



## Original Article

Rapidly decreasing prevalence of *Helicobacter pylori* among Japanese children and adolescents<sup>☆</sup>

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## ABSTRACT

**Background:** The secular trend in the prevalence of *Helicobacter pylori* (*H. pylori*) infection among children and adolescents in Japan has not been well documented.

**Materials and Methods:** We reviewed all relevant literature published between 1991 and 2017, focusing on the relationship between the prevalence of *H. pylori* infection and birth year. Our literature search covered all journal articles, conference proceedings and meeting abstracts that reported the prevalence of *H. pylori* infection in Japanese subjects under 20 years of age.

**Results:** We examined the prevalence of *H. pylori* infection according to birth year on the basis of data points, which comprised 20,269 subjects of 81 groups. Three-coefficient logistic regression analysis was performed to examine the trend in *H. pylori* prevalence. The prevalence was approximately 10% in the individuals born in 1985, but it decreased to 3% in the individuals born in 2011. The plot of *H. pylori* prevalence against birth year clearly indicated a birth-cohort effect: the earlier the birth year, the higher the prevalence.

**Conclusions:** Our analysis revealed a rapidly decreasing prevalence of *H. pylori* infection among Japanese children and adolescents over the past three decades.

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## 1. Introduction

*H. pylori*, a Gram-negative microaerophilic bacterium, was discovered in 1983 by Warren & Marshall [1]. *H. pylori* colonizes human gastric mucous and is known as a strong promoter of gastric carcinogenesis [2]. It is generally accepted that *H. pylori* infection mainly occurs in childhood and persists throughout life in the absence of eradication therapy or the development of atrophic gastritis [3–5]. Risk factors for *H. pylori* infection suggested by epidemiological studies include low socioeconomic status, domestic crowding [6] and recently, many studies have shown that the main infection route of *H. pylori* is from a parent to their child [4,7,8].

The prevalence of *H. pylori* has been markedly decreasing in Western countries with socioeconomical development over the course of the 20th century [9]. In Japan, the prevalence was as high as 72.7% among the adult population in 1974, but it decreased to around 40% in 2014 [10]. The observed changes in *H. pylori* prevalence in different age groups over time can be attributed to birth-cohort effects, which means that the prevalence is largely determined by an individual's birth year, with successive birth cohorts having different prevalence rates. The birth-cohort effect was plausible because of the unique features of *H. pylori* infection: the vast majority of *H. pylori* infections occur in early childhood and the infections are closely associated with hygiene and socioeconomical development. Wang and colleagues reported a decreasing trend in *H. pylori* prevalence in successive birth cohorts in a recent systematic review of studies conducted in Japan. However, that study involved mainly adult Japanese populations [11].

To our knowledge, few reports have comprehensively reviewed the prevalence of *H. pylori* infection in young Japanese, especially in

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children. We therefore conducted a comprehensive review focusing on the prevalence of *H. pylori* by birth year among Japanese children and adolescents.

## 2. Materials and Methods

We reviewed all relevant literature reporting on the prevalence of *H. pylori* infection in Japanese subjects who were under 20 years of age. Our search included PubMed and Ichushi-Web (Japan Medical Abstracts Society) searches, as well as hand-searching for conference proceedings and meeting abstracts (both in English and Japanese) that were submitted to the annual meetings of the Japanese Society for Helicobacter Research and the Japanese Society for Pediatric Gastroenterology, Hepatology and Nutrition held between 2001 and 2017. PubMed and Ichushi-Web searches were conducted using the following keywords: pylori [All Fields] AND (“epidemiology” [Subheading] OR “epidemiology” [All Fields] OR “prevalence” [All Fields] OR “prevalence” [MeSH Terms]) AND (“japan” [MeSH Terms] OR “japan” [All Fields]). We excluded abstracts or articles that did not describe the calendar year of the survey, the sample size or the diagnostic method. For all eligible articles, we extracted information on age, number of subjects, the test results of *H. pylori* infection, the diagnostic test and other relevant information.

*H. pylori* infection and birth year (calculated from the survey year and the average age of the subject at the time of survey) were plotted according to the diagnostic test and the sample size. JMP® 13.2.0 (SAS Institute Inc.) was used to generate scatter plots and regression lines. The three-coefficient logistic regression model was fitted using the nonlinear least squares method, with weighting determined by sample size. The size of the dot in the scatter diagram was changed according to the sample size, and the color of the dot was changed according to the diagnostic test.

## 3. Results

We identified nine full text articles (53 groups) and 41 meeting abstracts (75 groups), which were published from 2001 to 2017. We excluded those that do not describe the population number, the infection rate and the survey year. The groups including adults were also excluded. Seven articles (44 groups) and 19 abstracts (37 groups) were adopted (Table 1 and Fig. 1) [12–18]. Supplemental Table lists detailed information on 19 meeting abstracts which were not indexed in PubMed. Based on the descriptions of study subjects in individual studies, the vast majority of the study subjects were drawn from a general population when they underwent school health checks. Studies were excluded if children sought medical care due to gastrointestinal symptoms. Since detailed information on symptoms was not available in epidemiological studies, the possibility of inclusion of some symptomatic subjects could not be ruled out. In total, data points from 81 age groups (20,269 subjects) were extracted for the present analysis. The age ranged from 0 to 20 years old, and the birth year spanned from 1985 to 2011. The diagnostic methods included the urine antibody test, serum antibody test, stool antigen test and urea breath test.

Fig. 2 shows the scatter plot for the relationship between birth year and the proportion of positive *H. pylori* diagnostic tests. The highest infection rate was 18.8%, and the lowest was 0%. The prevalence of *H. pylori* infection was approximately 10% among subjects born in 1985, compared with about 2.7% among subjects born in 2011. A birth-cohort effect was therefore clear; the older birth cohorts (earlier years of birth) had a higher prevalence of *H. pylori* infection. More data were available for the birth cohorts between 1992 and 2002, in part because *H. pylori* screening

programs for junior high and high school students were carried out in some areas by local government during the same period.

## 4. Discussion

We conducted a comprehensive review focusing on *H. pylori* prevalence by birth year in the Japanese population under 20 years of age. We found that the prevalence was about 10% in the subjects born in 1985, but it approximated 3% in those subjects born in 2011. The prevalence has been decreasing rapidly, showing a clear birth-cohort effect among these young generations. These finding was similar to a recent systematic review on the prevalence of *H. pylori* in Japan [11]. However, the observed prevalence estimates in our study were lower compared with that study, in which the predicted prevalence estimates were 24.6% (23.5–25.8) for individuals born in 1980, 15.6% (14.0–17.3) for individuals born in 1990, and 6.6% (4.8–8.9) for individuals born in 2000 [11]. Several reasons might account for the differences in the prevalence estimates between these two studies. First, the target population might be different, because we included all literature published in both English and Japanese languages and meeting abstracts, while the previous systematic review excluded the literature published in Japanese and meeting abstracts. Second, we directly documented the prevalence by birth year based on the original studies, but the previous systematic review reported multivariable-adjusted prevalence, taking into account the between-study variations, such as source of population and diagnostic testing. Another possible reason is that the high multivariable-adjusted prevalence among individuals born between 1923 and 1943 may raise the overall prevalence in other age groups in the previous study.

When combining all data points, we noted that the data on the prevalence of *H. pylori* were not available for some birth years, making the estimates unstable for those subjects. Despite this limitation, our analysis corroborated the decreasing trend in the prevalence of *H. pylori* over the past three decades in young Japanese populations. A plot of the relationship between *H. pylori* prevalence and birth year demonstrated a clear birth-cohort effect; the earlier an individual's birth year, the higher the prevalence of *H. pylori*. Since *H. pylori* is the most potent etiological factor driving gastric carcinogenesis [2,19,20], the incidence of gastric cancer in these younger populations is expected to decrease in parallel with the decreasing prevalence of *H. pylori*, reaching a low level in future decades.

Our review showed that the prevalence ranged from 0% to 18.8% in the published studies targeting children and adolescents, suggesting a wide variation among young populations. Worldwide *H. pylori* infection in young generations exhibits a wide geographic variation, with a higher prevalence observed in developing countries compared with developed countries. For example, the prevalence was 80% among 5 years old children in Bolivia [21]. One major contributing factor may be the living conditions in childhood, given that living conditions or poor socioeconomic status has been closely linked with *H. pylori* infection during early childhood [6]. Another possibility is that the number of subjects in individual studies was relatively small, making prevalence estimates fluctuate.

In most developed countries, the prevalence of *H. pylori* has been decreasing over the past decades, albeit at different rates or at different times. Ozbey and colleagues reported that the overall prevalence of *H. pylori* among children in developed countries in recent years was 1.2%–12.2% [22]. Our review corroborated a rapid decrease in *H. pylori* prevalence over the past three decades in Japanese children and adolescents. Continuous improvements in the sanitation and living conditions from the 1950s onwards may be the main explanation for the declining prevalence in Japan. Increases in the introduction rates of water supply and sewage have

**Table 1**  
List of studies addressing the prevalence of *H. pylori* infection in Japanese children and adolescents.

Study ID	Birth year	Number of subjects	Prevalence (%)	Specimen	Measurement	Year of research	Mean Age (yrs)	Author
1	1985	149	18.8	Serum	NM	2002	17	Urita Y et al. [12]
2	1989	102	12.7	UBT	NM	2009	20	Horiuchi A et al. <sup>a</sup>
3	1990	192	7.8	Serum	NM	2002	12	Urita Y et al. [12]
4	1990	94	7.4	UBT	NM	2010	20	Horiuchi A et al. <sup>a</sup>
5	1991	182	4.9	Urine	NM	2001	10	Yarita Y et al. <sup>a</sup>
6	1991	147	15.6	Serum	NM	2002	11	Urita Y et al. [12]
7	1991	90	8.9	UBT	NM	2011	20	Horiuchi A et al. <sup>a</sup>
8	1991	409	3.4	Urine	RAPIRUN	2007	16	Akamatsu T et al. [13]
9	1992	153	4	Urine	URINELISA	2002	10	Naito Y et al. [14]
10	1992	85	18.8	UBT	NM	2012	20	Horiuchi A et al. <sup>a</sup>
11	1992	370	7.6	Urine	RAPIRUN	2008	16	Akamatsu T et al. [13]
12	1993	153	4.6	Urine	URINELISA	2003	10	Naito Y et al. [14]
13	1993	45	9	Stool	TestMate Pylori Antigen	2007	14	Booka M et al. <sup>a</sup>
14	1993	204	7.8	Urine	NM	2010	17.5	Mabe K et al. <sup>a</sup>
15	1993	445	4.9	Urine	RAPIRUN	2009	16	Akamatsu T et al. [13]
16	1994	160	5.6	Urine	NM	2001	7	Yarita Y et al. <sup>a</sup>
17	1994	78	7.7	Urine	NM	2010	16.5	Mabe K et al. <sup>a</sup>
18	1994	478	4.8	Urine	RAPIRUN	2010	16	Akamatsu T et al. [13]
19	1994	295	5.4	Serum	NM	2014	20	Okada H et al. <sup>a</sup>
20	1995	149	4.7	Urine	URINELISA	2002	7	Naito Y et al. [14]
21	1995	400	3	Urine	RAPIRUN	2011	16	Akamatsu T et al. [13]
22	1996	149	4	Urine	URINELISA	2003	7	Naito Y et al. [14]
23	1996	83	10.8	Stool	TestMate Pylori Antigen	2007	11	Booka M et al. <sup>a</sup>
24	1996	539	3.2	Urine	RAPIRUN	2012	16	Akamatsu T et al. [13]
25	1997	254	4.3	Urine	NM	2001	4	Yarita Y et al. <sup>a</sup>
26	1997	610	3.3	Urine	RAPIRUN	2013	16	Akamatsu T et al. [13]
27	1998	150	5.3	Urine	URINELISA	2002	4	Naito Y et al. [14]
28	1998	182	9.3	Stool	NM	2006	7.9	Okuda M et al. <sup>a</sup>
29	1998	203	4.9	Urine	URINELISA	2001	3.5	Booka M et al. <sup>a</sup>
30	1998	78	7.7	Serum	NM	2002	3.5	Urita Y et al. [12]
31	1998	317	5	Urine	NM	2010	12	Mabe K et al. <sup>a</sup>
32	1998	516	2.3	Urine	RAPIRUN	2014	16	Ito A et al. <sup>a</sup>
33	1999	150	6.7	Urine	URINELISA	2003	4	Naito Y et al. [14]
34	1999	68	1.5	Stool	NM	2006	6.8	Okuda M et al. <sup>a</sup>
35	1999	124	8.1	Stool	NM	2006	6.6	Okuda M et al. <sup>a</sup>
36	1999	150	4	Stool	TestMate Pylori Antigen	2007	8	Booka M et al. <sup>a</sup>
37	1999	337	5.6	Urine	NM	2012	13.5	Ueda J et al. <sup>a</sup>
38	1999	318	3.1	Urine	URINELISA	2012	13.5	Okuda M et al. <sup>a</sup>
39	1999	206	5.8	Serum	E-plate EIKEN	2012	13.5	Okuda M et al. <sup>a</sup>
40	1999	453	3.1	Serum	E-plate EIKEN	2012	13.5	Nakayama Y et al. [15]
41	1999	317	6	Urine	RAPIRUN	2013	14.5	Kondo H et al. <sup>a</sup>
42	1999	354	5.9	Urine	NM	2013	13.5	Igarashi Y et al. <sup>a</sup>
43	1999	530	2.6	Urine	RAPIRUN	2015	16	Ito A et al. <sup>a</sup>
44	1999	283	11.3	Urine	URINELISA	2014	15	Mabe K et al. [16]
45	1999	283	6.7	UBT	POC One	2014	15	Mabe K et al. [16]
46	2000	64	1.6	Stool	TestMate Pylori Antigen	2011	11	Okuda M et al. [17]
47	2000	220	3.6	Urine	URINELISA	2013	13.5	Okuda M et al. <sup>a</sup>
48	2000	354	4.5	Urine	NM	2014	14	Fujiwara S et al. <sup>a</sup>
49	2000	615	8.3	Urine	URINELISA	2015	15	Handa O et al. <sup>a</sup>
50	2001	82	4.9	Stool	TestMate Pylori Antigen	2011	10	Okuda M et al. [17]
51	2001	1764	6.6	Urine	NM	2014	13.5	Kaji E et al. <sup>a</sup>
52	2001	302	6	Urine	RAPIRUN	2014	13.5	Kondo H et al. <sup>a</sup>
53	2001	512	7.6	Urine	URINELISA	2014	13.5	Mabe K et al. [16]
54	2001	518	4.8	UBT	POC One	2014	13.5	Mabe K et al. [16]
55	2002	428	3.7	Stool	TestMate Pylori Antigen	2007	5	Booka M et al. <sup>a</sup>
56	2002	196	6.7	Stool	HpSA	2002	0	Okuda M et al. <sup>a</sup>
57	2002	90	3.3	Stool	TestMate Pylori Antigen	2010	8	Okuda M et al. [17]
58	2002	69	1.5	Stool	TestMate Pylori Antigen	2011	9	Okuda M et al. [17]
59	2002	274	2.9	Urine	RAPIRUN	2015	13.5	Kondo H et al. <sup>a</sup>
60	2002	1765	5.4	Urine	RAPIRUN	2015	13.5	Kusano C et al. [18]
61	2003	110	1.8	Stool	TestMate Pylori Antigen	2010	7	Okuda M et al. [17]
62	2003	100	1	Stool	TestMate Pylori Antigen	2011	8	Okuda M et al. [17]
63	2004	89	2.2	Stool	TestMate Pylori Antigen	2010	6	Okuda M et al. [17]
64	2004	71	1.4	Stool	TestMate Pylori Antigen	2011	7	Okuda M et al. [17]
65	2005	256	5.4	Stool	TestMate Pylori Antigen	2007	2	Booka M et al. <sup>a</sup>
66	2005	195	3.1	Stool	TestMate Pylori Antigen	2009	4	Booka M et al. <sup>a</sup>
67	2005	274	5.1	Stool	TestMate Pylori Antigen	2009	4	Booka M et al. <sup>a</sup>
68	2005	134	3.7	Stool	TestMate Pylori Antigen	2010	5	Okuda M et al. [17]
69	2005	120	3.3	Stool	TestMate Pylori Antigen	2011	6	Okuda M et al. [17]
70	2006	120	0.8	Stool	TestMate Pylori Antigen	2010	4	Okuda M et al. [17]
71	2006	115	0.9	Stool	TestMate Pylori Antigen	2011	5	Okuda M et al. [17]
72	2007	38	0	Stool	TestMate Pylori Antigen	2007	0	Booka M et al. <sup>a</sup>
73	2007	62	0	Stool	TestMate Pylori Antigen	2010	3	Okuda M et al. [17]
75	2008	36	0	Stool	TestMate Pylori Antigen	2010	2	Okuda M et al. [17]

**Table 1** (continued)

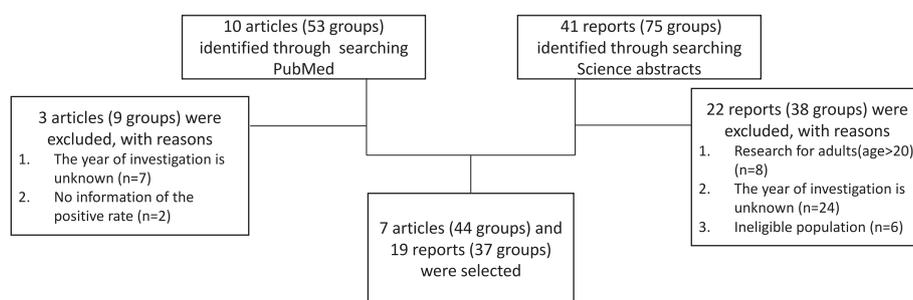
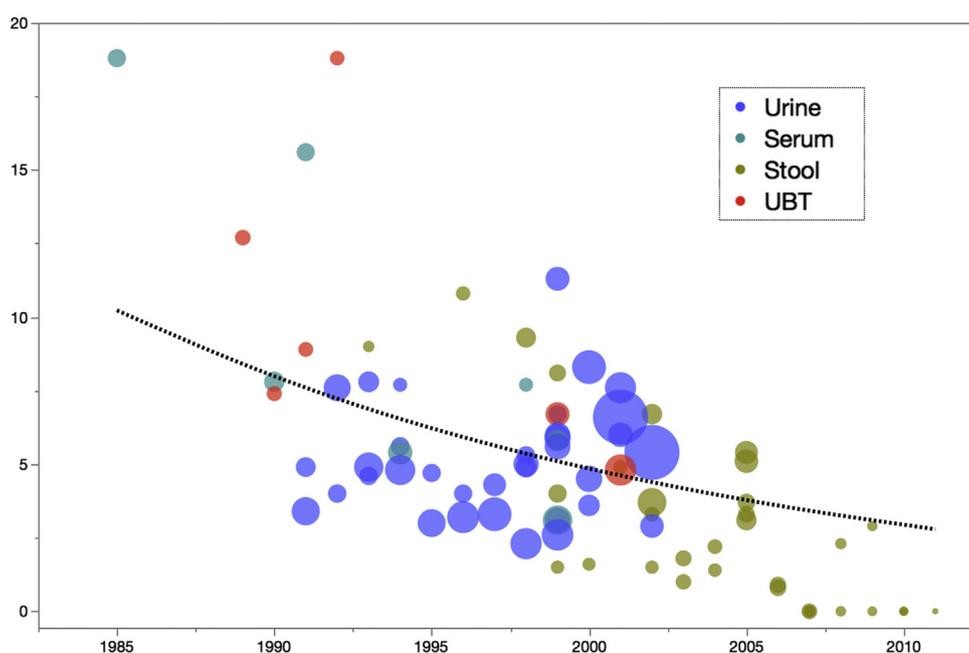
Study ID	Birth year	Number of subjects	Prevalence (%)	Specimen	Measurement	Year of research	Mean Age (yrs)	Author
76	2008	44	2.3	Stool	TestMate Pylori Antigen	2011	3	Okuda M et al. [17]
77	2009	29	0	Stool	TestMate Pylori Antigen	2010	1	Okuda M et al. [17]
78	2009	34	2.9	Stool	TestMate Pylori Antigen	2011	2	Okuda M et al. [17]
79	2010	19	0	Stool	TestMate Pylori Antigen	2010	0	Okuda M et al. [17]
80	2010	26	0	Stool	TestMate Pylori Antigen	2011	1	Okuda M et al. [17]
81	2011	6	0	Stool	TestMate Pylori Antigen	2011	0	Okuda M et al. [17]

UBT; Urea breath test, NM; not mentioned, RAPIRUN; Immunochromatography kit (Otsuka Pharmaceuticals, Tokyo, Japan), URINELISA; Enzyme-linked immunosorbent assay kit (Otsuka Pharmaceuticals Co., Tokyo, Japan), E-plate EIKEN; Enzyme immunoassay kit (Eiken Chemical Co., Tokyo, Japan), TestMate Pylori Antigen; Enzyme immunoassay kit (Wakamoto Pharmaceutical Co., Ltd., Tokyo, Japan), POC one; Infrared spectroscopy (Otsuka Electronics Co., Hirakata, Japan), HpSA; Enzyme-linked immunosorbent assay kit (Meridian Bioscience, Cincinnati, USA).

<sup>a</sup> Meeting abstracts, details are described in supplemental material.

been is linked to lower infection rate [23]. Another factor may be the decreasing birth rate [24], which has led to fewer children per family and thus decreased the possibility of intra-familial infection. Family size and the number of siblings have been shown to be positively associated with risk of *H. pylori* infection [25]. A Dutch study indicated that the decreasing trend in *H. pylori* prevalence has become stable in subsequent birth cohorts. Further studies are required to confirm whether similar stabilization of *H. pylori* prevalence will occur in subsequent cohorts in Japan.

Certain issues may need to be addressed to better capture the dynamics of *H. pylori* infection among children and adolescents. First, most of the included studies are cross-sectional studies involving a relatively small sample size. Few randomly selected samples or nationally representative samples were available, and prospective data collected at multiple time points for the same subject were also lacking. Second, detailed information on the measurement method, such as the kit used, was not available for most studies. Such information is important because even when

**Figure 1.** Flow diagram for selection of articles.**Figure 2.** Prevalence of *H. pylori* among Japanese children and adolescents by birth year.

the same diagnostic method is used, diagnostic accuracy may differ depending on the type of measurement kit. In addition, it remains controversial as to whether the cut-off points used to define *H. pylori* infection in adults can be readily applied to children when the serum antibody test is used for diagnosis. As for the urine antibody test, false positive results remain a concern [16]. Given these caveats, multiple non-invasive diagnostic methods should be used to confirm the infection.

In conclusion, our review indicated a rapidly decreasing trend in the prevalence of *H. pylori* infection among children and adolescents in Japan. With the continuous decrease in the prevalence of *H. pylori* infection in every age group, the incidence of gastric cancer is expected to continuously decrease, reaching a low level in future decades.

#### Author's contribution

All co-authors have contributed significantly to the study, and are in agreement with the content of the manuscript. The details of each author's contribution are as follows: RM, MO, YL AO and SK planned the study, RM and MO collected and reviewed papers, RM and KM analyzed the data, RM, MO, YL, AO and SK drafted the manuscript.

#### Conflicts of interest

Okuda M reports a personal lecture fee (Otsuka Pharmaceutical Co., Ltd. and EisCai o.Ltd.). Miyamoto R, Lin Y, Murotani K, Okumura A, and Kikuchi S declare no conflicts of interest.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jiac.2019.02.016>.

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