Preplanned Studies

Prevalence of Reproductive Tract Infections and Association with Human Papillomavirus Infection Among Reproductive-Age Women — Six Tertiary Hospitals, China, June 2021–December 2022

Di Gao[1]; Jiayue Li[2]; Gengli Zhao[1]; Zhaohui Liu[3]; Hui Bi[1]; Dai Zhang[1]; Fengxia Xue[4]; Chen Liu[5]; Hongtao Ma[6]; Bei Lin[7]; Xu Wang[1]; Xiaosong Zhang[1,#]; Linhong Wang[8,#]

Summary

What is already known about this topic?

Previous studies have indicated a possible association between reproductive tract infections (RTIs) and high-risk human papillomavirus (HPV) infection, but the evidence is still inconclusive.

What is added by this report?

This multicenter study found significantly higher positive rates of HPV, including general HPV, high-risk HPV, and HPV 16/18 infections, among women who tested positive for single or multiple RTIs compared to women who tested negative for RTIs in gynecological outpatient clinics.

What are the implications for public health practice?

Infection with HPV, especially high-risk types, is linked to RTIs and imbalances in the vaginal microbiota. Implementing standardized protocols for identifying and treating RTIs could support the establishment of a healthy vaginal microenvironment. This, in turn, may offer a novel approach to preventing cervical cancer.

Human papillomavirus (HPV) infections and reproductive tract infections (RTIs) are significant public health concerns that primarily spread through sexual activity, affecting women's health. Co-infection of HPV and RTIs can increase the risk of female reproductive tract infections and cervical cancer. This cross-sectional study, conducted in six tertiary hospitals in China from June 2021 to December 2022, aims to investigate the associations between various RTIs pathogens and HPV infections among women aged 18–49 years. The analysis included 3,133 women attending gynecology outpatient clinics. The overall rate of co-infection with HPV and RTIs was 13.2%. After adjusting for demographic factors, both the single-RTI-positive group [odds ratio (*OR*)=1.97, 95% confidence interval (*CI*): 1.59, 2.45] and the multiple-RTI-positive group (*OR*=4.85, 95% *CI*: 3.59, 6.56) showed significantly higher infection rates of HPV in general, as well as high-risk HPV (HR-HPV) and HPV 16/18. The study also found significant associations between RTI pathogens, including *Neisseria gonorrhoeae* (NG), *Chlamydia trachomatis* (CT), *Ureaplasma* species (UU), *Mycoplasma genitalium* (MG), *Mycoplasma hominis* (MH), and Herpes Simplex Virus Type II (HSV-2) infections, and HPV infections (general HPV, HR-HPV, and HPV 16/18). This research highlights the importance of understanding the relationship between RTIs and HPV infection, especially HR-HPV infection, in order to raise awareness of RTIs and HPV co-infection and facilitate early detection of disease-free latent infections.

RTIs can cause a range of symptoms and complications in the female reproductive tract, with potential long-term effects (*1*). Main pathogens include NG, CT, MG, and HSV-2, which are associated with conditions such as gonorrhea, chlamydial infections, and genital herpes. MH and UU, including *Ureaplasma urealyticum* (Uu) and *Ureaplasma parvum* (Up), are the most common *Mycoplasma* species in the reproductive tract and are also classified as RTIs in this study. In 2016, the World Health Organization (WHO) estimated 376.4 million new cases of chlamydia, gonorrhea, syphilis, and trichomoniasis globally (*2*). HPV is a significant sexually transmitted infectious pathogen, and persistent HR-HPV infection is a leading cause of cervical cancer. HPV types 16 and 18 are responsible for approximately 70% of all cervical cancer cases (*3*). The increasing prevalence of co-infections between HPV and other RTIs, coupled with changing modern lifestyles and sexual attitudes, highlights the need for

heightened attention in public health and medicine. RTI pathogens, such as NG, CT, and *Mycoplasma* species, have been found to potentially enhance HPV replication and persistence, leading to accelerated cervical neoplasia development (*4*). Therefore, it is crucial to detect and treat HPV and RTIs co-infections to develop targeted testing and screening programs, facilitate treatment and management strategies, and ultimately improve disease outcomes. Nevertheless, research on the association between RTI pathogens and HPV, as well as the prevalence of HPV-RTIs co-infections, is limited. Hence, this study aims to investigate the prevalence and association between various RTI pathogens and HPV to provide evidence and recommendations for the clinical diagnosis and management of vaginal and cervical infections.

This multicenter, cross-sectional study was conducted from June 2021 to December 2022 at six tertiary hospitals in China: Peking University First Hospital, Beijing Obstetrics and Gynecology Hospital, Shengjing Hospital of China Medical University, Tianjin Medical University General Hospital, Northwest Women's and Children's Hospital, and the Third Affiliated Hospital of Zhengzhou University. We recruited women of reproductive age (18–49 years) who attended the gynecology outpatient clinics at each hospital for either reproductive tract infection treatment or opportunistic screening for cervical cancer. Inclusion criteria included previous sexual history, pre-menopausal status, absence of menstruation at the time of sampling, and no sexual activity, vaginal medication, or douching within 3 days prior to sample collection. Exclusion criteria included pregnancy or within 8 weeks postpartum, vaginal bleeding, history of genital tract tumors, recent treatment for HPV infection or sexually transmitted diseases associated with pathogens, history of hysterectomy, cervical surgery, or pelvic radiotherapy, cervical ablation or excision treatment within the past 12 months, and antibiotic or probiotic use within the past month.

Based on previous studies, the estimated prevalence of co-infection between HPV and other RTIs in gynecology outpatients was approximately 15%. Therefore, we aimed to recruit a sample size of 2,242 participants for this cross-sectional study. Ultimately, cervical samples were collected from a total of 3,281 participants for HPV and RTI pathogens detection. After excluding samples that did not meet the qualification criteria or had missing results, 3,133 samples were included in the final analysis. HPV genotyping was performed using the 21 HPV GenoArray Diagnostic Kit (HBGA-21PKG; HybriBio Ltd., Chaozhou, China), which detects 14 HR-HPV types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68), 1 suspected HR-HPV type (HPV 53), and 6 low-risk HPV (LR-HPV) types (HPV 6, 11, 42, 43, 44, and CP8304). The STD6 GenoArray Diagnostic Kit (HBGA-STD6; HybriBio Ltd.) was used to detect 6 common RTI pathogens, including NG, CT, UU (Uu, Up1, Up3, Up6, Up14), MG, MH, and HSV-2.

Categorical variables were presented as numbers (*n*) and percentages (%), and the chi-square test was used to compare the co-infection of HPV and other RTI pathogens. Univariate and multivariate logistic regression models were used to analyze the association between common RTI pathogens and HPV infection, with calculation of *OR*s and 95% confidence intervals *CI*s. Statistical analyses were performed using STATA (version 14.0; Stata Corporation, College Station, TX, USA) and R (version 4.2.3; R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was determined using two-tailed tests with a significance level of 0.05. The study design underwent review and approval by the Biomedical Research Ethics Committee of Peking University First Hospital (2021KY069), and sample collection received authorization from the Human Genetics Resources Administration of China ([2022]CJ0124).

A total of 3,133 subjects were included in the study, with 13.2% having co-infections of both HPV and RTI pathogens. The co-infection rates varied across different demographic characteristics (Supplementary Table S1, available at https://weekly.chinacdc.cn/). The overall RTIs positive rate was 46.0%, with UU (42.1%), CT (4.9%), and MH (4.7%) being the most prevalent RTI pathogens. Of the 109 women (3.5%) with multiple RTIs co-infections, the most common combinations were MH+UU (43.1%), CT+UU (36.7%), and CT+MH (4.6%) (Figure 1C). The co-infection rates were 13.2% for HPV-positive, 11.4% for HR-HPV-positive, and 3.0% for HPV 16/18-positive (Table 1). HPV and RTI pathogens co-infections were found in 413 women (13.2%), with the most common combinations being HPV+UU (65.9%), HPV+MH+UU (9.9%), and HPV+CT+UU (9.2%) (Figure 1D). After adjusting for age group, ethnicity, education level, family monthly income, marital status, and parity, both the single-RTI-positive group (*OR*=1.97, 95% *CI*: 1.59, 2.45) and multiple-RTI-positive group (*OR*=4.85, 95% *CI*: 3.59, 6.56) had higher rates of HPV infection compared to the RTI-negative group. Furthermore, individuals infected

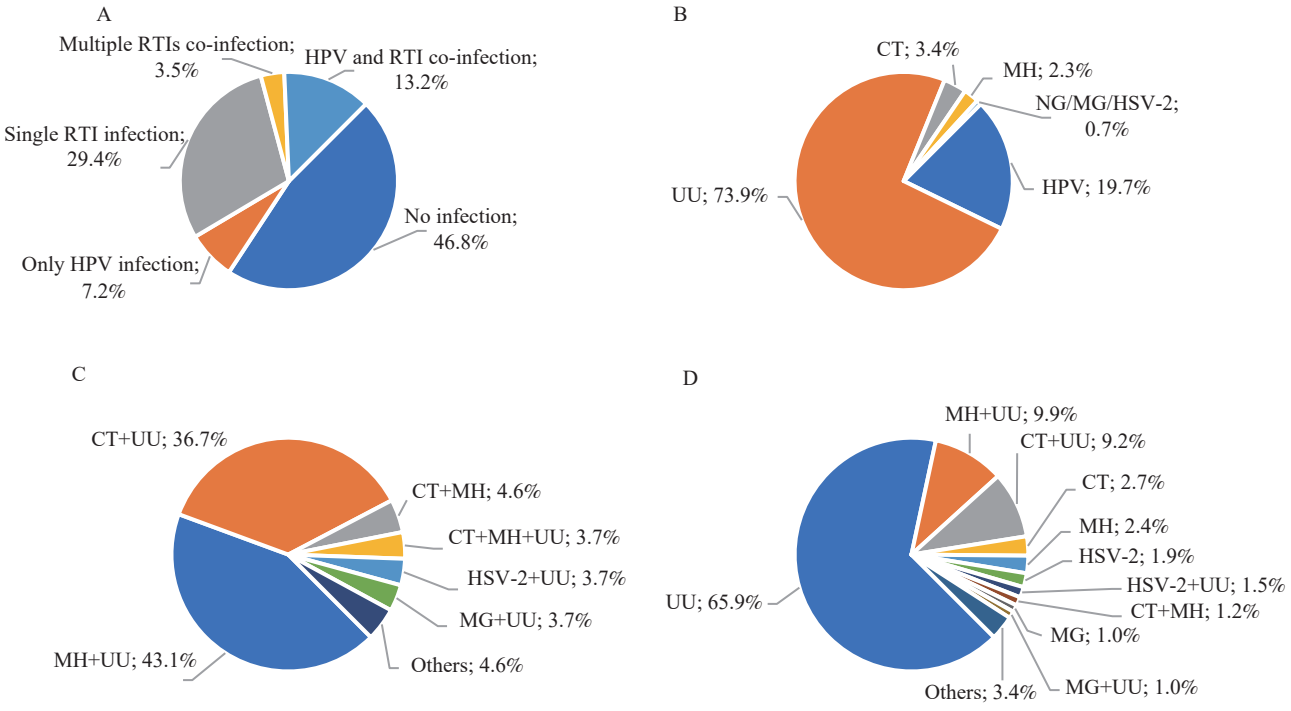


FIGURE 1. Patterns of RTI pathogens and HPV infection among reproductive-age women in six tertiary hospitals in China from June 2021 to December 2022. (A) Pattern of infection (*n*=3,133) (B) Pattern of single infection (*n*=1,146) (C) Multiple RTI co-infections (*n*=109); (D) HPV and RTI co-infection (*n*=413).
Note: RTI pathogens in our study included NG, CT, UU, MG, MH, and HSV-2.
Abbreviation: HPV=human papillomavirus; RTI=reproductive tract infection; NG=*Neisseria gonorrhoeae*; CT=*Chlamydia trachomatis*; UU=*Ureaplasma* species; MG=*Mycoplasma genitalium*; MH=*Mycoplasma hominis*; HSV-2=Herpes Simplex Virus Type II.

with NG, CT, Uu, Up1, Up3, Up6, any UU, MG, MH, or HSV-2 also had a significantly higher risk of HPV infection. Similar results were observed for HR-HPV and HPV 16/18 infections (Table 2). Significant correlations were also found between different HPV genotypes and RTI pathogens (Supplementary Figure S1, available at https://weekly.chinacdc.cn/).

DISCUSSION

The co-infection rate of HPV and RTI pathogens in this study was found to be 13.2%, emphasizing the importance of recognizing clinical co-infection of HPV and RTIs. Notably, the rates of general HPV infection, HR-HPV infection, and HPV 16/18 infection were significantly higher among women who tested positive for either single or multiple RTIs, compared to those who tested negative for RTIs. These findings indicate a positive association between HPV and RTIs, underscoring the need for prevention, detection, and proper management of RTIs. Preventing and treating reproductive tract infections may help reduce the prevalence of HPV infection, particularly HR-HPV infection.

The findings of this study provide support for the potential link between RTIs and HPV infection, which is consistent with recent research. However, previous studies have primarily focused on the presence of a single RTI pathogen. CT, a primary pathogen associated with HPV, has been extensively investigated. CT promotes HPV penetration into epithelial cells by inducing inflammation and altering the cervical microenvironment. In turn, HPV can facilitate the spread and multiplication of CT (*4*). This study also found a positive association between these two infections. Our current understanding of the relationships between NG, MG, HSV-2, and HPV remains limited. A meta-analysis revealed that MG was significantly associated with an increased risk of HR-HPV infection (*OR*=1.50, 95% *CI*: 1.11, 2.02) (*5*). Another cross-sectional study reported that individuals positive for HR-HPV had higher rates of HSV-2 seroprevalence and active infection compared to those who were negative. This may be attributed to co-infection of HSV-2 and HR-HPV, which disrupts local immune responses and promotes HPV-related

TABLE 1. Detection rate of different RTI pathogens and HPV co-infection among reproductive-age women in six tertiary hospitals in China from June 2021 to December 2022 [*n* (%)].

RTI pathogens	Total (*n*=3,133)	Co-infection with HPV	Co-infection with HR-HPV	Co-infection with HPV 16/18
NG-positive	10 (0.3)	6 (0.2)	5 (0.2)	2 (0.1)
CT-positive	152 (4.9)	61 (1.9)	49 (1.6)	12 (0.4)
UU-positive	1,320 (42.1)	371 (11.8)	322 (10.3)	79 (2.5)
Uu-positive	319 (10.2)	100 (3.2)	84 (2.7)	23 (0.7)
Up1-positive	169 (5.4)	48 (1.5)	44 (1.4)	9 (0.3)
Up3-positive	556 (17.7)	142 (4.5)	121 (3.9)	31 (1.0)
Up6-positive	424 (13.5)	137 (4.4)	122 (3.9)	30 (1.0)
Up14-positive	11 (0.4)	4 (0.1)	3 (0.1)	0 (0)
MG-positive	21 (0.7)	12 (0.4)	11 (0.4)	4 (0.1)
MH-positive	147 (4.7)	62 (2.0)	54 (1.7)	13 (0.4)
HSV-2-positive	27 (0.9)	18 (0.6)	18 (0.6)	3 (0.1)
Any RTIs-positive	1,442 (46.0)	413 (13.2)	357 (11.4)	93 (3.0)

Abbreviation: HPV=human papillomavirus; HR-HPV=high risk HPV; RTI=reproductive tract infection; NG=*Neisseria gonorrhoeae*; CT=*Chlamydia trachomatis*; UU=*Ureaplasma* species; Uu=*Ureaplasma urealyticum*; Up=*Ureaplasma parvum*; MG=*Mycoplasma genitalium*; MH=*Mycoplasma hominis*; HSV-2=Herpes Simplex Virus Type II.

disease progression (*6*). The findings of this study are consistent with the aforementioned positive associations.

Additionally, this study identified associations between UU and MH infections with both HPV and HR-HPV infections. UU, a common pathogen causing urinary tract infections, had controversial impact due to a lack of differentiation between Uu and Up subtypes. Previous studies have reported significant associations between UU and HPV, including HR-HPV (*5*,*7*), although Zhong et al. found no significant association (*8*). Despite these significant findings, the high rate of UU positivity in clinical practice limits its clinical diagnostic and treatment significance. Research has also shown a significant association between persistent MH infection and persistent HR-HPV infection ($P<0.05$), but no significant correlation between prevalent MH and prevalent HR-HPV infection (*9*). Overall, the associations between MH, UU, and HPV infections remain understudied. Further research is needed to investigate the impacts of UU and MH infection, specifically high-risk UU subtypes, on vaginal microecological balance, persistence and recurrence of HPV infection, and their contribution to cervical cancer development.

There are several limitations worth noting in this study. First, the cross-sectional design prevents us from establishing causal relationships between RTI pathogens and HPV infection, as well as determining their impact on persistent HPV infection. Second, the data collected for this study was limited to 6 hospitals in China, which may not be representative of the overall prevalence of HPV-RTI co-infection. However, this limitation does not affect the results pertaining to the relationship between HPV infection and RTIs. To gain a better understanding of the impact of specific subtypes of MH and UU on health, while excluding other traditional RTIs, further well-designed studies are needed. These studies will provide valuable information to guide routine testing and treatment recommendations.

In conclusion, this study found that the rates of general HPV, HR-HPV, and HPV 16/18 infections were significantly higher in both single-RTI-positive and multiple-RTI-positive groups. Additionally, specific RTI pathogens (NG, CT, UU, MG, MH, and HSV-2) were also associated with higher infection rates. These findings highlight the importance of standardizing the detection and treatment of RTI. By doing so, it may be possible to reduce the risk of high-risk and persistent HPV infection, providing a new approach to preventing cervical cancer and contributing to the goal of eliminating cervical cancer (*10*).

Conflicts of interest: No conflicts of interest.

Acknowledgments: All the participants and investigators from six tertiary hospitals: Peking University First Hospital, Beijing Obstetrics and Gynecology Hospital, Shengjing Hospital of China Medical University, Tianjin Medical University General Hospital, Northwest Women's and Children's Hospital, and the Third Affiliated Hospital of Zhengzhou University.

TABLE 2. Association between HPV infection and other RTI pathogens infection among reproductive-age women in six tertiary hospitals in China from June 2021 to December 2022.

RTI pathogens	Total	HPV-positive			HR-HPV- positive			HPV 16/18-positive		
		n (%)	Crude *OR* (95% *CI*)	Adjusted *OR* (95% *CI*)*	*n* (%)	Crude *OR* (95% *CI*)	Adjusted *OR* (95% *CI*)*	*n* (%)	Crude *OR* (95% *CI*)	Adjusted *OR* (95% *CI*)*
Neisseria gonorrhoeae										
Negative	3,123	633 (20.3)	Ref.	Ref.	558 (17.9)	Ref.	Ref.	137 (4.4)	Ref.	Ref.
Positive	10	6 (60.0)	5.90 (1.66, 20.97)	10.82 (2.04, 57.4)	5 (50.0)	4.60 (1.33, 15.93)	6.86 (1.49, 31.72)	2 (20.0)	5.45 (1.15, 25.9)	9.31 (1.70, 51.08)
Chlamydia trachomatis										
Negative	2,981	578 (19.4)	Ref.	Ref.	514 (17.2)	Ref.	Ref.	127 (4.3)	Ref.	Ref.
Positive	152	61 (40.1)	2.79 (1.99, 3.90)	2.64 (1.80, 3.86)	49 (32.2)	2.28 (1.60, 3.25)	2.18 (1.47, 3.24)	12 (7.9)	1.93 (1.04, 3.57)	2.14 (1.13, 4.05)
Ureaplasma species										
Negative	1,813	268 (14.8)	Ref.	Ref.	241 (13.3)	Ref.	Ref.	60 (3.3)	Ref.	Ref.
Positive	1,320	371 (28.1)	2.25 (1.89, 2.69)	2.13 (1.75, 2.59)	322 (24.4)	2.10 (1.75, 2.53)	1.96 (1.60, 2.41)	79 (6.0)	1.86 (1.32, 2.62)	1.73 (1.18, 2.54)
Ureaplasma urealyticum										
Negative	2,814	539 (19.2)	Ref.	Ref.	479 (17.0)	Ref.	Ref.	116 (4.1)	Ref.	Ref.
Positive	319	100 (31.3)	1.93 (1.49, 2.49)	1.97 (1.46, 2.65)	84 (26.3)	1.74 (1.33, 2.28)	1.67 (1.22, 2.29)	23 (7.2)	1.81 (1.14, 2.87)	1.59 (0.92, 2.72)
Ureaplasma parvum 1										
Negative	2,964	591 (19.9)	Ref.	Ref.	519 (17.5)	Ref.	Ref.	130 (4.4)	Ref.	Ref.
Positive	169	48 (28.4)	1.59 (1.13, 2.25)	1.45 (1.00, 2.12)	44 (26.0)	1.66 (1.16, 2.37)	1.58 (1.07, 2.32)	9 (5.3)	1.23 (0.61, 2.45)	1.01 (0.46, 2.24)
Ureaplasma parvum 3										
Negative	2,577	497 (19.3)	Ref.	Ref.	442 (17.2)	Ref.	Ref.	108 (4.2)	Ref.	Ref.
Positive	556	142 (25.5)	1.44 (1.16, 1.78)	1.36 (1.07, 1.73)	121 (21.8)	1.34 (1.07, 1.68)	1.23 (0.95, 1.58)	31 (5.6)	1.35 (0.90, 2.03)	1.16 (0.73, 1.85)
Ureaplasma parvum 6										
Negative	2,709	502 (18.5)	Ref.	Ref.	441 (16.3)	Ref.	Ref.	109 (4.0)	Ref.	Ref.
Positive	424	137 (32.3)	2.10 (1.68, 2.63)	1.93 (1.51, 2.48)	122 (28.8)	2.08 (1.64, 2.62)	1.97 (1.52, 2.54)	30 (7.1)	1.82 (1.20, 2.76)	1.76 (1.12, 2.78)
Ureaplasma parvum 14										
Negative	3,122	635 (20.3)	Ref.	Ref.	560 (17.9)	Ref.	Ref.	139 (4.5)		
Positive	11	4 (36.4)	2.24 (0.65, 7.67)	2.86 (0.80, 10.3)	3 (27.3)	1.72 (0.45, 6.49)	2.22 (0.57, 8.69)	0 (0)	–†	–†
Mycoplasma genitalium										
Negative	3,112	627 (20.1)	Ref.	Ref.	552 (17.7)	Ref.	Ref.	135 (4.3)	Ref.	Ref.
Positive	21	12 (57.1)	5.28 (2.22, 12.6)	3.17 (1.22, 8.22)	11 (52.4)	5.1 (2.16, 12.07)	3.06 (1.17, 7.99)	4 (19.0)	5.19 (1.72, 15.63)	6.09 (1.91, 19.49)

Continued

RTI pathogens	Total	HPV-positive			HR-HPV- positive			HPV 16/18-positive		
		n (%)	Crude *OR* (95% *CI*)	Adjusted *OR* (95% *CI*)*	*n* (%)	Crude *OR* (95% *CI*)	Adjusted *OR* (95% *CI*)*	*n* (%)	Crude *OR* (95% *CI*)	Adjusted *OR* (95% *CI*)*
Mycoplasma hominis										
Negative	2,986	577 (19.3)	Ref.	Ref.	509 (17.0)	Ref.	Ref.	126 (4.2)	Ref.	Ref.
Positive	147	62 (42.2)	3.05 (2.17, 4.28)	2.76 (1.87, 4.08)	54 (36.7)	2.83 (1.99, 4.00)	2.48 (1.66, 3.71)	13 (8.8)	2.20 (1.21, 4.00)	2.23 (1.15, 4.30)
Herpes simple virus type Ⅱ										
Negative	3,106	621 (20.0)	Ref.	Ref.	545 (17.5)	Ref.	Ref.	136 (4.4)	Ref.	Ref.
Positive	27	18 (66.7)	8.00 (3.58, 17.90)	6.67 (2.89, 15.36)	18 (66.7)	9.40 (4.20, 21.03)	7.94 (3.44, 18.29)	3 (11.1)	2.73 (0.81, 9.18)	2.38 (0.69, 8.25)
Any RTIs										
Negative	1,691	226 (13.4)	Ref.	Ref.	206 (12.2)	Ref.	Ref.	46 (2.7)	Ref.	Ref.
Single-RTI-positive	1,125	273 (24.3)	2.08 (1.71, 2.53)	1.97 (1.59, 2.45)	235 (20.9)	1.90 (1.55, 2.34)	1.82 (1.45, 2.28)	63 (5.6)	2.12 (1.44, 3.13)	2.17 (1.41, 3.34)
Multiple-RTI-positive	317	140 (44.2)	5.13 (3.94, 6.66)	4.85 (3.59, 6.56)	122 (38.5)	4.51 (3.45, 5.90)	4.17 (3.06, 5.68)	30 (9.5)	3.74 (2.32, 6.02)	3.47 (2.01, 6.00)

Abbreviation: HPV=human papillomavirus; HR-HPV=high risk HPV; RTI=reproductive tract infection; *OR*=odds ratio; *CI*=confidence interval.

* Adjusted for age group, ethnic group, education level, family monthly income, marital status, and parity.

† Regression was not possible because the sample size of the positive group was 0.

doi: 10.46234/ccdcw2024.038

[#] Corresponding authors: Xiaosong Zhang, zhangxiaosong@bjmu.edu.cn; Linhong Wang, linhong@chinawch.org.cn.

[1] Department of Obstetrics and Gynecology, Peking University First Hospital, Beijing, China; [2] School of Medicine, University College Dublin, Ireland; [3] Beijing Obstetrics and Gynecology Hospital, Beijing, China; [4] Tianjin Medical University General Hospital, Tianjin, China; [5] Northwest Women's and Children's Hospital, Xi'an City, Shaanxi Province, China; [6] Third Affiliated Hospital of Zhengzhou University, Zhengzhou City, Henan Province, China; [7] Shengjing Hospital of China Medical University, Shenyang City, Liaoning Province, China; [8] National Center for Chronic and Non-Communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, China.

Submitted: January 04, 2023; Accepted: February 27, 2024

REFERENCES

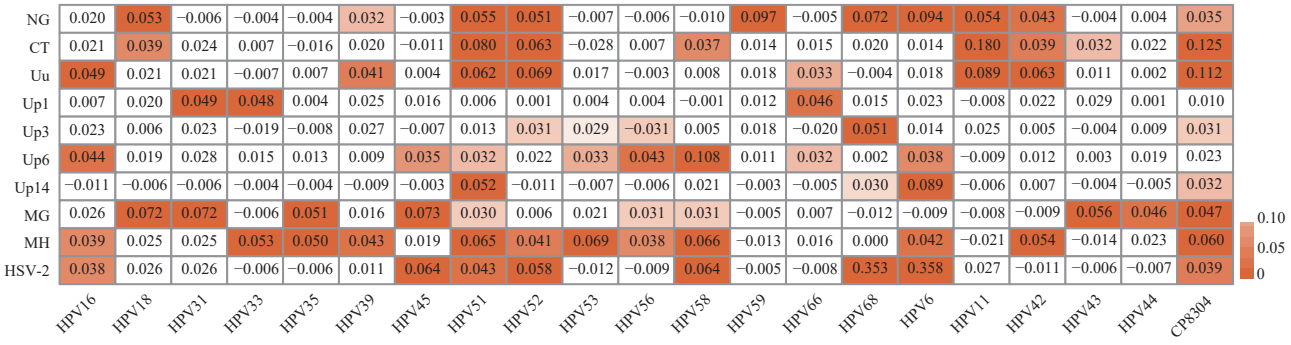
1. Van Gerwen OT, Muzny CA, Marrazzo JM. Sexually transmitted infections and female reproductive health. Nat Microbiol 2022;7(8):1116 – 26. https://doi.org/10.1038/s41564-022-01177-x.
2. Rowley J, Vander Hoorn S, Korenromp E, Low N, Unemo M, Abu-Raddad LJ, et al. Chlamydia, gonorrhoea, trichomoniasis and syphilis: global prevalence and incidence estimates, 2016. Bull World Health Organ 2019;97(8):548 – 62P. https://doi.org/10.2471/BLT.18.228486.
3. Crosbie EJ, Einstein MH, Franceschi S, Kitchener HC. Human papillomavirus and cervical cancer. Lancet 2013;382(9895):889 – 99. https://doi.org/10.1016/S0140-6736(13)60022-7.
4. Akbari E, Milani A, Seyedinkhorasani M, Bolhassani A. HPV co-infections with other pathogens in cancer development: a comprehensive review. J Med Virol 2023;95(11):e29236. https://doi.org/10.1002/jmv.29236.
5. Ye H, Song TG, Zeng X, Li L, Hou MM, Xi MR. Association between genital mycoplasmas infection and human papillomavirus infection, abnormal cervical cytopathology, and cervical cancer: a systematic review and meta-analysis. Arch Gynecol Obstet 2018;297(6):1377 – 87. https://doi.org/10.1007/s00404-018-4733-5.
6. Bahena-Román M, Sánchez-Alemán MA, Contreras-Ochoa CO, Lagunas-Martínez A, Olamendi-Portugal M, López-Estrada G, et al. Prevalence of active infection by herpes simplex virus type 2 in patients with high-risk human papillomavirus infection: a cross-sectional study. J Med Virol 2020;92(8):1246 – 52. https://doi.org/10.1002/jmv.25668.
7. Lu Z, Zhao PZ, Lu HJ, Xiao MF. Analyses of human papillomavirus, *Chlamydia trachomatis, Ureaplasma urealyticum, Neisseria gonorrhoeae*, and co-infections in a gynecology outpatient clinic in Haikou area, China. BMC Women's Health 2023;23(1):117. https://doi.org/10.1186/s12905-023-02259-6.
8. Zhong CY, Li XZ, Teng Y, Tian JY. Co-infection with *human papillomavirus* and sexually transmitted infections among Chinese individuals. Microb Pathog 2023;185:106395. https://doi.org/10.1016/j.micpath.2023.106395.
9. Adebamowo SN, Ma B, Zella D, Famooto A, Ravel J, Adebamowo C, et al. *Mycoplasma hominis* and *Mycoplasma genitalium* in the vaginal microbiota and persistent high-risk human papillomavirus infection. Front Public Health 2017;5:140. https://doi.org/10.3389/fpubh.2017.00140.
10. Wang LH. Accelerating cervical cancer prevention and control in China to achieve cervical cancer elimination strategy objectives. China CDC Wkly 2022;4(48):1067 – 9. https://doi.org/10.46234/ccdcw2022.215.

SUPPLEMENTARY MATERIALS

SUPPLEMENTARY TABLE S1. Demographic characteristics and co-infection of RTI pathogens with HPV among reproductive-age women in six tertiary hospitals in China from June 2021 to December 2022 [*n* (%)].

Characteristics	Total	HPV-positive & RTI-positive	HPV-positive & RTI-negative	HPV-negative & RTI-positive	HPV-negative & RTI-negative	χ^2	*P*
Overall	3,133	413 (13.2)	226 (7.2)	1029 (32.8)	1465 (46.8)		
Age group (years)						6.864	0.334
18–29	744	110 (14.8)	51 (6.9)	260 (34.9)	323 (43.4)		
30–39	1,628	202 (12.4)	124 (7.6)	519 (31.9)	783 (48.1)		
40–49	761	101 (13.3)	51 (6.7)	250 (32.9)	359 (47.2)		
Ethnic group*						9.504	0.023
Han	2,936	381 (13.0)	209 (7.1)	960 (32.7)	1,386 (47.2)		
Others	147	29 (19.7)	15 (10.2)	48 (32.7)	55 (37.4)		
Education level*						16.319	0.012
High school or below	533	84 (15.8)	31 (5.8)	172 (32.3)	246 (46.2)		
College	2,086	279 (13.4)	163 (7.8)	694 (33.3)	950 (45.5)		
Graduate or above	458	46 (10.0)	25 (5.5)	142 (31.0)	245 (53.5)		
Family monthly income (CNY)*						8.897	0.447
<5,000	572	75 (13.1)	37 (6.5)	190 (33.2)	270 (47.2)		
5,000–10,000	1,257	158 (12.6)	94 (7.5)	409 (32.5)	596 (47.4)		
10,001–20,000	836	115 (13.8)	65 (7.8)	256 (30.6)	400 (47.8)		
>20,000	322	43 (13.4)	21 (6.5)	125 (38.8)	133 (41.3)		
Marital status*						56.397	<0.001
Unmarried	621	125 (20.1)	50 (8.1)	210 (33.8)	236 (38.0)		
Married	2,407	264 (11.0)	169 (7.0)	781 (32.4)	1,193 (49.6)		
Divorce/others	80	19 (23.8)	5 (6.3)	28 (35.0)	28 (35.0)		
Parity*						65.536	<0.001
Nulliparous	800	154 (19.3)	74 (9.3)	290 (36.3)	282 (35.3)		
Multiparous	1,945	220 (11.3)	130 (6.7)	606 (31.2)	989 (50.8)		

Abbreviation: HPV=human papillomavirus; RTI=reproductive tract infection.
* There are missing values in the data.



SUPPLEMENTARY FIGURE S1. Heatmap of phi coefficients between different HPV genotypes and various RTI pathogens among reproductive-age women in six tertiary hospitals in China from June 2021 to December 2022.
Note: The number within each box indicates the phi correlation coefficient, while the color intensity of the boxes represents the magnitude of correlation. A white box indicates a correlation coefficient with a *P*-value greater than 0.01.
Abbreviation: HPV=human papillomavirus; RTI=reproductive tract infection; NG=*Neisseria gonorrhoeae*; CT=*Chlamydia trachomatis*;Uu=*Ureaplasma urealyticum*; Up=*Ureaplasma parvum*; MG=*Mycoplasma genitalium*; MH=*Mycoplasma hominis*; HSV-2=Herpes Simplex Virus Type II.