The global prevalence of and factors associated with Helicobacter pylori infection in children

a systematic review and meta-analysis

The global prevalence and risk factors for *Helicobacter pylori* infection in children: a systematic review and meta-analysis

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Summary

Background

The prevalence and risk factors for *Helicobacter pylori* infection (HPI) in children globally and in specific geographic regions are largely unknown. Randomised trials of oral recombinant vaccines against HPI are underway and showing vaccine efficacy. This study provides an estimate of the global and regional burden of paediatric HPI and risk factors to guide further research, development and implementation of HPI vaccine and other preventive measures that could reduce HPI.

Methods

Observational population-based studies, either cross-sectional or cohort in design, that reported the prevalence of HPI in children and adolescents aged 18 years and younger were included in the systematic review. From an initial list of 2247 bibliographic records, 193 articles containing 614 separate data points and involving 147317 children fulfilled the selection criteria. They were included in further meta-analysis of prevalence using multilevel mixed-effects meta-regression, and of risk factors significance using a random-effects meta-analysis.

Findings

An overall HPI prevalence in children worldwide was 32.4% (95% CI: 27.1-38.1). It significantly increased with advanced age, ranging from 24.0% (95% CI: 19.5-29.2) in children aged six years and under, to 43.5% (95% CI: 37.1-50.2) in those aged 13-18 years. It was higher in rural (49.7% [95% CI: 38.8-60.6]) than in urban areas (24.3% [95% CI: 17.0-33.4]). There were no differences between boys (35.6% [95% CI: 24.3-48.7]) and girls (34.4 % [95% CI: 23.4-47.4]). The prevalence of HPI in children steadily decreased by one-third globally, from 39.0% (95% CI: 32.3-46.0) before the year 2000 to 26.0% (95% CI: 18.5-35.2) in 2010 and later. The lowest HPI prevalence was found in samples obtained in health facilities (21.9% [95% CI: 15.4-30.2]) or tested by serology (28.1% [95% CI: 22.9-34.0]). Geographically, the highest HPI prevalence was found in the SEAR region (48.6% [95% CI: 28.1-69.6]), and the lowest in the WPR region (19.1% [95% CI: 10.4-32.4]). Advanced age, lower economic status, more siblings, room sharing, no access to sewage system, and infected mother were consistently associated with higher paediatric HPI prevalence in both HIC and LMIC. Additional risk factors included lower maternal or parental education, larger family size, smoking, drinking unboiled/non-treated water, consuming meals in unsanitary conditions, and infected father or siblings.

Interpretation

HPI is still highly prevalent in children and adolescents globally, but its prevalence is decreasing with improved education, urbanization, economic progress and improved nutrition, sanitation and standard of living worldwide. The prevalence is still high enough that it warrants large prevention and treatment programmes, such as vaccination, risk factors avoidance, screening and early antibiotic treatment.

Funding None.

Research in context

Evidence before this study

The prevalence of *Helicobacter pylori* infection (HPI) and risk factors for HPI in children globally and in specific geographic regions is largely unknown. However, the number of epidemiological investigations conducted on this topic world-wide has grown in the past 30 years. It should allow estimation of the prevalence and studying the role of possible risk factors. This is important, because randomised trials of oral recombinant vaccines against HPI are underway and they are showing vaccine efficacy. Providing an estimate of the global and regional burden of paediatric HPI and risk factors would, therefore, guide further research, development and implementation of HPI vaccine and other preventive measures that could reduce HPI.

Added value of this study

This study provided the first comprehensive and systematic estimate of the global and regional burden of paediatric HPI and risk factors. It showed that HPI prevalence in children worldwide was 32.4%, and that it significantly increased with advanced age, ranging from 24.0% in children aged six years and under, to 43.5% in those aged 13-18 years. The prevalence of paediatric HPI infection was higher in rural (49.7%) than in urban areas (24.3%). There were no differences between the prevalence in boys (35.6%) and girls (34.4%). The prevalence of HPI in children steadily decreased by one-third globally, from 39.0% before the year 2000 to 26.0% in 2010 and later. The lowest HPI prevalence was found in samples obtained in health facilities (21.9%) or tested by serology (28.1%). Geographically, the highest HPI prevalence was found in the SEAR region (48.6%), and the lowest in the WPR region (19.1%). Factors consistently associated with higher prevalence of HPI were advanced age, lower economic status, more siblings, room sharing, no access to sewage system, and infected mother, regardless of economic power of the countries in which the research took place. Additional risk factors included lower maternal or parental education, larger family size, smoking, drinking unboiled/non-treated water, consuming meals in unsanitary conditions, and infected father or siblings.

Implications of all the available evidence

HPI is still highly prevalent in children and adolescents globally, but its prevalence is decreasing with improved education, urbanization, economic progress and improved nutrition, sanitation and standard of living worldwide. The prevalence is still high enough that it warrants large prevention and treatment programmes, such as vaccination, risk factors avoidance, screening and early antibiotic treatment.

Introduction

Helicobacter pylori infection (HPI) is mostly acquired during childhood and often persists for life in the infected host.[1] How HPI transmits remains unclear, but intra-familial transmission appears to be the most important route.[2] While most children with HPI are asymptomatic, some may develop gastritis and peptic ulcer, as well as gastric adenocarcinoma and mucosa-associated lymphoid tissue lymphoma in adulthood.[3] About 8 in 10 of gastric cancer cases were attributable to HPI, making HPI one of the leading infectious causes of cancer globally.[4]

Although better sanitation, socio-economic status and living conditions particularly in high-income countries (HICs) may have resulted in a declining prevalence of HPI, the prevalence across many low- and middle-income countries (LMICs) is high.[5,6] Depending on geographical region and economic development, the prevalence of HPI in adults is reported to vary widely from 24% to 73% across populations, with a pooled global prevalence estimated at about 50%.[7] However, compared to adults, there are still uncertainties on the epidemiology of HPI in children. Many are asymptomatic with only 5% developing a peptic ulcer disease, gastritis or related gastrointestinal disorders.[6] Even with suggestions of a possible link with growth retardation and iron deficiency anaemia in children, limited evidence has affected research efforts.[6,8]

In a 2017 study,[9] a global prevalence of 33% was estimated for HPI in childhood, but without a breakdown by sub-regions, countries, and geographical settings which would be quite useful for preventive measures in specific settings. Moreover, no study has systematically reviewed the risk factors for HPI in children. This may provide further insights on the transmission patterns and prevention of HPI, and assist with ongoing studies. For example, a randomised phase 3 trial of an oral recombinant vaccine against HPI on 4403 Chinese children showed an efficacy of 72% in reducing HPI incidence at 1-year post-vaccination.[10] An accurate estimate of the global burden of paediatric HPI is therefore needed to update disease epidemiology relevant for response in different settings, including research and vaccine development. This could result in primary prevention of HPI and its potential elimination in the future.

Our primary aim is to estimate the global and regional prevalence of HPI in children and adolescents aged 18 years or younger. In addition, we aim to determine the risk factors for HPI in children , with variations estimated across HICs and LMICs.

Methods

This systematic review and meta-analysis was conducted and reported in accordance with the standards of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline [11]. The full review protocol is available in the PROSPERO database, registration number CRD42020209717.

Search strategy and study selection

We searched PubMed, Embase and Medline for observational population-based studies that were published until Sep 16, 2020, without language or geographical restrictions. The main search terms were related to HPI (e.g., "Helicobacter pylori", "Campylobacter pylori"), children (e.g., "children", "adolescents") and prevalence (e.g., "epidemiology", "prevalence"). The detailed search strategies for each database are available in the appendix. Reference lists of relevant reviews were additionally scrutinised to supplement the bibliographic database searches [Ref to add].

Observational population-based studies, either cross-sectional or cohort in design, that reported the prevalence of HPI in children aged 18 years and younger were included. Eligible studies should have provided the prevalence of HPI with uncertainty (confidence interval [CI] or standard error [SE]) or enough information to compute uncertainty (sample size and number of HPI cases). The investigated sample should not be purposely selected or clearly unrepresentative of the general paediatric population, such as children with specific conditions (e.g., type 1 diabetes, obesity or symptoms of disease). Investigations could have been organised in communities, schools or in the form of health check-ups in healthcare facilities. Moreover, the included studies should have employed active case ascertainment approaches and should not be based on self-reports. Case reports, reviews, or editorials that did not explicitly provide primary data were excluded.

Titles and abstracts of all identified records were independently screened by two authors (LH and YH) against the eligibility criteria. Then, the full text of all potentially suitable records was examined for final inclusion by the same two authors. Potentially relevant studies that were not published in English or Chinese were translated using Google Translate. Similar publications based on the same data source were carefully compared, and the one with the most comprehensive results or the most recent data was included.

Data extraction and quality assessment

Using a preconceived and standardised data extraction form, the following information was independently collected by the two authors (LH and YH) from the included articles: first author, year of publication, study characteristics (e.g., setting, country, study design, data collection period, sampling method), ascertainment methods of HPI, participants' characteristics (e.g., age range, sex), sample size, HPI cases and prevalence. A subset of included articles also explored potential associated factors for HPI using multivariable logistic regression, from which the definition and effect size (odds ratio [OR] and corresponding 95% CI) of each risk factor were extracted. Wherever possible, data on HPI prevalence were separately extracted for various age groups, sexes and settings.

To explore variations in HPI prevalence by geography and economy, we classified the included studies into regions as designated by the World Health Organization (WHO), including African region [AFR], region of the Americas [AMR], South-East Asia region [SEAR], European region [EUR], Eastern Mediterranean region [EMR], and Western Pacific region [WPR]). We also used the World Bank's classification to separate HICs from LMICs based on the relative size of their economies.

For articles that reported censored age range, the missing age band was imputed by taking the same width reported in other age ranges from the same article. In cases where investigation year was not reported, it was imputed as five years ahead of the year of publication, according to the average time-lag between investigation and publication from articles with available dates of both investigations and publications (see Appendix).

The quality of included articles was assessed by two independent authors (LH and YH) using a scale based on the Strengthening the Reporting of Observational Studies in Epidemiology statement [12] Five domains of study, namely study population, sample size, participation rate, outcome assessment, and analytical methods, were applied to evaluate the quality, with the score for each domain ranging from 0 (low quality) to 2 (high quality). The overall score of the five domains represents the overall quality (Appendix).

Any disagreements in review, data extraction and quality assessment were resolved through discussions with a senior investigator (YC).

Statistical analysis

According to our data extraction strategy, one individual article might have contributed multiple age-specific, sex-specific or setting-specific prevalence estimates (i.e., data points). To account for clustering of participants within the same study in the same country, we applied a multilevel mixed-effects meta-regression approach. After being transformed with the logit function, prevalence was first estimated for the global level, and then separately for HICs and LMICs. Then, a series of subgroup analyses was performed to explore variations in the pooled prevalence among age groups, sexes, settings (urban vs. rural), investigation period (before 2000, 2000-2010, 2010 and later), sampling sources (community-based, health facility-based, or school-based), test methods (serology, urea breath test, stool antigen test, or others) and WHO regions (AFR, AME, EUR, EMR, SEAR, or WPR). This was done for the global level, and then in HICs and in LMICs, respectively. Finally, pooled prevalence of HPI was generated for countries with two or more reported prevalence estimates.

For associated factors that had been provided in at least three articles, a random-effects (DerSimonian and Laird method) meta-analysis was adopted to synthesise their effect sizes (ORs) on HPI in children. Between-study heterogeneity was assessed using I^2 index and Cochran Q test. Meta-regression was used to check whether the pooled effect sizes of risk factors significantly differed between HICs and LMICs. For I^2 index, a value of 25% or lower, 26% to 50% and larger than 50% represented a low, moderate and high degree of heterogeneity, respectively. A two-sided $P<0.05$ was considered statistically significant in all analyses.

All analyses were conducted using Stata (version 14.0) and R (version 3.3.0).

Results

Study selection and characteristics

A total of 2247 bibliographic records were initially identified through searches of electronic databases. After removing 1216 duplicates and 562 irrelevant records in titles and abstracts, a full text of 420 articles was examined. Finally, 193 articles involving 147317 children fulfilled the selection criteria and were included in meta-analysis (Figure 1). The characteristics and quality of the included articles are given in the Appendix. Generally, more than one-third (37%, n=72) of the included articles were published in the last decade (2011 and onwards), and 72% (n=137) were conducted in rural–urban mixed settings. In addition, most samples were from communities (n=83, 43%) and schools (n=78, 40%), and the others were from check-ups in health facilities (n=32, 17%). The most commonly used tests for detecting HPI in children were serology (n=79, 41%) and urea breath test (n=60, 31%).

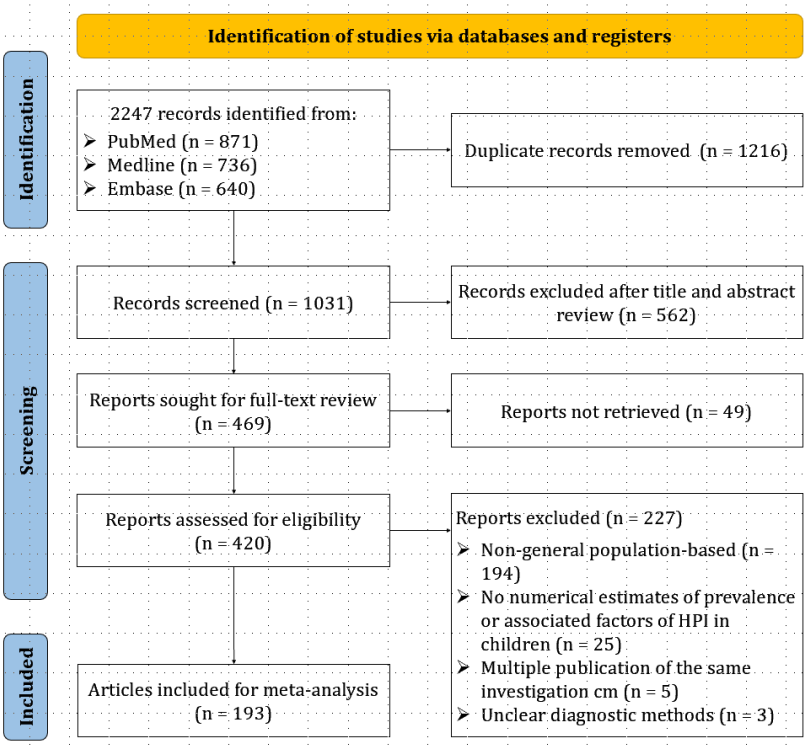

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Diagram of Literature Search and Study Selection

The included articles were generated from investigations in a total of 60 countries. Separating them by the country income level according to the World Bank's classification, the included articles came from HICs (46%, n=88) and LMICs (52%, n=100) quite evenly, while five articles reported prevalence of HPI in children for both HICs and LMICs. Geographically, most of the included articles were conducted in either EUR (34%, n=65) or AMR (28%, n=55). The geographic locations of the 193 included articles are shown in Figure 2.

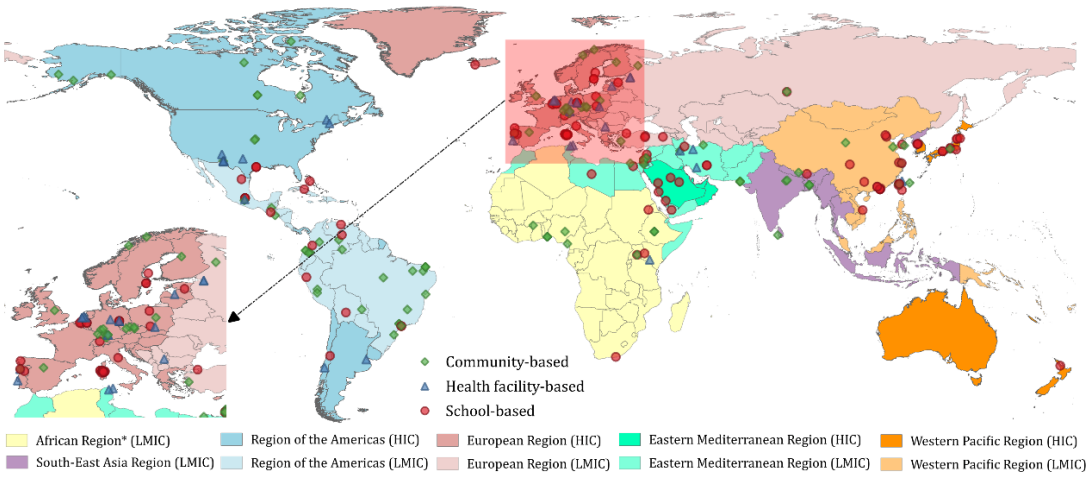

Figure 2. Geographic location of the included articles reporting the prevalence of HPI in children

*Note: * Seychelles is a high-income country according to the latest World Bank income classification, but we classified it together with the low-income and middle-income African Region countries due to its geographic location, small population size and unequal income distribution.*

Overall and stratified prevalence of HPI in children

Based on 614 data points from 193 articles, an overall HPI prevalence of 32.4% (95% CI: 27.1-38.1) was estimated in children worldwide from a multilevel mixed-effects meta-regression (Table 1). The stratified prevalence of HPI in children by age, sex, setting, investigation period, sampling source, test and WHO region was also estimated. Worldwide, the prevalence of HPI in children significantly increased with advanced age, ranging from 24.0% (95% CI: 19.5-29.2) in children aged six years and under, to 43.5% (95% CI: 37.1-50.2) in those aged 13-18 years. The prevalence of HPI in children did not differ between boys (35.6% [95% CI: 24.3-48.7]) and girls (34.4 % [95% CI: 23.4-47.4]), but was higher in rural areas (49.7% [95% CI: 38.8-60.6]) than in urban areas (24.3% [95% CI: 17.0-33.4]). In the past decades, the prevalence of HPI in children steadily decreased by one-third, from 39.0% (95% CI: 32.3-46.0) before 2000 to 26.0% (95% CI: 18.5-35.2) in 2010 and later. The prevalence of HPI in children was the lowest when samples were obtained in health facilities (21.9% [95% CI: 15.4-30.2]) or tested by serology (28.1% [95% CI: 22.9-34.0]). Geographically, the prevalence of HPI in children was the highest in the SEAR region (48.6% [95% CI: 28.1-69.6]), but the lowest in the WPR region (19.1% [95% CI: 10.4-32.4]).

The stratified prevalence in HICs and LMICs was also estimated by multilevel mixed-effects meta-regression. As shown in Table 1, the prevalence of paediatric HPI in LMICs was about two-fold higher than in HICs (43.5% [95% CI: 37.5-49.6] vs. 21.1% [95% CI: 15.5-28.0]). In HICs, the prevalence of HPI in children significantly increased with advanced age. It was relatively lower in urban than in rural settings, in health facilities than in communities, and when being tested by serology. By WHO region, the prevalence of HPI in children was the highest in EMR-HICs, but the lowest in EUR-HICs. In LMICs, the prevalence of HPI in children also significantly increased with advanced age. It was slightly higher in boys than in girls, and the lowest when detecting HPI with serology. Moreover, the prevalence of paediatric HPI in LMICs showed a decreasing secular trend from before 2000 to this decade. It didn't significantly vary among different settings (rural and urban), and regardless of sampling sources and WHO geographical regions.

Table 1. Estimated overall and stratified prevalence of HPI in children worldwide, in HICs and LMICs.

Group	No. of articles	No. of data points	No. of participants	No. of cases	Prevalence (%, 95% CI)	p value for subgroup difference
Worldwide						
Global analysis	193	614	147317	38773	32.4 (27.1-38.1)	-
Subgroup analysis						
Age group						
Overall	191	611	147072	38737	32.4 (27.1-38.2)	<0.0001
0-6 years	115	255	59038	11235	24.0 (19.5-29.2)	
7-12 years	111	239	56265	18667	35.3 (29.5-41.5)	
13-18 years	66	117	31769	8835	43.5 (37.1-50.2)	
Sex						
Overall	26	72	16501	4561	35.0 (23.9-48.0)	0.2134
Male	26	36	8370	2348	35.6 (24.3-48.7)	
Female	26	36	8131	2213	34.4 (23.4-47.4)	
Setting						
Overall	51	181	31787	9974	37.3 (28.6-46.9)	<0.0001

Group	No. of articles	No. of data points	No. of participants	No. of cases	Prevalence (%, 95% CI)	p value for subgroup difference
Urban	28	114	21751	6147	24.3 (17.0-33.4)	
Rural	26	67	10036	3827	49.7 (38.8-60.6)	
Investigation period						
Overall	192	612	147112	38766	32.9 (27.7-38.7)	
Before 2000	64	183	41273	8770	39.0 (32.3-46.0)	0.0015
2000-2009	100	312	70408	23475	31.2 (25.6-37.3)	
2010 and later	31	117	35431	6521	26.0 (18.5-35.2)	
Sampling source						
Overall	193	614	147317	38773	32.4 (27.1-38.1)	
Community-based	83	241	44041	15122	37.6 (30.6-45.2)	0.0049
Health facility-based	32	101	38309	7715	21.9 (15.4-30.2)	
School-based	78	272	64967	15936	31.9 (25.7-38.8)	
Test						
Overall	193	614	147317	38773	32.4 (27.1-38.1)	
Serology	79	252	61750	16319	28.1 (22.9-34.0)	
Urea breath test	60	158	48725	13213	39.3 (32.8-46.3)	<0.0001
Stool antigen test	38	125	16936	4888	29.6 (22.4-38.1)	
Other/mixed	26	79	19906	4353	41.5 (34.5-48.9)	
WHO region						
Overall	193	614	147317	38773	32.4 (27.1-38.1)	
AFR	13	45	5574	2072	44.2 (28.5-61.1)	
AMR	55	150	25354	9598	40.0 (30.2-50.8)	
EMR	23	86	14463	6685	43.6 (30.3-57.9)	0.0013
EUR	65	163	68002	14469	22.2 (16.2-29.6)	
SEAR	8	23	2038	823	48.6 (28.1-69.6)	
WPR	29	147	31886	5126	19.1 (10.4-32.4)	
			HICs			
Global analysis	90	229	87453	18742	21.1 (15.5-28.0)	-
Subgroup analysis						
Age group						
Overall	88	226	87208	18706	21.1 (15.5-28.1)	
0-6 years	44	91	34449	3994	11.4 (8.0-16.1)	<0.0001
7-12 years	45	91	31012	9621	23.9 (17.5-31.7)	
13-18 years	26	44	21747	5091	31.6 (23.7-40.7)	
Sex						
Overall	41	92	42690	11658	23.2 (15.6-33.2)	
Male	40	45	20011	5199	23.2 (15.5-33.1)	0.776
Female	40	47	22679	6459	23.3 (15.6-33.3)	
Setting						
Overall	15	45	15493	4422	27.8 (14.2-47.3)	
Urban	7	23	10023	2572	16.6 (8.0-31.4)	<0.0001
Rural	10	22	5470	1850	42.2 (24.1-62.7)	
Investigation period						
Overall	89	227	87248	18735	21.9 (16.2-28.9)	0.6754
Before 2000	34	88	27221	4568	22.1 (15.4-30.5)	

Group	No. of articles	No. of data points	No. of participants	No. of cases	Prevalence (%, 95% CI)	p value for subgroup difference
2000-2009	41	93	35962	10380	23.1 (16.6-31.3)	
2010 and later	15	46	24065	3787	18.6 (10.9-29.9)	
Sampling source						
Overall	90	229	87453	18742	21.1 (15.5-28.0)	
Community-based	32	81	20415	5812	28.7 (19.6-39.9)	0.0234
Health facility-based	19	37	29347	5333	15.1 (8.9-24.4)	
School-based	39	111	37691	7597	19.2 (13.3-27.0)	
Test						
Overall	90	229	87453	18742	21.1 (15.5-28.0)	
Serology	39	102	37734	9435	17.1 (12.1-23.6)	
Urea breath test	27	56	31943	6863	25.3 (18.2-34.0)	0.0001
Stool antigen test	17	38	5582	1381	28.9 (18.2-42.8)	
Other/mixed	13	33	12194	1063	19.8 (13.9-27.4)	
WHO region						
Overall	90	229	87453	18742	21.1 (15.5-28.0)	
AMR	17	38	6492	2650	38.2 (21.9-57.7)	
EMR	4	18	5218	2152	44.4 (18.2-74.1)	<0.0001
EUR	56	123	64662	12900	17.2 (12.0-24.1)	
WPR	13	50	11081	1040	38.2 (21.9-57.7)	
LMICs						
Global analysis	102	372	55835	19539	43.5 (37.5-49.6)	
Subgroup analysis						
Age group						
Overall	102	372	55835	19539	43.5 (37.5-49.6)	
0-6 years	68	151	20560	6749	37.3 (31.4-43.5)	<0.0001
7-12 years	68	148	25253	9046	46.1 (39.7-52.5)	
13-18 years	40	73	10022	3744	54.7 (48.2-61.1)	
Sex						
Overall	60	170	36404	12599	42.0 (34.4-50.0)	
Male	60	85	18072	6368	42.8 (35.1-50.8)	0.0146
Female	60	85	18332	6231	41.3 (33.7-49.3)	
Setting						
Overall	36	136	16294	5552	44.4 (40.0-49.0)	
Urban	21	91	11728	3575	46.5 (44.6-48.4)	0.188
Rural	16	45	4566	1977	39.1 (30.6-48.3)	
Investigation period						
Overall	102	372	55835	19539	43.5 (37.5-49.6)	
Before 2000	30	90	12400	3918	53.7 (46.0-61.2)	<0.0001
2000-2009	58	211	32069	12887	40.5 (34.1-47.3)	
2010 and later	16	71	11366	2734	32.8 (22.2-45.5)	
Sampling source						
Overall	102	372	55835	19539	43.5 (37.5-49.6)	
Community-based	51	159	23158	9182	44.7 (36.7-53.0)	0.288
Health facility-based	12	52	5401	2018	33.3 (21.5-47.7)	
School-based	39	161	27276	8339	45.5 (37.0-54.2)	

Group	No. of articles	No. of data points	No. of participants	No. of cases	Prevalence (%, 95% CI)	p value for subgroup difference
Test						
Overall	102	372	55835	19539	43.5 (37.5-49.6)	
Serology	41	146	22823	6832	37.0 (28.5-46.4)	
Urea breath test	30	93	13946	5910	40.0 (30.9-49.9)	<0.0001
Stool antigen test	21	87	11354	3507	42.4 (30.9-54.7)	
Other/mixed	13	46	7712	3290	80.3 (71.9-86.6)	
WHO region						
Overall	102	372	55835	19539	43.5 (37.5-49.6)	
AFR	13	45	5574	2072	43.0 (29.5-57.7)	
AMR	36	99	14833	6456	43.7 (33.8-54.2)	
EMR	19	68	9245	4533	45.1 (32.7-58.2)	0.5731
EUR	10	40	3340	1569	49.4 (31.9-67.2)	
SEAR	8	23	2038	823	48.4 (30.4-66.8)	
WPR	16	97	20805	4086	27.9 (15.3-45.4)	

Note: AFR, African region; AMR, region of the Americas; SEAR, South-East Asia region; EUR, European region; EMR, Eastern Mediterranean region; WPR, Western Pacific region.

As shown in Figure 3, the prevalence of HPI in children varied significantly, being as low as 2.0% (95% CI: 0.6-6.1) and 3.5% (95% CI: 0.4-22.4) in Finland and Iceland, respectively, but as high as >70% in Benin, Nepal and Peru. The estimated prevalence of HPI in the general paediatric population in 60 countries with available data is detailed in the Appendix.

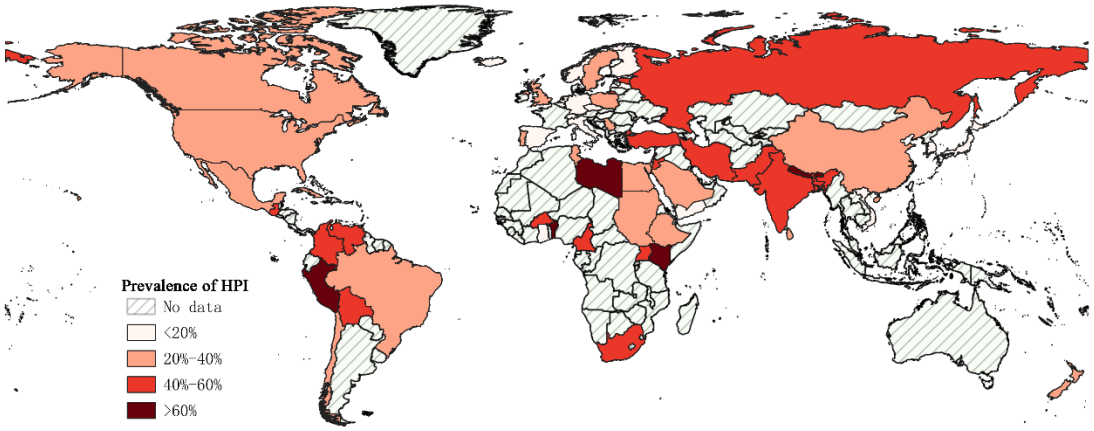

Figure 3. Estimated prevalence of HPI among children in 60 countries

Synthesised effect size of risk factors for HPI in children

A total of 29 associated factors that had been investigated in at least three articles were grouped into ten categories, covering a range of individual characteristics (e.g., age, sex, health behaviours), household characteristics (e.g., family characteristics, family transmission), and community characteristics (e.g., type of residence). Advanced age, lower economic status, more siblings, room sharing, no access to sewage system, and infected mother were consistently associated with paediatric HPI in both HIC and LMIC (Table 2). Additionally, lower education of mother's or both parents, larger family size, smoking, drinking unboiled/non-treated water, consuming meals in unsanitary conditions, infected father or siblings were also positively linked to HPI in children at the

global level. Diarrhoea was revealed as a symptom of paediatric HPI. The detailed results from individual articles that contributed to these meta-analyses are shown in appendix.

Table 2. Synthesised effect size of ten groups of associated factors of HPI in children that were investigated in at least three studies using multivariable design

Risk factor	Region	No. of studies	OR (95% CI)	I^2, %	p value	
					Q test	HIC vs. LMIC
Risk factor 1-Age (per year increase)						
	LMICs only	7	1.24(1.11-1.38)	71.8	0.002	-
Risk factor 2-Male Sex						
	Worldwide	27	1.08(0.99-1.19)	61.0	<0.001	
	HICs	12	1.10(0.97-1.25)	71.8	<0.001	0.549
	LMICs	15	1.06(0.92-1.22)	42.0	0.044	
Risk factor 3-Rural residence						
	Worldwide	4	1.18(0.91-1.53)	62.4	0.047	
	HICs	2	1.40(0.75-2.58)	72.3	0.057	0.589
	LMICs	2	1.10(0.78-1.54)	74.4	0.048	
Risk factor 4-Household aspects						
Lower economic status						
	Worldwide	16	1.63(1.46-1.82)	0	0.774	
	HICs	8	1.57(1.31-1.88)	25.4	0.226	0.884
	LMICs	8	1.65(1.37-1.98)	0	0.989	
Low mother's education						
	Worldwide	19	1.48(1.22-1.81)	59.4	0.001	
	HICs	2	1.95(0.11-33.63)	96.7	<0.001	0.908
	LMICs	13	1.38(1.23-1.55)	0	0.454	
Low father's education						
	Worldwide	8	1.25(0.71-2.21)	81.1	<0.001	
	HICs	2	0.85(0.06-11.74)	94.8	<0.001	0.340
	LMICs	6	1.52(1.26-1.84)	0	0.782	
Low both parents' education						
	Worldwide	5	1.73(1.28-2.33)	67.9	0.014	
	HICs	3	2.27(1.38-3.74)	71.5	0.03	0.209
	LMICs	2	1.29(0.83-1.98)	59.1	0.118	
Larger family size						
	Worldwide	10	1.24(1.01-1.53)	57.6	0.012	
	HICs	5	1.20(0.89-1.62)	53.5	0.072	0.925
	LMICs	5	1.27(0.90-1.79)	61.3	0.035	
More siblings/children						
	Worldwide	14	1.91(1.48-2.47)	77.2	<0.001	
	HICs	8	1.85(1.34-2.56)	81.6	<0.001	0.786
	LMICs	6	1.96(1.43-2.69)	24.7	0.249	
Bed sharing						
	LMICs only	6	1.40(0.99-1.99)	26.9	0.233	-
Room sharing						
	Worldwide	15	1.70(1.35-2.14)	51.0	0.012	
	HICs	3	1.71(1.14-2.56)	0	0.525	0.864
	LMICs	12	1.73(1.31-2.28)	59.5	0.004	

Risk factor	Region	No. of studies	OR (95% CI)	I^2, %	p value	
					Q test	HIC vs. LMIC
Ownership of domestic animal						
	Worldwide	10	1.16(0.98-1.38)	51.2	0.031	
	HICs	7	1.20(0.97-1.49)	66.9	0.006	0.626
	LMICs	3	1.07(0.76-1.50)	0	0.869	
No access to sewage system (including toilet)						
	Worldwide	8	1.60(1.22-2.10)	68.8	0.002	
	HICs	1	1.43(1.06-1.93)	-	-	0.699
	LMICs	6	1.78(1.14-2.77)	75.1	0.001	
Risk factor 5-Health behaviours						
Alcohol drinking						
	Worldwide	4	0.93(0.84-1.03)	5.7	0.365	
	HICs	3	0.89(0.76-1.05)	32.1	0.229	0.612
	LMICs	1	1.18(0.48-2.91)	-	-	
Smoking						
	Worldwide	4	1.12(1.04-1.21)	0	0.417	
	HICs	3	1.14(1.03-1.27)	6.8	0.342	0.459
	LMICs	1	0.91(0.55-1.50)	-	-	
Drinking unboiled/non-treated water						
	Worldwide	4	1.52(1.32-1.76)	13.8	0.323	
	HICs	2	1.58(1.41-1.78)	0	0.383	0.241
	LMICs	2	1.00(0.58-1.71)	0	0.986	
Consuming meals in unsanitised conditions						
	Worldwide	4	1.22(1.02-1.47)	78.9	0.003	
	HICs	3	1.24(0.96-1.61)	85.1	0.001	0.908
	LMICs	1	1.20(1.01-1.43)	-	-	
Risk factor 6-Day care attendance						
	Worldwide	7	1.51(0.96-2.35)	88.7	<0.001	
	HICs	4	1.57(0.74-3.36)	94.1	<0.001	0.918
	LMICs	3	1.44(1.12-1.85)	0	0.86	
Risk factor 7-Breastfeeding						
Ever breastfeeding						
	Worldwide	10	0.78(0.59-1.03)	63.5	0.003	
	HICs	4	0.66(0.41-1.07)	76.2	0.006	0.295
	LMICs	6	0.94(0.88-0.99)	0	0.426	
Exclusive breastfeeding						
	Worldwide	5	1.07(0.87-1.30)	22.8	0.274	
	HICs	2	1.28(0.83-1.96)	0	0.572	0.423
	LMICs	3	1.03(0.78-1.36)	22.8	0.274	
Risk factor 8-Family transmission						
Infected father						
	Worldwide	4	2.06(1.02-4.18)	7.7	0.355	
	HICs	2	2.87(1.41-5.83)	0	0.438	0.248
	LMICs	2	0.79(0.20-3.18)	0	0.836	
Infected mother						
	Worldwide	10	3.08(2.24-4.24)	0	0.659	0.310
	HICs	2	5.03(2.04-12.4)	17.3	0.271	

Risk factor	Region	No. of studies	OR (95% CI)	I^2, %	p value	
					Q test	HIC vs. LMIC
	LMICs	5	2.86(1.86-4.41)	0	0.412	
Infected sibling(s)						
	Worldwide	6	3.88(2.49-6.03)	0	0.512	
	HICs	4	4.21(2.18-8.13)	0	0.743	0.726
	LMICs	2	2.28(0.44-11.84)	65.7	0.088	
Risk factor 9-Symptoms						
Diarrhea						
	Worldwide	3	1.49(1.02-2.17)	62.7	0.068	
	HICs	2	1.57(0.91-2.69)	80.9	0.022	0.787
	LMICs	1	1.30(0.72-2.36)	-	-	
Abdominal pain						
	Worldwide	3	1.11(0.89-1.40)	63.8	0.063	
	HICs	2	1.05(0.83-1.34)	71.4	0.062	0.479
	LMICs	1	1.45(0.92-2.28)	-	-	
Nausea/Vomiting						
	Worldwide	3	1.31(0.76-2.26)	52.1	0.124	
	HICs	2	1.37(0.63-2.99)	75.7	0.043	0.951
	LMICs	1	1.28(0.41-4.01)	-	-	
Iron deficiency or anemia						
	LMICs only	4	1.03(0.90-1.18)	4.4	0.371	-
Poor appetite						
	HICs	2	0.89(0.76-1.04)	0	0.549	-
Risk factor 10-Short-term (within 6 months) antibiotic use						
	Worldwide	4	0.44(0.22-0.92)	86.9	<0.001	
	HICs	2	0.61(0.27-1.38)	92.7	<0.001	0.377
	LMICs	2	0.22(0.05-1.02)	53.5	0.143	

Discussion

This study provides the most comprehensive and systematic up-to-date estimation on the global prevalence of HPI in persons under 18 years of age. It is the first study that extensively explored possible risk factors for HPI in children. The amount of information that became available over the past 30 years seemed sufficient to produce estimates that look intuitive and reasonable in all of their main messages: the prevalence is higher in LMICs than in HICs, it is higher in rural than in urban areas, it increases with age and there are no detectable differences between the prevalence between boys and girls. Moreover, the prevalence of HPI is still relatively high in children and adolescents globally, but it has been decreasing over the past three decades with improved education, urbanization, economic progress and improved nutrition, sanitation and standard of living worldwide.

A special strength of this particular study is the reasonably large number of independent data points used for the estimates, as well as a sizeable total number of children and those who tested positive. In conjunction with numerous well-specified characteristics of the study population and setting, which is a consequence of increasingly high quality of reporting in observational studies, we were able to explore the possible effects of many different risk factors. All of them seemed to show effects that are in line with what was already known about the likely modes of transmission of the HP. This is reassuring, as

although the information and evidence for global health estimates is often scarce, patchy and of suboptimal quality, in this particular study we felt that the information allows us to develop a rather stable and plausible estimates – both for the levels of prevalence and for the roles of particular investigated risk factors. Our confirmation of these effects is novel in the literature.

Main findings

Specifically, our findings are in keeping with reported higher estimates of HPI in resource-constrained settings, with a two-fold higher prevalence in LMICs compared to HICs, and a significantly higher prevalence in rural compared to urban settings. This confirms earlier reports on a decreasing prevalence of HPI with rapidly improving socio-economic status including housing, water and sanitation facilities, and accessible standard health care – all important considerations for health promotion and policy response.[13,14]

Our global HPI prevalence of 32.4% (95% CI: 27.1-38.1) falls within previous estimates. In 2016, Zabala *et al*.[9] estimated a global childhood seroprevalence rate of 33% (95% CI: 27%-38%), while Zamani and colleagues[15] estimated a global prevalence 32.6% (95% CI: 28.4-36.8). According to Zabala *et al*.[9] although few longitudinal studies available in children did reveal some variability, most studies have consistently showed infection rates in the range 30%, suggesting one-third of children worldwide have HPI.

The prevalence of HPI varies significantly across geographical areas and time. We estimated that the prevalence of HPI in children decreased by one-third, from 39.0% before 2000 to 26.0% in 2010 and later, possibly due to improving states of social, economic, environmental and living conditions across world settings over this period, which has reflected in the better sanitation and decreased transmission over time.[16] HICs settings would largely account for this. In terms of regional variations, the highest prevalence of HPI among children were in the SEAR (48.6%), AFR (44.2%) and EMR (43.6%). We note that these regions also returned least data-points in our analysis. Although predominantly among adults and marked by lack of data from many LMICs, Hooi *et al*.[7] estimated highest prevalence of HPI in Africa at 70%, while Zamani *et al*.[15] estimated the highest prevalence in Latin America and the Caribbean (59%). Over the years, varying patterns in national HPI estimates have also been observed with highest estimates in Nigeria (90%), Serbia (88%), and South Africa (87%), and lowest in Yemen (9%), Indonesia (10%), and Belgium (11%)[15,17] Meanwhile, most studies observed no significant sex differences in HPI prevalence rate,[16] similar to the current study.

We reported a considerable increase in prevalence of HPI with advanced age in this study, increasing from 24.0% in 0-6 years to 43.5% in 13-18 years, which is apparently in keeping with the fact that adults have significantly higher infection rates compared to children.[15] However, some reports suggest a higher prevalence of HPI in children up to five years, with a declining prevalence observed thereafter.[18,19] The disparities with our estimates may reflect the method of case identification, treatment and re-infection status. For example, invasive studies, which are essentially facility-based, are likely among children that have been previously treated with reportedly low rates of re-infection.[20] Therefore, with different modes of identification of HPI among children in the current study, and a higher chance of spreading infection in the communities and schools where we have additional data, the possibility of an increase in prevalence from childhood to adolescents is most likely.[21]

Moreover, the higher estimates reported in communities compared to facilities may directly reflect the fact that more cases, mostly asymptomatic, would naturally be in the

population and schools compared to the few symptomatic cases that report to health facilities. In seven healthy cohort studies based on noninvasive direct detection methods, relatively higher infection rates were estimated among children ranging from 20-50% in children less than 5 years to 38-79% in children over 5 years.[9] To the best of our knowledge, this is the first time HPI prevalence variations by age is being studied among children, and therefore an important finding of this study.

Study limitations

As with many studies of this type, we recognise the limitations from a lack of data across several countries, geographical areas, and study period. In particular, we are still limited in our knowledge of the HPI from Africa and South East Asia, where studies are predominantly low, yet with reportedly higher burden. This should contribute a major point for research and policy in the response to the disease. We also note that this study includes varying study designs and methods of confirmation across different population settings, contributing to overall study heterogeneity. This is also an important consideration for research and practice, as many studies base their choice of diagnostic methods on access and cost, as observed, with a relative preference for serology in Asia, and urea breath test in North America.[15,22]

Odds ratio for some risk factors were only estimated in one or two studies. We clearly note the limitation of the power of synthesising the effect sizes of some of these selected risk factors. However, the strengths of this study are obvious – the first up-to-date estimates of HPI prevalence across the world, regions, geographical areas, study designs, case detection methods, age and sex. This is in addition to reporting variation in risk factors of HPI by world income categories, all from a robust dataset including 147317 children across 60 countries.

Research and policy implications

HPI is a substantial global health problem associated with spectrum of gastrointestinal disorders, especially among children. It also remains the most important established risk factor for stomach cancer.[23] Efforts targeted at improving hygiene, sanitary conditions and water sources are most-needed to reduce the burden of HPI globally, particularly in rural and resource-constrained world settings.[16] This would also be important considerations for schools, urban slums, crowded homes, marginalised communities and refugee camps.[24,25]

Appropriate use of current data and improved research across different levels will continue to be important steps towards better understanding and developing strategies to prevent spread of the disease. Considering the varying approaches to disease confirmation, there is a need to design and test guidelines to validate and correctly interpret current data. Serologic markers were employed across most studies, which do not necessarily determine an active infection, and has in fact returned low sensitivity among children,[13] partly responsible for a relatively low prevalence in this study.

Although there have been some considerable improvements in treatments with several consideration of alternative therapies,[26,27] understanding related antimicrobial resistance and adherence in different contexts, particularly among patients with multiresistant strains and treatment failure are important research considerations.[17] In a recent study,[28] the prevalence of resistance to first line triple therapy was high in many LMICs especially Africa, suggesting a need for more surveillance of susceptibility patterns in these settings.

Conclusions

Our study showed that HPI is still highly prevalent in children and adolescents globally, but its prevalence is decreasing with global development and reaching both the United Nations' Millennium Development Goals, as well as working further on Sustainable Development Goals. The prevalence is still high enough to warrant large prevention and treatment programmes, such as vaccination, risk factors avoidance, screening and early antibiotic treatment.

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Contributors

PS and YZ planned the study and IR and PS designed the methods. PS, YZ, ZF and HW contributed to the literature review and PS and YZ extracted data. PS, YZ and IR conducted statistical analyses. PS, TTL and DA prepared the first draft with important contributions from YC, KR, FJIF and FGRF. All authors interpreted results, commented on drafts of the paper and approved the final version.

Declaration of interests

We declare no competing interests.

Data sharing

All data generated or analysed in this study are included in the appendix.

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