

# Global Trends of Publication of Randomized Controlled Trials of Helicobacter Pylori Research

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## Research Article

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# Abstract

## Background

Since the first randomized controlled trial (RCT) on *H. pylori* was published in 1987, many RCTs were reported and major advances have been achieved in *H. pylori* research. This study aimed to use the PubMed to synthetically analyze the global trends of publication of the RCTs of *H. pylori* research from 1983 to 2020.

## Methods

A computerized literature search was performed based on PubMed (1983–Dec 31, 2020). The relevant RCTs on *H. pylori* research were identified. We analyzed the papers and calculated the data with the publishing items of RCTs.

## Results

The literature search involved 25,915 papers and 1,550 RCTs. These 1,550 RCTs were published from 1987 to 2020, with 2 ones in 1987 (the least) and 102 ones in 1999 (the most). These RCTs were published in 266 journals, with 259 ones in *Alimentary Pharmacology & Therapeutics (AP&T)*. These RCTs originated from 72 countries, with 236 from China, followed by 184 from Italy and 147 from Japan. The leading productive affiliation was Baylor College of Medicine (34 RCTs). The leading paper of the ten most highly-cited RCTs had 974 citations, and the mean number of citations was 584.

## Conclusions

The publication of *H. pylori* RCTs reached a peak at 1999 and then declined gradually after 2003. The leading journal publishing *H. pylori* RCTs was *AP&T*. The most productive countries were China, Italy, Japan, USA and UK. This bibliometric analysis can help relevant researchers take an overall view of global *H. pylori* research, and determine the direction of further research.

## 1. Introduction

A new era of research of gastroduodenal diseases has opened since the identification of *Helicobacter pylori (H. pylori)* by Warren and Marshall in 1983.<sup>1,2</sup> The bacterium was previously called *Campylobacter* genus, and was firstly named as *Helicobacter* in October 1989.<sup>3</sup> Currently, *H. pylori* infection remains one of the most common human infections all over the world.<sup>4</sup>

Rigorously designed and performed randomized controlled trials (RCTs) provide high-class evidence of the effect of health care interventions.<sup>5</sup> Consequently, RCTs have much more influence on health care

than other study designs. Thus, publications of RCTs could reflect the trend of clinical research. Since the first RCT on *H. pylori* was published in 1987,<sup>6,7</sup> over a thousand RCTs have been reported and major advances have been achieved in *H. pylori* research. In the present bibliometric study, we aimed to use the PubMed to synthetically analyze the global trends of publication of the RCTs of *H. pylori* research from 1983 to 2020, to help researchers have a historic perspective on the progress of worldwide *H. pylori* research, and determine the direction of further clinical research.

## 2. Methods

### 2.1 Literature search

A computerized literature search was performed based on the website, the PubMed (1983–2020). Although the RCTs published in 2020 have been included in PubMed, most of them have not been classified as “randomized controlled trial” with regard to the publication type. Thus, the literature search in 2020 was conducted manually after a simple search in PubMed. The citation search was conducted using the website, the Science Citation Index Expanded.<sup>8</sup> The language was restricted to English. There was no journal restriction.

The RCTs were identified using the search strategy: (Randomized Controlled Trial[ptyp]) and English[lang] and (*Helicobacter*[ti] OR *H. pylori*[ti] OR *campylobacter pylori*[TI] OR *C. pylori*[TI]). The literature search strategy in 2020: (*Helicobacter*[Title]) OR *H. pylori*[Title]) and English[lang] (randomized or randomised or randomly) 2020[dp].

### 2.2 Statistical Analysis

Descriptive statistical analyses were mainly used. We analyzed the involved papers and calculated the data with the following items: publication year, country of origin, journal, authorship, affiliation, terms and top citations.

## 3. Results

The literature search involved 25,915 papers and 1,550 RCTs using the website PubMed (1981–2020). The first two RCTs were both published in *Lancet* in 1987, which reported the failure of ofloxacin in *Campylobacter pylori* infection treatment and the relationship of this bacterium and recurrence of duodenal ulcers.<sup>6,7</sup>

These 1,550 RCTs were published from 1987 to 2020, with 2 ones in 1987 (the least) and 102 ones in 1999 (the most).(Fig. 1) However, the annual numbers of RCTs gradually reduced from 102 in 1999 to 32 in 2020. Besides, the annual proportions of RCTs to total papers of *H. pylori* were also showed in Fig. 1, with 2.49% in 1989 (the lowest) and 8.01% in 1999 (the highest). The annual proportions of RCT to total papers also gradually reduced from 8.01% in 1999 to 3.79% in 2020.

These 1,550 RCTs were published in 266 journals, with 259 ones in *Alimentary Pharmacology & Therapeutics (AP&T)*, followed by 141 ones in *Helicobacter* and 118 ones in *American Journal of Gastroenterology (AJG)*. (Table 1) The annual publications of *AP&T*, *Helicobacter* and *AJG* were showed in Fig. 2, which displayed a publishing climax of *AP&T* from 1998 to 2003. Nevertheless, there were few RCTs published in *AP&T* after 2007 and in *AJG* after 2005. 17 among the top 20 journals belonged to the journal category of Gastroenterology and Hepatology in the Journal Citation Reports, 1 to the journal category of infectious disease (*Journal of Antimicrobial Chemotherapy* with 12 RCTs), and 1 to the journal category of general medicine (*Lancet* with 24 RCTs). Besides, another two top journals, *New England Journal of Medicine (NEJM)* and *British Medical Journal (BMJ)* published and 8 and 11 RCTs, respectively.

Table 1  
Leading journals publishing the RCTs on *H. pylori* research

	<b>Journal</b>	<b>2019 Impact factor</b>	<b>Number of RCTs</b>
1	Alimentary Pharmacology & Therapeutics	7.515	259
2	Helicobacter	4.000	141
3	American Journal of Gastroenterology	10.171	118
4	European Journal of Gastroenterology & Hepatology	2.251	51
4	Journal of Gastroenterology and Hepatology	3.437	48
6	Gut	19.819	45
6	Digestive Diseases and Sciences	2.751	45
8	World Journal of Gastroenterology	3.665	44
9	Scandinavian Journal of Gastroenterology	2.130	40
10	Journal of Clinical Gastroenterology	2.973	32
11	Digestive and Liver Disease	3.570	27
12	Lancet	60.392	24
13	Hepato-Gastroenterology	-	23
14	Gastroenterology	17.373	21
15	Digestion	2.692	18
16	Turkish Journal of Gastroenterology	1.111	16
17	Indian Journal of Gastroenterology	-	14
18	Journal of Gastroenterology	6.132	13
19	Medicine	1.552	12
20	Journal of Antimicrobial Chemotherapy	5.439	12

These 25,915 papers came from 125 countries, with 3,658 ones from the United States (USA), followed by 3,132 ones from Japan and 2,828 ones from China.(Table 2) These RCTs originated from 72 countries, with 236 ones from China, followed by 184 ones from Italy and 147 ones from Japan.(Table 2) Although USA published the most papers about *H. pylori*, USA only published 124 RCTs. Among the top 20 countries, the proportions of RCT/total papers were the highest in Italy (184/1,682, 10.94%), followed by Turkey (64/665, 9.62%) and Switzerland (19/209, 9.09%).

Table 2  
Top Countries publishing the RCTs on *H. pylori* research

	Top countries	Number of RCTs	Number of papers	Proportion
1	China	236	2,828	8.35%
2	Italy	184	1,682	10.94%
3	Japan	147	3,132	4.69%
4	United States	124	3,658	3.39%
5	United Kingdom	96	2,178	4.41%
6	Korea	77	1,043	7.38%
7	Germany	76	1,422	5.34%
8	Turkey	64	665	9.62%
9	Iran	63	867	7.27%
10	Spain	36	472	7.63%
11	Netherlands	35	479	7.31%
12	France	25	631	3.96%
13	Australia	23	609	3.78%
14	Canada	21	498	4.22%
14	Sweden	21	617	3.40%
14	Brazil	21	368	5.71%
17	Switzerland	19	209	9.09%
18	Greece	18	231	7.79%
19	Finland	17	250	6.80%
19	India	17	522	3.26%

The annual publications of the top 5 countries were showed in Fig. 3. There were publication climaxes from 1999 to 2006 in China, from 1996 to 2006 in Italy, from 1998 to 2007 in Japan, from 1996 to 2003 in USA and from 1995 to 1999 in UK. Nevertheless, the numbers of RCTs reduced markedly after 2007 in Italy, USA and UK.

The top 20 productive affiliations in the world were listed in Table 3. The top three productive affiliations were Baylor College of Medicine (34 RCTs), National Yang Ming University (33 RCTs) and Peking University (29 RCTs). Among the top 20 affiliations, 10 ones were in China, with 3 in Italy, 3 in UK, 1 in

USA, 1 in Germany, 1 in Korea and 1 in Japan. Besides, the global origin map showed that the most productive areas were the West Europe and the East Asia. (Fig. 4)

Table 3  
Top affiliations producing the RCTs on *H. pylori* research

	<b>Affiliation</b>	<b>Countries</b>	<b>Number of RCTs</b>
1	Baylor College of Medicine	USA	34
2	National Yang Ming University	China	33
3	Peking University	China	29
4	Chinese University of Hong Kong	China	28
5	University of Hong Kong	China	27
5	Seoul National University	Korea	27
7	Kaohsiung Medical University	China	26
7	AstraZeneca	UK	26
7	University of Bologna	Italy	26
7	Shanghai Jiao Tong University	China	26
11	Catholic University of the Sacred Heart	Italy	25
12	GlaxoSmithKline	UK	24
12	Prince of Wales Hospital	China	24
14	Kaohsiung Veterans General Hospital	China	21
15	Otto von Guericke University	Germany	19
15	National Cheng Kung University	China	19
15	Sapienza University Rome	Italy	19
18	Chung Ho Memorial Hospital	China	18
18	University of Nottingham	UK	18
20	Hokkaido University	Japan	17

The ten most highly-cited RCTs were listed in Table 4, with 4 ones in published *NEJM*, 2 ones in *Lancet*, and the other journals were *Ann Intern Med*, *JAMA*, *J Natl Cancer Inst* and *Gastroenterology*. The leading paper had 974 citations, and the mean number of citations of the top ten papers was 584.

Table 4  
The most highly-cited RCTs on *H. pylori* research

RCT		Number of Citations
1	Graham DY, Lew GM, Klein PD, et al. Effect of treatment of <i>Helicobacter pylori</i> infection on the long-term recurrence of gastric or duodenal ulcer. A randomized, controlled study. <i>Ann Intern Med.</i> 1992;116:705–708.	974
2	Wong BC, Lam SK, Wong WM, et al. <i>Helicobacter pylori</i> eradication to prevent gastric cancer in a high-risk region of China: a randomized controlled trial. <i>JAMA.</i> 2004;291:187–194.	953
3	Hentschel E, Brandstätter G, Dragosics B, et al. Effect of ranitidine and amoxicillin plus metronidazole on the eradication of <i>Helicobacter pylori</i> and the recurrence of duodenal ulcer. <i>N Engl J Med.</i> 1993;328:308–312.	742
4	Fukase K, Kato M, Kikuchi S, et al. Effect of eradication of <i>Helicobacter pylori</i> on incidence of metachronous gastric carcinoma after endoscopic resection of early gastric cancer: an open-label, randomised controlled trial. <i>Lancet.</i> 2008;372:392–397.	729
5	Correa P, Fontham ET, Bravo JC, et al. Chemoprevention of gastric dysplasia: randomized trial of antioxidant supplements and anti- <i>Helicobacter pylori</i> therapy. <i>J Natl Cancer Inst.</i> 2000;92:1881–1888.	480
6	Chan FK, Chung SC, Suen BY, et al. Preventing recurrent upper gastrointestinal bleeding in patients with <i>Helicobacter pylori</i> infection who are taking low-dose aspirin or naproxen. <i>N Engl J Med.</i> 2001;344:967–973.	450
7	McCull K, Murray L, El-Omar E, et al. Symptomatic benefit from eradicating <i>Helicobacter pylori</i> infection in patients with nonulcer dyspepsia. <i>N Engl J Med.</i> 1998;339:1869–1874.	420
8	Blum AL, Talley NJ, O'Moráin C, et al. Lack of effect of treating <i>Helicobacter pylori</i> infection in patients with nonulcer dyspepsia. Omeprazole plus Clarithromycin and Amoxicillin Effect One Year after Treatment (OCAY) Study Group. <i>N Engl J Med.</i> 1998;339:1875–1881.	405
9	Lind T, Mégraud F, Unge P, et al. The MACH2 study: role of omeprazole in eradication of <i>Helicobacter pylori</i> with 1-week triple therapies. <i>Gastroenterology.</i> 1999;116(2):248–253.	348
10	Chan FK, Sung JJ, Chung SC, et al. Randomised trial of eradication of <i>Helicobacter pylori</i> before non-steroidal anti-inflammatory drug therapy to prevent peptic ulcers. <i>Lancet.</i> 1997;350:975–979.	334

## 4. Discussion

RCTs are often considered as the gold standard clinical evidence to measure an intervention's effect.<sup>9</sup> Designs of RCTs have become increasingly diversified as novel methods have been proposed to assess increasingly complex medical hypotheses. Based on the immense value of RCTs, RCTs are increasingly popular not only in medicine, but also in the social sciences.



Although *H. pylori* infection does not bring about illness in most infected persons, it is a critical risk factor for peptic ulcers and is responsible for the majority of gastroduodenal ulcers. In 1994, *H. pylori* was classified as a first-class carcinogen in humans by the International Agency for Research on Cancer,<sup>10</sup> despite there were conflicting results of carcinogenesis of *H. pylori* at the time. Since then, it has been widely accepted that *H. pylori* is an important pathogen of gastric malignancy and gastric mucosa-associated lymphoid tissue lymphoma.<sup>11</sup> Many RCTs have been published from many parts of the world over the past decades assessing different issues about *H. pylori* eradication therapy. This study provides attractive information about the global trends of the publication of RCTs on *H. pylori* research in the past decades.

Figure 1 showed that the number of RCTs increased markedly after 1992, reached a peak at 1999, and then declined gradually since 2003. In 2005, the two pioneers in *H. pylori* research, J.R. Warren and B.J. Marshall were given the Nobel Prize in Physiology or Medicine, which provided new stimulation for further research.<sup>12</sup> However, the number of RCTs continued to decrease after 2005. The trend of the publication of RCTs revealed that the clinical research on *H. pylori* fell into a low ebb in the past decade. However, there might be fewer RCTs in the several years due to the worldwide pandemic of COVID-19 influencing the conduction of RCTs.<sup>13</sup>

The top three journals published about 1/3 of all the RCTs, especially the *AP&T*, far more than other journals. However, *AP&T* and *AJG* published few RCTs after 2005. This might be attributed to the low ebb of RCTs of *H. pylori* research and that *H. pylori* was no longer a hot topic in gastrointestinal diseases. Besides, these two journals' impact factors rose rapidly in the past decade, maybe due to their disease speciality tendency to the hot points in gastrointestinal diseases. However, *H. pylori* research was once a hot medical issue and regularly published in the top general medical journals (*Lancet*, *NEJM* and *BMJ*).

The G7 industrial countries had the highest productivity of *H. pylori* research in the past decades.<sup>14</sup> However, in the list of *H. pylori* research RCTs, China (including mainland, Taiwan and Hong Kong) took the first place. The mainland of China presented a notable upward trend in many specialties based on the large size of the population, rapid economic development and huge investment into medical health in recent years.<sup>15-17</sup> In addition, Korea, Turkey and Iran entered the top ten list, and meanwhile France and Canada fell out of the top ten list. Figure 3 showed the annual publications of the top 5 countries, which revealed fast progress of China in the past decade, and in the contrast the numbers of RCTs reduced markedly after 2007 in the other four countries. West Europe and the East Asia were the most productive areas in the global origin map of *H. pylori* RCTs.

It was surprising that 10 of the top 20 productive affiliations in the world lied in China, with 5 in Taiwan, 3 in Hong Kong and 2 in mainland. Although mainland of China achieved great progress, considering the size of the population, it should be pointed out that mainland of China still has a long way to realize similar academic productivity of Taiwan and Hong Kong.

The ten most highly-cited RCTs were all published in top general or specialized journals, with 4 in *NEJM*, 2 in *Lancet* and 1 in *JAMA*, hinting great academic influence of these journals. Besides of the RCTs on *H. pylori* research, the most influential articles in *H. pylori* research were nearly all published in the top general or specialized journals.<sup>18</sup> The ten papers focused on the preventive effect of *H. pylori* treatment on peptic ulcers, bleeding, gastric dysplasia and cancer, which were the most important topics of *H. pylori* clinical research.

## 5. Conclusions

This study of global publication of *H. pylori* RCTs showed some interesting points concerning research performance from 1983 to 2020. The publication of *H. pylori* RCTs reached a peak at 1999 and then declined gradually after 2003. The top three journals were *AP&T*, *Helicobacter*, and *AJG*. The most productive countries were China, Italy, Japan, USA and UK. Besides, the most productive areas were the West Europe and the East Asia. This bibliometric analysis can help researchers take an overall view of global *H. pylori* research, and determine the direction of further clinical research.

## Declarations

**Ethics approval and consent to participate:** Not applicable.

**Consent for publication:** Informed consent was obtained in writing by all participates.

**Competing interests:** The authors declare that they have no competing interests.

**Availability of data and materials:** All data generated or analyzed during this study are included in this published article or are available from the corresponding author on reasonable request.

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**Authors' contributions:** SJ, SB and ZCM involved in study design, manuscript writing and revising. ZCM, CQT and WC involved literature search, data collection and statistical analysis and manuscript writing. ZCM and HYQ involved in creating figures and tables. All authors approved the final version of the article, including the authorship list.

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All data generated or analyzed during this study are included in this published article.

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# Figures

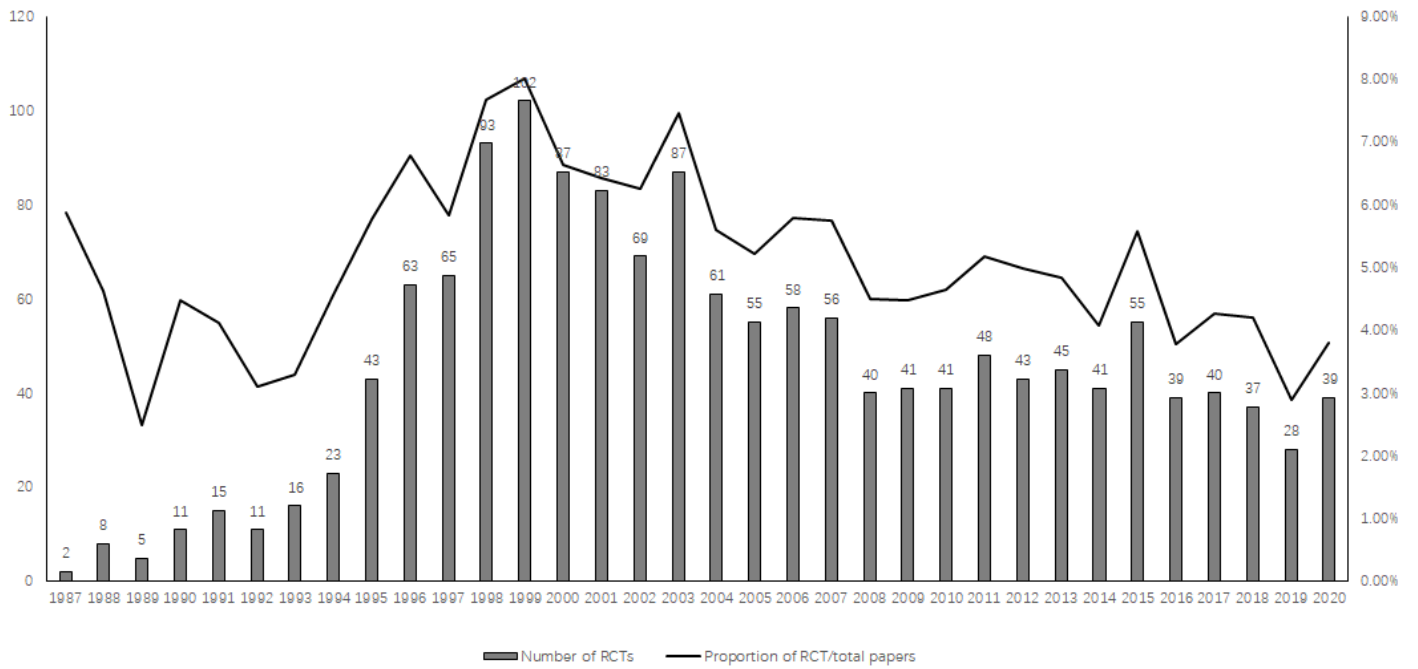


Figure 1

Number of RCTs and the proportion of RCT/total papers worldwide

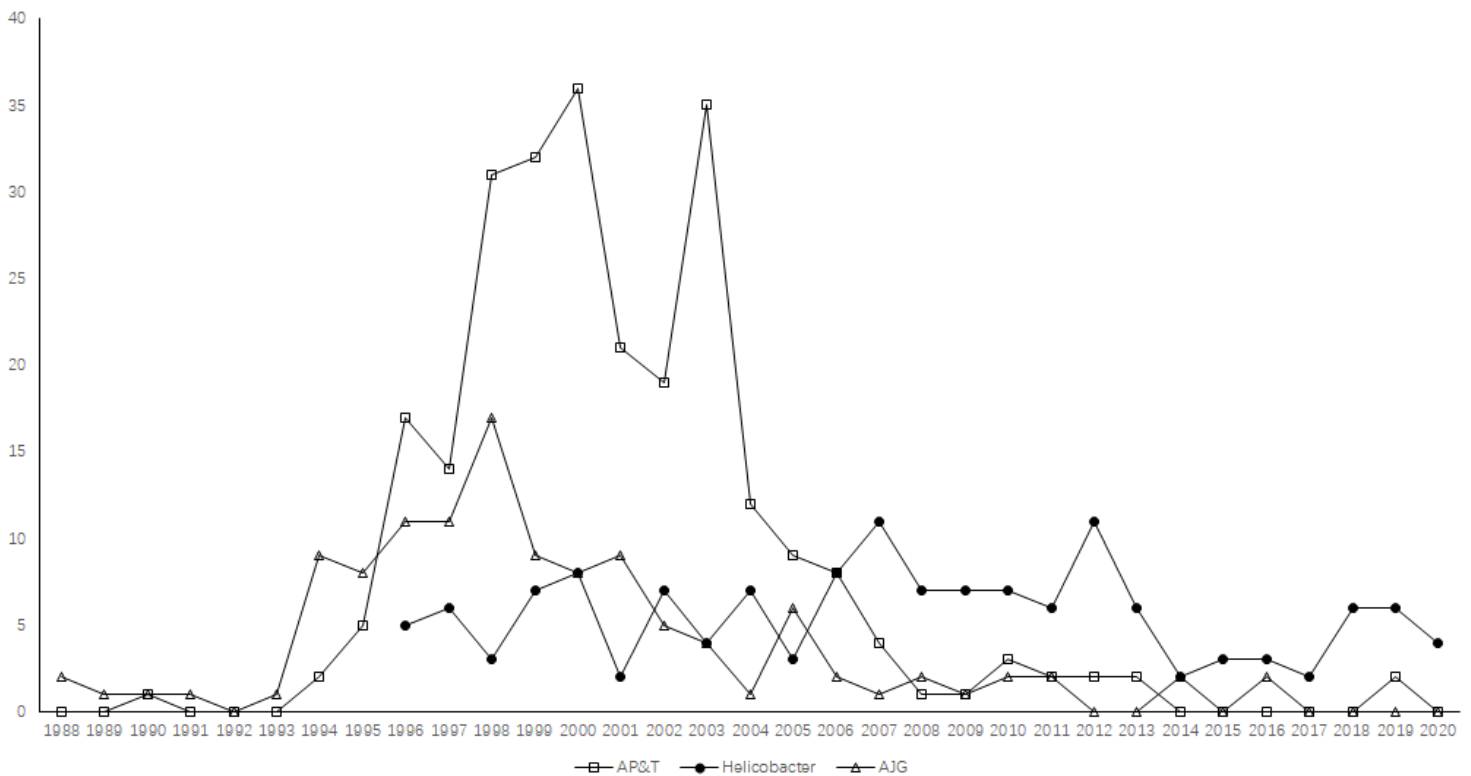


Figure 2

### Number of RCTs published in AP&T, Helicobacter and AJG

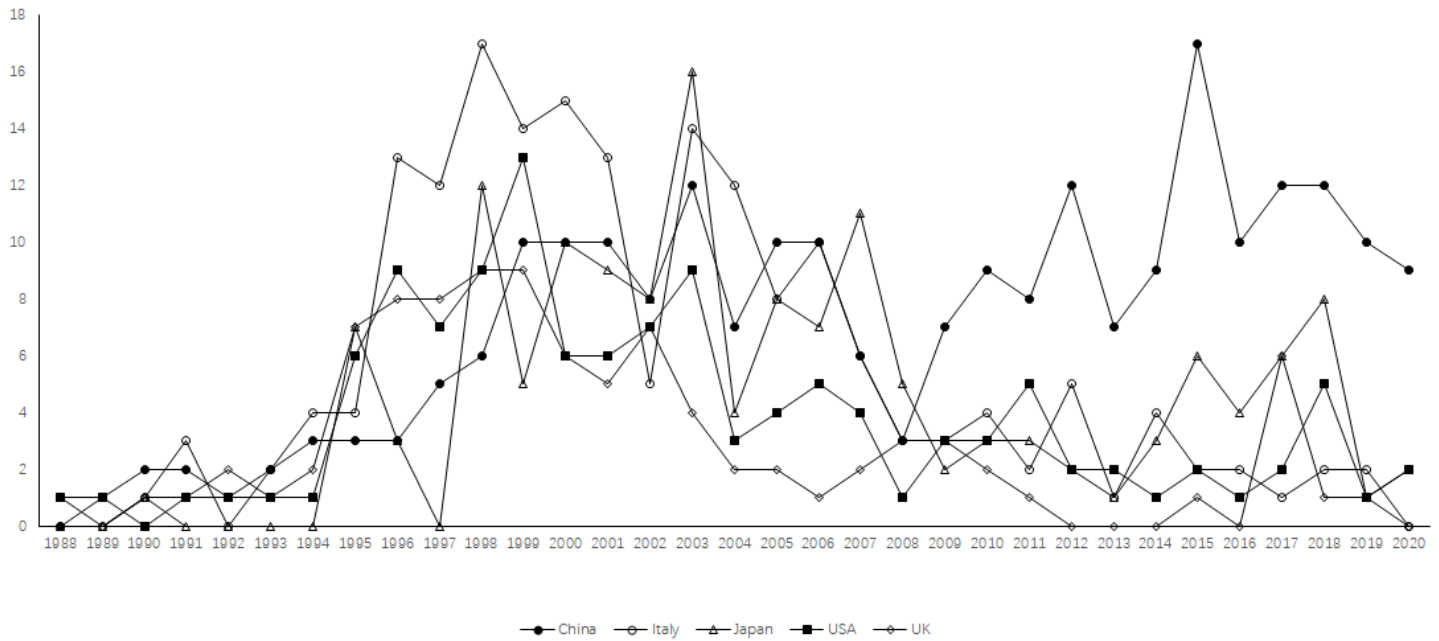


Figure 3

### Number of RCTs originated from China, Italy, Japan, USA and UK

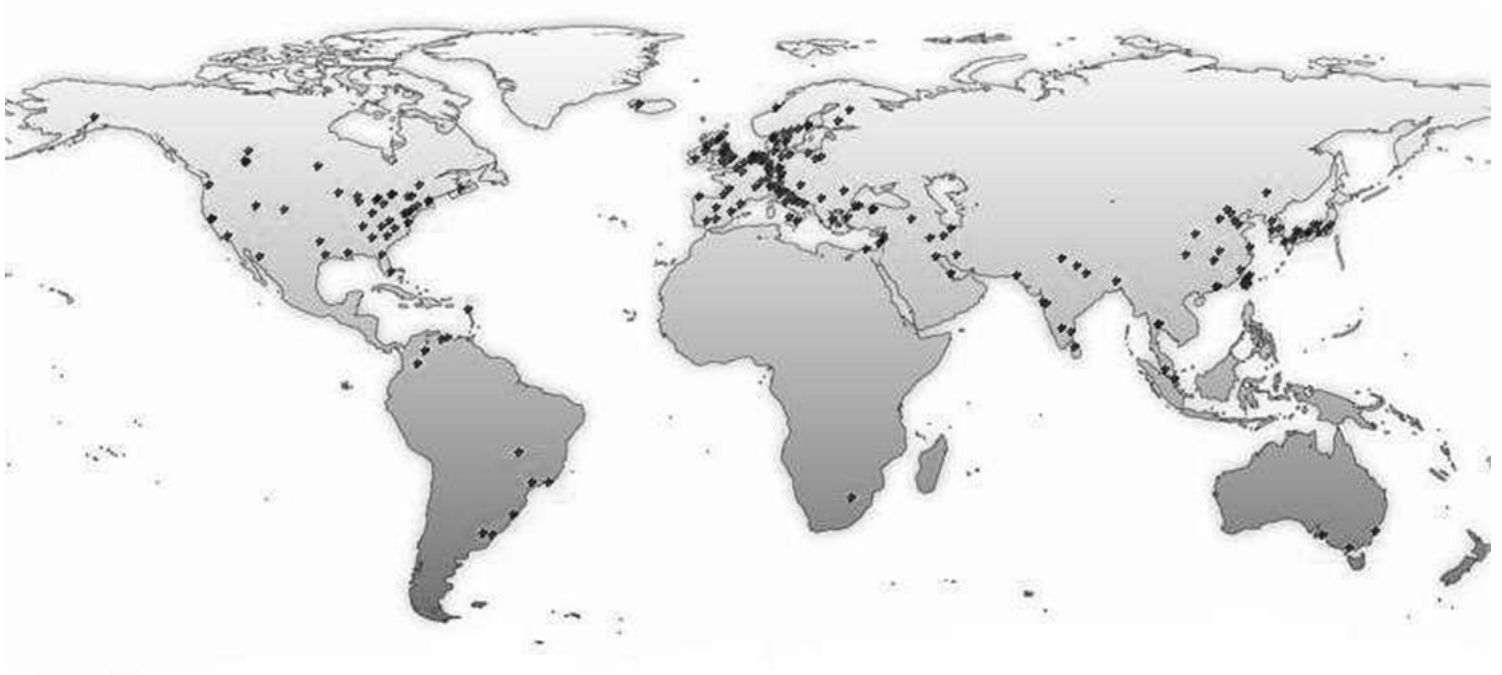


Figure 4

global origin map of the productive areas of Hp research RCTs Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its

authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.