

# Bibliometric Analysis of The Scientific Literature on Human Papillomavirus Vaccine Clinical Trials: Analysis of PubMed Database

Sushmitha Mohana Murali<sup>1\*</sup>, Karpagam Senthamarai Kannan<sup>2</sup>, Merrylda Claribel S<sup>3</sup>

<sup>1,2,3</sup>Independent Health Researcher, Chennai, India

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## ABSTRACT

**Background:** Cervical cancer is the 4<sup>th</sup> most common cancer in the world caused by human papillomavirus (HPV). A preventive measure for cervical cancer is immunization with the HPV vaccine. Hence globally many clinical trials on HPV vaccines are being performed to prevent HPV infection. This bibliometric analysis is done to determine the trend of clinical trials on HPV vaccines worldwide over the years.

**Methodology:** The articles on HPV vaccine clinical trials were extracted from the PubMed database (Mar 1999 – Sept 2022) and the bibliometric data analysis was done using Microsoft Excel.

**Result:** We extracted 308 articles from the PubMed database and obtained 296 clinical trial articles after removing the non-relevant ones. The majority of the papers were published by institutions in the United States of America (USA) among 39 countries (n=112, 37.8%). Most publications were done by the National Cancer Institute of the USA among 188 institutions worldwide (n=19, 6.4%). The majority of articles were published by more than five authors. Lehtinen M from the Department of Infections and Cancer, German Cancer Research Center has done the most number of publications (n=7). More publications were from the Vaccine journal (n=38). The first three highly cited articles had more than 2000 citations. The years 2015 and 2019 had the highest number of publications (n=25).

**Conclusion:** We can observe a gradual increase in clinical research on the HPV vaccine over the years that accounts for the reduction in cervical cancer cases.

**Keywords:** Bibliometrics, human papillomavirus, HPV, HPV vaccine, Clinical trials

## ARTICLE INFO

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**\*Correspondence:** Dr. Sushmitha Mohana Murali (Email: msushmi11@gmail.com)

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## INTRODUCTION

Human papillomavirus is the cause of cervical cancer, which is the 4<sup>th</sup> most common type of cancer in the world and the 2<sup>nd</sup> most common type of cancer in women in India.<sup>1,2</sup> There are about 150 genotypes of human papillomavirus, based on DNA sequence analysis, causing HPV infection with different clinical presentations.<sup>3</sup> Among them, the most common genotypes are types 6, 11, 16, and 18. Types 6 and 11 also cause anogenital warts (low-risk HPV infection) and types 16 and 18 cause cancer of the vagina, vulva, penis, anus, and oropharynx (high-risk HPV infection) by suppression of tumor suppressor gene. HPV infection spreads through sexual contact and by direct skin contact. HPV usually results in subclinical infection where the individual develops immunity, and the virus leaves the system in 2 years. But in some cases, with high-risk genotypes, the individual may develop cancer. Complicated HPV infection occurs in immunocompromised patients.<sup>4,5</sup>

Vaccines are highly effective in preventing infection when it is administered before the individual is exposed to the virus. It is recommended for adolescent females. There are 3 types of vaccines available to offer protection against the infection. They are bivalent, quadrivalent, and nonvalent vaccines. The bivalent vaccine (Cervarix-manufactured by GSK Biologicals) is effective against types 16 and 18 of HPV. The quadrivalent vaccine (Gardasil manufactured by Merck) is effective against types 6, 11, 16, and 18. The nonvalent vaccine (Gardasil 9 manufactured by Merck) is effective against 9 different genotypes of HPV- 6, 11, 16, 18, 31, 33, 45, 52, and 58.<sup>1,6</sup>

Numerous clinical trials are being conducted worldwide in different groups of populations to check the vaccine efficacy in that specific population. This is greatly helping in combating the disease. The result of these clinical trials is being published in many peer-reviewed journals. The pattern of publication of scientific evidence on the HPV vaccine clinical trials can be studied by bibliometric analysis. Here, we have done a bibliometric analysis of the scientific literature on HPV vaccine clinical trials from the PubMed database.

## METHODOLOGY

**Data Source:** We retrieved HPV vaccine clinical trial articles from the PubMed database (Mar 1999 – Sept 2022). The articles were published by around 188 institutions from 39 countries. The PubMed database is a free resource that provides access to abstracts and citations that have been issued in biomedical and life sciences journals and maintained by the National Center for Biotechnology Information (NCBI), at the U.S. National Library of Medicine (NLM), located at the National Institutes of Health (NIH).

We used some keywords in the PubMed database to retrieve the articles of our interest. They were “effi-

cacy”, “HPV vaccine”, “gardasil”, “gardasil 9” and “cervarix”

**Search Strategy:** We used the following search strategy in the PubMed database (efficacy) AND [(HPV vaccine) OR (gardasil) OR (gardasil 9) OR (cervarix)] Filters: Clinical Trial, Randomized Controlled Trial

**Study selection and data management:** We downloaded the data as an Excel file. The three independent reviewers reviewed the articles. We carefully evaluated the articles retrieved on HPV vaccine clinical trials and included them for analysis. We included data by reviewing the articles apart from the data downloaded for analysis under a few other variables. A final check on the data was done to not miss any differences in the same kind of data. For example, articles published by one author under different names (Giuliano AR and Anna R Giuliano) were categorized under the same name (Guiliano AR).

**Eligibility criteria:** We included only English articles that were published and indexed in the PubMed database under the keywords “efficacy”, “HPV vaccine”, “gardasil”, “gardasil 9” and “cervarix”. Only articles on HPV vaccine clinical trials were retrieved.

**Data extraction:** We extracted bibliometric data from the articles downloaded. The bibliometric data under the following variables were extracted, corresponding author name, corresponding author affiliation, number of authors, corresponding author’s country, publication year, article citations, and the journal in which the article was published. We retrieved the citation information from Google Scholar and journal information on the publisher’s name, impact factor, journal’s country of origin, frequency of publication, and the main theme of the journal.

**Data analysis:** Network and overlay visualization were done with the help of VOSviewer software. Visualization of country-wise publication was done using Maptitude software. Keywords cloud was done using the ChartExpo software in MS Excel. Other basic analysis was done using MS Excel. Analysis was done under the following variables, corresponding author name, corresponding author affiliation, number of authors, corresponding author’s country, co-authorship analysis, publication year, article citations, co-occurrence of keywords, and the journal in which the article was published. We ranked the top 10 data under every variable.

## RESULTS

We extracted 308 articles from the PubMed database and obtained 296 clinical trial articles after removing the non-relevant ones. Publications were done by 39 countries across the world (Figure 1a). The majority of the papers were published by institutions in the United States of America (USA) among 39 countries (n=112, 37.8%). Followed by the USA, the highest

number of publications were by China, Canada, Finland, and the UK. The listed top 10 countries pub-

lished more than two-thirds of the total publications (n=232, 78.3%) (Figure 1b).



Figure 1a: Country of origin of publications

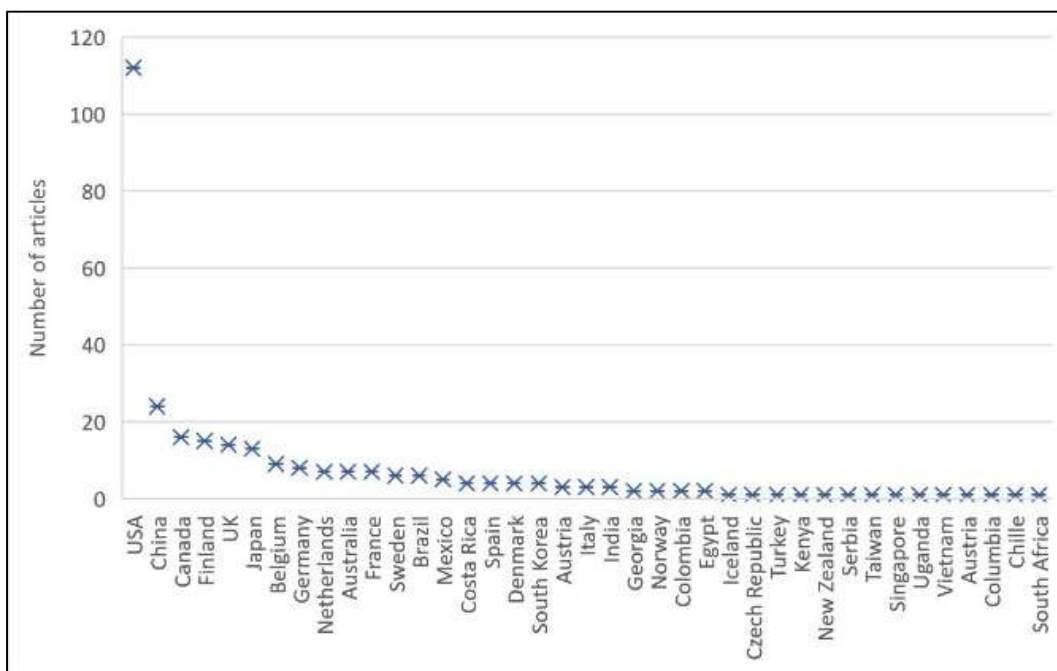


Figure 1b: Number of articles published according to the country of origin

Table 1: Top 10 institutions that published articles on HPV vaccine clinical trials

Institution	Publication (%)
National Cancer Institute	19 (6.41)
University of Tampere	10 (3.37)
Merck & Co, Inc.	7 (2.36)
Albert Einstein College of Medicine	7 (2.36)
University of Washington	7 (2.36)
GSK	6 (2.02)
The Chinese University of Hong Kong	5 (1.68)
Jichi Medical University	5 (1.68)
Chinese Academy of Medical Sciences and Peking Union Medical College	5 (1.68)
International Agency for Research on Cancer	5 (1.68)
Others	220 (74.32)

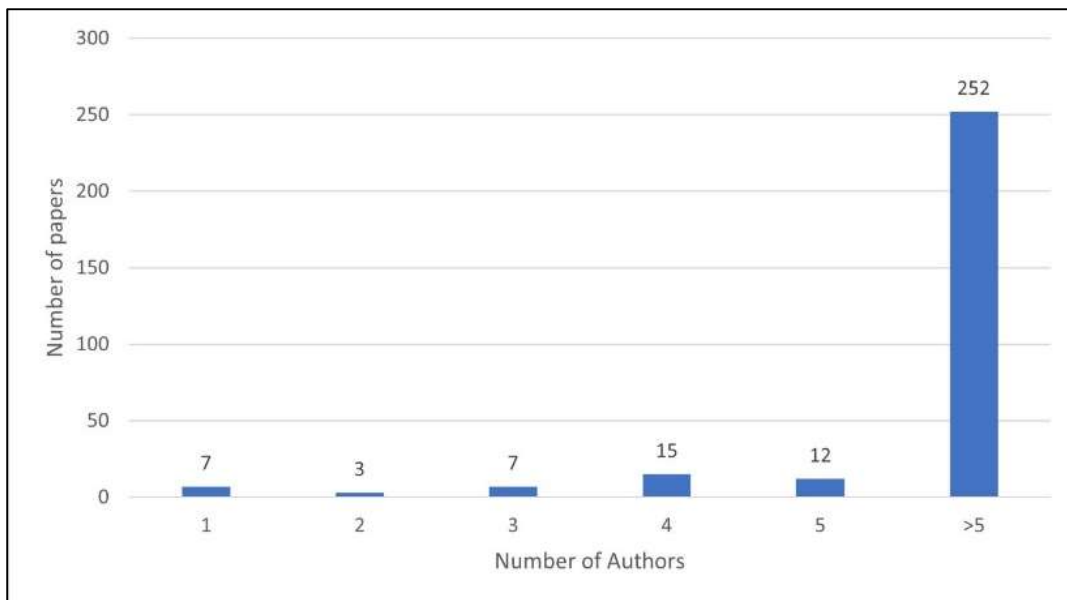


Figure 2: Author contribution to the publication of human papillomavirus vaccine clinical trials

Table 2: Corresponding authors with the highest number of publications

Corresponding Author	Publications (%)
Lehtinen M	7 (2.36)
Einstein MH	6 (2.02)
Konno R	5 (1.68)
Giuliano AR	5 (1.68)
Kreimer AR	5 (1.68)
Safaeian M	4 (1.35)
Pinto LA	4 (1.35)
Schwarz TF	4 (1.35)
Joura EA	4 (1.35)
Luxembourg A	4 (1.35)

Most publications were done by the National Cancer Institute of the USA among 188 institutions world-

wide (n=19, 6.4%). Among the 112 publications from the USA, 17% of the publications were by the National Cancer Institute. Followed by the National Cancer Institute, the highest number of publications were made by the University of Tampere from Finland, Merck & Co, Inc. from the USA, Albert Einstein College of Medicine from the USA, and the University of Washington also from the USA (Table 1).

The majority of articles were published by more than five authors (n=252, 85.13%) (Figure 2). The corresponding author, Lehtinen M from the Department of Infections and Cancer, German Cancer Research Center has done the most number of publications (n=7, 2.3%) (Table 2).

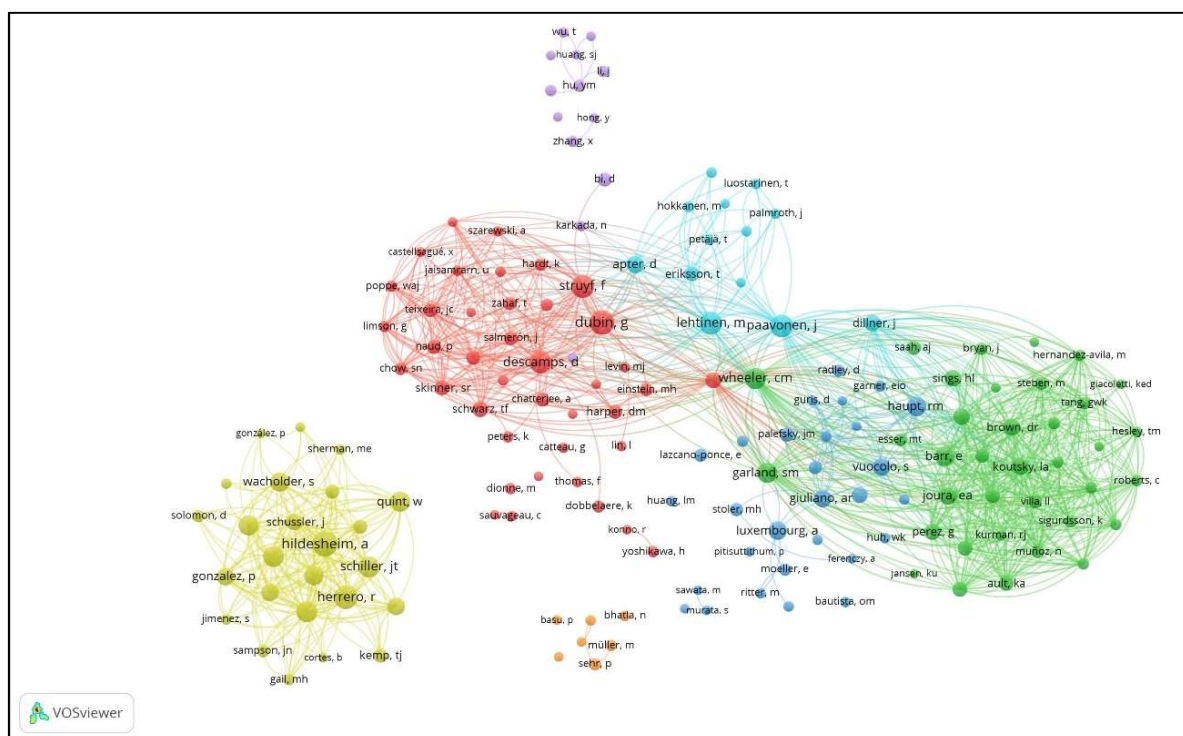
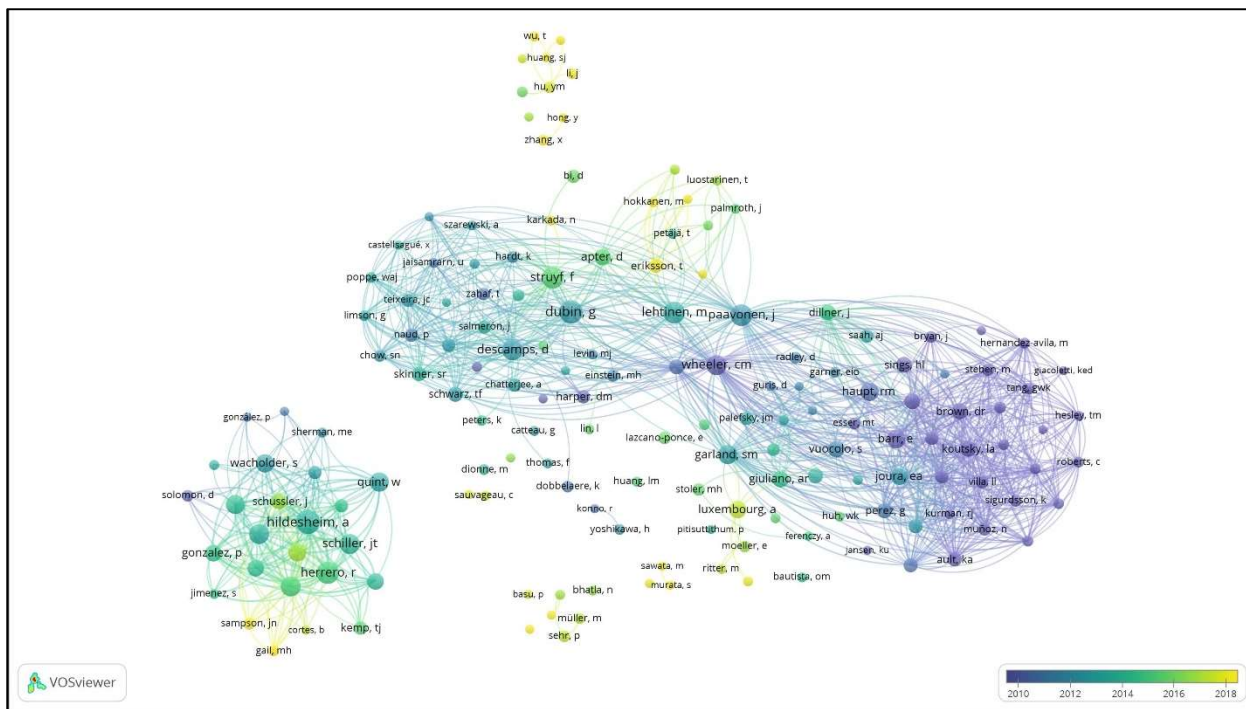


Figure 3a: Network visualization of co-authorship



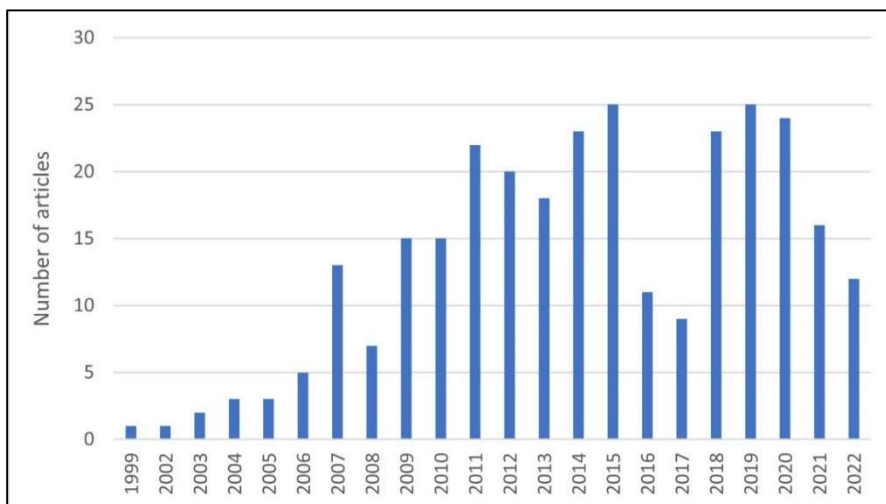
**Figure 3b: Overlay visualization of co-authorship**

Publication on HPV vaccine trials was done by 1979 authors, 163 authors met the threshold with minimum number of documents of five by an author. We can see the network visualization of co-authorship (Figure 3a). There is a total of seven clusters, each represents the close relationship among the authors represented by different colors. The size of nodes represents the number of article publications by the authors with total links of 2912 and total link strength of 10884. The highest number of publications was done by Hildesheim A from the Department of Cancer Epidemiology and Genetics, National Cancer Institute, USA with 34 publications. His main collaboration is with Porras C from the Department of Cancer Epidemiology and Genetics, National Cancer Institute, USA with link strength of 24. Overlay visualization (Figure 3b) shows the network map of co-authorship with relation to the articles published

between 1999 and 2022. The size of nodes represents the number of article publications by the authors.

More publications were from the Vaccine Journal and Human Vaccine Immunotherapeutic Journal (n=38, 12.8%). Followed by them, the highest number of publications were made in the Journal of Infectious Diseases, Pediatric Diseases Journal, and the International Journal of Cancer (Table 3).

The first three highly cited articles had more than 2000 citations. “A controlled trial of a human papillomavirus type 16 vaccine” authored by Koutsky LA has the highest citation of 2467 published in the New England Journal of Medicine (Table 4). The years 2015 and 2019 had the highest number of publications (n=25, 8.4%) (Figure 4).



**Figure 4: Number of articles published between 1999-2022**

**Table 3: Top 10 journals with the highest number of publications**

Journal	Publisher name	Impact factor	Publication Country	Frequency of journal publication	Main theme of the journal	Publications (%)
Vaccine	Elsevier	4.169	USA	Monthly	Vaccinology	38 (12.83)
Human Vaccines & Immunotherapeutic	Taylor and Francis	4.562	UK	Monthly	Vaccines and immunotherapeutic	38 (12.83)
Journal of Infectious Diseases	Oxford University Press	7.759	UK	Monthly	Infectious diseases	13 (4.39)
Pediatric Infectious Diseases Journal	Lippincott Williams & Wilkins	3.806	USA	Monthly	Pediatric Infectious Diseases	10 (3.37)
International Journal of Cancer	Wiley	7.316	USA	Bi-weekly	Oncology	10 (3.37)
Lancet Oncology	Elsevier	54.43	UK	Monthly	Oncology	8 (2.7)
Lancet	Elsevier	202.73	UK	Weekly	Medicine	8 (2.7)
Clinical Vaccine Immunology	American Society for Microbiology	2.598	USA	Monthly	Vaccine research and immunology	7 (2.36)
The New England Journal of Medicine	Massachusetts Medical Society	176.079	USA	Weekly	Medicine	7 (2.36)
PLoS One	Public Library of Science	3.752	USA	Bi-yearly	Interdisciplinary	7 (2.36)
Journal of National Cancer Institute	Oxford University Press	11.816	UK	Monthly	Oncology	7 (2.36)

**Table 4: Top 10 articles with the highest citations**

Title	First Authors	Corresponding Author	Journal/Book	Citations
A controlled trial of a human papillomavirus type 16 vaccine	Koutsky LA	Koutsky LA	N Engl J Med	2467
Quadrivalent vaccine against human papillomavirus to prevent anogenital diseases	Garland SM	Garland SM	N Engl J Med	2329
Quadrivalent vaccine against human papillomavirus to prevent high-grade cervical lesions	FUTURE II Study Group.	Laura A	N Engl J Med	2325
Efficacy of a bivalent L1 virus-like particle vaccine in prevention of infection with human papillomavirus types 16 and 18 in young women: a randomised controlled trial	Harper DM	Harper DM	Lancet	2285
Prophylactic quadrivalent human papillomavirus (types 6, 11, 16, and 18) L1 virus-like particle vaccine in young women: a randomised double-blind placebo-controlled multicentre phase II efficacy trial	Villa LL	Villa LL	Lancet Oncol	2274
Efficacy of human papillomavirus (HPV)-16/18 AS04-adjuvanted vaccine against cervical infection and pre-cancer caused by oncogenic HPV types (PATRICIA): final analysis of a double-blind, randomised study in young women	Paavonen J	Paavonen J	Lancet	1930
Efficacy of a prophylactic adjuvanted bivalent L1 virus-like-particle vaccine against infection with human papillomavirus types 16 and 18 in young women: an interim analysis of a phase III double-blind, randomised controlled trial	Paavonen J	Paavonen J	Lancet	1571
A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women	Joura EA	Joura EA	N Engl J Med	1372
Efficacy of quadrivalent HPV vaccine against HPV Infection and disease in males	Giuliano AR	Giuliano AR	N Engl J Med	1250
Vaccination against HPV-16 oncoproteins for vulvar intraepithelial neoplasia	Kenter GG	Kenter GG	N Engl J Med	1154



Keywords provided by the authors that occurred for five times and more in the PubMed database were used for analysis. The database contained a total of 963 keywords, out of which 137 met the threshold. The commonly used keywords were “humans” with total link strength of 3890 that was used 307 times that has a strong link with the keyword “human papillomavirus” with the link strength of 117 followed by “antibodies, viral” with the link strength of 113 (figure 5a). A word cloud was created with the keywords that occurred five times and more (figure 5b). It shows that the keyword “humans” is commonly used followed by “female”, “papillomavirus vaccines” and “papillomavirus infections”.

## DISCUSSION

The articles were published in the context of HPV vaccination trials among different populations across the world, of different age groups, some with associated co-morbidity, and others among the special population to study the safety, immunogenicity, and long-term effects. All these trials are being conducted to prevent even the thinnest chance of anyone being infected. The clinical trials have also helped to fix the vaccine dosage and frequency of administration. Few studies have also aimed to study the vertical transmission of the antibodies from mother to fetus following vaccination in mothers.<sup>7,8</sup> According to these studies, there is potential placental transmission of antibodies from mother to fetus.

The earliest study on the HPV vaccination was done in 1999 by C J Lacey et al<sup>9</sup> It was a phase IIa study. According to this study, a fusion protein vaccine was developed with HPV 6 L2E7 and Alhydrogel for the treatment of genital warts, given in 3 doses. Then emerged the era of prophylactic HPV vaccines. FDA approved three prophylactic vaccines for HPV infection following successful clinical trials. Gardasil was approved in 2006, Cervarix in 2009, and Gardasil 9 in 2014.<sup>10</sup> These vaccines provide essential protection against the infection by generating neutralizing antibodies but are ineffective when the individual is already infected.

In recent years, trials are being conducted in the development of therapeutic HPV vaccines. Therapeutic vaccines act by activating cellular immunity and eliminate the infected cells by acting on the oncoproteins E6 and E7. This can therefore be used as an adjunct to the surgical approach to cancer and prevent a recurrence. Different types of therapeutic vaccines are Live vector-based vaccines (2 subtypes-bacterial and viral vaccines), peptide and protein vaccines (2 subtypes-long and short peptide vaccines), nucleic acid vaccines (2 subtypes-DNA and mRNA vaccines), and Whole-cell vaccines (2 subtypes-Dendritic cell and Tumor vaccines).<sup>11,12</sup> Here, we could see the evolution of HPV vaccines over the years tried and implemented through clinical trials.

The main theme of the journals is Vaccinology, Oncology, medicine, and Infectious diseases since the article focuses on cervical cancer and HPV vaccinations. The top listed journals belong to the USA or the UK. The Lancet Journal has the highest impact factor of 202.73 among the top listed journals. The articles with the highest number of citations were published in the New England Journal of Medicine and the Lancet Journal. Most of the journals are published on a monthly frequency.

The first authors in the top ten articles were also the corresponding authors. Corresponding author Lehtinen M had the highest number of publications followed by Einstein MH. Half of the corresponding authors had at least four publications. More than two-thirds of the papers were published by more than 5 authors.

The National Cancer Institute of the USA has done extensive research on the HPV vaccines. The NCI is a USA federal government agency exclusively for cancer research. NCI is the part of National Institute of Health (NIH), a unit of the Department of Health and Human Services (HHS). The NCI is funding and conducting clinical trials on HPV vaccines in the USA.<sup>13</sup>

“A controlled trial of a human papillomavirus type 16 vaccine” authored by Koutsky LA has the highest citation of 2467 published in the New England Journal of Medicine.<sup>14</sup> According to this article, the study participants were administered HPV 16 virus-like particles in three doses. Following immunization, the vaccine protected against the HPV 16 infection which eventually reduces the incidence of cervical cancer caused by the HPV 16 virus.<sup>15,16</sup> The top 3 highest-cited articles were published in the New England Journal of Medicine with a high impact factor of 176.079.

## CONCLUSION

This bibliometric analysis of the HPV vaccine clinical trial shows a steady increase in the clinical research publication of the HPV vaccine. The USA has the highest number of publications, also the institution with the highest number of publications (National Cancer Institute) is from the USA. All of these research activities on the HPV vaccine across the world are ultimately aiding in reducing the incidence of the HPV infection. The strength of this study is that we have included all articles on HPV clinical trials irrespective of the year of publication to analyse the trend of publication and the advances over the years. The limitation of this study is that we have included articles from only the PubMed database.

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