%)	222 (10.4%)	0.86 [0.684-1.081]	0.190
Abdominal pain	340 (24.1%)	537 (25.1%)	0.94 [0.808-1.105]	0.461
Vomiting	76 (5.4%)	117 (5.5%)	0.98 [0.73-1.321]	0.896
Socioeconomic class				
Low socioeconomic status	145 (10.3%)	134 (6.3%)	1.71 [1.338-2.185]	0.001
Lower middle socioeconomic status	598 (42.3%)	722 (33.7%)	1.44 [1.253-1.653]	<0.001
Higher middle socioeconomic status	564 (39.9%)	1040 (48.6%)	0.7 [0.612-0.804]	< 0.001
Higher socioeconomic status	106 (7.5%)	242 (11.3%)	0.64 [0.5-0.807]	<0.001
Socioeconomic indicators				
Education level (both parents)				
Empty	14 (1.0%)	16 (0.7%)	1.33 [0.646-2.728]	0.442
Illiterate	85 (6.0%)	72 (3.4%)	1.84 [1.332-2.533]	<0.001
Primary	197 (13.9%)	174 (8.1%)	1.83 [1.473-2.27]	<0.001
Intermediate	214 (15.1%)	264 (12.3%)	1.27 [1.043-1.539]	0.018
High school	399 (28.2%)	583 (27.3%)	1.05 [0.903-1.219]	0.544
Bachelor	410 (29.0%)	857 (40.1%)	0.61 [0.529-0.706]	<0.001
Doctorate/Master	94 (6.7%)	172 (8.0%)	0.81 [0.628-1.057]	0.120
Family income ($)				
Empty	57 (4.0%)	103 (4.8%)	0.83 [0.597-1.156]	0.267
No income	84 (5.9%)	97 (4.5%)	1.33 [0.985-1.796]	0.063
<1500	293 (20.7%)	318 (14.9%)	1.5 [1.256-1.784]	<0.001
1500-2500	452 (32.0%)	585 (27.4%)	1.25 [1.078-1.446]	0.003
2500-5000	354 (25.1%)	713 (33.3%)	0.67 [0.575-0.776]	<0.001
5000-8000	114 (8.1%)	213 (10.0%)	0.79 [0.625-1.006]	0.054
>8000	59 (4.2%)	109 (5.1%)	0.81 [0.587-1.122]	0.202
Residential				
Empty	27 (1.9%)	29 (1.4%)	1.42 [0.835-2.403]	0.196
Traditional small house	234 (16.6%)	196 (9.2%)	1.97 [1.605-2.409]	<0.001
Apartment	461 (32.6%)	692 (32.4%)	1.01 [0.877-1.168]	0.894
Villa	684 (48.4%)	1207 (56.5%)	0.72 [0.632-0.828]	<0.001
Palace	7 (0.5%)	14 (0.7%)	0.76 [0.304-1.876]	0.542
Number of family members				
≤5	323 (22.9%)	564 (26.4%)	0.83 [0.707-0.968]	0.017
6-10	899 (63.6%)	1383 (64.7%)	0.95 [0.83-1.098]	0.483
≥11	191 (13.5%)	191 (8.9%)	1.59 [1.288-1.971]	<0.001
Growth parameters				
Weight <3rd percentiles (Underweight) %	172 (12.2%)	258 (12.1%)	1.010 [0.822-1.241]	0.937
Height <3rd percentile (short stature) %	192 (13.6%)	239 (11.2%)	1.249 [1.020-1.531]	0.033*
BMI <3rd percentile (%)	171 (12.1%)	244 (11.4%)	1.069 [0.868-1.316]	0.557
Weight Z-score (Mean±S.D)	-0.165±1.500	-0.135±1.448	0.954 [0.822-1.108]	0.537
BMI Z-score (Mean±S.D)	-0.0182±1.77	-0.0186±1.694	1.074 [0.975-1.183]	0.148
Height Z-score (Mean±S.D)	-0.484±1.300	-0.410±1.278	1.027 [0.924-1.141]	0.622
Age (yrs)				
≤6 yrs	19 (1.3%)	70 (3.3%)	0.4 [0.241-0.672]	< 0.001
7 yrs	59 (4.2%)	143 (6.7%)	0.61 [0.445-0.83]	0.002
8 yrs	104 (7.4%)	226 (10.6%)	0.67 [0.527-0.857]	0.448
9 yrs	132 (9.3%)	232 (10.9%)	0.85 [0.676-1.06]	0.143
10 yrs	153 (10.8%)	265 (12.4%)	0.86 [0.695-1.06]	0.152
11 yrs	181 (12.8%)	273 (12.8%)	1.0 [0.821-1.227]	0.984
12 yrs	201 (14.2%)	269 (12.6%)	1.15 [0.947-1.402]	0.162
13 yrs	164 (11.6%)	250 (11.7%)	0.99 [0.804-1.223]	0.925
14 yrs	186 (13.2%)	227 (10.6%)	1.28 [1.038-1.569]	0.021
>15 yrs	214 (15.2%)	183 (8.5%)	1.91 [1.546-2.352]	< 0.001

M=male; F=female; *After controlling for sociodemographic status, we did not find significant differences in the *H. pylori* positive and *H. pylori* negative groups (P=0.151, OR [95% CI] = 1.162 [0.946-1.428])

Table 5: Effect of region, socioeconomic class, age, and number of family members on distribution of *H. pylori* positive cases among Saudi Children (6-15 years)

Variable	Study cohort	*H. pylori* positive number %		P
	3551	1413	40%	
Region				
Center	421	224	53.2%	<0.001
South	464	225	48.5%	0.058
West	794	309	39%	0.707
East	1108	399	30.5%	0.040
North	738	245	33.2%	0.006
Socioeconomic class				
Low socioeconomic status	279	145	52%	0.006
Lower middle socioeconomic status	1320	598	45.3%	0.001
Higher middle socioeconomic status	1604	564	35.2%	0.001
Higher socioeconomic status	348	106	30.5%	0.011
Age group				
≤ 6 yrs	89	19	21.3%	0.011
7 yrs	202	59	29.2%	0.031
8 yrs	330	104	31.5%	0.030
9 yrs	364	132	36.3%	0.335
10 yrs	418	153	36.7%	0.347
11 yrs	454	181	40%	0.981
12 yrs	470	201	42.8%	0.358
13 yrs	414	164	40%	0.959
14 yrs	413	186	45%	0.135
>15 yrs	397	214	54%	<0.001
Number of family members				
≤5	887	323	36.4%	0.116
6-10	2282	899	39.4%	0.671
≥11	382	191	50%	0.006

has been changing over the last decades in many countries with a decline in the prevalence of the infection in parallel to improvement in SES.[23] The drop of *H. pylori* infection seroprevalence rate among healthy Saudi children to an intermediate range between developed and developing countries is mainly attributed to a combination of various factors including rapid economic growth, better education, improved housing and living conditions, and improved hygiene. Also, the widespread abuse of antibiotics to treat infectious during early childhood, when *H. pylori* infection is commonly acquired, could explain the decreasing *H. pylori* seropositivity levels in older children and adolescents. As Saudi Arabia is in a dynamic state of progression from a developing country into a developed country, it is anticipated that the pattern of prevalence of infection in Saudi Arabia will change further and each successive generation will experience a progressively lower rate of acquisition. It is important that preventive public health services be devoted to low SES communities via educational awareness campaigns, facilitating grant programs for wider housing with improved sanitation, and creating jobs for the poor jobless people to improve their income. Attainment of higher SES does not immediately change the epidemiology of *H. pylori* as it requires several generations for the pattern of acquisition of infection to change from that of a

developing country to a developed industrialized country. Based on our data, in comparison to a seroepidemiology data from Riyadh in 1989, it took 30 years for the *H. pylori*-IgG seropositivity in children to drop from 40% to 18%. Therefore, it may be valuable to study the seroprevalence of *H. pylori* infection every 2–3 decades to monitor prevalence trends and re-evaluate risk factors for *H. pylori* infection. Despite the significant drop in *H. pylori* seroprevalence rate among Saudi children, we still reserve two characteristics of developing countries: 1) Majority of the infected children had acquired the *H. pylori* infection during early childhood (20% are *H. pylori* infected by age 6 years), and 2) rapid increase of prevalence of *H. pylori* infection in older children and adolescents (Average of 3% increase in prevalence rate/year from 20% at age 6 years to 40% at age 15 years). In contrast, in developed countries *H. pylori* infection is low in childhood and slowly increases with age at a rate of less than 0.5–1% a year.[23] Long-term follow-up studies suggest that the age-dependent increase of *H. pylori* seropositivity is mainly attributable to a birth cohort phenomenon and a constant rate of new infections at all ages especially during childhood and adolescence that level off by 40–50 years of age.[27,29-32] These results support our assumption that a remarkable drop in *H. pylori* infection among Saudi Adults will probably follow the presently identified drop of *H. pylori* in children.

Variation in the prevalence of *H. pylori* infection reported across the world depends to a great extent on the SES, developmental stage of the country, and age of the studied population; however it could to some extent reflect differences in methodology of the studies, particularly the diagnostic method used. Large epidemiological studies using methods that directly detect the pathogen (stool antigen or urea breath test) over prolonged time-periods are considered the gold standard; however, these studies are logistically difficult to conduct and expensive compared to seroprevalence studies, and thus very infrequently conducted. An obvious limitation of the serology tests is that a positive result only indicates previous immunological exposure to *H. pylori* but cannot distinguish an active from an inactive *H. pylori* infection. Also another limitation is that a positive test result only indicates the presence of antibody to *H. pylori* and does not necessarily indicate that gastrointestinal disease is present. It is therefore recommended that serology tests are not used for diagnosis of *H. pylori* infection in clinical practice.[33] However, these tests have the advantages of being easy to perform, inexpensive, and the results are not affected by use of antibiotics or proton pump inhibitor within 1 month of testing. Also, several studies using *H. pylori* serology test demonstrated sensitivities over 90%

when compared to culture or histopathology-based studies.[21-23,26] These features made *H. pylori* serology test the most suited method for population-based *H. pylori* mass screening studies among healthy individuals, like our study. In a systematic review of the pediatric literature on population-based studies of the prevalence of *H. pylori* infection conducted during the period 2011–2016, the prevalence estimates from direct *H. pylori* detection studies and seroprevalence estimates in asymptomatic individuals did not differ significantly (30%–44% for direct detection versus 27%–38% for seroprevalence).[24] Also in the same systematic review, on analysis of the studies that tested for both seroprevalence and direct detection of infection in the same children, serology tended to find that about 10% of children had past infection and that about 10% of actively infected children were seronegative, indicating that serology results should be similar to those of direct detection methods, regardless of whether children were healthy or symptomatic. The authors concluded that the probability that overall seroprevalence represents true active *H. pylori* persistence rates in a large community appears to be high in childhood, considering the nearly 10% nonconcordance for both persistent and noninfected children. This may be a reflection of the observation that the majority of infections acquired early in childhood are persistent; follow-up data on *H. pylori* antibodies of same individuals showed that antibodies persisted in a great majority of those who had them 10–21 years earlier.[34,35] These data support that the seroprevalence of *H. pylori* infection reported in our study is very close to the true prevalence in the healthy Saudi pediatric population.

Majority of individuals infected with *H. pylori* produce a measurable systemic immune response, composed primarily of IgG Abs. Very few studies evaluated host immunological responses of IgA type against *H. pylori*. Data from these studies suggest that host immunological responses to *H. pylori* may vary in different populations; IgA-*H. pylori* Abs were usually detected in combination with elevated IgG antibodies in approximately two-thirds of infected subjects; however, isolated IgA response to *H. pylori* (negative IgG Abs) was detected in 2% of the population in Finland,[28] 4.9% of the population in Serbia,[22] and 7% of the population in the United States,[26] but not detected in Burkina Faso and Sweden.[25,27] The finding of high proportion of isolated anti-*H. pylori* IgA Abs production in response to *H. pylori* infection (≈55% of all *H. pylori* positive cases) is an interesting and unique finding in the Saudi Arabian population; the mechanisms behind this phenomenon remain to be studied. Therefore, measurement of only IgG Abs in the previous local population-based studies might have missed some cases of *H. pylori* infection and subsequently underestimated the true prevalence in the pediatric Saudi population.

The causal link between *H. pylori* and GC is now well established and the incidence of GC is generally in direct proportion to the prevalence of *H. pylori* infection. Over the past 2 decades, the age standardized incidence rate for GC among Saudis dropped from 3.7/100,000 population in 1994 to 2.1/100,000 population in 2014,[36] in parallel to the decline in *H. pylori* prevalence by 50% among Saudi children, as shown in the present study during the same time period. Similarly, in Japan, China, Korea, and throughout Europe, there has been a progressive and rapid decline in the prevalence of *H. pylori* infection as well as a fall in GC incidence.[37-42] However, from the global perspective, a lower incidence of GC is found in Saudi Arabia than in East Asia, some European countries, and Middle East countries despite the high prevalence and early childhood acquisition of *H. pylori* infection in the Saudi population over the past few decades.[36] Does the predominant IgA-type immunological response to *H. pylori* infection in the Saudi population offer protection against progression to peptic ulcer disease, atrophic gastritis, and GC? Some researchers reported that IgA anti-*H. pylori* antibodies can play a protective role against progression to severe *H. pylori* gastritis and atrophy[43] which legitimizes our question and provide a scientific plausibility to speculate on the low incidence of GC in Saudi Arabia.

Our data is in agreement with results from large epidemiologic studies on *H. pylori* infection, showing lack of relationship between *H. pylori* infection and gastrointestinal symptoms, including recurrent abdominal pains.[33,44,45] This emphasizes that gastrointestinal symptoms are unreliable for suggesting *H. pylori* infection. As the prevalence of *H. pylori* infection among Saudi children is becoming lower, pediatricians and family physicians need to re-evaluate when to test for and whether to treat *H. pylori*. Also, our data showed no association between *H. pylori* infection and growth impairment. Conflicting data were reported on the association between *H. pylori* infection and short stature. Several observational studies demonstrated that *H. pylori* infection may be associated with diminished growth of children; however after controlling for SES, the association between *H. pylori* infection and height was attenuated and was no longer statistically significant,[46,47] suggesting that *H. pylori* might be an indicator of living in suboptimal healthy and nutritional conditions. While the most updated consensus guidelines from the European and the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition recommend against diagnostic

testing for *H pylori* infection when investigating causes of short stature,[33] a recent systematic review proposed a weak recommendation to test and treat *H. pylori* infection in children with diminished growth.[48] Whether *H. pylori* eradication can be beneficial to children's growth is unclear, and evidence from randomized controlled clinical trials is lacking.

There are several limitations which should be acknowledged in this study. First, the relationship between *H. pylori* infection and its risk factors in the cross-sectional study could not be proven conclusively. However, this is an unavoidable limitation in the cross-sectional design of any study. Our current study was not designed to assess several important factors like lifestyle, living conditions, and dietary habits of the participants and their families, and whether there was previous *H. pylori* treatment or family history of *H. pylori* infection, peptic ulcer disease, and GC.

In conclusion, the prevalence of *H. pylori* infection among apparently healthy Saudi children has dropped by 50% over the past 3 decades to lay in the intermediate range between developed and developing countries. The Saudi pediatric population shows a predominant IgA-type immunological response to *H. pylori* infection. Further research is needed to uncover the clinical implication of this unique phenomenon and its impact on the outcome of *H. pylori* infection.

Conflicts of interest
There are no conflicts of interest.

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Supplementary Table 1: Mean level of *H. pylori* IgG and IgA titer according to age in the 430 positive *H. pylori* cases with combined positivity of IgG and IgA

Age	Mean level of IgG titer±SD	Mean level of IgA titer±SD	P
6 yr, *n* (%)	31.43±5.1	50.52±21.99	<0.001
7 yr, *n* (%)	42.14±12.34	47.47±19.59	<0.001
8 yr, *n* (%)	41.52±17.36	57.63±41.14	<0.001
9 yr, *n* (%)	36.36±11.16	55.91±32.52	<0.001
10 yr, *n* (%)	41.32±19.62	47.96±27.94	<0.001
11 yr, *n* (%)	49.29±22.11	45.53±26.51	0.024
12 yr, *n* (%)	44.86±17.12	50.32±33.9	0.003
13 yr, *n* (%)	42.57±16.2	53.7±29.88	<0.001
14 yr, *n* (%)	45.47±18.89	57.54±43.45	<0.001
15 yr, *n* (%)	46.95±20.64	61.1±48.12	<0.001

Supplementary Table 2: Comparison of the rate of isolated IgG-*H. pylori* positivity versus isolated IgA-*H. pylori* positivity across age groups

Variable	Isolated IgG *H. pylori* positive (*n*=212)		Isolated IgA *H. pylori* positive (*n*=771)		OR 95% CI	P
Gender F: M	105 (49.5%)/107 (50.5%)		374 (48.5%)/397 (51.5%)		0.960 [0.708-1.301]	0.792
Age (Mean±SD)	11.87±2.34		11.28±2.54		0.910 [0.855-0.968]	0.002
6 yr, *n* (%)	4	(1.9%)	9	(1.2%)	1.63 [0.496-5.34]	0.417
7 yr, *n* (%)	7	(3.3%)	47	(6.1%)	0.53 [0.234-1.181]	0.114
8 yr, *n* (%)	8	(3.8%)	72	(9.3%)	0.38 [0.18-0.803]	0.009
9 yr, *n* (%)	15	(7.1%)	85	(11.0%)	0.61 [0.347-1.088]	0.092
10 yr, *n* (%)	19	(9.0%)	93	(12.1%)	0.72 [0.427-1.206]	0.208
11 yr, *n* (%)	36	(17.0%)	102	(13.2%)	1.34 [0.886-2.031]	0.164
12 yr, *n* (%)	36	(17.0%)	98	(12.7%)	1.4 [0.926-2.13]	0.109
13 yr, *n* (%)	25	(11.8%)	86	(11.2%)	1.06 [0.663-1.71]	0.795
14 yr, *n* (%)	37	(17.5%)	89	(11.5%)	1.62 [1.067-2.46]	0.023
15 yr, *n* (%)	25	(11.8%)	90	(11.7%)	1.01 [0.631-1.621]	0.962