


ORIGINAL ARTICLE

Acceptability of and barriers to human papillomavirus vaccination in China: A systematic review of the Chinese and English scientific literature

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Abstract

Introduction: Widespread adoption of the human papillomavirus (HPV) vaccine will require population acceptance and tailoring of immunisation services to community needs and preferences. We examined peer-reviewed publications on the acceptability of and barriers to the HPV vaccine across China.

Methods: We searched English (MEDLINE, Embase, and Web of Science) and Chinese (CNKI, VIP, Wanfang data) databases between 1 January 2006 and 31 December 2017. We adopted a narrative approach for data synthesis.

Results: We identified 73 studies. The overall median acceptability of HPV vaccine was 71.8% (Q1–Q3: 58.6%–81%). Low levels of acceptability (<40%) of HPV vaccine were found in eastern regions of China. The largest differences of acceptability were observed between rural western regions (all >90%) and urban eastern regions (all <35%). Despite these regional variations, common barriers to HPV vaccine acceptance were concerns about vaccine safety, uncertainty over vaccine effectiveness, low perceived risk of cervical cancer and the price of the vaccine. The level of willingness to pay for the HPV vaccine (over 153 US dollars) was very low (<7%).

Conclusion: The acceptability of and attitudes towards HPV vaccine vary by regions and populations across China. HPV vaccination programmes will need to tailor service delivery as well as information materials to take account of regional concerns.

KEYWORDS

HPV vaccine, mainland China, safety concerns, vaccine acceptability, vaccine hesitancy

1 | INTRODUCTION

Cervical cancer is the second most common cancer in women aged 15–44 years in China, with an estimated 106,430 new cases and 47,739 deaths occurring annually (Bruni et al., 2018, 2019). The annual increase of incidence and mortality of cervical cancer was the

second highest among female cancers in the decade from 2000 to 2011 (Chen et al., 2016; Hu, Zheng, et al., 2014b). In 2018, the World Health Organization (WHO) launched a global strategy towards the elimination of cervical cancer and set three targets for the year 2030—90% coverage of HPV vaccination, 70% coverage of twice-lifetime screening, and 90% access to cervical precancer and cancer

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treatment services and palliative care' (Canfell et al., 2020). China's National Health Commission (NHC) has given full support to the WHO's global strategy. The Chinese Government's policy document Health China 2030—signalling the government's commitment to investing in health—included fast-tracking conditional approval of the nine-valent HPV vaccine and removing import tariffs on cancer drugs (F. Zhao & Qiao, 2019).

Imported vaccines against Human Papilloma Virus—Cervarix (bivalent vaccine) and Gardasil (quadrivalent and nine-valent vaccine)—were approved in China in 2016 (Pan et al., 2016), 2017 (Yin, 2017) and 2018 (Lin et al., 2019), respectively (Cao, 2020; Yin, 2017). A domestic vaccine—Cecolin—was approved in January 2020, with a two-dose schedule for adolescents aged 9–14 years, and three doses for females aged 15–45 years (Cao, 2020). In May 2020, Cecolin obtained WHO pre-qualification and was approved by the National Medical Products Administration (NMPA) for shipment of 100,000 doses to mainland China. However, the sole vaccine supply is inadequate to meet demand. Current government policy (Cao, 2020; Y. Xue, 2019) is that individuals can self-pay for the HPV vaccine through their private or employer insurance (Cao, 2020; Y. Xue, 2019)—a decision that may be determined by an individual perceptions of the HPV vaccine. A review of the global literature has suggested that women's choices over use of the HPV vaccine are influenced by multiple factors including the cost of vaccination, perceived efficacy and safety of the vaccine, and provision of information about vaccination (Santhanes et al., 2018).

Concerns about the safety and effectiveness of the HPV vaccine in China have been influenced by media reports of vaccine safety incidents between 2013 and 2018 (Hu et al., 2020; J. Ren et al., 2018; Yang et al., 2014). There is little evidence to support these concerns; however it has been difficult to assuage public doubts about HPV vaccination. Population characteristics affect acceptability; Lin et al. (2019) and You et al. (2020) reported socio-economic status was associated with a willingness to accept imported HPV vaccines among female undergraduates in China. A subsequent study in Shanghai reported migrants had lower confidence in the vaccine's benefits compared with the urban population, but were not as concerned about safety issues (J. Ren et al., 2018).

Despite an increasing focus on attitudes towards and acceptability of HPV vaccination in China, there is a dearth of comprehensive analysis, and limited data on any variation by demography or geography. To date, only one systematic review and meta-analysis (Y. Zhang et al., 2016) has been published on the knowledge and acceptability of the HPV vaccine among Chinese populations. The pooled acceptability of the HPV vaccine was 67.25%, with rates varied by sex, ethnicity and geographic regions. Safety of the vaccine was the main concern raised (Y. Zhang et al., 2016). However, variations of attitudes by region and socio-economic status of populations were not explored. The most recent and comprehensive survey among the Chinese population was a multicenter research study in 136 universities across eastern (78), central (27) and western (31) regions of China in 2019 (You et al., 2020). This study reported moderate acceptance (54%) of the HPV vaccine—the proportion of the sampled population

who say they would be willing to receive the HPV vaccine. Living in central and western regions and low socio-economic status were found to be associated with low levels of willingness to receive the HPV vaccination (You et al., 2020). However, barriers were not presented in terms of regional or socio-economic status (You et al., 2020).

We have carried out a systematic literature review of the acceptability of the HPV vaccine, and attitudes influencing the uptake of the HPV vaccine, across in the three regions (eastern, central and western) of China, and also reporting on variations in attitudes and acceptability by heterogeneous population groups, in order to inform targeted education strategies.

2 | MATERIALS AND METHODS

2.1 | Search strategy and selection criteria

We searched English-language databases: MEDLINE, Embase, and Web of Science and Chinese-language databases: China National Knowledge Infrastructure (CNKI), VIP Database for Chinese Technical Periodicals (VIP) and Wanfang data for relevant articles published between 1 January 2006 and 31 December 2017. The search terms are provided in Table S1. We included research studies if they included Chinese populations, assessed the acceptability of HPV vaccine and factors that may affect this level and were carried out in Mainland China, not in Hong Kong, Macao and Taiwan. Studies were excluded if they did not present original data (e.g., review), outcomes were not completely presented preventing data extraction, or only reported data on either knowledge or awareness of HPV and vaccine but did not report on acceptability and attitudes. The study selection followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009) and the selection process is displayed in Figure 1.

DuW, JD and BT independently reviewed the titles and abstracts in the Chinese databases. HO and DuW reviewed the English titles and abstracts. Disagreement on the records were discussed and clarified by DuW. The final decision was made by DuW for the inclusion of articles in the systematic review.

2.2 | Data synthesis

A standardised data extraction form was used (variables included study date, setting, participant characteristics, and the outcomes of each study). When identifying reported reasons for not accepting the HPV vaccine, we extracted the exact wording from English published papers, and translated Chinese wording into English from Chinese published papers. Four authors (DuW, HO, JD and BT) extracted the information from included studies and any disagreements were resolved through discussion. Study populations described in more than one paper were included as one research study, with any duplicate data excluded.

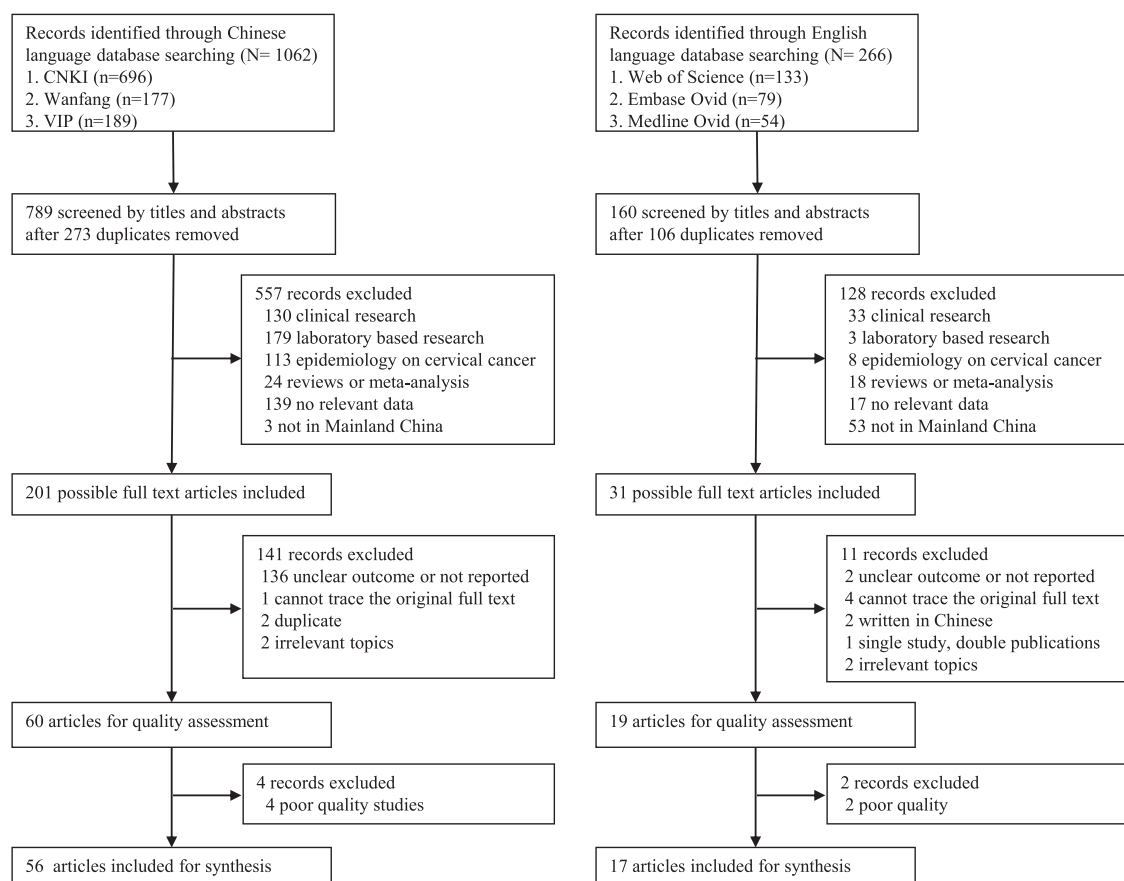


FIGURE 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram for selection of studies

An adapted version of Zaza's validated checklist (Zaza et al., 2000) (Table S2) was used to assess the quality of included studies. The checklist was translated from English into Chinese for quality assessment of the Chinese language studies, and assessed according to the checklist by three authors (DuW, JD and BT). Studies in English were assessed by HO and DuW; disagreements were resolved through discussion. Each study was graded as 'good', 'fair' or 'low' quality based on the scores generated by Zaza's checklist (Zaza et al., 2000). The outcome was presented in the Quality Assessment Tables (Table S3). 'Low' quality studies were removed for data synthesis.

A narrative approach was used to synthesise data (Ryan & Cochrane Consumers and Communication Review Group, 2020). Given the heterogeneity between studies (e.g., geographical regions, study populations and methods), and analytical strategies (adjustment for different confounders), meta-analysis of data was not feasible. The rationale for using narrative synthesis instead of meta-analysis is summarised in Table S4. We reported HPV vaccine acceptability and reasons for not taking HPV vaccine among people across geographical regions (eastern, central and western China). Table S5 summaries socio-demographic characteristics of the regions in China. The full results from each study, including stratification by rurality, by gender, by population subgroups (i.e., undergraduates, parents and medical providers) were

summarised in supplementary materials, grouped according to whether studies presented acceptability for oneself, or for a daughter or son, willingness to pay for the HPV vaccine by price ranges, and the reasons for not accepting the HPV vaccine. We used box plots to describe regional variation. For each region, we presented summary figures (the median with the first quantile and the third quantile) showing the acceptability of the HPV vaccine by rural/urban residence, and gender. For studies reporting results on reasons to accept or decline the HPV vaccine, we extracted the exact wording of reasons from English language papers and translated the wording of reasons into English from Chinese language papers and then summarised the results by multiple/single choice answers, populations and region. There was sufficient similarity in wording across studies to allow collation and comparison of findings. For studies reporting results of acceptability variation by the price of the vaccine, we extracted data that provided the acceptability by price ranges (i.e., under 15.3(¥100), 15.3–45.9(¥300), 45.9–76.5 (¥500), 76.5–153(¥1,000), and over 153 US dollars), grouping data by the lowest threshold of paying for the HPV vaccine (<3.06 (¥20), <7.65(¥50), <15.3, <45.9, <76.5 US dollars), and summarised the results by the most commonly used price range (>15.3, >153 US dollars). For studies exploring acceptability of domestic versus imported vaccines, we summarised the result by the most commonly used price range (<76.5, >76.5 US dollars).

The protocol of this study is registered with PROSPERO, number CRD42018085894. R software (version 3.5.2; <https://www.r-project.org/>) was used for descriptive analysis.

3 | RESULTS

3.1 | Characteristics of included studies

A total of 1062 records from Chinese language and 266 from English language searches were identified. Seventy-three studies (56 Chinese language and 17 English language), covering 24 provincial regions across mainland China and presenting data for 110,754 individuals, were selected for inclusion in the review (Figure 1).

The characteristics and results of the studies are summarised in Tables 1 and S6. All 73 included studies used a cross-sectional survey approach. The median sample size was 757 participants (range 104–13,024), with the majority of studies (73, 80.2%) having less than 2000 participants. Articles were published from 2007 to 2017. Many studies examined multiple topics including awareness of HPV, and understanding of the HPV vaccine. We report on acceptability, and barriers influencing acceptability of the vaccine.

3.1.1 | Geographical distribution

Of the 73 studies, the majority (40) were conducted in eastern China (Guangdong, Beijing, Hebei, Zhejiang, Liaoning, Shandong, Shanghai,

TABLE 1 Characteristics of included studies

Study	Region	Study setting	People	Sex
Feng SW 2010 (S. Feng et al., 2012)	Eastern	Rural/urban hospital	Rural/urban women outpatients	Female
Hong Y, 2013 (Hong et al., 2013)	Eastern	Community	Female sex workers	Female
Zhao FH, 2012 (F. H. Zhao et al., 2012)	Mixed	Urban/rural hospital	General population, government officials and healthcare providers	Mixed
Zhou YQ 2016 (Y. Q. Zhou, Yang, & Wu, 2016b)	Eastern	Urban hospital	Healthcare providers	Female
Ma D 2012 (X. J. Ma, Meng, et al., 2013b)	Eastern	Urban hospital	Healthcare providers	Mixed
Wang HQ 2011	Eastern	Urban hospital	Healthcare providers	NA
Gao J 2017 (Gao, Zhen, & Liu, 2017a)	Central	Urban community	Healthcare providers	NA
Li J 2011(J. Li, 2011)	Eastern	Rural/urban hospital	Healthcare providers and government officials	Mixed
Fu CJ, 2014(Fu et al., 2014)	Western	Medical university	Medical students	Mixed
Ma D 2013 (D. Ma, Wei, et al., 2013a)	Eastern	College	Medical students	Mixed
Gu C, 2015 (Gu et al., 2015)	Central	Medical university	Medical students	Female
Pan XF, 2014 (Pan et al., 2014)	Western	Medical university	Medical students	Mixed
Zou H, 2016 (Zou, Meng, et al., 2016a)	Eastern	Sexual health clinic	Men	Male
Zhang YY 2016 (Y. Y. Zhang, 2016)	Eastern	School	Parents of children	Female
Zhang SK, 2015 (S. K. Zhang et al., 2015)	Mixed	Middle school, junior	Parents of teenagers	Mixed
Hu HS 2014 (Hu, Ren, et al., 2014a)	Eastern	Middle school	Parents of teenagers	Mixed
Zhang H 2014 (H. Zhang, Yu, et al., 2014a)	Central	School	Parents of teenagers	Mixed
Wang W, 2015 (W. Wang, Ma, et al., 2015b)	Eastern	Middle school, junior	Parents of teenagers	Mixed
Yu Y, 2016 (Y. Yu et al., 2016)	Eastern	High school, primary, junior, senior	Parents of teenagers	Female
Yan J 2013 (J. Yan et al., 2013)	Western	Rural community	Rural adult women	Female
Ye JR 2011 (Ye, 2011)	Eastern	Rural community	Rural adult women	Female
Zhang XX 2014 (X. X. Zhang, Zhao, et al., 2014c)	Eastern	Rural hospital	Rural adult women	Female
Cheng Y 2017 (Cheng et al., 2017)	Central	Rural community	Rural adult women	Female
Song D 2007 (Song, 2007)	Central	Rural community	Rural adult women	Female
Li J, 2015 (J. Li et al., 2015)	Central	Villages	Rural adult women	Female
Yu J 2013 (J. Yu et al., 2013)	Western	Rural/urban community	Rural adult women, government officials and healthcare providers	Mixed
Wang XM 2012 (X. M. Wang et al., 2012)	Central	Rural community/urban hospital	Rural women residents/urban women outpatients	Female

TABLE 1 (Continued)

Study	Region	Study setting	People	Sex
Cui B 2010 (Cui, 2010)	Eastern	Rural community/urban hospital	Rural women/urban women patients	Female
Xue L, 2018 (L. Xue et al., 2018)	Eastern	Middle school, junior	Teenagers	Mixed
Wang SM, 2014 (S. M. Wang, Zhang, et al., 2014a)	Mixed	University	Undergraduate students	Mixed
Zeng XM 2015 (Zeng et al., 2015)	Eastern	College	Undergraduate students	Mixed
He X 2010 (X. He et al., 2010)	Central	College	Undergraduate students	Mixed
Zhu YR 2017 (Y. R. Zhu et al., 2017)	Central	College	Undergraduate students	Mixed
Zhou Y 2012 (Y. Zhou et al., 2012)	Central	College	Undergraduate students	Mixed
Gong FQ 2014 (Gong, 2014)	Eastern	College	Undergraduate students	Mixed
Xu J 2014 (Xu & Li, 2014)	Western	College	Undergraduate students	Mixed
Yang J 2016 (J. Yang et al., 2016)	Western	College	Undergraduate students	Female
Zou H, 2016 (Zou, Wang, et al., 2016b)	Eastern	University	Undergraduate students	Mixed
Huang H 2013 (H. Huang et al., 2013)	Western	College	Undergraduate students	Mixed
Liu RJ 2017 (R. J. Liu et al., 2017)	Eastern	College	Undergraduate students	Mixed
Li M 2013 (M. Li et al., 2013)	Eastern	NA	Undergraduate students and parents of teenagers	Mixed
Liu Q 2015 (Q. Liu et al., 2015)	Central	College	Undergraduate students and parents of teenagers	Mixed
Lu J 2016 (Lu et al., 2016)	Eastern	College/urban community/hospital	Undergraduate students/government/HCPs	Mixed
Tian T 2017 (Tian, 2017)	Western	NA	Urban adult men	Male
Zhu JH 2016 (J. H. Zhu et al., 2016)	Eastern	Urban CDC	Urban adult men	Male
Huang YH 2014 (Y. H. Huang et al., 2014)	Eastern	Urban community	Urban adult men and women	Mixed
Li J 2008 (J. Li et al., 2009)	Eastern	Urban community	Urban adult women	Female
Zhang SK 2014 (S. K. Zhang, Huang, et al., 2014b)	Mixed	NA	Urban adult women	Female
Lei JH 2015 (Lei & Zhong, 2015)	Eastern	Urban hospital	Urban adult women	Female
Meng LP 2015 (Meng et al., 2015)	Eastern	Urban community	Urban adult women	Female
Yang GQ 2013 (G. Q. Yang et al., 2013)	Eastern	Urban hospital	Urban adult women	Female
Zhou YQ 2016 (Y. Q. Zhou, Yang, & Wu, 2016b)	Eastern	Urban community	Urban adult women	Female
Ran LM 2014 (Ran et al., 2014)	Western	Urban hospital	Urban adult women	Female
Liu XW 2016 (X. W. Liu et al., 2016)	Eastern	Urban hospital	Urban adult women	Female
Ma XJ 2013 (X. J. Ma, Meng, et al., 2013b)	Eastern	Urban hospital	Urban adult women	Female
Zhao DJ 2010 (D. J. Zhao et al., 2010)	Eastern	Urban community	Urban adult women	Female
Shao SJ 2013 (Shao et al., 2013)	Eastern	Urban hospital	Urban adult women	Female
Hu SY, 2011 (S. Y. Hu et al., 2011)	Eastern	Rural (Binhai), suburban (Jintan) and urban (Xuzhou)	Urban and rural women	Female
Li J, 2009 (J. Li et al., 2009)	Mixed	Urban community cluster and rural areas	Urban and rural women	Female
Feng S, 2012 (S. Feng et al., 2012)	Eastern	Urban/rural hospital	Urban and rural women	Female
Wu Y 2011 (Wu, 2011)	Eastern	NA	Urban women adults	Female
Chang IJ, 2013 (Chang et al., 2013)	Mixed	Companies and universities	Urban women and undergraduate students	Female
He M 2011 (M. He et al., 2011)	Mixed	Urban hospital	Urban women outpatients/urban hps	Female
Xiao W 2010 (Xiao & Bian, 2009)	Eastern	Urban hospital	Urban women patients	Female
Huang GF 2011 (G. F. Huang, 2011)	Eastern	Urban hospital	Urban women patients	Female
Xie WL 2015 (Xie et al., 2015)	Central	Urban hospital	Urban women patients	Female
Fan BJ 2009 (Fan, 2009)	Eastern	Urban hospital	Urban women patients	Female
Su Q 2016 (Su et al., 2016)	Western	Urban hospital	Urban women patients	Female

(Continues)

TABLE 1 (Continued)

Study	Region	Study setting	People	Sex
Wang X 2014 (X. Wang, Lei, et al., 2014b)	Western	Urban hospital	Urban women patients	Female
Zhu QY 2015 (Q. Y. Zhu et al., 2015)	Eastern	Urban hospital	Urban women patients	Female
Fatima 2014 (Fatima, 2014)	Western	Rural community	Uyghur rural adult women	Female
Ren CL 2011 (C. L. Ren et al., 2011)	Western	NA	Uyghur/Hui/Han women adults	Female
Wang L 2015 (L. Wang, Ouyang, & Wang, 2015a)	Central	Urban hospital	Medical students	Female

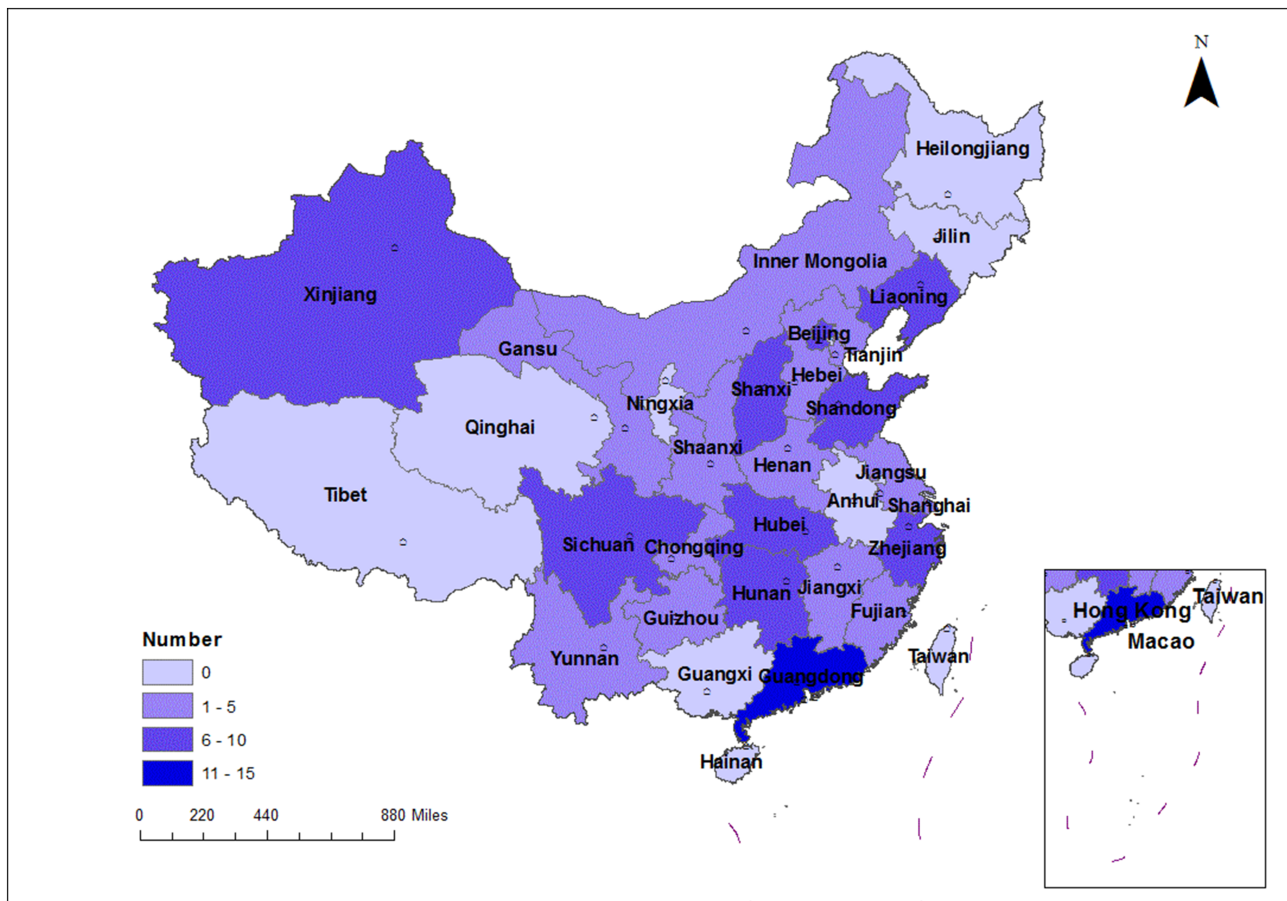


FIGURE 2 Map of mainland China, showing the number of studies in each province and region

Tianjin and Jiangsu), 13 studies in western China (Xinjiang, Yunnan, Chongqing, Shaanxi, Gansu, Inner Mongolia, Guizhou and Sichuan) and 13 in central China (Hunan, Jiangxi, Shanxi, Hubei and Henan). Seven studies were multicenter, recruiting participants across two or three regions of China. Publications from three areas—Beijing, Guangdong and Zhejiang—predominated (27 in total) (Figure 2).

3.1.2 | Study participants

The majority of studies (39 in total) were conducted among adult women, 20 among undergraduate students, seven among parents of teenagers, six among healthcare providers, four among adult men, two

among Uyghur people and one among teenagers (aged 11–18 years). Studies examining the views of ethnic minority groups (Uyghur, Mongolian and Hui peoples) were only found from western China (Tables 1 and S6). Most studies (38) were undertaken in urban areas, with 10 in rural areas, and 9 in both urban and rural areas (Table S7).

3.2 | Quality of included studies

Overall, 23 studies were of ‘good’ quality, 50 were ‘fair’ and 14 were ‘low’ (Table S3). Low quality studies were excluded from data synthesis. Studies carried out in western China were more likely to be of lower quality whereas those reporting data from eastern China were

more likely to clearly describe the study population, outcomes, statistical tests and study instruments. Full details are available in Tables S3 and S4.

3.3 | Acceptability of the HPV vaccine

Fifty-eight studies assessed the level of acceptability of the HPV vaccine. Acceptability of HPV vaccine was generally defined as the proportion of people willing to have HPV vaccine.

The overall median rate of acceptability of the HPV vaccine was 71.8% (Q1–Q3: 58.6%–81%). Regional variation was observed: studies from western China reported a higher acceptability (median: 84.7%, Q1–Q3: 74.3%–94.1%) compared with those from eastern China (median: 68.4%, Q1–Q3: 56.8%–76.4%) and central China (median: 59.9%, Q1–Q3: 50.6%–75.5%) (Figure 3). In 52 of 58 studies, the acceptability of the HPV vaccine was over 50% (Table S7). Ten studies reported over 80% baseline acceptability of HPV vaccine (Fan, 2009; Fatima, 2014; Fu et al., 2014; He et al., 2011; Liu et al., 2016; Ren et al., 2011; Tian, 2017; Yan et al., 2013; Zhao et al., 2012). In contrast, eight studies from eastern China reported low levels of acceptability of HPV vaccine (less than 40% willingness) (Hong et al., 2013; Hu, Ren, et al., 2014a; Ma et al., 2012; Ma, Meng, et al., 2013b; Y. Yu et al., 2016; S. K. Zhang et al., 2015; Y. Y. Zhang, 2016; Zou, Meng, et al., 2016a) across various population groups including female sex workers (Hong et al., 2013), healthcare providers (D. Ma et al., 2012), parents of teenagers (Y. Yu et al., 2016; S. K. Zhang et al., 2015; Y. Y. Zhang, 2016) and urban men (Y. H. Huang et al., 2014; Zou, Meng, et al., 2016a) and women (Ma, Meng, et al., 2013b). For example, Yu et al. (2016), Zhang (2016) and Ma, Meng, et al. (2013b) found that 24.7%–33% of respondents indicated that they would be willing to

take the HPV vaccine in urban and rural areas of Shandong and Fujian. Ma et al. (2012) found that 25%–37% healthcare providers in urban Hebei indicated a willingness to accept the vaccine. Zhang et al. (2015) found low overall intention of accepting the HPV vaccine (36.2%) in seven provinces in both western and eastern China: however, it is not possible to disaggregate the results by region (S. K. Zhang et al., 2015) (Table S7).

When taking account of rurality and regional location, the largest differences in acceptability were observed between rural western and urban eastern groups. For example, Fatima (2014), Yan et al. (2013) and Yu et al. (2013) reported high levels of acceptability of HPV vaccine (exceeding 90%) in rural western China, whereas Yu Y 2016, Zhang YY 2016 and Ma XJ 2013 reported levels of acceptability of HPV vaccine of no more than 35% in urban eastern China (Table S7).

Five studies (Fatima, 2014; Fu et al., 2014; Y. H. Huang et al., 2014; Wang, Zhang, et al., 2014a; L. Xue et al., 2018) stratified level of acceptability of the HPV vaccine by gender. In each study, the authors found women were more likely to express a willingness to be vaccinated than men. Two studies among undergraduates found that 73.2%–87.5% of females and 68.3%–81.8% of males would accept the HPV vaccine (Fu et al., 2014; Wang, Zhang, et al., 2014a) (Table S7).

Twenty-five studies assessed the level of parental acceptability of the HPV vaccine for a child (Chang et al., 2013; Cui, 2010; Fan, 2009; Fatima, 2014; Fen, 2010; M. He et al., 2011; Hong et al., 2013; Hu, Ren, et al., 2014a; Lei & Zhong, 2015; J. Li, 2011; J. Li et al., 2015; J. Li et al., 2009; M. Li et al., 2013; D. Ma et al., 2012; Pan et al., 2014; C. L. Ren et al., 2011; Su et al., 2016; Wang, Ma, et al., 2015b; Xiao & Bian, 2009; Xie et al., 2015; Zhang, Yu, et al., 2014a; Zhang, Huang, et al., 2014b; S. K. Zhang et al., 2015; Y. Y. Zhang, 2016; Zhao et al., 2010; F. H. Zhao et al., 2012; Zhou, Fan, et al., 2016a; Zou,

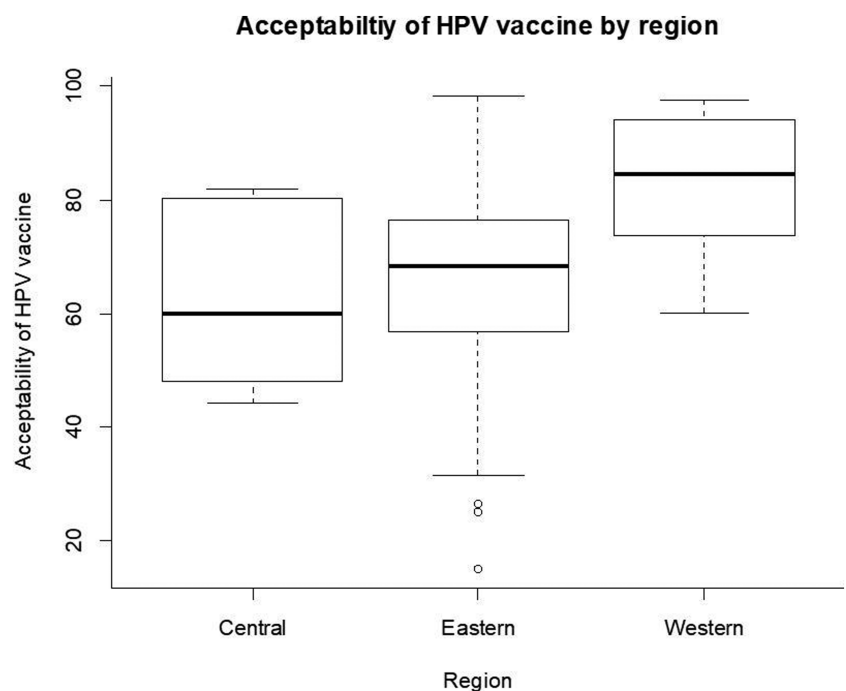


FIGURE 3 Acceptability of human papillomavirus (HPV) vaccine by region

Wang, et al., 2016b). The majority of studies (19 of 25) reported levels of acceptability of the HPV vaccine for either a daughter or a son exceeded 50%. Seven studies (Fan, 2009; Fatima, 2014; M. He et al., 2011; J. Li, 2011; J. Li et al., 2015; J. Li et al., 2009; C. L. Ren et al., 2011) reported high levels of acceptability of the HPV vaccine (over 80% acceptability). However, it is important to note that many of these studies (19 of 25) were carried out among health care providers, gynaecology patients, or undergraduates, with respondents having either adult daughters or sons, or no children at present. Only six studies were carried out among parents of teenagers: among these studies, the level of acceptability of the HPV vaccine was lower, ranging from 8.2% to 42.8%; (Hu, Ren, et al., 2014a; M. Li et al., 2013; Wang, Ma, et al., 2015b; H. Zhang, Yu, et al., 2014a; S. K. Zhang et al., 2015; Y. Y. Zhang, 2016). One study in Fujian (Y. Y. Zhang, 2016) reported a higher acceptability of 58% for their daughters (Table S8).

3.4 | Barriers to uptake of the HPV vaccine

Studies reporting barriers affecting the acceptability of HPV vaccine are summarised in Table S9. The four most commonly reported barriers to HPV vaccine acceptance were concerns about vaccine safety, questions regarding vaccine effectiveness, low perceived risk of cervical cancer, and the price of the vaccine.

Thirty-seven studies reported the reasons people would not be willing to accept the HPV vaccine (Table S10). In general, the level of concerns about vaccine varied widely across different populations and regions. Undergraduates (Gong, 2014; Gu et al., 2015; H. Huang et al., 2013; Lu et al., 2016; Pan et al., 2014; Zeng et al., 2015; Zou, Wang, et al., 2016b), parents of teenagers (Chang et al., 2013; Hu, Ren, et al., 2014a; W. Wang, Ma, et al., 2015b; Y. Yu et al., 2016; H. Zhang, Yu, et al., 2014a; S. K. Zhang, Huang, et al., 2014b) and urban adult women (Chang et al., 2013; Cui, 2010; Fan, 2009; S. Feng et al., 2012; M. He et al., 2011; Y. H. Huang et al., 2014; Lei & Zhong, 2015; X. W. Liu et al., 2016; Wu, 2011; S. K. Zhang, Huang, et al., 2014b; D. J. Zhao et al., 2010; F. H. Zhao et al., 2012) reported high levels of worry about vaccine safety, concerns about the vaccine's effectiveness and concerns that the vaccine has not been widely used in China. Higher levels of worry about the vaccine's safety were found among undergraduates (Zou, Wang, et al., 2016b) in Shandong and by Gong FQ 2014 (Gong, 2014) in Liaoning (83.3% and 92.1% respectively). Two studies (H. Huang et al., 2013, and Chang et al., 2013) reported lower rates (57.5% and 58.3% respectively), with lower rates among male undergraduates (safety: male vs. female: 49.3% vs. 67.7%; effectiveness: male vs. female: 19.7% vs. 36.5%) (H. Huang et al., 2013). However, other studies reported inconsistent gender differences (Fu et al., 2014; Pan et al., 2014; Zou, Wang, et al., 2016b) (Table S10). Parents of teenagers (Hu, Ren, et al., 2014a; W. Wang, Ma, et al., 2015b; Y. Yu et al., 2016; H. Zhang, Yu, et al., 2014a; S. K. Zhang et al., 2015) also reported high levels of concern about the vaccine's safety and the rates varied less widely from 62.4% to 78.2%; these studies were from urban areas of seven

provinces. Zhang SK (S. K. Zhang et al., 2015) noted that mothers worried more than fathers about the vaccine's safety (67.9% vs. 62.4%), but this gender difference in parental attitudes was not reported in other studies (Table S11).

Patterns of concerns about HPV vaccine among rural adult women were inconsistent and differed from other populations. Of the eight studies exploring attitudes among rural women (Cui, 2010; Cheng et al., 2017; Fatima, 2014; S. Feng et al., 2012; J. Li et al., 2009; Song, 2007; J. Yan et al., 2013; F. H. Zhao et al., 2012), five (Cui, 2010; Fatima, 2014; J. Li et al., 2015; Song, 2007; J. Yan et al., 2013) reported an unwillingness based on a low perceived risk of cervical cancer, followed by concerns about the vaccine's safety, and the high price of the vaccine. The levels of perceived low risk for cervical cancer among rural women varied widely across regions: 34.8% in Liaoning (Cui, 2010), 67.8% in Shanxi (Song, 2007), 78.4% in Gansu (J. Yan et al., 2013), 84.3% in Xinjiang (Fatima, 2014) and 31.8% for daughters in Shanxi (J. Li et al., 2015). Two studies (Cheng et al., 2017, and F. H. Zhao et al., 2012) found rural women reported different patterns of concerns about the HPV vaccine in comparison with urban women—the high price of the vaccine was the major concern of rural women, while concerns about the vaccine's safety was more predominant among urban women (Table S10).

3.5 | Cost of the HPV vaccine

Twenty-eight studies examined respondents' willingness to pay for the HPV vaccine. The level of willingness of paying over 100 Chinese yuan (15.3 US dollars) for the HPV vaccine varied widely. Low levels of willingness (range: 6.1%–16.2%) were found in seven studies (Li et al., 2008; Song, 2007; Su et al., 2016; Xiao & Bian, 2009; J. Yang et al., 2016; D. J. Zhao et al., 2010): three (range: 7.8%–16.2%) in the western region (two in Shaanxi (Su et al., 2016; J. Yang et al., 2016), one in Xinjiang (Fatima, 2014)) with the lowest threshold of paying less than 50 Chinese yuan (7.65 US dollars); four (6.1%–15.8%) published before 2010 (J. Li et al., 2008; Song, 2007; Xiao & Bian, 2009; D. J. Zhao et al., 2010) with the lowest threshold of paying less than 20 Chinese yuan (3.06 US dollars). Higher rates (19.2%–51.1%) of willingness of paying over 100 Chinese yuan (15.3 US dollars) were found in the other three studies in central and eastern regions (two in Hebei (X. W. Liu et al., 2016; D. Ma et al., 2012), one in Shanxi (X. M. Wang et al., 2012)), published after 2010 with the lowest threshold of paying less than 50 Chinese yuan (7.65 US dollars) (Table S12).

For the willingness of paying over 1,000 Chinese yuan (153 US dollars) for the HPV vaccine, all (Fu et al., 2014; H. Huang et al., 2013; W. Wang, Ma, et al., 2015b; Wu, 2011; Y. Y. Zhang, 2016; Zou, Wang, et al., 2016b) but two (Lu et al., 2016; Y. R. Zhu et al., 2017) reported very low levels of willingness: less than 7% people (range: 2.0%–6.5%) would be willing to pay over 1000 Chinese yuan (153 US dollars) for the HPV vaccine. The exceptions were undergraduates in Hunan where the level of willingness to pay over 1000 Chinese yuan (153 US dollars) ranged from 8.2% to 17.7% for domestic and

38.1%–41.4% for imported vaccines.(Y. R. Zhu et al., 2017). Another study, health providers and government officials (Lu et al., 2016) in Shanghai also reported acceptability of a high cost (Table S12).

Ten studies compared domestic and imported HPV vaccines and found that people would be willing to pay more for imported vaccines (Table S12) (M. He et al., 2011; H. Huang et al., 2013; M. Li et al., 2013; Lu et al., 2016; Pan et al., 2014; Wang, Zhang, et al., 2014a; W. Wang, Ma, et al., 2015b; J. H. Zhu et al., 2016; Y. R. Zhu et al., 2017; Zou, Wang, et al., 2016b). For example, Zhu YR 2017 (Y. R. Zhu et al., 2017) found that if the vaccine was less than 500 Chinese yuan (76.5 US dollars), 27.2% versus 62.8% of undergraduates were willing to pay for imported and domestic vaccines respectively, but if the vaccine was over 1000 Chinese yuan (153 US dollars), the willingness increased to 39.8% for imported vaccines and dropped to 12.6% for domestic ones. Zhu JH 2016 (J. H. Zhu et al., 2016) reported the acceptable price for imported HPV vaccine was 755 Chinese yuan (115.5 US dollars) but 604 Chinese yuan (92.4 US dollars) for domestic vaccine.

4 | DISCUSSION

This review explored the acceptability of and attitudes towards HPV vaccine among 110,754 Chinese people living in 24 provinces across mainland China, from 73 included studies, from both the Chinese- and English- language literature. The acceptability of and barriers to HPV vaccination vary across regions (eastern, central and western) and different demographic populations in China. The most common barriers affecting acceptability of the HPV vaccine include concerns about the vaccine's safety, effectiveness, price and an individual's perceived risk.

Compared with a previous systematic review(Y. Zhang et al., 2016), we have reported variation of acceptability of the HPV vaccine by region, different populations and by price range. Zhang et al published a meta-analysis of 58 studies in Mainland China in 2016, showing a pooled willingness to take the HPV vaccine of 67.25% of studies' participants—very close to our overall estimate. However, comparison should be made with caution given the differences in inclusion criteria. In our review, low levels of acceptability of the HPV vaccine were most commonly found in eastern China irrespective of population groups, while studies from western China showed much higher acceptance levels. When rurality is considered, participants from rural western regions had nearly three times the level of HPV vaccine acceptability compared to urban eastern people (who are mostly better-educated and with higher income) (Table S5). This finding was consistent with Liu et al.'s research who found that people who were 'relatively well-educated, had higher incomes and lived in urban areas' had more vaccine hesitancy (D. Hu et al., 2020). Papers published since 2017 report similar or contradictory findings. Wagner AL (Wagner et al., 2019) and Lin Y (Lin et al., 2019) reported similar findings—people in low and middle-income regions were less vaccine hesitant and had fewer safety concerns than people in high-income regions of China. However, this contrasts with You D's finding that low level of willingness was found in lower income groups and

rural residents in central and western regions of China (You et al., 2020). However, we also noted variations in reasons for concern about HPV vaccine among different populations. Vaccine safety was the greatest concern raised by urban women, and those in the eastern provinces.

Interpretation of our findings should take into account different immunisation services in respective populations and regions (Hu, Ren, et al., 2014a; W. Wang, Ma, et al., 2015b; Y. Yu et al., 2016). For example, eastern China, including Guangdong and Shandong, should consider providing a focus of health education on the vaccine's safety particularly to parents; while provinces in western China such as Xinjiang and Gansu should consider subsidising part of the cost of the vaccine, or initiate a two-dose instead of a three-dose schedule to reduce the cost. Overall, there is little research on the relationship between vaccine acceptability and socio-economic status in China; therefore, the findings should be interpreted according to the specific context.

Additionally, many studies did not take account of vaccine price in examining the overall acceptability of HPV vaccine, and results may reflect an expectation that the vaccine would be free of charge. In those studies that did include price, the level of acceptability was 6.1%–51.1% if the price was over 15.3 US dollars, lower (6.1%–16.2%) in people in Shaanxi (Su et al., 2016; J. Yang et al., 2016) and Xinjiang (Fatima, 2014), particular lower (2%–6.5%) (Fu et al., 2014; H. Huang et al., 2013; W. Wang, Ma, et al., 2015b; Wu, 2011; Y. Y. Zhang, 2016) if the vaccine's price was over 153 US dollars—but the price was still much lower than the market price in China (Yin, 2017). A similar downward trend was shown in a study based in Hong Kong (Z. Wang et al., 2018), where acceptability dropped to 14.9%–27.4% from 51.6%–63.0% if the vaccine was at a market price. Moreover, we found that when the vaccine price was over 76.5 US dollars, Chinese people preferred to pay more for imported vaccines than domestic ones (Figure 4). This is a common cost threshold in a number of Chinese studies which is close to the cost-effective price per vaccinated woman (\leq \$50 [¥350]) suggested by Levin CE (Levin et al., 2015). However, in China, the imported HPV vaccine costs as much as \$271–571 (¥1806–4,000) (Cao, 2020; Yin, 2017), compared to \$94–170 (¥658–987) for the domestic HPV vaccine (Cecolin) (Cao, 2020). This gap between the acceptable or cost-effective price, and the real cost, highlights the need for strategies to reduce the HPV vaccine cost, particularly in rural areas and less resourced provinces.

Economic development varies within each region/province and may contribute to the variation in HPV vaccine acceptability. In addition, the respective region/province's vaccine safety history must be taken into account (R. T. Yang et al., 2014). HPV vaccine safety events in Shenzhen (Guangdong) in 2013 (R. T. Yang et al., 2014), in Shandong in 2016, and in Changchun Changsheng Biotechnology company in 2018 (D. Hu et al., 2020) led to a public trust crisis, resulting in a decline in the vaccination rate afterwards and documented vaccine hesitancy (D. Hu et al., 2020; X. L. Yan, 2016). Some vaccine safety events were misrepresented (and exaggerated) in the media (R. T. Yang et al., 2014), some arose from lack of supervision and professional management of cold chain logistics (R. T. Yang et al., 2014).

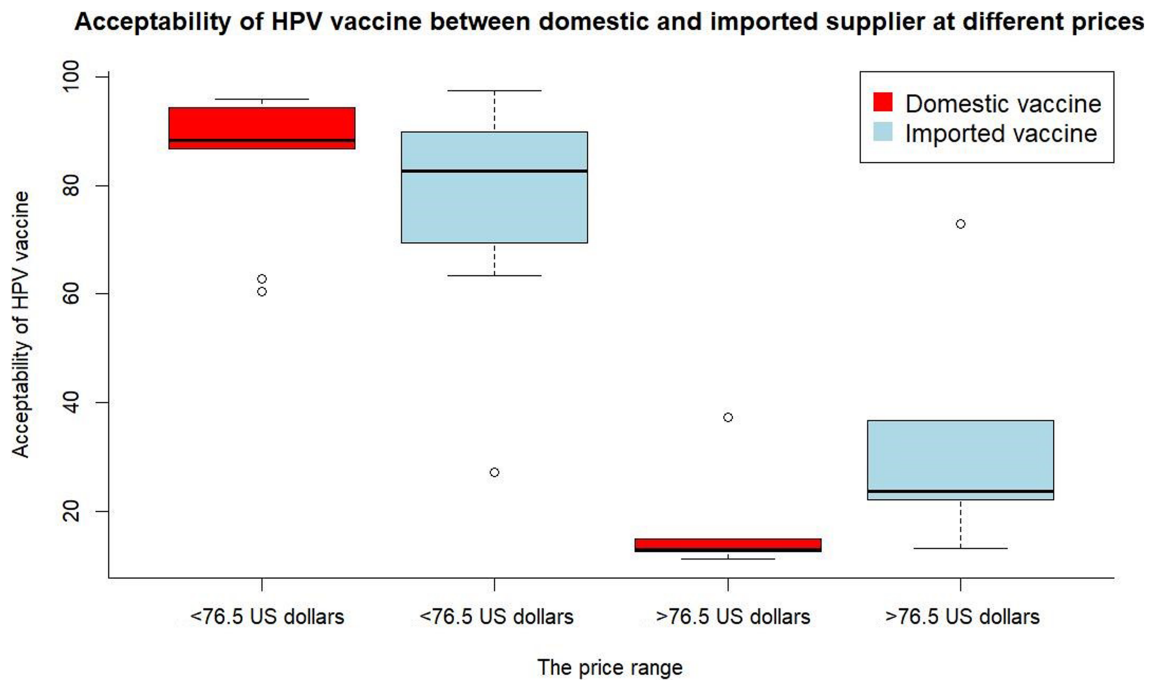


FIGURE 4 Acceptability of human papillomavirus (HPV) vaccine between domestic and imported supplier at different prices

That these safety events occurred mostly in eastern provinces may partially explain our findings in this region: the lowest level of acceptability of vaccine and high levels of worries about the vaccine's safety were in eastern China (a more affluent region). Well educated people and those on higher incomes (female undergraduates and parents of teenagers in urban areas) were groups with the most hesitancy. Similarly, Liu et al. reported people who were 'relatively well-educated, had higher incomes and lived in urban areas' had more vaccine hesitancy (D. Hu et al., 2020). However, we note that information on the vaccine's safety and effectiveness may not have been available to parents of teenagers in studies from western China, and there is a need to investigate whether the safety incidents will affect acceptability of HPV vaccine in the long term. At present, concerns about vaccine safety are relatively limited, and better public understanding of the HPV vaccine (including evidence of effectiveness, safety profile, informing health care providers of health status prior to vaccination), is needed, particularly in eastern China (e.g., Shandong and Guangdong). Public health officials should provide transparent evidence-based information following any vaccine scares and tailor public health messages to individuals with different education levels.

Our study was comprehensive and systematic, but did have some limitations. Firstly, we focused our analysis on regional variations across China because government policy or national programmes are mostly frequently launched or located by region and province: the three regions themselves represent socio-economic inequalities because they were originally divided based on disparities in economic progress (Gao, Zhou, et al., 2017b). However, region-level data are crude, and variation within region based on rurality and sex could not always be assessed because of lack of data on these subgroups in the

included studies. Secondly, we used median, first quantile and third quantile for our estimates of regional level of acceptability because studies are heterogeneous in population groups. Median, first, and third quantiles are not weighted by sample size, and region-level data require cautious interpretation. However, our review was carried out according to PRISMA guidance, following a registered protocol and assessing the quality using modified quality assessment criteria. Most of the studies included in this review used quantitative study designs with robust sample sizes. Additionally, comparable results among sub-populations and regions were observed. Thus, this review provides a valid summary of the existing evidence on acceptability of and attitudes towards HPV vaccine in China. We recognise that there was no common definition of the term 'effectiveness' in the included studies; we list the wording used (in English and Chinese) in Table S9. Finally, studies since 2017 were not included in the systematic review, but we have compared findings in contemporary literature published since 2017 with our findings.

5 | CONCLUSIONS AND IMPLICATIONS

To our knowledge, this is the first and most comprehensive systematic review to explore regional and demographic variations in acceptability of HPV vaccine in China and our review highlights important differences in willingness and barriers to accept the HPV vaccine between different populations and regions of China. Our findings indicate that barriers affecting the willingness to take HPV vaccine are complex, involving multiple factors. Overall, for rural women, particularly in western regions, low perceived risk of cervical cancer and the high

vaccine price were the most prominent barriers, while for undergraduates and parents of teenagers in urban areas, particularly in the eastern region, the major concerns were the safety and effectiveness of the HPV vaccine.

Our review highlights potential strategies for policy makers. It is currently government policy (Cao, 2020; Y. Xue, 2019) that individuals can pay for the HPV vaccine out of pocket or through private or employer insurance (Cao, 2020; Y. Xue, 2019). Subsidising vaccines, particularly for rural western regions, should be considered. Moreover, high rates of HPV vaccination coverage are necessary to achieve global targets for elimination (four or fewer cases per 100,000 women-years). Elimination rates will be much lower if only screening and treatment are used without vaccination (Brisson et al., 2020; Canfell et al., 2020). Our findings may help inform policy in other regions and populations that have not yet been included in academic studies, although we recommend that research in these provinces and communities is carried out.

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CONFLICT OF INTEREST

All authors declared no conflicts of interests. The funder of the study had no role in the study design, data collection, data analysis, data interpretation or writing of the report. The corresponding authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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